European Commission

Combined Draft Renewal Assessment Report prepared according to Regulation (EC) N° 1107/2009
and
Proposal for Harmonised Classification and Labelling (CLH Report) according to Regulation (EC) N° 1272/2008

Penconazole (ISO)

1-[2-(2,4-dichlorophenyl)pentyl]-1*H*-1,2,4-triazole

Volume 1

Rapporteur Member State: Norway
Co-Rapporteur Member State: Germany

Version History

When	What
11th of June 2021	Initial dRAR to co-RMS (DE)
12th of November 2021	Initial dRAR submitted to EFSA

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Level 1

Penconazole

1. STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THIS REPORT HAS BEEN PREPARED AND BACKGROUND INFORMATION ON THE APPLICATION

1.1 CONTEXT IN WHICH THIS DRAFT ASSESSMENT REPORT WAS PREPARED

1.1.1 Purpose for which the draft assessment report was prepared

Penconazole is already an approved substance under Commission Regulation (EC) No. 1107/2009. This renewal assessment report (RAR) is prepared to evaluate the dossier submitted to support the renewal of the approval of penconazole.

Syngenta Crop Protection AG, on behalf of Syngenta Crop Protection AG and Ascenza Agro SA, submitted an application and a dossier to support the renewal of the approval of penconazole. This was in accordance with Commission Regulation (EU) 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009. Norway, acting as the RMS, evaluated all aspects of the renewal dossiers via a Renewal Assessment Report (RAR).

A proposal for a new MRL-setting is also included, as well as a proposal for new Classification & Labelling.

1.1.2 Arrangements between rapporteur Member State and co-rapporteur Member State

Norway, as RMS, made the assessment and prepared the RAR. Germany, acting as Co-RMS, agreed to review the RAR before the submission to the Commission and EFSA.

1.1.3 EU Regulatory history for use in Plant Protection Products

Penconazole was included as a New Active Substance in Annex I of EU Council Directive 91/414/EEC on 1 January 2010 (Commission Directive 2009/77/EC, 1 July 2009 and amended in Commission Directive 2010/34/EU, 31 May 2010). Syngenta was the sole data submitter in support of Annex I inclusion. Germany acted as Rapporteur Member State (RMS).

EFSA sent to the Commission its conclusion regarding the peer review of the pesticide risk assessment of the active substance penconazole (23 September 2008).

The Commission presented a Review Report (SANCO/4461/09 – rev 3, 26 February 2009, updated 26 January 2021) in support to the consideration of Annex I inclusion. The Review Report was updated 27 November 2009 confirming the reference specification purity set by the RMS in the evaluation report on the finalisation of the reference specification of penconazole (September 2009), as well as revision 2 was taken note of 11 May 2010 due to extension of inclusion as laid down in Chapter 1. It was also updated 26 January 2021 to include the agreed reference values and residue definitions for the triazole derived metabolites.

Penconazole was (and is currently) approved under Commission Regulation (EC) No. 1107/2009 (repealing Council Directive 91/414/EEC) via Commission Implementing Regulation (EU) No. 540/2011 of 25th May 2011. By way of derogation from the Implementing Regulation (EU) No 540/2011, the expiry dates for approval of certain active substances, including penconazole, was extended to 31 December 2022 (Commission implementing regulation (EU) 2021/1449). This allowed applicants to prepare, and for the Commission to then consider, applications for renewal of this active substance.

EFSA has published a Review of the existing maximum residue levels for penconazole according to Article 12 of Regulation (EC) No 396/2005 (EFSA Journal 2017; 15(6):4853).

1.1.4 Evaluations carried out under other regulatory contexts

The RMS is not aware of any other relevant EU-evaluations of penconazole carried out in the framework of other relevant EU-legislation (e.g. biocides, flavourings, food additives, cosmetics).

Penconazole is included in the Inventory of Evaluations performed by the Joint Meeting on Pesticide Residues (JMPR), where the most recent report is from 2015.

The RMS did not find any recent evaluation of penconazole from EPA (USA) or PMRA (Canada).

1.2 APPLICANT INFORMATION

Members of the Penconazole Task Force are: Syngenta Crop Protection AG and Ascenza Agro SA.

1.2.1 Name and address of applicant(s) for approval of the active substance

The contact point for the Penconazole Task Force is

Address:	Syngenta Crop Protection AG Rosentalstrasse 67 4058 Basel Switzerland
Contact (all sources):	[redacted]
Telephone number:	[redacted]
E-mail:	[redacted]

1.2.2 Producer or producers of the active substance

Syngenta

Address:	Syngenta Crop Protection AG Rosentalstrasse 67 4058 Basel Switzerland
Contact (all sources):	[redacted]
Telephone number:	[redacted]
E-mail:	[redacted]

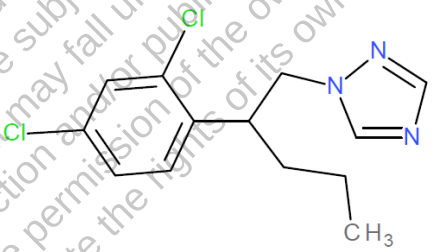
Ascenza

Address:	Ascenza Agro S.A. Avenida do Rio Tejo Herdade das Praias 2910-440 Setúbal Portugal
Contact (all sources):	[redacted]
Telephone:	[redacted]
Fax :	[redacted]
E-mail:	[redacted]

1.2.3 Information relating to the collective provision of dossiers

For the renewal of approval of penconazole, a task force was established. Members of the Penconazole Task Force are: Syngenta Crop Protection AG and Ascenza Agro SA. The dossier was submitted by Syngenta Crop Protection AG, on behalf of the task force.

1.3 IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1 Common name proposed or ISO-accepted and synonyms	Penconazole
1.3.2 Chemical name (IUPAC and CA nomenclature)	
IUPAC	1-[2-(2,4-dichlorophenyl)pentyl]-1*H*-1,2,4-triazole
CA	1-[2-(2,4-dichlorophenyl)pentyl]-1*H*-1,2,4-triazole
1.3.3 Producer's development code number	CGA71818 (also known as CGA071818)
1.3.4 CAS, EEC and CIPAC numbers	
CAS	66246-88-6
EEC	266-275-6
CIPAC	446
1.3.5 Molecular and structural formula, molecular mass	
Molecular formula	$C_{13}H_{15}Cl_2N_3$
Structural formula	
Molecular mass	284.2 g/mol
1.3.6 Method of manufacture (synthesis pathway) of the active substance	CONFIDENTIAL information - data provided separately (Vol.4) by the Penconazole Task Force members.
1.3.7 Specification of purity of the active substance in g/kg	≥ 950
1.3.8 Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1 Additives	CONFIDENTIAL information - data provided separately (Vol.4) by the Penconazole Task Force members.
1.3.8.2 Significant impurities	CONFIDENTIAL information - data provided separately (Vol.4) by the Penconazole Task Force members.
1.3.8.3 Relevant impurities	The relevance of impurities is still unclear/not concluded on. See Volume 4.
1.3.9 Analytical profile of batches	CONFIDENTIAL information - data provided separately (Vol.4) by the Penconazole Task Force members.

1.4 INFORMATION ON THE PLANT PROTECTION PRODUCT

1.4.1	**Applicant**	
1.4.2	**Producer of the plant protection product**	Address: Syngenta Crop Protection AG Rosentalstrasse 67 4058 Basel Switzerland Contact (all sources): [redacted] Telephone number: [redacted] E-mail: [redacted]
1.4.3	**Trade name or proposed trade name and producer's development code number of the plant protection product**	Topas 100 EC A6209G
1.4.4	**Detailed quantitative and qualitative information on the composition of the plant protection product**	
1.4.4.1	***Composition of the plant protection product***	CONFIDENTIAL information - data provided separately (Vol.4; Syngenta)
1.4.4.2	***Information on the active substances***	
1.4.4.3	***Information on safeners, synergists and co-formulants***	CONFIDENTIAL information - data provided separately (Vol.4; Syngenta)
1.4.5	**Type and code of the plant protection product**	Emulsifiable concentrate [EC]
1.4.6	**Function**	Fungicide
1.4.7	**Field of use envisaged**	Penconazole is a fungicide for foliar application to control diseases in fruits, berries and vegetables.

1.4.8 Effects on harmful organisms	Penconazole is a fungicide used in agriculture for control of powdery mildews in various crops such as grape, pome fruits, stone fruits, strawberry, cucumber and other vegetables. When taken up by the plant, penconazole acts on the fungal pathogen during penetration and haustoria formation. It stops the development of fungi by interfering with the biosynthesis of sterols in cell membranes. Interference with sterol biosynthesis leads to disruption of membrane function, leakage of cytoplasmic contents and hyphal death. Penconazole belongs to the triazole class of chemistry and its mode of action is similar to other triazoles (sterol demethylation inhibitors = DMIs). Its main biochemical mode of action is the inhibition of cytochrome P-450 sterol 14α-demethylase (P-45014DM), a key enzyme of the sterol biosynthetic pathway of fungi, which stops the development of fungi by interfering with the biosynthesis of sterols in cell membranes. It is thus classified by FRAC (Fungicide Resistance Action Committee) as a Sterol Biosynthesis Inhibitor (SBI: class 1) with other triazoles like difenoconazole, tebuconazole and myclobutanil. Triazole fungicides are systemic or translaminar compounds with quick uptake and acropetal translocation in the xylem, resulting in good distribution in the plant tissue and protection from being washed off. When taken up by the plant, penconazole acts on the fungal pathogen during penetration and haustoria formation.

1.5 DETAILED USES OF THE PLANT PROTECTION PRODUCT

1.5.1 Details of representative uses

Crop and/or situation (a)	Member State	Product Name	FGI (b)	Pests or group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (m)	Remarks
					Type (d-f)	Conc of a.i. g/kg (i)	Method kind (f-h)	Growth stage and season (j)	Number min max (k)	Interval between applications (min)	Kg a.i./hl min max (g/hl) (l)	Water l/ha min max	Kg a.i./ha min max (*) (g/ha) (l)		
Pome fruit: apple, pear, quince	EU	TOPAS 100 EC (A6209G)	F	*Podosphaera leucotricha*	EC	100 g/L	Foliar spray, mist blower	BBCH 71–89	2	10	2.7-8.0	500-1500	40	14	Only tractor mounted applications
Grapes, table and wine	EU	TOPAS 100 EC (A6209G)	F	*Uncinula necator*	EC	100 g/L	Foliar spray	BBCH 13-85	2	8	3.0-20	150-1000	30	14 (28 in NEU and France)	Only tractor mounted applications
Cucumber	EU	TOPAS 100 EC (A6209G)	F	*Erysiphe Cichoracearum, Sphaerotheca fuliginea*	EC	100 g/L	Foliar spray	BBCH 51-89	3	8	4.2-25	200-1200	50	3	Only tractor mounted applications
Cucumber	NEU	TOPAS 100 EC (A6209G)	F	*Cichoracearum, Sphaerotheca fuliginea*	EC	100 g/L	Foliar spray	BBCH 51-89	1	n/a	2.9-17.5	200-1200	35	3	Only tractor mounted applications

(a) For crops, the EU and Codex classification (both) should be taken into account ; where relevant, the use situation should be described (e.g. fumigation of a structure)

(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)

(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g.

(c) *e.g.* biting and sucking insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes – GIFAP Technical Monograph N° 2, 1989
(f) All abbreviations used must be explained
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant – type of equipment used must be indicated

fluoroxypyr). **In certain cases, where only one variant synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application

(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha
(m) PHI - minimum pre-harvest interval

1.5.2 Further information on representative uses

See 1.5.1. for details. The timing of application is not normally influenced by the growth stage of the crop, rather by the development of the disease. In this respect, the recommendations are normally to apply at the first sign of disease and at intervals varying between 7 and 14 days thereafter. The activity of penconazole is such that protection is provided during the interval between applications up to a maximum of 14 days. Where application by horizontal boom sprayers: Avoid spraying/application within 5 m of the field boundary to reduce effects on non-target insects or other arthropods. Where application is by broadcast sprayers: The best available application technique, which minimises offtarget drift should be used to reduce effects on non-target insects or other arthropods.

1.5.3 Details of other uses applied for to support the setting of MRLs for uses beyond the representative uses

Not relevant

1.5.4 Overview on authorisations in EU Member States

Penconazole is widely authorised in European countries including Estonia, Finland, Latvia, Lithuania, Sweden, Norway, Austria, Belgium, Czech Republic, Germany, Hungary, Netherlands, Poland, Romania, Slovakia, Slovenia, Bulgaria, Cyprus, France, Greece, Italy, Portugal, Spain, Croatia, as well as UK.

The currently authorised uses of the formulations containing penconazole are provided in the following:
Syngenta formulation: A6209G, containing 100 g/L penconazole as an EC formulation
Syngenta formulation: A9246B, containing 200 g/L penconazole as an EW formulation
Ascenza Agro, S.A. formulation: SAP811F, containing 100 g/L penconazole as an EC formulation

Penconazole can be used in a number of crops across such as apple, pear, quinace, peach, apricot, nectarine, black currant, red currant, gooseberry, blackberry, raspberry, artichoke, cucumber, eggplant, gherkin, grapes (table and wine), melon, peppers, pumpkin, strawberries, tobacco, tomatoes, watermelon, zucchini, ornamentals, cherries, forest nursery, fruit nursery, nut trees, hop, chili, squash.

Level 2

Penconazole

2. SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

Summary of methodology used by the applicant for literature review and for all sections:

- A very broad search was conducted in a number of scientific source databases for penconazole and its metabolites. Details regarding the databases and search terms are listed in Volume 3CA B2 (Appendix 1), Volume 3CA B6 (Appendix 1), Volume 3CA B7 (Appendix 2), Volume 3CA B8 (B.8.6.1), and Volume 3CA B9 (Appendix 1). A separate search was also conducted for impurity/impurities in penconazole technical materials. Details of this literature search are summarised in Syngenta's Volume 4.
- Duplicate titles from within each database were automatically removed from the output.
- A rapid relevance assessment of the titles was conducted to remove any additional duplicates and any obviously irrelevant titles (where enough information was available from the title alone).
- Summary abstracts were requested for the remaining titles and a further rapid relevance assessment was conducted where again any clearly irrelevant titles were removed.
- A detailed assessment of the full-text documents for the remaining titles was conducted using the criteria developed for study relevance.
- Any relevant papers were highlighted and assessed for reliability.

A more extensive search has also been conducted using more specific endocrine disruption search terms and an extended duration to ensure that all available literature have been located. This additional search was carried out to identify *in vitro* and *in vivo* studies designed to assess the effects of penconazole on the endocrine system.

2.1 IDENTITY

2.1.1 Summary or identity

Data provided separately by the Penconazole Task Force members. See RAR Vol. 4 for each task force member.

2.2 PHYSICAL AND CHEMICAL PROPERTIES [EQUIVALENT TO SECTION 7 OF THE CLH REPORT TEMPLATE]

2.2.1 Summary of physical and chemical properties of the active substance

Table 1: Summary of physicochemical properties of the active substance

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20 °C and 101,3 kPa	**Pure active substance** colour: white aspect: powder odour: odourless **Technical grade active substance** colour: off-white aspect: powder with lumps odour: weak	*Das R. 2000a* *Das R. 2000b*	Sensory observations
Melting/freezing point	60.3 °C to 61.0 °C	*Das R. 1999*	Measured
Boiling point	> 360 °C at 101.325 kPa 99.2°C at 1.9 Pa	*Das R. 2000*	Measured
Relative density	Not required under EU Regulation No 283/2013		
Vapour pressure	0.224 mPa at 25 °C 0.094 mPa at 20 °C	*Vijayakumar C. 2018*	Measured
Surface tension	53.2 mN/m at 20.0 ± 0.5 °C	*O'Connor B., 2015*	

Property	Value	Reference	Comment (e.g. measured or estimated)
Water solubility	77 mg/L at 20 °C	*Halarnakar R. 2018*	Measured
Partition coefficient n-octanol/water	P_{ow} = 6421 (± 94) log P_{ow} = 3.8 at 20 °C	*Halarnakar R. 2018a*	Measured
Henry's law constant	$3.4 \cdot 10^{-4}$ Pa.m^3/mol at 20 °C	*RAR Vol. 3 B.2.2/02*	Calculated from measurements in Halarnakar R. 2018 and Vijayakumar C. 2018
Flash point	Data lacking	-	Waiving of testing based on penconazole's melting point, i.e. > 40°C
Flammability	Non-flammable	*Jackson W. 2017*	Measured
Explosive properties	Not explosive	*Jackson W. 2017*	Measured, or Waiving of testing based on penconazole's exothermic decomposition energy
Self-ignition temperature	Data lacking	-	Waiving of testing based on experience of handling
Oxidising properties	Non-oxidising	*Jackson W. 2017*	Measured
Granulometry	No data	-	-
Solubility in organic solvents and identity of relevant degradation products	Solubility at 20 °C: acetone > 500 g/L dichloromethane > 500 g/L ethyl acetate > 500 g/L hexane 16 g/L methanol > 500 g/L octanol 350 g/L toluene > 500 g/L	*Vijayakumar C. 2018a*	Measured
Dissociation constant	pKa = 1.51 at 20°C	*Jäkel K. 1987b*	Measured
Viscosity	Not required under EU Regulation No 283/2013		
Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity	**Instrument parameters** UV: methanol (solvent) IR: KBr pellet 13C-NMR: 75 MHZ, CDCl3 1H-NMR: 300 MHz, CDCl3 Mass Spectra: EI **UV Absorption Characteristics**	*Oggenfuss P. 1999*	Measured

Property	Value	Reference	Comment (e.g. measured or estimated)
	The molar extinction coefficients at different wavelengths were determined to be: Solution / Wavelength [nm] / Molar extinction coeff. [L/mol · cm] neutral 220 10564 273 437 281 401 acidic 220 10741 273 410 281 376 basic 220 9607 273 453 281 417 No absorption maximum between 290 nm and 750 nm was observed.		

Study reports for determination of the partition coefficient (n-octanol/water) (CA B.2.7) for three of the metabolites included in the residue definition for surface water, ground water and soil (2.14.1) are not acceptable. For the metabolites CGA179944 and CGA71019 the study report does not contain analytical certificates for the batches used. For CGA91305 no study report is provided whatsoever. For penconazole and the rest of the metabolites in the residue definition, adequate studies has been provided for determination of the partition coefficient.

2.2.1.1 Evaluation of physical hazards [equivalent to section 8 of the CLH report template]

2.2.1.1.1 Explosives [equivalent to section 8.1 of the CLH report template]

Table 2: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
UN Test 2(b)	Effect of heating under confinement: The tube was unchanged "O" after five minutes of heating applying orifice plate diameter of 1 mm. The test gave a negative "–" result.	Penconazole is not explosive within the criteria of this study.	*Jackson W. 2017* TC; Purity 98.1% w/w
UN Test 2(c)(i)	Effect of ignition under confinement: The substance, penconazole, failed to produce a pressure greater than the upper threshold of 2070 kPa,	Penconazole is not explosive within the criteria of this study.	*Jackson W. 2017* TC; Purity 98.1% w/w

Method	Results	Remarks	Reference
	the rise time could not be determined. The test gave a negative "–" result.		
ASTM E537	Heat of decomposition: 584 J/g	Series 2 type (a) test of sensitivity to detonative shock is not required if the exothermic decomposition energy of organic materials is less than 800 J/g (CR (EU) No 1272/2008; p. 52)	*Jackson W. 2017* TC; Purity 98.1% w/w

2.2.1.1.1.1 Short summary and overall relevance of the provided information on explosive properties

Penconazole does not fulfil the criteria of the screening procedure as the substance contains chemical groups, e.g. contiguous nitrogen atoms, which can react to produce very rapid increase in temperature or pressure. Therefore the acceptance procedure (Test series 2 to 4; section 10.3 of ST/SG/AC.10/11/Rev.7), i.e. determining whether or not a product offered for transport is a candidate for Class 1, have to be performed (CR (EU) No 1272/2008; p. 52).

The explosive properties of penconazole (TC of purity 98.1% w/w) were studied using recommended test methods referred to in ST/SG/AC.10/11/Rev.7, i.e. Test 2(b; Koenen test) and Test 2(c)(i; Time/Pressure test). The tests were carried out as outlined in ST/SG/AC.10/11/Rev.7. In agreement with CR (EU) No 1272/2008 (p. 52) Test 2(a), i.e. UN gap test was waived based on Penconazole's decomposition energy of 584 J/g (< 800 J/g) determined by using method ASTM E537 (Differential Scanning Calometry).

The effect observed when heating penconazole for five minutes under confinement applying orifice plate diameter of 1 mm was «O» - Tube unchanged. The end of the reaction was well within five minutes.

The highest pressure achieved in the time/pressure test was 453 kPa which is well within the upper threshold of 2070 kPa. Hence, the rise time could not be determined.

Penconazole's exothermic decomposition energy and the negative ("–") outcome of the Koenen test and the Time/Pressure test, i.e. sensitivity towards shock, heating and ignition, respectively, concludes the substance is too insensitive for acceptance into Class 1 (ST/SG/AC.10/11/Rev.7).

2.2.1.1.1.2 Comparison with the CLP criteria

A substance is considered for classification as explosive where a positive result is obtained in a test series as outlined in Figure 2.1.2 of CR (EU) No 1272/2008, i.e. sensitivity towards heat, shock, or friction. Therefore, comparison with CLP criteria would not result in classification of the substance given the exothermic decomposition energy and the negative outcome from Test 2(b; Koenen test) and Test 2(c)(i; Time/Pressure test).

2.2.1.1.1.3 Conclusion on classification and labelling for explosive properties

Not classified – conclusive but not sufficient for classification

2.2.1.1.2 Flammable gases (including chemically unstable gases) *[equivalent to section 8.2 of the CLH report template]*

Hazard class not applicable, substance is a solid

2.2.1.1.3 Oxidising gases [equivalent to section 8.3 of the CLH report template]

Hazard class not applicable, substance is a solid

2.2.1.1.4 Gases under pressure [equivalent to section 8.4 of the CLH report template]

Hazard class not applicable, substance is a solid

2.2.1.1.5 Flammable liquids [equivalent to section 8.5 of the CLH report template]

Hazard class not applicable, substance is a solid

2.2.1.1.6 Flammable solids [equivalent to section 8.6 of the CLH report template]

Table 3: Summary table of studies on flammable solids

Method	Results	Remarks	Reference
UN Test N.1	Preliminary screening test: The test substance, formed into an unbroken powder train, melted and ignited but did not propagate combustion along 200 mm train (within two minutes). The full burning time over 200 mm could not be determined.	Penconazole is not a flammable solid within the criteria of this test.	*Jackson W. 2017* TC; Purity 98.1% w/w

2.2.1.1.6.1 Short summary and overall relevance of the provided information on flammable solids

The flammable properties of penconazole (TC of purity 98.1% w/w) were studied using recommended test methods referred to in ST/SG/AC.10/11/Rev.7, i.e. Test N.1 (test method for flammable solids). The tests were carried out as outlined in ST/SG/AC.10/11/Rev.7.

The preliminary screening test showed that penconazole melted and ignited but did not propagate combustion along the 200 mm of the train. The full test programme was not required as the full burning time over 200 mm is less than 2 minutes (could not be determined).

2.2.1.1.6.2 Comparison with the CLP criteria

A flammable solid shall be classified for this class using test N.1. The burning rate test was, however, waived due to the outcome of the preliminary screening test. Therefore, comparison with CLP criteria according to Table 2.7.1 in CR (EU) No 1272/2008 would not result in classification of the substance.

2.2.1.1.6.3 Conclusion on classification and labelling for flammable solids

Not classified – conclusive but not sufficient for classification

2.2.1.1.7 Self-reactive substances [equivalent to section 8.7 of the CLH report template]

Table 4: Summary table of studies on self-reactive substances

Method	Results	Remarks	Reference
Differential scanning calorimetry	Heat of decomposition: 755 J/g	Penconazole is not a self-reactive substance within	*Jackson W. 2021* TC; Purity 98.1% w/w

Method	Results	Remarks	Reference
		the criteria of this test. An earlier study showed a heat of decomposition of 584 J/g (TC of purity 98.1% w/w; see section 2.2.1.1.1)	
UN Test H.4	Self-Accelerating decomposition temperature (SADT): >75 °C	Penconazole is not a self-reactive substance within the criteria of this test.	*Jackson W. 2021* TC; Purity 98.1% w/w

2.2.1.1.7.1 Short summary and overall relevance of the provided information on self-reactive substances

UN test series A to H are required only for substances considered for classification. According to CLP, substances and mixtures must be considered for classification in the hazard class as a self-reactive substance or mixture unless:

- their heat of decomposition is less than 300 J/g, or
- their Self-Accelerating Decomposition Temperature (SADT) is greater than 75°C for a 50 kg package.

The heat of decomposition and self-accelerating decomposition temperature were studied for Penconazole (TC of purity 98.1% w/w) using recommended test methods referred to in ST/SG/AC.10/11/Rev.7, i.e., differential scanning calorimetry and UN Test H.4, respectively. Results showed a heat of decomposition of 755 J/g, and a self-accelerating decomposition temperature greater than 75 °C.

2.2.1.1.7.2 Comparison with the CLP criteria

Self-reactive substances or mixtures are classified in one of the seven categories of types A to G using UN Test Series A to H in ST/SG/AC.10/11Rev.5 (pp. 217-296). In agreement with CR (EU) No 1272/2008 (p. 63) the classification procedure was waived as penconazole:

- is not explosive (2.2.1.1.1)
- is not oxidising (2.2.1.1.13)
- is not an organic peroxide (2.2.1.1.14)
- has shown a heat of decomposition above 300 J/g
- has a SADT greater than 75 °C for a 50 kg package

Therefore, comparison with CLP criteria according to Section 2.8.2.3 in CR (EU) No 1272/2008 would not result in classification of the substance.

2.2.1.1.7.3 Conclusion on classification and labelling for self-reactive substances

Not classified – conclusive but not sufficient for classification

2.2.1.1.8 Pyrophoric liquids [equivalent to section 8.8 of the CLH report template]

Hazard class not applicable, substance is a solid.

2.2.1.1.9 Pyrophoric solids [equivalent to section 8.9 of the CLH report template]

2.2.1.1.9.1 Short summary and overall relevance of the provided information on pyrophoric solids

No data derived in accordance with the recommended test method in CR (EU) No 1272/2008 have been provided.

Penconazole has, however, been handled in air in other studies conducted and referred to in this dossier, where no incidences of self-ignition when exposed to air have been reported. In agreement with Section 2.10.4.1 of CR (EU) No 1272/2008 (p. 68), the classification procedure for pyrophoric solids need not be applied given the experience stated above (i.e. the substance is stable at room temperature for prolonged periods of time (days)).

2.2.1.1.9.2 Comparison with the CLP criteria

A pyrophoric solid shall be classified using test N.2 in ST/SG/AC.10/11Rev.7. This testing was waived based on the experience stated in above subsection (2.2.1.1.9.1). Therefore, comparison with CLP criteria according to Table 2.10.1 in CR (EU) No 1272/2008 (p. 68) would not result in classification of the substance.

2.2.1.1.9.3 Conclusion on classification and labelling for pyrophoric solids

Not classified – conclusive but not sufficient for classification

2.2.1.1.10 Self-heating substances [equivalent to section 8.10 of the CLH report template]

2.2.1.1.10.1 Short summary and overall relevance of the provided information on self-heating substances

No data derived in accordance with the recommended test method in CR (EU) No 1272/2008 have been provided.

It is, however, referred to ECHA-17-G-21-EN (subsection 2.11.4.2) stating *«substances or mixtures with a low melting point, i.e. < 160 °C, should not be considered for classification in this class since the melting process is endothermic and the substance-air surface is drastically reduced. However, this criterion is only applicable if the substance or mixture is completely molten up to this temperature.»*

The melting point of penconazole has been studied (Das R., 1999; CGA71818/4305) and reported in this dossier (RAR vol.4 3CA B2). Results showed a melting range starting at 60°C and was completely molten at 61°C.

In agreement with ECHA-17-G-21-EN, the classification procedure for self-heating substances need not be applied given penconazole's melting point.

2.2.1.1.10.2 Comparison with the CLP criteria

The self-heating substance or mixture shall be classified using test N.4 in ST/SG/AC.10/11Rev.7. This testing was waived (ECHA-17-G-21-EN) based on penconazole's melting point that is well below 160°C. Therefore, comparison with CLP criteria according to Table 2.11.1 in CR (EU) No 1272/2008 (p. 69) would not result in classification of the substance.

2.2.1.1.10.3 Conclusion on classification and labelling for self-heating substances

Not classified – conclusive but not sufficient for classification

2.2.1.1.11 Substances which in contact with water emit flammable gases *[equivalent to section 8.11 of the CLH report template]*

2.2.1.1.11.1 Short summary and overall relevance of the provided information on substances which in contact with water emit flammable gases

No data derived in accordance with the recommended test method in CR (EU) No 1272/2008 have been provided.

The chemical structure of penconazole does, however, not contain metals or metalloids. Further, penconazole has been handled in water in other studies, where no incidences of violent reaction and emission of flammable gases have been reported. In agreement with Section 2.12.4.1 of CR (EU) No 1272/2008 (p. 63), the classification procedure for substances or mixtures which in contact with water emit flammable gases need not be applied given the information and experience stated above.

2.2.1.1.11.2 Comparison with the CLP criteria

A substance or mixture which, in contact with water, emits flammable gases shall be classified in one of the three categories for this class, using test N.5 in ST/SG/AC.10/11Rev.7. This testing was waived based on the experience stated in above subsection (2.2.1.1.11.1). Therefore, comparison with CLP criteria according to Table 2.12.1 in CR (EU) No 1272/2008 (p. 72) would not result in classification of the substance.

2.2.1.1.11.3 Conclusion on classification and labelling for substances which in contact with water emit flammable gases

Not classified – conclusive but not sufficient for classification

2.2.1.1.12 Oxidising liquids [equivalent to section 8.12 of the CLH report template]

Hazard class not applicable, substance is a solid.

2.2.1.1.13 Oxidising solids [equivalent to section 8.13 of the CLH report template]

Table 5: Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
UN Test O.1	Mean burning times (s); n =5 Test substance penconazole:cellulose* / Reference Bromate:cellulose 4:1 / 1:1 / 3:7 449 / 541 / 70 * total weight: 30 g The test substance ignited and burned fully with a flame. Mean burning times of the test substance are both greater than the mean burning time of the reference.	Penconazole is not an oxidising solid within the criteria of this test.	*Jackson W. 2017* TC; Purity 98.1% w/w

2.2.1.1.13.1 Short summary and overall relevance of the provided information on oxidising solids

Penconazole contain chlorine but since chlorine is chemically bonded only to carbon, the classification procedure for this class shall not apply according to subsection 2.1.4.4.1 of CR (EU) No 1272/2008. Regardless, the oxidative properties of penconazole (TC of purity 98.1% w/w) were studied using recommended test methods referred to in ST/SG/AC.10/11/Rev.7, i.e. Test O.1 (test for oxidising solids). The tests were carried out as outlined in ST/SG/AC.10/11/Rev.7.

The substance, penconazole, in the 4:1 and 1:1 sample-to-cellulose ratio (by mass) tested, exhibited a mean burning time less than the mean burning time of a 3:7 mixture (by mass) of potassium bromate and cellulose, i.e. category 3 in Table 2.14.1 in CR (EU) No 1272/2008). Consequently, the criteria for Categories 1 and 2 are not met and burning time of 2:3 and 3:2 mixture (by mass) of potassium bromate and cellulose is waived.

2.2.1.1.13.2 Comparison with the CLP criteria

An oxidising solid shall be classified for this class using test O.1 (subsection 34.4.1) outlined in ST/SG/AC.10/11/Rev.7. Test results showed that penconazole does not meet the CLP criteria according to Table 2.14.1 in CR (EU) No 1272/2008.

2.2.1.1.13.3 Conclusion on classification and labelling for oxidising solids

Not classified – conclusive but not sufficient for classification

2.2.1.1.14 Organic peroxides [equivalent to section 8.14 of the CLH report template]

Hazard class not applicable, the substance is not an organic peroxide.

2.2.1.1.15 Corrosive to metals [equivalent to section 8.15 of the CLH report template]

2.2.1.1.15.1 Short summary and overall relevance of the provided information on oxidising solids

No data derived in accordance with the recommended test method in CR (EU) No 1272/2008 have been provided.

2.2.1.1.15.2 Comparison with the CLP criteria

A substance or mixture corrosive to metals is classified using UN Test C.1 in ST/SG/AC.10/11Rev.7 unless it is impracticable to perform the test.

This testing was waived based on penconazole's melting point that is approximately 60°C (see Table 1) and above the test temperature (cut-off temperature) of 55°C (ECHA-17-G-21-EN). Therefore, comparison with CLP criteria according to Table 2.16.1 in CR (EU) No 1272/2008 (p. 80) would not result in classification of the substance.

2.2.1.1.15.3 Conclusion on classification and labelling for self-heating substances

Not classified – conclusive but not sufficient for classification

2.2.2 Summary of physical and chemical properties of the plant protection product

The representative formulation A6209G is an emulsifiable concentrate (EC). Its appearance is that of a colorless clear liquid with a sweetish odor.

A6209G need not be classified for explosive, oxidizing or flammable properties under CLP (CR (EU) No 1272/2008): The formulation's heat of decomposition was determined as 38 J/g. Waiving of further testing is acceptable, since the heat of decomposition was below 500 J/g. The formulation is not an oxidizing liquid

within the criteria of UN test O.2 nor flammable as the formulation's flashpoint was determined as 62.5 ± 5°C by the use of ISO 1523 Pensky-Martens closed cup testing. Also, the auto-ignition temperature was determined as 210 ± 10°C (performance of the test as described in IEC 60079-20-1; not useful for classification under CLP).

The pH of a 1 % dilution was determined to 6.5. The alkalinity (calculated as NaOH) was determined to be less than 0.01 %.

The viscosity of the formulation was determined to 9.08 mPa·s at 20 °C and 4.88 mPa·s at 40 °C. The viscosity is not significantly depending on the shear rate. Therefore, the test item can be considered as a Newtonian liquid.

The surface tension (σ) of the formulation at 20 °C was determined with the plate method to 33.3 mN/m (0.5 % w/v), 34.7 mN/m (0.1 % w/v) and 30.6 mN/m (undiluted).

The relative density of the liquid formulation was determined to be 0.986 g/cm^3 at 20 °C ($RD_{20\,°C/4\,°C}$ = 0.986).

Heat stability studies (accelerated storage) on the formulation showed that the formulation was physically and chemically stable for 2 weeks at 54 °C in package made from High Density Polyethylene (HDPE).

Low temperature stidies showed no separation after 7 days storage at 0 °C. Testing of emulsion properties at 30 °C after 7 days storage at 0 °C show no changes in emulsifiability, emulsion stability and re-emulsifiability compared to the emulsion properties of the fresh formulation.

Shelf life studies following two years storage of the formulation at ambient temperature (20 °C) showed no change of the content of the active ingredient (0 % change). Except for a reduction of the pH value of a 1 % dilution from 6.5 to 5.8, no other tested phys-chem property showed any change after two years compared with the initial results. Evaluation of the HDPE packaging (1 L) used for the shelf life studies showed some panelling and a 0.07 % gross weight increase. Else, none of the other packaging evaluation criteria changed after storage. The formulation AG6209G is considered chemically and physically stable following two years storage at 20 °C in a package made from High Density Polyethylene (HDPE).

The persistence of foaming of the formulation was tested according to CIPAC MT 47.3. The formulation was diluted with CIPAC water D. For a concentration of 0.5 % (v/v) the foaming was determined to be 12 mL after 1 min and 8 mL after 12 min. For a concentration of 0.1 % (v/v) the foaming was determined to be 32 mL after 1 min and 22 mL after 12 min. The FAO/WHO pesticide specifications recommends a limit of max. 60 mL foaming when tested with CIPAC MT 47.3.

The emulsion properties of the formulation was tested at 30 °C at concentrations 0.5 % (v/v) and 0.1 % (v/v) diluted with CIPAC water A and D. Emulsifiability was spontaneous and re-emulsifiability was complete for all cases. The emulsion stability test showed no cream and/or oil after 0.5 h and 2 h for all cases. However, after 24 h, trace cream at the bottom was observed at concentration 0.5 % (v/v) for CIPAC water A and D. No oil was observed. At concentration 0.1 % (v/v) after 24 h no cream and/or oil was observed for both waters. The emulsion stability test 0.5 h after re-emulsifiability show no cream and/or oil.

Studies regarding physical and chemical compatibility of tank mixes are not submitted as there are no tank mix recommendations proposed in the AIR supplementary dossier.

2.3 DATA ON APPLICATION AND EFFICACY

2.3.1 Summary of effectiveness

When taken up by the plant, penconazole, contained in the representative product A6209G, acts on the fungal pathogen during penetration and haustoria formation. It stops the development of fungi by interfering with the biosynthesis of sterols in cell membranes. Interference with sterol biosynthesis leads to disruption of membrane function, leakage of cytoplasmic contents and hyphal death.

Penconazole has been tested in field development trials and has demonstrated efficacious activity. A6209G has been registered in many EU countries based on detailed national assessments of the efficacy package in compliance with Regulation (EC) No. 545/2011 and according to the Uniform Principles (Regulation (EC) No. 546/2011), with which Member States authorities were satisfied.

2.3.2 Summary of information on the development of resistance

Penconazole is an ergosterol biosynthesis inhibitor (SBI) from the chemical class of the triazoles (FRAC group 3) blocking the demethylation of eburicol. It is active on a broad range of plant pathogens on many crop plants. Due to the supposed oligo-genetic mechanism of resistance the resistance risk is estimated as medium by the Fungicide Resistance Action Committee (FRAC, www.frac.info).

Baseline sensitivity and resistance to DMI fungicides (Penconazole)

More than 40 SBI fungicides are available to control many plant pathogens. Because the mechanism of resistance is mostly controlled by the accumulation of several independent mutations and is referred to as "quantitative resistance", the inherent resistance risk to DMI fungicides has been classified as medium risk. The resistance factors associated to single mutations at target gene (cyp51) are relative small. Resistance to DMI's has been shown to be in the form of small shifts occurring over a long period of time and the phenotype rather corresponds to reduced sensitivity than to resistance. Only in rare cases truly resistant isolates have been found to follow a disruptive resistance (e.g. *Ramularia collo-cygni*). In the majority of the cases, a combination of target site mutations on the cyp51 gene (cytochrome p450), overexpression or duplication of the cyp51 gene and effects on ABC transporters detoxifying the organism have been found to be the most common mechanisms of resistance to DMIs. In addition, it was demonstrated in several studies that DMIs have no cross resistance to any of the other major fungicide classes e.g. MBCs, QoIs, or SDHIs.

Prominent examples for the shifting behaviour of DMI fungicides are *Zymoseptoria tritici* (aka *Mycosphaerella graminicola*) and *Venturia inaequalis*. There are ample reports for shifting in Erysiphe species on cereals and *Cercospora beticola* in sugar beet. Several reports are also available for *Uncinula necator* and *Podosphaera fuliginea*. The exact mechanism conferring the resistance to DMIs for the diseases relevant for penconazole are not completely understood. Recent studies with *Uncinula necator* indicated that resistance seems to be due to at least two mechanisms, cyp51 over-expression and target-site mutation in CYP51.

Extensive resistance monitoring studies are conducted in Europe by several companies and the results are discussed at the FRAC meeting on an annual basis. In general, DMI sensitivity of *Uncinula necator*, *Podosphaera fuliginea*, *Erysiphe cichoracearum* and *Podosphaera leucotricha* is stable since many years after having experienced a sensitivity shift in the past.

Resistance risk assessment for TOPAS 100 EC (A6209G)

For estimating the risk of fungicide resistance three major components need to be evaluated: 1) the intrinsic risk of pathogens (determined by the biology of the pathogen), 2) the risk of active ingredients (determined by the mode of action) and 3) the agronomic risk (determined by the cultural practice and the use strategy).

Factors relating directly to disease epidemiology, and indirectly to disease management, combine with genetic factors to form the pathogen risk. The most important factors determining pathogen risk appear to be life cycle, reproduction, gene flow and mutation rate. Moreover, pathogen risk ranking into high, medium or low risk to evolve fungicide resistance consider the following aspects:

High:

- **resistance is known in the species from other crops**
- **close relation (genus) to with species developing resistance**
- **abundant sexual and asexual propagation and strong epidemics**

Medium:

- **lower probability of selection due to moderate epidemics**
- **no resistance found, despite usage in the same crop to control other diseases**

Low :

- **mechanistic block of evolution of resistance**
- **low spread and no sexual recombination (e.g. soil borne pathogens)**

The fungicide resistance risk varies for fungicide classes depending from specific mode of action. The combined risk a fungicide to evolve resistance should consider the agronomic risk that is based on weather conditions, fertilization, irrigation, cultural practices, crop density and degree of resistance of cultivars.

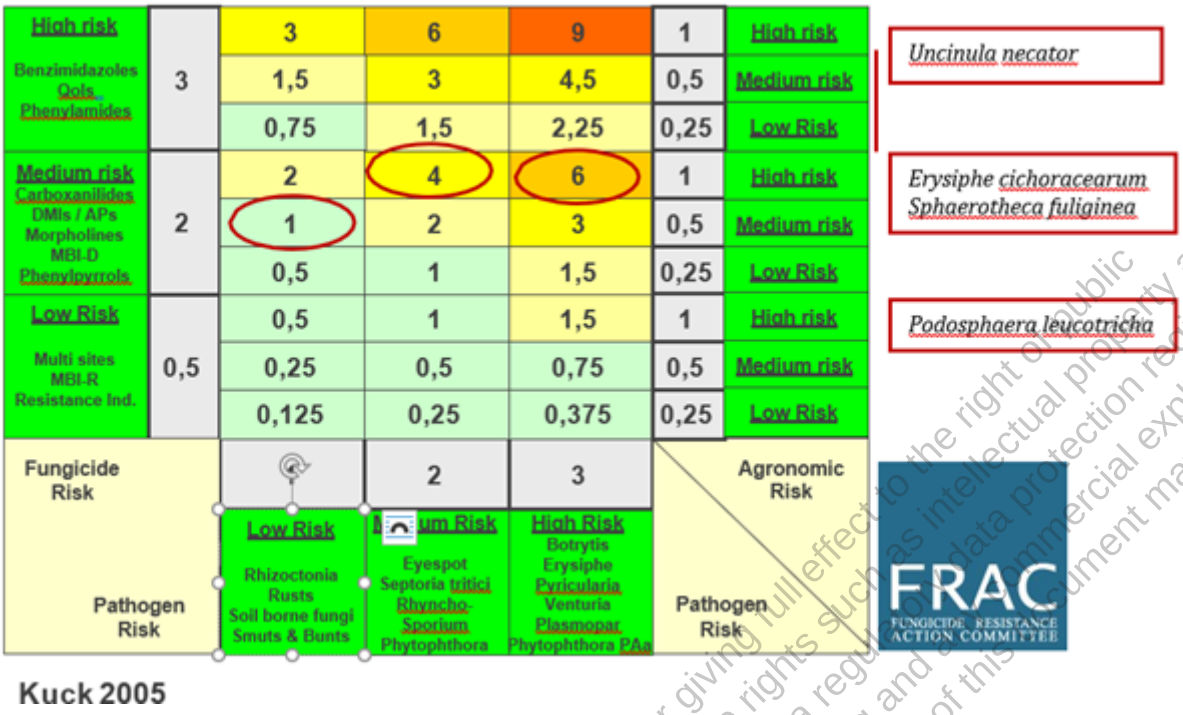
Members of the Fungicide Resistance Action Committee (FRAC) monitor the sensitivity changes towards DMI fungicides and provide guidelines for the use of DMI fungicides in different crops. General and specific guidelines for a responsible use of DMI fungicides are available under http://www.frac.info/.
Based on the multi-allelic and polygenic nature of resistance, the risk of resistance to DMIs can be considered as moderate. Risk assessment of sensitivity shifts to DMI fungicides in selected vegetable pathogens is shown in the **Summary table** below.

Use recommendation for TOPAS 100 EC (A6209G)
The Fungicide Resistance Action Committee (FRAC) has made the following general recommendations to minimize the risk of resistance occurring to the SBI fungicides (of which the DMI's are one class).

- **Repeated application of SBI fungicides alone should not be used on the same crop in one season against a high-risk pathogen in areas of high disease pressure for that particular pathogen.**
- **For crop/pathogen situations where repeated spray applications (e.g. orchard crops/powdery mildew) are made during the season, alternation (block sprays or in sequence) or mixtures with an effective non cross-resistant fungicide are recommended (see FRAC Code List).**
- **Where alternation or the use of mixtures is not feasible because of a lack of effective or compatible non cross-resistant partner fungicides, then input of SBI's should be reserved for critical parts of the season or crop growth stage.**
- **If the performance of SBIs should decline and sensitivity testing has confirmed the presence of less sensitive isolates, SBIs should only be used in mixture or alternation with effective non cross-resistant partner fungicides.**
- **The introduction of new classes of chemistry offers opportunities for more effective resistance management. The use of different modes of action should be maximized for the most effective resistance management strategies.**
- **Users must adhere to the manufacturers' recommendations. In many cases, reports of "resistance" have, on investigation, been attributed to cutting recommended use rates, or to poorly timed applications.**
- **Fungicide input is only one aspect of crop management. Fungicide use does not replace the need for resistant crop varieties, good agronomic practice, plant hygiene/sanitation, etc.**
- **Exclusive frequency measurements of single cyp51 mutations are not sufficient to describe the sensitivity situation towards DMIs but can help to better understand the background of sensitivity shifts.**

Table 6: Summary table: Risk assessment of sensitivity shifts to DMI fungicide in selected pathogens

Pathogen	Resistance situation	Risk assessment
Podosphaera leucotricha	Stable	Low
Uncinula necator	Stable	Medium
Erysiphe cichoracearum	Stable	High
Podosphaera fuliginea	Stable	High



Kuck 2005

2.3.3 Summary of adverse effects on treated crops

Penconazole has been applied in all EU member states for many years without reports of phytotoxic effects on target or succeeding crops. Consequently no negative impact is expected on treated crops.

2.3.4 Summary of observations on other undesirable or unintended side-effects

There is no evidence of any undesirable or unintended side-effects.

2.4 FURTHER INFORMATION

2.4.1 Summary of methods and precautions concerning handling, storage, transport or fire

Active substance – penconazole

Handling

Avoid contact with skin and eyes. When using, do not eat, drink or smoke. Wash hands and exposed skin before eating, drinking or smoking and when the handling of the substance is completed.

This material is capable of forming flammable dust clouds in air, which, if ignited, can produce a dust cloud explosion. Flames, hot surfaces, mechanical sparks and electrostatic discharges can serve as ignition sources for this material. Electrical equipment should be compatible with the flammability characteristics of this material. The flammability characteristics will be made worse if the material contains traces of flammable solvents or is handled in the presence of flammable solvents.

This material can become readily charged in most operations.

Storage

Keep in original containers, tightly closed, in a dry, cool and well-ventilated place. Keep out of reach of children. Keep away from food, drink and animal feeding stuffs.

Transport

UN Number:	UN3077
Transport hazard class:	9
Classification code:	M7
Hazard Identification Number:	90
Packaging Group:	III
Proper shipping name:	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (PENCONAZOLE)

Fire

Suitable extinguishing media:
Extinguishing media - small fires: Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.
Extinguishing media - large fires: Use alcohol-resistant foam or water spray.

Extinguishing media which shall not be used for safety reasons:
Do not use a solid water stream as it may scatter and spread fire.

Specific hazards during fire fighting:
As the product contains combustible organic components, fire will produce dense black smoke containing hazardous products of combustion. Exposure to decomposition products may be a hazard to health.

Special protective equipment for firefighters:
Wear full protective clothing and self-contained breathing apparatus.

The representative formulation – A6209G

Handling
Storage
Requirements for storage areas and containers:
No special storage conditions required.
Keep containers tightly closed in a dry, cool, and well-ventilated place.
Keep out of the reach of children.
Keep away from food, drink, and animal feeding stuffs.

Advice on safe handling:
No special protective measures against fire required.
Avoid contact with skin and eyes.
When using do not eat, drink, or smoke.
For personal protection see Safety data sheet

Transport
Land transport
ADR/ RID:

UN-Number:	UN 3082
Class:	9
Labels:	9
Packaging group	III
Proper shipping name:	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (PENCONAZOLE)

Sea transport
IMDG:

UN-Number:	UN 3082
Class:	9
Labels:	9
Packaging group:	III
Proper shipping name:	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (PENCONAZOLE)
Marine pollutant :	Marine pollutant

Air transport

IATA-DGR

UN-Number:	UN 3082
Class:	9
Labels:	~~9~~ Miscellaneous
Packaging group:	III
Proper shipping name:	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (PENCONAZOLE)

Fire

Suitable extinguishing media:
Extinguishing media - small fires: Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.
Extinguishing media - large fires: Use alcohol-resistant foam or water spray.
Extinguishing media which shall not be used for safety reasons: Do not use a solid water stream as it may scatter and spread fire.

Specific hazards during fire fighting: As the product contains combustible organic components, fire will produce dense black smoke containing hazardous products of combustion. Exposure to decomposition products may be a hazard to health. Flash back possible over considerable distance.

Special protective equipment for firefighters: Wear full protective clothing and self-contained breathing apparatus.

Further information minimise the hazards arising: Do not allow run-off from fire fighting to enter drains or water courses. Cool closed containers exposed to fire with water spray.

Hazardous decomposition products likely to be generated in the event of fire: Combustion or thermal decomposition will evolve toxic and irritant vapours.

2.4.2 Summary of procedures for destruction or decontamination

Active substance – penconazole

Where possible, recycling is preferred to disposal or incineration. It must undergo special treatment e.g. at suitable disposal site to comply with local regulations.

As the halogen content of penconazole is below the 60% trigger value, high temperature incineration is the preferred means of disposal for the active substances, formulated products, contaminated materials or contaminated packaging. Incineration should be carried out in a licensed incinerator operating at a temperature above 800°C and with a minimum gas phase residence time of two seconds.

Further details are available in the safety data sheet for penconazole.

The representative formulation – A6209G

Neutralisation procedure
In the event of accidental spillage, neutralisation (with acid or base to neutral pH) is not an effective procedure for the destruction or decontamination of the formulation.

Therefore, the spilled liquid formulation should first be adsorbed onto a solid, such as sand, inert clay filler, saw dust or soil, before being swept up into a safe container to await disposal.

Controlled incineration
As the halogen content of A6209G is below the 60% trigger value, high temperature incineration is the preferred means of disposal for the active substances, formulated products, contaminated materials or contaminated packaging. Incineration should be carried out in a licensed incinerator operating at a temperature above 800°C and with a minimum gas phase residence time of two seconds.

2.4.3 Summary of emergency measures in case of an accident

Active substance – penconazole

Personal Precautions
Ensure suitable personal protection during removal of spillages (for details see safety data sheet).

Environmental Precautions
Do not flush into surface water or sanitary sewer system. If the product contaminates rivers and lakes or drains inform respective authorities.

Methods of Cleaning Up:
Contain spillage, pick up with an electrically protected vacuum cleaner or by wet-brushing and transfer to a container for disposal according to local regulations. Do not create a powder cloud by using a brush or compressed air. Clean contaminated surface thoroughly.

The representative formulation – A6209G

a) Containment of spillages

Containment and/or segregation is the most reliable technical protection measure if exposure cannot be eliminated. The extent of these protection measures depends on the actual risks in use. Maintain air concentrations below occupational exposure standards.

Where necessary, seek additional occupational hygiene advice.

b) Decontamination of areas, vehicles and buildings

Environmental precautions:
Prevent further leakage or spillage if safe to do so. Do not flush into surface water or sanitary sewer system.

Methods for cleaning up:
Contain spillage, and then collect with non-combustible absorbent material (e.g. sand, earth, diatomaceous earth, vermiculite) and place in container for disposal according to local/national regulations.
If the product contaminates rivers and lakes or drains inform respective authorities.

Do not contaminate ponds, waterways or ditches with chemical or used container.
Do not dispose of waste into sewer.
Where possible recycling is preferred to disposal or incineration.
If recycling is not practicable, dispose of in compliance with local regulations.

Additional advice:
If the product contaminates rivers and lakes or drains inform respective authorities.

c) Disposal of damaged packaging, absorbents and other materials

Contaminated packaging:
Empty remaining contents.
Triple rinse containers.
Empty containers should be taken to an approved waste handling site for recycling or disposal.
Do not re-use empty containers.

d) Protection of emergency workers and residents, including bystanders

Protective measures:
The use of technical measures should always have priority over the use of personal protective equipment.
When selecting personal protective equipment, seek appropriate professional advice. Personal protective equipment should be certified to appropriate standards.

Respiratory protection:
No personal respiratory protective equipment normally required. When workers are facing concentrations above the exposure limit, they must use appropriate certified respirators.

Hand protection:
Nitrile rubber gloves, >480 min breakthrough time, 0.5 mm thickness. The selected protective gloves have to satisfy the specifications of EU Directive 89/686/EEC and the standard EN 374 derived from it.

Eye protection:
Wear tightly fitting safety goggles. Always wear eye protection when the potential for inadvertent eye contact with the product cannot be excluded.

Skin and body protection:
Choose body protection in relation to its type, to the concentration and amount of dangerous substances, and to the specific work-place. Remove and wash contaminated clothing before re-use. Wear as appropriate: Impervious clothing.

e) First aid measures

General advice:
Have the product container, label or Material Safety Data Sheet with you when calling the Syngenta emergency number, a poison control centre or physician, or going for treatment.

Inhalation:
Immediately move to fresh air. If breathing is irregular or stopped, administer artificial respiration. Keep patient warm and at rest. Call a physician or Poison Control Centre immediately.

Skin contact:
Take off all contaminated clothing immediately. Wash off immediately with plenty of water. If skin irritation persists, call a physician. Wash contaminated clothing before re-use.

Eye contact:
Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Remove contact lenses. Immediate medical attention is required.

Ingestion:
If swallowed, seek medical advice immediately and show this container or label. Do NOT induce vomiting.

Medical advice:
There is no specific antidote available. Treat symptomatically.

2.5 METHODS OF ANALYSIS

2.5.1 Methods used for the generation of pre-authorisation data

Adequate methods have been used for the analysis of penconazole in the representative formulation (A6209G), and of penconazole and significant impurities in technical materials (Syngenta and Ascenza separately).

Adequate methods have been used for the generation of pre-approval data required for the risk assessment of and penconazole and its metabolites in the toxicology, residue, and environmental fate and behaviour section.

In a PPP study, the reliability of the measured test concentration generated in the acute toxicity testing of carp could not be concluded. The same analytical method was considered fit for purpose in an equivalent study i.e., acute toxicity testing of rainbow trout. However, the apparently low precision of the method could be due to the performance of the analytical method or the experimental set up. Otherwise, adequate methods have been used for the generation of pre-approval data required for the risk assessment of and penconazole and its metabolites in the ecotoxicology section.

2.5.2 Methods for post control and monitoring purposes

Adequate methods and ILV have been provided for monitoring of penconazole residues in commodities of plant origin, in commodities of animal origin, in soil and water, in air and in body fluids and tissues. Analytical methods and ILV for monitoring of the metabolite CGA179944, included in the residue definition for monitoring of groundwater, is also provided and found adequate.

However, the Task Force has not provided analytical methods for post control and monitoring purposes for all the metabolites listed in the definition of residues for monitoring (2.14.2). This concerns the metabolite CGA71019 (1,2,4-Triazole) included in the residue definition for soil and groundwater, metabolite penconazole-OH included in the residue definition for bodily tissues fluids and tissues.

2.6 EFFECTS ON HUMAN AND ANIMAL HEALTH

2.6.1 Summary of absorption, distribution, metabolism and excretion in mammals *[equivalent to section 9 of the CLH report template]*

Table 7: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Distribution, Degradation and Excretion of CGA 71818 in the Rat Pre-OECD 417 (1984) Pre-GLP	**Distribution** after 144 hours (6 days): Widely distributed in tissues, but in low amounts, the highest residues in liver, lungs and kidneys. **Metabolism:** Metabolised extensively. Polar metabolites in urine (0-24 h). **Excretion** after 144 hours (6 days): *Urinary:* 62-85% (urinary excretion was higher and faster in ♀ compared to ♂) *Faecal:* 14-39%, *Expired air:* <0.1% *Total excreted:* 99-105 No distinct excretion-profiles between low and high dose	**Test substance**: CGA 71818 (penconazole) Radiochemical: LOT not reported >98% purity Oral route/Dose (average mg/kg bw): Single low dose 0.5 Single high dose 25 Sampling up to 144 hours Rat: [redacted] RAI f (SPF) Group size: 2 rats/sex/dose Only 2 rats/sex/dose were used; GI-tract was not examined; A biliary or an IV study was not performed, although >20% of the radioactivity was excreted in the faeces; TLC results for metabolic profiles were insufficiently documented	[redacted] (1980) K-CA 5.1.1/01 Document No. 41/80 (supplementary)
The Major Urinary Metabolites of CGA 71818 in the Rat Pre-OECD 417 (1984) Pre-GLP	**Metabolism** (0-48 h urine)**:** The urinary metabolite U_{o3} was identified as free triazole (CGA 71019). U_{o3} accounted for 24% of the urinary radioactivity. The carboxylic acid metabolites identified were $U_{o7\text{-}1}$ (CGA 177279, pentanoic acid), $U_{o7\text{-}2}$ (CGA 177280, butyric acid) and $U_{o4\text{-}1}$ (CGA 179944, propanoic acid). The α-hydroxy carboxylic acid metabolites identified were $U_{o6\text{-}1}$ (CGA 177281, α-hydroxy pentanoic acid) and $U_{o6\text{-}2}$ (hydroxylated CGA 17780, α-hydroxy butyric acid). The urinary metabolites U_{o7}, U_{o4} and U_{o6} accounted for 31, 10, and 8% of urinary radioactivity, respectively.	**Test substance**: CGA71818 (penconazole) Non-labelled: LOT not reported >98% purity Radiochemical: LOT not reported >98% purity Oral route/Dose (average mg/kg bw): Single high dose 25 Sampling up to 48 hours Rat: [redacted] RAI f (SPF) Group size: 20 ♂ rats Only ♂ rats were examined; compounds which have been characterized in excreta as comprising 5% or greater of the administered dose should be identified. However, this was not always done; no data available on MS or NMR examinations; TLC results for metabolic profiles were insufficiently documented	[redacted] (1982) K-CA 5.1.1/02 Report No. 15/82 (supplementary)
The Metabolic Fate of CGA71818 in the Rat. Pre-OECD 417 (1984) Pre-GLP	**Metabolism:** The most abundant metabolites, each accounting for >10% of dose, were 1, 2, 4-triazole (CGA 71019) and the carboxylic acid metabolite CGA177279. Free triazole was eliminated in both urine and faeces. Some unchanged penconazole (0.8% of dose) was identified in faeces and is considered to represent unabsorbed dose.	**Test substance**: CGA71818 (penconazole) Non-labelled: LOT not reported >98% purity Radiochemical: LOT not reported >98% purity Oral route/Dose (average mg/kg bw): Single high dose 25 Sampling up to 48 hours Rat: [redacted] RAI f (SPF)	[redacted] (1984) K-CA 5.1.1/03 Report No. 23/83 (supplementary)

Method	Results	Remarks	Reference
	Excretion after 48 hours: *Urinary:* 62% *Faecal:* 33% *Total excreted:* 95%	Group size: 20 ♂ rats Only ♂ rats were examined; compounds which have been characterized in excreta as comprising 5% or greater of the administered dose should be identified. However, this was not always done and only 50% of the dose was characterized in terms of chemical structure; the documentation of results does not comply with current standards.	
Sex Dependency of the Metabolite Pattern of CGA71818 after Oral Administration to Rats. Pre-OECD 417 (1984) Pre-GLP	**Metabolism:** Urinary fractions were identified as conjugates with glucuronic acid, free 1,2,4-triazole and several carboxylic acid metabolites. In total, ♂ rats excrete 13% of a dose of CGA 71818 as free 1,2,4-triazole in their 0-48 hours urines, whilst ♀ rats do so to a much lower extent. ♀ rats excreted much higher proportions of polar metabolites (glucuronide conjugates) than ♂ rats in urine. **Excretion** after 144 hours (6 days) – already presented in a previous study (RAR 1.1/01): *Urinary:* 62-85% (urinary excretion was higher and faster in ♀ compared to ♂) *Faecal:* 14-39%, *Expired air:* <0.1% *Total excreted:* 99-105	**Test substance**: CGA71818 (penconazole) Radiochemical: LOT not reprorted >98% purity Oral route/Dose (average mg/kg bw): Single low dose 0.5 Single high dose 25 Sampling up to 144 hours Rat: [redacted]RAI f (SPF) Group size: 2 rats/sex/dose Only 2 rats/sex/dose were used; GI-tract was not examined; A biliary or an IV study was not performed, although >20% of the radioactivity was excreted in the faeces; Compounds which have been characterized in excreta as comprising 5% or greater of the administered dose should be identified; however, this was not always done; only TLC was used for structural identification	[redacted] (1985) K-CA 5.1.1/04 Report No. 1/85 – addendum to [redacted] (1980), Report No. 41/80 (supplementary)
Acute Kinetic Study with CGA71818 Technical in Albino Rats. No applicable guideline; however mainly in line with OECD 417 (2010) GLP	**Excretion** after 48 hours: *Urinary:* 46-90% (urinary excretion was higher and faster in ♀ compared to ♂) *Faecal:* 9-27% There were no marked differences in excretion profiles across the range of dose levels investigated	**Test substance**: CGA71818 (penconazole) Non-labelled: FL-840833 98.7% purity Radiochemical: GAN-IX-83 >98% purity Oral route/Dose Penconazole 0, 10, 100, 300, 500, 1000 or 2400 ppm Single dose + [3,5-^{14}C -triazole]-penconazole 0.1 mg Single dose Sampling up to 48 hours after the [^{14}C]-dose Rat: Sprague Dawley: [redacted]CD (SD) BR Group size: 5 rats/sex/dose Mass balance should be determined by summation of the percent of the administered (radioactive) dose excreted in urine, faeces, and expired air, and the percent present in tissues,	[redacted] (1987) K-CA 5.1.1/05 Report No. [redacted] 6117-123 (accepted with lim.)

Method	Results	Remarks	Reference
		residual carcass, and cage wash; however, air and tissue was not examined, and total recoveries of administered test substance was below 90% in males and therefore considered to be inadequate; A biliary or an IV study was not performed, although >20% of the radioactivity was excreted in the faeces in males	
90-Day Subchronic Dietary Toxicity and Kinetic Study in Albino Mice with CGA71818 Technical. No applicable guideline; however mainly in line with OECD 417 (2010) GLP	**Excretion** after 48 hours: *Urinary after IV dose:* 47-66% in ♂ and 67-77% in ♀ *Faecal after IV dose:* 20-31% ♂ and 9-14 % in ♀ *Urinary after oral dose:* 47-62% in ♂ and 63-78% in ♀ *Faecal after oral dose:* 19-28% ♂ and 11-17% in ♀ ♀ excreted a higher proportion of the dose in urine and less via faeces than ♂. There were no marked differences in excretion profiles across the range of dose levels investigated or between administration of IV or oral dose.	**Test substance**: CGA71818 (penconazole) Non-labelled: FL-840833 98.7% purity Radiochemical: GAN-IX-83 >98% purity Oral route/Dose 0, 10, 100, 300, 500, 1000 or 2400 ppm repeated for at least 90 days in the diet + [3,5-^{14}C-triazole]-penconazole 25 µg Single oral gavage or single intravenous dose Sampling up to 48 hours after the [^{14}C]-dose Mice [redacted] CD-1(ICR)BR Groupe size: 5 mice/sex/dose (20 mice/sex ctrl) Although the test guideline refers to the rat (6-12 weeks) as the test species, mice (21 days) were used; Mass balance should be determined by summation of the percent of the administered (radioactive) dose excreted in urine, faeces, and expired air, and the percent present in tissues, residual carcass, and cage wash; however air and carcass were not examined, and total recoveries of administered test substance was below 90% in several of the groups and therefore considered to be inadequate	[redacted] (1987) K-CA 5.1.1/06 Report No. [redacted] 6117-121 (supplementary)
Kinetic Study in Albino Rats with CGA71818 Technical. No applicable guideline; however mainly in line with OECD 417 (2010) GLP	**Excretion** after 48 hours: *Urinary after IV dose:* 49-53% in ♂ and 73-77% in ♀ *Faecal after IV dose:* 22-29% ♂ and 12-17% in ♀ *Urinary after oral dose:* 48-59% in ♂ and 74-79% in ♀ *Faecal after oral dose:* 26-31% ♂ and 13-16% in ♀ ♀ excreted a higher proportion of the dose in urine and less via faeces than ♂. There were no marked differences in excretion profiles across the range of dose levels investigated or between administration of IV or oral dose.	**Test substance**: CGA71818 (penconazole) Non-labelled: FL-840833 98.7% purity Radiochemical: GAN-IX-83 >98% purity Oral route/Dose 0, 10, 100, 300, 500, 1000 or 2400 ppm repeated for at least 90 days in the diet + 0.1 mg [3,5-^{14}C-triazole]-penconazole Single oral gavage or single intravenous dose Sampling up to 48 hours after the [^{14}C]-dose	[redacted] (1987a) K-CA 5.1.1/07 Report No. [redacted] 6117-122 (supplementary)

Method	Results	Remarks	Reference
		Rat Sprague Dawley: [redacted] CD (SD) BR Group size: 5 rats/sex/dose Normally, the rats should be 6-12 weeks at the time of dosing; however, these rats were younger; Mass balance should be determined by summation of the percent of the administered (radioactive) dose excreted in urine, faeces, and expired air, and the percent present in tissues, residual carcass, and cage wash; however, air and carcass were not examined, and total recoveries of administered test substance was below 90% in several of the groups and therefore considered to be inadequate	
Penconazole: [U-^{14}C]-Phenyl CGA 71818: Absorption, Distribution, Excretion and Metabolism after Single and Repeated Oral Administration to the Rat. EPA 85-1 (1984) GLP	**Absorption:** The 2-5% of the dose present in faeces of bile duct cannulated rats, was assumed to represent the unabsorbed dose. **Distribution** after 96 hours: Widely distributed in tissues, but in low amounts, the highest residues in liver, kidney, adrenal gland, skin, carcass, blood and plasma **Metabolism:** CGA127841 (and/or conjugated CGA127841) was identified in urine, faeces, kidneys, liver and bile and CGA189659 (and/or conjugated CGA189659) in faeces, kidneys and liver; however, four urinary and one faecal metabolite present at over 5% in one or more of the groups, remained unidentified. **Excretion** 1)In single-dosed rats after 96 hours: ♂ excreted similar amounts of the dose in urine (47% of low dose) and faeces (44%), ♀ excreted a higher amount in urine (69%) than in faeces (21%). 2)In bile-canulated rats after 48 hours: *Urinary:* 28% in ♂ and 48% in ♀ *Faecal:* 5% in ♂ and 2% in ♀ *Biliary:* 55% in ♂ and 40% in ♀ 3)Repeated dose study: Similar excretion profile as single-dosed rats	**Test substance**: CGA71818 (penconazole) Non-labelled: P2 >99% purity Radiochemical: GB-XXIX-57 B1 98% purity 1)Balance study: [phenyl-U-^{14}C]-penconazole 0.5 or 50 mg/kg Single dose Sampling up to 96 hours after the [^{14}C]-dose 2)Bile excretion study: [phenyl-U-^{14}C]-penconazole 0.5 mg/kg Single dose Sampling up to 48 hours after the [^{14}C]-dose 3)Repeated dose study: Penconazole 0.5 mg repeated for 14 days Single dose + [phenyl-U-^{14}C]-penconazole 0.5 mg/kg Single oral dose Sampling up to 96 hours after the [^{14}C]-dose Rat Wistar, KFM-WIST outbred (SPF) Group size: 5 rats/sex/dose in balance and repeated dose studies, only 3 rats/sex in bile excretion study) In the bile duct cannulation experiment, a group size of 3 male and 3 female rats was used, instead of a minimum group size of 4 animals per sex; A number of metabolites accounting for >5% of the administered dose in excreta have not been identified/characterised	[redacted] (1988) K-CA 5.1.1/08 Report No. [redacted] 075666 (accepted)
Blood Kinetics, Tissue Distribution and Depletion Kinetics of [Phenyl-U-^{14}C]-CGA71818	**Plasma kinetics:** ♂: C_{max} 7.76 ppm T_{max} 4.0 h $T_{½}$ 17 h	**Test substance**: CGA 71818 (penconazole) Non-labelled: AMS 204/102 99.5% purity Radiochemical: ILS-207.1 >98.5% purity	[redacted] (1999) K-CA 5.1.1/09

Method	Results	Remarks	Reference
in the Rat after Oral Administration. OECD 417 (1984) GLP	$AUC_{0-48\ h}$ 141 µg·h /g ♀: C_{max} 7.37 ppm T_{max} 6.0 h $T_{½}$ 9.0 h $AUC_{0-48\ h}$ 70 µg·h /g **Distribution**: ♂: Rapid widely distributed in tissues, concentrations reached a maximum after 6 hours, with the highest concentration in the penis, followed by liver and kidney. $T_{½}$ = 7-12 h (22 h in penis) ♀: Rapid widely distributed in tissues, concentrations reached a maximum after 4 hours, with the highest concentration in the adrenal gland, followed by liver and kidney. $T_{½}$ = 3-8 h.	[3,5-^{14}C-triazole]-penconazole 50 mg/kg Single dose Sampling up to 48 hours after the [^{14}C]-dose Rat [redacted] RAI f (SPF) Group size: 6 rats/sex, only 3 rats/sex in blood kinetic study Groups of three rats instead of four were used in the blood kinetic study. A total of six animals/sex were used in the radioluminography study; however, results from each time point is based on measurement of a single specimen (as one male and one female were terminated at each time point). The GI-tract was not examined	Report No. 039AM01 (accepted)
1)Identification of Metabolites of the Fungicide Penconazole in Human Urine 2) Development of a Biomarker for Penconazole: A Human Oral Dosing Study and a Survey of UK Residents' Exposure No test guidline Not GLP	**Metabolism:** 1)RAR 6.1.1/10: Seven metabolites were identified in the urine. The most abundant metabolite became penconazole-OH (~0.80). 2)RAR 6.1.1/11: Penconazole-OH was excreted conjugated and is considered to be a significant metabolite (25%–47% of the administered dose, comprising approximately 80% of the total metabolites). Penconazole-COOH is excreted largely unconjugated and accounts for 7%–8% of the dose.	**Test substance**: CGA71818 (penconazole) Non-labelled: LOT not reported, 98.7% purity (RAR 6.1.1/10) (Not reported for RAR 6.1.1/11) 1) Mercadante R. et al. (2016), K-CA 5.1.1/10: No exposure data, sampling 24 h after the application of penconazole in a vineyard (five urine samples from agricultural workers who worked with and were exposed to penconazole (no exposure details given). 2) Sams C. et al. (2016), K-CA 5.1.1/11: Penconazole 0.03 mg/kg Single dose Sampling from 24 h pre-dose to 48 hours post-dose determined and quantified potential penconazole biomarkers from an oral dosing study of three human volunteers Both publications are not performed according to any test guideline, and they do not comply with the data requirements given in Commission Regulation (EU) No 283/2013, which states, among others, that: Tests involving the deliberate administration of the active substance or the plant protection product to humans and non-human primates shall not be performed for the purpose of this Regulation. Despite this, RMS consider these publications as supplementary information.	1) Mercadante R. et al. (2016) K-CA 5.1.1/10 Report No. Chemical research in toxicology (2016) 29(7):1179-86 (supplementary) and 2) Sams C. et al. (2016) K-CA 5.1.1/11 Report No. Toxics (2016) 4, 10 (supplementary)
Penconazole - *In Vitro* Comparative Metabolism of [Phenyl-U-^{14}C]Penconazole and [Triazolyl-U-^{14}C]Penconazole in	**Metabolism:** The metabolism was almost complete in rat after 60 min incubation, with only 1.4 % of [phenyl-U-^{14}C] and 3.8% of [triazolyl-U-^{14}C] penconazole remaining. In human, 66.6% and	**Test substance**: CGA 71818 (penconazole) Non-labelled: AMS 204/103 99.3% purity Radiochemical: [Phenyl-U-^{14}C]penconazole NP-III-11 99.5% purity	Daniel, P. (2019) K-CA 5.1.2/01 Report No. JT65VB (supplementary)

Method	Results	Remarks	Reference
Human and Rat Liver Microsomes No test guideline GLP	69.3% of the respective doses remained. Incubations with [phenyl-U-^{14}C]penconazole resulted in up to 15 radio-HPLC peaks. The major metabolite was R5, present at 64.7% in rat and 24.9% in human. Up to 13 peaks were observed after incubation with [triazolyl-U-^{14}C]penconazole. The major metabolite was R8, present at 68.9% in rat and 26.8% in human. R5 and R8 contained three hydroxyl-metabolites of penconazole, CGA132465 (a mixture of two diastereoisomers CGA132465a and CGA132465b) and CGA127841. The metabolism of [^{14}C]penconazole in human liver microsomes was not as extensive as rat over a period of 60 minutes, but qualitatively comparable. No unique human metabolites were detected.	[Triazolyl-U-^{14}C]penconazole NP-III-13 98.3% purity **Concentration:** 10 µM **Positive control:** [^{14}C]-testosterone, Radiochemical purity >99 % 100 µM **With enzyme cofactor NADPH:** Concentration 2 mM **Analysed** by HPLC and LC-MS **Recovery of Total radioactivity:** 99.0 - 102% **Liver microsomes:** **Human**: mixed gender, pooled from 150 donors **Rat**: Wistar, mixed gender, pooled from 65♂ and 24♀ The study was conducted according to criteria proposed by ECPA (P. Whalley et al 2017) and is mainly in line with key elements discussed on the EFSA Workshop on *in vitro* comparative metabolism studies in regulatory pesticide risk assessment (nov.2018). However, the recommendation of using a broad species spectrum (i.e. rat, dog, mice, rabbit) was not fulfilled. Furthermore, in the previous evaluation of penconazole, ADI and AOEL were based on studies from dogs, whereas ARfD was based on rabbit studies; consequently, RMS consider the comparison of only rat and human insufficient.	

2.6.1.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Together, twelve toxicokinetic studies were evaluated. Several of the studies were considered supplementary only, and the major deviations are listed under remarks in the table above. Despite the deviations, the studies present relevant toxicokinetic data as summarized below.

Absorption

Irrespective of dose or sex, a single or repeat oral dose of penconazole was extensively absorbed. The oral absorption of total radioactivity from an oral dose of [^{14}C]-penconazole was around 85%, in male and female rats ([redacted] (1988), K-CA 5.1.1/08). This was estimated from the percentage of dose recovered in urine, bile and carcass (without gastrointestinal tract) from bile duct-cannulated male and female rats, following single oral gavage administration of ^{14}C-penconazole. The majority of an oral dose was systemically available, based on the urinary excretion ratio following oral and intravenous (iv) administration and the excretion profile ([redacted] (1987), K-CA 5.1.1/06; [redacted] (1987a), K-CA 5.1.1/07). The oral:iv urinary excretion ratio was ca. 1:1, calculated from ca 50% of a 0.1 mg/kg oral dose and ca 50% of a 0.1 mg/kg iv dose excreted in urine (RAR 6.1.1/07). The excretion profile showed that less than <1% of a 25 mg/kg oral dose was excreted unchanged in faeces and penconazole was not present in urine ([redacted] (1984), K-CA 5.1.1/03)

Distribution

Irrespective of dose or sex, penconazole and its metabolites are widely distributed in body tissues ([redacted] (1980), K-CA 5.1.1/01; [redacted] (1988), K-CA 5.1.1/08; [redacted] (1999), K-CA 5.1.1/09), with a trend towards higher levels and longer elimination half-lives in males than in females ([redacted] (1999), K-CA 5.1.1/09). All tissue residues of the parent and/or its

metabolites were either below or close to the limit of determination 4 - 6 days after dosing ([redacted] (1980), K-CA 5.1.1/01; [redacted] (1988), K-CA 5.1.1/08; [redacted] (1999), K-CA 5.1.1/09). There was no indication of a potential for accumulation. The time course of tissue residues closely resembled the profiles in blood ([redacted] (1999), K-CA 5.1.1/09). The highest concentrations in both sexes were present in liver and kidneys, followed by adrenal gland and abdominal fat ([redacted] (1988), K-CA 5.1.1/08; [redacted] (1999), K-CA 5.1.1/09). Residues in male rats tended to be higher than in female tissues. The calculated half-life for elimination of tissue residues ranged from 7 to 12 hours in males and 3 to 8 hours in females ([redacted] (1999), K-CA 5.1.1/09).

Excretion

Irrespective of dose or sex, a single oral dose of penconazole was rapidly excreted. Excretion was nearly complete within 72 h with >95% excreted ([redacted] (1985), K-CA 5.1.1/04); [redacted] (1988), K-CA 5.1.1/08). In females, 69 - 85% of the administered radioactivity was excreted via urine and 14 - 31% via faeces. In males, 41 - 60% of the administered radioactivity was excreted via urine and 35 - 46% via faeces. Excretion was faster by females, irrespective of dose or position of radiolabelling. Radioactivity recovered in expired air was negligible.

Biliary elimination accounted for 55% of a 0.5 mg/kg [^{14}C-triazole]-dose in males and 40% in females. Urinary excretion by the bile duct-cannulated rats accounted for 28% of the dose in males and 48% in females, with faecal excretion representing less than 5% of the dose. These results therefore confirmed the almost quantitative absorption of an oral dose of penconazole and also showed that some biliary metabolites were subject to reabsorption in both sexes. Whilst there was a sex difference in excretion profiles, there was no pronounced difference in excretion profiles between the contrasting dose levels of 0.5 and 25 or 50 mg/kg or between the two radiolabelled forms of the molecule.

Metabolism

Some of the experiments performed in order to elucidate the metabolic fate of penconazole in rats have been performed in the early to mid-1980s and they do not fully comply with current standards. Although considerable effort has been undertaken, the structure of relevant metabolites could only partly be disclosed, while for a substantial part (ca. 50%) of radioactivity found in the excreta, such attempts were not successful. A single oral dose of 0.5, 25 or 50 mg [^{14}C]-penconazole/kg to rats was subject to extensive biotransformation (RAR 6.1.1/03; RAR 6.1.1/04; RAR 6.1.1/08). Metabolites were isolated from urine and faeces of male and female rats administered a single oral dose of 0.5 or 50 mg [^{14}C-phenyl] and [^{14}C-triazole]-penconazole/kg, or a 0.5 mg/kg dose after 14 daily oral doses of 0.5 mg/kg of unlabelled penconazole (RAR 6.1.1/04; RAR 6.1.1/08). Whilst there were no qualitative differences in metabolite profiles, there were quantitative differences.

Primary metabolic reactions involved in the biotransformation of penconazole included cleavage of the triazole ring to CGA71019 (1,2,4-triazole) and oxidation of the ω-position of the alkane chain to form the respective carboxylic acid, CGA177279 (RAR 6.1.1/03). Both CGA71019 and CGA177279 accounted for >10% of the dose in male urine. Other metabolites observed were those following oxidation of the alkane chain to form mono and dihydroxy derivatives and oxidation of the triazole ring. Secondary metabolic reactions include α-oxidation of the carboxylic acids to form α-hydroxy carboxylic acids, decarboxylation, following oxidation to α-ketocarboxylic derivative, oxidation of the 3,4-dihydroxy derivatives to produce the corresponding 3- or 4-keto derivatives and conjugation with glucuronic acid of all alkanol derivatives. No unchanged parent compound was detected in urine, but a small amount of parent penconazole was identified in faeces and was considered to represent unabsorbed dose.

CGA127841 appeared as the main female metabolite (RAR 6.1.1/08), also identified as one of the major metabolites in a recent *in vitro* study of rat and human liver microsomes (RAR 6.1.1/12). Recent studies in human showed that penconazole-OH was the most abundant metabolite comprising approximately 80% of the total urinary metabolites (RAR 6.1.1/10; RAR 6.1.1/11).

2.6.2 Summary of acute toxicity

2.6.2.1 Acute toxicity - oral route [equivalent to section 10.1 of the CLH report template]

Table 8: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
Report On Acute Oral LD_{50} In The Rat Of Technical CGA71818 Guideline not reported; earliest OECD 401 version (May	Rat, [redacted] RAIf (SPF) M and F 5/sex/group	Penconazole Tech. Purity: 88.4% Batch: P.2+3	500, 1000, 2000, 4000 mg/kg bw Administration orally by gavage Observed for 1 h following treatment, hourly for the first day,	oral LD_{50} (combined sexes) = 2125 mg/kg bw, for males only: 1000 mg/kg bw < LD_{50} < 2000 mg/kg bw	[redacted] (1980) K-CA 5.2.1/01 Report No. 800553

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
1981) not yet available at time of study According to the most recent OECD guidelines 420, 423 and 425, several deviations exist, among which the most severe are the excess use of animals in this study in addition to the administration of too high doses Study is acceptable			and twice daily for 14 days		
Report On Acute Oral LD_{50} In The Hamster Of Technical CGA 71818 Guideline not reported; earliest OECD 401 version (May 1981) not yet available at time of study According to the most recent OECD guidelines 420, 423 and 425, several deviations exist, among which the most severe are the excess use of animals in this study in addition to the administration of too high doses Study is acceptable	Hamster Chinese hamsters M and F 5/sex/group	Penconazole Tech. Purity: 88.4% Batch: P.2+3	2000, 4000, 5000 mg/kg bw Administration orally by gavage Observed for 1 h following treatment, hourly for the first day, and twice daily for 14 days	oral LD_{50} for combined sexes ~ 5000 mg/kg bw. For females only 4000 < LD_{50} <5000 mg/kg bw. For males only LD_{50} >5000 mg/kg bw	[redacted] (1980a) K-CA 5.2.1/02 Report No. 800555
Report On Acute Oral LD_{50} In The Rabbit Of Technical CGA 71818 Guideline not reported; earliest OECD 401 version (May 1981) not yet available at time of study According to the most recent OECD guidelines	Rabbit New Zealand white rabbits M and F 3/sex/dose	Penconazole Tech. Purity: 88.4% Batch: P.2+3	Ctr, 600, 1000, 2000 mg/kg bw Administration orally by intubation Observed for 1 h following treatment, hourly for the first day, and for the following 14 days	oral LD_{50} in rabbits is 971 mg/kg bw	[redacted] (1981) K-CA 6.2.1/03 Report No. 800554

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
420, 423 and 425, several deviations exist, among which the most severe are the excess use of animals in this study in addition to the administration of too high doses Study is acceptable					
Report On Acute Oral LD_{50} In The Mouse Of CGA 71818, Technical Guideline not reported; earliest OECD 401 version (May 1981) not yet available at time of study According to the most recent OECD guidelines 420, 423 and 425, several deviations exist, among which the most severe are the excess use of animals in this study in addition to the administration of too high doses Study is acceptable	Mice [redacted] MAG (SPF) mice M and F 5/sex/dose	Penconazole Tech. Purity: 88.4% Batch: P.2+3	1500, 2000, 3000, 5000 mg/kg bw Administration orally by gavage Observed for 1 h following treatment, hourly for the first day, and twice daily for 14 days	oral LD_{50} in mice is 2444 mg/kg bw	[redacted] (1980) K-CA 6.2.1/04 Report No. 800552

Table 9: Summary table of human data on acute oral toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

Table 10: Summary table of other studies relevant for acute oral toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

2.6.2.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Four different studies were conducted, on rat, hamster, rabbit, and mice. All studies were conducted before the earliest version of any OECD guideline was available. The most severe differences to the OECD guidelines 420,

423, and 425 effective today are the excess use of animals and the administration of too high doses. Despite this, the studies are acceptable.

In all 4 studies, penconazole tech. (purity 88.4%) was administered orally by gavage/intubation. In rat (5/sex/group), polyethylene glycol was used as vehicle, and four different doses (500, 1000, 2000 and 4000 mg/kg bw) were given. In hamster (5/sex/group), polyethylene glycol was used as vehicle, and three different doses (2000, 4000 and 5000 mg/kg bw) were given. In rabbit (3/sex/dose), carboxymethyl-cellulose 2% (w/v) in water was used as vehicle, and four different doses (ctr, 600, 1000 and 2000 mg/kg bw) were given. In mice (5/sex/dose), polyethylene glycol was used as vehicle, and four different doses (1500, 2000, 3000 and 5000 mg/kg bw) were given.
In two studies, rat and rabbit, the doses administered were toxic, leading to deaths of 5/5 male and 4/5 female rats at 4000 mg/kg bw, and 3/5 males and 0/5 females at 2000 mg/kg bw, and 3/3 male and female rabbits at 2000 mg/kg bw, and 2/3 male and female rabbits at 1000 mg/kg bw. For rat, acute oral LD_{50} (combined sexes) = 2125 mg/kg bw, and for males only: 1000 mg/kg bw/day < LD_{50} < 2000 mg/kg bw/day. For rabbit, acute oral LD_{50} is 971 mg/kg bw.

In the studies with hamster and mice, the doses administered were less toxic, leading to deaths of 1/5 male and 3/5 female hamsters at 5000 mg/kg bw, and 5/5 male and female mice at 5000 mg/kg bw, 4/5 male and 5/5 female mice at 3000 mg/kg bw, and 0/5 male and female mice at 2000 mg/kg bw. For hamster, acute oral LD_{50} for combined sexes ~ 5000 mg/kg bw for. For females only, acute oral LD_{50}: 4000 < LD_{50} <5000 mg/kg bw. For males only, acute oral LD_{50} >5000 mg/kg bw. For mice, acute oral LD_{50} is 2444 mg/kg.

2.6.2.1.2 Comparison with the CLP criteria regarding acute oral toxicity

According to the CLP criteria, classification for acute oral toxicity is warranted if the LD_{50} (experimentally derived ATE) of a substance is ≤ 2000 mg/kg bw. For rat, acute oral LD_{50} (combined sexes) = 2125 mg/kg bw, and for males only: 1000 mg/kg bw/day < LD_{50} < 2000 mg/kg bw/day. For rabbit, acute oral LD_{50} is 971 mg/kg bw. For hamster, acute oral LD_{50} for combined sexes ~ 5000 mg/kg bw for. For females only, acute oral LD_{50}: 4000 < LD_{50} <5000 mg/kg bw. For males only, acute oral LD_{50} >5000 mg/kg bw. For mice, acute oral LD_{50} is 2444 mg/kg. Overall, the rat is the preferred species for acute oral toxicity studies with 1000 mg/kg bw/day < LD_{50} < 2000 mg/kg bw/day. However, other species can also be used, and an ATE-value should be chosen from the most sensitive species. For penconazole, the most sensitive species was the rabbit, with LD_{50} = 971 mg/kg bw; thus, ATE = 971 mg/kg bw, and classification as 'harmful if swallowed' H302 according to Regulation (EC) No. 1272/2008 is warranted.

For rat and rabbit, classification as 'harmful if swallowed' H302 according to Regulation (EC) No. 1272/2008 is warranted. For hamster and mice, no classification according to Regulation (EC) No. 1272/2008 is warranted. Taken together, classification as 'harmful if swallowed' H302 according to Regulation (EC) No. 1272/2008 is warranted.

2.6.2.1.3 Conclusion on classification and labelling for acute oral toxicity

Harmonised classification proposed. Classification as Acute tox. 4 "Harmful if swallowed" (H302) is considered appropriate. ATE = 971 mg/kg bw

2.6.2.2 Acute toxicity - dermal route [equivalent to section 10.2 of the CLH report template]

Table 11: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations[1] if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Value LD_{50}**	**Reference**
Report On Acute Dermal LD_{50} In The Rat Of Technical CGA 71818 Guideline not reported; earliest OECD 402 version (May 1981) not yet available at time of study	Rat [redacted] RAIf (SPF) M and F 5/sex/dose	Penconazole Tech. Purity: 88.4% Batch: P.2+3	0, 2000, 2500, 3000 mg/kg bw for 24 hours	dermal LD_{50} >3000 mg/kg bw	[redacted] (1980b) K-CA 5.2.2/01 Report No. 800559

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
According to the most recent OECD guideline 402 several deviations exist, among which the most severe are the excess use of animals in this study in addition to the administration of too high doses. Study is acceptable					

Table 12: Summary table of human data on acute dermal toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

Table 13: Summary table of other studies relevant for acute dermal toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

2.6.2.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

Groups of 5 male and 5 female rats were administered a single dermal dose (0, 2000, 2500 or 3000 mg/kg bw) of penconazole tech., purity 88.4% in polyethylene glycole vehicle. The treated area was covered with an occlusive dressing that was fastened around the trunk of the animals by elastic bandage. Exposure lasted 24 hours, thereafter the dressing was removed and the skin rinsed with water and soap. Animals were observed for 1 hour following treatment and at hourly intervals for the remaining day 1. For the following 14 days, observations took place twice a day. No animal deaths were recorded up to the highest achievable dose of 3000 mg/kg bw. The most common clinical symptoms were dyspnoea, ruffled fur, and curved body position. All symptoms were reversible within 8 days after treatment. Gross pathology did not show any particular findings in any organ or tissue at necropsy.

2.6.2.2.2 Comparison with the CLP criteria regarding acute dermal toxicity

According to the CLP criteria, a substance is classified for acute dermal toxicity if the LD_{50} value is ≤ 2000 mg/kg bw. The acute dermal LD_{50} for penconazole (ISO) in rat is >3000 mg/kg bw, thus, no classification is warranted according to Regulation (EC) No. 1272/2008.

2.6.2.2.3 Conclusion on classification and labelling for acute dermal toxicity

Data conclusive but not sufficient for classification.

2.6.2.3 Acute toxicity - inhalation route [equivalent to section 10.3 of the CLH report template]

Table 14: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations[1] if any	**Species, strain, sex, no/group**	**Test substance, form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value LC_{50}**	**Reference**
OECD TG 433 (2018) Deviations: - the use of ten animals (5 males and 5 females) instead of five (only males, or the most sensitive sex) in one dose group - only one concentration tested (the highest attainable and close to the limit concentration for classification of aerosols) - a slightly higher mass median equivalent aerodynamic diameter (4.4 µm) than the recommended (4 µm). These deviations are considered not to influence the quality or integrity of the present study. Study is acceptable.	Rat, [redacted] RAIf (SPF) M, F 5/dose level	Penconazole Aerosol MMAD = 3.5 – 5.4 (mean: 4.4)	4.046 mg/l air (technical highest attainable concen-tration) (4 hr, nose-only, aerosol)	LC_{50} (dust, nose only) >4.046 mg/L air/4h (technical highest attainable concentration)	[redacted] (1987) Report No. 871169

Table 15: Summary table of human data on acute inhalation toxicity

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No studies available				

Table 16: Summary table of other studies relevant for acute inhalation toxicity

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No studies available				

2.6.2.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

The study follows the OECD TG 433 (adopted 25th June 2018), with the following deviations:

- the use of ten animals (5 males and 5 females) instead of five (only males, or the most sensitive sex) in one dose group

- only one concentration tested (the highest attainable and close to the limit concentration for classification of aerosols)
- a slightly higher mass median equivalent aerodynamic diameter (4.4 µm) than the recommended (4 µm).

In RMS's opinion, these deviations do not influence the quality or integrity of the present study. The study was conducted as a limit test with 10 animals. In contrast, the TG currently in force recommends an approach avoiding using death/ moribundity of animals as either an exclusive or an intended endpoint by incorporating evident clinical signs of toxicity at one of a series of fixed dose levels, as an endpoint on which to base classification of the test chemical. Notably, no animal deaths were recorded upon exposure to the highest achievable penconazole dose of 4.05 mg/L air. When testing aerosols according to OECD TG 433 (2018), the primary goal should be to achieve a respirable particle size (i.e. an MMAD of ≤4 µm). This is possible with most test chemicals at a concentration of 2 mg/L. Aerosol testing at greater than 2 mg/L should only be attempted if a respirable particle size can be achieved.

The study is considered acceptable. As no animal deaths were recorded upon exposure to the highest achievable penconazole dose of 4046 mg/m^3, the acute rat inhalation LC_{50} (dust, nose only) should be >4.046 mg/L air/4h.

2.6.2.3.2 Comparison with the CLP criteria regarding acute inhalation toxicity

Classification for acute inhalation toxicity under Regulation (EC) No 1272/2008 (Section 3.1 of Annex I) is required for substances (dusts and mists) with an acute inhalation LC_{50} value of ≤5 mg/L. The acute rat inhalation LC_{50} (dust, nose only) was >4.046 mg/L air/4h (highest achievable concentration) and penconazole (ISO) thus does not fulfil the CLP classification criteria for inhalation toxicity. Based on the available data, no classification is required for acute inhalation toxicity according to Regulation (EC) No 1272/2008.

2.6.2.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Data conclusive but not sufficient for classification.

2.6.2.4 Skin corrosion/irritation [equivalent to section 10.4 of the CLH report template]

Table 17: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations[1] if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Results** **- Observations and time point of onset[2]** **- Mean scores/animal** **- Reversibility**	**Reference**
Report On Skin Irritation In The Rabbit After Single Application Of Technical CGA71818 EPA 163.81-5 (1978); earliest OECD 404 version (May 1981) not yet available at time of study No GLP Accepted	Rabbit New Zealand white 3M and 3F	Penconazole P.2+3, 88.4% purity	0.5 g 24 h	- Time 0, 24, 48 and 72 h upon removal of the pads, and after 7 days of study initiation - very slight erythema of treated skin was noted in all animals at patch removal (time 0). All 24-72 h mean scores were 0	K-CA 5.2.4/01

Table 18: Summary table of human data on skin corrosion/irritation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

Table 19: Summary table of other studies relevant for skin corrosion/irritation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

2.6.2.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

Skin irritation was investigated in groups of 3 male and 3 female New Zealand White rabbits after exposure to 0.5 g of penconazole tech. (88.4%) (penconazole concentration 50% in vehicle 70:30 v/v propylene glycol + saline) for 24 h. The study was conducted in 1980, prior to GLP, and there are some deviations from the current OECD 404 guideline (2015), e.g., exposure time was 24 hours instead of 4 hours; however, this is considered a worst-case as compared to a 4 h exposure period. Despite the deviations, the study is considered acceptable. The results show a slight erythema of treated skin on both intact and scarified skin areas in all animals at patch removal (time 0 h); however, no irritation effects were noted at any other time point. The mean scores for erythema or oedema at 24, 48 and 72 hours were zero. According to CLP Regulation (EC) No. 1272/2008, penconazole tech. should not be classified as a skin irritant.

2.6.2.4.2 Comparison with the CLP criteria regarding skin corrosion/irritation

A substance is irritant to skin when it produces reversible damage to the skin following its application for up to 4 hours. The criteria for the irritation category 2 are that at least 2 of 3 tested animals have a mean score of ≥2.3 and ≤4.0 for erythema/eschar or for oedema from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions. Classification is also required for inflammation that persists to the end of the observation period (normally 14 days) in at least 2 animals, particularly taking into account findings such as alopecia, hyperkeratosis, hyperplasia, and scaling. Classification may also be required in some cases where there is pronounced variability of response among animals. In the single study available, the mean scores for erythema or oedema at 24, 48 and 72 hours were zero. According to CLP Regulation (EC) No. 1272/2008, penconazole (ISO) should not be classified as a skin irritant.

2.6.2.4.3 Conclusion on classification and labelling for skin corrosion/irritation

Data conclusive but not sufficient for classification.

2.6.2.5 Serious eye damage/eye irritation [equivalent to section 10.5 of the CLH report template]

Table 20: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results - Observations and time point of onset[2] - Mean scores/animal - Reversibility	Reference
CGA71818 - Primary Eye Irritation	Rabbits	Penconazole FL 840833, 98.7% purity	100 mg	The eyes were examined at 1, 24, 48 and 72 hours post dosing and after 4, 7, and 10 days using the recommended scoring system.	K-CA 5.2.5/01

Study In Rabbits. Similar to OECD 405 GLP Acceptable	New Zealand White 3 M and 6 F		3 F: 30 sec in washed group 3 F + 3 M: unwashed	The washing of eyes (3 F) was performed too early; hence, the results of these animals were not used in the scoring. **Mean scores** (24-72 h): Corneal opacity: M: 0-0-0.67 F: 0-0-0.33 Iris lesions: M: 0.33-0.67-0.33 F: 0.33-0.33-0.33 Conjunctivae redness: M: 1.0-1.0-1.0 F: 1.0-1.0-1.0 Conjunctivae chemosis: M: 0.67-1.0-0.67 F: 0.67-0.67-1.0 Recovery was complete after 10 days.	

Table 21: Summary table of human data on serious eye damage/eye irritation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

Table 22: Summary table of other studies relevant for serious eye damage/eye irritation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

2.6.2.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

In an eye irritation study, groups of 3 male and 6 female New Zealand White rabbits, received an instillation of 100 mg penconazole tech. into the conjunctival sac of the right eye. The study was conducted in 1988, according to GLP, but there are some deviations from the current OECD 405 guideline (2020). Despite these deviations, the study is considered acceptable.

Examination of the eyes for corneal opacity, iris lesions and conjunctiva redness and chemosis showed slight ocular irritation. The rinsing of eyes was performed too early (already 30 sec after instillation of the test material) in 3 female rabbits. For this reason, only the results of the unwashed groups (3 males + 3 females) were used for overall scoring. According to the criteria defined in the CLP Regulation (EC) No. 1272/2008, the mean scores for corneal opacity, iritis, conjunctival redness and conjunctival chemosis (oedema), following grading at 24, 48 and 72 hours after installation of the test material, were below the trigger for classification as an eye irritant. Therefore, penconazole tech. is regarded as non-irritant to the eye and no classification is proposed.

2.6.2.5.2 Comparison with the CLP criteria regarding serious eye damage/eye irritation

A substance is to be classified in category 1 (serious eye damage) if it produces a) in at least one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or b) in at least 2 of 3 tested animals, a positive response of: (i) corneal opacity ≥3 and/or (ii) iritis >1.5 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

A substance is to be classified in category 2 (eye irritation) if it produces in at least in 2 of 3 tested animals, a positive response of: (a) corneal opacity ≥1 and/or (b) iritis ≥1, and/or (c) conjunctival redness ≥2 and/or (d) conjunctival oedema (chemosis) ≥2 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days

Examination of the eyes for corneal opacity, iris lesions and conjunctiva redness and chemosis showed slight ocular irritation. Mean scores (24-72 h) were: Corneal opacity: M: 0-0-0.67 F: 0-0-0.33; Iris lesions: M: 0.33-0.67-

0.33 F: 0.33-0.33-0.33; Conjunctivae redness: M: 1.0-1.0-1.0 F: 1.0-1.0-1.0; Conjunctivae chemosis: M: 0.67-1.0-0.67 F: 0.67-0.67-1.0. Recovery was complete after 10 days. Penconazole (ISO) does therefore not require classification for serious eye damage (Category 1) or for eye irritation (Category 2) according to Regulation (EC) No 1272/2008.

2.6.2.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

Data conclusive but not sufficient for classification.

2.6.2.6 Respiratory sensitisation [equivalent to section 10.6 of the CLH report template]

Table 23: Summary table of animal studies on respiratory sensitisation

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results	Reference
No studies available					

Table 24: Summary table of human data on respiratory sensitisation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

Table 25: Summary table of other studies relevant for respiratory sensitisation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

2.6.2.6.1 Short summary and overall relevance of the provided information on respiratory sensitisation

No relevant findings on respiratory sensitisation from the studies provided.

2.6.2.6.2 Comparison with the CLP criteria regarding respiratory sensitisation

Hazard class not assessed in this dossier.

2.6.2.6.3 Conclusion on classification and labelling for respiratory sensitisation

Hazard class not assessed in this dossier.

2.6.2.7 Skin sensitisation [equivalent to section 10.7 of the CLH report template]

Table 26: Summary table of animal studies on skin sensitisation

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
CGA71818 Tech. – Skin Sensitization In The Guinea Pig	Albino Guinea pig Himalayan Spotted (GOHI)	CGA71818, Penconazole Tech. Purity: 96%	Intradermal induction: 5% in peanut oil, Epidermal	Erythema: 2/20 animals at 24 h and 3/20 animals at 48 h. Oedema: 1/20 animals at 24 and 48 h. Overall, 2/20 animals (24 h) and 3/20 animals (48 h) were affected. The sensitisation rate of	[redacted] (1998) K-CA 5.2.6/01

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
(Maximization Test) OECD 406 (1992) Study is acceptable	M and F 10 animals in control and 20 animals in test group (4 additional animals, 2 M + 2 F, were used in the pre-test)	Batch: EN 603012	induction: 50% in vaseline (48 h exposure) Epidermal challenge: 20% in vaseline (24 h exposure)	penconazole in this maximisation test system was 15%	Report No. 983118

Table 27: Summary table of human data on skin sensitisation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

Table 28: Summary table of other studies relevant for skin sensitisation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

2.6.2.7.1 Short summary and overall relevance of the provided information on skin sensitisation

Penconazole tech., purity 96%, was tested on 20 (penconazole-treated) and 10 (vehicle control) female albino Guinea Pigs of the GOHI strain (Himalayan Spotted) using the maximisation method. During intradermal induction pre-test, doses of 0.5, 1.0, 3.0, and 5.0% penconazole tech. in peanut oil were administered. During epidermal induction pre-test, doses of 10, 20, 30, and 50% penconazole tech. in vaseline were administered. According to the results, 5% penconazole tech. in peanut oil was used for intradermal induction, 50% penconazole tech. in vaseline was used for epidermal induction, and 20% penconazole tech. in vaseline was used for epidermal challenge. At day 0, an area of 5x5 cm was shaved, and three pairs of injections of 0.1 mL of the test article (5.0% in peanut oil) were then given in the shaved area so that one injection of each pair was on each side of the midline:

- 0.1 mL FCA/saline (1:1 v/v)
- 0.1 mL peanut oil (control) or 5% penconazole tech. in peanut oil (treatment group)
- 0.1 mL peanut oil, 50% w/v with 1:1 adjuvant/physiological saline mixture (control) or 5% penconazole tech. in 1:1 FCA/saline mixture

At day 8, a filter paper patch was fully loaded (approximately 0.4 g) with 50% test article in vaseline (treated group) or vaseline vehicle alone (control) and held in place with the occlusive dressing for 48 h. At day 21, the flanks of all animals were shaved immediately prior to treatment. One chamber loaded with the 20% test article in vaseline (highest non-irritating dose, approximately 0.35 mL) was placed on one flank (test flank) and one chamber loaded with the vehicle alone was placed on the other flank (vehicle flank) of the animals of both groups. The chambers were held in place with an occlusive dressing for 24 h. 24 and 48 h after the challenge application, dermal reactions (erythema and oedema) were examined and graded according to the Draize scoring scale. Body weights were recorded at the start and end of the test. Clinical symptoms and mortality were checked daily. Application sites were examined for skin irritation reactions 1 h after removal of the epidermal induction dressing on day 10.

For the pre-test, intradermal injection of penconazole tech. in peanut oil caused erythema and oedema (grade 1) at concentrations of 0.5, 1.0, 3.0 and 5%. When administered epidermally in vaseline, penconazole did cause erythema of skin (but no oedema) at concentrations of 30% and 50%, but not at 10 or 20%. For the main test, positive dermal skin reactions were observed on all animals that received the test material, but not in the vehicle controls. After challenge application, erythema was evident at the application site in 2/20 animals at 24 h and in 3/20 animals at 48 h. Oedema was evident at the application site in 1/20 animals at 24 h and in 1/20 animals at 48 h. Based on these observations, the sensitisation rate of penconazole in this maximisation test system was 15%. There were no skin responses among the vehicle control group. There was neither mortality nor remarkable clinical signs in the guinea pigs of the control or test group, and body weights were not affected by treatment.

2.6.2.7.2 Comparison with the CLP criteria regarding skin sensitisation

In accordance with the CLP criteria, a substance is classified if there are positive results from an appropriate animal test, i.e. redness (Score ≥1) in ≥30% of the test animals. The sensitisation rate of penconazole in this maximisation test system was 15% only. According to Regulation (EC) No. 1272/2008 no classification is warranted.

2.6.2.7.3 Conclusion on classification and labelling for skin sensitisation

Data conclusive but not sufficient for classification.

2.6.2.8 Phototoxicity

Table 29: Summary table of studies on phototoxicity

Method, guideline, deviations[1] if any	Test substance	Dose levels duration of exposure	Results	Reference
Penconazole – *In Vitro* 3T3 NRU Phototoxicity Test OECD 432 (2004) Study is acceptable	CGA71818 (penconazole) Purity: 99.3% Lot/batch: AMS204/3	1000; 316; 100; 31.6, 10.0; 3.16; 1.00 and 0.316 µg/mL 60 min incubation + 50 min irradiation	No phototoxic potential. PIF = 0.9	Gehrke H. (2015) K-CA 5.2.7/01 Report No: 146848

Table 30: Summary table of human data on phototoxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

Table 31: Summary table of other studies relevant for phototoxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

2.6.2.8.1 Short summary and overall relevance of the provided information on phototoxicity

Under the experimental conditions reported, the test item penconazole did not possess any phototoxic potential. A PIF of 0.9 was calculated.

The study is acceptable. With exception of two minor deviations, the study follows OECD TG 432 (2004), which was in force at the time when the supplemental dossier was submitted, as well as the revised version of this TG, adopted in 2019 (OECD TG 432, 2019). One minor deviation from the TG is a change of the type of serum added to the cell culture medium (10% calf serum instead of the recommended 10% Newborn calf serum) since cells cultivated with several new NCS batches failed the acceptance criteria. A second minor deviation is the applicant's reference to the half-effective concentration (EC_{50}) instead of the added concentration of the test chemical at which the response amounts to 50% of the original value (IC_{50}). According to the study report, no distinction is normally made in practical applications between the EC_{50} representing the bio-available concentration of the substance which is actually sensed by target and the IC_{50}. In RMS opinion, none of these deviations influence the quality or integrity of the present study.

Although RMS agrees with the assessment and conclusions of the applicant, there are some concerns to consider this study as relevant to evaluate phototoxicity. According to the available UV/VIS results, no absorption maximum between 290 nm and 750 nm was observed at any pH for penconazole (Batch AMS 204/102, purity 99.5%). Absorption was seen in the range of 220-281 nm at acidic, neutral and alkaline conditions. The irradiation wavelength used in the test for phototoxicity (>330 nm) may therefore be considered as not appropriate for the assessment of the phototoxicity of penconazole. To RMS's opinion, the phototoxicity of penconazole can therefore not be concluded. However, in the context of risk assessment this is of no importance since penconazole will be exposed to the visible spectrum where the lower irradiation wavelengths of the UV spectrum are not relevant.

2.6.2.8.2 Comparison with the CLP criteria regarding phototoxicity

N/A

2.6.2.8.3 Conclusion on classification and labelling for phototoxicity

Data inconclusive.

2.6.2.9 Aspiration hazard [equivalent to section 10.13 of the CLH report template]

Table 32: Summary table of evidence for aspiration hazard

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No study available				

2.6.2.9.1 Short summary and overall relevance of the provided information on aspiration hazard

No evidence of aspiration hazard.

2.6.2.9.2 Comparison with the CLP criteria regarding aspiration hazard

Hazard class not applicable.

2.6.2.9.3 Conclusion on classification and labelling for aspiration hazard

Hazard class not applicable.

2.6.2.10 Specific target organ toxicity-single exposure (STOT SE) [equivalent to section 10.11 of the CLH report template]

Table 33: Summary table of animal studies on STOT SE (specific target organ toxicity-single exposure)

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
Acute Aerosol Inhalation Toxicity In The Rat OECD 403 -the use of ten animals (5 males and 5 females) instead of five (only males, or the most sensitive sex) in one dose group -only one concentration tested (the highest attainable and close to the limit concentration for classification of aerosols) -a slightly higher mass median equivalent aerodynamic diameter (4.4 µm) than the recommended (4 µm). Rat [redacted] RAIf (SPF) M, F 5/sex/group	Penconazole Tech. (EN 603012, 96.1%) Inhalation, nose-only control group: 2472 mg F1/m^3 air; 4046 mg penconazole/m^3 air 4 hours	Acute rat inhalation LC_{50} (dust, nose only) >4.046 mg/L air/4h, no classification for acute inhalation is required. No animal deaths, symptoms included slight to moderate sedation, moderate to severe dyspnoea, curved body position and ruffled fur, which were observed in all animals at the end of the 4 h inhalation exposure and thereafter. Furthermore, in rats exposed to penconazole, symptoms were of a slightly more severe grade than in the vehicle control group and lasted 2 days longer. All rats had recovered completely on day 5 (vehicle control group) and on day 7 post-exposure (test group), respectively.	[redacted] (1987) K-CA 5.2.3/01 Report No. 871169

Table 34: Summary table of human data on STOT SE (specific target organ toxicity-single exposure)

Type of data/report	**Test substance**	**Route of exposure Relevant information about the study (as applicable)**	**Observations**	**Reference**
No study available				

Table 35: Summary table of other studies relevant for STOT SE (specific target organ toxicity-single exposure)

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No study available				

2.6.2.10.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure (STOT SE)

No relevant findings on specific target organ toxicity – single exposure

2.6.2.10.2 Comparison with the CLP criteria regarding STOT SE (specific target organ toxicity-single exposure)

According to the CLP criteria, classification for STOT-SE is appropriate when it has been demonstrated from human or animal data that specific non-lethal target organ toxicity arises from a single exposure to a substance. STOT-SE Category 1 and 2 is assigned on the basis of findings of 'significant' or 'severe' toxicity. In this context 'significant' means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. 'Severe' effects are generally more profound or serious than 'significant' effects and are of a considerably adverse nature with significant impact on health. Both factors have to be evaluated by weight of evidence and expert judgement. Category 3 is specifically assigned for transient effects on the respiratory system and/or narcotic effects. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included

2.6.2.10.3 Conclusion on classification and labelling for STOT SE (specific target organ toxicity-single exposure)

Data conclusive but not sufficient for classification.

2.6.3 Summary of repeated dose toxicity (short-term and long-term toxicity) [section 10.12 of the CLH report]

2.6.3.1 Specific target organ toxicity-repeated exposure (STOT RE) [equivalent to section 10.12 of the CLH report template]

Table 36: Summary table of animal studies on repeated dose toxicity (short-term and long-term toxicity) STOT RE (specific target organ toxicity - repeated exposure)

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
28-Day Oral Cumulative Toxicity Study In Rats OECD 407: -doses were increased after one week of treatment -functional parameters reactivity to stimuli, grip strength and motor activity were not measured -bile acids were not measured -epididymis, prostate + seminal vesicles with coagulating glands and heart were not weighed Supportive only (as dose levels were increased on day 8 of treatment) Rat [redacted] RAIf (SPF) (Sprague-Dawley-derived) M, F 10/sex/dose	Penconazole (91.7%, P. 11-14), Oral (gavage), First week 0, 20, 100, 500 mg/kg bw/day From 2nd week: 0, 100, 500, 1000 mg/kg bw/day Doses were increased after one week of treatment. 28 days	NOAEL: 20 < 100 LOAEL: 100 < 500 **Target organ:** Liver. **Mortality:** No deaths. **Clinical signs:** 3/10 (F/M) at top dose (vs. 0 in ctr): marked apathy, lateral body position after dose increase. Recovered after a few days. **Ophthalmology:** No relevant findings. **Body weight:** M high dose (-13%) **Bw gain:** M high dose 1st week (-8.9%), F (-17%, -21%) and M (-16%, -35%) at both top doses after 2nd week. **Food consumption:** M/F top dose weeks 2-4 (-19%, -12%). **Water consumption:** F top dose (+31%). **Haematology:** F two top doses (Haemoglobin: -4.2%, -6.3%; Haematokrit: -4.7%, -7.0%). M 500 mg/kg-group (Haemoglobin: -3.2%, Haematokrit: -2.3%). **Clinical chemistry:** Albumin: M top dose (+15%), F top dose (+9.0%); ALAT: M/F top dose (+48%); Bilirubin: M top dose (+267%);	[redacted] (1984) K-CA 5.3.1/01 Report No. 820822

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
		Creatinin: M top dose (+11%); Globulin: F two top dose-groups (+16%, +27%); K^+: F top dose (-32%); Phosphate: F top dose (+32%); Total protein: M top dose (+11%), F two top dose-groups (+6.6%, +17%). **Urine volume:** M top dose (+70%), F two top dose-groups (+38%, +108%). **Organ weight:** Liver: M two top dose-groups (abs. +46%, +67%; rel. +56%, +102%), F two top-dose groups (abs. +39%, +76%; rel. +50%, +102%); Kidney: M two top dose-groups (rel. +16%, +24%), F two top dose groups (abs. +17%, +22%; rel. +27%, +41%); Adrenal: F two top dose-groups (abs. +13%, +12%). **Macro- and histopathology:** Enlarged liver, hepatocyte hypertrophy: M/F top dose 10/10 (vs. 0/10 in ctr), 500 mg/kg-group: 8/10 M, 3/10 F.	
28-Day Subacute, Oral Toxicity Study In Rats OECD 407: -For each batch of test material only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level -functional parameters reactivity to stimuli, grip strength and motor activity were not measured -epididymis, prostate + seminal vesicles were not weighed -only a limited number of organs/tissues were examined histopathologically Supportive only (as only two dose levels were tested, and because of the deficiencies in dose level selection; toxicity already at the low dose and excessive toxicity at the high dose) Rat	Penconazole Batch A: 96.2% (w/w); batch B: 96.1% (w/w), Batch A: op. 3-23.01.90; batch B: EN 603012 Oral (gavage) 0-100-500 mg/kg bw/day 28 days	NOAEL: <100 LOAEL: 100 **Target organ:** Liver. **Mortality:** M top dose 1/10 (B) sacrificed, F top dose 1/10 (A) and 2/10 (B) sacrificed. **Clinical signs:** F top dose (B): Hunch-backed posture, piloerection, laboured breathing. **Body weight/BW gain:** No significant, dose-dependent relevant findings. **Food consumption:** F top dose (-3.3% (A), -4.2% (B)). **Haematology:** Platelets: M top dose (+30% (A), +25% (B)); Prothrombin time: M top dose (-17% (A/B), F top dose (-15% (A), -18% (B)). **Clinical chemistry:** Glucose: F top dose (+44% (A), +39% (B)); Urea: M top dose (+37% (A)), F top dose (+19% (A)); Total protein: M top dose (+9.3% (A), +7.6% (B)), F 100 mg/kg-group (+5.3% (A), +4.1% (B)) 500 mg/kg-group (+7.1% (A), +8.7% (B)); Globulin: M top dose (+14% (A), +12% (B)), F top dose (+10.6% (A), +16% (B)); Cholesterol: M top dose (+44% (A), +25% (B)), F top dose (+60% (A), +91% (B)); ALAT: M top dose (+40% (A), +62% (B)), F top dose (+18% (A), +39% (B)). **Organ weight:** Liver: M 100 mg/kg-group (abs. +9.3% (A), +11% (B), rel. +10.2% (A), +9.0% (B)), M 500 mg/kg-group (abs. +43% (A), +58% (B), rel. +45% (A), +60% (B)), F 100 mg/kg-group (abs. +14% (B), rel. +13% (B)), F 500 mg/kg-group (abs. +46% (A), +56% (B), rel. +46% (A), +52% (B)); Kidney: M top dose (abs. +14% (A), +18% (B), rel. +16% (A), +19% (B)), F top dose (abs. +23% (A), +20% (B), rel. +22%	[redacted] (1991) K-CA 5.3.1/02 Report No. 901026

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
Tif:RAIf (SPF) (Sprague-Dawley-derived) M, F 10/sex/dose		(A) +17% (B)); Adrenal: M top dose (abs. +18% (A), +14% (B)); Thyroids: M 100 mg/kg-group (abs. +9.9% (A) +43% (B), rel. +10.9% (A), +40% (B)), M 500 mg/kg-group (abs. +32% (A), +50% (B), rel. +34% (A), +53% (B)). **Macro- and histopathology:** Hepatocyte hypertrophy: M top dose 10/10 (A), 9/10 (B) (vs. 0/10 in ctr), F top dose 7/10 8A), 8/10 (B) (vs. 0/10 in ctr); Hepatocellular necrosis: M top dose 2/10 (A), 3/10 (B) (vs. 0/10 in ctr); Thyroid follicle epithelium hypertrophy: M top dose 7/10 (A), 10/10 (B) (vs. 2/10 in ctr), F top dose 2/10 (A), 8/10 (B) (vs. 0/10 in ctr).	
3-Month Toxicity Study In Rats Guideline not reported, OECD 408 came into force shortly after study start -dose intervals exceeded the recommended optimum (2-4) but were within recommended maximum (10). -grip strength and motor activity were not assessed, but this may be considered as in agreement with the guideline in absence of clinical signs indicating any functional deficits. -thyroid hormones (T4, TSH, T3), LDL and HDL were not measured. -oestrus cycle stage was not determined at sacrifice. -the following organs were not weighed: epididymis, prostate + seminal vesicles with coagulating glands as a whole complex), uterus, pituitary gland and thyroid gland. -no histopathological examination was conducted on the vagina, cervix and the coagulating glands. Supportive only	Penconazole (91.7%, P. 11-14) Oral (diet) (0-30-300-3000 ppm) M: 0-2.0-19.4-202 mg/kg bw/day; F: 0-2.1-20.7-209 mg/kg bw/day 90 days	NOAEL: (300) M: 19.4; F: 20.7 LOAEL: (3000) M: 202; F: 209 **Target organ:** Liver. **Mortality:** No deaths occurred. **Clinical signs:** No clinical signs noted. **Ophthalmology:** No treatment-related effects. **Body weight/BW gain:** F top dose week 13 (-16%), F top dose weeks 1-13 (-26%). **Food consumption:** M top dose week 1 (-10.6%), F top dose weeks 1-13 (-9.9%). **Water consumption:** M top dose week 12 (+15%), F top dose week 12 (+24%). **Haematology:** Nucleated RBC-normoblasts F two top doses (0.25 and 0.30 vs 0.05 in ctr). **Clinical chemistry:** No dose-dependent, significant relevant changes compared with ctr. **Organ weight:** Liver: M 300 ppm-group (abs. +10.85, rel. +7.0%), M 3000 ppm-group (abs. +22%, rel. +28%), F 300 ppm-group (abs. +7.4%, rel. +8,0%), F 3000 ppm-group (abs. +21%, rel. +40%). **Macro- and histopathology:** Hepatocyte hypertrophy M top dose 20/20, F top dose 9/20 (vs. 0/20 in ctrs).	[redacted] (1982) K-CA 5.3.2/01 Report No. 801194

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
(due to deviations from the test guideline currently in place) Rat, [redacted] RAIf; 20M+20F			
3-Month Toxicity Study In Rats OECD 408 -grip strength and motor activity were not assessed, but this may be considered as in agreement with the guideline in absence of clinical signs indicating any functional deficits. -thyroid hormones (T4, TSH, T3), LDL and HDL were not measured. -oestrus cycle stage was not determined at sacrifice. -the following organs were not weighed: epididymis, prostate + seminal vesicles with coagulating glands as a whole complex), uterus, pituitary gland and thyroid gland. -no histopathological examination was conducted on the vagina, cervix and the coagulating glands. Supportive only (due to deviations from the test guideline currently in place) Rat, [redacted] RAIf; 20M+20F	Penconazole (91.7%, P. 11-14) Oral (diet) (0-10-30-100 ppm) M: 0-0.8-2.1-7.1 mg/kg bw/day; F: 0-0.8-2.1-7.3 mg/kg bw/day 90 days	NOAEL: (>100) M: 7.1; F: 7.3 **Mortality:** No deaths during test period. **Clinical signs:** No treatment-related clinical signs. **Ophthalmology:** No treatment-related incidences. **Body weight and bw gain:** Comparable to ctr in all treatment groups, except increased weight (+9.8%) and weight gain in F 30 ppm-group. **Food and water consumption:** Comparable to ctr in all groups. **Haematology:** No treatment-related dose-dependent findings. **Clinical chemistry:** Urea-N: F top dose (-14%); Total proteins: M top dose (+2.5%) w/increasing trend, F top dose (+4.1%) w/increasing trend; Phosphate inorg.: M top dose (-13.7%) w/decreasing trend. **Organ weight:** Liver: M 10 ppm and 30 ppm-groups (abs. +14%, +23%, rel. +11%, +15%), but not evident at top dose. **Macro- and histopathology:** No treatment-related dose-dependent findings.	[redacted] (1983) K-CA 5.3.2/02 Report No. 821054
90-Day Subchronic Toxicity Study In Albino Rats FIFRA § 82-1; while not being referenced in the report OECD 408 (1981) was in force at the time of the study	Penconazole (98.7%, FL-840833) Oral (diet) (0-10-100-300-500-1000-2400 ppm) M: 0-0.8-7.5-23.2-37.5-72-179 mg/kg bw/day; F: 0-1.0-9.8-	NOAEL: (300) M: 23.2; F: 28.3 LOAEL: (500) M: 37.5, F: 45.2 **Target organ:** Liver. **Mortality:** No deaths. **Clinical signs:** No treatment-related clinical signs. **Ophthalmology:** No incidences.	[redacted] (1987b) K-CA 5.3.2/03 Report No. [redacted] 6117-120

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
-histopathological examination was limited to the liver as a target organ. -grip strength and motor activity were not assessed. However, this may be considered as in agreement with the guideline in absence of clinical signs indicating any functional deficits. -thyroid hormones (T4, TSH, T3), LDL and HDL were not measured. -oestrus cycle stage was not determined at sacrifice. -the following (and several other) organs were not weighed: epididymis, prostate + seminal vesicles with coagulating glands as a whole complex), uterus, pituitary gland and thyroid gland. Supportive only (due to deviations from the test guideline currently in place) Rat, [redacted] CD(SD)BR 15M+15F	28.3-45.2-86-209 mg/kg bw/day 90 days	**Body weight and bw gain:** Bw F two top doses (-6.2% and -10%), bw gain F two top doses (-8.9% and -15%). **Food consumption:** F top dose (-8.9%). M all groups deceased food consumption (-8-12%), no dose-dependent effect. **Haematology:** No treatment-related effects on any parameter compared with ctr. **Clinical chemistry:** Urea-N: M two top doses (+35% and +22%). **Organ weight:** Liver: M 1000 ppm-groups (re. +13%), M top dose (abs. +29%, rel. +31%, rel. to brain +32%), F 500 ppm-group (rel. +10.2%), F 1000 ppm-group (abs. +18%, rel. +20%, rel. to brain +18%), F top dose (abs. +18%, rel. +29%, rel. to brain +17%). **Macro- and histopathology:** Hepatocellular hypertrophy: M 1000 ppm-group 12/15, M/F 2400 ppm-group 15/15, F 1000 ppm-group 10/15 (vs. 0/15 in ctrs); Hepatocellular degeneration: M 2400 ppm-group 5/15, F 2400 ppm-group 7/15 (vs. 0/15 in ctrs); Hepatocytic vacuolization: M 2400 ppm-group 11/15 (vs. 0/15 in ctr).	
Toxicity Study In Dogs Not reported; guidelines in force at the time the study was performed: OECD 409 (1981) -length of acclimatisation period is not formally reported (animals bred in-house/same site). -animals were observed daily for mortality and signs of local or systemic toxicity, while the guideline states that all animals should be inspected for signs of morbidity and	Penconazole (91.7%, P. 11-14) Oral (diet) (0-100-500-5000/2500 ppm) M**: 0-3.4-18.2-132 mg/kg bw/day; F**: 0-3.8-19.4-137 mg/kg bw/day 90 days	NOAEL: (100) M: 3.3; F: 3.8 LOAEL: (500) M: 17.5; F: 18 **Target organ:** Liver. **Mortality:** No deaths during test period. **Clinical signs:** Diarrhoea observed in all groups, also ctr. Vomiting in the 5000 ppm-group (M/F). **Ophthalmology:** Spot on cornea (one F), spot on lens (one F). **Body weight and bw gain:** M/F top dose body weight loss (-9-12%). **Food consumption:** M top dose (-34%), F top dose (-36%). **Haematology:** Hb: M top dose (-9.3%); RBC: M top dose (-10.3); Lymphocytes: M top dose (+9.1%), F top dose (+12%); Eosinophils: M top dose (-75%); Platelets: M top dose (+9.2%), F top	[redacted] (1984); K-CA 5.3.2/04 Report No. 801187

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
mortality at least twice daily. -urine analysis was not performed midway through the study. -urine volume was not investigated as urine was collected via catheterisation. -The following organs were not weighed: gall bladder, uterus, thymus and spleen (unclear whether gall bladder was included in liver weight and whether parathyroids were weighed together with thyroids). Study is acceptable. Dog, Beagle 4M+4F		dose (+35%). Of note, most values within HCD mean. **Clinical chemistry:** Glucose: M top dose (-13%); OCT: M top dose (+418%), F top dose (+480%); Urea-N: F top dose (-32%); Globulin: M top dose (+12%); inorganic PO_4: M top dose (+11%), F top dose (+36%); ALP: M top dose (+390%), F top dose (+366%); γ-GT: M top dose (+1800%), F top dose (+932%); AST: M top dose (+154%), F top dose (+143%); ALT: M top dose (+790%), F top dose (+808%). **Organ weight:** Liver: M 500 ppm-group (abs. +20%, rel. +15%), M 5000 ppm-group (abs. +30%, rel. +75%), F 500 ppm-group (abs. +15%, rel. +24%), F 5000 ppm-group (abs. +22%, rel. +88%); Kidney: M top dose (abs. +16%, rel. +60%), F top dose (abs. +18%, rel. +55%); Gonads: M top dose (abs. -47%, rel. -27%), F top dose (abs. -37%, rel. -17%). **Macro- and histopathology:** M/F top dose: Emaciation of all animals except one M; Cytoplasmic vacuolisation liver: M top dose 2/4 (vs. 0/4 in ctr); Inflammatory cell infiltration liver: M/F top dose 4/4 (vs. 0/4 in ctrs); Hepatocyte necrosis: M/F top dose 4/4 (vs. 0/4 in ctrs); Reduced spermatogenesis: M top dose 4/4 (vs. 0/4 in ctr); Epididymis cellular debris: M top dose 4/4 (vs. 0/4 in ctr).	
Toxicity Study In Dogs Not reported; guidelines in force at the time the study was performed: OECD 409 (1981) and OECD 452 (1981) -the deviations listed for the 90-day part of the study concerning length of acclimatisation period, clinical signs and urine volume -the following clinical pathology parameters were not determined: MCV, MCH, MCHC, activated partial thromboplastin time, total cholesterol -the following organs were not weighed: uterus and spleen (unclear whether parathyroids were weighed together	Penconazole (91.7%, P. 11-14) Oral (diet) (0-100-500-5000/2500 ppm) M**: 0-3.0-16.8-108 mg/kg bw/day; F**: 0-3.2-16.5-110 mg/kg bw/day 1 year	NOAEL: (100) M: 3.1; F: 3.3 LOAEL: (500) M: 16.9; F: 16.7 **Target organ:** Liver. **Mortality:** No deaths during test period. **Clinical signs:** Diarrhoea observed in all groups, also ctr, less frequent towards end of study period. Vomiting in the 5000 ppm-group (M/F), only in F after dose reduction. **Ophthalmology:** Spot on lens (one F). **Body weight and bw gain:** Bw F top dose (-13%), bw gain M top dose (-44%), bw gain F top dose (-58%). **Food consumption:** M top dose (-11%), F top dose (-5.8%). Drastically reduced during first weeks of study, gradually improved, especially after dose reduction. **Haematology:** Platelets: M top dose (+44%), F top dose (+40%), no clear dose response. **Clinical biochemistry:** OCT: M top dose (+1273%), F top dose (+1700%); Globulin: M top dose (+16%); ALP: M 500 ppm-group (+60%), M top dose (+425%), F top dose (+381%); γ-GT: M top dose (+504%), F top dose (+313%); AST: M	[redacted] (1984); K-CA 5.3.2/04 Report No. 801187

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
with thyroids) -there was no histopathological examination of cervix, coagulating gland, seminal vesicles, vagina and the Harderian gland. Study is acceptable. Dog, Beagle 4M+4F and 2M+4F for recovery		top dose (+157%), F top dose (+109%); ALT : M top dose (+454%), F top dose (+683%). **Organ weight:** Liver: M top dose (abs. +27%, rel. +35%), F 500 ppm-group (abs. +27%, rel. +28%), F top dose (abs. +46%, rel. +21%); Kidney: M top dose (abs. +12%, rel. +21%), F 500 ppm-group (abs. +15%, rel. +15%), F top dose (abs. +25%, rel. +39%); Adrenals: M top dose (abs. +12%, rel. +22%), F top dose (abs. +34%, rel. +54%). **Macro- and histopathology:** Cytoplasmic vacuolisation liver: M/F top dose 2/4 (vs. 0/4 in ctrs); Inflammation with fibrosis liver: M/F top dose 4/4 (vs. 0/4 in ctrs); Hepatocyte necrosis: F top dose 2/4 (vs. 0/4 in ctr); Reduced spermatogenesis: M top dose 2/4 (vs. 0/4 in ctr); Tubular atrophy testis: M top dose 2/4 (vs. 0/4 in ctr).	
90-Day Subchronic Dietary Toxicity And Kinetic Study In Albino Mice EPA guideline No. 82-1; OECD 408 (1981) not referenced but was in force at the time of the study -histopathological examination was limited to the liver (expected target organ). -grip strength and motor activity were not assessed, but this may be considered as in agreement with the guideline in absence of clinical signs indicating any functional deficits. -thyroid hormones (T4, TSH, T3), LDL and HDL were not measured. -oestrus cycle stage was not determined at sacrifice. -the following organs were not weighed: testes, epididymis, prostate + seminal vesicles with coagulating glands as a whole complex), uterus, thymus, pituitary gland and thyroid gland.	Penconazole (98.7%, FL-840833) Oral (diet) (0-10-100-300-500-1000-2400 ppm) M: 0-1.7-17.1-51.8-84.7-163-423 mg/kg bw/day; F: 0-2.5-23.9-72.2-115.6-237-614 mg/kg bw/day 90 days	NOAEL: M: (500) 85; F: (1000) 237 LOAEL: M: (1000) 163; F: (2400) 614 **Target organ:** Liver **Mortality:** Two F (2400 ppm and 1000 ppm-group), one M (500 ppm-group). **Clinical signs:** No clinical signs reported. **Ophthalmology:** No incidences. **Body weight gain:** M top dose (-13%), F top dose (-17%) (vs pooled week 0 data). **Food consumption:** No differences to ctr, trend to slightly higher consumption in F top dose (+8.5%). **Haematology:** No differences to ctr. **Clinical chemistry:** Total protein: M 1000 ppm-group (-8.3%), M top dose (-6.7%), F top dose (-10%); Albumin: F top dose (-14%); A/G ratio: F top dose (-13%); Cholesterol: M 1000 ppm-group (-31%), M top dose (-61%), F 1000 ppm-group (-36%), F top dose (-40%); ALT: M top dose (+170%); γ-GT: M 500 ppm-group (-75%), M 1000 ppm-group (-92%), M top dose (-100%). **Organ weight:** Liver: M 500 ppm-group (abs. +11%, rel. +10.5%), M 1000 ppm-group (abs. +21%, rel. +17%), M top dose (abs. +34%, rel. +42%), F top dose (abs. +24%, rel. +32%); Kidney: F top dose (abs. -11.5%). **Macro- and histopathology:** Hepatocyte hypertrophy: M 1000 ppm-group (6/15), M top dose (14/15), F top dose 7/15 (vs. 0/15 in ctrs); Hepatocyte degeneration: M top dose 7/15 (vs. 0/15 in ctr); Hepatocyte vacuolisation: M top dose	[redacted] (1987) K-CA 5.3.2/05 Report No. [redacted] 6117-121

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
Supportive only Mouse, [redacted] CD-1(ICR)BR 15M+15F		10/15 (vs. 0/15 in ctr); Coagulative necrosis liver: M top dose 4/15 (vs. 0/15 in ctr).	
90 Day Preliminary Carcinogenicity Study In Mice This study was conducted as a preliminary carcinogenicity study and was not intended to comply with any regulatory guidelines. OECD 408 (1998) was in force at the time of the study. -No haematology and no ophthalmological examination performed. -histopathological examination was limited to the adrenals, brain, epididymis, ovary, kidney, liver and testis. -grip strength and motor activity were not assessed. -thyroid hormones (T4, TSH, T3), LDL, HDL, sodium, potassium, blood urea nitrogen, were not measured. -oestrus cycle stage was not determined at sacrifice. -the following organs were not weighed: prostate + seminal vesicles (with coagulating glands as a whole complex), thymus, pituitary gland and thyroid gland. Supportive only (considering the purpose of the study and due to deviations from the test guideline currently in place) Mouse, C57BL/10J	Penconazole (97.7%, WS007001) Oral (diet) (0-100-500-1500-3000-5000 ppm) M: 0-14-69-229-437-837 mg/kg bw/day; F: 0-18-87-274-545-983 mg/kg bw/day 90 days	NOAEL: (500) M: 69; F: 87 LOAEL: (1500) M: 229; F: 274 **Target organ:** Liver **Mortality:** 5000 ppm-group: All animals killed for humane reasons. Two additional animals died/were killed (3000 ppm-group and 500 ppm-group). **Clinical signs:** No treatment-related clinical signs in surviving animals. **Body weight gain:** M/F 5000 ppm-group (-11-17%, before killing in second week). M 1500 ppm-group (-19%), M 3000 ppm-group (-52%), F 1500 ppm-group (-9.8%), F 3000 ppm-group (-38%). **Clinical chemistry:** Cholesterol: M 500 ppm-group (-10%), M 1500 ppm-group (-43%), M 3000 ppm-group (-54%), F 100 ppm-group (-13%), F 500 ppm-group (-29%), F 1500 ppm-group (-42%), F 3000 ppm-group (-58%); ALP: M 1500 ppm-group (+22%), F 3000 ppm-group (+25%); Albumin: F 1500 ppm-group (-5.7%), F 3000 ppm-group (-6.5%); Total protein: F 1500 ppm-group (-7.7%), F 3000 ppm-group (-8.1%); Triglycerides: M/F 3000 ppm-group (-20%); Calcium: F 3000 ppm-group (-4.4%). **Organ weight:** Liver (adjusted for body weight): M 500 ppm-group (+12%), M 1500 ppm-group (+33%), M 3000 ppm-group (+48%), F 1500 ppm-group (+10%), F 3000 ppm-group (+28%). Adrenals (adjusted for body weight): F 3000 ppm-group (+52%); Epididymides: M 3000 ppm-group (abs. -21%, rel. -5.8%, adjusted for body weight -22%). **Macro- and histopathology:** Hepatocyte hypertrophy: M ≥1500 10/10, F 3000 ppm-group 4/10 (vs. 0/10 in ctrs); Increased nuclear pleomorphism liver: M ≥1500 10/10 (vs. 0/10 in ctr).	[redacted] (2002) K-CA 5.3.2/06 Report No. CTL/PM12 35

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
fCD-1 10M+10F			
21-Day Repeated Dose Dermal Toxicity Study in Rabbits OECD 410 -Initial weight was 1.5-3 kg versus the recommended 2-3 kg. -ornithine decarboxylase was not measured Study is acceptable Rabbit, NZW; 5M+5F	Penconazole (91.7%, P. 11-14) Dermal M/F: 0-1000-1500-2000 mg/kg bw/day 21 days	NOAEL: M/F: 2000 **Mortality:** No deaths. **Clinical signs:** No treatment-related clinical signs. **Body weight and bw gain:** Not affected by treatment. **Haematology and Clinical chemistry:** No treatment-related, dose-dependent, biologically relevant findings. **Organ weight:** No treatment-related, dose-dependent, biologically relevant findings. **Macro- and histopathology:** No treatment-related, dose-dependent, biologically relevant findings.	[redacted] (1983) K-CA 5.3.3/01 Report no 820206.

* exceeding the range of historical control data provided by the applicant for the renewal
** based on recalculated intake of penconazole during the renewal

Table 37: Summary table of human data on repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

Type of data/report	Test substance	Route of exposure Relevant information about the study (as applicable)	Observations	Reference
No study available				

Table 38: Summary table of other studies relevant for repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No study available				

2.6.3.1.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure (short-term and long-term toxicity)

The short-term oral toxicity of penconazole was evaluated by means of two 28-day (gavage) and three 90-day (diet) studies in rats, two 90-day dietary studies in mice, and by means of a combined 90-day and one-year capsule feeding study in the dog. In all three species, the liver was the main target organ following oral administration of penconazole. In addition, some evidence for a disturbance of protein and lipid metabolism was found in all species. Histopathological evidence for organ toxicity was accompanied by reductions in body weight gain and food consumption.

In the 28-day gavage studies in rats, clinical signs and/or mortality, reduced body weight development and food consumption, and some changes in haematology parameters (not necessarily consistent between the two available studies) were seen at dose levels ≥500 mg/kg bw/day. Changes in clinical pathology parameters – at least partly associated with an induced liver function (increased ALAT, increased albumin, globulin or total protein, increased cholesterol) - were most marked at 1000 mg/kg bw/day, with occasional changes seen already at 500 mg/kg bw/day.

Liver weights were increased at ≥100 mg/kg bw/day and associated with hepatocyte hypertrophy and other histopathological findings at ≥500 mg/kg bw/day. Kidney and adrenal weights were increased at ≥500 mg/kg bw/day, but only the latter was associated with adrenal cortical atrophy in females in one study at 500 mg/kg bw/day. Observed variations in thyroid weight were inconsistent between the two studies and the two sexes: in the 1st study, thyroid weights were increased in females and somewhat decreased in males (at 1000 mg/kg bw/day) while the situation was reversed in the 2nd study, where an increase in thyroid weight was seen in males and a slight decrease in females (500 mg/kg bw/day). However, in the 2nd study, increased incidences of thyroid follicular hypertrophy were seen in both sexes at 500 mg/kg bw/day. Considering both available 28-day studies, the NOAEL is considered to be between 20 and 100 mg/kg bw/day.

In the 90-day feeding studies in rats, reduced body weight gain and food consumption was seen at ≥1000 ppm primarily in females (only slight effects at 3000 ppm in males). Water consumption was increased in both sexes at 3000 ppm. A number of clinical pathology parameters achieved statistical significance in the available studies at higher dose levels, but most of these variations were within the range of available historical control data (HCD), except from increased cholesterol (3000 ppm) and blood urea nitrogen (≥1000 ppm). Absolute and relative liver weights were increased at ≥1000 ppm and associated with increased incidences of hepatocyte hypertrophy (both sexes), hepatocyte vacuolation (males) and hepatocytic degeneration (males). Low incidences of hepatocyte hypertrophy and hepatocytic vacuolisation were also seen at 500 ppm-treated males in one study.
Considering the three available 90-day studies, the overall subchronic NOAEL for rats is considered to be 300 ppm, corresponding to 19.4/20.7 and 23/28 mg/kg bw/day in males/females from two of the studies, respectively. This is in line with the previous evaluation (DAR, 2007) and EFSA's conclusion on the peer review of penconazole (EFSA, 2008), where the relevant overall oral NOAEL in rats was set to 25 mg/kg bw/d (90-d rat, overall NOAEL).

Two 90-day oral (feeding) toxicity studies are available in mice. Excessive toxicity (body weight loss) was observed at 5000 ppm in the 2nd study and animals were sacrificed in the 2nd week. Reduced body weight gain was seen in the 1st study at 2400 ppm and at ≥1500 ppm in the 2nd study. Food utilisation was also reduced in the 2nd study at ≥1500 ppm. Changes in blood biochemistry parameters were also seen at higher dose levels and comprised reduced total protein and albumin (more marked in females), reduced A/G ratio (1st study only), reduced cholesterol, increased ALT (1st study in males only), and reduced triglycerides (2nd study). The liver was the primary target organ with increased weight (≥500 ppm) and histopathological findings (e.g. hepatocyte hypertrophy also at ≥500 ppm) with males showing more marked effects as compared to females. However, during the reassessment, it has been noted that the reported effects at 500 ppm were quite mild with an increase in liver weight of 10-12% compared to controls, associated with only a slight increase in hepatocyte hypertrophy in the 1st study. In contrast to the conclusion during the previous evaluation (DAR, 2007), these changes at 500 ppm can be considered as an adaptive response to the increased metabolic load, and not adverse. During the previous evaluation it was concluded that the overall NOAEL in short term mouse studies was 300 ppm, corresponding to an intake value of 52 mg/kg bw/day. When considering both available 90-day studies in mice, it is now proposed that the overall subchronic NOAEL for mice should be 500 ppm, corresponding to an intake value of 69 mg/kg bw/day.

A combined 90-day/1-year oral (feeding) toxicity study is available in dogs. Due to excessive toxicity (body weight loss, markedly reduced food consumption) the top dose level had to be reduced from 5000 to 2500 ppm from week 20 onwards. While top dose animals then partly compensated for the earlier body weight loss in the remaining treatment period (up to 1 year), overall body weight development was still reduced. A relation to treatment was not excluded for a slightly lower body weight gain over the 1-year period at 500 ppm (females) but could also have been due to the slightly higher body weight at start of the study in this group. At the top dose level, haemoglobin and erythrocyte count and blood glucose were transiently decreased (90-day part) but normalised after the dose level had been reduced towards the end of the 1-year treatment period. However, several changes were seen consistently at the top dose level within the 90-day part of the study and after the dose level had been reduced to 2500 ppm (1-year part of the study): increased globulin and inorganic phosphate (males), and markedly increased liver-related enzymes in both sexes. Liver weights were increased at ≥500 ppm and were associated with histopathological findings at the top dose level, both at the 90-day and 1-year sacrifice (cytoplasmatic vacuolisation, inflammatory cell infiltration (90-day) or inflammation with fibrosis (1-year), hepatocyte necrosis). Increased kidney weight (at 90-day and 1-year sacrifices) at the top dose level was not associated with any histopathological findings. Reduced testes weight and reduced spermatogenesis (90-day and 1-year sacrifices) and tubular atrophy (1-year sacrifice), as well as cellular debris in the epididymis (90-day sacrifice only) was noted at the top dose level. These effects may be considered due to the body weight loss during the first 19 weeks of the study (sensitive time window during sexual maturation of dogs) and/or indicate an adverse endocrine effect. Also, a slight increase in c-cell hyperplasia was noted at the top dose level only at the 90-day sacrifice. Based on the reduced body weight gain and hepatotoxicity observed in the combined 90-day/1-year study, the subchronic NOAEL for dogs was considered to be 100 ppm, corresponding to 3.4 and 3.8 mg/kg bw/day for males and females for the 90-day part of the study, and 3.0 and 3.2 mg/kg bw/day for males and females for the 1-year part of the study, respectively. The relevant overall

NOAEL in dogs, based on this combined 90-day/1-year study, will still be 3 mg/kg bw/day, as previously concluded (EFSA, 2008).

The subchronic toxicity of penconazole was also studied by the dermal route in rabbit. In the available 21-day dermal toxicity study, no relevant treatment-related findings were noted up to the top dose level of 2000 mg/kg bw/day. Consequently, the NOAEL for local irritation was 2000 mg/kg bw/day, and the NOAEL for systemic toxicity higher than 2000 mg/kg bw/day. However, as pointed out earlier (Penconazole addendum DAR, 2008), these results are compromised by the fact that the test material was applied as a solid powder moistened with water, in which penconazole is known to be only poorly soluble.

2.6.3.1.2 Comparison with the CLP criteria regarding STOT RE (specific target organ toxicity-repeated exposure)

According to the CLP criteria, effects considered to support classification for specific target organ toxicity following repeated exposure are:

- **Morbidity or death resulting from repeated or long-term exposure**

  Morbidity resulting in sacrifisation were seen in one 28-days study in rats and one 90-days study in mice, both at the top dose level.

- **Significant functional changes in the central or peripheral nervous systems or other organ systems**

  No relevant findings in any of the studies affecting the nervous system. Functional changes in the liver occurred in the 28-days studies in rats, 90-days studies in mice and 1-year study in dogs, all at the top dose level.

- **Any consistent and significant adverse changes in clinical chemistry, haematology or urinalysis parameters**

  Significant changes in clinical chemistry, mostly related to liver function, was seen at the higher doses in all studies. Changes in haematology were seen in some of the studies at the top doses, and also some changes in urinalysis parameters.

- **Significant organ damage noted as necropsy and/or subsequently seen or confirmed at microscopic examination**

  Hepatocyte hypertrophy and other histopathological findings were seen in all studies at the top doses.

  In the combined 90-days/1-year study in dogs, cytoplasmatic vacuolisation, inflammatory cell infiltration (90-day) or inflammation with fibrosis (1-year), and hepatocyte necrosis were observed. In addition, some incidences of adrenal and thyroid hypertrophy at the top doses were reported.

  In the 90-day oral rat study, evidence of hepatotoxicity was also found. Observations included dose-related centrilobular hypertrophy of hepatocytes (in males 0/15, 3/15, 12/15 and 15/15 for 300, 500, 1000 and 2400 ppm, weaker in females), hepatocellular degeneration around the central vein, and an increase in the incidence of hepatocytic vacuolisation (in males 0/15, 1/15, 5/15 for 500, 1000 and 2400 ppm, weaker in females).

- **Multifocal or diffuse necrosis, fibrosis or granuloma formation in organs with regenerative capacity**

  No relevant findings

- **Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction**

  No relevant findings

- **Evidence of appreciable cell death in vital organs incapable of regeneration**

  No relevant findings.

In summary, among the reported repeated dose toxicity studies on rats (three studies), mice (two studies) and dogs (two studies), the dog appeared to be the most sensitive species, with an overall NOAEL of 3 mg/kg bw/day (100 ppm). Severe liver changes, below the guidance value, are noted at 500 ppm in dog studies (necrosis in 1 male out of 4 in the 90-day study and fibrosis in the 1-year study) and hepatic degeneration is also observed in one rat 90-day study at 1000 ppm (72 mg/kg bw/day) and the effective dose level of 500 ppm (16.9-18 mg/kg bw/day).

2.6.3.1.3 Conclusion on classification and labelling for STOT RE (specific target organ toxicity-repeated exposure)

Harmonised classification proposed. The Committee for Risk Assessment (RAC) previously (RAC, 2012) concluded that classification for specific target organ toxicity after repeated exposure to penconazole is considered not required according to Classification Regulation (EC) No 1272/2008. The reported liver changes in dogs at 500 ppm and in rats at 1000 ppm (below the guidance value) were considered as only adaptive responses to the increased metabolic load, and it was pointed out that although some of these effects could be considered as severe (necrosis and fibrosis in dogs and hepatic degeneration in rats), they appeared as isolated cases. In RMS' opinion, it should be rediscussed whether the observed cases with fibrosis in dogs should be considered as isolated cases. Awaiting the outcome of further discussion on this, RMS proposes that classification and labelling for STOT RE Cat. 2, H373 (liver) is warranted according to Regulation (EC) No. 1272/2008.

2.6.4 Summary of genotoxicity / germ cell mutagenicity [equivalent to section 10.8 of the CLH report template]

The genotoxicity of penconazole has been investigated in several guideline- and GLP-compliant *in vitro* tests and one *in vivo* bone marrow micronucleus tests using different batches of penconazole.

As the phototoxicity test revealed no phototoxic potential of penconazole, a photomutagenicity test is not required, in accordance with EFSA technical report 2016 (Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology, EFSA Supporting publication 2016:EN-1074).

In vitro

The gene mutation potential of penconazole has been investigated *in vitro* in bacterial gene mutation studies (Ames tests) and in HPRT mammalian cell gene mutation assay (V79 cells). The clastogenic potential of penconazole was investigated *in vitro* in an chromosomal aberration assay (CHO), which is considered supplementary. An unscheduled DNA synthesis test was conducted, also considered supplementary.

Table 39: Summary table of genotoxicity/germ cell mutagenicity tests *in vitro*

Method, guideline, deviations[1] if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
Salmonella/Mammalian-Microsome Mutagenicity Test 1st Ames test; OECD 471 GLP Only four bacterial strains (all *S. typhimurium* strains) were tested, instead of five as recommended;	Penconazole Tech. (91.7%, P.11-14)	*S. typhimurium* TA98, TA100, TA1535, TA1537), plate incorporation assay, ±S9 5 concentrations from 10 to 2560 µg/plate (progression factor 4), acetone (three replicates)	Negative (±S9) Cytotoxicity at 2560 µg/plate Positive controls induced the appropriate increases in mutant frequencies	Deparade (1984) K-CA 5.4.1/01 Report No 830750

Method, guideline, deviations[1] if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
Strain *E. coli* WP2 or *S. typhimurium* TA102 was not included; The historical negative (solvent/vehicle) and positive control data were not provided Supplementary				
Salmonella and Escherichia/ Mammalian-Microsome Mutagenicity Test 2nd Ames test; OECD 471 GLP Acceptable	Penconazole Tech. (96.1%, EN 603012)	*S. typhimurium* (TA98, TA100, TA102, TA1535, TA1537), *E.coli* (WP2 uvrA), plate incorporation and pre-incubation assay, ±S9 *S.typhimurium* strains: Range-finding assay: 20.6 – 5000 µg/plate (±S9), original assay: 125 - 2000 µg/plate (±S9), 1st confirmatory assay: 61.73 - 5000 µg/plate (-S9), 24.69 - 2000 µg/plate (+S9), 2nd confirmatory assay: 31.25 - 500 µg/plate (-S9), 12.5 - 200 µg/plate (+S9), 3rd confirmatory assay: 61.73 - 5000 µg/plate (+S9). *E. coli* WP2 uvrA: Range-finding assay: 20.6 - 5000 µg/plate (±S9), original assay 312.5 - 5000 µg/plate (±S9), 1st confirmatory assay 61.73 - 5000 µg/plate (±S9)	Negative (±S9) Precipitation at 5000 µg/plate in *S.t. strains* (±S9) Cytotoxicity at 1667 and 5000 µg/plate in *S.t. strains* (±S9) 1st confirmatory assay: Growth inhibition observed in a wide concentration range in strains TA100, TA102, and TA1537 and (±S9), a 2nd confirmatory experiment was conducted in these strains with concentrations of 12.5 to 500 µg/plate. Appropriate positive & solvent controls gave the expected results	Deparade (1999) K-CA 5.4.1/02 Report No 983114
Reverse Mutation Assay using Bacteria (*Salmonella typhimurium*) 3rd Ames test	Penconazole Tech. (100.15%, 0704)	*S. typhimurium* (TA98, TA100, TA102, TA1535, TA1537), plate	Negative (±S9) Experiment 1 : cytotoxicity at ≥316 µg/plate for TA100, TA1535 and TA102 (+/-S9) and	Donath (2010) K-CA 5.4.1/03 Report No 100829

Method, guideline, deviations[1] if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
OECD 471 GLP Acceptable		incorporation and pre-incubation assay, ±S9 Pre-test (TA98, TA100), +/-S9: 3.16, 10, 31.6, 100, 316, 1000, 2500, 5000 µg/plate Experiment 1, all strains, +/S9: 3.16, 10, 31.6, 100, 316, 1000, (2500 TA98 +S9 only) µg/plate Experiment 2, all strains, +/S9: 1, 3.16, 10, 31.6, 100, 316, 1000 µg/plate, DMSO (three replicates)	for TA98 and TA1537 (-S9), and at ≥1000 µg/plate for TA98 and TA1537 (+S9). Experiment 2 (pre-incubation method): cytotoxicity at ≥316 µg/plate for TA98 (+/ S9) and at ≥100 µg/plate for TA100 (+/ S9). In tester strains TA1535, TA1537 and TA102, cytotoxicity was noted at ≥100 µg/plate (-S9), and at ≥316 µg/plate (+S9). Appropriate positive & solvent controls gave the expected results	
Mutagenicity study in the *Salmonella Typhimurium* reverse mutation assay 4th Ames test OECD 471 GLP Acceptable	Penconazole Tech. (100.15%, 0704)	*S. typhimurium* (TA98, TA100, TA102, TA1535, TA1537), plate incorporation and pre-incubation assay, ±S9 Preliminary tests (plate incorporation and preincubation methods), TA100, -S9: 0.316-5000 µg/plate Experiment 1 (plate incorporation), all strains, +/S9: 1.0, 3.16, 10, 31.6, 100, 316 µg/plate Experiment 2 (preincubation), all strains, +/S9: 0.316, 1.0, 3.16, 10, 31.6, 100 µg/plate	Negative (±S9) Cytotoxicity at concentrations ≥316 µg/plate (plate incorporation) and ≥100 µg/plate (preincubation) in both experiments in all strains (±S9). Appropriate positive & solvent controls gave the expected results	Flügge (2010) K-CA 5.4.1/04 Report No 25505

Method, guideline, deviations[1] if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
		(three replicates)		
Cytogenetic Test On Chinese Hamster Ovary Cells Chromosome aberrations OECD 473 GLP Only 200 metaphases scored (vs. recommended 300); cytotoxicity not measured as Relative Population Doubling (RPD) or Relative Increase in Cell Count (RICC), but by mitotic index (MI); positive HCD not included in report. Supplementary	Penconazole Tech. (96%, EN 603012)	CHO cells, ±S9 Test concentrations between 0.78 and 100 µg/mL; except in the original assay (6.25-800 µg/mL) (Quadruplicate cultures)	Negative* (±S9) Cytotoxicity at 50 µg/mL, the highest concentration evaluated for chromosome aberrations was 25 µg/mL (except in experiment 1 (3h/18h recovery, -S9) 50 µg/ml was used as the highest concentration). *A significant increased number of metaphases with specific chromosomal aberrations was observed (4%) at 25 µg/ml (experiment 4, 3h/18h recovery, +S9); negative HCD range 0-6%, however HCD was not contemporary to the study being evaluated (e.g. within a period of up to around 5 years of the study) and the 95% confidence limits were not calculated. Positive and negative controls gave the expected results.	[redacted] (1999) K-CA 5.4.1/05 Report No 983116
Gene mutation in mammalian cells, HPRT assay OECD 476 GLP Target range of 10-20% cloning efficiency (CE) after treatment corresponding to 80-90% relative survival (RS) was not quite met; concurrent negative control should ideally be within the 95% control limits of the negative HCD, and the results should be within the distribution of the negative HCD; the observed mutant frequencies for the confirmatory experiment in presence of S9 the concurrent control and the two lowest concentrations of penconazole exceeded the HCD range;	Penconazole Tech. (96%, EN 603012)	V79 cells ±S9 Test concentrations in the preliminary cytotoxicity tests (both with and without S9) ranged from 0.39 to 800 µg/mL (separated by 2-fold intervals), in the mutagenicity assays concentrations ranged between 10 to 80 µg/mL and 8.75 to 70 µg/mL(-S9), and 5 to 40 µg/mL (+S9)	Negative* (±S9) The maximum concentration used was based on cytotoxicity (80 µg/ml (original), 70 µg/ml (confirmatory) +S9, and 40 µg/ml (orginal and confirmatory) -S9)) although the highest concentration did not meet the 20-10% RS. The dose spacing between the highest concentrations, however, was narrow and covered the range up to excessive cytotoxicity and the target range for cytotoxicity are therefore considered acceptable. *In the confirmatory experiment, +S9, the observed mutant frequencies in the concurrent control and the two lowest concentrations of penconazole exceeded the HCD range; however the mutant frequencies were well below the range of the positive HCD. Positive and negative controls gave the expected results (the positive control, S9, in the original experiment was below the range of the positive	[redacted] (1999) K-CA 5.4.1/06 Report No 983115

Method, guideline, deviations[1] if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
The period during which the historical control data were built up was not provided Acceptable			HCD, but the mutagenicity frequency was sufficiently increased above background and the response was considered valid).	
DNA-repair/Unscheduled DNA synthesis Conducted prior to OECD 482 The results of the original experiment were not verified in an independent experiment; Data from the preliminary study (cytotoxicity test) were not reported. Supplementary (The study is not a data requirement in Commission Regulation No 283/2013)	Penconazole Tech. (91.7%, P.11-14)	Primary hepatocytes Toxicity test: 5 to 320 µg/mL; UDS test: 0.32, 1.6, 8.0, and 40 µg/mL (concentrations selected based on the cytotoxicity results in the preliminary toxicity test), DMSO	Negative Cytotoxicity: highest usable concentration was calculated to be 40 µg/mL The original report and the re-evaluation of the slides showed that penconazole did not induce induction of DNA damage in primary hepatocytes cultured *in vitro*. Positive and negative controls gave the expected results	Puri (1984) K-CA 5.4.1/07 Report No 811522

Penconazole did not reveal any genotoxic potential in all available *in vitro* studies. All tests were considered acceptable except for one out of four Ames tests, the chromosome aberration assay and an unscheduled DNA synthesis test, which were considered supplementary. The negative Ames tests and the *in vitro* HPRT mammalian cell gene mutation test confirm that penconazole does not induce gene mutations in bacterial cells and in mammalian cells. In addition to the supplementary chromosomal aberration assay, a negative *in vitro* micronucleus test with technical penconazole spiked for several impurities is available in the RAR (Volume 4). The *in vitro* micronucleus test confirms the absence of both aneugenic and clastogenic potential for penconazole and the negative result for clastogenicity in the supplementary chromosomal aberration assay.

In vivo

The potential of penconazole to induce chromosomal damage in rodents has been investigated *in vivo* in one bone marrow micronucleus test (mice).

Table 40: Summary table of genotoxicity/mutagenicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations[1] if any	Test substance	Relevant information about the study (as applicable)	Observations/Results	Reference
Bone marrow micronucleus assay OECD 474 GLP	Penconazole Tech. (96.1%, EN 603012)	Mouse orally by gavage, M: 200-800 mg/kg bw, F: 125-500 mg/kg bw Doses were selected based on	Mortality: at 2000 mg/kg bw, within 3 h (F) to about 20 h (M) following administration (pre-test/ tolerability test).	[redacted] (1999a) K-CA 5.4.2/01 Report No 983117

Method, guideline, deviations[1] if any	Test substance	Relevant information about the study (as applicable)	Observations/Results	Reference
2000 polychromatic (immature) erythrocytes were scored per animal; The study was conducted using 5 animals of each sex; Blood samples were not taken at appropriate times to demonstrate that exposure of the bone marrow occurred. Supplementary		the maximum tolerated dose (MTD) as determined in a preliminary range-finding/tolerability test.	Clinical signs: reduced locomotor activity, ventral recumbency and hunched posture at 800 mg/kg bw in M in the main study (and pre-test) and at 500 mg/kg bw in F in the pre-test. No notable effect of treatment on body weights was reported. Blood samples were not taken at appropriate times to demonstrate that exposure of the bone marrow occurred; however, statistically significant reductions of PCE/NCE and PCE/(PCE+NCE) ratios (at high dose 48 h, M & F), clinical signs, and available additional ADME information in mice support the exposure of the bone marrow. No evidence for clastogenic or aneugenic effects, however the number of analysed cells is too low (only 2000 polychromatic (immature) erythrocytes were scored per animal) Positive and negative controls gave the expected results	

Penconazole was investigated for its ability to induce micronucleated immature erythrocytes in the bone marrow of ICO:CD1(CRL) mice.

Doses were selected based on the maximum tolerated dose (MTD), and dose range was determined according to a stepwise fixed-dose procedure, one male and one female at each step. In the tolerability assay, one male and one female were exposed to penconazole dissolved in 0.5% w:v carboxymethyl-cellulose (CMC) at the highest dose level of 2000 mg/kg bw by gavage (dosing volume 10 mL/kg). Based on the results from the preliminary range-finding/tolerability test, five male mice received oral doses of 200, 400, or 800 mg/kg bw, and five females 125, 250, or 500 mg/kg bw in the micronucleus assay. Suspensions of penconazole in the vehicle or the vehicle alone (negative control) were applied once by gavage. Cyclophosphamide (64 mg/kg bw) provided the positive control. Groups of animals treated at the highest dose or with the vehicle alone were killed 24 and 48 hours after administration, whereas animals administered the intermediate or lowest dose, or the positive control substance, were sacrificed 24 hours after administration. The animals were sacrificed by CO2 asphyxiation.

In the high dose animals at both sampling times, males showed occasionally signs of toxicity (ventral recumbence, hunched posture, reduced locomotion activity). In all dose groups, animals exposed to penconazole showed no significant increase in micronucleus frequencies at any dose level, investigation time, or sex. The exact Linear-by-linear trend test for an increase with all groups included was not statistically significant for both males and females at 24 hours sacrifice ($p=0.129$ and $p=0.210$, respectively). The positive control, cyclophosphamide, induced a drastic and statistically significant 100-fold increase in the frequencies of micronuclei in both male and female animals when compared to vehicle controls ($p < 0.05$). Regarding bone marrow exposure, evidence of test article-induced toxicity to the bone marrow was noted with reductions of PCE/NCE and PCE/(PCE+NCE) ratios at the high dose at 48h in both sexes. The clinical signs at MTD and above also supports evidence for systemic bioavailability, and available additional ADME data in CD1 mice (comparing the excretion pattern after single

radiolabelled oral (gavage) or iv application at 0.25 mg/kg bw in groups of 5 male and 5 female mice after 90 days of pre-treatment at different dietary dose levels of non-radiolabelled penconazole) supports that exposure of the bone marrow occurred.

It should be noted, that only 2000 instead of 4000 PCEs were evaluated per animal. The study was conducted using 5 animals of each sex and there are therefore data from 10 animals from each of the 3 dose levels in the study. The low, mid, high dose levels however used for males and females were not quite identical as males were more tolerant than females and could therefore be treated at higher dose levels. According to OECD 474 (2016) a study should be performed using a minimum of 5 analysable animals of one sex, or of each sex if both are used, per group. Therefore, 4000 PCEs should have been evaluated per animal.

Nevertheless, under the conditions of the study, penconazole was not genotoxic *in vivo* in mice.

Table 41: Summary table of human data relevant for genotoxicity / germ cell mutagenicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No study available				

2.6.4.1 Short summary and overall relevance of the provided information on genotoxicity / germ cell mutagenicity

Penconazole has been tested for potential genotoxic properties in a standard battery of *in vitro* assays and one *in vivo* assay.

There was no evidence that the different batches of penconazole was mutagenic or clastogenic in the available *in vitro* tests.

The genotoxicity of penconazole was tested *in vivo* in one supplementary bone marrow micronucleus test conducted in mice.

There is no evidence from the available data set that penconazole is a somatic cell mutagen, and there is therefore no reason to believe that penconazole would have the potential to induce mutations in germ cells.

2.6.4.2 Comparison with the CLP criteria regarding genotoxicity / germ cell mutagenicity

In accordance with the CLP criteria, penconazole did not demonstrate any genotoxic potential in six *in vitro* and one *in vivo*, guideline- and GLP-compliant studies, and therefore the criteria for classification are not met.

2.6.4.3 Conclusion on classification and labelling for genotoxicity / germ cell mutagenicity

Not classified - data conclusive but not sufficient for classification

2.6.5 Summary of long-term toxicity and carcinogenicity [equivalent to section 10.9 of the CLH report template]

Table 42: Summary table of animal studies on long-term toxicity and carcinogenicity

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
OECD TG 453 (adopted 25th June 2018) Mouse [redacted] MAGf (SPF)/ 80 M/F	Penconazole (91.7%, P. 11-14) 0, 5, 75, 150 and 300 ppm, equivalent to:	NOAEL (ppm) mg/kg bw/day : (300) 41/36 (M/F) No LOAEL. At 300 ppm only weak effects without clear toxicological significance: prothrombin time ↑, albumin ↑	[redacted] (1985). K-CA 5.5/01 Report No. 811414

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
Several deviations, the most severe is that the selected dose levels are too low to produce significant toxicological effects Supportive only	0 - 0.8/0.7 - 9.8/8.8 - 19.3/17.2 - 41/36 mg/kg bw/day (M/F) duration of exposure: 106 and 107 weeks (M, F)	Prostate and adrenal wt ↑ (M) at ≥75 ppm, but without associated histopathological findings. No effect on survival or tumour incidence.	
OECD 451 Mouse C57BL/10JfCD-1 50 M/F Acceptable	Penconazole (97.7%, WS007001[CH]) 0, 25, 200, 1500 ppm, equivalent to: 0 - 2.7/3.5 - 21.7/28.2 - 177.7/221.5 mg/kg bw/day (M/F) duration of exposure: 80 weeks	NOAEL (ppm) mg/kg bw/day: 21.7/28.2 (M/F) Effects at LOAEL: bw ↓, liver wt ↑, kidney wt ↓, increased incidence and severity of hepatocyte vacuolation (M+F) No effect on survival or tumour incidence.	[redacted] (2004). K-CA 5.5/02. Report No. PM1239
OECD TG 453 Rat [redacted] RAIf (SPF) 50 M/F Several deviations are noted, the most severe is that the selected dose levels are too low to produce significant toxicological effects Supportive only	Penconazole (91.7%, P. 11-14) 0, 5, 75, 150, 300 ppm, equivalent to 0 – 0.2/0.2 – 2.7/2.9 – 5.0/5.7 – 10.4/11.9 mg/kg bw/day (M/F) duration of exposure: 116 and 117 weeks (M, F)	NOAEL (ppm) mg/kg bw/day: (300) 10.4/11.9 (M/F) No LOAEL. No relevant treatment-related effects at the highest dose level tested No effect on survival or tumour incidence.	[redacted] (1985a). K-CA 5.5/03. Report No. 811415

Table 43: Summary table of human data on long-term toxicity and carcinogenicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

Table 44: Summary table of other studies relevant for long-term toxicity and carcinogenicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

2.6.5.1 Short summary and overall relevance of the provided information on long-term toxicity and carcinogenicity

Three carcinogenicity bioassays have been performed with Penconazole. Details (if not presented here) including study design, a description of the results (including information on incidences and severities of findings and extent of changes relative to controls, etc.) are given in the RAR (section B.6.5.1-2).

In two of these studies ([redacted] (1985), K-CA 5.5/01; [redacted] (1985a), K-CA 5.5/03), one in mice and one in rats, the highest tested dose was 300 ppm (corresponding to 40.8 mg/kg bw/day (M) and 35.7 mg/kg bw/day (F) and to 10.4 mg/kg bw/day (M) and 11.9 mg/kg bw/day (F) for mice and rats, respectively). No adverse findings, including tumours, were seen in these studies. However, as no toxicity was seen at the top dose, it was previously concluded (DAR, 2007) that the tested doses were too low and that the studies could only be considered supportive.

In the mouse study by ([redacted] (1985), K-CA 5.5/01), change in prothrombin time (PT), albumin concentration and prostate and adrenal weight was noted. Statistical tests were performed at significance level 0.05 (noted with a star) (comparison between control and treated group, dose levels 0; 5; 75; 150 and 300 ppm) or 0.01 (trend from control to highest dose group at 300 ppm).

Prothrombin time (PT)
In males, PT showed a statistically significant ($p \leq 0.01$) positive trend from control to highest dosage group in week 27 (PT 11.4; 11.2 (-1.8%); 11.7* (+2.6%); 11.6 (+1.8%); 11.7 (+2.6%) for dose level 0; 5; 75; 150; 300, respectively), week 81 (PT 11.4; 12.0 (+5.2%); 11.9 (+4.4%); 11.8* (+3.5%); 12.2 (+7%) for dose level 0; 5; 75; 150; 300, respectively) and week 105 (PT 11.5; 11.5 (+/-0%); 11.0 (-4.4%); 11.6 (+0.9%); 12.0* (+4.3%) for dose level 0; 5; 75; 150; 300, respectively). No such trends were observed at week 14 or 52. In females, PT showed a statistically significant ($p \leq 0.01$) positive trend from control to highest dosage group in week 81 (PT 11.0; 11.1 (+1.0%); 11.2 (+1.8%); 11.1 (+1.0%); 11.4* (+3.6%) for dose level 0; 5; 75; 150; 300, respectively) and week 105 (PT 10.9; 10.9 (+/-0%); 11.1 (+1.8%); 11.1 (+1.8%); 11.4 (+4.6%) for dose level 0; 5; 75; 150; 300, respectively). No such trends were observed at week 14 or 52.

Importantly, the available HCD confirm that the variations seen in the penconazole study for prothrombin time were within the normal biological variation.

Albumin
Albumin concentrations showed a statistically significant ($p \leq 0.01$) negative trend from control to highest dosage group in males in week 27 (Albumin g/L 30.8; 30.1 (-2.3%); 29.3 (-4.9%); 28.7* (-6.8%); 29.2* (-5.2%) for dose level 0; 5; 75; 150; 300, respectively) and in females in week 81 (Albumin g/L 31.7; 30.4 (-4.1%); 30.5 (-3.8%); 30.1 (-5%); 29.6* (-6.6%) for dose level 0; 5; 75; 150; 300, respectively). No such trends were observed at week 81 or 105.
Importantly, the available HCD confirm that the variations seen in the penconazole study for albumin levels were within the normal biological variation.

Prostate weight
At terminal sacrifice (wk 106), prostate weights showed a statistically significant ($p \leq 0.01$) negative trend from control to highest dosage group. Absolute prostate weight was 111; 117 (+5.4%); 135* (+22%); 147* (+32%) and 157* (+41%) mg at dose level 0;5,75,150 and 300 ppm, respectively. Relative prostate weight was 2.46; 2.51 (+2%); 3.02* (+23%); 3.10* (+26%) and 3.42* (+39%) at dose level 0; 5; 75; 150 and 300 ppm, respectively. While prostate weight at the interim sacrifice were also higher than controls in all treated groups, these variations never reached statistical significance and were in absence of any dose relationship.

Adrenal weight
A statistically significant trend was noted for increased absolute and realtive adrenal weights at the terminal sacrifice in males (for dose level 0; 5; 75; 150 and 300 ppm, the corresponding absoulte adrenal weight was 15.8; 16.6; (+5.1%); 19.4* (+23%); 17.4 (+10%) mg, wheras the corresponding realtive adrenal weight was 0.37; 0.36 (-2.2%); 0.41 (+9.9%); 0.42* (+13%); 0.38 (+3%). However, this was in absence of a dose relationship, not associated with relevant histopathological changes and the values were within the range of available HCD. Variations in adrenal weights achieving statistical significance in females (decrease at terminal sacrifice) were in absence of a dose relationship.

In rats, the only dose-related finding of potential toxicological relevance that attained statistical significance was a slight increase in absolute and relative liver weight in females of the mid- and high-dose groups. Statistical tests were performed at significance level 0.05 (noted with a star) (comparison between control and treated group, dose

levels 0; 5; 75; 150 and 300 ppm) or 0.01 (trend from control to highest dose group at 300 ppm). A significant trend from control to highest dose group at 300 ppm was observed in females in week 52 (absolute and relative) and week 104 (relative). For dose level 0; 5; 75; 150 and 300 ppm the corresponding absolute liver weight in female rats in week 52 was 12.4; 13.7 (+11%); 13.2 (+6.5%); 14.1 (+14%) and 14.8* (+20%). The relative liver weight in female rats in week 52 was 2.97; 2.99 (+0.5%); 3.08 (+3.5%); 3.37* (+13) and 3.41* (+15%), wheras the relative liver weight in week 104 was 3.19; 3.19 (+0.2%); 3.29 (+3.3%); 3.29 (+3.1%) and 3.66 (+15%). Absolute liver weights in week 52 for top dose females also exceeded mean +- SD (13.0+/-1.2) and the range (10.8-13.7) of available limited HCD. However, these findings lacked a biochemical or histopathological correlate and were therefore not considered adverse.

In the third study in mice ([redacted] (2004), K-CA 5.5/02), a top dose of 1500 ppm, corresponding to 178 mg/kg bw/day (M) and 222 mg/kg bw/day (F), was used. This dose caused toxic effects but no tumours. At 1500 ppm, the body weight development was reduced and an increase in liver weight was associated with an increase in hepatocyte vacuolisation.

Statistical tests were performed at significance level 0.05 and 0.01, noted with one or two stars, respectively (comparison between control and treated group, dose levels 0; 25; 200 and 1500 ppm).

Body weight
There was an effect on bodyweight development in both sexes at 1500 ppm. The maximum difference from control of adjusted body weights were at week 73 (males) and weeks 33/37 (females). Bodyweights and bodyweight gain in g and % variation to controls were noted. Body weight in male control was 21.1; 22.7; 28.8; 31.8; 37.1; 38.0; 40.5; 41.9 and 41.9 for week, 1; 2; 8; 15; 33; 37; 51; 73 and 81 respecively. The corresponding effect at the highest dose level (1500 ppm) in male was 21.1 (+/-0); 21.8** (-4.0); 27.3** (-5.2); 29.3** (-7.9); 32.8** (-12); 33.4** (-12); 35.0** (-14); 35.7** (-15) and 36.5** (-13). Body weight in female control was 17.2; 18.0; 22.6; 25.1; 29.2; 30.1; 31.2; 32.6 and 33.0 for week, 1; 2; 8; 15; 33; 37; 51; 73 and 81 respecively. The corresponding effect at the highest dose level (1500 ppm) in female was 17.3 (+0.6); 17.5** (-2.8); 21.3** (-5.8); 23.4** (-6.8); 26.4** (-9.6); 27.2** (-9.6); 28.8** (-7.7); 30.2** (-7.4) and 30.5** (-7.6), respectively. There were no effects on bodyweight in males receiving 200 ppm penconazole. Small differences in adjusted bodyweight in the 200 ppm females occasionally achieved statistical significance but the maximum difference from control was as low as 2-3%. There were no effects on bodyweight in either sex in the 25 ppm group.

Liver weight
Liver weights were increased in top dose males. Absolute weight was 1.88 g **(+11%), adjusted weight 2.10** (+27%) and relative weight 5.17 (+28 %), while values in control was 1.69, 1.65 and 4.03, respectively. After excluding the high value for female 273 (25 ppm group), there was evidence of slightly higher liver weights (approximately 5% higher than control) in females receiving 1500 ppm, but the value did not reach statistical significance. There were no effects on liver weight in either sex in the 25 and 200 ppm groups.

Hepatocyte vaculation
There was an increase in the incidence and severity of hepatocyte vacuolation of the liver in the high dose (1500 ppm) males and females. Minimal, slight, moderate and marked vaculation was reported in 13/50; 15/50; 9/50 and 0/50 high dose male (in total 37/50). In comparison, the incidence in male control was 6; 6; 1 and 0 (in total 13/50). In high dose females 9/50 showed minimal, 6/50 slight, 1/50 moderate and 0/50 slight vaculation (in total 16/50), wheras only 1/50 of the female control was affected (minimal hypertrophy).

Kidney weight
Kidney weights were lower than controls in both sexes receiving 1500 ppm penconazole. However, in males, the difference was no longer evident after adjustment for bodyweight, and in females, there was no difference from control after exclusion of high values obtained for female 223 (control) and female 275 (25 ppm).

EFSA previously concluded (EFSA, 2008) that penconazole had no carcinogenic potential and did not need to be tested at higher doses in rats. Furthermore, the Committee for Risk Assessment (RAC) previously (RAC, 2012) concluded that classification for carcinogenicity after exposure to penconazole is considered not required according to Classification Regulation (EC) No 1272/2008. According to RAC, the negative result of the 2004 study in mice ([redacted] (2004), K-CA 5.5/02), together with the supportive 1985 studies in mice ([redacted] (1985), K-CA 5.5/01) and rats ([redacted] (1985a), K-CA 5.5/03) indicates no carcinogenic potential of penconazole. In RMS' opinion, it should be re-discussed to what extent these three available long term studies are sufficient to exclude a carcinogenic potential of penconazole, and whether additional testing of long-term toxicity and carcinogenesis at higher doses in rats may be needed. To support this discussion, a statement concerning the justification for the dose selection of the long-term toxicity and carcinogenesis studies, has been provided by the applicant upon request from the RMS (see summary in section B.6.5 in Volume 3 of the RAR). To further substantiate a conclusion and to avoid

unnecessary testing in animals, other properties of or aspects concerning the toxicity of penconazole could be taken into account, including the genotoxic potential of penconazole, that further data is requested to address potential thyroid effects of penconazole and the classification of other triazole substances. At the current stage, it is not possible to conclude on classification for genotoxicity according to Regulation (EC) No 1272/2008 as amended and RMS is of the opinion that sufficiency on thyroid effects may be discussed.

2.6.5.2 Comparison with the CLP criteria regarding carcinogenicity

Annex I Section 3.6.1.1 of the CLP Regulation defines a carcinogen as a substance which induces cancer or increases its incidence. Substances which have induced benign and malignant tumours in well-performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans. Carcinogenic substances are allocated to Category 1 (known or presumed human carcinogens) or Category 2 (suspected human carcinogens).

A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. Substances known to have carcinogenic potential for humans (based largely on human evidence) are classified in Category 1A. Substances presumed to have carcinogenic potential for humans (based largely on animal evidence) are classified in Category 1B. In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.

The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations. Such evidence may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

Since no increased incidence in tumours were seen, classification for carcinogenicity is not proposed. However, in RMS's opinion, it should be re-discussed to what extent these three available long-term studies are sufficient to exclude a carcinogenic potential of penconazole, and whether additional testing of long-term toxicity and carcinogenesis at higher doses in rats may be needed.

Table 45: Compilation of factors to be taken into consideration in the hazard assessment

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
N/A								

2.6.5.3 Conclusion on classification and labelling for carcinogenicity

Data lacking. Since no increased incidence in tumours were seen, classification for carcinogenicity is not proposed. However, in RMS's opinion, it should be re-discussed to what extent these three available long-term studies are sufficient to exclude a carcinogenic potential of penconazole, and whether additional testing of long-term toxicity and carcinogenesis at higher doses in rats may be needed.

2.6.6 Summary of reproductive toxicity [equivalent to section 10.10 of the CLH report template]

2.6.6.1 Adverse effects on sexual function and fertility – generational studies [equivalent to section 10.10.1 of the CLH report template]

Table 46: Summary table of animal studies on adverse effects on sexual function and fertility – generational

studies

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for sexual function and fertility, parents)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
Two-generation reproduction toxicity study Similar to OECD 416 Non-GLP Supplementary Rat, [redacted] RAIf(SPF) 20M+20F	Penconazole: P. 11-14, 91.7% purity 0-80-400-2000 ppm Oral: diet about 110 days of treatment	Systemic NOAEL (adults, pups) 400 ppm corresponding to 29.9 (♂) and 29.7 (♀) mg/kg bw/day Reproductive NOAEL 400 ppm corresponding to 29.7 mg/kg bw/day P (F0): **Mortality:** No deaths during pre-mating period. Mortality after parturition: 1 F 400 ppm-group, 3 F 2000 ppm-group. **Clinical signs:** No clinical signs during pre-mating. **Body weight gain:** M similar to ctr group, F top dose (-8.3% during premating, -7.7 during gestation, -94% on lactation day 1 compared with gestation day 0). **Food consumption:** M similar to ctr, F top dose (-4.5% during premating, -5.1% during gestation.) **Length of pre-coital interval:** Comparable to ctr. **Mating and gestation data:** Duration of gestation in F top dose increased (21.8 vs. 21.1 in ctr). Other parameters comparable to ctr. F1, F2: **Mortality:** No deaths during pre-mating period. Mortality after parturition: 1 F ctr-group, 1 F 400 ppm-group, 3 F 2000 ppm-group. **Clinical signs:** No clinical signs during pre-mating. **Body weight gain:** M top dose (-10.6%), F top dose (-6.9% during premating, -16% during gestation, -75% on lactation day 1 compared with gestation day 0). **Food consumption:** M top dose (-7.1%), F top dose (-4.2 during premating, -8.8% during gestation). **Length of pre-coital interval:** Comparable to ctr. **Mating and gestation data:** Comparable to ctr. **Litter parameters:** Comparable to ctr. **Pup body weight/bw gain:** Bw comparable to ctr. Bw gain F1 M top dose (-22.6%), F top dose (-15.9%). **Offspring development:** General development, behavioural tests, and sexual development concidered comparable to ctr. **Organ weights:** Liver: F1 adults F top dose (abs. +29%, rel. +37%), F1 weanlings M top dose (abs. +11%, rel. +31%) F top dose (abs. +8.2%, rel. +28%), F2 weanlings M top dose (abs. +21%, rel. +28%) F top dose (abs. +16%, rel. +22%). **Macro- and histopathology:** Hepatocyte hypertrophy: F1 M top dose 17/20 (ctr. 0/20), F1 F 400 ppm-group 14/16, F top dose 16/16 (ctr 0/18).	[redacted] (1983) K-CA 5.6.1/01, /02, /03 Report No 811416
Two-generation reproduction toxicity study EPA guideline No 83-4; comparable with OECD guideline 416 (1983) Supplementary Rat [redacted] COBS CD (Sprague Dawley) M and F	Penconazole tech. Purity: 98.7% Batch: FL 840833 0, 25, 250 and 2500 ppm Orally via diet Duration of exposure for 63 days (9 weeks, F0) and 84 days (12 weeks, F1) prior to mating, during the maximum 3 weeks mating period through to termination, i.e. after	Systemic and reproductive NOAEL of 250 ppm (corresponding to 21.2 (males) and 22.7 (females) mg/kg bw/day) P (F0): **Mortality:** 1 M top dose (week 11) **Clinical signs:** No clinical signs. **Body weight gain:** F top dose Premating (-21%) **Food consumption:** F top dose Premating (-7.1%), F top dose Gestation (-7.0). **Pre-coital intervals:** Comparable to ctr. **Mating and gestation data:** Comparable to ctr. **Organ weight:** Comparable to ctr. Increased rel. ovary weight at top dose due to decreased F body weight.	[redacted] (1983) K-CA 5.6.1/04 Report No. 382-119

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for sexual function and fertility, parents) - target tissue/organ - critical effects at the LOAEL	Reference
30/sex/dose F0 and F1 generation	the litters had weaned.	F1, F2: **Mortality:** No deaths **Clinical signs:** No clinical signs. **Body weight gain:** M top dose premating (-6.9%), mating (-24%), overall (-10.5%). F top dose premating (-7.1%). **Food consumption:** F top dose Premating (-7.6%). **Pre-coital intervals:** Comparable to ctr. **Mating and gestation data:** Post-implantation loss: Top dose 2.0 (16.7%) per dam (vs. 1.5 (10.2%) in ctr). **Litter parameters:** Total pups stillborn: F1 top dose 11 /vs. 1 in ctr), F2 top dose 24 (vs. 11 in ctr). Mean live pups/dam F1 top dose M pups 5.3 (vs. .0 in ctr). Not seen in F2. No. live pups day4/day 0: F1 top dose 96.1% (vs. 98.4% in ctr), F2 top dose 95.6% (vs. 98.8% in ctr). **Pup body weight gain:** F1 M top dose (-7.1%), F1 F top dose (-8.0%), F2 M top dose (-12%), F2 F top dose (-9.0%). **Offspring development:** Comparable to ctr, apart from No. pups that died or born dead: F1 top dose 13 (vs. 3 in ctr), F2 top dose 29 (vs. 11 in ctr). **Organ weight:** Comparable to ctr. Increased rel. ovary weight (F1 adults) at top dose due to decreased F body weight. **Macro- and histopathology:** Comparable to ctr.	

Table 47: Summary table of human data on adverse effects on sexual function and fertility

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

Table 48: Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

2.6.6.1.1 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility – generational studies

Two 2-generation reproductive studies in rat were delivered. Both had major deviations from OECD guideline 416 (2001), the most severe being (in one or both studies) using too high dose intervals, not continuing dosing 10 weeks before mating period, oestrous cycle length was not evaluated, testis and epididymis weight not recorded, sperm count, motility and morphology not evaluated, anogenital distance was not measured, not all organs from both generations were weighed at termination, histopathological examinations were not conducted for all organs from both generations and the number of corpora lutea were not determined.

In both studies, similar unspecific toxicity was seen at the top dose level (reduced body weight gain and food consumption in adults). For females, this was most pronounced during premating, but also during gestation in the first study ([redacted] 1983). Males were only affected in the F1 generation. Reduced body weight gain of pups during lactation was reported in both generations in the second study ([redacted] 1987) at the top dose of 2500 ppm. Furthermore, an increase in liver weight was noted at the top dose level in the first study for adults and weanlings, associated with hepatocyte hypertrophy in adults.

In the first study, an increase in dam mortality at/shortly after parturition and during lactation was noted, as well as a slight prolongation of gestation period. An increase in post-implantation loss was seen at 2500 ppm in the second study. In both generations, the mean number of dead pups at birth/pups that died (until day 4) was slightly but not statistically higher at 2500 ppm when compared with control.

Taken together, systemic NOAELs of the two studies were 400 ppm (29.7/29.9 mg/kg bw/day for males/females) in the first study ([redacted] 1983) and 250 ppm (21.2/22.7 mg/kg bw/day° for males/females) in the second study ([redacted] 1987). The reproductive NOAELs were 400 ppm (29.9 mg/kg bw/day for females) in the first study ([redacted] 1983) and 250 ppm (22.7 mg/kg bw/day for females) in the second study ([redacted] 1987).

2.6.6.1.2 Comparison with the CLP criteria regarding adverse effects on sexual function and fertility

According to the CLP criteria, adverse effects on sexual function and fertility include those that interfere with the reproductive system, onset of puberty, gamete production/transport, reproductive cycle, sexual behaviour, fertility, parturition, pregnancy outcome, reproductive senescence or any other function that is dependent on the reproductive system. Not all of these effects have been sufficiently investigated, as several critical reproductive endpoints were not addressed in the available studies.
Considering the adverse findings, only a slight prolongation of the gestation period and an increase in dam mortality at/shortly after parturition and during lactation at the top dose, both findings from the first study, are related to sexual function and fertility. However, due to the fact that these findings are not reproduced in the second study where a higher top dose of penconazole (ISO) with higher purity was applied, these findings are not consistent enough to lead to a classification.
Thus, penconazole (ISO) does not meet the criteria for classification for adverse effects on sexual function and fertility.

2.6.6.1.3 Conclusion on classification and labelling for sexual function and fertility

Data conclusive but not sufficient for classification

2.6.6.2 Adverse effects on development [equivalent to section 10.10.4 of the CLH report template]

Table 49: Summary table of animal studies on adverse effects on development

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for parent, offspring and for developmental effects)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
Developmental toxicity Earliest OECD 414 version (1981) not yet available at time of study Acceptable Rat [redacted] RAIf (SPF) F Preliminary study: 10/dose Main study: 25/dose Supplementary study :15/dose	Penconazole tech. Purity: 88.4% Batch: P. 2+3 Administered orally by gavage Preliminary study: 0, 300 mg/kg bw/day (days 6-15 of gestation) Main study: 0, 30, 100, 300 mg/kg bw/day (days 6-15 of gestation) Supplementary study: 0, 300, 450 mg/kg bw/day (days 10-14 of gestation)	Maternal and developmental NOAEL of 100 mg/kg bw/day Mortality at 300 (2/25 (8%) and 4/15 (26%) dams in main and supplementary study, respectively) and 450 mg/kg bw (2/15 (13%) dams). Bw gain ↓, food ↓ in dams Postimplantation loss ↑ Dead foetuses ↑ (450 mg/kg bw) Foetal weight ↓ Skeletal anomalies ↑	[redacted] (1981) K-CA 5.6.2/01 Report No. 800549
Developmental toxicity OECD 414 (1981), EPA guideline 83-3 (1982) Acceptable Rat	Penconazole tech. Purity: 98.7% Batch: FL840833 Administered orally by gavage	Maternal and developmental NOAEL of 100 mg/kg bw/day Mortality at 500 mg/kg bw (3 dams) Clinical signs: stomach and intestinal lesions, crusty eye(s), crusty nose and/or muzzle, damp and yellow/brown-stained fur in perianal and/or	[redacted] (1985) K-CA 5.6.2/03 Report No. 450-2087

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for parent, offspring and for developmental effects) - target tissue/organ - critical effects at the LOAEL	Reference
Sprague Dawley F 25/dose	0, 5, 100, 500 mg/kg bw/day (days 6-15 of gestation)	abdominal region, staggered gait, emaciation, loose stool, weakness, and/or lethargy. Bw gain ↓, food ↓ in dams Postimplantation loss ↑ Life foetuses per dam ↓ Runt foetuses ↑ Skeletal findings ↑	
Developmental toxicity OECD 414 GLP Acceptable Rabbit Chinchilla 20 F/dose	Penconazole: P. 11-14; 91.7% purity 0-25-75-150 mg/kg bw/d (days 6 - 18 p.c.) Oral: diet	Maternal and developmental NOAEL of 75 mg/kg bw/day Bw gain ↓, food ↓ in dams Internal Hydrocephalus 2/125 foetuses, 2/16 litters	[redacted] (1982) K-CA 5.6.2/04, /05 Report No. 911354
Developmental toxicity OECD 414 GLP Acceptable Rabbit New Zealand White 20F /dose	Penconazole: FL840833; 98.7% purity 0-10-50-200 mg/kg bw/d (days 7 - 19 p.i.) Oral: diet	Maternal and developmental NOAEL of 50 mg/kg bw/day Bw gain ↓, food ↓ in dams Embryonic resorptions compared to HCD mean ↑, post implantation loss compared to HCD mean ↑, live foetuses/litters compared to HCD mean ↓, % of foetuses with hyoid body and/or arches unossified and reduced ossification of the skull ↑, Bw in offspring ↓	[redacted] (1985) K-CA 5.6.2/06 Report No. [redacted] 82004

Table 50: Summary table of human data on adverse effects on development

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

Table 51: Summary table of other studies relevant for developmental toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No studies available				

2.6.6.2.1 Short summary and overall relevance of the provided information on adverse effects on development

Two developmental studies were conducted in rats. Both had several deviations from the current OECD guideline 414 (2018), the most severe being (in one or both studies) that test substance should be administered from implantation day onwards to one day prior to the day of scheduled humane killing, weight and histopathological

assessment of the thyroid gland should be taken, number of corpora lutea should be determined, the anogenital distance should be measured, and blood samples should be collected to assess thyroid hormones and TSH.

In both available developmental toxicity studies in rats, unspecific maternal toxicity was shown by mortality, reduced body weight development and food consumption at the top doses of 300/450 mg/kg bw/day in the first study ([redacted] 1981) and 500 mg/kg in the second study ([redacted] 1985). In the second study, clinical signs were also reported. Increases in post-implantation loss were seen in both studies, partly exceeding available HCD, and leading to a reduced number of live foetuses in the second study. In the first study, an increase in dead foetuses were seen at 450 mg/kg bw/day. Reduced foetal weights were reported in both studies. An increase in runt foetuses were reported in the second study. Skeletal findings were reported in both studies, mainly increases in incomplete ossification and occurrence of extra ribs. However, the individual skeletal findings contributing to these increases were not reproducible within the same study nor between the two studies except for some indications for delayed ossification. Taken together, both maternal and developmental NOAELs in both studies are 100 mg/kg bw/day.

In the first study in rats ([redacted] 1981), four different doses of penconazole technical (0, 30, 100 and 300 mg/kg bw/day) were given to 25 mated female rats ([redacted] RAIf (SPF)) per group orally via gavage (GD 6-15) (main study). The report also includes a preliminary study with treatment of 10 mated female rats at 0 and 300 mg/kg bw/day (GD 6-15) and a supplementary study to further investigate the foetal skeletal development with treatment at 0 and 300 mg/kg bw/day (GD 6-15), and with 450 mg/kg bw/day (GD 10-14).

Further details (if not presented here) including study design, a description of the results (including information on incidences and severities of findings and extent of changes relative to controls, etc.) are given in the RAR (section B.6.5).

Mortality was seen at 300 mg/kg bw/day (2/25 (8%) and 4/15 (26%) dams in main and supplementary study, respectively) and 450 mg/kg bw/day (2/15 (13%) dams in supplementary study). Autopsy did not reveal any obvious pathological condition, but deaths are considered to be related to treatment. Further general toxicity was observed via consistently reduced body weight development and food consumption at ≥300 mg/kg bw/day. Maternal body weight gain corrected for gravid uterus weight was also markedly decreased at ≥300 (See table below).

Table 52: Maternal body weights and food consumption

	Main study			Supplementary study			
mg/kg bw/day	**0**	**30**	**100**	**300**	**0**	**300**	**450°°**
Body weight [g] (% change vs controls)							
GD 0	200	199 (-0.5)	200 (+/-0)	198 (-1.0)	197	198 (+0.5)	201 (+2.0)
GD 6	225	225 (+/-0)	224 (-0.4)	226 (+0.4)	223	220 (-1.3)	226 (+1.3)
GD 10					240		247 (+2.9)
GD 15					272		270 (-0.7)
GD 16	291	287 (-1.4)	287 (-1.4)	287 (-1.4)	282	267 (-5.3)	280 (-0.7)
GD 21	356	355 (-0.3)	358 (+0.6)	350 (-1.7)	337	312 (-7.4)	335 (-0.6)
GD21°	265	261 (-1.5)	266 (+0.4)	260 (-1.9)	244	230 (-6.0)	241 (-1.5)
Body weight gain [g] (% change vs controls)							
GD 0-6	25	26 (+4.0)	24 (-4.0)	28 (+12.0)	26	22 (-15.4)	25 (-3.8)
GD 6-16	66	62 (-4.6)	63 (-4.5)	61 (-7.6)	59	47 (-20.3)	54 (-8.5)
GD 10-15					32		23 (-28.1)
GD 16-21	65	68 (+4.6)	71 (+9.2)	63 (-3.1)	55	45 (-18.2)	55 (+/-0)
GD 6-21	131	130 (-0.8)	134 (+2.3)	124 (-5.3)	114	92 (-19.3)	109 (-4.4)
GD 6-21°	39.4	35.7 (-9.4)	42.2 (+7.1)	34.6 (-12.2)	20.9	9.4 (-54.9)	15.2 (-27.6)
Gravid uterus weight [g] (% change vs controls)							
GD 21	91.5	93.8 (+2.5)	92.0 (+0.5)	89.6 (-2.1)	92.7	82.3 (-11.2)	94.7 (+2.1
Food consumption [g/animal/day] (% change vs controls)							
GD 0-6	20.9	21.7 (+3.8)	21.2 (+1.4)	20.9 (+/-0)	19.9	20.0 (+0.5)	21.2 (+6.5)

GD 6-11	24.5	22.7 (-7.3)	22.2 (-9.4)	20.5 (-16.3)	22.3	18.6 (-16.6)	22.0 (-1.3)
GD 11-16	26.2	25.3 (-3.4)	25.1 (-4.2)	25.6 (-2.3)	21.2	21.0 (-0.9)	19.9 (-6.1)
GD 16-21	23.5	23.6 (+0.4)	24.2 (+3.0)	24.5 (+4.3)	21.1	18.8 (-10.9)	19.3 (-8.5)
GD 6-16	25.3	24.0 (-5.3)	23.6 (-6.9)	23.0 (-9.1)	22.7	19.8 (-12.8)	20.9 (-7.9)

° corrected for uterus weight, °° treatment for gestation days 10-14

Slightly higher post-implantation loss was seen at ≥300 mg/kg bw/day in all studies, due to an increase in early resorptions. Post-implantation loss exceeded limited HCD in preliminary study only. The number of dead foetuses was increased at 450 mg/kg bw/day, but were comparable to control for the other treatment groups. Foetal weights were decreased at ≥300 mg/kg bw/day in supplementary study only (see selected Caesarean section observations in the table below). Foetal sex ratio was not affected by penconazole treatment.

Table 53: Selected Caesarean section observations

study	**preliminary**		**main**				**supplementary**			**HCD**
mg/kg bw/day	**0**	**300**	**0**	**30**	**100**	**300**	**0**	**300**	**450**	**Mean +/- SD (range)**
Resorptions/dam										
- Early/embryonic (% of implantations)	1.5 (10.1)	2.3 (15.1)	0.7 (4.8)	0.8 (5.9)	1.1 (8.1)	1.3 (9.0)	0.7 (5.0)	1.2 (9.8)	1.0 (7.1)	7.4 +/- 2.8 (2.7-15)
- Late/foetal	0	0.1	0	0.04	0	0.05	0	0.1	0.1	0.4 +/- 0.9 (0-5.1)
Live Foetuses/Dam	13.4	12.9	12.8	12.7	12.3	12.9	12.7	10.9	12.6	12.6 +/- 1.0 (10.1-14.9)
Dead Foetuses/group	0	1	1	0	0	2	1	2	5	
Dead foetuses [% of implantations]										0.04+/-0.11 (0-0.5)
Post-implantation loss [%]	10.1	16.5	5.2	6.2	8.1	10.0	5.4	12.5	10.4	7.8 +/- 2.9 (3.5-15.0)
Mean foetal weight [g] (% change vs control)	5.19	5.35 (+3.0)	5.17	5.31 (+2.7)	5.38 (+4.1)	5.32 (+2.8)	5.26	5.03* (-4.5)	4.96* (-5.8)	5.29 +/- 0.11 (5.11-5.5)

* $p < 0.05$ (t-test)

The overall number of skeletal anomalies was increased at 300 mg/kg bw/day (main study only) and 450 mg/kg bw/day (supplementary study). The individual skeletal findings contributing to these increases were not reproducible between the main and supplementary study. A slight increase in the number of still unossified phalangeal nuclei of the hindlimb at the mid and high dose was observed (main study, within HCD range). An increase in the number of still unossified phalangeal nuclei of the forelimb (supplementary study, 450 mg/kg bw/day, outside the HCD range), hindlimb and calcaneous (at ≥300 mg/kg bw/day, within HCD range). In addition, wide sutures of the fronto-parietal region was seen in 11 fetuses from one litter at 450 mg/kg bw/day. No external nor visceral anomalies related to treatment were observed. (See selected findings on foetal abnormalities and incidences of individual skeletal findings in the table below).

Table 54: Selected foetal examinations - Foetuses with abnormalities (% of total examined) and Incidences of individual skeletal findings

	Main study				**Supplementary study**			**Limited HCD**
mg/kg bw/day	**0**	**30**	**100**	**300**	**0**	**300**	**450**	**mean/ range (%)**
with skeletal anomalies:	2/187 (1.1)	2/211 (0.9)	2/197 (1.0)	11/182 (6.0)	1/191 (0.5)	0/98 (0)	12/164 (7.3)	(0.63), (0-2.3)
Phalangeal nuclei unossified								(0-12.3),
Forelimb (%)	1 (0.5)	1 (0.5)	4 (2.0)	4 (2.2)	7 (3.7)	3 (3.1)	22 (13)	(0-10.7)
Hindlimb (%)	27 (15)	41 (19)	72 (37)	45 (25)	42 (25)	51 (52)	82 (50)	(4.5-65.6)
Wide sutures foetuses (%)	0	0	0	0	0	0	11 (6.7)	(0-1.4)
Litter (%)	0	0	0	0	0	0	1 (7.7)	

In the second study in rats ([redacted] 1985), four different doses of penconazole technical (0, 5, 100 and 500 mg/kg bw/day) were given to groups of 25 mated female rats (Sprague-Dawley) via oral gavage (GD 6-15).
Mortality was observed in one gravid female at 5 mg/kg bw/day and two gravid and one non-gravid females at 500 mg/kg bw/day.
Clinical signs were observed at 500 mg/kg bw/day and comprised stomach and intestinal lesions, crusty eye(s), crusty nose and/or muzzle, damp and yellow/brown-stained fur in perianal and/or abdominal region, staggered gait, emaciation, loose stool, weakness, and/or lethargy.
Additional maternal toxicity observed at 500 mg/kg bw/day was reduced body weight development (absolute and corrected for gravid uterus weight) and food consumption. Body weight gain on GD 6-20 in top-dose females was -19% compared with controls. Corrected body weight gain on GD 6-20 was reduced by 41% and gravid uterus weights were 12% lower than concurrent controls in high-dose females. Body weight development in the low and mid-dose groups was not relevantly affected by treatment. A slightly lower food consumption on GD 6 for mid-dose animals were reported, but is not considered adverse.
Post-implantation loss was increased at 500 mg/kg bw/day (due to both early (2.2 per dam vs. 0.3 in ctr) and late (0.6 per dam vs. 0.0 in ctr) resorptions) (18.9% vs. 2.2% in ctr), and a slightly lower number of live foetuses per dam were reported at 500 mg/kg bw/day (12.2 vs. 14.6 in ctr).
Foetal weights were also reduced at this dose (M -5.9%, F -3.1%).
Pre-implantation loss and sex ratio were unaffected by treatment at all dose levels, as well as post-implantation loss, number of foetuses per dam and foetal weight in the low and mid-dose groups.
Increases in runt foetuses were seen at 500 mg/kg bw/day (4.3% vs 0.6% in ctr). Some other external findings were reported, including shortened tail and umbilical hernia, but these were not considered to be treatment related. Incidences of overall visceral findings were unaffected by treatment and within the range of historical controls.
Skeletal findings at 500 mg/kg bw/day included occurrence of ribs from cervical sternebrae and dual ossification centres of sternebrae, incomplete ossification of frontals and parietals and an increase in 14th ribs, all reported to be outside the range of HCD. See table below.

Table 55: Selected foetal skeletal findings

mg/kg bw/day	**0**	**5**	**100**	**500**	**HCD°**
Foetuses/litter examined	174/23	155/21	162/22	109/16	

Ribs from cervical vertebrae	foetuses (%) litter (%)	1 (0.6) 1 (4.3)	2 (1.3) 1 (4.8)	0 0	8 (7.3) 5 (31)	Not available
Dual ossification centres sternebrae	foetuses (%) litter (%)	0 0	0 0	1 (0.6) 1 (4.5)	3 (2.8) 2 (12.5)	(0-0.6)
Incompletely ossified Frontals+parietals	foetuses (%) litter (%)	3 (1.7) 3 (13.0)	8 (5.2) 5 (24)	8 (4.9) 6 (27)	15 (13.8) 9 (56)	(0-8.8)
14th ribs	foetuses (%) litter (%)	2 (1.1) 2 (8.7)	3 (1.9) 2 (9.5)	1 (0.6) 1 (4.5)	16 (14.7) 8 (50)	(0-10.7)

° HCD data only available for foetal incidences (not for litter incidences); based on results from 9 studies provided by the laboratory within the report of the penconazole study

Two developmental studies were conducted in rabbits. Both had several deviations from the current OECD guideline 414 (2018), the most severe being (in one or both studies) that test substance should be administered from implantation day onwards to one day prior to the day of scheduled humane killing, each test and control group should contain a sufficient number of females to result in approximately 20 female animals with implantation sites at necropsy, weight of the thyroid gland and histopathological assessment of the thyroid gland should be taken, and brain, nasal passages and tongue should be examined from one-half of the foetuses.

In both available developmental toxicity studies in rabbits, unspecific maternal toxicity was shown by reduced body weight development and food consumption during treatment at the top doses of 150 mg/kg bw/day in the first study ([redacted] 1982) and 200 mg/kg bw/day in the second study ([redacted] 1985). In addition, clinical signs were reported in the second study. Post-implantation loss was observed in the second study, exceeding HCD mean, but not exceeding HCD range; however, the number of live foetuses per litter were slightly reduced. Moreover, two foetuses were dead in the second study. In the first study, the incidences of internal hydrocephalus slightly exceeded available HCD. This was not seen in the second study. In addition, three foetuses in the first study had microphthalmia (within the range of HCD), including two which also had hydrocephalus. In the second study, foetuses with hyoid body and/or arches unossified and reduced ossification of the skull were observed and exceeded available HCD ranges. Taken together, both maternal and developmental NOAELs were 75 and 50 mg/kg bw/day in the first study ([redacted] 1982) and in the second study ([redacted] 1985), respectively.

In the first study ([redacted] 1982), CGA71818 (dose levels of 0, 25, 75 and 150 mg/kg bw/day) was administered orally, via gavage, to Chinchilla rabbits. The major findings of the study regarding general toxicity at the high dose of 150 mg/kg bw/day were reduced food consumption (GD 6-11 (-22%), GD 11-15 (-12%), GD 6-19 (-13%)) and body weight development (GD 6-19 (-11%), GD 0-28 corrected for gravid uterus weight (-7.4%)) during the treatment period. Two high-dose dams died during the gestation period, but so did one control. Consequently, these deaths can be considered spontaneous.

Pregnancy parameters were comparable to controls. Number of corpora lutea and implantations, pre- and post-implantation loss, number of live or dead foetuses, foetal weights and sex ratio were similar in treated and control groups. A slightly higher number of early resorptions (9.7% vs 4.8% in ctr) was observed at the high dose (but within the range of HCD). However, the number of implantations and live foetuses was also higher (as compared to controls). Hence, the higher number of resorptions is considered unrelated to treatment.
External findings were comparable between groups. Bilateral microphthalmia were seen in three high-dose foetuses (in two foetuses, microphthalmia was associated with internal hydrocephalus). The total incidence of microphthalmia in foetuses and litter was within the range of HCD; however, mean +/-SD was exceeded. The incidence of internal hydrocephalus at the high dose was with two affected foetuses slightly above the range of HCD, both for foetuses and litter. See table below.

Table 56: Selected foetal visceral findings

mg/kg bw/day		0	25	75	150	HCD°°
Foetuses/litter examined		113 / 16	104 / 15	102 / 15	125 / 16	
Individual findings						
Microphthalmia	foetuses	0	0	0	3° (2.4)	(0.5+/-1.2, 0-4.1)°°°
(%)		0	0	0	2 (12.5)	(1.8+/-4.1, 0-12.5)
(bilateral)	litter (%)					
Internal	foetuses	0	0	0	2° (1.6)	(0.2+/-0.3, 0-0.9)°°°
(%)		0	0	0	2 (12.5)	(1.1+/-2.5, 0-7.1)
hydrocephaly	litter (%)					

° both foetuses with internal hydrocephalus also had microphthalmia

°° limited information based on 16 studies (same laboratory/rabbit strain/breeder) the applicant has access to: mean +/-standard deviation, range (% incidences)

°°° including one foetus that had internal hydrocephalus and microphthalmia

In the second study ([redacted] 1985), CGA71818 (dose levels of 0, 10, 50 and 200 mg/kg bw/day) was administered orally, via gavage, to New Zealand White rabbits. Two females (both gravid) died during the course of the study: one in the top dose group on day 18 and one in the vehicle control group on day 28. During the treatment period, decreased defecation and urination were seen in the majority of the high dose group animals.
The major findings regarding general toxicity at the high dose of 200 mg/kg bw/day were reduced food consumption and body weight development, most markedly in the first week of treatment. See table below.

Table 57: Maternal body weight development and food consumption

mg/kg bw/day	0	10	50	200
Body weight [g] (% variation to controls)				
GD 0	4093	4057 (-0.9)	4021 (-1.8)	4086 (-0.2)
GD 7	4276	4136 (-3.3)	4132 (-2.7)	4239 (-0.9)
GD 20	4276	4139 (-3.2)	4243 (-0.8)	4058 (-5.1)
GD 29	4144	4088 (-1.4)	4105 (-0.9)	4087 (-1.4)
GD 29°	3717	3837 (+3.2)	3748 (+0.8)	3844 (+3.4)
Body weight gain [g] (% variation to controls)				
GD 0-7	183	79* (-57) [105 (-43)]°°	140 (-23)	153 (-16)
GD 7-10	2	-12	23	-104**
GD 10-14	85	45	95	-19**
GD 14-20	-87	-30	-37	-36
GD 7-20	1	4	81	-150
GD 20-29	-114	-51	-159	29
GD 0-29	78	31 (-60) [77 (-1.3)]°°	48 (-38)	27 (-65)
GD 0-29°	-349	-208	-304	-175
Gravid uterus weight [g] (% variation to controls)				
GD 29	426.6	348.5 (-18)	410.5 (-3.8)	289.5 (-32)
Food consumption [g/rabbit/day] (% variation to controls)				
GD 0-7	194	157** (-19)	184 (-5.2)	181 (-6.7)
GD 7-10	185	154 (-17)	177 (-4.3)	106** (-43)
GD 10-14	182	142** (-22)	165 (-9.3)	83** (-54)
GD14-20	125	115 (-8.0)	144 (+15)	106 (-15)
GD 7-20	157	133 (-15)	158 (+0.6)	99** (-37)
GD 20-29	82	97 (+18)	76 (-7.3)	113 (+38)
GD 0-29	143	127 (-11)	138 (-3.5)	123 (-14)

* p <0.05, ** p <0.01

° corrected for gravid uterus weight

°° excluding dam 3850 (10 mg/kg bw/day)

Five dams delivered 1-2 days prior to the scheduled Caesarean section in absence of a dose relationship (2 each in low and mid dose group, 1 in high dose group). All the foetuses were normal and necropsy findings were negative. The incidence of dams delivering prior to CS are within the range of HCD.
The number of embryonic (early) resorptions (16 vs. 9 in ctr) and post-implantation loss (21.4% vs. 9.2% in ctr) was higher at the top dose, and live foetuses/dam (4.8 vs. 6.9 in ctr) was reduced at the top dose compared to control. The numbers were within the range of HCD but exceeded the mean +/-SD and may be related to treatment. In addition, two dead foetuses were recorded at the top dose (vs. 0 in ctr).
External findings were limited to mostly single incidences in the control and mid dose group and did not show any dose-relationship. The % of foetuses with hyoid body and/or arches unossified and reduced ossification of the skull exceeded the range of HCD at the top dose level while the litter incidences of both findings were well within the range of HCD. See table below.

Table 58: Selected skeletal variations

mg/kg bw/day		0	10	50	200	HCD°
Foetuses/litter examined		118/17	76/13	87/12	77/14	
Hyoid body and/or arches unossified	foetuses	1 (0.8)	1 (1.3)	3 (3.4)	6 (7.8)	(0.7+/-1.6, 0-7.0)°°°
	(%) litter (%)	1 (5.9)	1 (7.7)	3 (25)	2 (14)	(3.2+/-7.2, 0-30)
Reduced ossification of skull	foetuses	0	0	0	5 (6.5)	(0.5+/-1.2, 0-5.3)
	(%) litter (%)	0	0	0	1 (7.1)	(2.8+/-6.1, 0-25)

° mean +/-standard deviation, range; based on HCD information in Appendix D of report: 25 studies using NZW rabbits performed by the laboratory starting July 1980 to February 1985; assumption that incidence was 0 where finding was not listed for an individual study

°°° includes reduced ossification of hyoid body and/or arches

2.6.6.2.2 Comparison with the CLP criteria regarding adverse effects on development

According to the CLP criteria, developmental toxicity includes any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during pre-natal development, or postnatally, to the time of sexual maturation. The major manifestations of developmental toxicity include death of the developing organism, structural abnormality, altered growth and functional deficiency.

Several adverse findings in the respective top dose groups from all four studies were related to developmental effects. Increases in post-implantation loss were seen in both rat studies and in the second rabbit study. In the first rat study, an increase in dead foetuses were seen at 450 mg/kg bw/day. Reduced foetal weights were reported in both rat studies. In the second rabbit study, two foetuses were dead, and the number of live foetuses per litter were reduced.

An increase in runt foetuses were reported in the second rat study. Skeletal findings were reported in both rat studies, mainly increases in incomplete ossification and occurrence of extra ribs. However, the individual skeletal findings contributing to these increases were not reproducible within the same study nor between the two studies except for some indications for delayed ossification. In the first rabbit study, the incidences of internal hydrocephalus slightly exceeded available HCD. This was not seen in the second study. In addition, three foetuses in the first study had microphthalmia (within the range of HCD), including two which also had hydrocephalus. In the second rabbit study, foetuses with hyoid body and/or arches unossified and reduced ossification of the skull were observed and exceeded available HCD ranges.

Taken together, these findings contribute to the need for classification in a weight of evidence assessment. Since the data are from animal studies only and are not sufficiently convincing to classify in category 1b, classification in category 2 is warranted. Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance in Category 1A is largely based on evidence from humans. For Penconazole (ISO), only evidence from animal studies is provided. The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered

not to be a secondary non-specific consequence of other toxic effects. For Penconazole (ISO), the adverse effects are not consistent enough throughout the different species and studies to classify it in Category 1b. Moreover, the evidence for adverse effects on development are present, and all data taken together in a weight of evidence approach, warrants classification. Development of the offspring throughout gestation and during the early postnatal stages can be influenced by toxic effects in the mother either through non-specific mechanisms related to stress and the disruption of maternal homeostasis, or by specific maternally-mediated mechanisms. The studies in rats showed some maternal toxicity at the top dose, such as some mortalities, clinical signs, reduced weight gain and food consumption. The maternal toxicity in rabbits was milder, primarily affecting body weight gain and food consumption. The maternal toxicity is not considered severe enough to explain the adverse effects on development of the offspring seen in all the studies. Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification.
The fact that other triazoles are classified for developmental effects could also be considered supportive.

2.6.6.2.3 Conclusion on classification and labelling for reproductive toxicity

Harmonised classification proposed. Classification for adverse effects on development of the offspring, category 2, H361d, is warranted.

2.6.6.3 Adverse effects on or via lactation [equivalent to section 10.10.7 of the CLH report template]

Table 59: Summary table of animal studies on effects on or via lactation

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
No relevant findings on or via lactation from the studies provided			

Table 60: Summary table of human data on effects on or via lactation

Type o data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No studies available				

Table 61: Summary table of other studies relevant for effects on or via lactation

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No studies available				

2.6.6.3.1 Short summary and overall relevance of the provided information on effects on or via lactation

No relevant findings on or via lactation from the studies provided.

2.6.6.3.2 Comparison with the CLP criteria regarding effects on or via lactation

Hazard class not assessed in this dossier.

2.6.6.3.3 Conclusion on classification and labelling for reproductive toxicity

Hazard class not assessed in this dossier.

2.6.7 Summary of neurotoxicity

Table 62: Summary table of animal studies on neurotoxicity

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results: - NOAEL/LOAEL - target tissue/organ -critical effect at LOAEL	Reference
No studies available			

No relevant findings on neurotoxicity from the studies provided.

2.6.7.1 Comparison with the CLP criteria regarding effects on neurotoxicity

Hazard class not assessed in this dossier.

2.6.7.2 Conclusion on classification and labelling for reproductive toxicity

Hazard class not assessed in this dossier.

2.6.8 Summary of other toxicological studies

2.6.8.1 Toxicity studies of metabolites and impurities

Toxicity studies are available with metabolites CGA179944, CGA91305, CGA132465 and several common triazole metabolites: 1,2,4-Triazole (1,2,4-T, CGA71019), triazole alanine (TA, CGA131013), triazole acetic acid (TAA, CGA142856) and triazole lactic acid (TLA, CGA205369).

The common triazole metabolites have been recently evaluated in the EU[1]. From the common triazole metabolites, only TAA exceeds the limit in groundwater modelling that triggers a non-relevance case. Therefore, only this common triazole metabolite is potentially relevant. Study summaries for TAA are not repeated in this document as recently evaluated in the EU; however, details of the studies relied on (reports) have been provided. Toxicity studies with the remaining common triazole metabolites are not included within this submission (please refer to the existing EU evaluations).

Further toxicity studies are available with CGA91305 (tentatively identified in groundwater) but as a non-relevance case is not triggered, the toxicity studies are not included within this submission (see list of non-submitted studies).

Several genotoxicity studies with CGA179944 were also already evaluated at EU as part of the last evaluation of tetraconazole due to the fact that CGA179944 is also a metabolite of tetraconazole (CGA179944 is called 'M14360-acid' within tetraconazole DAR). In addition to the studies previously presented, an additional Ames test and developmental toxicity studies were performed since the last EU evaluation and the negative response in the existing *in vivo* micronucleus test was supported by further work (trend test calculation, updated HCD, slide re-evaluation).[2]

For metabolite CGA132465, genotoxicity data and a 28-days oral toxicity study in rats are available.

Toxicological relevance of several dietary metabolites (excluding the common triazole metabolite above) - CGA190503, CGA132465, CGA127841, CGA177279, CGA177281, CGA179944, CGA189659 - is further discussed in a statement based on structural relationship and available QSAR modelling as compared to penconazole. Essentially, all dietary metabolites evaluated were similar to parent in QSAR modelling. However, concerning CGA127841, CGA132465, CGA177279 and CGA177281, one of the models is out of the applicability domain and therefore may not be reliable to support read-across to parent. CGA179944 and CGA190503 would support a read-across to parent and the use of penconazole toxicological reference values for risk assessment for the dietary metabolites, if required. The latter is supported by the absence of a relevant genotoxic potential for CGA132465 for which studies are available.
Upon request from the RMS, the available QSAR information was additionally presented in agreement with the EFSA template for reporting QSAR.

[1] European Commission: Peer review of the pesticide risk assessment for the triazole derivative metabolites in light of confirmatory data submitted, 29th June 2018
Triazole Derivative Metabolites: Addendum – Confirmatory Data; B.5 Methods of analysis, B.6 Mammalian Toxicology & Metabolism, B.7 Residues, revised May 2016 and February 2018

[2] With the exception of the Ames test done by Isagro with M14360-acid = CGA179944, as the applicant has performed another Ames test showing the same results: negative +/-S9. Also not included is a tolerability study in non-pregnant rabbits.

Additionally, during the last EU review, CGA127841 was considered as a major rat metabolite covered by the studies performed with penconazole. CGA132465 and CGA190503 were considered likely to be of the same or lower toxicity than penconazole, based on their structural similarity with the parent compound and some rat metabolites[3].

CGA179944 was negative in the available Ames test. The existing *in vitro* mammalian cell gene mutation study was considered to be equivocal by RMS and should be repeated to confirm a clearly negative outcome. Notably, a positive outcome of this test would have triggered a requirement to conduct a Comet assay or a Transgenic Rodent Assay. The chromosome aberration test was reconfirmed to be positive. Overall, a novel *in vitro* mammalian cell gene mutation study should be provided, and a justification regarding *i.p.* administration in the *in vivo* micronucleus assay should be provided.

After 7 days of oral application of CGA179944, dose levels up to 1000 mg/kg bw/day (gavage) and 10000 ppm (via diet, 737 mg/kg bw/day) were well tolerated in the rat without relevant signs of toxicity. Minimal and/or transient maternal effects were seen in the preliminary and main developmental toxicity at 10000 ppm, except for body-weight gain corrected for gravid uterus weight at 10000 ppm, and to a lesser degree at 3000 ppm, which was markedly reduced. Concerning foetal toxicity, early intrauterine deaths showed a dose-response, with a marked increase at 3000 and 10000 ppm compared with control, although not statistically significant. Accordingly, post-implantation loss is elevated at 3000 and 10000 ppm compared with control. An increase in minor abnormalities and variant findings are seen at both 3000 and 10000 ppm. RMS suggests a maternal and a developmental NOAEL of 1000 ppm (84 mg/kg bw/day).

In the main rabbit study, there was one death related to treatment in the high-dose group, in addition to one death in the control group. Maternal toxicity was further manifested as body weight loss from day 6 to day 12, lower body weight gain and food intake at the top dose compared with control. Concerning foetal toxicity, there was a slight increase in the number of late intra-uterine deaths and the number of litters affected in the group given 600 mg/kg/day. At 600 mg/kg bw/day, group mean foetal weights (total, males and females) were statistically significantly lower than controls. Litter weight was also decreased at 600 mg/kg bw/day compared with control. Different major foetal abnormalities were seen in all treatment groups. However, at 600 mg/kg bw/day, two cases of incomplete interventricular septum were detected. Different variations were seen in all treatment groups; however, cerv vert, odontoid process, extra 13th rib and forelimb epiphyses not ossified were markedly elevated in 600 mg/kg bw/day compared with control, with statistical significance, and in some cases also at 300 mg/kg bw/day. RMS suggests a maternal NOAEL of 300 mg/kg bw/day and a developmental NOAEL of 100 mg/kg bw/day.

RMS suggests a classification for CGA179944 according to Regulation (EC) No. 1272/2008: H361d, "Suspected of damaging the unborn child», similar to the classification for penconazole. The NOAEL for CGA179944 is comparable with the NOAEL for penconazole from the developmental studies on rat (100 mg/kg bw/day). For rabbit, both maternal and developmental NOAEL is higher for CGA179944 in rabbit compared with penconazole (75 and 50 mg/kg bw/day for developmental studies in rabbit).

Another available study – tolerability in non-pregnant rabbits - with CGA179944 was not submitted (included in list of non-submitted studies), as it was considered not to add relevant information required for the evaluation of CGA179944[4].

CGA142856 (TAA) was negative in the available genotoxicity studies (Ames, mammalian cell gene mutation, chromosome aberration). It is therefore considered non-genotoxic and a classification for genotoxicity is not required.

The available acute and repeated dose toxicity studies in rats and mice indicate that CGA142856 (TAA) is less toxic (with NOAELs at or close to the limit dose) than the parent penconazole.
The latter was confirmed by the available reproductive toxicity studies (2-generation study in rats, rat and rabbit developmental toxicity studies) not showing relevant reproductive or developmental effects and NOAELs again being higher as compared to the respective penconazole studies.
The recent EU evaluation resulted in an ADI and ARfD of 1 mg/kg bw/day for CGA142856 (TAA) based on the NOAELs of 100 mg/kg bw/day of the available reproductive toxicity (rat) and developmental toxicity (rabbit) studies.

[3] EFSA (2016). Scientific Report of EFSA on scientific support for preparing an EU position in the 48th Session of the Codex Committee on Pesticide Residues (CCPR). EFSA Journal 2016;14(8):4571.
[4] While it contained additional TK information (as compared to the submitted studies), the latter was not used to set the dose levels for the submitted studies (dose levels based on toxic effects).

CGA132465 was negative in the available genotoxicity studies (Ames, mammalian cell gene mutation, *in vitro* micronucleus). It is therefore considered non-genotoxic and a classification for genotoxicity is not required.

Available QSAR indicates that CGA132465 should not be more toxic than the parent penconazole; however, one of the models is out of applicability domain and may not be reliable. A 28-days oral (feeding) study in rats confirmed the modelling prediction revealing the liver as target organ (increased liver weight and hepatocellular necrosis comparable with effects seen with penconazole) and a NOAEL of 1000 ppm equivalent to 75/74 mg/kg bw/day which was also comparable with the NOAEL seen in 28-days studies with penconazole (20 < NOAEL < 100 mg/kg bw/day). Therefore, CGA132465 is considered similar to parent and it is considered justified to use the reference doses based on studies with penconazole for risk assessment of CGA132465 as well.

2.6.8.2 Supplementary studies on the active substance

The potential immunotoxic effects of penconazole were evaluated based on results from 14 existing repeated dose data studies. Studies with penconazole that were reviewed include short-term, subchronic and chronic studies in rats, mice, rabbits and dogs and multi-generation reproduction studies in rats. The following parameters were investigated in some or all of the studies: spleen, thymus and adrenal organ weights, haematology parameters, plasma globulin levels, micropathology in immune-related tissues, tumour increase in immune-related tissues, and enhanced infections.
Generally, very few immune-related findings were revealed; thus, the investigated studies show no immunotoxic potential of penconazole.

A supplementary study on liver enzyme induction was conducted with penconazole in rats and mice. The animals were given daily oral doses of penconazole via gavage for 14 days (dose levels of 10, 80, 160, or 320 mg/kg bw/d). The treatment caused a marked liver enlargement in both species at 80 mg/kg bw/day and higher (dose-dependent). Proliferation of smooth endoplasmic reticulum membranes, and a pronounced induction in the activity of several hepatic xenobiotic metabolising enzymes (ethoxycoumarin-O-deethylase, epoxide hydrolase, UDP-glucuronosyl-transferase, glutathione-S-transferase) was seen. The results suggested that in both species liver enlargement was due to a combination of both hyperplasia and hypertrophy of the hepatocytes. They also indicated that, like other triazole derivatives, penconazole belongs to the phenobarbital class of monooxygenase inducers. Taken together, RMS proposes a NOAEL of 80 mg/kg bw/day in both rats and mice.

An open literature article on transcriptionally altered cancer-related genes induced by penconazole was considered to be relevant and reliable by RMS and included as a supplementary study on the active substance. Cells from the T-47D cell line were treated with commercial penconazole or penconazole-contaminated grape extracts for 4 h at doses close to the MRL. The whole-genome transcriptomic profile was assessed by using genome 44 K oligo-microarray slides. The analysis returned a set of genes involved in Thyroid Cancer Pathway as common genes significantly altered from both treatments and showing the same trend of modulation. Due to the fact that the experiment was performed in a cell line, and only one cell line was applied, RMS considers these finding supplementary only, but recognizes that the findings might contribute to a weight of evidence setting.

2.6.9 Summary of medical data and information

Medical surveillance on manufacturing plant personnel and monitoring studies
The applicant has maintained a data base of incidents involving chemical exposure of workers since 1983. A query of the Syngenta internal database in January 2019 for penconazole produced one record of adverse health effects reported in February 2016. A bitter taste following access to samples of formulated products in a non-extracted fume cupboard. The taste was quickly eliminated following the use of mouthwash. The investigation concluded that the symptoms were most likely to be associated with volatile solvent rather than penconazole technical material. No other cases have been reported during the manufacture or formulation of penconazole-containing products over a 32-year period.

Data collected on humans
The applicant did not perform any studies that would collect data from humans.
A number of publications appeared in the literature search that may have been potentially relevant as potentially containing information on adverse health effects in humans. However, they were considered insufficiently reliable to be included here and/or a relation between penconazole exposure and reported indications for adverse health effects could not be established.

Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical test

Penconazole is of low acute toxicity. Intoxication is only likely if large quantities are ingested. In animal studies, symptoms of acute poisoning were non-specific.

Proposed treatment: first aid measures, antidotes, medical treatment
General advice: Have the product container, label or Material Safety Data Sheet with you when calling the Syngenta emergency number, a poison control center or physician, or going for treatment.
Inhalation: Move the victim to fresh air. If breathing is irregular or stopped, administer artificial respiration. Keep patient warm and at rest. Call a physician or poison control centre immediately.
Skin contact: Take off all contaminated clothing immediately. Wash off immediately with plenty of water. If skin irritation persists, call a physician. Wash contaminated clothing before re-use.
Eye contact: Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Remove contact lenses. Immediate medical attention is required.
Symptoms: No information available
Ingestion: If swallowed, seek medical advice immediately and show this container or label. Do NOT induce vomiting.
Medical advice: There is no specific antidote available. Treat symptomatically. No antidote is known, apply symptomatic treatment.

Expected effects of poisoning
Penconazole is of low toxicity in animals (and humans) as indicated by available animal studies and the absence of relevant health effects reported in medical surveillance of manufacturing facilities.

2.6.10 Toxicological end points for risk assessment (reference values)

Table 63: Overview of relevant studies for derivation of reference values for risk assessment

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
Dog	Toxicity Study In Dogs, 90-days/1 year Orally via diet	Penconazole (91.7%, P. 11-14)	Target organ: Liver 90 days: Bw gain ↓; liver: weight ↑, hepatocyte necrosis 1 year: Bw gain ↓; liver: weight ↑, hepatocyte necrosis, inflammation, fibrosis	90 days: (100) M: 3.3; F: 3.8 1 year: (100) M: 3.1; F: 3.3	90 days: (500) M: 17.5; F: 18 1 year: (500) M: 16.9; F: 16.7	[redacted] (1984); K-CA 5.3.2/04 Report No. 801187
Rabbit	Developmental toxicity GD 7-19 Orally via diet	Penconazole: FL840833; 98.7% purity	Bw gain ↓, food ↓ in dams Embryonic resorptions compared to HCD mean ↑, post implantation loss compared to HCD mean ↑, live foetuses/litters compared to HCD mean ↓, % of foetuses with hyoid body and/or arches unossified and reduced ossification of the skull ↑, Bw in offspring ↓	Maternal and developmental NOAEL of 50 mg/kg bw/day		[redacted] (1985) K-CA 5.6.2/06 Report No. [redacted] 82004

2.6.10.1 Toxicological end point for assessment of risk following long-term dietary exposure – ADI (acceptable daily intake)

In line with the previous evaluation (DAR, 2007), the ADI is based on the NOAEL (3 mg/kg bw/day) from the 90 days/1 year toxicity study in dogs. From a comparison of NOAELS/LOAELs potentially relevant for setting an ADI, i.e. those from short-term, long-term and reproduction toxicity studies, it was concluded that the species most sensitive to repeated administration of penconazole was the dog, with the most relevant NOAEL of ca. 3 mg/kg bw/day, being derived from the combined 90-day/1-year oral gavage study ([redacted] 1984) on the basis of reduced body weight development and hepatotoxicity at about 17 mg/kg bw/day and above.

With respect to safety factors, it was previously (DAR, 2007) decided to use a default value of 100 (accounting for potential interspecies as well as for intraspecies variation), resulting in an ADI of 0.03 mg/kg bw/day. During this re-assessment an extra safety factor of 2 is proposed to be applied, to account for the extrapolation from sub-chronic to chronic studies. Notably, the histopathological findings in the combined 90-day/1-year oral gavage study indicate a time-dependent increase in the number of animals with inflammation with fibrosis in the liver. In addition, more severe effects in the liver are seen at lower penconazole levels after 1 year compared with 90 days.

In total, three chronic/long term studies were conducted (two in mice and one in rats). However, in line with the previous evaluation (DAR, 2007), it was concluded that the tested doses in two of these studies ([redacted] 1985,

and [redacted] 1985a) were too low and that the studies could only be considered supportive, as no toxicity was seen at the top dose. In the third long-term study in mice ([redacted] 2004), a NOAEL of 21.7 mg/kg bw/day was derived, based on reduced body weight development and an increase in liver weight associated with an increase in hepatocyte vacuolisation at the highest dose tested. Notably, a NOAEL of 69 mg/kg bw/day was derived for a 90 - Day Preliminary Carcinogenicity Study In Mice ([redacted] 2002), based on reduced body weight development and an increase in liver weight associated with an increase in hepatocellular hypertrophy at increasing dose.

The proposed ADI was calculated as follows:

ADI = NOAEL 90-day/1-year, dog/ SF = (3 mg/kg bw/day)/200 = 0.015 mg/kg bw/day.

2.6.10.2 Toxicological end point for assessment of risk following acute dietary exposure - ARfD (acute reference dose)

During the previous evaluation (DAR, 2007), the setting of an ARfD for penconazole was considered unnecessary, based on an evaluation in accordance with recommendations of the WHO published in 2004 (JMPR, 2004. Guidance for the derivation of an acute reference dose, pesticide residues in food-2004, Report of the JMPR, FAO Plant Production and Protection Paper, 178).

During the current evaluation, an ARfD of 50 mg/kg bw/day is proposed, based on the NOAEL from a developmental toxicity study in rabbit ([redacted] 1985). With respect to uncertainty factors, it is proposed to use a default value of 100, accounting for potential interspecies as well as for intraspecies variation. Based on the comparative intravenous (iv) vs. oral data, the oral absorption of penconazole can be assumed to be practically complete, and no additional correction factor is proposed.

The proposed ARfD was calculated as follows:

ARfD = NOAEL dev. Tox rabbit /SF = (50 mg/kg bw/day)/100 = 0.5 mg/kg bw/day

2.6.10.3 Toxicological end point for assessment of occupational, bystander and residents risks – AOEL (acceptable operator exposure level)

In line with the previous evaluation (DAR, 2007), the AOEL is based on the NOAEL (3 mg/kg bw/d) from the 90 days/1 year toxicity study in dogs. From a comparison of potentially relevant NOAELs/LOAELs for short-term and reproduction toxicity, the combined 90-d/1-yr study in dogs ([redacted] 1984) was chosen as being the most relevant one for the setting of the systemic AOEL (AOEL-S). As oral absorption of penconazole exceeded 80%, no need was seen to use an additional correction factor.

With respect to safety factors, it is, in line with the previous evaluation (DAR, 2007), decided to use a default value of 100, accounting for potential interspecies as well as for intraspecies variation. Based on the comparative intravenous (iv) vs. oral data, the oral absorption of penconazole can be assumed to be practically complete, and no additional correction factor is proposed.

The proposed AOEL was calculated as follows:

AOEL-S = NOAEL 90-day/1-year, dog /SF = (3 mg/kg bw/day)/100 = 0.03 mg/kg bw/day

2.6.10.4 Toxicological end point for assessment of occupational, bystander and residents risks – AAOEL (acute acceptable operator exposure level)

An EU-wide harmonised approach for the derivation of the AAOEL is still pending. However, based on the Commission Guidance Document SANTE-108322015 rev. 1.7, 24 January 2017, the ARfD is suggested as a value for the AAOEL.

The proposed AAOEL was calculated as follows:

AAOEL = NOAEL dev. Tox rabbit /SF = (50 mg/kg bw/day)/100 = 0.5 mg/kg bw/day

2.6.11 Summary of product exposure and risk assessment

The representative plant protection product "Topas" A6209G is an emulsifiable concentrate (EC) containing 100 g penconazole/L intended for use as a fungicide on pome fruit, grapes and cucumber.

Operator exposure:
According to the intended uses submitted by the applicant, the maximum applied dose is 40 g a.s./ha in pome fruit, 30 g a.s./ha in grapes, and 50 g a.s./ha in cucumber, with a minimum volume of 500 L/ha in pome fruit, 150 L/ha in grapes, and 200 L/ha in cucumber. The exposure estimates according to the different scenarios are summarized in the tables below.
EFSA Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products [EFSA Journal 2014;12(10):3874 [55 pp.] has been used as a model to estimate exposure.

Table 64: Summary of estimated operator exposure to penconazole (longer term exposure)

Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Tractor-mounted/trailed broadcast air assisted spray application outdoors to high crops-pome fruit			
Application rate		0.04 kg a.s./ha	
Spray application (AOEM**;** 75th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and App.	0.0069	22.87
Tractor-mounted/trailed broadcast air assisted spray application outdoors to high crops grapes			
Application rate		0.03 kg a.s./ha	
Spray application (AOEM**;** 75th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and App.	0.0053	17.76
Tractor-mounted boom spray application outdoors to low crops-cucumber			
Application rate		0.05 kg a.s./ha	
Spray application (AOEM**;** 75th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and App.	0.0024	7.92

Table 65: Summary of estimated operator exposure to penconazole (acute exposure)

Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AAOEL**
Tractor-mounted/trailed broadcast air assisted spray application outdoors to high crops-pome fruit			
Application rate		0.04 kg a.s./ha	
Spray application (AOEM**;** 95th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and App.	0.0217	4.34
Tractor-mounted/trailed broadcast air assisted spray application outdoors to high crops grapes			
Application rate		0.03 kg a.s./ha	
Spray application (AOEM**;** 95th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and App.	0.0164	3.28
Tractor-mounted boom spray application outdoors to low crops-cucumber			
Application rate		0.05 kg a.s./ha	

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AAOEL
Spray application (AOEM**;** 95th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and App.	0.0203	4.07

Therefore, according to the model calculations, it can be concluded that the risk for the operator using A6209G for the proposed uses is acceptable without the use of personal protective equipment.

Worker:

Workers may enter field cultivations of pome fruit, grapes and cucumbers after treatment to perform tasks such as crop inspections, pruning or harvesting.

Table 66: Estimated worker exposure to penconazole

Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Reaching, picking pome fruit Outdoor Work rate: 8 hours/day(1), DT_{50}: 30 days(2) DFR: 3 µg/cm²/kg a.s./ha(2) Interval between treatments: 10 days			
Number of applications and application rate		2 × 0.04 kg a.s./ha	
Body weight: 60 kg	(3)Work wear (arms, body and legs covered) TC: 4500 cm²/person/h	0.0284	94.71
Reaching, picking grapes Outdoor Work rate: 8 hours/day(1), DT_{50}: 2.38 days(4) DFR: 2.0 µg/cm²/kg a.s./ha(4) Interval between treatments: 8 days			
Number of applications and application rate		2 × 0.03 kg a.s./ha	
Body weight: 60 kg	(3)Work wear (arms, body and legs covered) TC: 10100 cm²/person/h	0.0195	65.02
Reaching, picking cucumber Outdoor Work rate: 8 hours/day(1), DT_{50}: 30 days(2) DFR: 3 µg/cm²/kg a.s./ha(2) Interval between treatments: 8 days			
Number of applications and application rate		3 × 0.05 kg a.s./ha	
Body weight: 60 kg	(3)Work wear (arms, body and legs covered) TC: 2500 cm²/person/h	0.0277	92.48

(1) 8 h/day for professional applications for harvesting, pruning, tying, thinning or weeding activities
(2) EFSA Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products [EFSA Journal 2014;12(10):3874 [55 pp.]
(3) no PPE: Worker wearing shoes, socks, long-sleeved shirt, and long trousers
(4) DFR value derived from experimental data.

It is concluded that there is no unacceptable risk anticipated from penconazole for the worker wearing adequate work clothing (but no PPE), when re-entering crops treated with A6209G. As a standard rule, it should be mentioned on the label that treated crops should not be re-entered before spray deposits on leaf surfaces have completely dried.

Bystander and residents:

The acute exposure assessment for bystanders covers the exposure that a resident could reasonably be expected to incur in a single day. Therefore, there is no need for a separate acute risk assessment for residents. Resident exposure is therefore determined by average exposure over a longer duration, and higher exposures on one day will tend to be offset by lower exposures on other days.

Table 67: Summary of estimated bystander (acute) exposure to penconazole

Model data		**Total absorbed dose (mg/kg bw/day)**	**% of systemic AAOEL**
Tractor-mounted/trailed broadcast air assisted spray application outdoors to high crops-pome fruit Buffer zone: 5(m) Drift reduction technology: no DFR: 3 µg/cm²/kg a.s./ha and DT50: 30 days			
Application rate		0.04 kg a.s./ha	
Bystander child Body weight: 10 kg	Drift (95th perc.)	0.0056	1.12
	Vapour (95th perc.)	0.0011	0.21
	Deposits (95th perc.)	0.0008	0.17
	Re-entry (95th perc.)	0.0027	0.53
Bystander adult Body weight: 60 kg	Drift (95th perc.)	0.0031	0.62
	Vapour (95th perc.)	0.0002	0.05
	Deposits (95th perc.)	0.0003	0.06
	Re-entry (95th perc.)	0.0015	0.30
Tractor-mounted/trailed broadcast air assisted spray application outdoors to high crops-grapevines Buffer zone: 5(m) Drift reduction technology: no *DFR: 2.0 µg/cm²/kg a.s./ha and DT50: 2.38 days			
Application rate		0.03 kg a.s./ha	
Bystander child Body weight: 10 kg	Drift (95th perc.)	0.0140	2.81
	Vapour (95th perc.)	0.0011	0.21
	Deposits (95th perc.)	0.0002	0.03
	Re-entry (95th perc.)	0.0008	0.16
Bystander adult Body weight: 60 kg	Drift (95th perc.)	0.0078	1.55
	Vapour (95th perc.)	0.0002	0.05
	Deposits (95th perc.)	0.0001	0.01
	Re-entry (95th perc.)	0.0005	0.09

*Experimentally derived value. See Section CP 6.4.3.1

Table 68: Summary of estimated resident (longer term) exposure to penconazole

Model data		**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**
Tractor-mounted/trailed broadcast air assisted spray application outdoors to high crops-pome fruit Buffer zone: 5(m) Drift reduction technology: no DFR: 3 µg/cm^2/kg a.s./ha and DT50: 30 days			
Number of applications and application rate		2 × 0.04 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.0025	8.17
	Vapour (75th perc.)	0.0011	3.57
	Deposits (75th perc.)	0.0003	1.04
	Re-entry (75th perc.)	0.0027	8.88
	Sum (mean)	0.0050	16.66
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0014	4.52
	Vapour (75th perc.)	0.0002	0.77
	Deposits (75th perc.)	0.0001	0.39
	Re-entry (75th perc.)	0.0015	4.93
	Sum (mean)	0.0024	7.90
Tractor-mounted/trailed broadcast air assisted spray application outdoors to high crops-grapes Buffer zone: 5(m) Drift reduction technology: no *DFR: 2.0 µg/cm^2/kg a.s./ha and DT50: 2.38 days			
Number of applications and application rate		2 × 0.03 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.0061	20.42
	Vapour (75th perc.)	0.0011	3.57
	Deposits (75th perc.)	0.0001	0.24
	Re-entry (75th perc.)	0.0008	2.72
	Sum (mean)	0.0058	19.35
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0034	11.31
	Vapour (75th perc.)	0.0002	0.77
	Deposits (75th perc.)	0.00002	0.09
	Re-entry (75th perc.)	0.0005	1.51
	Sum (mean)	0.0028	9.43

*Experimentally derived value. See Section CP 6.4.3.1

It is concluded that there is no undue risk to any bystander or resident from penconazole during and following local application of A6209G.

2.7 RESIDUE

2.7.1 Summary of storage stability of residues

The potential for degradation of residues of penconazole during freezer storage in plant commodity categories applicable to representative uses (i.e., High Water and High Acid) has been assessed in the framework of the peer review for penconazole.

The second interim report for the new study (Homazava, N, 2020, VV-244513) demonstrates freezer storage stability for penconazole across all 5 plant commodity categories for at least 18 months. This tested period of 18

months thereby covers the actual period of freezer storage prior to analysis in all the residue and processing trials to support representative uses.
A new storage stability study for crop metabolites (CGA132465, CGA127841 and CGA190503) has been conducted (Connor, 2020, VV-743150). This study demonstrates storage stability for each analyte across all 5 plant commodity categories for the maximum duration of the studies. The study demonstrates stability for the metabolites for at least 24 months in High Water (cucumber), High Oil (oil seed rape seed), High Protein (dry beans) and High Starch (cereal grain) commodities, and at least 30 months in High Acid (grapes) commodities.

Storage stability of penconazole in crops:
The maximum period of freezer storage prior to analysis for penconazole in residue trials is 10 months for representative uses and 5.1 months for supplementary data crops. Since all samples analysed and presented belong to High Water or High Acid groups, the penconazole analyses are covered by Homazava, (2020).

Storage stability of metabolites in crops:
The maximum period of freezer storage prior to analysis for crop metabolites (CGA132465, CGA127841 and CGA190503, after deconjugation) in residue trials is 24 months for representative uses and 13 months for supplementary data crops. Since all samples analysed belong to High Water or High Acid groups, the crop metabolite analyses are covered by the new crop metabolite storage stability study (Connor, 2020).

Storage stability of penconazole and metabolites in processed crop commodities:
The maximum period between first sampling and last analysis for freezer storage, prior to analysis for penconazole, in magnitude of residue processing studies reported prior to 2018 is 16 months. The maximum periods for freezer storage for penconazole and crop metabolites in the latest grape (Brown, 2019) and apple (Brown, 2019a) magnitude of residue processing studies reported are approximately 15 and 10 months, respectively. Correspondingly, demonstration of storage stability for parent and crop metabolites is covered by Connor (2020).

Table 69: Summary of stability data for metabolites (CGA132465, CGA127841 and CGA190503) in plant commodities

Commodity Category	Commodity	Maximum Storage Period	Report Reference	EU reviewed
High Acid Content	Grapes	30 months*	225935 (**Conner, S., 2020**; VV-743150)	No
High Water Content	Cucumber	24 months*		
High Oil	Oilseed rape seed			
High Protein	Dried beans			
High Starch	Wheat grain			

* Storage at -20ºC

Table 70: Summary of stability data for total residues of CGA71818 and its metabolites containing the 2,4-dichlorobenzyl moiety in plant commodities

Commodity Category	Commodity	Maximum Storage Period	Report Reference	EU reviewed
High Acid Content	Grapes	6 months*	ABR-85051 (**Kahrs, R. A., 1985**; CGA71818/0844)	No

* Storage at -15ºC

Except for sample preparation and the removal of a sub-sample for analysis, the samples in the residue trials were stored at or below -18°C for a maximum period of 9.9 months (301 days) from sampling to analysis of penconazole residues.

2.7.2 Summary of metabolism, distribution and expression of residues in plants, poultry, lactating ruminants, pigs and fish

Metabolism studies conducted with three different crops from the fruit/fruiting vegetable group (tomatoes, apples and cucumbers; the only metabolic group applicable to the presented GAP) based on the commercially recommended use pattern, i.e. post emergence foliar treatment, have provided a detailed understanding of the metabolism of penconazole (CGA71818) in food commodities. The metabolic pathways in the studies are similar, and, consequently, the available crop metabolism studies fully support the current proposed uses of CGA71818 on fruit/fruiting vegetable crops.

Penconazole (CGA71818) was present in all commodities. Levels of penconazole in food commodities ranged from 7.2% to 19.0% TRR in tomato fruit, 11.6% in whole apples and 12.5% to 20.1% in cucumbers.

Metabolism was extensive in most crops and the metabolites identified in tomatoes and apples included cleaved molecules (see Figure below). The principal metabolic transformations of penconazole in tomatoes and apples occurred via oxidation of the propyl side chain of the parent molecule to produce predominately the hydroxylation product CGA132465 as a mixture of diastereomers. Additional hydroxylation products CGA190503 and CGA127841, as well as further oxidation products, were present at much lower levels. Identified metabolites were found in both their conjugated and/or their free non-conjugated form.

In tomatoes and apples, cleavage of the triazole ring led only to trace amounts of free triazole. Triazole conjugates CGA131013, and to a lesser extent CGA205369 (triazolyllactic acid), CGA142856 and CGA205373 (triazolylglycolic acid) were observed at higher levels.

In cucumbers, with the exception of Unk-1, all residues were <0.01 mg/kg and were not identified. Unk-1 (31.1% to 36.9% TRR, 0.011 to 0.012 mg/kg), obtained by hydrolysis of the aqueous extracts was also not identified. However, Unk-1 was characterized subsequently by the same TLC system used for an unknown soil degradate and the resulting chromatograms were very similar. Since CGA132465 elutes in the same place as Unk-1 and was also the major metabolite in all plant metabolism studies by the applicant, the structure of "Unk-1" was assigned to CGA132465.

The metabolism of ^{14}C-triazolyl- and ^{14}C-phenyl-penconazole was measured in foliar-applied tomato whole fruit and leaves 7 and 40 days after four applications, 4 x 40 g a.s./ha (1X nominal rate). Total radioactivity from the fruits was calculated by combination of surface methanol rinses, followed by combustion for penetrated radioactivity.

The level of metabolism in surface washes of tomato fruit was minimal, with penconazole as the most significant residue detected accounting for 71.0 - 92.6% of the radioactivity in the surface wash (equitable to (12.5 – 13.0% TRR (7 days PHI) and 1.7 – 2.2% TRR (40 days PHI) in whole fruit). Metabolism in the washed whole tomato fruit was much more extensive. Hydrolysis of the combined plant surface rinse and fruit extracts with aqueous HCl produced predominantely free CGA132465 as a mixture of diastereomers (61.6 – 66.9% TRR (7 days PHI) and 55.2 – 63.0% TRR (40 days PHI)). Similar levels of penconazole (7.8 – 8.7% TRR (7 days PHI) and 0.3 – 4.1% TRR (40 days PHI)) and CGA132465 (64.4 – 67.4% TRR (7 days PHI) and 59.9 – 70.1% TRR (40 days PHI)) were observed in the hydrolysed leaf extracts.

Minor metabolites CGA127841 and CGA190503 were observed in both leaves and fruit. With the exception of CGA190503 in leaves (10.8 – 16.4% TRR), both accounted for ≤4.3% TRR in any sample.

The only significant cleavage product detected was CGA131013 in 40 days PHI fruit samples (15.4% TRR). Residues of CGA131013 (leaves), CGA205369, CGA142856 and CGA71019 were also observed in 40 days PHI fruit and leaves; however, at levels of ≤2.3% TRR.

In addition, in the same tomato metabolism study, an exaggerated foliar application of [triazole-U-^{14}C]-penconazole to tomato plants at 4 x 200 g ai/ha (5X, nominal) was performed to produce metabolites for identification. The total achieved rate was 766.5 g ai/ha. Foliage, immature and mature fruit were harvested 40 days after last application for analysis. The metabolic profiles of the exaggerated rate (5X) were qualitatively similar to those obtained at the lower application rate (1X).

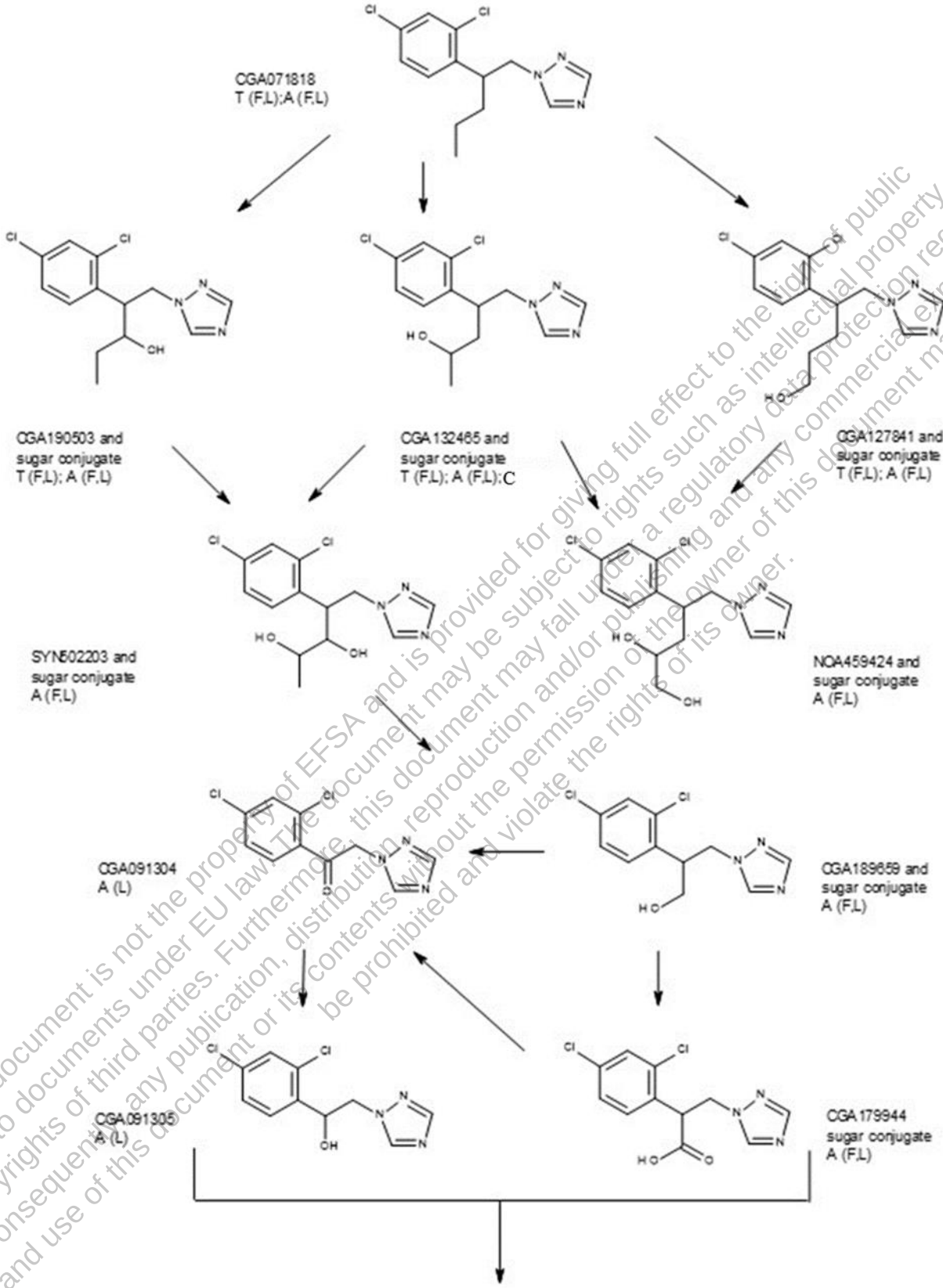
Following ten foliar applications at 2.5 g ai/hL and after a 34 days PHI, the level of metabolism of ^{14}C-triazolyl-penconazole was the most extensive in apples.

The principal metabolic transformation product of penconazole in apple whole fruit occurred via conjugation of free triazole to produce CGA131013 (23.0% TRR). An additional triazole conjugation product, CGA205369 (leaves: 2.4% TRR; apple peels: 5.0% TRR and apple pulp (7.6% TRR) was observed in both leaves and fruit. Other significant residues included parent penconazole (whole fruit: 11.6% TRR and leaves: 6.8% TRR) and hydroxylation product CGA132465 (whole fruit: 14.3% TRR and leaves: 37.9% TRR) as a mixture of diastereomers. The latter was present in both free and conjugated forms. Multiple minor residues, including CGA127841, CGA142856, CGA190503, CGA205373, CGA189659, CGA179944 and mixtures of propyl-dihydroxy parent were also detected in the fruit, none exceeding 5.6% TRR. A similar metabolic pattern was observed in leaves, although quantitatively different.

RMS did not evaluate the studies on grape. (The meeting of experts considered that the grape data were not acceptable, and they were not considered further.) ***EFSA Scientific Report*** **(2008) 175, 1-104 Conclusion on the peer review of penconazole.**

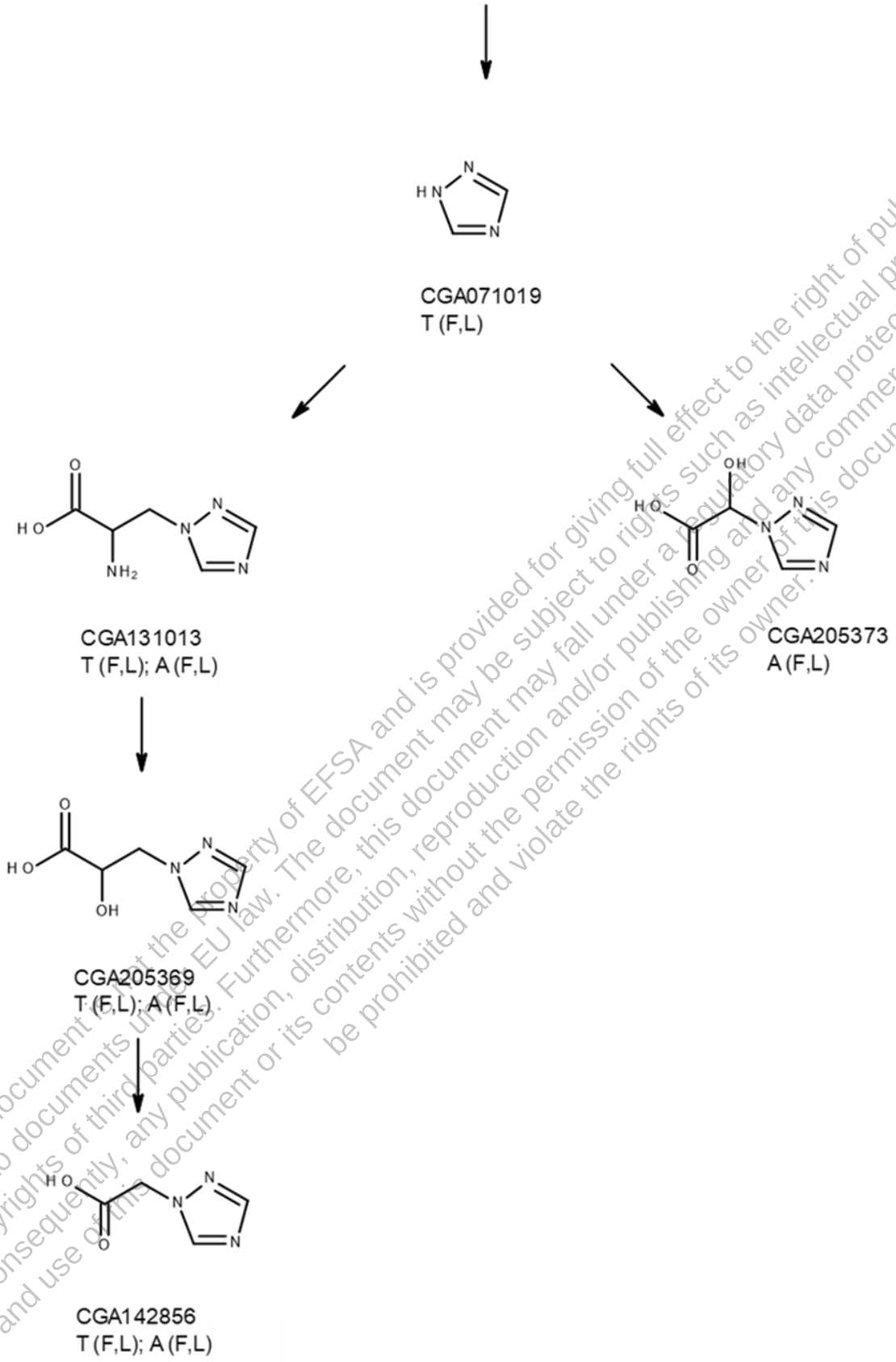
Cucumber plants were treated three times with [phenyl-^{14}C]-penconazole or [triazole-^{14}C]-penconazole emulsion concentrate formulated product (100 g/L EC) at a rate of ca 50 g active ingredient (ai) per hectare (ha). The plants were treated based on a worst case of a minimum pre-harvest interval of 3 days and an interval of 12-14 days between each application. With the exception of Unk-1, all residues were <0.01 mg/kg and were not identified. Unk-1 (31.1% to 36.9% TRR, 0.011 to 0.012 mg/kg), obtained by hydrolysis of the aqueous extracts was also not identified, but was consistent chromatographically with the major metabolite in all plant metabolism studies by the applicant. As such, the structure of "Unk-1" was assigned to CGA132465.
Overall, it is evident that hydroxylation of the parent molecule and degradation to triazole conjugates represent the principle metabolic transformations (see Figure below) observed in all crops. Additional metabolism into multiple lower residue components was also reported.

Proposed metabolic pathway for penconazole in crops



T = tomato; A = apple (F = fruit; L = leaves); C = cucumber

Proposed metabolic pathway for penconazole in crops (continued)



T = tomato; A = apple (F = fruit; L = leaves)

Poultry

The representative uses are not considered to be poultry feed items in the EU. Therefore, poultry studies are not required. Nevertheless, the applicant submitted a metabolism study in hens following oral administration (capsule) for completeness. RMS did not evaluate this study.

Livestock ruminants

According to existing EU guidance, investigating the metabolism of penconazole in ruminants is not required, Nevertheless, the applicant submitted the metabolism of penconazole in lactating goat for completeness. RMS did not evaluate this study.

Pigs

Since the commodities that may be derived from the representative crops are not considered relevant to pigs feeding, metabolism and feeding studies in pigs are not required.

Fish

Since the commodities that may be derived from the representative crops are not considered relevant to fish feeding, metabolism and feeding studies in fish are not required.

2.7.3 Definition of the residue

The existing Residues Definitions for Monitoring in commodities of plant are parent penconazole, only (**EFSA Scientific Report (2008) 175, 1-104**). No changes are proposed to the Monitoring Residue Definitions. Since metabolism and residue studies in ruminants, poultry and pigs are not required, the Residue Definition for Risk Assessment in livestock commodities is also proposed to be parent, only.

The existing Residue Definition for Risk Assessment in plant commodities (fruit and fruiting vegetables, only) is the sum of penconazole and free and conjugated CGA132465, CGA190503 and CGA127841, expressed as penconazole (**EFSA Scientific Report (2008) 175, 1-104 and EFSA Journal 2017;15(6):4853**). No changes are proposed to the residue definition for risk assessment in plants. However, this needs to be confirmed after toxicological risk assessment. The rationale for the proposed dietary residue definitions is outlined below.

The toxicological relevance of several dietary metabolites (including CGA132465, CGA190503, CGA127841, CGA179944, CGA177279 and CGA177281) has been thoroughly discussed. Quantitative Structure–Activity Relationship modelling was performed and should be considered as weight of evidence. For CGA132465, indexes in CAESAR are below the cut-off value for compounds to be considered within the Applicability Domain of the model. Therefore, the prediction may not be reliable. CGA179944 and CGA190503 are classified with a higher reliability.

Genotoxicity studies with CGA132465 and down-stream metabolite CGA179944, support read-across to parent and between the dietary metabolites evaluated: the dietary metabolites are considered non-genotoxic and not to be more toxic than the parent. Of note, CGA179944 is considered to possess comparable developmental toxicity to penconazole, and RMS suggests the same classification for CGA179944 with regard to developmental toxicity, H361d. For CGA132465, a 28-days oral toxicity study was assessed, and the metabolite possesses comparable toxicity as parent penconazole.

EFSA Scientific Report in preparation for the 48th CCPR (**EFSA Scientific Report (2016a) 14, 4571**): "*During the EU peer review, CGA127841 was considered as a major rat metabolite covered by the studies performed with penconazole. CGA132465 and CGA190503 were considered likely to be of the same or lower toxicity than penconazole, based on their structural similarity with the parent compound and some rat metabolites.*"

In conclusions, it is therefore considered justified to use the toxicological reference values of the parent for the evaluated dietary metabolites.

Definition of the Residue in Plants

The metabolism of penconazole was investigated for foliar application to apples and tomatoes using ^{14}C-triazole and ^{14}C-phenyl-labelled-penconazole. Studies have been conducted using ^{14}C-triazole-labelled penconazole under hydrolytic conditions to investigate the effect of processing on the nature of penconazole. Penconazole was shown to be stable under hydrolytic conditions, and this has also been demonstrated for crop metabolites CGA132465, CGA190503 and CGA127841 (***Kelly, D***, 2019, VV-733090; ***Kelly, D***, 2019a, VV-733072; and ***Mound, R***, VV-733065). The metabolism of penconazole in rotational crops was investigated in leafy vegetables (lettuce), root and

tuber vegetables (radish) and cereals (wheat). The metabolites identified in the rotational crop studies were the same as determined in the metabolism studies on primary crops:

EFSA Scientific Report for Penconazole (**EFSA Scientific Report (2008) 175, 1-104**): "*The peer review agreed to establish for fruiting crops the residue definition for enforcement as the parent compound. The current residue definition set in Regulation (EC) No 396/2005 is identical to the residue definition for enforcement derived in the peer review. For risk assessment, the residue definition was set as penconazole + CGA132465 + CGA190503 + CGA127841 and the conjugates of the metabolites, expressed as penconazole. For fruits and fruiting vegetables, a conversion factor (CF) of 6 from enforcement to risk assessment residue definition was established to consider the three metabolites. Pending the submission and assessment of the confirmatory data on TDMs requested for triazole pesticides, the residue definition should be regarded as provisional*."

The metabolism studies in tomatoes with 4 applications demonstrate that following the critical representative uses, penconazole should not lead to significant residues of any TDM in edible commodities. Whilst triazole alanine (TA) comprises 15% TRR in tomato fruit (K-CA 6.2.1/01; 1X study), residues of TA are only 0.004 mg/kg. For the other TDMs, tomato fruit residues are <10% TRR and ≤0.001 mg/kg (report K-CA 6.2.1/01; 1X study). In the apple metabolism study, higher levels of TDMs were discovered. However, penconazole was applied excessively compared to representative GAP. Correspondingly, the TDMs are not considered suitable for inclusion within Residue Definitions for Monitoring or Risk Assessment in Primary Crops or honey and bee products.

Recognising that residues of TDMs may be significant in rotational crops following treatment of penconazole (K-CA 6.2.1/01), the TDMs are considered applicable to penconazole's Residue Definition for Risk Assessment in Rotational Crops (relevant to representative uses on cucumbers). However, based on the findings in rotational metabolism and residue studies, no penconazole-specific residues are expected to be detectible in food (<0.01 mg/kg), and penconazole-specific residues in feed are not expected to meet the OECD (2018) trigger of 0.05 mg/kg.

The metabolism studies were all previously reviewed (**EFSA Scientific Report (2008) 175, 1-104**), except for KCA 6.2.1/09 [^{14}C]-Penconazole: Metabolism in Cucumber. The tomato metabolism studies were conducted at 4 × 40 g/ha (1X rate; reports 97JS25 and 97JS26) and 4 x 200 g/ha (5X rate; report 97JS25), which correspond to total seasonal rates of 160 g/ha and 800 g/ha, respectively. Representative uses have GAPs of up to 3 × 50 g/ha (total seasonal rate of 150 g/ha). Representative uses during the Peer Review (**EFSA Scientific Report (2008) 175, 1-104**) had GAPs of up to 4 × 50 g/ha (total seasonal rate of 200 g/ha). The tomato metabolism studies sampled fruit after 7 and 40 days PHI. Representative uses, and most authorised uses considered during the review of MRLs (**EFSA Journal 2017;15(6):4853**), have PHIs of ≤28 days.

During the review of existing MRLs under the Article 12 process, a concern was raised that crop metabolism studies might be under-dosed compared to the critical GAPs that had been selected at that time (**EFSA, Journal 2017;15(6):4853**). However, based on the assessment below, it may be concluded that the same metabolic profile was seen in tomato fruit when penconazole was applied to tomatoes at the 5X rate as when the 1X rate was applied.

Following the 1X rate, the sum amounts of II_{13} and II_{16} in tomato fruit pre-hydrolysis are approximately 69% TRR at 7 days PHI and 44% TRR at 40 days PHI (summarised in the table below). Similarly, following the 5X rate, the sum amounts of II_{13} and II_{16} in fruit pre-hydrolysis is 55% TRR at 40 d PHI. When acid hydrolysis was applied to tomato samples from the 1X rate tomato studies, II_{13} and II_{16} are substantively replaced by free CGA132465 (see table below). Although the 5X rate tomato metabolism study did not use a hydrolysis step, it is reasonable to conclude that free CGA132465 would have been the predominate residue found if a hydrolysis step had been used (at PHIs similar to 7 or 40 days).

Taking into consideration the similarity of GAPs, the Peer Review (**EFSA Scientific Report (2008) 175, 1-104**) and the 1X rate tomato studies, the metabolism studies are considered to support residue definitions for penconazole in plants (fruit and fruiting vegetables metabolism group) for the representative uses. Taking into consideration the similarity of metabolic profile across the 1X and 5X rate tomato studies, it is further proposed that the metabolism studies support GAPs that are more critical, such as those presented in the review of existing penconazole MRLs (**EFSA Journal 2017;15(6):4853**).

The residue definition for monitoring in plants is proposed to be parent penconazole, only. The residue definition for risk assessment in plants is proposed to be the sum of penconazole + CGA132465 + CGA190503 + CGA127841, and the conjugates of the metabolites, expressed as penconazole (fruit and fruiting vegetables, only). The residue definition for risk assessment in processed plant commodities (fruit and fruiting vegetables, only) is proposed to be the same as for unprocessed plant commodities.

Table 71: Summary of tomato residue level changes for selected analytes following hydrolysis

Selected analytes	%TRR in tomato fruit harvested at PHIs of 7 or 40 d PHI								
	Pre-hydrolysis					Post-hydrolysis			
	7 d		40 d			7 d		40 d	
	1X Rate				5X Rate	1X Rate			
	Ph.	Tri.	Ph.	Tri.	Tri.	Ph.	Tri.	Ph.	Tri.
Parent	15.0	18.6	6.1	11.8	6.6	15.1	19.0	7.2	12.6
CGA132465/CGA127841	0.4	n/a	0.1	n/a	n/a	61.6	n/a	63.0	n/a
CGA132465	n/a	0.8	n/a	0.8	0.8	n/a	66.9	n/a	55.2
CGA127841	n/a	ND	n/a	ND	ND	n/a	ND	n/a	ND
II_{13}	15.3	17.6	27.8	28.4	27.6	ND	ND	<0.1	0.3
Total II_{16}	58.2	46.0	14.8	17.0	27.0	0.3	ND	ND	0.1
II_{13} + total II_{16}	73.5	63.6	42.6	45.4	54.6	0.3	ND	<0.1	0.4
Mean II_{13} + total II_{16}	68.6		44.0			0.3		<0.3	

Ph.: Results from Phenyl-labelled tomato study 97JS26.
Tri.: Results from Triazole-labelled tomato study 97JS25.

In order to support residue trials that have only measured penconazole, a Conversion Factor (CF) approach has been taken making use of residue trials for which the full proposed $RD_{(RA)}$ has been analysed (penconazole and, after deconjugation, total CGA127841, CGA132465 and CGA190503). In order to support robust proposals, CFs were calculated using residue trials with representative crops and supplementary crops with residue data according to the $RD_{(RA)}$ (sweet/bell peppers and raspberries). All crops for which CFs were calculated are members of the fruit and fruiting vegetables metabolism group.

In line with guidance within the template for MRL Evaluations under "new" data requirements (Section 3.1.3; EFSA, 2015a https://ec.europa.eu/food/plant/pesticides/max_residue_levels/guidelines_en#council):

- CFs were calculated across each sampling intervals (PHIs) for which the RAC was sampled.
- Each CF was calculated by dividing total residues according to the proposed $RD_{(RA)}$ by the proposed $RD_{(Mo)}$, penconazole.
- CF proposals considered the overall evolution of the CF values at the different PHIs.

In line with advice on dealing with <LOQ results within EFSA, 2015a and Scholz, 2018 (European database of processing factors for pesticides. EFSA supporting publication 2018: EN-1510. 50 pp.), a CF was only calculated where a detectable residue of penconazole was found.

A CF was calculated per crop, per PHI, per trial, or as a combined value across crops per PHI, per trial. Subsequently, median CFs were calculated per PHI, and then summarised in the table below. Finally, in line with EFSA (2015a), it was assessed whether single CF values could be proposed to cover the applicable fruit and fruiting vegetables crop group.

Table 72: Median CF estimated at th**e different PHIs in the supervised residue trials**[a]

RAC	Statistic[a]	PHI[b] (days)									
		0	**1**	**3**	**5**	**6-7**	**10**	**13-14**	**21-22**	**27-28**	**21-28**
Pome fruits	CF	2.00	-	-	-	2.50	2.50	3.25	3.25	-	3.25
	n	8 (Mo: 0.02; 0.03 x5; 0.04 x2) (RA: 0.05; 0.06 x5; 0.07 x2)	-	-	-	6 (Mo: 0.01 x2; 0.02 x2; 0.03 x2) (RA: 0.04; 0.05 x3; 0.06 x2)	4 (Mo: 0.02 x3; 0.04) (RA: 0.05 x3; 0.07)	8 (Mo: 0.01 x4; 0.02; 0.03; 0.04 x2) (RA: 0.04 x4; 0.05; 0.06; 0.07; 0.08)	2 (Mo: 0.01; 0.02) (RA: 0.04; 0.05)	-	2 (Mo: 0.01; 0.02) (RA: 0.04; 0.05)
Grapes[c]	CF	1.50	-	1.68	-	2.25	-	3.00	4.00	3.50	4.00
	n	8 (Mo: 0.01; 0.03; 0.04; 0.06 x2; 0.07; 0.09; 0.25) (RA: 0.04; 0.06; 0.07; 0.09 x2; 0.10; 0.13; 0.29)	-	4 (Mo: 0.02; 0.04; 0.05; 0.09) (RA: 0.05; 0.07; 0.08; 0.13)	-	6 (Mo: 0.02 x2; 0.03 x3; 0.08) (RA: 0.05 x2; 0.06 x2; 0.08; 0.14)	-	7 (Mo: 0.01 x2; 0.02 x4; 0.03) (RA: 0.04 x2; 0.05 x2; 0.06 x2; 0.07)	3 (Mo: 0.01 x2; 0.02) (RA: 0.04; 0.05; 0.06)	2 (Mo: 0.01; 0.03) (RA: 0.05; 0.06)	5 (Mo: 0.01 x3; 0.02; 0.03) (RA: 0.04; 0.05 x2; 0.06 x2)
Cucumbers[d]	CF	2.00	2.50	2.50	4.00	-	-	-	-	-	-
	n	10 (Mo: 0.01; 0.02; 0.03 x5; 0.04; 0.05 x2) (RA: 0.04; 0.05; 0.06 x5; 0.07; 0.08 x2)	10 (Mo: 0.01 x2; 0.02 x6; 0.03 x2) (RA: 0.04 x2; 0.05 x6; 0.06 x2)	9 (Mo: 0.01 x4; 0.02 x4; 0.03) (RA: 0.04 x4; 0.05 x4; 0.06)	2 (Mo: 0.01 x2) (RA: 0.04 x2)	-	-	-	-	-	-
Sweet / bell peppers	CF	2.67	2.67	3.00	3.00	-	-	-	-	-	-
	n	4 (Mo: 0.02 x2; 0.03; 0.05) (RA: 0.06 x2; 0.07; 0.09)	4 (Mo: 0.01; 0.02; 0.03 x2) (RA: 0.05; 0.06; 0.07 x2)	5 (Mo: 0.01 x2; 0.02 x2; 0.04) (RA: 0.04; 0.05 x2; 0.06; 0.07)	1 (Mo: 0.02) (RA: 0.06)	-	-	-	-	-	-
Raspberries	CF	1.15	1.27	1.38	1.63	-	-	-	-	-	-
	n	2 (Mo: 0.2; 0.21) (RA: 0.23; 0.24)	2 (Mo: 0.1; 0.13) (RA: 0.13; 0.16)	4 (Mo: 0.02; 0.07; 0.09; 0.21) (RA: 0.05; 0.10; 0.12; 0.24)	2 (Mo: 0.04; 0.06) (RA: 0.07; 0.09)	-	-	-	-	-	-
Combined (all 5	CF	2.00	2.50	**2.50**	3.00	2.50	2.50	**3.00**	4.00	3.50	**4.00**
	n	32	16	22	5	12	4	15	5	2	7

crops above)											

(a): Median CFs calculated at the supported PHIs are underlined and in bold.
(b): 0 for samples collected just after the last application.
(c): Grape CFs were calculated for plots that had received either 2 or 3 applications.
(d): B.7.3.4 has been excluded since it uses a less-critical cucurbits (edible peel) GAP than B.7.3.3.
n: Number of CFs calculated at the respective PHI (i.e. the number of trials with detectible penconazole residues).

Based on the information within the table, CFs tend to increase moderately as PHIs increase, and median CFs are similar across crops for a given PHI. Correspondingly, CF proposals for calculating residues according to the proposed $RD_{(RA)}$ when only penconazole is measured have been based on the combined dataset. In summary, for when only penconazole is measured, CFs of 2.5, 3.0, and 4.0 are proposed for PHIs of 3 days, 14 days and 21-28 days, respectively.

Definition of the Residue in Livestock

The dietary burden triggering the submission of livestock metabolism studies is >0.004 mg/kg bw/d for the active substances falling under Regulation (EU) No 283/2013. Calculated dietary burden calculations for feed-related representative crops (apple, only) are below the trigger in Regulation (EU) No 283/2013 (>0.004 mg/kg bw/d) for ruminants, and zero for poultry, pigs and fish. Therefore, residue definitions for monitoring and risk assessment in animal commodities are not required.

All proposed residue definitions are summarised in the table below.

Table 73: Dietary Residue Definitions for Penconazole

Endpoint	EU agreed endpoint[(a)]	Proposed endpoint
Residue Definition for Monitoring in plants	Penconazole	Penconazole (sum of all constituent isomers) (limited to fruit crops only)[(b)]
Residue Definition for Risk Assessment in treated plants, and processed plant commodities	Penconazole + CGA132465 + CGA190503 + CGA127841 and the conjugates of the metabolites, expressed as penconazole	Sum of penconazole and free and conjugated CGA132465, CGA190503 and CGA127841, expressed as penconazole[(b)]
Residue Definition for Risk Assessment in rotational plants	Not required	Triazole Derivative Metabolites
Residue Definition for monitoring in animal commodities	Not required	Not required
Residue Definition for Risk Assessment in animal commodities	Not required	Not required

(a): Definitions from the Peer Review (EFSA, 2008; EC, 2010).
(b): This definition matches the definition in the review of existing MRLs (**EFSA Journal 2017;15(6):4853**). This needs to be confirmed after toxicological risk assessment.

2.7.4 Summary of residue trials in plants and identification of critical GAP

Four trials on apple and four trials on pear from both Northern and Southern Europe are presented, thus covering the minimum of 8 trials required per residue zone.

Table 74: Overview of the available residue trials data

Commodity	Residue region, Outdoor/ Indoor	Reviewed/ new	Individual trial results (mg/kg)	STMR (mg/kg) (d)	HR (mg/kg) (d)	MRL (mg/kg) (d-f)
			Enforcement[a] & Risk assessment[b]			
Pome fruit	NEU, outdoor	New	**GAP: 2 ´ 40 g a.s./ha, 10 d interval, 14 d PHI** Mo: 3 x <0.01, 2 x 0.01, 0.02, 0.03, 0.04 RA: 3 x <0.04, 2 x 0.04, 0.05, 0.06, 0.08	**Mo: 0.01** **RA: 0.04**	**Mo: 0.04** **RA: 0.08**	**Mo: 0.07**
	SEU, outdoor	New	**GAP: 2 ´ 40 g a.s./ha, 10 d interval, 14 d PHI** Mo: 5 x <0.01, 2 x 0.01, 0.04 RA: 3 x <0.04, 2 x 0.04, 2 x 0.05, 0.07	**Mo: 0.01** **RA: 0.04**	**Mo: 0.04** **RA: 0.07**	**Mo: 0.06**
	Combined[c]	New	**GAP: Identical in both zones** Mo: 8 x <0.01, 4 x 0.01, 0.02, 0.03, 2 x 0.04 RA: 6 x <0.04, 4 x 0.04, 3 x 0.05, 0.06, 0.07, 0.08	**Mo: <u>0.01</u>** **RA: <u>0.04</u>**	**Mo: <u>0.04</u>** **RA: <u>0.08</u>**	**Mo: <u>0.06</u>**

(a): The proposed residue definition for monitoring (Mo) is parent penconazole only.
(b): The proposed residue definition for risk assessment (RA) is penconazole + CGA132465 + CGA190503 + CGA127841 and the conjugates of the metabolites, expressed as penconazole.
(c): In accordance with the results of the U-Test (EFSA, 2015), the NEU and SEU datasets can be combined.
(d): Values selected for use in risk assessments have been underlined.
(e): Calculated using the OECD method (ENV/JM/MONO(2011)3); rounded value.
(f): Values presented according to (b) are presented to support the calculation of the TMDI.

Sixteen trials on grapes from Northern Europe and eight trials on grapes from Southern Europe are presented, thus covering the minimum of 8 trials required per residue zone.

Table 75: Overview of the available residue trials data

Commodity	Residue region, Outdoor/ Indoor	Reviewed/ new	Individual trial results (mg/kg)	STMR (mg/kg) (c)	HR (mg/kg) (c)	MRL (mg/kg) (c-e)
			Enforcement[a] & Risk assessment[b]			
Grape	NEU, outdoor[f]	New	**GAP: 2 × 30 g a.s./ha, 8 d interval, 28 d PHI** Mo: 8 x <0.01, 3 x 0.01, 2 x 0.02, 2 x 0.03 RA: **2 x <0.04**, 3 x <0.04, **2 x 0.04**, 2 x 0.04, 0.05, 0.06, **2 x 0.08**, 0.08, **0.12**	**Mo: 0.01** **RA: 0.04**	**Mo: 0.03** **RA: <u>0.12</u>**	**<u>Mo: 0.05</u>**
	SEU, outdoor	New	**GAP: 2 × 30 g a.s./ha, 8 d interval, 14d PHI** Mo: 2 x <0.01, 2 x 0.01, 3 x 0.02, 0.03 RA: 2 x <0.04, 0.04, 3 x 0.05, 2 x 0.06	**Mo: 0.015** **RA: <u>0.05</u>**	**Mo: 0.03** **RA: 0.06**	**Mo: 0.05**

(a): The proposed residue definition for monitoring (Mo) is parent penconazole only.
(b): The proposed residue definition for risk assessment (RA) is penconazole + CGA132465 + CGA190503 + CGA127841 and the conjugates of the metabolites, expressed as penconazole. The proposed Conversion Factors (CFs) from monitoring to risk assessment at 14- and 28-days PHI (3.0 and 4.0, respectively) were used with 7 NEU trials that only quantified penconazole (in **bold** for identification), and with TMDI calculations.
(c): Values selected for use in risk assessments have been underlined.
(d): Calculated using the OECD method (ENV/JM/MONO(2011)3); rounded value.
(e): Values presented according to (b) are presented to support the calculation of the TMDI.
(f): The value of 0.26 mg/kg penconazole (KCA 6.3.2/01) has been excluded as an outlier (please see text below).

Fourteen trials on cucumber and courgettes (3 applications) from Northern Europe and eight trials from Southern Europe are presented, thus covering the minimum of 8 and 4 trials required within the NEU and SEU, respectively.

Table 76: Overview of the available residue trials data

Commodity	Residue region, Outdoor/ Indoor	Reviewed/ new	Individual trial results (mg/kg)	STMR (mg/kg) (d)	HR (mg/kg) (d)	MRL (mg/kg) (d-f)
			Enforcement(a) & Risk assessment(b)			
cucumbers (3 applications)	NEU, outdoor	New	**GAP: 3 × 50 g a.s./ha, 8 d interval, 3 d PHI**	**Mo: 0.01 RA: 0.04**	**Mo: 0.03 RA: 0.075**	**Mo: 0.05**
			Mo: 7 x <0.01, 0.01, 5 x 0.02, 0.03 RA: **2 x <0.025**, 4 x <0.04, 2 x 0.04, 3 x 0.05, **2 x 0.05**, **0.075**			
	SEU, outdoor	New	**GAP: 3 × 50 g a.s./ha, 8 d interval, 3 d PHI**	**Mo: 0.01 RA: 0.04**	**Mo: 0.03 RA: 0.06**	**Mo: 0.05**
			Mo: 4 x <0.01, 2 x 0.01, 0.02, 0.03 RA: 4 x <0.04, 2 x 0.04, 0.05, 0.06			
	Combined(c)	New	**GAP: Identical in both zones**	**Mo: <u>0.01</u> RA: <u>0.04</u>**	**Mo: <u>0.03</u> RA: <u>0.075</u>**	**<u>Mo: 0.05</u>**
			Mo: 10 x <0.01, 4 x 0.01, 6 x 0.02, 2 x 0.03 RA: 2 x <0.025, 8 x <0.04, 4 x 0.04, 6 x 0.05, 0.06, 0.075			

(a): The proposed residue definition for monitoring (Mo) is parent penconazole only.
(b): The proposed residue definition for risk assessment (RA) is penconazole + CGA132465 + CGA190503 + CGA127841 and the conjugates of the metabolites, expressed as penconazole. The proposed conversion factor from monitoring to risk assessment at 3-day PHI is 2.50 and it was used with 5 NEU residue trials (in **bold** for identification), and MRLs.
(c): In accordance with the results of the U-Test (EFSA, 2015), the NEU and SEU datasets can be combined.
(d): Values selected for use in risk assessments have been underlined.
(e): Calculated using the OECD method (ENV/JM/MONO(2011)3); rounded value.
(f): Values presented according to (b) are presented to support the calculation of the TMDI.

Sixteen trials on cucumber and courgettes (1 application) from Northern Europe are presented, thus covering the minimum of 8 trials required within the NEU.

Table 77: Overview of the available residue trials data

Commodity	Residue region, Outdoor/ Indoor	Reviewed/ new	Individual trial results (mg/kg)	STMR (mg/kg)	HR (mg/kg)	MRL (mg/kg) (c-e)
			Enforcement(a) & Risk assessment(b)			
Cucumber	NEU, outdoor	New	**GAP: 1 × 35 g a.s./ha, 3 d PHI** Mo: 7 x <0.01, 6 x <0.01, 0.01, 0.01, 0.02 RA: **6 x <0.025**, **0.025**, 7 x <0.04, 2 x 0.04	**Mo: 0.01** **RA: 0.04**	**Mo: 0.02** **RA: 0.05**	**Mo: 0.02**

(a): The proposed residue definition for monitoring (Mo) is parent penconazole only.
(b): The proposed residue definition for risk assessment (RA) is penconazole + CGA132465 + CGA190503 + CGA127841 and the conjugates of the metabolites, expressed as penconazole. The conversion factor from monitoring to risk assessment at 3-day PHI is 2.50 and it was used with 7 residue trials (in **bold** for identification), and the MRL.
(c): Calculated using the OECD method (ENV/JM/MONO(2011)3); rounded value.
(d): Values presented according to (b) are presented to support the calculation of the TMDI (Volume 1, 2.7.9.).
(e): The residues associated with this GAP are less critical than those obtained in cucumber with three applications and are therefore not included in the dietary risk assessments.

2.7.5 Summary of feeding studies in poultry, ruminants, pigs and fish

Penconazole is proposed for use on cucumbers, grapes and pome fruit. Apple wet pomace might be fed to livestock. The median and maximum dietary burdens have been calculated for the different groups of livestock using the methodology described by the OECD (OECD, 2013) based on residues in apple.

On the basis of the OECD feeding tables only apple wet pomace is considered to form part of livestock diets in the EU. Since apple wet pomace may be bulked/blended prior to consumption by livestock and applications to apple trees are made pre-harvest, the STMR is the appropriate statistic for both median and maximum dietary burden calculations.

Table 78: Penconazole residue values used for calculation of livestock dietary burdens based on the residue definition for risk assessment (a)

Commodity	Maximum dietary burden		Median dietary burden	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Apple pomace wet (By-products group)	0.128	STMR for risk assessment (0.04 mg/kg x measured PF (3.19)	0.128	STMR for risk assessment (0.04 mg/kg) x measured PF (3.19)

(a): The proposed residue definition for monitoring is parent penconazole only. The proposed residue definition for risk assessment is penconazole + CGA132465 + CGA190503 + CGA127841 and the conjugates of the metabolites, expressed as penconazole.

All dietary burden calculations were performed using the tool published on the Guidelines - Maximum Residue levels page of the Europa.eu website[5] in 2017 (pesticides_mrl_guidelines_animal_model_2017.xls).

Poultry
The representative uses are not considered to be poultry feed items in the EU. Therefore, poultry studies are not required. Nevertheless, a feeding study was subitted by applicant for completeness. RMS did not evaluate this study.

[5] https://ec.europa.eu/food/plant/pesticides/max_residue_levels/guidelines_en#council

Ruminants

Calculated dietary burdens relating to the representative uses do not trigger the need for mammalian livestock studies. Nevertheless, a feeding study was submitted by applicant for completeness. RMS did not evaluate this study.

Pigs

Since the commodities that may be derived from the representative crops are not considered relevant to pigs feeding, metabolism and feeding studies in pigs are not required.

Fish

Since the commodities that may be derived from the representative crops are not considered relevant to fish feeding, metabolism and feeding studies in fish are not required.

2.7.6 Summary of effects of processing

Residues of penconazole, CGA132465, CGA190503 and CGA127841 in Raw Agricultural Commodities are each ≥0.01 mg/kg. Correspondingly, the nature of the residue for penconazole and its dietary metabolites (CGA132465, CGA190503 and CGA127841) have been determined under conditions representative of pasteurisation, baking/brewing/boiling and sterilisation.

Penconazole and its dietary metabolites (CGA132465, CGA190503 and CGA127841) were hydrolytically stable under conditions representative of pasteurisation, baking/brewing/boiling and sterilisation.

Guidance on defining how to handle <LOQ findings in processing studies (Scholz, 2018. European database of processing factors for pesticides. EFSA supporting publication 2018: EN-1510. 50 pp) was taken into consideration when calculating Processing Factors within studies Brown, 2019 and Brown 2019a, and when deriving median Processing Factors. Individual Processing Factors for studies Brown, 2019 and Brown 2019a, were defined as being "less than" a numerical value if all the corresponding analytes quantified in the processed commodity were <LOQ. Similarly, when calculating median Processing Factors for grape and apple commodities, they were defined as being "less than" a numerical value if all the corresponding individual Processing Factors had been defined as being "less than".

An overview of available Processing Factors for the proposed Residue Definition for Monitoring in primary crops (penconazole, only) and for total residues according to the proposed Residue Definition for Risk Assessment in primary crops[6] for grape and apple commodities is presented in the tables below.

Table 79: Summary of Processing Factors for the proposed Residue Definition for Monitoring in primary crops (penconazole, only) in grape commodities

Crop	Commodity	Study	Review status	Processing Factor	
				Value	Median
Grape	Must	***Anderson and Mason, 2007*** (CGA71818/4786)	Acceptable	1.22	0.59
				0.40	
		Brown (2019) (VV-733683)	Acceptable	0.71	
				0.47	
	Juice	***Brown (2019)*** (VV-733683)	Acceptable	< 0.27	< 0.27
				< 0.29	
				< 0.13	
	Wine	***Anderson and Mason, 2007*** (CGA71818/4786)	Acceptable	0.19	0.23
				< 0.27	
		Brown (2019) (VV-733683)	Acceptable	< 0.29	
				< 0.13	

[6] Sum of penconazole and free and conjugated CGA132465, CGA190503 and CGA127841, expressed as penconazole.

Crop	Commodity	Study	Review status	Processing Factor	
				Value	Median
	Raisins	***Brown (2019)*** (VV-733683)	Acceptable	3.20 1.71 2.29	2.29
	Dry pomace	***Anderson and Mason, 2007*** (CGA71818/4786)	Acceptable	11 8.36	8.66
		Brown (2019) (VV-733683)	Acceptable	8.95 5.11	
	Wet pomace	***Anderson and Mason, 2007*** (CGA71818/4786)	Acceptable	4.11 2.40	3.72
		Brown (2019) (VV-733683)	Acceptable	4.29 3.32	
	Seed	***Brown (2019)*** (VV-733683)	Acceptable	2.93 16.29 4.84	4.84
	Oil	***Brown (2019)*** (VV-733683)	Acceptable	8.00 39.14 11.03	11.03

Table 80: Summary of Processing Factors for penconazole in apple commodities

Crop	Commodity	Study	EU review status	Processing Factor	
				Value	Median
Apple	Juice	***Boxwell, 2007*** (CGA71818/4761)	Acceptable	< 0.07	< 0.19
		Brown (2019a) (VV-733255)	Acceptable	< 0.19 < 0.33	
	Sauce	***Boxwell, 2007*** (CGA71818/4761)	Acceptable	0.17	< 0.19
		Brown (2019a) (VV-733255)	Acceptable	< 0.19 < 0.33	
	Canned	***Brown (2019a)*** (VV-733255)	Acceptable	< 0.19 < 0.33	< 0.26
	Dried	***Brown (2019a)*** (VV-733255)	Acceptable	3.2 6.0	4.6
	Dry pomace	***Boxwell, 2007*** (CGA71818/4761)	Acceptable	8.52	9.0
		Brown (2019a) (VV-733255)	Acceptable	12.4 9.0	
	Wet pomace	***Boxwell, 2007*** (CGA71818/4761)	Acceptable	2.32	4.0
		Brown (2019a) (VV-733255)	Acceptable	5.4 4.0	

Table 81: Summary of Processing Factors for the proposed Residue Definition for Risk Assessment in primary crops[7] in grape commodities

Crop	Commodity	Study	Review status	Processing Factor	
				Value	Median
Grape	Must	***Brown (2019)*** (VV-733683)	Acceptable	0.51	0.51
				0.69	
				0.43	
	Juice	***Brown (2019)*** (VV-733683)	Acceptable	< 0.37	0.46
				< 0.50	
				0.46	
	Wine	***Brown (2019)*** (VV-733683)	Acceptable	0.55	0.55
				0.63	
				0.38	
	Raisins	***Brown (2019)*** (VV-733683)	Acceptable	4.32	2.54
				2.38	
				2.54	
	Dry pomace	***Brown (2019)*** (VV-733683)	Acceptable	6.56	6.56
				7.38	
				4.27	
	Wet pomace	***Brown (2019)*** (VV-733683)	Acceptable	1.69	2.29
				3.08	
				2.29	
	Seed	***Brown (2019)*** (VV-733683)	Acceptable	1.56	2.34
				9.50	
				2.34	
	Oil	***Brown (2019)*** (VV-733683)	Acceptable	3.59	4.72
				19.38	
				4.72	

[7] Sum of penconazole and free and conjugated CGA132465, CGA190503 and CGA127841, expressed as penconazole.

Table 82: Summary of Processing Factors for the proposed Residue Definition for Risk Assessment in primary crops[8] in apple commodities

Crop	Commodity	Study	Review status	Processing Factor	
				Value	Median
Apple	Juice	***Brown (2019a)*** (VV-733255)	Acceptable	< 0.48	< 0.58
				< 0.67	
	Sauce	***Brown (2019a)*** (VV-733255)	Acceptable	< 0.48	< 0.58
				< 0.67	
	Canned	***Brown (2019a)*** (VV-733255)	Acceptable	< 0.48	< 0.58
				< 0.67	
	Dried	***Brown (2019a)*** (VV-733255)	Acceptable	2.88	3.36
				3.83	
	Dry pomace	***Brown (2019a)*** (VV-733255)	Acceptable	10.88	8.11
				5.33	
	Wet pomace	***Brown (2019a)*** (VV-733255)	Acceptable	3.88	3.19

2.7.7 Summary of residues in rotational crops

The principal metabolic transformations of penconazole in all rotated crop commodities occurred via oxidation of the parent molecule to produce CGA132465, CGA127841 and CGA179944 and by conjugation of CGA71019 to produce CGA13013, CGA142856 and CGA205369 ([1,2,4]-triazol-1-yl-lactic acid).

The metabolism of penconazole was measured in two confined rotational crop studies conducted separately with [Triazole-(U)^{14}C]- and [Phenyl-(U)^{14}C]-penconazole. In both studies, single spray application was made to soil at a nominal application rate of 240 g a.s./ha. The radiochemical was formulated as an emulsifiable concentrate (EC) containing 100 g ai/L. Treatment plots were maintained outdoors.

In the [Triazole-(U)^{14}C]-penconazole study, the greatest uptake of total radioactive residues was found in cereal commodities. Total radioactive residues in spring wheat were: ≤0.231 mg/kg (whole tops), ≤1.39 mg/kg (fodder) and ≤3.28 mg/kg (grain). Residues in winter wheat were markedly lower, 0.171, 0.084, 0.337 and 0.418 mg/kg for whole tops (25% maturity), whole tops (50% maturity), fodder and grain, respectively. Relatively low uptakes were observed in lettuce (≤0.072 mg/kg) and radish tops and root (≤0.084 mg/kg). There was no clear correlation between residue levels and planting interval.

Solvent extractability with methanol was within the range 61-99% TRR for all commodities. A further 1-18% was released by microwave extraction of the PES. Unextracted residues accounted for <16% TRR in lettuce, ≤7.9% TRR in radish (roots and tops), <11% TRR in wheat whole tops, <17% TRR in wheat fodder and <28% TRR in wheat grain.

Parent penconazole was identified, with the exception of 179 DAT wheat (3.3% TRR, 0.011 mg/kg), only in small amounts (<0.01 mg/kg) and was predominantly found at the first planting interval. CGA131013, CGA205369 and CGA142856 were the major metabolites identified. CGA131013 was a major metabolite in wheat, lettuce and radishes with highest residues in grain (highest in 126 DAT grain: 57.4% TRR, 1.89 mg/kg). CGA142856 was a minor residue in lettuce and radishes (≤1.7% TRR, 0.001 mg/kg). Residues were more significant in wheat commodities with the highest residues observed in wheat grain (highest in 126 DAT grain: 26.4% TRR, 0.868 mg/kg). CGA205369 ([1,2,4]-triazol-1-yl-lactic acid) was a major metabolite in lettuce, wheat tops and wheat fodder and tops and a minor (<0.01 mg/kg) metabolite in radishes and wheat grain. Highest residues were observed in 126 DAT spring wheat fodder (38.3% TRR, 0.532 mg/kg). CGA71019 was a minor metabolite in wheat and radishes and not detected in lettuce. The highest residue was observed in 126 DAT spring wheat fodder (4.1% TRR, 0.057 mg/kg). No other metabolites were present in significant amounts.

Non-extractable radioactivity, once characterised, was found to be made up of CGA13013, CGA142856 and CGA71019 and several polar components.

In the [Phenyl-(U)^{14}C]-penconazole study, the greatest uptake of radioactive residues was found in cereal commodities. Total radioactive residues in spring wheat were: ≤0.035 mg/kg (whole tops), ≤0.286 mg/kg (fodder) and ≤0.132 mg/kg (grain). Residues in winter wheat were markedly lower, 0.027, 0.012, 0.077 and 0.005 mg/kg for

[8] Sum of penconazole and free and conjugated CGA132465, CGA190503 and CGA127841, expressed as penconazole.

whole tops (fall cutting), whole tops (50% maturity), fodder and grain, respectively. Relatively low uptakes were observed in lettuce (≤0.071 mg/kg) and radish tops and root (≤0.032 mg/kg).

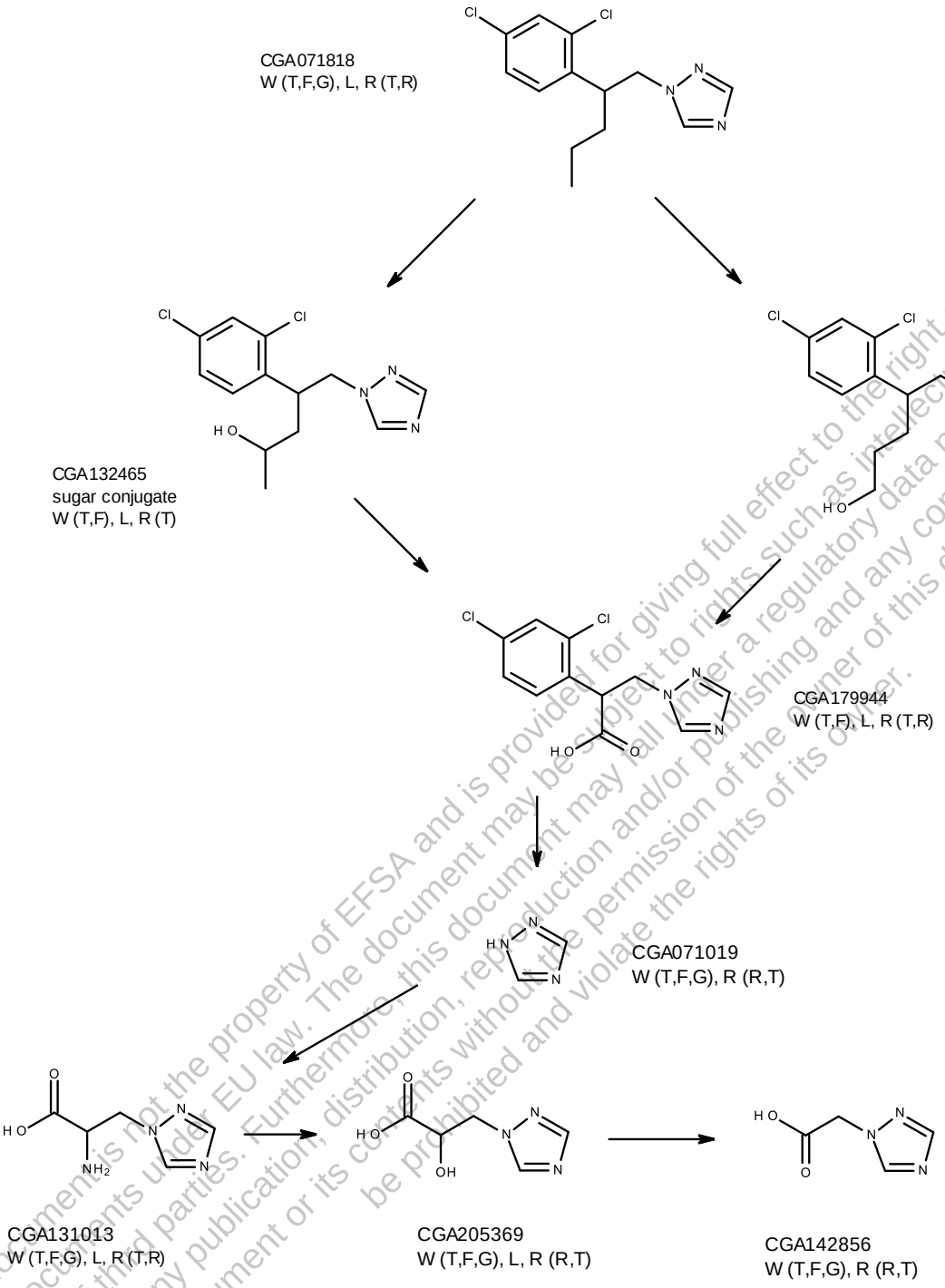
In lettuce and radish, residue levels decreased at longer planting intervals; however, for wheat, there was no clear correlation between residue levels and planting interval.

Solvent extractability with methanol within the range 53-95% TRR was achieved for all commodities, apart from wheat grain; where low extractability of 22-47% was obtained. A further 11-20% was released by microwave extraction of the PES of wheat grain samples. Unextracted residues accounted for 2.8% TRR in lettuce, ≤10% TRR in radish (roots and tops), ≤33% TRR in wheat whole tops, <36% TRR in wheat fodder and <64% TRR in wheat grain.

None of the characterised metabolite fractions exceeded 0.05 mg/kg. Parent penconazole was identified only in trace amounts (≤0.004 mg/kg) and was predominantly found at the first planting interval. Conjugates of CGA132465 and CGA127841 co-eluted and were the major identified metabolites in nearly all commodities. They were not detected in wheat grain or radish roots and the highest residue observed was in 126 DAT wheat fodder (16.8% TRR, 0.048 mg/kg). The 32 DAT wheat fodder extract was hydrolysed with aqueous HCl and the resulting ratio of unconjugated CGA132465 to CGA127841 was determined to be approximately 6:1. CGA179944 was a major metabolite in all plant parts, with the exception of grains, where it was not present. The highest residue observed was in 126 DAT wheat fodder (6.6% TRR, 0.019 mg/kg). No other metabolites were present in significant amounts.

In summary, the qualitative nature of the residues in rotated crops is similar to and consistent with the pathways found in the representative primary crops. A proposed overall metabolic pathway for penconazole in confined rotational crops is presented in the Figure below.

Proposed overall metabolic pathway for penconazole in confined rotational crops



W = wheat (T = tops, F = fodder, G = grain), L = lettuce, R = radish (T = tops, R = roots)

In conclusion, Tier II rotational field trials with penconazole are not required by penconazole-specific residues in order to support the GAPs described in **Volume 1**.

Nevertheless, Tier II rotational field trials quantifying penconazole, 1,2,4-triazole (CGA071019), triazole alanine (CGA131013), triazole acetic acid (CGA142856) and triazole lactic acid (CGA205369) have been previously performed and are presented as additional information in this submission.

In summary, penconazole was applied, as A6209G, as one application to soil with lightly sown grass at an over-dosed TSR of 200 g a.s./ha (1.3X) in the NEU (A7402T_10154) and SEU (A7402T_10149). Residues of penconazole were ≤0.01 mg/kg, or <0.008 mg/kg after scaling to the TSR of 158 g/ha/year. Based on findings scaled

to the TSR, no detectible penconazole-specific residues in food are expected. In conclusion, the results of these Tier II rotational field trials are considered to align with the results of the Tier I rotational studies, and the potential relevance of penconazole-specific residues in rotational crops can be considered negligible.

2.7.8 Summary of other studies

Effect on the residue level in pollen and bee products

The data requirement objective of these studies is to determine the residue in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom.

According to available guidelines (Commission Services, 2018), all representative crops within GAP are considered to possess melliferous capacity. In accordance with GAP, penconazole may be applied before or during flowering. Thus, honey residue trials are appropriate to generate residue data for dietary risk assessment.

Some criteria for the study are fulfilled, but there are several limitations according to the guideline. The trial is conducted in rape oil seed, it can be regarded as a worst-case culture.

Austrian site: The dose of 4 x 50 mg a.i./ ha mirrors the GAP. The bee hive was placed in the tunnel the day before the third spraying and the last spraying was before the end of flowering. Honey was collected at the end of flowering. No residues of penconazole, or CGA127841, CGA132465 and CGA190503 (after deconjugation), at or above the limit of quantification (LOQ, 0.01 mg/kg) were found in the untreated or treated honey samples.

Italian site: The dose of the test item 2 x 50 mg a.i./ ha was applied at the BBCH stage 64 and after end of flowering. It thus does not mirror the GAP. There was also very little honey to analyse from the treated beehive and the origin of the honey was not well documented. The analytical results from the Italian site cannot be relied on.

There are not enough data in honey to derive an MRL for penconazole for honey. A minimum of 4 trials are required.

2.7.9 Estimation of the potential and actual exposure through diet and other sources

In accordance with the EFSA Scientific Report for Penconazole (**EFSA Scientific Report (2008) 175, 1-104**), a 6-fold Conversion Factor (CF) may be used to convert between measurements of parent in crop commodities to the full proposed Residue Definition for Risk Assessment (penconazole + CGA132465 + CGA190503 + CGA127841 and the conjugates of the metabolites, expressed as penconazole). Residue data for each of CGA132465, CGA190503 and CGA127841 (total, after deconjugation) have been prepared and presented, and were used where applicable. In order to support robust proposals, novel CFs were calculated using residue trials with representative crops and supplementary crops with residue data according to the $RD_{(RA)}$ (sweet/bell peppers and raspberries). All crops for which CFs were calculated are members of the fruit and fruiting vegetables metabolism group. In summary, for when only penconazole is measured, CFs of 2.5, 3.0, and 4.0 are proposed for PHIs of 3 days, 14 days and 21-28 days, respectively.

Chronic and acute exposure calculations for penconazole were performed using revision 3.1 of the EFSA Pesticide Residues Intake Model (PRIMo[9]). Although apples are EU feed items within the OECD feeding tables, livestock commodities are excluded from the risk assessment. This exclusion is conducted because representative uses lead to calculated livestock dietary burdens of <0.004 mg/kg bw/d.

Acceptable Daily Intake (ADI) and Dietary Exposure Calculation

The current ADI for penconazole is 0.03 mg/kg bw/day (**EFSA Scientific Report (2008) 175, 1-104**. Following a review of the available toxicological data for penconazole and penconazole's metabolites, RMS proposes an ADI of 0.015 mg/kg bw/d.

Theoretical Maximum Daily Intake (TMDI) and International Estimated Daily Intake (IEDI) are calculated based on the proposed uses according to this document. The residue levels used for each commodity is based on either the calculated MRL (× CF) for TMDI calculations, or the STMR (using a CF for subsets of residue trials only measuring penconazole[10]) for IEDI calculations. In the table below, the input values for the chronic exposure as entered in the EFSA PRIMo model are presented.

The TMDI and IEDI calculations are presented below. According to the TMDI calculation, the survey population with the highest calculated exposure is the NL Toddler at 20% of ADI (the highest contributing commodity is apples at 13%). The highest chronic exposure according to the IEDI is 5% of ADI for the NL toddler survey population (the highest contributing commodity is apples at 3%).

The results indicate that there is no unacceptable chronic risk to human health from the consumption of commodities treated with penconazole according to the uses considered.

[9] EFSA (European Food Safety Authority), 2017. Guidance document on the use of the EFSA Pesticide Residue Intake Model (EFSA PRIMo revision 3). EFSA Journal 2018;16(1):5147, 45 pp. doi:10.2903/j.efsa.2018.5147

[10] 7/15 NEU grape trials, and 5/14 NEU trials supporting cucumbers with 3 applications (more critical than the 1-application cucumber GAP).

Table 83: Input Values for Penconazole Chronic Risk Assessment

Commodity	Chronic risk assessment		
	Input value (mg/kg)		Comment
	MRL	STMR	
Penconazole + CGA132465 + CGA190503 + CGA127841 and the conjugates of the metabolites, expressed as penconazole			
Apples	0.06 × CF (3.0)	0.04	
Pears			
Quinces			
Medlar			
Loquats/Japanese medlars			
Other pome fruit			
Table grapes	0.05 × CF (4.0)	0.05	
Wine grapes	0.05 × CF (4.0) × YF (0.7)	0.05 × YF (0.7)	
Cucumbers	0.05 × CF (2.50)	0.04	
Gherkins			
Courgettes			
Other cucurbits – edible peel			
Honey[a]	<0.04	<0.04	

(a): Due to adverse weather conditions in 2019, only 2 of the 4 initiated honey residue trials were able to generate residue data at the applicable GAP and as such, 2 additional trials are underway in 2020.
CF: Conversion Factor derived from available residue trials
YF: In line with the conclusions of EFSA (EFSA Journal 2016;14(7):4553), a Yield Factor (YF) of 0.70 has been applied to the chronic risk assessment to account for 100 kg of wine grapes being used to produced 70 kg of wine.

TMDI calculation :

European Food Safety Authority
EFSA PRIMo revision 3.1; 2019/03/19

Penconazole

LOQs (mg/kg) range from:		to:	
Toxicological reference values			
ADI (mg/kg bw/day):	0,015	ARfD (mg/kg bw):	0,5
Source of ADI:	M-CA 5	Source of ARfD:	M-CA 5
Year of evaluation:	2019	Year of evaluation:	2019

Comments: TMDI based on calculated MRLs.

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : ---

Calculated exposure (% of ADI)	MS Diet	Expsoure (µg/kg bw per day)	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities
20%	NL toddler	3,06	13%	Apples	5%	Pears
18%	DE child	2,73	15%	Apples	2%	Table grapes
10%	NL child	1,51	7%	Apples	1%	Pears
5%	DK child	0,78	3%	Apples	1%	Cucumbers
5%	DE women 14-50 yr	0,70	3%	Apples	0,8%	Wine grapes
5%	FR toddler 2 3 yr	0,69	4%	Apples	0,4%	Pears
4%	PT general	0,66	2%	Wine grapes	1%	Apples
4%	DE general	0,66	3%	Apples	0,8%	Wine grapes
4%	RO general	0,58	2%	Apples	2%	Wine grapes
4%	GEMS/Food G11	0,55	2%	Apples	1,0%	Wine grapes

IEDI calculation:

EFSA PRIMo revision 3.1; 2019/03/19

Penconazole			
LOQs (mg/kg) range from:		to:	
Toxicological reference values			
ADI (mg/kg bw/day):	0,015	ARfD (mg/kg bw):	0,5
Source of ADI:	M-CA 5	Source of ARfD:	M-CA 5
Year of evaluation:	2019	Year of evaluation:	2019

Comments:

Refined calculation mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : ---

	Calculated exposure (% of ADI)	MS Diet	Exposure (µg/kg bw per day)	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities
	5%	NL toddler	0,69	3%	Apples	1%	Pears
	4%	DE child	0,63	3%	Apples	0,5%	Table grapes
	2%	NL child	0,34	2%	Apples	0,3%	Table grapes
	1%	DK child	0,19	0,6%	Apples	0,4%	Cucumbers
	1%	DE women 14-50 yr	0,17	0,7%	Apples	0,2%	Wine grapes
	1%	FR toddler 2 3 yr	0,16	0,8%	Apples	0,1%	Pears
	1%	PT general	0,16	0,6%	Wine grapes	0,3%	Apples
on)	1%	DE general	0,16	0,6%	Apples	0,2%	Wine grapes

Acute Reference Dose (ARfD) and Dietary Exposure Calculation

The ARfD for penconazole is 0.5 mg/kg bw according to EFSA Scientific Report for Penconazole (**EFSA Scientific Report (2008) 175, 1-104**). Following a review of the available toxicological data for penconazole and penconazole's metabolites, the ARfD is proposed to remain as 0.5 mg/kg bw.

International estimated short-term intake (IESTI) values are calculated based on the proposed uses according to this document. The residue levels used for each commodity is based on either the HR or STMR depending on the commodity in question (×CF for subsets of residue trials only measuring penconazole[11]). In the table below, the input values for the acute exposure as entered in the EFSA PRIMo model are presented.

The results of the IESTI calculation for penconazole are shown below. The highest IESTI for the consumption of Raw Agricultural Commodities is for pears by children, representing 2% of ARfD. The highest IESTI for the consumption of Processed Commodities is for 'Courgettes / boiled', by children, representing 0.5% of ARfD.

The results indicate that there is no unacceptable acute risk to human health from the consumption of commodities treated with penconazole according to the uses considered.

Table 84: Input Values for Penconazole Acute Risk Assessment

Commodity	Acute risk assessment		
	Input value (mg/kg)		Comment
	STMR	HR	
Penconazole + CGA132465 + CGA190503 + CGA127841 and the conjugates of the metabolites, expressed as penconazole			
Apples	*Not applicable*	0.08	
Pears			
Quinces			
Medlar			

[11] 7/15 NEU grape trials, and 5/14 NEU trials supporting cucumbers with 3 applications (more critical than the 1-application cucumber GAP).

Loquats/Japanese medlars			
Other pome fruit			
Apple juice	0.04 × PF (0.6)	*Not applicable*	
Pear juice	0.04 × PF (0.6)		
Quinces / jam[a]	0.04		
Table grapes	*Not applicable*	0.03 × CF (4.0)	
Wine grapes		Children: 0.03 × CF (4.0) × YF (0.75)	
		Adults: 0.03 × CF (4.0) × YF (0.70)	
Table grapes / raisins		0.03 × CF (4.0) × PF (2.54)	
Wine grapes / wine		0.03 × CF (4.0) × PF (0.55)	
Wine grapes / juice	0.05 × PF (0.46)	*Not applicable*	
Cucumbers	*Not applicable*	0.03 × CF (2.50)	
Gherkins			
Courgettes			
Other cucurbits – edible peel			
Gherkins / pickled		0.03 × CF (2.50) × 1 (PF)	
Courgettes / boiled		0.03 × CF (2.50) × 1 (PF)	
Honey[b]	-	<0.04	

(a): No Processing Factor (PF) is applicable to quinces jam because pome fruit jam is not a required processing step according to OECD (2008) guidance, and in addition, residues and exposures would not trigger investigating jamming of quinces (acute exposures from quinces are less <10% ARfD, and contributions from quinces to the TMDI are <10% ADI).
(b): Due to adverse weather conditions in 2019, only 2 of the 4 initiated honey residue trials were able to generate residue data at the applicable GAP and as such, 2 additional trials are underway in 2020.
CF: Conversion Factor derived from available residue trials (CF = 2.50 or 4.0).
PF: Processing Factor
YF: In line with the conclusions of EFSA (EFSA Journal 2012;10(6):2769), Yield Factors (YF) of 0.70 and 0.75 have been applied to acute risk assessments to account for 100 kg of grapes being used to produce 70 kg of wine (adult exposure assessment) or 75 kg of juice (child exposure assessment), respectively.

IESTI calculation:

Show results for all crops

Unprocessed commodities

Results for children No. of commodities for which ARfD/ADI is exceeded (IESTI): ---				**Results for adults** No. of commodities for which ARfD/ADI is exceeded (IESTI): ---			
IESTI				**IESTI**			
Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
2%	Pears	0 / 0,08	11	0,8%	Table grapes	0 / 0,12	4,1
2%	Table grapes	0 / 0,12	8,8	0,5%	Pears	0 / 0,08	2,4
2%	Apples	0 / 0,08	8,6	0,4%	Apples	0 / 0,08	2,2
1,0%	Cucumbers	0 / 0,08	4,9	0,4%	Cucumbers	0 / 0,08	2,1
0,7%	Courgettes	0 / 0,08	3,5	0,4%	Wine grapes	0 / 0,08	2,0
0,4%	Quinces	0 / 0,08	2,0	0,3%	Courgettes	0 / 0,08	1,7
0,2%	Medlar	0 / 0,08	1,1	0,2%	Quinces	0 / 0,08	1,2
0,2%	Wine grapes	0 / 0,09	0,84	0,1%	Medlar	0 / 0,08	0,55
0,04 %	Gherkins	0 / 0,08	0,21	0,09 %	Gherkins	0 / 0,08	0,45
0,04 %	Honey and other	0 / 0,05	0,18	0,01 %	Honey and other	0 / 0,05	0,07
Expand/collapse list							
Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)							

Processed commodities

Results for children No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---				**Results for adults** No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---			
IESTI				**IESTI**			
Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
0,5%	Courgettes / boiled	0 / 0,08	2,7	0,343%	Courgettes / boiled	0 / 0,08	1,7
0,3%	Gherkins / pickled	0 / 0,08	1,7	0,07 %	Table grapes / raisins	0 / 0,27	0,34
0,1%	Wine grapes / juice	0 / 0,01	0,59	0,06 %	Wine grapes / juice	0 / 0,01	0,28
0,1%	Apples / juice	0 / 0,01	0,41	0,05 %	Wine grapes / wine	0 / 0,03	0,26
0,0%	Pears / juice	0 / 0,01	0,25	0,05 %	Apples / juice	0 / 0,01	0,25
0,0%	Quinces / jam	0 / 0,04	0,12	0,01 %	Quinces / jam	0 / 0,04	0,05

2.7.10 Proposed MRLs and compliance with existing MRLs

EU MRLs for penconazole are currently detailed in the **Regulation (EC) No 2019/89**.

The data presented in this document demonstrate that the proposed representative use of penconazole does not lead to an exceedance of the recommended MRLs for pome fruits, grapes and cucumbers (or cucurbits with edible peel), or those for products of animal origin. Whilst residues in raspberries exceed the existing MRL for that crop, new MRLs for raspberries (and blackberries by extrapolation) have been proposed to Germany separately to penconazole's renewal process.

EU MRLs for the commodities relevant to the representative crop use of penconazole are detailed in the table below. The applicant has provided novel studies with regard to residues in plants. The calculated MRLs presented by the applicant based on these novel studies are lower compared with the current EU MRLs.

Table 85: Current and proposed EU MRLs for penconazole for representative crops

Code	Commodity	Current EU MRL[(a-b)] (mg/kg)	Proposed EU MRL[(c)] (mg/kg)
0130000	Pome fruits (excluding Loquats/Japanese medlars)	0.15	0.06
0130050	Loquats/Japanese medlars	0.07	
0151000	Grapes	0.5	0.05
0232010	Cucumbers	0.06	0.05[d]
			0.02[e]
1000000	Products of animal origin – terrestrial animals	0.01*	0.01[f]
1040000	Honey and other apiculture products	0.05*	No MRL proposal
1100000	Fish, fish products and any other marine and freshwater food product	None established	None required[(g)]
1200000	Products or part of products exclusively used for animal feed production	None established	None required[(h)]

(a): The current and proposed residue definition for monitoring is parent penconazole only.
(b): Regulation (EU) 2019/89.
(c): Calculations based on representative uses; rounded OECD values presented.
(d): Results of the calculation for the 3-application cucumber GAP.
(e): Results of the calculation for the 1-application cucumber GAP.
(f): The MRLs are proposed, based on negligible livestock dietary burdens, to be at the LOQ.
(g): Penconazole is not applied to crops within the fruit and fruiting vegetables metabolism group considered to form components of fish feed (B.7.2.5; **EFSA Journal 2017;15(6):4853**).
(h): Penconazole is not applied to crops within the fruit and fruiting vegetables metabolism group that provide commodities that are considered to be exclusively fed to animals in the EU.
*: These MRLs are currently set at respective LOQs.

The QuEChERS method is proposed for the monitoring of penconazole in crops with a limit of analytical determination of 0.01 mg/kg (see reports S14-02175 and 20140165). The QuEChERS method is also proposed for the monitoring of penconazole in animal commodities with a limit of analytical determination of 0.01 mg/kg (see reports 20180148 and MS73PS).

2.7.11 Proposed import tolerances and compliance with existing import tolerances

Not applicable. The crop residue data lead to calculated, rounded OECD MRLs that do not exceed MRLs within Regulation

2.8 FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1 Summary of fate and behaviour in soil

Aerobic laboratory studies

Data on the route and rate of degradation of penconazole in soils were previously submitted and evaluated in context of the first EU review of penconazole (2007). The route of aerobic soil degradation was investigated in seven studies (Völkl, 2002, Glänzel, 1999, Knoch, 1993, Abildt, 1989, 1989a and 1989b and Keller, 1982) in six different soils (pH 7.0-7.5, OC 1.4 – 5.8) incubated at 15-25 °C with ^{14}C-penconazole labelled at either the triazole-ring or the phenyl ring. In these studies, the major metabolite formed by microbial degradation was CGA71019 (1,2,4-triazole), a metabolite common to many azole active substances. Another major metabolite occurring > 10% AR was CGA179944. Following the previous EU evaluation, it was discovered that the penconazole metabolite CGA179944 is a common metabolite with a metabolite of tetraconzole, namely M14360-acid.

In the study by Knoch, 1993, an unknown metabolite (U1) was formed in amounts > 10% AR. The metabolite was later, as part of confirmatory data, identified to be CGA142856 (triazole acetic acid; TAA). The RMS considers that this conclusion is still valid. Additionally, two new soil metabolism studies (Dobson, 2010 and Brands, 2010) investigated whether the unknown U1 metabolite may be formed and identified. In both studies, CGA142856 was confirmed at low levels well below 5% AR. However, in Dobson (2010), an unidentified metabolite (M9) was present up to 7.5% of applied radioactivity at the study end on day 60 (3.3% on day 30) in a soil dosed with a high rate of penconazole. A retrospective elucidation study was conducted (Edwards, 2019) to identify unknown M9. The retrospective elucidation work assigned the identity of the unknown soil metabolite (M9) as CGA91305.

The penconazole task force also submitted two new soil metabolism studies (Crabtree, 2016; Corral and Brands, 2009) that were instigated to determine the behaviour of penconazole over a wider pH range than the old studies and at an application rate closer to the current rate. No new metabolites were identified in either of these studies.

The table below shows the different penconazole laboratory studies that were performed and the formation of metabolites, CO_2 and bound residues in these studies.

Table 86: Overview of the formation of metabolites, CO2 and bound residues in the penconazole laboratory aerobic route of degradation studies (needs to be updated)

Reference	Soil, application rate	Soil type	pH	Label	CGA71019 (1,2,4-triazole)	CGA179944	CGA142856 (triazole acetic acid; TAA)	CGA91305	CO_2	NER
					Max occurrence (%AR) at (day)				% AR after 100 days	
Völkl S, 2002	Weide, 209 g/ha	Silt loam	7.5(1	TRZ	19.5 (188)	2.0 (28) (***	-	-	2.8 (120) 6.8 (188)	17.1 (120) 27.3 (188)
	Pappelacker, 209 g/ha	Sandy loam	7.44(1	TRZ	38.6 (188)	7.2 (58)	-	-	5.4 (120) 9.6 (188)	25.5 (120) 35.8 (188)
Glänzel A. 1999	Gartenacker, 320 g/ha	Loam	7.18(1	TRZ	34.8 (180)	1.8 (14) (***	3.6 (90) (***	-	2.3 (90) 4.1 (210)	12.6 (90) 35.1 (210)
Knoch E., 1993	Itingen, 63 g/ha	Silt loam/loam	7.4(1	TRZ	14.3 (56)	13.1 (56)	-	-	6.4 (105)	18.4 (105) 40.2 (364)

Reference	Soil, application rate	Soil type	pH	Label	CGA71019 (1,2,4-triazole)	CGA179944	CGA142856 (triazole acetic acid; TAA)	CGA91305	CO_2	NER
					Max occurrence (%AR) at (day)				% AR after 100 days	
									26.9 (364)	
	Itingen, 630 g/ha	Silt loam/loam	7.4(1	TRZ	5.5 (182)	10.9 (364)	12.5 (364)	-	3.5 (105) 11.0 (364)	14.5 (105) 23.7 (364)
Abildt U, 1989	Les Barges (Strassenacker), 727 g/ha	Sandy loam/loam	7.0(2	PH	-	5.3 (56)	-	-	19.3 (84)	13.3 (84)
Abildt U, 1989a	Les Barges (Strassenacker), 727 g/ha	Sandy loam/loam	7.0(2	PH	-	13.4 (182)	-	-	15.3 (182)	14.6 (182)
Abildt U, 1989b	Les Barges (Strassenacker) , 735 g/ha (*	Sandy loam/loam	7.0(2	TRZ	20.3 (546)	10.2 (364)	-	-	0.4 (130)	17.8 (130)
Keller A, 1982	Les Barges, 750 g/ha	Sandy loam	7.3(2	TRZ	29 (336)	-	-	-	1.4 (84)	15.2 (84)
Crabtree G et al., 2016	Gartenacker, 50 g/ha (*	Loam	7.4(3	PH	-	2.2 (59) (***	-	-	1.2 (105)	35.7 (76)
	18 Acres, 50 g/ha	Sandy clay loam	7.2(3	PH	-	3.9 (120) (***	-	-	0.7 (105)	13.1 (105)
	Hepler, 50 g/ha	Silt loam	6.2(3	PH	-	1.0 (90) (***	-	-	5.7 (45)	32.6 (120)
	East Anglia, 50 g/ha	Sandy loam	7.6(3	PH	-	3.1 (120) (***	-	-	0.4 (90)	22.6 (120)
	Capay, 50 g/ha	Clay loam	6.7(3	PH	-	0.7 (76) (***	-	-	1.0 (45)	52.8 (120)
Corral E. and Brands C, 2009	Speyer 2.2, 100 g/ha	Loamy sand	5.4(4	TRZ	-	-	-	-	0.1 (122)	15.5 (122)
	Speyer 2.3, 100 g/ha	Sandy loam	6.4(4	TRZ	-	-	-	-	0.5 (122)	34.4 (60)
	Speyer 6S, 100 g/ha	Clay	7.2(4	TRZ	-	-	-	-	0.1 (14)	19.2 (60)
Dobson R, 2010(**	Stolpe, 65 g a.s./ha	Sand	5.5(4	TRZ	3.3 (60) (***	3.0 (60) (***	-	2.0 (60) (***	0.2 (28)	4.5 (60)
	Fislis, 65 g a.s./ha	Silt loam	7.3(4	TRZ	15.4 (60)	0.9 (60) (***	-	3.7 (28) (***	5.5 (60)	22.0 (60)
	Fislis, 650 g a.s./ha	Silt loam	7.3(4	TRZ	7.8 (60)	3.9 (28) (***	-	7.5 (60)	1.3 (60)	14.4 (60)

TRZ: triazole ring label, PH: Phenyl ring label

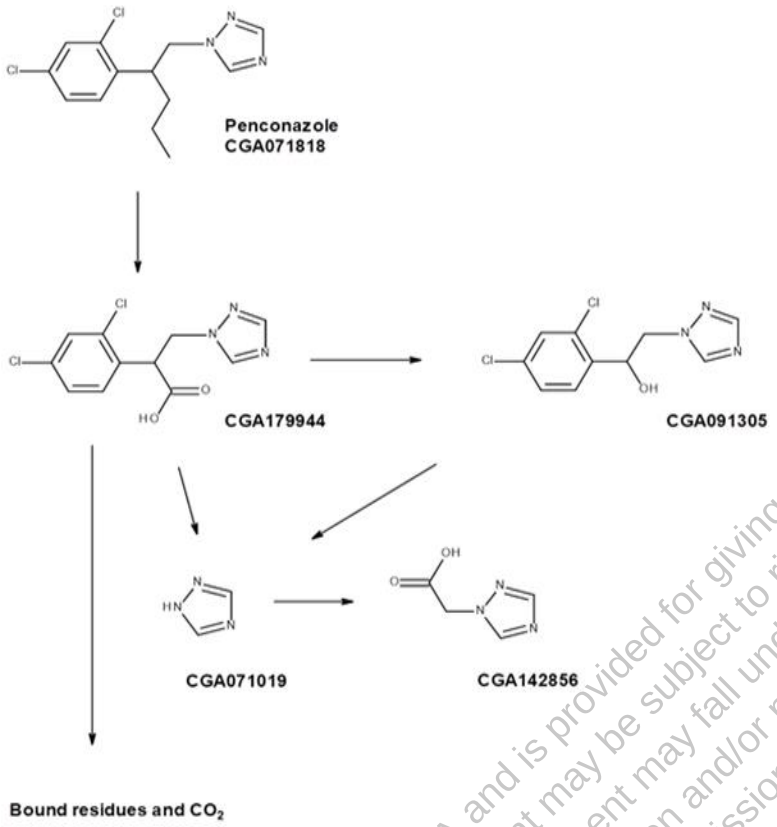
(1 pH in KCl; (2 pH medium not stated; (3 pH in H_2O; (4 pH in $CaCl_2$

(*suggested to be excluded from the results (see Vol 3 CA Part B.8 for full study summary and evaluation) – will be removed from this vol. 1 summary if agreed upon in peer review

(** study only to be used for supporting information – will be removed from this vol. 1 summary if agreed upon in peer review

(*** metabolites that do not exceed 5% AR in the study. Will be removed from table after peer review.

The proposed metabolic pathway for penconazole in soil incubated under aerobic condition, based on the results obtained, is presented in the following scheme:



Penconazole is essentially stable in soil to photolysis and under anaerobic conditions (see summary of anaerobic laboratory studies below). Under sterile conditions, penconazole was not significantly degraded (Keller, 1982). This indicates that the degradation of penconazole is microbially driven.

Penconazole degraded slowly in aerobic soil. Mineralization was relatively low (0.1-19.3% AR after up to 120 days). Volatiles were formed at very low levels and were in most cases not observed >LOD of the respective studies. Bound residues amounted to a maximum of 52.5% AR after 120 days.

The results from the laboratory aerobic degradation studies of penconazole in soil are summarized in Table 80. Please refer to the individual study summaries in Vol. 3 B.8 CA for more details.

The degradation rates of the metabolites CGA179944, CGA71019, CGA142856 and CGA91035 are given in Table 81 to 84. Formation fractions are given in Table 85. Please refer to the individual study summaries in Vol. 3 B.8 CA for more details.

Table 87: Summary of kinetic evaluation of laboratory data on aerobic degradation of penconazole in soil.

Study	Soil	pH	Persistence endpoint				Modelling endpoint (20°C, pF2)			
			Best fit model	DT50, days	DT90, days	χ^2 error, %	Model	Factor to normalize moisture	Factor to normalize temperatur	DT50, days
Völkl S, 2002	Weide, silt loam	7.5(1	SFO	154	511	3.2	SFO	1	1	154
	Pappelacker, sandy loam	7.44(1	SFO	54.2	180	3.3	SFO	1	1	54.2
Glänzel A. 1999	Gartenacker, loam	7.18(1	SFO	77.2	256	4.1	SFO	1	1	77.2

Study	Soil	pH	Persistence endpoint				Modelling endpoint (20°C, pF2)			
			Best fit model	DT50, days	DT90, days	χ^2 error, %	Model	Factor to normalize moisture	Factor to normalize temperatur	DT50, days
Knoch E., 1993	Itingen (low dose 20°C/60%), silt loam	7.4(1	DFOP	108	515	4.8	SFO	0.699	1	92.4
	Itingen (high dose 10°C/60%), silt loam	7.4(1	SFO	484	1610	3.02	-	-	-	-
	Itingen (high dose 20°C/30%), silt loam	7.4(1	SFO	474	1580	3.42	-	-	-	-
Abildt U, 1989	Les Barges (Strassenacker), 25°C/75%FC, sandy loam	7.0(2	DFOP	103	683	4.93	SFO	0.818	1.606	192
Abildt U, 1989b	Les Barges (Strassenacker), 15°C/75%FC, sandy loam	7.0(2	SFO	301	999	5.26	SFO	0.818	0.623	154
Keller A, 1982	Les Barges, sandy loam	7.3(2	SFO	132	438	2.18	SFO	0.818	1.606	169
Crabtree G et al., 2016	18 Acres, sandy clay loam	7.2(3	SFO	418	1390	1.35	SFO	1	1	418
	Hepler, silt loam	6.2(3	DFOP	193	806	2.88	SFO	0.959	1	197
	East Anglia, sandy loam	7.6(3	DFOP	227	850	1.55	SFO	1	1	228
	Capay, clay loam	6.7(3	DFOP	126	651	2.51	DFOP k2	0.868	1	196
Corral E. and Brands C, 2009	Speyer 2.2, loamy sand	5.4(4	SFO	628	2090	1.54	SFO	1	1	628
	Speyer 2.3, sandy loam	6.4(4	SFO	239	792	1.78	SFO	0.798	1	191
	Speyer 6S, clay	7.2(4	DFOP	700	2640	3.74	SFO	0.469	1	298
Geometric mean (n=14)										180.6

(1 pH in KCl; (2 pH medium not stated; (3 pH in H_2O; (4 pH in $CaCl_2$

Table 88: Summary of kinetic evaluation of laboratory data on aerobic degradation of the metabolite **CGA179944 in soil.**

Study	Soil	pH	Persistence endpoint				Modelling endpoint (20°C, pF2)			
			Best fit model	DT50, days	DT90, days	χ^2 error, %	Model	Factor to normalize moisture	Factor to normalize temperature	DT50, days
Völkl S, 2002	Weide	7.5(1	SFO-SFO	45.5	151	11.0	SFO-SFO	1	1	45.5
Knoch E., 1993	Itingen (high dose)	7.4(1	SFO-SFO	247	820	13	SFO-SFO	0.699	1	173
	Itingen (low dose)	7.4(1	SFO-SFO	-	-	-	SFO-SFO	-	-	-
Abildt U, 1989	Les Barges (Strassenacker),	7.0(2	SFO-SFO	16.4	54.6	20.5	SFO-SFO	0.818	1.606	21.0

Study	Soil	pH	Persistence endpoint				Modelling endpoint (20°C, pF2)			
			Best fit model	DT50, days	DT90, days	χ^2 error, %	Model	Factor to normalize moisture	Factor to normalize temperature	DT50, days
	25°C/75%FC, sandy loam									
Abildt U, 1989b	Les Barges (Strassenacker), 15°C/75%FC, sandy loam (*	7.0(2	SFO-SFO	196	650	6.54	SFO-SFO	0.818	0.623	101
Crabtree, 2016	18 Acres, sandy loam	7.2(3	SFO-SFO	1000*	3320	16.4	SFO-SFO	1	1	1000*
	East Anglia, sandy loam	7.6(3	SFO-SFO	1000*	3320	19.0	SFO-SFO	1	1	1000*
Völkl, 2002a	Weide, silt loam	7.5(1	HS	39.8	61.8	1.34	SFO	1	1	25.8
	Pappelacker, sandy loam	7.44(1	HS	27.6	49.5	0.97	SFO	1	1	21.5
	Gartenacker, silt loam	7.3(1	HS	21.3	37	1.83	SFO	1	1	16.2
Hurst, 2011	18 Acres, sandy clay loam	6.0(4	SFO	23.6	78.4	4.2	SFO	1	1	23.6
	Ohio, clay loam	5.6(4	FOMC	22.3	113	3.8	SFO	1	1	26.2
	Frensham, sandy loam	5.0(4	HS	23.0	198	4.2	HS	1	1	101
Scacchi and Pizzingrilli, 2000	Speyer 2.1, sand	6.0(4	SFO	218	724	3.0	SFO	0.9765	1	213
	Speyer 2.2, loamy sand	5.8(4	DFOP	316 (k2 slow phase)	748	1.2	DFOP	1	1	316
	Speyer 2.3, sandy loam	6.6(4	SFO	114	380	1.4	SFO	0.8711	1	99.3
Corral and Brands, 2009a	Speyer 2.2, loamy sand	5.4(4	SFO	31.0	103	8.7	SFO	1	1	31.0
	Speyer 2.3, sandy loam	6.4(4	SFO	31.8	106	3.7	SFO	0.798	1	25.4
	Speyer 6S, clay	7.2(4	SFO	112	373	4.7	SFO	0.469	1	52.5
Geometric mean (n=20)										**71.8**

-No reliable degradation half-lives could be determined.
(1 pH in KCl; (2 pH medium not stated; (3 pH in H_2O; (4 pH in $CaCl_2$
* DT50 fixed to extrapolate ffm

Table 89: Summary of kinetic evaluation of laboratory data on aerobic degradation of the metabolite CGA142856 in soil.

Study	Soil	pH	Persistence endpoint				Modelling endpoint (20°C, pF2)			
			Best fit model	DT50, days	DT90, days	χ^2 error, %	model	Factor to normalize moisture	Factor to normalize temperature	DT50, days
Scacchi and Pizzingrilli, 2003	SP-2.1, sand	5.2(1	HS[a)]	8.47	14.2	14.9	HS[a)]	1	1	4.28 [b), c)]
	SP-2.2, loamy sand	5.6(1	HS[a)]	10.7	14.9	7.21	HS[a)]	1	1	4.49 [b), c)]

Study	Soil	pH	Persistence endpoint				Modelling endpoint (20°C, pF2)			
			Best fit model	DT50, days	DT90, days	χ^2 error, %	model	Factor to normalize moisture	Factor to normalize temperature	DT50, days
	SP-2.3, sandy loam	6.3(1	HS[a)]	16.3	21.6	8.10	HS[a)]	1	1	6.51 [b), c)]
Mainolfi and Colombini, 2019	IGM, loamy sand	7.9(1	HS[a)]	19.2	30.1	2.01	HS[a)]	1	1	9.07 [b)]
Geometric mean (n=4)										**5.80**

(1 pH in $CaCl_2$

a) Initial break point value was manually set prior to free optimisation

b) DT_{50} derived from lag phase hockey stick DT_{90}/3.32 according to FOCUS kinetics guidance (2006, 2016a)

c) Soils not normalised for moisture as a conservative assumption

Table 90: Summary of kinetic evaluation of laboratory data on aerobic degradation of the metabolite CGA71019 (1,2,4-triazole) in soil.

Study	Soil	pH	Persistence endpoint				Modelling endpoint (20°C, pF2)			
			Best fit model	DT50, days	DT90, days	χ^2 error, %	Model	Factor to normalize moisture	Factor to normalize temperature	DT50, days
Slangen, 2000	Laacher Hof AXXa, sandy loam	6.9(1	DFOP	59.2	78.5	5.1	DFOP	0.798	1	47.2
	BBA 2.2, loamy sand	6.19(1	DFOP	247.6	512.5	5.1	DFOP	1	1	247.6
	Laacher Hof AIII, silt loam	7.88(1	DFOP	20.6	33.9	4.5	DFOP	0.666	1	13.7
Geometric mean (n=3)										**54.3**

(1 pH in H_2O

Table 91: Summary of kinetic evaluation of laboratory data on aerobic degradation of the metabolite CGA91305 in soil.

Study	Soil	pH	Persistence endpoint				Modelling endpoint (20°C, pF2)			
			Best fit model	DT50, days	DT90, days	χ^2 error, %	Model	Factor to normalize moisture	Factor to normalize temperature	DT50, days
Cashmore, 2020	18 Acres, sandy loam	6.2(1	SFO	25.7	85.4	3.62	SFO	0.97	1	24.9
	Gartenacker, loam	7.5(1	SFO	8.59	28.5	7.84	SFO	0.94	1	8.07
	East Anglia, sandy loam	7.1(1	SFO	34.1	113	4.35	SFO	0.97	1	33.1
Geometric mean (n=3)										**18.8**

(1 pH in $CaCl_2$

Table 92: Summary of formation fractions from kinetic modelling of penconazole and its metabolites

Soil	Formation fraction estimates in each soil			
	Penconazole → CGA 179944	Penconazole → CGA71019	Penconazole → CGA91305	Penconazole → CGA142856
Weide	-			

Itingen (high dose)	0.2436			
Strassenacker(*	0.4855			
Strassenacker(*	0.4004			
18 Acres	0.2069			
East Anglia	0.1056			
Fislis, normal dose			0.235	
Fislis, high dose			0.453	

(*suggested to be excluded from the results (see Vol 3 CA Part B.8 for full study summary and evaluation) – will be removed from this vol. 1 summary if agreed upon in peer review
- No acceptable estimate of formation fraction determined

Anaerobic laboratory studies

Two studies were submitted investigating the anaerobic transformation of penconazole in soil. Under anaerobic soil conditions, the degradation of penconazole was much slower than under aerobic conditions and no rate of degradation could be established due to its stability. Metabolite CGA71019 (1,2,4-triazole) was formed, principally during the initial aerobic phase of the experiment, in amounts exceeding 5% AR (max 27.2% AR). Minor amounts of metabolite CGA142856 (triazole acetic acid; max 5.5 % AR at one time point) and CGA 179944 (max 0.5 % AR) were formed. Penconazole and metabolite CGA71019 were mainly found in the soil phase. Non-extractable residues reached a maximum of 22.1 % AR after 133 days. Mineralisation was low under anaerobic conditions and did not exceed 1.7% AR.

The anaerobic degradation of metabolite CGA71019 was further investigated in one study. Degradation was slower than under aerobic conditions. The DT50 was 80.6 days. One metabolite, CGA142856 (TAA) was formed at levels up to 50.3% AR at study end (122 days after flooding). Several other minor metabolites were observed but occurred at <5% AR. CGA71019 was mainly found in the soil phase, while metabolite CGA142856 was found in slightly higher amounts in the water phase than the soil phase. Non-extractable residues reached a maximum of 21.4 % AR after 60 days. Mineralisation was low under anaerobic conditions and CO_2 levels did not exceed 1.3% AR.

Photochemical transformation

Two studies were provided on the photochemical transformation of penconazole in soil, Mamouni (2003a) and Spare (1987). Both were previously evaluated and accepted in the DAR (2007). The two studies show similar results, however the RMS is uncertain whether Spare (1987) should still be considered acceptable due to the shortcomings of the study and because it is of lower quality than the study by Mamouni (2003). The RMS therefore suggest that the study by Spare (1987) should be considered as supportive information only.

In the study by Mamouni (2003a) penconazole is slowly broken down under artificial sunlight conditions. Penconazole accounted for mean 95% of AR by the end of the study duration under irradiated conditions, no phototransformation products were observed, unextracted residues reached a maximum mean value of 4.4% AR and CO_2 accounted for a maximum mean value of 4.5% AR. Similar results were obtained in the dark control as well. Degradation half-life was calculated to be 282 days (corrected for latitudes equivalent to summer sunlight days at 30-50°N).

Field studies

Soil dissipation studies

Five soil dissipation studies were performed with penconazole, Offizorz (1990, 1991, 1991a, 1991b) and Tournayre (1985). Quantifiable residues of penconazole were detected in the first 20 cm of the soils. No residue above the LOQ were detected at depth 10-20 cm in any sample at any of the five sites. Altogether, although the studies have several shortcomings, they indicated that penconazole does not show any significant tendency to move into deeper soil layers indicating low potential to leach to groundwater.

None of the studies were by the RMS and co-RMS considered to be of good enough quality to estimate dissipation and degradation rates and are only considered as supporting information (Tournayre (1985) is considered not acceptable). Therefore, none of the studies should be used for risk assessment or the assessment of the P-criteria. The main shortcomings were lack of replicates and that there were too few datapoints for field studies with several other shortcomings. As the DT50-values for penconazole are greater than 60 days in laboratory studies, field studies are considered required in accordance with Commission Regulation (EU) No 283/2013, this is therefore considered a data gap by the RMS. However, we would like the opinion of the other MS and EFSA on this matter.

Four new field dissipation studies were provided for the metabolite CGA17994, Ahrens (2019 and 2020), Ahrens and Bisharat (2020 and 2020a). The Ahrens (2019) study is considered as supportive only and cannot be used to derive dissipation/degradation endpoints due to questionable data quality of the residues data.

Kinetic assessment and the persistency and modelling endpoints were assessed in Hardy and Agostini 2021 and 2021a, respectively. PEARL was used to calculate the daily moisture content of the top 10 cm of the soil and used for normalisation, instead of the actual measured moisture data in all three studies. Based on comments from co-RMS the applicant was requested to provide a comparison of the measured and simulated moisture content and detailed calculations of the time-step normalisation, refer to grey commenting boxes in 3CA B8 (section B.8.1.1.5.1.). The persistency DT50 endpoints range from 22.3 – 118 days. However, we would like the opinion of the other MS and EFSA on the choice of kinetic model for the persistency endpoints. For modelling, normalized DT50 endpoints range from 45.3 – 125, with a geomean of 72.2 days. All studies indicate that residues of CGA179944/M14360-acid declined in soil under field conditions.

A soil storage stability study at -18°C (Soddu, 2020) showed that the CGA179944 residues were stable at 18 months.

Field dissipation of the metabolite CGA71019 (1,2,4-Triazole) has been summarized and assessed in the CRD 2013 report "*Triazole Derived Metabolite: 1,2,4-Triazole. Proposed revision to DT50. Summary, Scientific Evaluation and Assessment. July 2011, revised September 2011 (after comments from MS and EFSA) and further revised January 2013 (minor clarifications added post-commenting)*". This report is still considered valid, and no new assessment has been performed. The persistency DT50 endpoints range between 6.8 – 28.1 days. The normalized DT50 endpoints for modelling range between 0.5 – 4.6 days (geomean 1.68 days) for fast phase and 25.1 – 126.0 days (geomean 60.5 days) for the slow phase and "g" range between 0.365 – 0.655 (arithmetic mean 0.489).

Table 93: Summary of kinetic evaluation of field dissipation data of the metabolite CGA179944 in soil.

Compound	Soil type	Location (country or USA state)	pH[a)]	Persistence endpoint				Modelling endpoint			
				Best fit model	χ^2 error, %	DT50, days	DT90, days	Model	t. oC / % MWHC	χ^2 error, %	DT50 (d) Norm[b)].
CGA179944	Loam	Spain	7.57	SFO	9.0	28.8	95.7	SFO	20°C / pF2	11.9	66.4
	Sandy loam	Portugal	4.60	DFOP	20.1	22.3	117	SFO	20°C / pF2	19.0	45.3
	Sandy loam	UK	6.67	SFO	13.7	118.0	547	SFO	20°C / pF2	14.3	125
Geometric mean (n=3)											**72.18**

[a)] Measured in 0.01M $CaCl_2$ solution
[b)] Normalised using a Q10 of 2.58 and Walker equation coefficient of 0.7, values are DegT50matrix

Table 94: Summary of kinetic evaluation of field dissipation data of the metabolite CGA71019 (1,2,4-Triazole) in soil.

Compound	Soil type	Location (country or USA state)	pH[a)]	Persistence endpoint				Modelling endpoint			
				Best fit model	χ^2 error, %	DT50, days	DT90, days	Model	t. oC / % MWHC	χ^2 error, %	DT50 (d) Norm[b)].
CGA71019 (1,2,4-Triazole)	Silt loam	Germany	6.36	FOMC	15.2	7.8	366.7	DFOP	20°C / pF2	18.8	2.5/70.7 (0.655)[c)]
	Silty clay loam	Italy	7.56	DFOP	10.7	21.2	207.4	DFOP	20°C / pF2	10.6	1.4/59.8 (0.364)[c)]
	Sandy loam	UK	7.37	DFOP	17.8	6.8	109.3	DFOP	20°C / pF2	18.1	0.5/25.1 (0.458)[c)]
	Loam	Spain	5.81	DFOP	13.3	28.1	717.6	DFOP	20°C / pF2	12.7	4.6/126.0 (0.489)[c)]

Geometric mean (n=4) ("g" arithmetic mean)	**1.68/60.5 (0.489) [c)]**

[a)] Measured in 0.01M $CaCl_2$ solution
[b)] Normalised using a Q10 of 2.58 and Walker equation coefficient of 0.7, values are DegT50matrix
[c)] Fast phase/slow phase ("g")

Soil accumulation studies

Ten existing studies were included in the previous EU evaluation of penconazole. The studies are considered again for the renewal of approval of penconazole.

Several long-term soil residue trials were performed in grapes and in apple or pear orchards applying various penconazole formulations according to common agricultural practice. The application rates covered a broad spectrum reflecting the wide range of different uses, e.g. the annual treatment in grapes ranged from 3 x 37 = 111 to 5 x 103 = 515 g as/ha, in apples from 3 x 25 = 75 to 14 x 70 = 980 g as/ha and in pears from 9 x 25 = 225 to 11 x 25 = 275 g as/ha.

Four studies were considered acceptable as supportive information (Kuhne-Thu 1997 and 1997a, Formica 1992 and 1992a), while six were rejected because they were outdated, or the data was unreliable.

In the opinion of the RMS, the only thing that can be concluded with certainty from these supporting studies is that penconazole or its metabolites had not been completely degraded between the last application of the season and the date of soil sampling (48-119 days after last application).

According to the data requirements of the commission regulation (EU) No 283/2013, soil accumulation studies shall provide estimates of the time required for dissipation of 50 % and 90 % (DisT50 field and DisT90 field).

This is not the case for these studies. The RMS asked the applicant to fulfil this data requirement by model calculations instead. Review of the reported residue data for the soil accumulation studies indicates that the calculation of $DT_{50/90}$ is not possible. Single yearly residue analysis at various times does not allow for kinetic evaluations. Thus, this data requirement is not filled.

Two soil storage stability studies were submitted (Emburey 2004 and Shadrick et al. 1999). They showed that the residues of penconazole and CGA179944 were stable at ≤-18°C for 12 months, and the residues of CGA71019 were stable at -25°C for 3.5 years.

Assessment in relation to the P-criteria

The criteria for persistence in soil, as stated in Annex II to Reg (EC) 1107/2009:

- DT50 120 days (PBT)
- DT50 180 days (POP and vPvB)

RMS has based the assessment in relation to the P-criteria on the DG SANCO Working Document on «Evidence Needed to Identify POP, PBT and vPvB Properties for Pesticides» rev. 3, September 2012. According to this document:

- The kinetic model that gives the best description of the chemical's behaviour should be selected. Guidance provided in FOCUS Degradation Kinetics Guidance (Sanco/10058/2005, ver 2.0, June 2006) on how to derive best fit DT50 should be applied.
- Laboratory studies: DT50 values should be normalised to a temperature of 20°C, as this is the current practice in recent assessments of soil degradation rates of active substances.
- DT50 values from different studies should not be aggregated. A Weight of Evidence approach should be used for the evaluation of laboratory and/or field studies. Significant variations among studies should be described and explained to inform decision making by risk managers.

The maximum DT50 estimated for penconazole in soil from laboratory studies is 700 days (DFOP best fit, non-normalised, study conducted at 20°C). When considering degradation at 20°C 11 of 14 laboratory DT50 values are above the criteria for PBT (126 – 700 days) and 7 of 14 DT50 values above the criteria for POP and vPvB (193 – 700 days). The 3 DT50 values that are below both criteria range from 54.2 – 108 days. Additionally, DT50 values from two studies that were conducted at a different temperature, and where normalisation to 20°C have not been done, are available, 484 days (SFO best fit, 10°C) and 103 days (DFOP best fit, 25°C).

There was no simple and apparent explanation to the variation in degradation rate in terms of soil characteristics. It should be noted that the DT50 of 700 days was estimated in a clay soil (which is not one of the recommended representative soils in the OECD 307 Guidance) and that the initial microbial biomasses and decrease towards the end of incubation were quite high in the study (Corral and Brands, 2009). However, this was discussed with co-RMS and it was decided that the results were reliable and the study results should be used.

Based on a WoE approach, as the degradation of penconazole is slow in most cases and the longest DT50 values is 700 days, RMS is of the opinion that both criteria for persistence in soil (PBT: 120 days; POP/vPvB: 180 days) are fulfilled.

The SANCO Working Document also states that field dissipation studies should be included in the assessment if it is possible to derive degradation half-lives from them and that data on photolysis should also be considered when relevant. None of the field studies provided for penconazole were by the RMS and co-RMS considered to be of good enough quality to estimate dissipation and degradation rates and are only considered as supporting information. From a study on soil photolysis a half-life (DegT50) of 282 days was calculated (corrected for latitudes equivalent to summer sunlight days at 30-50°N) and it showed that penconazole is slowly broken down under artificial sunlight conditions and can be considered to be stable to sunlight irradiation on soil surfaces.

Adsorption, desorption, and mobility in soil

Two studies on adsorption/desorption of penconazole were available, Keller (1982a) and Martinson (1988). Both studies were previously evaluated and accepted in the DAR (2007). Both are summarised in the table below.

Table 95: Adsorption of **penconazole.**

Study	Soil	OC %	pH	K_F ml/g	r^2 *	1/n	$K_{F,oc}$ ml/g
Keller, 1982a	Silt loam (Collombey)	1.3	7.8	10.03	n.s.	0.89	786
	Sandy loam (Vetroz)	3.2	6.7	69.80	n.s.	0.75	2149
	Silt clay loam (Les Evouettes)	2.1	6.1	33.45	n.s.	0.77	1602
	Silt loam (Lakeland)	0.7	6.3	24.42	n.s.	0.86	3508
Martinson, 1988	California clay loam	1.1	7.8	11.2	0.999	0.798	998
	California sandy loam	0.75	4.9	31.3	0.977	0.844	4120
	Arkansas silt loam	0.29	5.9	7.28	0.999	0.801	2510
	New York loam	1.8	6.5	35.9	0.997	0.816	1970
Arithmetic mean (n=8)						**0.82**	**-**
Geometric mean (n=8)						**-**	**1931**

n.s. not stated
* calculated by RMS

Adsorption/desorption data were evaluated for metabolites CGA179944, CGA142856, CGA71019, and CGA91305. Out of nine studies, two (Mamouni 2003b, Hawkins 1988) had been previously evaluated and accepted in the DAR (2007). Three new studies (Scacchi and Pizzingrilli 1999, with further work in Rizzo 2010, and Scacchi et al 2002) were rejected by the RMS. The studies deemed acceptable are summarised in the three tables below. For metabolite CGA142856, it was not possible to accurately determine Kd values with the batch equilibrium method. The RMS recommends using a conservative default value for very mobile substances in environmental exposure modelling of CGA142856. In the one study on metabolite CGA71019 (Hawkins 1988), one soil (Lakeland) was excluded by the RMS due to its low organic carbon content.

Table 96: Adsorption of metabolite CGA179944.

Study	Soil	OC %	pH	K_F ml/g	r^2	1/n	$K_{F,oc}$ ml/g
Mamouni A, 2003b	Weide, silt loam	2.14	7.5	0.36	0.9954	0.89	17
	Vetroz, silt loam	5.0	7.2	0.55	0.9984	0.93	11
	Gartenacker, loam	2.59	7.13	0.26	0.9750	0.84	10
	Borstel, loamy sand	1.5	5.8	0.19	0.9717	0.71	12

Hurst L, Alderman D, Gilbert J, 2011	18 Acres, sandy clay loam	2.2	6.0	0.44	0.9993	0.8913	20
	Ohio, clay loam	2.9	5.6	1.06	0.9997	0.8598	37
	Frensham, sandy loam	1.8	5.0	0.61	0.9995	0.8684	34
Corral E and Brands C, 2009b	Speyer 2.2, loamy sand	2.16	5.4	0.678	0.990	0.82	31.4
	Speyer 2.3, sandy loam	0.98	6.4	0.177	0.942	0.84	18.1
	Speyer 6S, clay	1.75	7.2	0.322	0.962	0.88	18.4
Arithmetic mean (n=10)						**0.85**	**-**
Geometric mean (n=10)						**-**	**18.9**

Table 97: Adsorption of metabolite CGA71019.

Study	**Soil**	**OC %**	**pH**	**K_F ml/g**	**r^2**	**1/n**	**$K_{F,oc}$ ml/g**
	Silt clay (Alpaugh)	0.7	8.8	0.833		0.897	120
	Clay loam (Hollister)	1.7	6.9	0.748		0.827	43
	Silty clay (Lawrenceville)	0.7	7.0	0.722		0.922	104
	Sandy loam (Pachappa)	0.8	6.9	0.720		1.016	89
Arithmetic mean (n=4)						**0.92**	**-**
Geometric mean (n=4)						**-**	**83.1**

n.s. not stated
* calculated by RMS

Table 98: Adsorption of metabolite CGA91305.

Study	**Soil**	**OC %**	**pH**	**K_F ml/g**	**r^2**	**1/n**	**$K_{F,oc}$ ml/g**
	Loamy sand (Pappelacker)	1.2	7.2	2.01		0.92	165
	Silt loam (Gartenacker)	1.7	7.4	2.13		0.93	122
	Silty clay (Marsillargues)	1.0	7.6	3.19		0.89	305
Arithmetic mean (n=3)						**0.91**	**-**
Geometric mean (n=3)						**-**	**183.1**

n.s. not stated
* calculated by RMS

pH dependency of sorption

There is an indication of sorption being pH dependent for penconazole and its metabolites CGA179944 and CGA71019. There is too little data to conclude on metabolite CGA91305. The co-RMS analyzed the pH-dependence of adsorption according to the recommendations described in the draft "Considering pH-dependent degradation and adsorption in soil for groundwater leaching assessment" (UBA, 1. April 2021) using the accompanying pHADe tool. For the active substance penconazole and its metabolites CGA179944 (excluding soils from Scacchi and Pizzingrilli, 1999) and CGA71019 (excluding the soil Lakeland) the co-RMS found indications for pH-dependent adsorption behavior. For details, please see the Excel file "pH dependence sorption".

The evaluations with the pHADe-tool require pKa values. For the active substance, a value of 1.51 is reported in the LoEP. Avery different value was found in the literature (5.2, see Cadková et al. (2013)[12]) which fits much better to the adsorption data. It has not been finalised which value is correct and should be used for risk assessment.

2.8.2 Summary of fate and behaviour in water and sediment [equivalent to section 11.1 of the CLH report template]

Route of degradation in the aquatic compartment

Hydrolytic degradation

[12] Eva Cadkova et al. (2013) pKa constant determination of two triazole herbicides : Tebuconazole and Penconazole. Journal of Solution Chemistry, Springer Verlag (Germany), 2013, 42, pp.1075-1082.

Two studies were provided for the hydrolysis of penconazole (van der Gaauw, 2002 and Spare, 1987a). One study showed that penconazole was stable to hydrolysis at pH 4, 5, 7, and 9 at 50 °C for 7 days and the other study at pH 5, 7 and 9 at 25 °C for 30 days. Penconazole is therefore considered as hydrolytically stable under environmentally relevant pH conditions. No hydrolysis products were detected in either of the studies.

Two studies were also provided for the hydrolysis of the metabolite CGA179944 (Mamouni 2002 and Oudhoff, 2008). One study showed that CGA17994 was stable to hydrolysis at pH 4, 7, and 9 at 50 °C for 5 days and the other study at pH 5, 7 and 9 at 50 °C for 5 days. CGA179944 is therefore considered as hydrolytically stable under environmentally relevant pH conditions.

For the metabolite CGA71019 one study was provided (Spare, 1983), however this was only considered as supportive information, but indicate that CGA71019 is stable to hydrolysis at pH 5, 7, and 9 at 25 °C for 30 days.

Direct and indirect photochemical degradation

Data to address the data requirement for direct photochemical degradation are not required since the molar absorption coefficient ε is < 10 L / (mol · cm). Data on indirect photochemical degradation is not required either.

Rate of degradation in the aquatic compartment

Ready biodegradability

The "ready biodegradability" of penconazole was investigated in one study, Grade (1999), which was assessed and accepted during the previous EU evaluation, DAR (2007). The study was conducted following the OECD guideline 301/B (CO_2 evolution test). Inoculum was prepared at concentration 25.3 mg sludge/L (activated sludge was collected from a sewage treatment plant) and was dosed with 41.1 and 40.8 mg/l penconazole, incubated for 29 days at 20 ±2ºC. Validation criteria were met. Penconazole reached a mean of -9% $ThCO_2$ by day 29 (negative values are a consequence of comparison of values obtained in the blank controls and the low values obtained in presence of test item) and can be considered «not readily biodegradable».

Aerob mineralisation in surface water

One new study was submitted considering aerobic mineralisation of penconazole in surface water, Hurst and Sutcliffe (2015). The mineralisation rate and route for degradation of penconazole was investigated in Fountains Abbey natural water plus suspended sediment system at two concentrations (nominal rates of 10 and 95 µg/L). Both systems were incubated under aerobic conditions at 20°C for 59 days. The study shows that mean levels of penconazole remained similar throughout the incubation period for both low and high concentration and no significant degradation of penconazole was observed, therefore no characterisation of metabolites was required. Penconazole was measured to range from mean 92.7- 97.0% AR (low concentration) and 93.3-95.8% AR (high concentration). Low levels of volatile radioactivity were observed, < 1.5% AR. This suggest that penconazole is stable to aerobic mineralisation in surface water. The degradation rates (DT_{50}) of penconazole were estimated using CAKE software by fitting single first-order kinetics (SFO) to the data. However, the degradation rates could not be accurately determined due to high prob > t values.

Degradation in water/sediment systems

Two studies were provided for evaluating the degradation in water/sediment systems, Mamouni (1998) assessed and accepted in DAR (2007) and a new study Brands (2009). In both studies two different water/sediment systems were incubated under aerobic conditions at 20°C, in the dark. In Mamouni (1998) samples were incubated for up to 706 days and in Brands (2009) 100 days. Both studies show that penconazole dissipated rapidly from the water phase to sediment. In Mamouni (1998) the route of degradation was similar in both water/sediment systems with CGA179944 as the major degradation product observed. In one of the water/sediment systems the metabolite reached a maximum of 22.1% AR in the total system, in the other system a maximum of 5.8% AR. In Brands (2009) no metabolites were detected in either the water layer or the sediment extract of both systems.

New kinetic analysis for both studies is presented in Hardy and Agostini (2019e) for the sake of renewal. The kinetic analysis shows that penconazole is degraded slowly in sediment and is stable in the two systems in both Mamouni (1998) and Brands (2009). Refer to Table 93 and 94 for persistence and modelling endpoints (DT50-values) for penconazole in water and total system.

Assessment in relation to the P-criteria

The criteria for persistence in water and sediment, as stated in Annex II to Reg (EC) 1107/2009, are:

- Water: DT50 40 days (freshwater in PBT), 60 days (POP, marine water in PBT, and all water in vPvB),
- Sediment: DT50 120 days (freshwater sediment in PBT), 180 days (POP, marine sediment in PBT, and

all sediments in vPvB).

No data was available for marine water or sediment. This is not considered as a data gap since data from marine compartments are not routinely required.

Penconazole is hydrolytically stable and not readily biodegradable. A study showed that penconazole is stable to aerobic mineralisation in surface water, however reliable degradation rates could not be determined. The results from the water/sediment studies (OECD 309) indicate that distribution to sediment is an important aspect of the dissipation of penconazole in aquatic systems. Penconazole dissipate rapidly from the water phase to sediment where it is degraded slowly and kinetic assessment show that penconazole i stable in water/sediment systems. The half-lives for water in the water/sediment systems did not exceed the criteria for persistency in water (however the rates in water reflect both degradation as well as distribution to another environmental compartment). The DT50-values for the whole systems represent both degradation in water and sediment, but as penconazole is rapidly distributed to the sediment RMS has compared the DT50-values for whole system against the P-criteria for sediment. $DT50_{whole\ system}$ indicates that both criteria for persistence in fresh water (PBT: 120 days; POP/vPvB: 180 days) are exceeded. Refer to section 2.8.2.2.4 for summary of the water/sediment system studies and Table 93 and 94 for endpoints.

2.8.2.1 Rapid degradability of organic substances

Relevant studies on degradation of penconazole are listed in the table below. These studies show that penconazole is hydrolytically stable, not readily biodegradable and is not rapidly degraded in aquatic systems. In natural water system penconazole is stable and in water/sediment systems penconazole rapidly dissipate to sediment where it is slowly degraded.

Table 99: Summary of relevant information on rapid degradability

Method	Results*	Key or Supportive study	Remarks	Reference
Ready biodegradability. 29 days, 20 ± 2°C Penconazole (96.6% purity). OECD 301/B. GLP.	Penconazole measure -9% of the theoretical CO_2 within 29 days (negative values are a consequence of comparison of values obtained in the blank controls and the low values obtained in presence of test item). Penconazole can be considered not readily biodegradable.	Acceptable	The reference substance reached the pass level of >60% $ThCO_2$ within a 10-day time window.	Grade (1999a)
Hydrolysis. Incubation temperature was 50°C, for 7 days at pH 4, 5, 7 and 9. ^{14}C-phenyl penconazole at a concentration of 2 mg a.s./L was investigated. OECD 111. GLP.	Hydrolytically stable at pH 4, 5, 7 and 9 for up to 7 days at 50°C.	Acceptable	Only minor transformation products (<1.2% AR) were observed.	van der Gaauw (2002)
Hydrolysis. Incubation temperature was 25°C, for 30 days at pH 5, 7 and 9. ^{14}C-triazole penconazole at a concentration of 10 mg a.s./L was investigated.	Hydrolytically stable at pH 5, 7 and 9 for up to 30 days at 25°C.	Acceptable	Analysis for transformation products was not performed since no hydrolysis was observed.	Spare (1987a)

Method	Results*	Key or Supportive study	Remarks	Reference
OECD 111. GLP.				
Aerobic mineralisation in surface water. Aerobic conditions in the dark at 20°C for up to 59 days. Sterile controls were maintained under the same conditions. Application rates of 10 and 95 µg/L ^{14}C-phenyl penconazole (radiochemical purity: >98.3%). OECD 309. GLP.	The parent compound remained stable throughout the test. Levels of parent ranged from 92.7 to 97.0% AR (low concentration) and 93.3 to 95.8% AR (high concentration) AR at the end of the incubation period (59 DAT).	Acceptable	The degradation of sodium ^{14}C-benzoate to ^{14}C-carbon dioxide indicated a viable microbial population was established (average 82.8 and 92.8 % AR at 14 and 59 days after treatment, respectively). No significant degradation of ^{14}C- penconazole was observed under the test conditions.	Hurst and Sutcliffe (2015)
Degradation in water/sediment systems. ^{14}C-phenyl penconazole at a nominal rate of 0.092 mg/550 mL water = 0.167 mg/L water (equivalent to a field rate of 500 g a.s./ha, assuming a uniform distribution in a water body of 30 cm depth), radiochemical purity: > 99%, maintained in dark conditions at 20 ± 1 °C for up to 706 days. OECD 308. GLP.	Recalculated DT50 values were 1.88 days and 5.32 days for river and pond systems, respectively. Total system half-lives were 563 and 1150 days for river and pond systems, respectively.	Acceptable	The mean mass balance from all aerobic water/sediment systems was 100.2% AR (range 94.1 to 105.8% AR). Maximum mineralisation and $^{14}CO_2$ evolved was 8.4% and 4.6% AR in the River and Pond systems, respectively, by the end of the incubation. Maximum levels of bound residues for River and Pond systems were 17.6% and 18.7% AR, respectively.	Mamouni (1998) Hardy and Agostini (2019e)
Degradation in water/sediment systems. ^{14}C-triazole penconazole at a nominal rate of 38.1 µg/L (Goorven) or 39.0 µg/L (Schoonrewordsewiel), maintained in dark conditions at 20 ± 2 °C for up to100 days. Radiochemical purity: 99.86%. OECD 308. GLP.	Recalculated DT_{50} values were 8.77 days, Goorven and 17.1 days, Schoonrewordsewiel. Corresponding total system half-lives were 2010 days and >10,000 days, respectively.	Acceptable	The mean mass balance were between 96.2-106.1% AR for the Goorven system and between 96.5- 101.8% AR for the Schoonrewoerdsewiel system. Mineralization was negligible ≤ 0.1% AR in both test systems. Bound residues accounted for maximum 15% (Goorven) and 11% AR (Schoonrewoerdsewiel).	Brands (2009) Hardy and Agostini (2019e)

** data on full mineralization should be reported*

2.8.2.1.1 Ready biodegradability

The “ready biodegradability” of penconazole was investigated in one study, Grade (1999), which was assessed and accepted during the previous EU evaluation, DAR (2007). It is concluded that penconazole can be considered as “not readily biodegradable”.

Grade (1999)
The study was conducted following the OECD guideline 301/B (CO2 evolution test). The test was conducted with penconazole (molecular formula: $C_{13}H_{15}Cl_2N_3$, a purity of 96.6% and organic carbon content of 54.94%). Inoculum was prepared at concentration 25.3 mg sludge/L (activated sludge was collected from a sewage treatment plant (CH-4153 Reinach), treating predominantly domestic wastewater) and was dosed with 41.1 and 40.8 mg penconazole, incubated for 29 days at 20 ±2ºC.

The percentage degradation of the reference compound, sodium benzoate, reached the pass level of 60% ThCO2 within a 10-day window. The 10-d window begins when the degree of biodegradation has reached 10% ThCO2 and must end before day 28 of the test. By day 3 it had reached 53% and by day 13, 96% ThCO2, confirming the suitability of the inocula used. Based on the toxicity test (test substance + reference compound) the test substance is not assumed to be inhibitory, more than 25% ThCO2 is reached by day 14. Validation criteria were met. Penconazole reached a mean of -9% $ThCO_2$ by day 29 (negative values are a consequence of comparison of values obtained in the blank controls and the low values obtained in presence of test item), meaning there was no biodegradation of penconazole. Based on these findings penconazole can be considered «not readily biodegradable».

2.8.2.1.2 BOD5/COD

No data provided.

2.8.2.2 Other convincing scientific evidence

2.8.2.2.1 Aquatic simulation tests

One new study was submitted considering aerobic mineralisation of penconazole in surface water, Hurst and Sutcliffe (2015). The study shows that mean levels of penconazole remained similar throughout the incubation period for both low and high concentration and that no significant degradation of penconazole was observed. Low levels of volatile radioactivity were measured (< 1.5% AR). This suggest that penconazole is stable to aerobic mineralisation in surface water.

Hurst and Sutcliffe (2015)
The study was conducted following OECD guideline 309 Aerobic Mineralisation in Surface Water – Simulation Biodegradation Test (13 April 2004). The mineralisation rate and route for degradation of ^{14}C-phenyl labelled penconazole (specific radioactivity: 2.12 MBq/mg, radiochemical purity: 98.3 %) was investigated in Fountains Abbey natural water plus 0.02 g/L suspended sediment systems. ^{14}C-phenyl labelled penconazole was applied in acetonitrile to the water at nominal rates of 10 and 95 µg/L (low and high, respectively). The 95 µg/L rate was also applied to sterilised test systems (natural water plus 0.02 g/L suspended sediment), for examining possible abiotic degradation or other non-biological removal of the test substance. The systems were incubated under aerobic conditions and maintained in dark conditions at 20°C for 59 days. Duplicate samples were collected for each system at 0, 6, 14, 28, 45 and 59 DAT. Sterilised samples were collected at 59 DAT.

Reference samples (natural water plus 0.02 g/L suspended sediment) treated with 10 µg/L sodium benzoate, to confirm viable microbial activity and blank control (natural water and 0.02 g/L suspended sediment), to measure water quality, were similarly incubated. Reference samples were collected at 3, 6, 9, 12, 14, 21, 28, 35, 42, 49, 56 and 59 DAT. Blank controls were collected at 0, 6, 14, 28, 45 and 59 DAT.

At each sampling interval, the quantity of radioactivity in the water and suspended sediment was determined by liquid scintillation counting (LSC). The water was aspirated into a pot containing acetonitrile (50 mL) and centrifuged to separate the water and sediment. The water was analysed by reverse phase high performance liquid chromatography (HPLC), with gradient elution, whilst the suspended sediment was not analysed further.

The test vessels and magnetic stirrer bar were rinsed with methanol:water (80:20 v/v, ca 100 mL) and the quantity of radioactivity in the organic wash was determined by LSC. The organic rinse of the test vessel was not further analysed as it contained <3% of the applied radioactivity (AR) at all sampling intervals.

Any volatile radioactivity was continuously flushed from the vessels, collected in 2M NaOH traps and quantified by LSC. A mass balance was determined for each sample.

The overall mean mass balance for low concentration ranged from 94.9-97.9% AR, with an overall mean of 96.6 ± 1.1% AR. For the high concentration the range was between 96.0-97.3% AR, with an overall mean of 96.6 ± 0.5% AR. The mean mass balance for the sterilised test system was 102.6% AR.

Penconazole was measured to range from mean 92.7- 97.0% AR (low concentration) and 93.3-95.8% AR (high concentration). For the sterilised samples, the mean level of penconazole was 99.9% AR at 59 DAT.

No significant degradation of penconazole was observed within this study and therefore no characterisation of metabolites was required. Penconazole was mineralised to a small amounts of volatile radioactivity (< 1.5% AR in both treatment rates), this was assumed to be CO_2.

The degradation of sodium ^{14}C-benzoate to ^{14}C-carbon dioxide (82.8% AR at 14 DAT and 92.8% AR at 59 DAT) indicated a viable microbial population was established.

The degradation rates (DT_{50}) of penconazole were estimated using CAKE software by fitting single first-order kinetics (SFO) to the data. However, the degradation rates could not be accurately determined due to high prob > t values.

2.8.2.2.2 Field investigations and monitoring data (if relevant for C&L)

No data provided.

2.8.2.2.3 Inherent and enhanced ready biodegradability tests

No data provided. Penconazole is not readily biodegradable.

2.8.2.2.4 Soil and sediment degradation data

Two studies were provided for evaluating the degradation in water/sediment systems, both following OECD Guideline 308, April 2002. Mamouni (1998) assessed and accepted in DAR (2007) and a new study Brands (2009). Kinetic assessments for both studies are presented in Hardy and Agostini (2019e). Both studies show that penconazole dissipate rapidly from the water phase to the sediment, where degradation is slow. The kinetic assessment show that penconazole is very stable in both systems, in both studies.

Mamouni (1998)
The study was conducted with ^{14}C-phenyl labelled penconazole (specific radioactivity: 2.12 MBq/mg; radiochemical purity: > 99%). The rout and rate of degradation of ^{14}C-penconazole was investigated in two different water/sediment systems, River (Rhine) and Pond (Judenweiher). ^{14}C-labelled penconazole was applied dissolved in acetone to the surface water using a Hamilton syringe at a nominal rate of 0.092 mg penconazole/550 mL water = 0.167 mg/L water (equivalent to a field rate of 500 g a.s./ha, assuming a uniform distribution in a water body of 30 cm depth). Samples were incubated under aerobic conditions at 20 ± 1°C, in the dark for 706 days. Samples were taken at 0, 1, 3, 7, 14, 28, 56, 120, 188, 240, 365 DAT. Additional samples were taken after 678 and 686 (river) and 706 (pond) days. Radioactivity in the water layers and the sediment extracts were quantified by LSC. Aliquots of the water layers were analysed by HPLC and TLC. Sediment extracts containing >1% AR were concentrated via rotary evaporation and the resulting extracts were quantified by LSC then analysed, primarily, by HPLC. Confirmatory analysis was performed by TLC. The remaining radioactivity content of the sediment residues after the extraction steps was determined by combustion.

Mean mass balance of the River system was 98.4% AR (ranging from 84.5-103.7% AR) and 102.0% AR (ranging from 95.5-105.8% AR) in the Pond system.

Penconazole dissipated rapidly from the water phase to the sediment in both systems. In water by day 28 penconazole represented 7.1% AR in the River system and by day 14 10.9% AR in the Pond system. At the end of the study duration penconazole represented 1.3% and 1.2% AR in the River and Pond system, respectively. Penconazole initially increased in the sediment reaching a maximum of 91.9% AR at day 14 in the River system and 92.7% AR at day 56 in the Pond system, the levels in the sediment then declined towards the end of the study. The route of degradation was similar in both water/sediment systems with CGA179944 as the major degradation product observed. In the River system CGA179944 was detected at maximum mean levels of 17.3 and 4.8% AR in the water and sediment phases, respectively, with a maximum of 22.1% AR in the total system. In the Pond system CGA17994

reached a maximum of 5.8% AR at 246 DAT in the total system. A minor metabolite (M1) was observed but occurred at <5% AR in the total system in all sampling intervals.

Maximum $^{14}CO_2$ evolved was 8.4% and 4.6% AR in the River and Pond systems, respectively, by the end of the incubation.

Bound residues increased throughout the incubation period. Maximum levels for River and Pond systems were found to be 17.6% and 18.7% AR, respectively.

The half-lives (DT50) of penconazole are presented in the two tables below, under Hardy and Agostini (2019e).

Brands (2009)

The rout and rate of degradation of ^{14}C-triazole labelled penconazole (specific radioactivity: 2.18 GBq/mmol, radiochemical purity: 99.86%) was investigated in two different water/sediment systems, Goovern (GV) and Schoonrewordsewiel (SW). ^{14}C-labelled penconazole was applied dissolved in acetonitrile. The initial test substance concentration in the water layer was 38.1 µg/L (GV) and 39.0 µg/L (SW). The aquatic sediment systems were incubated under aerobic conditions, in the dark at 20 ± 2°C for up to 100 days. Duplicate samples were taken for analysis after 0, 3, 7, 14, 29, 60 and 100 days. Volatiles were trapped by polyurethane foam, ethylene glycol monoethyl ether and NaOH traps. The water layer and the sediment layer were analysed (extraction of sediment with 80/20 (v/v) acetonitrile/Milli-Q water). Bound residues were determined by combustion. Extracts were analysed by HPLC. 14C-penconazole was identified based on comparison of retention time with a reference standard; identification was confirmed by TLC.

The mean mass balance were between 96.2-106.1% AR for the Goorven system and between 96.5- 101.8% AR for the Schoonrewoerdsewiel system.

In the GV system, mean 11.3% AR was recovered in the water layer and 83.0% AR in the sediment extract after 14 days of incubation. At study end 8.7% AR was found in the water layer and 81.2% AR in sediment. In the SW system, 16.6% AR was recovered in the water layer after 14 days of incubation which gradually decreased to 5.6% AR at the end of incubation. In the sediment extract penconazole increased to 71.4% AR after 14 days, and measured 82.4% AR at the end of incubation. No metabolites were detected in either the water layer or the sediment extract of both systems.

Mineralisation was negligible (≤0.1%). Bound residues (non-extractable) accounted for maximum 15% (GV) and 11% (SW) AR.

The half-lives (DT50) for penconazole are presented in the two tables below, under Hardy and Agostini (2019e).

Hardy and Agostini (2019e)

In this study, the data from Brands (2009) and Mamouni (1998) were re-evaluated using the FOCUS guidance (2006 and 2014) and modelling using CAKE v. 3.3 (2016). Revised calculated DT50 values are shown in the tables below.

Table 100: Summary of persistence endpoint DT50 values for penconazole

Reference	System	Derivation of DT_{50}	DT_{50} (days)
Mamouni, (1998)	Pond Judenweiher, water	FOMC	2.39
Mamouni, (1998)	River Rhine, water	HS	1.87
Brands, (2009)	Goovern, water	DFOP	2.49
Brands, (2009)	Schoonrewoerdsewiel, water	HS	4.12
Worst-case water column			**4.12**
Mamouni, (1998)	Pond Judenweiher, Total system	SFO	1150
Mamouni, (1998)	River Rhine, Total system	SFO	563
Brands, (2009)	Goovern, Total system	SFO	2010
Brands, (2009)	Schoonrewoerdsewiel, Total system	SFO	>10000
Worst-case whole system			**>10000**

Table 101: Summary of modelling endpoint DT50 values for penconazole

Reference	System	Derivation of DT_{50}	DT_{50} (days)
Mamouni, (1998)	Pond Judenweiher, water	FOMC DT_{90}/3.32	5.32
Mamouni, (1998)	River Rhine, water	HS DT_{90}/3.32	1.88
Brands, (2009)	Goovern, water	DFOP DT_{90}/3.32	8.77
Brands, (2009)	Schoonrewoerdsewiel, water	HS DT_{90}/3.32	17.1
Geometric mean water column			**6.2**
Mamouni, (1998)	Pond Judenweiher, Total system	SFO	1150
Mamouni, (1998)	River Rhine, Total system	SFO	563
Brands, (2009)	Goovern, Total system	SFO	2010
Brands, (2009)	Schoonrewoerdsewiel, Total system	SFO	>10000
Geometric mean whole system			**>1000**

2.8.2.2.5 Hydrolysis

Two studies were provided for the hydrolysis of penconazole, van der Gaauw (2002) and Spare (1987), both previously submitted and accepted in DAR (2007). Both studies suggest that penconazole can be considered as hydrolytically stable under environmentally relevant pH conditions. No hydrolysis products were detected in either of the studies.

van der Gaauw (2002)
The test was conducted with ^{14}C-phenyl labelled penconazole (specific radioactivity: 2.3 MBq/mg; radiochemical purity: 98.2 %), dissolved in buffer solutions at a concentration of 1.80 to 1.85 mg penconazole/L, at 50°C for 7 days. Samples were taken at 0, 1, 3, 5 and 7 DAT. Sterility was confirmed at 0 DAT and at study termination. Mean observed levels of penconazole at day 7 was measured to be 90.9%, 95.1%, 90.1% and 93.5% AR at pH 4, 5, 7 and 9, respectively. Mean mass balance for the respective pH- levels were 96.1 ± 3.2 %, 95.5 ± 3.2 %, 95.8 ± 3.5 %, and 94.5 ± 3.3 % AR. Individual metabolites were observed at a maximum mean level of 1.2% AR. Less than 10 % of hydrolysis is observed after day 7, penconazole can therefore be considered hydrolytically stable at pH 4, 5, 7 and 9.

Spare (1987a)
The test was conducted with ^{14}C-triazole labelled penconazole (specific radioactivity: 0.77 MBq/mg; radiochemical purity: 98.3 %), the nominal test concentration was 10 mg penconazole/L for all pH values tested and was incubated at 25 ± 1°C for a duration of 30 days. Samples were taken at 0, 1, 3, 7, 14, and 30 DAT. Sterility was not confirmed. Mean observed levels of penconazole at day 30 was measured to be 89.7%, 92.6% and 92.5% AR at pH 5, 7 and 9, respectively. Mean mass balance for the respective pH-levels were 102.5 ± 7.3%, 98.2 ± 4.4% and 91.8 ± 4.4%. Analysis for transformation products was not performed since no hydrolysis was observed. Despite deviations from the current guideline (the study was conducted before the current guideline, OECD 111, was implemented), these do not affect the study results, which are confirmed by the newer study, van der Gaauw (2002). Penconazole can be considered to be hydrolytically stable at pH 5, 7 and 9.

2.8.2.2.6 Photochemical degradation

Data to address the data requirement for direct photochemical degradation are not required since the molar absorption coefficient ε is < 10 L / (mol · cm). Data on indirect photochamical degradation is not required either.

2.8.2.2.7 Other / Weight of evidence

No data provided.

2.8.2.3 *Comparison with the CLP criteria*

Penconazole is considered “not readily biodegradable”, as no degradation was observed over a 29-day test period, following OECD guideline 301/B. Penconazole is considered hydrolytically stable under environmentally relevant pH conditions.

In natural water system penconazole was stable to aerobic mineralisation as mean levels of penconazole remained

similar throughout the study period. In water/sediment systems penconazole dissipated rapidly from the water phase to the sediment, where degradation was slow. Penconazole is stable in water/sediment systems with half-lives for the whole system ranging from 563 to >10,000 days (n=4).

Penconazole is therefore considered to be **not** rapidly degradable for the purpose of classification according to the CLP Criteria Guidance Document (ECHA, 2017).

2.8.3 Summary of fate and behaviour in air

2.8.3.1 Hazardous to the ozone layer

Table 102: Summary table of studies on hazards to the ozone layer

Method	Results	Remarks	Reference
Atmospheric oxidation of penconazole by hydroxy radicals, rate estimation, derived by the Atmospheric Oxidation Programme (AOP, v. 1.85 and 1.91) based on Atkinson model.	DT_{50} of 1.32 days, assuming OH (12 h) concentration = $1.5x10^6$ [OH x cm^{-3}] DT_{50} of 1.99 days, assuming OH (24 h) concentration = $0.5x10^6$ [OH x cm^{-3}]	Acceptable	Stamm, 1999
Volatilization of penconazole from bean leaves. ^{14}C-triazole labelled penconazole. 19 - 21°C, 36 - 40 % relative humidity for 24 hours. Air exchange per hour = 220, indirect method. BBA guideline, July 1990 (outdated). Non GLP.	Penconazole sprayed to young bean plants volatilised at a rate of 50% of the initial residues under laboratory conditions during a 24-hour period.	Not acceptable	Sandmeier, 1992
Volatilization of penconazole from soil surfaces. ^{14}C-triazole labelled penconazole. 20°C, 35 % relative humidity for 24 hours. Velocity of 0.003 m/s, direct and indirect method. Velocity of 1 m/s indirect method. BBA guideline, July 1990 (outdated). Non GLP.	Summarising all of the results, penconazole is considered to be non-volatile from soil surfaces at an air velocity between 0.003 and 1 m/sec.	Not acceptable	Schulze-Aurich, 1993

2.8.3.1.1 Short summary and overall relevance of the provided information on hazards to the ozone layer

The half-life of penconazole in the atmosphere was calculated to be 1.32 days at an assumed average atmospheric OH concentration of 1.5×10^6 cm^{-3} for a 12-hour day, and 1.99 days assuming an average atmospheric concentration of 0.5 x 10^6 OH radicals cm^{-3} for a 24-hour day (Stamm, 1999). This was determined using the Atmospheric Oxidation Program (AOP, version 1.85 and 1.91), based on the Atkinson model. Both derived DT50-values are below the trigger value of 2 days (FOCUS, 2008)[13], further consideration of long-range transport is therefore not necessary for penconazole as it is unlikely. The dominant degradation process for penconazole in the atmosphere is considered to be via reaction with OH (via alkyl hydrogen abstraction and aromatic–ring-addition mechanisms).

[13] FOCUS (2008) Pesticides in Air, SANCO/10553/2006 Rev. 2 June 2008

Two studies were provided on the transport via air, Sandmeier (1992) and Schulze-Aurich (1993), neither are considered acceptable. Penconazole has a low vapour pressure of 9.4×10^{-5} Pa at 20°C. This is under the trigger for volatilisation from soil, but over the trigger for volatilisation from plants[14]. If a step 4 calculation for FOCUS Surface water becomes necessary, input values on volatilization for modelling can be calculated based on the vapour pressure with the EVA tool.

2.8.3.1.2 Comparison with the CLP criteria

According to the CLP Criteria Guidance Document (ECHA, 2017) "any substances having an Ozone Depleting Potential (ODP) greater or equal to the lowest ODP (i.e. 0.005) of the substances currently listed in Annex I to Regulation (EC) No 1005/2009 should be classified as hazardous to the ozone layer (category 1)".

The ODP is not reported for penconazole, hence a comparison with the CLP criteria cannot be made. The hazard is not considered further in this report.

2.8.3.1.3 Conclusion on classification and labelling for hazardous to the ozone layer

Data conclusive but not sufficient for classification.

2.8.4 Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

A groundwater monitoring programme (Naeb and Liss 2018) was conducted in prominent sugar beet and cereal areas in Germany. The aim of the study was to assess residue concentrations of the metabolite 1,2,4-triazole in groundwater following the use of azole fungicides in agricultural crops. None of the analysed samples showed 1,2,4-triazole concentrations >0.1 µg/L. Please refer to Vol. 3 B.8 CA for more information.

2.8.5 Definition of the residues in the environment requiring further assessment

Compartment	Residue definition
Soil	Penconazole CGA179944 CGA142856 (triazole acetic acid; TAA) CGA91305 CGA71019 (1,2,4-triazole)
Groundwater	Penconazole CGA179944 CGA142856 (triazole acetic acid; TAA) CGA91305 CGA71019 (1,2,4-triazole)
Surface water	Penconazole CGA179944 CGA142856 (triazole acetic acid; TAA) CGA91305 CGA71019 (1,2,4-triazole)
Sediment	Penconazole
Air	Penconazole

2.8.6 Summary of exposure calculations and product assessment

To be completed with updated calculations, hence has not been summarised here by the RMS. For current calculations see Volume 3 CP B.8 of the dRAR.

[14] Commission Regulation (EU) No 283/2013

The table below shows a comparison of endpoints in the draft supplied by the applicant (old endpoint, currently used in modelling) and the endpoints suggested by RMS (new endpoints). In the opinion of the RMS the modelling needs an update, but we will leave the final decision up to the MS and EFSA during/after the peer review.

If deemed necessary by MS/EFSA the following adjustments should also be made for the new modelling:

- PECsoil using geometric mean lab DT50. For PECsoil modelling, field DT50 values were used. The soil dissipation studies that this DT50 value was based on have not been approved by the RMS. Modelling should be done with geometric mean laboratory DT50 values
- PECgw and cucumber using "spring cereals" as a surrogate crop (based on co-RMS commenting table, comment 59)
- PECsw Steps 1-2 calculations covering the entire application period. See RMS' grey commenting box in Vol. 3CP B.8, under section B.8.5 for an overview of the additional modelling that should be provided.
- Any new calculations provided for metabolite CGA91305 should be conducted using the correct molecular weight of 258.1 g/mol.

Table 103: Comparison of old endpoints (used in modelling) and new endpoints suggested by RMS

Substance	Endpoint old or new?	Laboratory DT50 (d) 20 ºC pF2 (geometric mean)	Formation fraction (arithmetic mean)	Degr. pH dep.?	Kfoc (mL/g) (geometric mean)	1/n (arithmetic mean)	Sorption pH dep.?
Penconazole	Old	179	-	No	1931	0.82	No
	New	180.6	-	No	1931	0.82	Yes
CGA179944	Old	71.3	0.256	No	26.5	0.85	No
	New	71.8	0.288	No	18.9	0.85	Yes
CGA142856	Old	5.80	1	No	0	1	No
	New	5.80	1	No	0	1	No
CGA71019	Old	*	*	-	83.1	0.92	No
	New	*	*	-	83.1	0.92	Yes
CGA91305	Old	19.6	0.288	No	183.1	0.91	No
	New	18.8	0.344	No	183.1	0.91	Maybe

*No reliable lab DT50 or f.f. values. Field data used in modelling.

2.9 EFFECTS ON NON-TARGET SPECIES

2.9.1 Summary of effects on birds and other terrestrial vertebrates

Birds

Acute toxicity

Four acute oral studies with birds exposed to penconazole have been evaluated by the RMS. Two of the studies have been accepted, while one of the studies ([redacted] **1980a; CGA71818/0062)** was only considered supportive due to several deviations from the test guideline, non-compliance with GLP and lack of certificate of analysis. The last study ([redacted] **1980a; CGA71818/0060)** was considered not acceptable due to regurgitation among the threated birds. The geomean between the two acceptable acute oral studies ([redacted] **1984; CGA71818/0067**, [redacted] **1984a; CGA71818/0066)** of **1998 mg/kg bw** has been used in the acute risk assessment. Two additionally acute oral studies with the metabolites CGA71019 ([redacted] **&** [redacted] **2014; CGA071019_50000)** and CGA142856 ([redacted] **2003; VV_510365)** have been used as supportive information in the avian risk assessment of these metabolites.

Short-term toxicity

Several short-term studies with birds have been submitted and the endpoints from these studies are only considered supportive. Such studies with penconazole are not a data requirement under **Commission Regulation (EU) No**

283/2013, as the mode of action, or results from mammalian studies do not indicate a potential for the dietary LD_{50} measured by the short term dietary (5-day) studies to be lower than the LD_{50} based on an acute oral studies. Furthermore, the results from the short-term studies do not indicate higher toxicity than what was observed in the acute oral studies with birds. Two of the studies with the metabolite CGA 131013 have been used as supportive information in the avian risk assessment of this metabolite.

Reproductive toxicity

Two reproductive studies with birds have been evaluated by the RMS. Only one of the studies ([redacted] **1985; CGA71818/0068**) is still considered acceptable since two of the validity criteria were not fulfilled in the second study ([redacted] **1985a; CGA71818/0069**). The **EFSA Guidance Document on Risk Assessment for Birds and Mammals (2009)** states that the acute $LD_{50}/10$ should be used as an endpoint in long-term risk assessment when it is lower than the long-term endpoint. For penconazole the lowest endpoint from the reproduction studies (28.9 mg a.s./kg bw) will be used in risk assessment since this endpoint is lower than the acute geomean $LD_{50}/10$ ($LD_{50}/10$ = 200 mg a.s./kg bw).

The endpoints relevant for the avian risk assessment are summarised in the table below.

Table 104: Summary of acceptable and supportive endpoints for birds exposed to penconazole. Endpoints in **bold** are used in the risk assessment.

Organism	Test item	Test type	Endpoints	Reference (author, date, Document No.)
Acute oral				
Mallard duck (*Anas platyrhynchos*)	Penconazole	Acute oral	**LD_{50} >1590 mg/kg bw[a]*** NOEL = 1590 mg/kg bw	[redacted] ***1984; CGA71818/0067***
Bobwhite quail (*Colinus virginianus*)	Penconazole	Acute oral	**LD_{50} >2510 mg/kg bw[a]*** NOEL < 398 mg/kg bw mg/kg bw	[redacted] ***1984a; CGA71818/0066***
Japanese quail (*Coturnix japonica*)	Penconazole	Acute oral	LD_{50} = 2424 mg/kg bw NOEL = 600 mg/kg bw	[redacted] ***1980a; CGA71818/0062[b]***
Bobwhite quail (*Colinus virginianus*)	CGA71019	Acute oral	LD_{50} = 770 mg/kg bw NOEL = 245 mg/kg bw	[redacted] **&** [redacted] ***2014; CGA071019_50000[d]***
Bobwhite quail (*Colinus virginianus*)	CGA142856	Acute oral	LD_{50} = >2000 mg/kg bw NOEL = 2000 mg/kg bw	[redacted] ***2003; VV_510365[d]***
Dietary short term				
Mallard duck (*Anas platyrhynchos*)	Penconazole	Dietary short term [c]	LD_{50} >1845 mg/kg bw/d) NOEL = 987 mg/kg bw/day*	[redacted] ***1985; CGA71818/0065***
Peking duck (*Anas domestica*)	Penconazole	Dietary short term [c]	LC_{50} >1000 mg/kg feed NOEC = 1000 mg/kg feed	[redacted] ***1980b; CGA71818/0061***
Japanese quail (*Coturnix japonica*)	Penconazole	Dietary short term [c]	LC_{50} >1000 mg/kg feed NOEC = 1000 mg/kg feed	[redacted] ***1980c; CGA71818/0063***
Mallard duck (*Anas platyrhynchos*)	CGA131013	Dietary short term [c]	LD_{50} >1404 mg/kg bw/d NOEL = 1404 mg/kg bw/day	[redacted] ***&*** [redacted] ***1983; CGA131013/0034***
Bobwhite quail (*Colinus virginianus*)	CGA131013	Dietary short term [c]	LD_{50} >1342 mg/kg bw/d NOEL = 1342 mg/kg bw/day	[redacted] ***&*** [redacted] ***1983a; CGA131013/0033[b]***

Organism	Test item	Test type	Endpoints	Reference (author, date, Document No.)
Acute oral				
Reproductive				
Mallard duck (*Anas platyrhynchos*)	Penconazole	Sub-chronic toxicity and reproductive	**NOAEL = 28.9 mg/kg bw/d***	[redacted] ***1985; CGA71818/0068***

[a] Used in the geomean calculation of the acute endpoint: LD_{50}(geomean) =1998 mg/kg bw
[b] Study only considered supportive due to several deviations from the test guideline, non-compliance with GLP and lack of certificate of analysis.
[c] Study only considered supportive. Dietary short-term studies no longer a data requirement under **Commission Regulation (EU) No 283/2013.**
[d] Study not previously evaluated.
* Note that the batch used is not equivalent with the reference specification (finalised September 2009 by RMS Germany) or the appli-cants proposed technical specification (global specification). However, studies are still considered protective when used in the risk assessment with regard to the representative uses. For further details, see Volume 3 (AS) B.9.11 and Volume 4 (Syngenta).

Mammals

Acute toxicity

The acute oral study with the representative formulation A6209G ([redacted] **1996; CGA71818/1239**) shows 3.8 times higher toxicity than the corresponding lowest endpoint from the studies with the active substance (based on a.s. content). Therefore, the acute risk assessment for wild mammals has been conducted both with endpoints derived from studies with the active substance and the product (LD_{50} = **971 and 257 mg as/kg bw**, respectively**)**. Endpoints are available from three acute oral studies with the metabolites CGA131013, CGA142856 and CGA205369 ([redacted] **1981; CGA71818/0764,** [redacted] **1980; CGA71818/0763** and [redacted] **1980a; CGA71818/0693)** Furthermore, two new 7-day tolerability studies with pregnant rats exposed to the metabolite CGA179944 ([redacted] **2017; CGA179944_10014** and [redacted] **2017; CGA179944_10015)** have been submitted. Studies with rabbits exposed to CGA179944 (developmental study; [redacted] **2018, CGA179944_10027**) and rats exposed to CGA132465 (28-day oral toxicity study; [redacted] ***2019,* 01166003**) have also been submitted. Data from the studies above have been used as supportive information in the mammalian risk assessment of the relevant metabolites.

The acute endpoints relevant for the mammalian risk assessment are summarised in the table below.

Table 105: Summary of acute oral toxicity endpoints for mammals. Endpoints in **bold** are used in the risk assessment.

Organism	Test item	Test type	Endpoints	Reference (author, date, File No.)
Rabbit	Penconazole	Acute oral	**LD_{50} = 971 mg a.s./kg bw**	[redacted] ***1981; CGA71818/0764***
Rat	Penconazole	Acute oral	LD_{50} = 2125 mg a.s./kg bw	[redacted] ***1980; CGA71818/0763***
Chinese hamster	Penconazole	Acute oral	LD_{50} = 5000 mg a.s./kg bw	[redacted] ***1980a; CGA71818/0693***
Mouse	Penconazole	Acute oral	LD_{50} = 2444 mg a.s./kg bw	[redacted] ***1980; CGA71818/0707***
Rat	A6209G (Topas 100 EC)	Acute oral	**LD_{50} = 2574 mg A6209G/kg bw, corresponding to 257 mg a.s./kg bw**	[redacted] ***1996; CGA71818/1239 TOX 96-50626***

Organism	Test item	Test type	Endpoints	Reference (author, date, File No.)
Rat	CGA131013	Acute oral	LD_{50} >5000 mg/kg bw	[redacted] ***1982; CGA131013/0030***[b]
Rat	CGA142856	Acute oral	LD_{50} >5000 mg/kg bw	[redacted] ***1984; CGA142856/0001***[b]
Rat	CGA205369	Acute oral	LD_{50} >2000 mg/kg bw	[redacted] ***2006; CGA205369/000***[c]***1***
Rat	CGA179944	7-day tolerability and TK in non-pregnant rat (gavage)	Dose levels up to 1000 mg/kg bw/day well tolerated	[redacted] ***2017; CGA179944_10014***[a]
Rat	CGA179944	7-day tolerability and TK in non-pregnant rat (dietary)	Dose levels up to 10000 ppm (737 mg/kg bw/day) well tolerated	[redacted] ***2017; CGA179944_10015***[a]

[a] Studies evaluated in **section B.6**
[b] Evaluated and accepted during the previous EU evaluation of penconazole
[c] Reviewed in triazole derivative metabolite assessment (COP no. 2011.00502)

Reproductive toxicity

The endpoints relevant for the ecotoxicological risk assessment are summarised in the table below. In terms of the chronic endpoint, the NOAEL of **21.2 mg a.s./kg bw**/d is considered the most relevant ecological endpoint for use in the mammalian risk assessment. This endpoint is based on reduced body weights for both adults and pups during lactation. Please refer to **Volume 3 (PPP) - B.9.2.2.1** for details on the selection of the ecotoxicologically relevant endpoint.

Table 106: Summary of short-term dietary and long-term endpoints for mammals. Endpoints in **bold** are used in the risk assessment.

Organism	Test item	Test type	Endpoints[a]	Reference (author, date, File No.)
Rat	Penconazole	2-generation reproduction study	NOAEL = 29.9 (males) and 29.7 (females) mg/kg bw/day	[redacted] ***1983; CGA71818/0755***
Rat	Penconazole	2-generation reproduction study	**NOAEL= 21.2 (males)** and 22.7 (females) **mg/kg bw/day**	[redacted] ***1987; CGA71818/0756***
Rat	Penconazole	Developmental study	NOAEL = 100 mg/kg bw/day	[redacted] ***1981; CGA71818/0751***
Rat	Penconazole	Developmental study	NOAEL = 100 mg/kg bw/day	[redacted] ***1985; CGA71818/0752***
Rabbit	Penconazole	Developmental study	NOAEL = 75 mg/kg bw/day	[redacted] ***1982; CGA71818/0753***
Rabbit	Penconazole	Developmental study	NOAEL = 50 mg/kg bw/day	[redacted] ***1985; CGA71818/0754***

Organism	Test item	Test type	Endpoints[a]	Reference (author, date, File No.)
Rat	Penconazole	28-day oral toxicity study	NOAEL = 20/100 mg/kg bw/day	[redacted] ***1984; CGA71818/0759***
Rat	Penconazole	28-day oral toxicity study	NOAEL < 100 mg/kg bw/day	[redacted] ***1991; CGA71818/0837***
Rat	Penconazole	Sub-chronic oral toxicity study	NOAEL = 19.4 (males) and 20.7 (females) mg/kg bw/day	[redacted] ***1982; CGA71818/0714***
Rat	Penconazole	Sub-chronic oral toxicity study	NOAEL = 7.1 (male) and 7.3 (female) mg/kg bw/day	[redacted] ***1983; CGA71818/0715***
Rat	Penconazole	Sub-chronic oral toxicity study	NOAEL = 23.2 (males) to 28.3 (females) mg/kg bw/day	[redacted] ***1987; CGA71818/0716***
Dog	Penconazole	Sub-chronic oral toxicity study	NOAEL = 3.4 (males) and 3.8 (females) mg/kg bw/day	[redacted] ***1984; CGA71818/0718***
Dog	Penconazole	Sub-chronic oral toxicity study	NOAEL = 3.0 (males) and 3.2 (females) mg/kg bw/d	[redacted] ***1984; CGA71818/0718***
Mouse	Penconazole	Sub-chronic oral toxicity study	NOAEL = 85 (male) and 237 (female) mg/kg bw/day	[redacted] ***1987; CGA71818/0717***
Mouse	Penconazole	Sub-chronic oral toxicity study	NOAEL = 69 (males) and 87 (females) mg/kg bw/d	[redacted] ***2002; CGA71818/4393***
Rat	CGA132465	28-day oral toxicity study	NOAEL = 75 and 74 mg/kg bw/day	[redacted] ***2019; 01166003***[b]
Rat	CGA131013	2-generation reproduction	NOAEL = 100 mg/kg bw/day	[redacted] ***et.al., 1986; CGA131013/0020***[b]
Rat	CGA71019	2-generation reproduction	NOAEL = 34.4 mg/kg bw/day	[redacted] ***et.al., 2005; CGA71019/0084***[c]
Rabbit	CGA179944	Developmental study (OECD 414) Dose levels 0, 100, 300 and 600 mg/kg/day (gavage)	Maternal NOAEL = 300 mg/kg bw/day; foetal/developmental NOAEL = 600 mg/kg bw/day	[redacted] ***2018; CGA179944_10027***[a]

[a] Study evaluated in **Volume 3 - B.6 (AS)**
[b] Evaluated and accepted during the previous EU evaluation of penconazole
[c] Reviewed in triazole derivative metabolite assessment (COP no. 2011.00502)

2.9.2 Summary of effects on aquatic organisms [section 11.5 of the CLH report]

Since penconazole is not intended solely for use in enclosed spaces, studies to address the data requirements in accordance with **Commission Regulation (EU) No 283/2013** and **Commission Regulation (EU) No 284/2013** have been provided.

Toxicity data have been provided for penconazole, relevant metabolites and the formulation A6209G. Many of the studies were already available during the previous evaluation (Penconazole B9: Ecotoxicology, June 2007, Volume 3 DAR and DAR addenda (April 2008, November 2009). Updated study summaries have been included in **Volume 3 - B.9 (AS)** and **Volume 3 - B.9 (PPP)** and the studies have been re-evaluated according to recent guidelines and standards. In addition, new studies with penconazole metabolites have been provided to meet specific data gaps.

2.9.2.1 Bioaccumulation [equivalent to section 11.4 of the CLH report template]

Table 107: Summary of relevant information on bioaccumulation

Method	Species	Test material	Results	Relevant study	Remarks	Reference
OECD 107 (shake flask method)	NA	Penconazole technical Purity: 99.3 % Batch: AMS 204/3	log P_{ow} = 3.8 at 20 °C	Reliable (key study)	Measured partition coefficient n octanol/water	Halarnakar R. 2018; CGA071818/10590

[a] Evaluated according to OECD 305 (2012)

2.9.2.1.1 Estimated bioaccumulation

Not relevant, see paragraph 2.9.2.1.2.

2.9.2.1.2 Measured partition coefficient and bioaccumulation test data

A study on Bioaccumulation should always be provided for substances with a log K_{ow} >3. As penconazole fulfils this criterion (Log K_{ow} = 3.8), a study has been provided.

The metabolites which are considered relevant and need to be addressed in the aquatic risk assessment are CGA179944, CGA71019, CGA142856 and CGA91305. None of these metabolites have a log K_{ow} >3 (see Volume 3 (CA) B2 and the table below).

	Penconazole	CGA71019*	CGA179944*	CGA142856**	CGA91305***
Log Kow	3.8 at 20 °C and pH 6.9	-0.62 at pH 5 -0.71 at pH 7 -0.68 at pH 9	0.26 at pH 5 -1.3 at pH 7 -1.7 at pH 9	-1.4 at 25°C and pH 4 -2.22 at 25°C and pH 7	2.1 at pH 7.5 to 8.7

* Log P_{ow}-value not finally verified, seeVolume 3 (CA) B2
** Log P_{ow}-value verified, see Volume 3 (CA) B2
*** Log P_{ow}-value not verified. Needs further confirmation by applicant, see Volume 3 (CA) B2

[redacted] (2018), Report No. SMG14669, Data point: K-CA 2.7/01
The measured logarithmic n-octanol/water partition coefficient of penconazole is 3.8 (log K_{ow} = 3.8 at 20 °C).

[redacted] (1988) Report No. 85-2-1729, Data point: K-CA 8.2.2.3/01
One bioaccumulation study with the bluegill sunfish, *Lepomis macrochirus*, is available (not included in the summary table). In this study, a maximum whole fish bioconcentration factor (BCF) of 320 was derived.

In the current study TOC was not measured during the test. Organic matter content, quantified as total organic carbon (TOC) and dissolved organic carbon (DOC) can have a significant effect on the amount of freely dissolved test substance during flow-through fish tests, especially for highly lipophilic substances. A metabolism study with a 7-day semi static exposure was available, and during this part of the study partitioning of penconazole between the aqueous and organic phase in water was investigated. The results show that 85-98% of ^{14}C-residues were extracted from the organic phase. Sorption of the test substance to organic matter may reduce its bioavailability and therewith result in an underestimation of the BCF[15]. In total, this brings uncertainty about the accuracy of calculated BCF.

In addition, there was a lack of lipid and growth measurements which prevented normalisation of the BCF, and the calculation of the BCF was not done according to the guideline. The BCF was instead calculated based on the mean maximum concentration in fish and the concentration in fish was highest at the start of the exposure period. RMS asked coRMS DE for their opinion regarding the validity of the study, and received the following comment (excerpt): *(...) In our opinion, this study should not be considered valid. The relation of the BCF to the high concentration at the beginning might be conservative, but might also be due to the fact that the test substance was not completely bioavailable in the further course of the study. Consequently, there is a high uncertainty attributed to the BCF. (…)*

RMS thus consider the study not valid, and recommend a new valid study is conducted to conclude on the BCF. For further details, see **Volume 3 - B.9.2.2.3 (AS).**

Fulfilment of the data requirements (PPP-legislation)
According to **Commission Regulation (EU) No 283/2013** data requirement *8.2.2.3. Bioconcentration in fish: The test on bioconcentration in fish shall provide the **steady-state bioconcentration factors**, **uptake rate constants** and **depuration rate constants**, **incomplete excretion**, **metabolites formed in fish** and, if available, information on **organ-specific accumulation**.*
*All data shall be provided with **confidence limits** for each test substance. Bioconcentration factors shall be expressed as a **function of both total wet weight and of the lipid content of the fish**.*

The available study reports a maximum BCF in whole fish, muscle and viscera, and also includes a metabolite study. The study does not report a **steady state BCF**, **uptake or depuration rate constants,** and the BCF is instead based on the mean maximum concentration in fish **(**highest at the start of the exposure period). Further, **confidence intervals (CI)** of the reported BCF are not included, and neither is the **growth or the lipid content** of fish. In addition, the study has not been regarded as reliable by RMS, due to lack of measurements of TOC and uncertainties about the bioavailability of penconazole in water. The data requirement is thus not considered fulfilled.

CLP
For a comparison with the CLP-criteria, please see section 2.9.2.4.

2.9.2.1.3 Assessment of bioaccumulation (B)-criteria, in Annex II to Regulation (EC) 1107/2009

The criteria for bioaccumulation in aquatic organisms, as stated in Annex II to Regulation (EC) 1107/2009, is BCF or BAF > 2000 (PBT) and > 5000 (POP and vBvP). As indicated above, the available study on bioaccumulation is not regarded reliable by RMS. A decision regarding the bioaccumulative potential can thus not be reached.

2.9.2.2 Acute aquatic hazard [equivalent to section 11.5 of the CLH report template]

In the table, studies regarded as acceptable and supportive for risk assessment and hazard classification are

[15] OECD (2017). Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation. ENV/JM/MONO(2017)16

listed. Studies regarded as not acceptable have not been included.

Table 108: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results	Relevant study	Remarks	Reference
OECD 203 (1981) [a] GLP	Rainbow trout (*Oncorhynchus mykiss*)	**A6209G** (Topas 100 EC) Purity: 100 g/L penconazole Batch: Not reported	96 h (static) **LC_{50} > 5.6 mg formulation/L (nom)** **(**LC_{50} < 6.8 mg formulation/L (nom)) Equivalent to: **LC_{50} > 0.56 mg a.s./L (nom)** **(**LC_{50} < 0.68 mg formulation/L (nom))	Reliable	Unknown batch used Expiry date of batch not reported In the study report, the LC_{50} is estimated to be 6.8 mg prod/L (nom), however concentrations were not maintained within ± 20 % of nominal for all treatments. In addition, concentrations were only measured in 3 of 5 treatments, and it is thus not possible to calculate the endpoint based on mean measured concentrations. As only 10 % mortality was observed at the second highest test-concentration of 5.6 mg prod/L (nom) and a 100% mortality was observed at the top dose of 10 mg prod./L, the endpoint is established to be LC_{50} > 5.6 mg formulation/L (nom) but < 6.8 mg prod/L (nom).	[redacted] 1984; CGA71818/0005
OECD 203 (1981) [a] GLP	Carp (*Cyprinus carpio*)	**A6209G** (Topas 100 EC) Purity: 99% Batch: P 401013	96 h (flow-through) LC_{50} > 10 mg formulation/L (nom) **(**LC_{50} < 12.1 mg formulation/L (nom)) Equivalent to: LC_{50} >1.0 mg a.s./L) (nom) **(**LC_{50} < 1.21 mg formulation/L (nom))	Reliable	Unknown batch used Expiry date of batch not reported In the study report, the LC_{50} is estimated to be 12.1 mg prod/L (nom). Concentrations were not maintained within ± 20 % of nominal for all	[redacted] 1984a; CGA71818/0006

Method	Species	Test material	Results	Relevant study	Remarks	Reference
					treatments. In addition, concentrations were only measured in 3 of 5 treatments, and it is thus not possible to calculate the endpoint based on mean measured concentrations. As only 10% mortality was observed at test-concentration of 10 mg prod/L (nom) and a 100% mortality was observed at the test concentrations 18 and 32 mg mg prod./L, the endpoint is established to be LC50 > 10 mg formulation/L (nom) and < 12.1 mg formulation/L.	
OECD 203 (1981) [a]	Rainbow trout (*Onchorynchus mykiss*)	**Penconazole Tech.** Purity: 87.3% Batch: FL 30634	96 h (static) **LC_{50} ≤ 1.3 mg a.s./L (im)**	Supportive for risk assessment Reliable for hazard classification (please see justification in section 2.9.2.4.1)	No analytical measurement at the end of the study, endpoint thus established to be either equal or lower than the derived endpoint	[redacted] 1984; CGA71818/0073
OECD 203 (1981) [a]	Carp (*Cyprinus carpio*)	**Penconazole Tech.** Purity: 99% Batch: P 401013	96 h (static) LC_{50} = 3.8 mg a.s./L (nom)	Reliable	Not GLP Expiry date of technical penconazole not reported	[redacted] 1984a; CGA71818/0076
OECD 203 (1981) [a]	Rainbow trout (*Onchorynchus mykiss*)	**CGA71019** (1,2,4-Triazole) Purity: 91.9% Batch: EN 38530	96 h (static) **LC_{50} = 529 mg/L (mm)**	Reliable	Not GLP Expiry date of technical penconazole not reported	[redacted] 1983; CGA71019/0024
OECD 203 (1992) [a] GLP	Fathead minnow (*Pimephales promelas*)	**CGA179944** Purity: 99 ± 2% Batch: MLA-437/1,3,4	96 h (static) **LC_{50} > 60 mg/L (nom)**	Reliable		[redacted] & [redacted] 2001; CGA179944/0009

Method	Species	Test material	Results	Relevant study	Remarks	Reference
OECD 203 (1992) [a] GLP	Fathead minnow (*Pimephales promelas*)	**CGA179944** Purity: 99.44 % Batch: PH18I	96 h (static) LC_{50} >100 mg/L (nom)	Reliable		[redacted] & [redacted] 2010; CGA179944_10032
OECD 203 [a] Directive 92/69/EEC, C.1 [a] GLP	Rainbow trout (*Oncorhynchus mykiss*)	**CGA142856** (triazole acetic acid) Purity: 96.95% wt/wt Batch: FCF/T/197-0 1 (ex 20689117)	96 h (static) **LC_{50} >100 mg/L (nom)**	Reliable		[redacted] & [redacted] 2003; CGA142856/0025
OECD 203 (1992) [a] GLP	Rainbow trout (*Oncorhynchus mykiss*)	**CGA91305** Purity: 99 ± 2% Batch: KI 6437/2	96 h (static) **LC_{50} = 23.7 mg/L (nom)**	Reliable		[redacted] 2001; CGA77502/0001
OECD 202 (1984) [b] GLP	*Daphnia magna*	**A6209G** (Topas 100 EC) Purity: 100 g/L (nominal); 108 g/L (analysed) Batch: P.609143	**48 h (static)** **EC_{50} = 36 mg /L** **Equivalent to:** **EC_{50} = 3.88 mg a.s./L (nom)**	Reliable		Palmer et al, 2001; CGA71818/4379
US EPA-660/3-75-009 [b]	*Daphnia magna*	**Penconazole tech.** Purity: NA Batch: P. 11-14	**48 h (static)** **EC_{50} = 6.75 mg/L (nom)**	Supportive	Not GLP Purity unknown The batch not equivalent with the reference specification (finalised September 2009 by RMS Germany) or the applicants proposed technical specification (global specification). See Volume 4 (Syngenta).	Hitz, 1981; CGA71818/0079
OECD 202 (1984) [b] Dir	*Daphnia magna*	**CGA71019** (1,2,4-	48 h (static) **EC_{50} >100 mg/L (nom)**	Reliable		Bell, 1995; CGA169374/2320

Method	Species	Test material	Results	Relevant study	Remarks	Reference
92/69/EEC, C.2 (1992) GLP		Triazole) Purity: 100.8 % Batch: JC 16/215854 /3				
OECD 202 (1984) [b] GLP	*Daphnia magna*	**CGA179944** Purity: MLA-437/1,3,4 Batch: 99 ± 2%	48 h (static) **EC_{50} >120 mg/L (nom)**	Reliable		Swarbrick & Woodyer, 2001a; CGA179944/0011
OECD 202 (1984) [b] Dir 92/69/EEC, C.2 (1992) GLP	*Daphnia magna*	**CGA179944** Purity: 99.75% Batch: PH18I	48 h (static) **EC_{50} >120 mg/L (nom)**	Reliable		Kuhl & Wydra, 2009; CGA179944_10031
OECD 202 (1984) [b] Dir 92/69/EEC, C.2 (1992) GLP	*Daphnia magna*	**CGA142856** (triazole acetic acid) Purity: 96.95% Batch: FCF/T/197-01 (ex 20689/17)	48 h (static) **EC_{50} >100 mg/L (nom)**	Reliable		Hertl & Breitwieser, 2003a; CGA142856/0026
OECD 202 (1993) [b] GLP	*Daphnia magna*	**CGA91305** Purity: 99 ± 2% Batch: KI 6437/2	48 h (static) **EC_{50} >110 mg/L (nom)**	Reliable		Wallace, 2001a; CGA77502/0002
OECD 201 (1984) [c] GLP	Green algae *(Scenedesmus subspicatus)*	**A6209G** (Topas 100 EC) Purity: 100 g/L (nominal) Batch: OP 211 052	72 h (static) **E_rC_{50} = 7.9 mg/L (nom)** **Equivalent to:** **E_rC_{50} = 0.79 mg a.s./L (nom)** E_rC_{20} = 4.3 mg/L (nom) E_rC_{10} = 3.1 mg/L (nom) E_bC_{50} = 3.9 mg/L (nom) E_bC_{20} = 2.1 mg/L (nom) E_bC_{10} = 1.6 mg/L(nom) NOEC = 1.0 mg a.s./L (nom)	Reliable		Memmert & Knoch, 1994; CGA71818/1234 & Schuster, 2016; A6209G_11142 [d]
OECD 201 (1984) [c] OPPTS 850.5400, C.3 (1996)	Green algae *(Pseudokirchneriella subcapitata)*	**Penconazole tech.** Purity: NA Batch: WS00700	72 h (static) E_rC_{50} = 4.9 mg/L (mm) E_rC_{20} = 2.94 mg/L (mm)	Reliable	Purity unknown	Desjardins et al, 2001; CGA71818/4378 & Schuster,

Method	Species	Test material	Results	Relevant study	Remarks	Reference
GLP		1	E_rC_{10} = 2.39 mg/L (mm) E_bC_{50} = 2.0 mg/L (mm) E_bC_{20} = 0.78 mg/L (mm) E_bC_{10} = 0.50 mg/L (mm) NOEC = 0.56 mg a.s./L (mm)			2016; CGA071818_10472 [d]
OECD 201 (2006) [c] GLP	Green algae *(Pseudokirchneriella subcapitata)*	**Penconazole tech.** Purity:99.86% Batch: 0701	72 h (static) **E_rC_{50} = 3.41 mg/L (mm)** E_rC_{20} = 0.62 mg/L (mm) E_rC_{10} = 0.26 mg/L (mm) E_yC_{50} = 0.42 mg/L (mm) E_yC_{20} = 0.16 mg/L (mm) E_yC_{10} = 0.10 mg/L (mm) NOEC = 0.234 mg/L (mm)	Reliable		Kley & Wydra, 2009: CGA071818_10633 & Lührs & Wydra, 2018: CGA071818_10633 [d]
OECD 201 (2006/2011) [c]	Green algae *(Pseudokirchneriella subcapitata)*	**Penconazole tech.** Purity: NA Batch: NA	72 h (static) E_rC_{50} = 3.62 mg/L (measured)	Supportive	Study from open literature Not GLP Batch/purity/expiry date not reported Concentrations of penconazole measured, but not reported Validity criteria not reported	Durjava et al., 2013: ATLA, 41:65-75.
OECD 201 (1984) [c] O.J. No. L383A, Method C.3 (1992) OPPTS 850.5400, C.3 (1996) GLP	Green algae *(Pseudokirchneriella subcapitata)*	**CGA71019** (1,2,4-Triazole) Purity: 99 ± 2% Batch: R200	72 h (static) **E_rC_{50} >31 mg/L (mm)** E_rC_{20} = 11.3 mg/L (mm) E_rC_{10} = 8.3 mg/L (mm) E_bC_{50} = 13 mg/L (mm) E_bC_{20} = 7.2 mg/L (mm) E_bC_{10} = 5.9 mg/L (mm) NOEC = 3.1 mg/L (mm)	Reliable		Palmer et al, 2001; CGA71019/0044 & Hefner, 2014; CGA071019_10010 [d]
OPPTS	Green algae *(Pseudokirc*	**CGA179944**	72 h (static)	Reliable	Deviations in pH. Study still	Swarbrick & Woodyer,

Method	Species	Test material	Results	Relevant study	Remarks	Reference
850.5400, C.3 (1996) [c] GLP	*hneriella subcapitata)*	Purity: MLA-437/1,3,4 Batch: 99 ± 2%	**E_rC_{50} > 32 mg/L (mm)** E_bC_{50} > 32 mg/L (mm) NOEC >32 mg/L		considered acceptable (see RAR Volume 3CA, B.9.)	2001b; CGA179944/ 0010
OPPTS 850.5400, C.3 (1996) [c] GLP	Green algae *(Selenastrum capricornutum)*	**CGA91305** Purity: 99 ± 2% Batch: KI 6437/2	72 h (static) **E_rC_{50} = 19.1 mg/L (nom)** E_rC_{20} = 11.5 mg/L (nom) E_rC_{10} = 8.9 mg/L (nom) E_bC_{50} = 9.6 mg/L (nom) E_bC_{20} = 6.7 mg/L (nom) E_bC_{10} = 4.7 mg/L(nom) NOEC =3.2 mg/L (nom)	Reliable		Wallace & Woodyer, 2001; CGA77502/0003 & Hefner, 2014a; CGA091305_1011
OECD 221 (2006) [e] US EPA Proposed Guidelines for Registering Pesticides in the United States, Subpart J, 1980; Holst RW and TC Ellwanger, 1982	*Lemna gibba*	**Penconazole tech.** Purity: 87.3% Batch: FL-830634	14 days (static) E_bC_{50} = 0.19 mg/L (frond number) E_bC_{50} = 0.096 mg/L (dry weight)	Not acceptable Included in table for completeness, as the study was considered the key study in the RAC opinion from 2012	The validity criteria in OECD 221 (2006) were not fulfilled: frond doubling time were 2.6 days and average specific growth rate 0.268d-1, whereas the validity criteria require a doubling time of less than 2.5 days and an average specific growth rate of 0.275 d-1. No analytical measurement of test substance during the test.	Hughes J.S., 1985a; CGA71818/ 0082

[a] Evaluated according to OECD 203 (2019)
[b] Evaluated according to OECD 202 (2004)
[c] Evaluated according to OECD 201 (2006/2011)
[d] Statistical re-analysis to determine EC_{10}- and/or EC_{20}-estimates.
[e] Evaluated according to OECD 221 (2006)
Bold values represent the lowest endpoint for the respective organism group and test substance.

2.9.2.2.1 Acute (short-term) toxicity to fish

Five studies with penconazole technical and five studies with metabolites (CGA71019/1,2,4-Triazole, CGA179944, CGA142856/triazole acetic acid and CGA91305) have been provided. In addition, two studies with the representative formulation A6209 (Topas EC 100) are available. Reliable and supportive studies are summarised in the table, above. Full study summaries and the assessment and conclusion by the applicant and by RMS are available in **Volume 3 - B.9 (AS)** and **Volume 3 - B.9 (PPP)**.

According to **Commission Regulation (EU) No 283/2013** studies performed to obtain data on the properties or safety with respect to animal health and the environment *shall be* conducted in accordance with the **GLP-principles** (principles laid down in Directive 2004/10/EC of the European Parliament and of the Council (OJ L 50, 20.2.2004, p. 44)). Two of the fish studies (study with penconazole technical and CGA71019) were however not conducted according to GLP. As a *way of derogation from this requirement* studies with vertebrates may be integrated into the

assessment, when accepted by the competent authorities as scientifically valid, thereby removing the need for repeating animal tests. Both non-GLP studies fulfils the validity criteria of the OECD guideline, and the studies are thus considered reliable.

Penconazole

One Reliable study ([redacted] (1985), fulfilling the validity criteria of OECD TG 203, however non-GLP) with penconazole technical considered suitable for use in hazard classification and risk assessment is presented below. Four fish studies did not fulfill all of the OECD TG 203 validity criteria, as penconazole was measured initially, however no measurements were performed at the end of the test. It is thus not possible to determine if concentrations were maintained, and an accurate LC_{50} cannot be estimated with certainty, which is necessary in order to conclude on the risk. Three of these studies were thus not considered further, and regarded as not reliable. The fourth study ([redacted] 1984) was conducted with rainbow trout, and was also the study providing the lowest endpoint of the available fish studies. As concentrations were measured at test start, it can be concluded with certainty that the LC_{50} from this study is either equal to or lower than the established endpoint. The study also fulflled the remaining validity criteria, and was conducted according to the OECD TG. In the data requirements for AS (Commission regulation 283/2013), a study with rainbow trout shall be conducted. RMS is of the opinion that the study provides relevant information for deciding on the endpoint to be used in the risk assessment for fish, and the study has thus been regarded as supportive information for the risk assessment. RMS also consider the study as reliable for use in hazard classification, and a justification for classification purposes have been included in see section 2.9.2.4.

[redacted] (1984), Report No. BW-84-5-1583, Data Point: K-CA 8.2.1/01 **(supportive for risk assessment, reliable for classification)**

The 96-hour semi-static study was conducted with Rainbow trout (*Oncorhynchus mykiss)* exposed to penconazole technical with a nominal exposure range of 0.77, 1.7, 2.3, 3.6 or 6.0 mg a.s./L. Exposure solutions were prepared with the aid of the solvent Dimethyl formamide (DMF) and a solvent control was included. Initial measured concentrations were 0.45, 1.0, 1.6, 2.1 and 6.5 mg/L, corresponding to 58 to 108% of nominal concentrations. The estimated LC_{50} were derived using the initial measured concentrations. Two of three validity criteria in OECD TG 203 (2019) was fulfilled, and the remaining study conditions were considered acceptable. One validity criteria was not fulfilled, as the concentrations were not measured at test end. It is thus not possible to determine an accurate LC_{50}. However, the endpoint can with certainty be estimated to be either equal to or lower than the **1.3 mg a.s./L_{im}**, which is the LC_{50} estimated in the study. In the previous EFSA conclusion (2008) it was decided that the estimated LC_{50} should be corrected for the low purity of test material used in this study (87.3%), however, this is not necessary when measured concentrations are used (see EFSA Supporting publication 2019:EN-1673).Thus, RMS consider the relevant endpoint to be **≤ 1.3 mg a.s./L_{im}** instead of 1.13 mg a.s./L_{im} agreed in the previous EFSA conclusion (2008). The 96-hour endpoint was estimated to be:

96h, *Oncorhynchus mykiss*, **LC50 ≤ 1.3 mg a.s./L_{im}** with 95 % confidence limits of ≤ 1.0 to ≤ 1.6 mg/L

[redacted] (1985), Report No. 840736, Data Point: K-CA 8.2.1/05

The 96-hour semi-static study was conducted with Carp *(Cyprinus carpio)* exposed to penconazole technical with a nominal exposure range of 0.5, 1.0, 1.8, 3.2 or 5.8 mg a.s./L. Exposure solutions were prepared with the aid of the solvent Dimethyl formamide (DMF) and Arkopal N150 and a solvent control was included. Study conditions were considered acceptable. Measured concentrations were within ± 20 % of the nominal concentration, except for the treatment with the lowest concentration at test end, which were 76% of nominal. As the estimated LC_{50}-value lies between the two treatments with the highest concentrations (5.8 and 3.2 mg a.s./L_{nom}), the slight reduction below ± 20% of nominal in the lowest test concentration at 96h is not expected to affect the estimated LC_{50}. The LC_{50} values were thus derived using nominal concentrations. It is noted that the study is a **non-GLP-study,** however, as the study fulfills the validity criteria it is considered sufficiently robust and to be valid. The 96-hour endpoint was estimated to be:

Cyprinus carpio, 96h LC50 = 3.8 mg a.s./L with 95 % confidence limits of 2.5 to 5.2 mg/L

Metabolites

Five reliable studies (fulfilling the validity criteria of OECD TG 203) with penconazole metabolites considered suitable for use in hazard classification and risk assessment are presented below.

[redacted] (1983), Report No. 82 14 18, Data Point: K-CA 8.2.1/06

The 96-hour semi-static study was conducted with *Oncorhynchus mykiss* (rainbow trout) exposed to the metabolite CGA71019 (1,2,4-Triazole) with a nominal exposure range of 100, 180, 320, 580 and 1000 mg/L and a dilution water control. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable. Measured concentrations were 47 to 67% of nominal at the end of the study period and results were

based on mean measured concentrations. This is considered conservative and acceptable for the purpose of hazard classification.The 96-hour endpoint was estimated to be:
Oncorhynchus mykiss, 96h LC_{50} = 529 mg CGA71019 (1,2,4-Triazole)/L_{mm} with 95 % confidence limits of 472 to 592 mg CGA71019 (1,2,4-Triazole)/L.

[redacted] & [redacted] (2001), Report No. BL7204/B, Data Point: K-CA 8.2.1/07
The 96-hour semi-static study was conducted with Fathead minnow *(Pimephales promelas)* exposed to the metabolite CGA179944 with a nominal exposure range of 7.5, 15, 30, 60 and 120 mg CGA179944/L and a dilution water control. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable, except for the top concentration wich were excluded due to low pH in the exposure water of 4.12 and a 100% mortality. The recommended pH for fathead minnow is 6.0-8.5, and it cannot be exlcuded that the mortality is caused by the very low pH. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. This is considered conservative and acceptable for the purpose of hazard classification.The 96-hour endpoint was estimated to be:
Pimephales promelas, 96h LC50 > 60 mg CGA179944/L < 120 mg CGA179944/L

[redacted] & [redacted] (2010), Report No. 55391230, Data Point: K-CA 8.2.1/08
The 96-hour semi-static study was conducted with Fathead minnow *(Pimephales promelas)* exposed to the metabolite CGA179944 with a nominal exposure of 100 mg CGA179944/L and a dilution water control. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. This is considered conservative and acceptable for the purpose of hazard classification.The 96-hour endpoint was estimated to be:
Pimephales promelas, 96h LC50 > 100 mg CGA179944/L

[redacted] & [redacted] (2003), Report No. TM 92 14361230, Data Point: K-CA 8.2.1/09
The 96-hour semi-static study was conducted with *Oncorhynchus mykiss* (rainbow trout) exposed to the metabolite CGA142856 (triazole acetic acid) with a nominal exposure of 100mg/L and a negative control. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. This is considered conservative and acceptable for the purpose of hazard classification.The 96-hour endpoint was estimated to be:
Oncorhynchus mykiss, 96h LC_{50} = 100 mg CGA142856/L_{nom}

[redacted] (2001), Report No. BL7153/B, Data Point: K-CA 8.2.1/10
The 96-hour semi-static study was conducted with *Oncorhynchus mykiss* (rainbow trout) exposed to the metabolite CGA142856 (triazole acetic acid) with a nominal exposure range of 5.6, 10, 18, 32 and 56 mg R116857/L and a dilution water control. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. This is considered conservative and acceptable for the purpose of hazard classification.The 96-hour endpoint was estimated to be:
Oncorhynchus mykiss, 96h LC50 = 24 mg CGA91305/L_{nom} with 95 % confidence limits of 18 to 32 mg CGA91305/L_{nom}

Representative formulation A6209G (Topas EC 100)
Two reliable studies (fulfilling the validity criteria of OECD TG 203) with the representative formulation A6209 (Topas EC 100) considered supportive for use in hazard classification and suitable for use in risk assessment are presented below.

[redacted] (1984), Report No. AFT-84-056, Data Point: K-CP 10.2.1/01 (*O. mykiss*) &
[redacted] (1984a), Report No. AFT-84-07, Data Point: K-CP 10.2.1/02 (*C. carpio*)
One 96-hour flow-through study was conducted with *Oncorhynchus mykiss* (rainbow trout) exposed to the representative formulation A6209 (Topas EC 100) with a nominal exposure range of 0.94, 1.88, 3.28, 5.62 and 10 mg A6209/L and a dilution water control. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable.

In addition, one 96-hour flow-through study was conducted with *C. carpio* (rainbow trout) exposed to the representative formulation A6209 (Topas EC 100) with a nominal exposure range of of 3.2, 5.6, 10, 18 and 32 mg A6209/L and a dilution water control. Exposure solutions were prepared without the aid of a solvent. Study

conditions were considered acceptable. Based on nominal concentrations, the 96-hour LC_{50} of A-6209G for rainbow trout (*O. mykiss*) was 6.8 mg formulation/L (equivalent to 0.68 mg as/L) and 96-hour LC50 of A-6209G for carp (*C. Carpio*) was 12.1 mg formulation/L (equivalent to 1.21 mg as/L).

In both studies there were some uncertainties with regard to the analytical verification of the test substance, as concentrations were not maintained within ± 20% of nominal at all dose levels tested (mean measured concentrations were 73.6-100.2% and 61-93 in study with for *O. mykiss* and *C. carpio*, respectively). Ideally, the mean measured concentrations should be used to derive the endpoint. However, this was not possible as concentrations were not measured at all dose levels. In the study with *O. mykiss* mortality was mainly observed at the highest dose level (100%), and only 10% was observed at the second highest dose level. Thus, RMS has proposed to set the endpoint as higher than the second highest test concentration. This is considered sufficient protective, and in the interest of limiting further vertebrate studies (in-keeping with Article 62 of Regulation (EC) 1107/2009). A similar approach was taken for the study with *C. carpio*.

O. mykiss 96 h (static), LC50 > 5.6 mg A6209G/L_{nom}, equivalent to >0.56 mg a.s./L_{nom}
C. carpio 96 h (static), LC50 > 10 mg A6209G/L_{nom}, equivalent to >1.0 mg a.s./L_{nom}

Fulfilment of the data requirements (PPP-legislation)
According to **Commission Regulation (EU) No 283/2013** data requirement *8.2.1. Acute toxicity to fish: A study shall be provided on the acute toxicity to fish (LC50) and details of observed effects. (...) A test on rainbow trout (Oncorhynchus mykiss) shall be carried out.* As no valid study with rainbow trout (*O. mykiss*) and technical penconazole was available, RMS propose to use the endpoint from the study with representative formulation A6209G and *O. mykiss* to address the **Commission regulation (EU) 283/2013** data requirement *8.2.1. Acute toxicity to fish*. This will ensure that toxicity to a sensitive salmonid species is addressed and removing the need for repeating a vertebrate animal test. The information provided is also sufficient to address the **Commission regulation (EU) 283/2013** data requirement *8.2.6.1. Acute toxicity to fish* with regard to the penconazole metabolites CGA71019/1,2,4-Triazole, CGA179944, CGA142856/triazole acetic acid and CGA91305.

CLP
For a comparison with the CLP-criteria and justification for the use of endpoints, please see chapter **2.9.2.4. Comparison with the CLP criteria.**

2.9.2.2.2 Acute (short-term) toxicity to aquatic invertebrates

One study with penconazole technical and five studies with metabolites have been provided. In addition, one study with the representative formulation A6209 (Topas EC 100) is available. Valid studies are summarised in the table, above. Study summaries and the assessment and conclusion by the applicant and by RMS are available in **Volume 3 - B.9 (AS)** and **Volume 3 - B.9 (PPP)**.

One **non-GLP** acute toxicity study with Daphnia and **penconazol technical** was available (*D. magna* 48 h (static) EC_{50} = 6.75 mg/L_{nom}; Hitz, 1981). According to **Commission Regulation (EU) No 283/2013** studies performed to obtain data on the properties or safety with respect to animal health and the environment *shall* be conducted in accordance with the GLP-principles (principles laid down in Directive 2004/10/EC of the European Parliament and of the Council (OJ L 50, 20.2.2004, p. 44)). The study was not a GLP-study, however, is considered *supportive* as it fulfils the validity criteria of OECD 202 (2004). In addition, valid studies with aquatic invertebrates (*D. magna*) are available for all **relevant aquatic metabolites**. The studies indicate that the metabolites are not acutely toxic to aquatic invertebrates (LC_{50} in the range >100 mg/L to >120 mg/L), and less toxic than the active substance. For further details, see **Volume 3 - B.9 (AS).**

Penconazole
One study (non-GLP) with penconazole technical considered supportive for use in hazard classification and risk assessment is presented below.

Hitz H.R.. (1981) Report No. 810763, Data point : CA 8.2.4.1/01 **(supportive)**
The 48-hour static study was conducted with *Daphnia magna* (water flea) exposed to penconazole technical with a nominal exposure range of 0. 2.3, 3.4, 5.1, 7.6, 10 and 15 mg a.s./L. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. Study conditions were considered acceptable and the study fulfilled the validity criteria. However, the study were poorly reported and was a **non- GLP**-study. The batch not equivalent with the reference specification (finalised

September 2009 by RMS Germany) or the appli-cants proposed technical specification (global specification), for details, see Volume 4 (Syngenta). In an overall assessment the study is considered **supportive only**. The supportive 48-hour endpoint was estimated to be:
Daphnia magna, 48h EC_{50} = 6.75 mg a.s. /L (95% C.I.: 5.76 - 8.01)

Metabolites
Five reliable studies (fulfilling the validity criteria of OECD TG 202) with penconazole metabolites considered suitable for use in hazard classification and risk assessment are presented below.

Bell G. (1995) Report No. ENVIR/95/52, AGV 50(b)/952181, Data point: K-CA 8.2.4.1/02
The 48-hour static study was conducted with *Daphnia magna* (water flea) exposed to penconazole metabolite CGA71019 (1,2,4-Triazole) with a nominal exposure of 100 mg/L and a dilution water control. Exposure solutions were prepared without the aid of a solvent. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. The 48-hour endpoint was estimated to be:
Daphnia magna, 48h EC_{50} > 100 mg CGA71019 (1,2,4-Triazole)/L

Swarbrick R.H. & Woodyer J.M. (2001a) Report No. BL7205/B, Data point: K-CA 8.2.4.1/03
The 48-hour static study was conducted with *Daphnia magna* (water flea) exposed to penconazole metabolite CGA179944 with a nominal exposure of 120 mg/L and a dilution water control. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. The 48-hour endpoint was estimated to be:
Daphnia magna, 48h EC_{50} > 120 mg CGA179944/L

Kuhl R. & Wydra V. (2009) Report No. 42552220, Data point: K-CA 8.2.4.1/04
The 48-hour static study was conducted with *Daphnia magna* (water flea) exposed to penconazole metabolite CGA179944 with a nominal exposure of 120 mg/L and a dilution water control. Exposure solutions were prepared without the aid of a solvent.Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. The 48-hour endpoint was estimated to be:
Daphnia magna, 48h EC_{50} > 120 mg CGA179944/L

Hertl J. & Breitwieser H. (2003a) Report No. TM 93 14362220, Data point: K-CA 8.2.4.1/05
The 48-hour static study was conducted with *Daphnia magna* (water flea) exposed to penconazole metabolite CGA142856 (triazole acetic acid) with a nominal exposure of 100 mg/L and a dilution water control. Study conditions were considered acceptable. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. The 48-hour endpoint was estimated to be:
Daphnia magna, 48h EC_{50} > 100 mg CGA142856 (triazole acetic acid /L

Wallace S.J. (2001a) Report No. BL7154/B, Data point: K-CA 8.2.4.1/06
The 48-hour static study was conducted with *Daphnia magna* (water flea) exposed to penconazole metabolite CGA91305 with a nominal exposure range of 10, 18, 32, 56, 100 and 180 mg R116857/L and a dilution water control. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. The 48-hour endpoint was estimated to be:
Daphnia magna, 48h EC_{50} = 110 mg CGA91305/L (95 % c.i.: 99-130 mg/L)

Representative formulation A6209G (Topas EC 100)
One acceptable study (fulfilling the validity criteria of OECD TG 202) with the representative formulation A6209 (Topas EC 100) considered supportive for use in hazard classification and suitable for use in risk assessment are presented below.

Palmer et al. (2001) Report No. 528A-106, Data point: K-CP 10.2.1/03
The 48-hour static study was conducted with *Daphnia magna* (water flea) exposed to penconazole metabolite A-6209G (TOPAS 100 EC) with a nominal exposure range of 7.5, 15, 30, 60 and 120 mg/L A-6209G and a dilution water control. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period

and results were based on nominal concentrations. The 48-hour endpoint was estimated to be: *Daphnia magna*, 48h EC_{50} = 36 mg A-6209G /L_{nom} equivalent to 3.88 mg a.s./L_{nom}

Fulfilment of the data requirements (PPP-legislation)
According to **Commission Regulation (EU) No 283/2013** data requirement *8.2.4.1. Acute toxicity to Daphnia magna: A test shall be provided on the 24- and 48-hour acute toxicity of the active substance to Daphnia magna, expressed as the median effective concentration (EC50) for immobilisation, and where possible, the highest concentration causing no immobilisation.* As the study with aquatic invertebrates (*D. magna*) and technical penconazole was considered *supportive only*, RMS has preliminary accepted the endpoint from the study with the representative formulation A6209G and *D. magna* (Palmer et al. (2001) Report No. 528A-106, Data point: K-CP 10.2.1/03) to address the **Commission regulation (EU) 283/2013** data requirement *8.2.4.1. Acute toxicity to Daphnia magna*. However, EFSA should consider whether a new valid study with *D. magna* and penconazole technical should be provided. The study is also used to address **Commission regulation (EU) 284/2013** data requirement *10.2.1: Acute toxicity to fish, aquatic invertebrates, or effects on aquatic algae and macrophytes* for the representative formulation.

The information provided is also sufficient to address the **Commission regulation (EU) 283/2013** data requirement *8.2.4.1. Acute toxicity to Daphnia magna* with regard to the penconazole metabolites CGA71019/1,2,4-Triazole, CGA179944, CGA142856/triazole acetic acid and CGA91305.

CLP
For a comparison with the CLP-criteria, please see section 2.9.2.4.

2.9.2.2.3 Acute (short-term) toxicity to algae or aquatic plants

Please see Section 2.9.2.3.3 'Chronic toxicity to algae or aquatic plants' where both acute (short-term) and chronic toxicity to algae and aquatic plants are discussed.

Penconazole
Two reliable studies (fulfilling the validity criteria of OECD TG 201) with penconazole technical considered suitable for use in hazard classification and risk assessment is presented in chapter 2.9.2.3.3. A study from open literature is also available. The study could not be fully verified according to the validity criteria in OECD TG 201, however it provide an endpoint in the same range as the two valid studies and are thus considered supportive. One study with *Lemna gibba* is avaliable, however was considered as not reliable, as it did not fulfill the validity criteria in OECD TG 221, please see section 2.9.2.3.3.2 for a summary of this study.

Desjardins D., Kendell T.Z. & Krueger H.O. (2001) Report No. 528A-112, Data point: K-CA 8.2.6.1/01
Pseudokirchneriella subcapitata, 72 h E_rC_{50} = 4.9 mg a.s./L_{mm} (95 % c.i.: 4.9 -5.0 mg/L_{mm})

Kley A. & Wydra V. (2009) Report No. 42541210, Data point: K-CA 8.2.6.1/03a
Pseudokirchneriella subcapitata, 72 h E_rC_{50} = 3.41 mg a.s./L_{mm} (95 % c.i.: 2.63– 4.61 mg/L_{mm})

Durjava, M.K., Kolar, B., Arnus, L., Papa, E., Kovarich, S., Sahlin, U., Peijnenburg, W. (20014) Report ATLA, 41:65-75., Data Point: K-CA 8.2.6.1/14 **(Supportive)**
Pseudokirchneriella subcapitata, 72 h E_rC_{50} 3.62 mg a.s./$L_{measured}$

Metabolites
Three valid studies (fulfilling the validity criteria of OECD TG 201) with penconazole metabolites considered suitable for use in hazard classification and risk assessment is presented below.

Palmer S.J., Kendall T.Z. & Krueger H.O. (2001) Report No. 528A-101, Data point: K-CA 8.2.6.1/04
Pseudokirchneriella subcapitata, 72 h E_rC_{50} > 31 mg/L mg CGA71019 (1,2,4-Triazole)/L_{nom}

Swarbrick R.H. & Woodyer J.M. (2001b) Report No. BL7206/B, AJ0287/D, Data point: K-CA 8.2.6.1/08
Pseudokirchneriella subcapitata, 72 h E_rC_{50} > 32 mg/L mg a. CGA179944/L_{nom}

Wallace S.J. & Woodyer J.M. (2001) Report No. BL7155/B, AJ0228/D, Data Point: K-CA 8.2.6.1/12
Pseudokirchneriella subcapitata, 72 h ErC50 = 19.1 mg CGA91305/L_{nom} (95% confidence limits = 16.6 – 21.7 mg CGA91305/L_{nom})

Representative formulation A6209G (Topas EC 100)
One reliable study (fulfilling the validity criteria of OECD TG 201) with the representative formulation A6209 (Topas EC 100) considered supportive for use in hazard classification and suitable for use in risk assessment are presented below.

Memmert U. & Knoch E. (1994) Report No. RCC 428916, Data Point: K-CP 10.2.1/04
Scenedesmus subspicatus, 72 h
E_rC_{50} = 7.9 mg A6209G L_{nom} (95 % c.i.: 3.3 – 18.5 mg A6209G **/L),** equivalent to 0.79 mg a.s./L

CLP
For a comparison with the CLP-criteria, please see section 2.9.2.4.

2.9.2.2.4 Acute (short-term) toxicity to other aquatic organisms
No acute toxicity data to other aquatic organisms are available.

2.9.2.3 Long-term aquatic hazard [equivalent to section 11.6 of the CLH report template]

Table 109: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results	Relevant study	Remarks	Reference
Test was conducted to an internal protocol [a] GLP	Fathead minnow (*Pimephales promelas*)	**Penconazole tech.** Purity: 87.3% Batch: FL 830634	Early life stage, 35 d (flow-through) **NOEC = 0.36 mg a.s./L (mm)** **$EC_{10;\ weight}$=0.43 mg a.s./L_{mm}** $EC_{20;weight}$=0.603 mg a.s./L_{mm}	Reliable	Expiry date of technical penconazole not reported Age of embryos at test start: <48 hours. According to the TG the test should start as soon as possible after the eggs have been fertilized and no later than 12 h post fertilisation to ensure exposure during early embryonic development. The batch not equivalent with the reference specification (finalised September 2009 by RMS Germany) or the applicants proposed technical specification (global specification). See Volume 4	[redacted] 1984c; CGA71818/0074 & [redacted] 2016; CGA071818_10494[b]

Method	Species	Test material	Results	Relevant study	Remarks	Reference
					(Syngenta).	
No specific guideline reported. [a] Embryo development, 4 h post-fertilisation – 96 h post hatch, semi-static	Zebrafish (*Danio rerio*)	**Topas 100 EC** Purity: NA Batch: NA	NOEC < 0.8 mg a.s./L LC_{50} ≤ 3.73 mg penconazole/L	Supportive	Study from open literature Not GLP Could not be determined whether the validity criteria of the relevant OECD test guideline (OECD 210) were fulfilled No measurement of test concentrations	Aksakal & Ciltas, 2018; Chemosphere, 200:8-15.
OECD 234, draft ver. 2 (2010) GLP	Fathead minnow (*Pimephales promelas*)	**Penconazole tech.** Purity: 97.4% Batch: SSH4D030	98 d (flow-through) $NOEC_{apical\ endpoints}$ = 0.60 mg a.s./L (mm) ($NOEC_{mechanistic,\ VTG}$ = 0.28 mg a.s./L (mm))	Reliable	No significant (apical) effects were observed on embryo time to hatch, embryo hatching success, sex ratio, length, weight, abnormal behaviour, morphological abnormalities, or survival. ↓vitellogenin observed in male and female fish at concentrations above 0.28 mg/L (mm) Age of embryos at test start: <24 hours. According to the TG the test should start as soon as possible after the eggs have been fertilized and no later than 12 h post fertilisation to ensure exposure during early embryonic development.	[redacted] 2012; CGA71818_10278

Method	Species	Test material	Results	Relevant study	Remarks	Reference
OECD 215 (2000) GLP	Rainbow trout (*Oncorhynchus mykiss*)	**CGA71019** Purity: 99.9 % Batch: NLL 7052-1	28 d (semi-static) NOEC = 3.2 mg/L (nom)	Supportive	Study is no longer a data requirement (European Commission (EU) 283/2011) and has thus been regarded as supportive	[redacted] & [redacted] 2002; CGA71019/0052
Internal method US EPA-660/3-75-009 GLP	*Daphnia magna*	**Penconazole tech.** Purity: 87.3% Batch: FL-830634	21 d (flow-through) **NOEC ≤ 0.069 mg a.s./L (mm)**	Supportive for risk assessment Reliable for hazard classification (please see r justification in section 2.9.2.4.2)	As there are some uncertainties regarding the applied statistics, the lowest dose tested (0.069 mg a.s./L) may actually be the LOEP, rather than the NOEC. The study has thus been regarded supportive for use in risk assessment. The study is still considered relevant for hazard classification purposes. The applicant intends to provide new data to clarify the correct endpoint.	Surprenant, 1984d; CGA71818/0080
OECD 202 (1984) GLP	*Daphnia magna*	**A6209G** (Topas 100 EC) Purity: 100 g/L penconazole (nom) Batch: Op 211 052	21 d (semi-static) **NOEC = 0.32 mg prod./L (nom)** Equivalent to: **NOEC = 0.032 mg a.s./L** **EC_{10} = 0.49 mg prod./L** Equivalent to: **EC_{10} = 0.049 mg a.s./L** EC_{20} = 0.81 **mg prod./L** Equivalent to: **EC_{20} = 0.081 mg a.s./L**	Reliable	Expiry date of technical penconazole not reported	Memmert & Knoch, 1994a; CGA71818/1235
OECD, Proposal for Toxicity Test	*Chironomus riparius*	**Penconazole tech.** Purity:	28 d (static) <u>Water-spiked:</u>	Reliable	All validity criteria not fulfilled, but	Grade, 1999; CGA71818/1390

Method	Species	Test material	Results	Relevant study	Remarks	Reference
with Chironomidae (May 1998) [d]		97.4% Batch: EN 603012	NOEC = 0.8 mg/L (im) Sediment-spiked: NOEC = 25.2 mg/kg sed dw (nom) EC_{10} = 41.8 mg /kg sed dw (nom) EC_{20} = 50.2 mg /kg sed dw (nom)		study still regarded as acceptable. 60 individuals used, whereas 80 should be used to determine the NOEC according to the guideline. Deviations in regard to emergence (more emerged than introduced). Using a WoE approach the study has still been considered acceptable (see RAR Volume 3CA, B.9.)	& Kümmich, 2016b; CGA071818_10483
OECD 201 (1984) [c] GLP	Green algae *(Scenedesmus subspicatus)*	**A6209G** (Topas 100 EC) Purity: 100 g/L (nominal) Batch: OP 211 052	72 h (static) **E_rC_{50} = 7.9 mg/L (nom)** **Equivalent to:** **E_rC_{50} = 0.79 mg a.s./L (nom)** E_rC_{10} = 3.1 mg/L (nom) E_rC_{20} = 4.3 mg/L (nom) E_bC_{50} = 3.9 mg/L (nom) E_bC_{20} = 2.1 mg/L (nom) E_bC_{10} = 1.6 mg/L(nom) **NOEC = 1.0 mg a.s./L_{nom}**	Reliable		Memmert & Knoch, 1994; CGA71818/1234 & Schuster, 2016; A6209G_11142 [d]
OECD 201 (1984) [c] OPPTS 850.5400, C.3 (1996) GLP	Green algae *(Pseudokirchneriella subcapitata)*	**Penconazole tech.** Purity: NA Batch: WS007001	72 h (static) E_rC_{50} = 4.9 mg/L (mm) E_rC_{20} = 2.94 mg/L (mm) E_rC_{10} = 2.39 mg/L (mm) E_bC_{50} = 2.0 mg/L (mm) E_bC_{20} = 0.78 mg/L (mm) E_bC_{10} = 0.50 mg/L (mm) NOEC = 0.56 mg a.s./L_{mm}	Reliable	Purity unknown	Desjardins et al, 2001; CGA71818/4378 & Schuster, 2016; CGA071818_10472 [d]
OECD 201 (2006) [c]	Green algae *(Pseudokirc*	**Penconazole tech.**	72 h (static)	Reliable		Kley & Wydra, 2009:

Method	Species	Test material	Results	Relevant study	Remarks	Reference
GLP	*hneriella subcapitata)*	Purity:99.86 % Batch: 0701	**E_rC_{50} = 3.41 mg/L (mm)** E_rC_{20} = 0.62 mg/L (mm) **E_rC_{10} = 0.26 mg/L (mm)** E_yC_{50} = 0.42 mg/L (mm) E_yC_{20} = 0.16 mg/L (mm) E_yC_{10} = 0.10 mg/L (mm) **NOEC = 0.234 mg/L (mm)**			CGA071818_10633 & Lührs & Wydra, 2018: CGA071818_10633 [d]
OECD 201 (1984) [c] O.J. No. L383A, Method C.3 (1992) OPPTS 850.5400, C.3 (1996) GLP	Green algae *(Pseudokirchneriella subcapitata)*	**CGA71019** (1,2,4-Triazole) Purity: 99 ± 2% Batch: R200	72 h (static) **E_rC_{50} >31 mg/L (mm)** E_rC_{20} = 11.3 mg/L (mm) E_rC_{10} = 8.3 mg/L (mm) E_bC_{50} = 13 mg/L (mm) E_bC_{20} = 7.2 mg/L (mm) E_bC_{10} = 5.9 mg/L (mm) **NOEC = 3.1 mg/L (mm)**	Reliable		Palmer et al, 2001; CGA71019/0044 & Hefner, 2014; CGA071019_10010 [d]
OPPTS 850.5400, C.3 (1996) [c] GLP	Green algae *(Pseudokirchneriella subcapitata)*	**CGA179944** Purity: MLA-437/1,3,4 Batch: 99 ± 2%	72 h (static) **E_rC_{50} > 32 mg/L (mm)** E_bC_{50} > 32 mg/L (mm) **NOEC >32 mg/L**	Reliable	Deviations in pH. Study still considered acceptable (see RAR Volume 3CA, B.9.)	Swarbrick & Woodyer, 2001b; CGA179944/0010
OPPTS 850.5400, C.3 (1996) [c] GLP	Green algae *(Selenastrum capricornutum)*	**CGA91305** Purity: 99 ± 2% Batch: KI 6437/2	72 h (static) **E_rC_{50} = 19.1 mg/L (nom)** E_rC_{20} = 11.5 mg/L (nom) E_rC_{10} = 8.9 mg/L (nom) E_bC_{50} = 9.6 mg/L (nom) E_bC_{20} = 6.7 mg/L (nom) E_bC_{10} = 4.7 mg/L(nom) **NOEC =3.2 mg/L (nom)**	Reliable		Wallace & Woodyer, 2001; CGA77502/0003 & Hefner, 2014a; CGA091305_1011
US EPA Proposed Guidelines for Registering Pesticides in the United States, Subpart J, 1980; Holst	*Lemna gibba*	**Penconazole tech.** Purity: 87.3% Batch: FL-830634	14 days (static) E_bC_{50} = 0.19 mg/L (frond number) E_bC_{50} = 0.096 mg/L (dry weight)	Not valid. Included in table for completeness, as the study was considered the key study in the RAC	The validity criteria in OECD 221 (2006) were not fulfilled: frond doubling time were 2.6 days and average specific growth rate	Hughes J.S., 1985a; CGA71818/0082

Method	Species	Test material	Results	Relevant study	Remarks	Reference
RW and TC Ellwanger, 1982 [e]				opinion from 2012	0.268d-1, whereas the validity criteria require a doubling time of less than 2.5 days and an average specific growth rate of 0.275 d-1. No analytical measurement of test substance during the test.	

[a] Evaluated according to OECD 210 (2013)
[b] Statistical re-analysis to determine EC_{10}- and/or EC_{20}-estimates.
[c] Evaluated according to OECD 211 (2012)
[d] Evaluated according to OECD 218 and OECD 219 (2004)
[e] Evaluated according to OECD 221 (2006)
mm: mean measured; nom: nominal concentration; im: immediately measured
Bold values represent the lowest endpoint for the respective organism group and test substance.

2.9.2.3.1 Chronic toxicity to fish

Four studies investigating chronic effects of penconazole, or relevant metabolite(s) have been provided. One study from open literature is also available. Valid studies are summarised in the table above. Study summaries and the assessment and conclusion by the applicant and by RMS are available in **Volume 3 - B.9 (AS)** and **Volume 3 - B.9 (PPP)**.

Penconazole
Two reliable studies (fulfilling the validity criteria of the respective OECD TG) with penconazole technical considered suitable for use in hazard classification and risk assessment is presented below. One study from open literature is considered supportive. To further investigate the effects of endocrine disruption, a **fish full life-cycle study** has been initiated. Preliminary results are available **Volume 3 - B.9 (AS)**. However, as the final study report is not available, these results cannot be verified by RMS at the current stage of the evaluation.

[redacted] (1984c) Report No. BW-84-7-1600, Data point: K-CA 8.2.2.1/01
A 35-day (30 days post-hatch) flow-through **early life stage (ELS) test** with fathead minnow (*Pimephales promelas*) exposed to penconazole technical with a nominal exposure range of 0.25, 0.5, 1.0, 2.0 and 4.0 mg a.s./L. Exposure solutions were prepared with the aid of the solvent Dimethyl formamide (DMF). A solvent and a dilution water control were included. Mean measured concentrations were 68-88% of nominal, and the mean measured concentrations have been used to derive the endpoint. Study conditions were considered acceptable. The batch not equivalent with the reference specification (finalised September 2009 by RMS Germany) or the appli-cants proposed technical specification (global specification), for details, see Volume 4 (Syngenta). Statistically significant effects on growth (mean total length and average wet weight) were observed at the dose levels 0.68 and 1.5 mg a.s./L_{mm}. At the top dose (3 mg a.s./L_{mm}) the % egg hatchability/survival was 0%. The validity criteria are either fulfilled or considered acceptable. The endpoint was estimated to be:
35 d, *P. promelas*, NOEC = 0.36 mg a.s./L_{mm}.

Aksakal, F.I., Ciltas, A. (2018) Report No. Chemosphere, 200:8-15, Data point: K-CA 8.2.2.1/03 **(Open literature, supportive data)**
One study from open literature have assessed the embryo development of Zebrafish (*Danio rerio*) after exposure to penconazole Embryos were exposed 4 h post-fertilisation – 96 h post hatch in a semi-static test regime. There were no analytical verification during or prior to the test it cannot be determined whether exposure were maintained at ± 20 percent of nominal concentrations According to the study authors, the LC_{50} of penconazole to zebrafish embryos

was calculated to be 3.73 mg penconazole/L. However, as concentrations of penconazole have not been analytically verified, the endpoint is set to ≤ 3.73 mg penconazole/L. The effects on mortality (>10% - >30%) was observed at all test concentrations (0.8, 1.2 and 2.4 mg a.s./L_{nom}). Body length, heartbeat rate and malformations were significantly affected at the two top dose-levels compared to the control. Gene expression levels of various genes were affected at all test concentrations compared to the control. The study was evaluated according to the relevant validity criteria of OECD 210, however, the validity criteria was not fully met. The results are in line with the valid chronic toxicity tests with penconazole and is considered as *supportive* information. According to the applicant, the study is reliable with restrictions, with a Klimisch score of 2. The RMS consider the study supportive. The **supportive** endpoint was estimated to be:
96h, *D. rerio* NOEC < 0.8 mg a.s./L_{nom}
LC_{50} of penconazole to zebrafish embryos ≤ 3.73 mg penconazole/L

[redacted] (2012) Report No. 1781.6770, Data point: K-CA 8.2.3/03
To assess the potential for endocrine disruption of penconazole, a 98 d sexual development test (FSDT) with fathead minnow (*P. promelas*) exposed to penconazole technical with a nominal exposure range of 0.038, 0.075, 0.15, 0.30 and 0.60 mg/L under flow-through conditions. Measured concentrations were within ± 20 % of the nominal concentration, and nominal consentrations were used to derive the endpoint. The study indicates *no effects* on the apical endpoints: survival, growth (length, weight) or histological sex ratio at doses up to the top dose (0.6 mg a.s./L). However, a significant reduction in vitellogenin (VTG) levels were observed for both males and females at the top dose. In addition, a clear dose response curve was observed for this parameter also at lower doses, however these reductions were not statistically significant. Already at the lowest dose level (0.041 mg a.s./L) a decrease in VTG levels compared to the control can be visually observed. The endpoint was estimated to be:
98 d, *P. promelas*, NOEC = 0.60 mg a.s./L_{mm}

Metabolites
One juvenile growth test (28 d) with the metabolite CGA71019/1,2,4-triazole have been provided. The study was considered valid according to the assessment in the RAR of Metconazole (August 2019). As the study is no longer a data requirement in **Commission Regulation (EU) No 283/2013,** the study is considered *supportive only*, by RMS.

Representative formulation A6209G (Topas EC 100)
One prolonged flow-through test (OECD TG 204) with the representative formulation A6209 (Topas EC 100) and fish has been provided. The study is no longer a data requirement and has thus not been evaluated by RMS. RMS note that the endpoint is in the same range as the endpoint from the ELS study and technical penconazole.

Fulfilment of the data requirements (PPP-legislation)
According to **Commission Regulation (EU) No 283/2013** data requirement *8.2.2.1. Fish early life stage test: A fish early life stage toxicity test shall determine effects on development, growth and behaviour, and details of observed effects on fish early life stages. The EC10 and EC20 shall be reported together with the NOEC. Where EC10 and EC20 cannot be estimated, an explanation shall be provided.* The information provided is sufficient to address the **Commission regulation (EU) 283/2013** data requirement *8.2.2.1. Fish early life stage test*.

For the assessment of available data to address the potential endocrine disruption for fish, please see section 2.10 in this document.

CLP
For a comparison with the CLP-criteria, please see section 2.9.2.4.

2.9.2.3.2 Chronic toxicity to aquatic invertebrates

Two studies investigating the chronic toxicity of penconazole technical to aquatic invertebrates have been provided, one study with *Daphnia magna* and one with the sediment dwelling Chironomidae *Chironomus riparius*. In addition, one chronic study with the representative formulation A6209G and *Daphnia magna* is available. Acceptable studies are summarised in the table, above. Study summaries and the assessment and conclusion by the applicant and by RMS are available in **Volume 3 - B.9 (AS)** and **Volume 3 - B.9 (PPP)**.

Studies to estimate EC_{10}- and EC_{20}-values have also been provided, and where reliable EC_x-estimates were derived, they have been included in the table, above.

2.9.2.3.2.1 Daphnia magna

Penconazole
One study (fulfilling the validity criteria of OECD TG 211) with penconazole technical is available. However, it was pointed out by coRMS during commenting, that there are some uncertainties with the applied statistics, and co RMS points out that the NOEC derived from the study may actually be the LOEC. RMS has thus concluded that the NOEC from this study is either equal to or lower than the derived NOEC. In order to conclude on the risk with high certainty, a lower-than endpoint cannot be used in the risk assessment. The study is thus regarded as supportive for risk assessment. However, as the study fulfills the validity criteria, and the endpoint can be established to be either equal to or lower than the derived endpoint, it is regarded to provide valuable information for hazard classification and is considered reliable for hazard classification purposes. Please see section 2.9.2.4 comparison with the CLP criteria for further details.

Surprenant D.C. (1984d) Report No. BW-84-8-1614, Data point: K-CA 8.2.5.1/01 (**supportive for risk assessment and reliable for hazard classification**)
A 21-day flow-through study with the aquatic invertebrate *Daphnia magna* exposed to penconazole technical at nominal exposure range of 0.25, 0.5, 1.0, 2.0 and 4.0 mg a.s./L. Exposure solutions were prepared with the solvent dimethyl formamide (DMF). A dilution water and a solvent control were included. Measured concentrations were not maintiained witihn ± 20% of nominal, and mean measured concentrations (0.069, 0.39, 0.73, 1.6 and 3.6 mg a.s./L) are thus used to derive the endpoint. Mean percent survival was 0% at the top dose (3.6 mg a.s./L_{mm}) and mean cumulative offspring/female was significantly reduced at the dose levels 0.39, 0.73 and 1.6 mg a.s./L_{mm}. The NOEC generated from the study was thus 0.069 mg/L. The applicant tried to calculate an EC_{10} which were estimated to be 0.1 mg a.s./L. However, the EC_{10} was not accepted as the lower limit of the confidence interval could not be derived. The OECD validity criteria and the study conditions were considered acceptable.

The statistical evaluation performed in the study report was however questioned by the coRMS. CoRMS states that a possible re-evaluation of the statistical data might result in a LOEC of 0.069 mg/L. A question was sent to the applicant to clarify this the 22nd of September 2021. The following comment was received by the applicant the 13th of October 2021:

> *The applicants thank DE for their comments and acknowledge that the existing Daphnia chronic exposure study (CGA71818/0080) has some limitations according to today's standards. Therefore, the Penconazole Task Force intend to conduct a new study according to OECD TG 211, which fully complies with current guidance, with the data ready to be delivered on request by Q2 2022. Calculation of the ECx values will be included in this new report.*
>
> *We also note the additional statistical deficiencies raised within the existing report (comparison of controls, choice of statistical test and use of mean values) and will ensure that these are addressed in the new study.*
>
> *In the meantime, a statistical re-evaluation will be performed to confirm the correct NOEC/LOEC values based on the existing data.*

A statistical re-evaluation was however not submitted prior to sending the RAR to EFSA (autumn 2021). In order to take account for the uncertainty raised by coRMS, RMS concludes that the NOEC from this study should be set to either equal to or lower than 0.069 mg a.s/L. EFSA and/or ECHA should thus consider requesting the statistical re-evaluation and/or the new study according to OECD TG 211 referred to by the applicant, above.

The relevant endpoint is:
21 d, *D. magna*, NOEC ≤ 0.069 mg a.s./L_{mm}

Representative formulation A6209G (Topas EC 100)
One reliable study (fulfilling the validity criteria of OECD TG 211) with the representative formulation A6209 (Topas EC 100) is considered suitable for use in hazard classification and risk assessment are presented below.

Memmert U. & Knoch E. (1994a) Report No. 428938, Data point: K-CP 10.2.2/03
A 21-day semi-static study with the aquatic invertebrate *Daphnia magna* exposed to A6209G (Topas EC 100) a nominal exposure range of 0.1, 0.32, 1.0, 3.2 and 10.0 mg/L A-6209G and a dilution water control. Exposure solutions were prepared without the use of a solvent. For semi-static tests where the concentration of the test substance is expected to remain within ± 20 per cent of the nominal it is recommended that, as a minimum, the highest and lowest test concentrations should be analysed when freshly prepared and at the time of renewal on one occasion during the first week of the test, and this should be repeated at least at weekly intervals thereafter. This is not fully fulfilled. Analytical data may also indicate that concentrations in test solutions contining algae fell somewhat below ± 20% of nominal (74% of nominal at the lowest test concentration in old water at sampling day 19. Concentrations measured at the top dose were maintiained witihn ± 20% of nominal. Endpoint is thus based on nominal concentrations. Study conditions were considered acceptable. Mean percent survival was 20% at the top

dose (10 mg A6209G/L_{nom} and mean cumulative offspring/female was significantly reduced at the dose levels 10, 3.2 and 1 mg /L_{nom}. The endpoint was estimated to be:
21 d, *D. magna*, NOEC = 0.32 mg A6209G/L_{nom} (equivalent to 0.032 mg a.s./L_{nom}).

Fulfilment of the data requirements (PPP-legislation)
According to **Commission Regulation (EU) No 283/2013** data requirement *8.2.5 Long-term and chronic toxicity to aquatic invertebrates: The aim of the test on reproductive and development toxicity to Daphnia magna shall be to measure adverse effects such as immobilisation and loss of reproductive capacity and to provide details of observed effects. The EC_{10}, and EC_{20} shall be reported together with the NOEC. Where EC_{10} and EC_{20} cannot be estimated, an explanation shall be provided.* The information provided is sufficient to address the **Commission regulation (EU) 283/2013** data requirement *8.2.5. Long-term chronic toxicity to aquatic invertebrates.*

CLP
For a comparison with the CLP-criteria, please see section 2.9.2.4.

2.9.2.3.2.2 Chironomus riparius

Penconazole
One reliable study (fulfilling the validity criteria of OECD TG 218 and 219) with penconazole technical considered suitable for use in hazard classification and risk assessment is presented below.

Grade R. (1999) Report No. 983757, Data point: K-CA 8.2.5.3/01
A 28-day static study with the sediment dwelling Chironomidae *Chironomus riparius* exposed penconazole technical with a nominal exposure range of 0.50, 1.0, 2.0, 4.0, 8.0 and 16 mg/L (water spiked) and 25.2, 50.4, 100.8, 201.5 and 403 mg/kg dry sediment (sediment spiked), together with a diultion water control for both exposure routs. In the sediment spiked test acetone was used as a solvent, and a solvent control was thus also included. Concentrations in the water-spiked test was not maintained within ± 20% of nominal. However, RMS has concluded that using the initial measured concentrations in water, as suggested by the applicant, will provide a conservative endpoint (initial measured concentrations are lower than the mean measured concentrations). There were several deviations, however, in an overall assessment these have been considered acceptable by RMS. For further details, see **Volume 3 - B.9.5.4 (AS)**.
In the test emergence and development rate were investigated. Development rate was the most sensitive endpoint in the water spiked test, whereas emergence rate gave the lowest NOEC in the sediment spiked test. No effects were observed on the average weight of larvae. The endpoints were estimated to be:
C. riparius, 21 d
Water spiked: NOEC = 0.8 mg a.s./L_{im}
Sediment spiked: NOEC = 25.2 mg/kg sed dw_{nom}

Fulfilment of the data requirements (PPP-legislation)
According to Commission regulation (EU) 283/2013, *8.2.5.4. Sediment dwelling organisms: **When accumulation of an active substance in aquatic sediment is indicated or predicted by environmental fate studies**, the impact on a sediment-dwelling organism shall be assessed. The chronic risk to Chironomus riparius or Lumbriculus spp. shall be determined. An appropriate alternative test species may be used where a recognised guideline is available. The active substance shall be applied to **either** the water or the sediment phase of a water/sediment system and the test shall take account of the major route of exposure. The key endpoint from the study shall be presented in terms **of mg substance/kg dry sediment** and **mg substance/L** water and the EC_{10} and EC_{20} shall be reported together with the NOEC.*

The Guidance on tiered risk assessment for edge-of-field surface waters (AGD; EFSA Journal 2013;11(7):3290) gives further guidance to assess this requirement. According to the AGD, the test shall be required when the water/sediment study show > 10 % of applied radioactivity (AR) at or after day 14 present in the sediment and chronic daphnia test (or other comparable study with insects) EC10 (or NOEC) < 0.1 mg/L

Water/sediment-studies show that penconazole dissipated preliminary by partitioning to the sediment, and that 80-90% of the AR is present in sediment after 14 days. Preliminare investigations of the e-fate data indicate that penconazole has a DT_{50} of 1.86 – 4.12 days in water, and a DT_{50} between 565 and >10 000 days in sediment. The , DT_{90} is between 1870 og > 10 000 in sediment (for further details, see Volume 3 - B.8 (AS). The 21 day chronic daphnia study gave a NOEC = 0.06 mg a.s./L, and thus fulfills the second part of the requirement.

The main metabolite in the water/sediment studies was CGA179944. The metabolite was present in the water phase up to 17.3% of the AR after 365 days, however, only accounted for a maximum of 4.8% of the applied rate in

sediment. The metabolite M1 (3-(1,2,4-triazol-1-yl)-L-alanine) is also present in the water/sediment studies, however, at levels <5% of the AR. This metabolite is not considered a major metabolite, neither in water or soil. Acute toxicity studies with the aquatic invertebrate *Daphnia magna* is available for the metabolites CGA71019 (1,2,4-Triazole), CGA179944, CGA142856 (triazole acetic acid) and CGA91305. None of the metabolites acutely toxic to *Daphnia magna* and all are much less toxic than the active substance. Thus, further investigations of sediment dwelling organisms with the metabolites are not needed.

It is concluded that the circumstances for when **Commission Regulation (EU) 283/2013** data requirement *8.2.5.4. Sediment dwelling organisms* need to be addressed are fulfilled. In addition, the information provided is sufficient to address the requirement.

RMS notes that *Lumbriculus* is recommended in AGD as the most relevant species for a.s. with fungicidal activity (such as penconazole).

2.9.2.3.3 Chronic toxicity to algae or aquatic plants

Three studies with penconazole technical and six studies with metabolites have been provided. In addition, one study with the representative formulation A6209 (Topas EC 100) are available. One study with penconazole technical and the aquatic plant *Lemna gibba* was also provided. Reliable studies are summarised in the table, above. The study on *Lemna gibba* which was not regarded as reliable by RMS is included on request by ECHA and for completeness, as it was the key study in the hazard classification in the RAC opinion 2012. Study summaries and the assessment and conclusion by the applicant and by RMS are available in **Volume 3 - B.9 (AS)** and **Volume 3 - B.9 (PPP)**.

2.9.2.3.3.1 Algae

Two toxicity studies with green algae (*Pseudokirchneriella subcapitata*) and **penconazol technical** was available (*P. subcapitata* 72h (static) E_rC_{50} = 4.9 mg/L_{mm} and ***P. subcapitata* 72h (static) E_rC_{50} = 3.41 mg/L_{mm}**). Both studies were considered reliable and fulfilled the validity criteria of OECD 201 (2006, 2011). One study from open literature was considered *supportive only*, as the data was insufficient to assess whether the validity criteria were fulfilled. The endpoint in the study from open literature was in the same range as the two valid studies. In addition, valid studies with green algae (*P. subcapitata* or *Selenastrum capricornutum*) were available for the **relevant aquatic metabolites** CGA71019/1,2,4-Triazole, CGA179944 and CGA91305. The studies indicate that the metabolites are less toxic to than technical penconazole (E_rC_{50} in the range 19.1 mg/L to >32 mg/L). *No valid study* with the metabolite CGA142856 (triazole acetic acid) was available, and the need for requesting further data for this metabolite should be considered. In total, three studies with green algae were considered not reliable. Two studies, with CGA71019 (1,2,4-Triazol) and CGA142856 (triazole acetic acid), did not fulfil the validity criteria for section-by-section specific growth rate, and one study with CGA179944 was disregarded due to a non-monotonic dose response pattern. For further details, see **Volume 3 - B.9 (AS)**.

In addition, one study with the **representative formulation A6209 (Topas EC 100)** and green algae (***Scenedesmus subspicatus* 72 h (static) ErC50 = 7.9 mg/L_{nom}, equivalent to 0.79 mg a.s./L_{nom}**) was available in the dossier. The study is considered reliable. For further details, see **Volume 3 - B.9 (PPP)**.

Studies to estimate EC_{10}- and EC_{20}-values has also been provided, and where reliable EC_x-estimates were derived, they have been included in the table, above.

Penconazole

Two reliable studies (fulfilling the validity criteria of OECD TG 201) and one supportive study with penconazole technical considered suitable for use in hazard classification and risk assessment are presented below.

Desjardins D., Kendell T.Z. & Krueger H.O. (2001) Report No. 528A-112, Data point: K-CA 8.2.6.1/01

The 96-hour static study was conducted with *Pseudokirchneriella subcapitata* exposed to penconazole technical with a nominal exposure range of 0.56, 1.1, 2.3, 4.5 and 9.0 mg a.s./L and a culture medium control. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. The validity criteria in OECD 201 was fulfilled both when investigating the data for 72h and 96h. According to the test guideline, the 72h endpoint is the preferred endpoint. The 72-hour endpoint was estimated to be:

Pseudokirchneriella subcapitata, 72 h

E_rC_{50} = 4.9 mg a.s./L_{mm} (95 % c.i.: 4.9 -5.0 mg/L_{mm})

E_rC_{20} = 2.94 mg a.s./L_{mm} (95 % c.i.: 2.8 – 3.1 mg/L)*

E_rC_{10} = 2.49 mg a.s./L_{mm} (95 % c.i.: 2.2 – 2.6 mg/L)*
NOEC = 0.56 mg a.s./L_{mm}

*$EC_{10 \text{ and } 20}$-values were calculated by Schuster 2016 (Report No. S16-02793, Data point: CA 8.2.6.1/02).

Kley A. & Wydra V. (2009) Report No. 42541210, Data point: K-CA 8.2.6.1/03a
The 72-hour static study was conducted with *Pseudokirchneriella subcapitata* exposed to penconazole technical with a nominal exposure range of 0.08, 0.25, 0.80, 2.5 and 8.0 mg test item/L and a test water control. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable. Measured concentrations were 73-108% and results were based on mean measured concentrations. The 72-hour endpoint was estimated to be:
Pseudokirchneriella subcapitata, 72 h
E_rC_{50} = 3.41 mg a.s./L_{mm} (95 % c.i.: 2.63– 4.61 mg/L_{mm})
E_rC_{10} = 0.26 mg a.s./L_{mm} (95 % c.i.: 0.12 – 0.42 mg/L)
E_rC_{20} = 0.62 mg a.s./L_{mm} (95 % c.i.: 0.38 – 0.87 mg/L)*
NOEC = 0.234 mg a.s./L_{mm}

*EC_{20}-values were calculated by Lührs U. & Wydra V. 2018 (Report No. 42541210, Data point: CA 8.2.6.1/03b). As these calculations were based on nominal rather then mean measured concentrations, the EC_{20} was recalculated by RMS

Durjava, M.K., Kolar, B., Arnus, L., Papa, E., Kovarich, S., Sahlin, U., Peijnenburg, W. (20014) Report ATLA, 41:65-75., Data Point: K-CA 8.2.6.1/14 **(Supportive data)**
The 96-hour static open literature study was conducted with *Pseudokirchneriella subcapitata* exposed to the penconazole technical. Dilution water control, two positive controls and at least five nominal concentrations (concentrations not reported) arranged in a geometric series. Test concentrations were measured by chemical analysis (values not reported). The concentration range at which effects were likely to occur was determined on the basis of results from range-finding experiments. It was ensured that the lowest concentration selected did not have any observed effect on the growth of the algae. The validity criteria could not be assessed with the data avilable in the study report. The study is not conducted according to GLP. Reliable with restrictions. According to the applicant, the study design is appropriate for the determination of penconazole effects on algal growth and methodology is adequately documented, and the study has a \Klimisch score of 2. The reported EC_{50} is in line with data available in the dossier of penconazole. The study is by the RMS regarded as supportive. The 72-hour **supportive** endpoint was estimated to be:
Pseudokirchneriella subcapitata, 72 h E_rC_{50} 3.62 mg a.s./$L_{measured}$

Metabolites
Three acceptable studies (fulfilling the validity criteria of OECD TG 201) with penconazole metabolites considered suitable for use in hazard classification and risk assessment are presented below.

Palmer S.J., Kendall T.Z. & Krueger H.O. (2001) Report No. 528A-101, Data point: K-CA 8.2.6.1/04
The 96-hour static study was conducted with *Pseudokirchneriella subcapitata* exposed to the penconazole metabolite CGA71019 (1,2,4-Triazole) with a nominal exposure range of 1.9, 3.8, 7.5, 15 and 30 mg 1,2,4-triazole/L and a culture medium control. Exposure solutions were prepared without the aid of a solvent. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. Study conditions were considered acceptable. The validity criteria in OECD 201 was fulfilled both when investigating the data for 72h and 96h. According to the test guideline, the 72h endpoint is the preferred endpoint. The 72-hour endpoint was estimated to be:
Pseudokirchneriella subcapitata, 72 h
E_rC_{50} > 31 mg/L mg CGA71019 (1,2,4-Triazole)/L_{nom}
E_rC_{20} = 11.33 mg CGA71019 (1,2,4-Triazole) /L (95% confidence limits = 10.7-12.0 mg CGA71019 (1,2,4-Triazole) /L)*
E_rC_{10} = 8.31 mg CGA71019 (1,2,4-Triazole)/L (95% confidence limits = 8.03-8.58 mg CGA71019 (1,2,4-Triazole) /L)*
NOEC = 3.1 mg CGA71019 (1,2,4-Triazole) /L_{nom}

*$EC_{10 \text{ and } 20}$-values were calculated in Volume 3 – B9: Ecotoxicology in the RAR of Metconazole (August 2019) by RMS BE

Swarbrick R.H. & Woodyer J.M. (2001b) Report No. BL7206/B, AJ0287/D, Data point: K-CA 8.2.6.1/08

The 96-hour static study was conducted with *Pseudokirchneriella subcapitata* exposed to the penconazole metabolite CGA179944 with a nominal exposure range of 3.2, 5.6, 10, 18, 32, 56, 100 and 180 mg/L and a culture medium control. Exposure solutions were prepared without the aid of a solvent. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. Study conditions were considered acceptable, except for the three top concentrations wich were excluded due to low pH (5.21- 8.26, 3.75-4.1 and 3.54-3.56 at 56, 100 and 180 mg/L, respectively). It is not known whether the growth of algae has been affected by the low pH, however this cannot be excluded. The validity criteria in OECD 201 was fulfilled both when investigating the data for 72h and 96h. According to the test guideline, the 72h endpoint is the preferred endpoint. The 72-hour endpoint was estimated to be:
Pseudokirchneriella subcapitata, 72 h E_rC_{50} > 32 mg/L mg a. CGA179944/L_{nom}
NOEC> 32 mg CGA17994/L_{nom}

Wallace S.J. & Woodyer J.M. (2001) Report No. BL7155/B, AJ0228/D, Data Point: K-CA 8.2.6.1/12
The 96-hour static study was conducted with *Pseudokirchneriella subcapitata* exposed to the penconazole metabolite CGA91305 (R116857) with a nominal exposure range of 0.56, 1.0, 1.8, 3.2, 5.6, 10, 18 and 32 mg /L and a culture medium control. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. The validity criteria in OECD 201 was fulfilled both when investigating the data for 72h and 96h. According to the test guideline, the 72h endpoint is the preferred endpoint. The 72-hour endpoint was estimated to be:
Pseudokirchneriella subcapitata, 72 h
E_rC_{50} = 19.1 mg CGA91305/L_{nom} (95% confidence limits = 16.6 – 21.7 mg CGA91305/L_{nom})
E_rC_{20} = 11.5 mg/L_{nom} (95% confidence limits = 10.4 - 12.6 mg/L_{nom})*
E_rC_{10} = 8.9 mg/L_{nom} (95% confidence limits = 7.7 - 9.9 mg/L_{nom})
NOEC = 3.2 mg/L_{nom}

*EC_{20}-values were calculated by Hefner N. 2014a (Report No. D79317H, Data point: K-CA 8.2.6.1/13.

Representative formulation A6209G (Topas EC 100)
One reliable study (fulfilling the validity criteria of OECD TG 201) with the representative formulation A6209 (Topas EC 100) is considered suitable for use in hazard classification and risk assessment and are presented below.

Memmert U. & Knoch E. (1994) Report No. RCC 428916, Data Point: K-CP 10.2.1/04
The 72-hour static study was conducted with *Scenedesmus subspicatus* exposed to the Representative formulation A6209G (Topas EC 100) with a nominal exposure range of 0.032, 0.10, 0.32, 1.0, 3.2 and 10.0 mg/L mg A-6209G/L and a culture medium control. Exposure solutions were prepared without the aid of a solvent. Study conditions were considered acceptable. Measured concentrations were within ± 20 % of the nominal concentration at the end of the study period and results were based on nominal concentrations. The validity criteria in OECD 201 was fulfilled. The 72-hour endpoint was estimated to be:
Scenedesmus subspicatus, 72 h
E_rC_{50} = 7.9 mg A6209G L_{nom} (95 % c.i.: 3.3 – 18.5 mg A6209G **/L),** equivalent to 0.79 mg a.s./L
E_rC_{20} = 4.3 mg A6209G /L_{nom} (95 % c.i.: 4.25 – 4.33 mg A6209G /L)*
E_rC_{10} = 3.1 mg A6209G./L_{nom} (95 % c.i.: 3.0 – 3.2 mg A6209G /L)
NOEC = 1.0 mg a.s./L_{nom}

*EC_{20}-values were calculated by Schuster A.K. 2016 (Report No. S16-02797, Data point: K-CP 10.2.1/05

Fulfilment of the data requirements (PPP-legislation)
According to **Commission Regulation (EU) No 283/2013** data requirement *8.2.6.1. Effects on growth of green algae: A test shall be provided establishing EC10, EC20, EC50 for green algae and corresponding NOEC values for algal growth rate and yield, based on measurements of biomass or surrogate measurement variables.* The information provided is considered sufficient to address the **Commission regulation (EU) 283/2013** data requirement *8.2.6.1. Effects on growth of green algae* for penconazole technical and the metabolites CGA71019/1,2,4-Triazole, CGA179944 and CGA91305. The information provided is also considered sufficient to address the **Commission regulation (EU) 283/2013** data requirement *10.2.1: Acute toxicity to fish, aquatic invertebrates, or effects on aquatic algae and macrophytes* for the representative formulation. A **data gap** has been identified for the metabolite CGA142856/triazole acetic acid and green algae, and it should be considered whether additional data is needed to address the toxicity of this metabolite.

CLP
For a comparison with the CLP-criteria, please see section 2.9.2.4.

2.9.2.3.3.2 Aquatic plants

One study with the aquatic plant *Lemna gibba* and **penconazole technical** was provided, but was considered not reliable. A study summary has still been provided for completeness, as requested by ECHA.

Hughes J.S. (1985a) Report No. MPI-267-22-1100-2, Data Point: K-CA 8.2.7/01 (**Study not reliable**)
The 14-d static study was conducted with *Lemna gibba* exposed to penconazole technical with a nominal exposure range of 0.05, 0.10, 0.20, 0.40 and 0.80 mg/L mg a.s./L and a culture medium control. Exposure solutions were prepared with the solvent aceton. No analytical verification of the test substance was performed and it was not possible to verify if the concentrations had been maintained throughout the test. The RMS also investigated the fulfilment of the validity criteria in OECD TG 221 using the statistical software ToxRat Professional 3.3.0 for the interval 0-7 days. The validity criteria were however not fulfilled (frond doubling time were 2.6 days and average specific growth rate 0.268d^{-1}, whereas the validity criteria require a doubling time of less than 2.5 days and an average specific growth rate of 0.275 d^{-1}). The study could thus not be regarded as valid and not reliable for in the risk assessment nor hazard classification purposes.
The endpoint listed in the LoEP of Penconazole (2008):
Lemna gibba, 14-day :
$\mathbf{E_bC_{50\ :dry\ weight\ =}}$ **0.096 mg a.s./L_{nom}** (endpoint listed in the EFSA Journal (2008), 175, 1-104, re-calculated to 100% purity of active substance to account for the low purity of test material used in this study (87.3%).
NOEC = 0.096 mg a.s./L_{nom}
Note, that as the study does not fulfill the validity criteria, only a very brief evaluation of the study have been performed by the RMS, e.g. suitability of the study conditons according to the OECD TG, the applied statistics and whether the estimated ECx/NOEC are correct have not been controlled by RMS

Fulfilment of the data requirements (PPP-legislation)
According to **Commission Regulation (EU) No 283/2013** data requirement *8.2.7 Effects on aquatic macrophytes: (...) A laboratory test with Lemna species shall be performed for **herbicides** and **plant growth regulators** and for substances where there is evidence from information submitted under point 8.6 of Part A of this Annex or point 10.6 of Part A of the Annex to Regulation (EU) No 284/2013 that the test substance has **herbicidal activity**. (...).* Penconazole is a fungicide, and there is no evidence of herbicidal activity in tests with terrestrial non-target higher plants (see **Volume 3 - B.9.11 (PPP)**). However, the non-reliable study with *Lemna gibba* may indicate that penconazole technical is toxic to aquatic plants at concentrations below 1 mg a.s./L. Thus, requesting a new study on aquatic plants and technical penconazole may be warranted. This should be further considered by EFSA.

CLP
For a comparison with the CLP-criteria, please see section 2.9.2.4.

2.9.2.3.4 Chronic toxicity to other aquatic organisms

No chronic toxicity data to other aquatic organisms are available.

2.9.2.3.5 Assessment of the toxicity (T) -criteria, in Annex II to Regulation (EC) 1107/2009

Penconazole fulfils the criteria for a toxic substance according to the criteria Annex II to Regulation (EC) 1107/2009:

- An active substance is toxic for aquatic organisms if the long-term no-observed effect concentration for marine and freshwater organisms is less than 0.01 mg/L. From laboratory studies on the toxicity of penconazole to aquatic organisms the preliminary long-term NOEC for daphnia is ≤ 0.069 mg a.s./L. Hence, the T-criterion is currently not fulfilled for penconazole. However, the study is regarded as supportive, due to uncertainty regarding the applied statistics. The applicant has informed RMS that the Penconazole Task Force intend to conduct a new study according to OECD TG 211, which fully complies with current guidance, with the data ready to be delivered on request by Q2 2022. Thus, the assessment for toxicity to marine or freshwater organisms may still change.
- the substance is not classified as carcinogenic (category 1A or 1B) or mutagenic (category 1A or 1B);

however, the substance is toxic for reproduction (category 2) pursuant to Regulation (EC) No 1272/2008

- there is evidence of chronic toxicity, as identified by the classification as STOT RE 2 pursuant to Regulation (EC) No 1272/2008 (Please see Section 2.6.3.1.)

2.9.2.4 Comparison with the CLP criteria

2.9.2.4.1 Acute aquatic hazard

Table 110: Summary of information on acute aquatic toxicity relevant for classification (the most critical study per trophic level)

Method	Species	Test material	Results	Key or Supportive study	Remarks	Reference
OECD 203 (1981) [a]	Carp (*Cyprinus carpio*)	**Penconazole Tech.** Purity: 99% Batch: P 401013	96 h (static) LC_{50} = 3.8 mg a.s./L (nom)	Supportive	Not GLP Expiry date of technical penconazole not reported	[redacted] 1984a; CGA71818/0076
OECD 203 (1981) [a]	Rainbow trout (*Onchorynchus mykiss*)	**Penconazole Tech.** Purity: 87.3% Batch: FL 30634	**96 h (static)** **LC_{50} ≤ 1.3 mg a.s./L (im)**	Key study	No analytical measurement at the end of the study, endpoint thus established to be either equal or lower than the derived endpoint	[redacted] 1984; CGA71818/0073
OECD 203 (1981) [a] GLP	Rainbow trout (*Onchorynchus mykiss*)	**A6209G** (Topas 100 EC) Purity: 100 g/L penconazole Batch: Not reported	96 h (static) **LC_{50} > 5.6 mg formulation/L (nom)** **(**LC_{50} < 6.8 mg formulation/L (nom)) Equivalent to: **LC_{50} > 0.56 mg a.s./L (nom)** **(**LC_{50} < 0.68 mg formulation/L (nom))	Supportive	Unknown batch used Expiry date of batch not reported	[redacted] 1984; CGA71818/0005
OECD 203 (1981) [a] GLP	Carp (*Cyprinus carpio*)	**A6209G** (Topas 100 EC) Purity: 99% Batch: P 401013	96 h (flow-through) LC_{50} > 10 mg formulation/L (nom) **(**LC_{50} < 12.1 mg formulation/L (nom)) Equivalent to: LC_{50} >1.0 mg a.s./L) (nom) **(**LC_{50} < 1.21 mg formulation/L (nom))	Supportive	Unknown batch used Expiry date of batch not reported	[redacted] 1984a; CGA71818/0006

Method	Species	Test material	Results	Key or Supportive study	Remarks	Reference
US EPA-660/3-75-009 [b]	*Daphnia magna*	**Penconazole tech.** Purity: NA Batch: P. 11-14	**48 h (static)** **EC_{50} = 6.75 mg/L (nom)**	Key study	Not GLP Purity unknown	Hitz, 1981; CGA71818/0079
OECD 202 (1984) [b] GLP	*Daphnia magna*	**A6209G** (Topas 100 EC) Purity: 100 g/L (nominal); 108 g/L (analysed) Batch: P.609143	48 h (static) EC_{50} = 36 mg /L (**equivalent to 3.88 mg a.s./L**) (nom)	Supportive		Palmer et al, 2001; CGA71818/4379
OECD 201 (2006) [c] GLP	Green algae *(Pseudokirchneriella subcapitata)*	**Penconazole tech.** Purity:99.86% Batch: 0701	**72 h (static)** **E_rC_{50} = 3.41 mg/L (mm)**	Key study		Kley & Wydra, 2009: CGA071818_10633 & Lührs & Wydra, 2018: CGA071818_10633 [d]

[a] Evaluated according to OECD 203 (2019)
[b] Evaluated according to OECD 202 (2004)
[c] Evaluated according to OECD 201 (2006/2011)
[d] Statistical re-analysis to determine EC_{10}- and/or EC_{20}-estimates.
mm: mean measured, nom: nominal. **Bold** provides the two lowest endpoints, both the lowest among the key studies and among the supportive studies performed on technical penconazole.

Acute aquatic hazard
According to the Guidance on the Application of the CLP Criteria (2017)[16] fish, crustacea and aquatic plants represents the 'base-set' in most hazard profiles and represent a minimum dataset for a fully valid description of hazard. The lowest of the available toxicity values will normally be used to define the hazard category. Reliable studies with fish (*Cyprinus carpio* and *O. mykiss*) and green algae (*Pseudokirchneriella subcapitata*) are available for penconazole technical. In addition, a supportive study with crustacea (*Daphnia magna*) is available. Studies conducted with penconazole metabolites provide higher toxicity endpoints than studies with penconazole technical and have thus not been considered further with regard to the classification.

Algae/aquatic plants:
In the RAC opinion for penconazole (2012)[17], the endpoint derived from a study with *Lemna gibba* (**14-day EC_{50} = 0.096 mg/l based on frond numbers**) provided the lowest acute endpoint, and the reason penconazole was classified as: Aquatic hazard - category Acute 1 with an M-factor of 1. RMS has re-evaluated the Lemna-study and have regarded the study as not reliable due to major deficiencies: the validity criteria of OECD TG 221 were not fulfilled and exposure concentrations were not analytically verified, thus the endpoint cannot be considered reliable. RMS is thus of the opinion that this endpoint cannot be used for classification purposes anymore. However, RMS is of the opinion that there remains uncertainty regarding the toxicity for Lemna sp. and has proposed that EFSA should consider requesting a new study with Lemna.

Of the reliable studies with algae, the study by Kley and Wydra (2009) provided the lowest endpoint (***P. subcapitata* 72h (static) E_rC_{50} = 3.41 mg/L_{mm})** is regarded as the key study for this organism group**.**

Aquatic invertebrates:
Only one acute (48h) study with *D. magna* (EC_{50} = 6.75 mg a.s. /L) and technical penconazole by Hitz (1981) is available. The study is not considered fully reliable, as it is not conducted according to GLP. However, the study does fulfil the validity criteria of the OECD TG 202. Further, the available study with the representative formulation A6209G support (*D. magna*, EC_{50} = 36 mg A-6209G /L_{nom} equivalent to 3.88 mg a.s./L_{nom}) supports that the endpoint

[16] ECHA 2017. Guidance on the Application of the CLP Criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures Version 5.0. July 2017.
[17] Committee for Risk Assessment Opinion proposing harmonised classification and labelling at EU level of Penconazole. ECHA/RAC/CLH-O-0000002679-61-01/F

is in the range established in the supportive study with penconazole technical. The study by Hitz (1981) is thus regarded as the key study for this organism group.

Fish:
In the dossier a study with rainbow trout (**96h, *Oncorhynchus mykiss*, LC_{50} ≤ 1.3 mg a.s./L_{im}**) provides the lowest endpoint of the available fish studies, and the endpoint is ~ three time as low as the available study with carp (***Cyprinus carpio*, 96 h (static) LC_{50} = 3.8 mg a.s./L_{nom}**). In the study with rainbow trout, no measurement of the test substance was performed at the end of the test. However, in all other aspects, the study was conducted according to the requirements in OECD TG 203 and considered valid. When concentrations are only measured at the start of the test, it is not known whether the concentrations were maintained at test end. If concentrations at test end are not within ± 20% of nominal, the endpoint should be based on mean measured concentrations. In the current study, the initial measured concentration of the top dose was 108% of nominal, wheras the remaining 4 concentrations were between ~60-70% of nominal. When we look at the whole dataset for aquatic studies conducted with penconazole technical (excet the study on *O. myikss* and excluding those studies considered not reied on), endpoints from two studies were in the end based on nominal concentraions (concentrations were maintained within ± 20% of nominal in these studies), wheras endpoints from eight studies were based on mean measured concentrations (one of these were based on initial measured). Thus, it can be concluded that in the majority of the studies concentrations were not maintained. This further supports the RMS view that it cannot be excluded that the true endpoint of the study with *O. mykiss* may be below 1 mg a.s./L.

In another line of evidence, we may look at the two fish studies in the dossier with the representative formulation A6209G. In these studies it was concluded that in the study with ***O. mykiss* 96 h (static), the LC_{50} was below 6.8 mg A6209G/L_{nom} and above 5.6 mg A6209G/L_{nom}** (equivalent to < 0.68 mg a.s./L_{nom} and >0.56 mg a.s./L_{nom}). In the study with ***C. carpio* 96 h (static) the LC_{50} was below 12.1 mg A6209G/L_{nom} and above 10 mg A6209G/L_{nom}** (equivalent to <1.21 mg a.s./L_{nom} and >1.0 mg a.s./L_{nom}). The endpoints derived from these studies also indicate that rainbow trout is a more sensitive species than carp, and that relying on the active substance study with carp for classification is not conservative. The endpoint from the study with the representative formulation and *O. mykiss* is below 1 mg a.s./L, when expressed in terms of the active substance. However, there seem to be a general trend that the studies conducted with the representative formulation provides lower endpoints when expressed in terms of active substance, than the studies conducted with the active substance (technical). Thus relying on the *O. mykiss* product study alone for classification of the active substance, should be made with cation.

Another relevant isse is that the active substance study with carp is not conducted according to a GLP protocol (a non-GLP study). In the plant protection regulation, there is an independent requirement to reduce the need for repeating vertebrate studies. RMS has thus accepted the study to be sufficiently reliable, as the study do fulfill the the validity criteria of the relevant OECD TG. However, this may also be considered in the weight of evidence when deciding which endpoint to rely on for fish.

In an overall weight of evidence, RMS is thus of the opinion that the study with *O. mykiss* and penconazole technical cannot be disregarded for classification purposes. The study provides the lowest acute endpoint, and it can be established that the study with *O. mykiss* and penconazole technical provide an endpoint close to, but possible also below 1 mg/L. RMS is of the opinion that the study with *O. mykiss* should be regarded the key study for classification for this organism group.

The acute study providing the lowest toxicity value is the study with rainbow trout (**96h, *Oncorhynchus mykiss*, LC_{50} ≤ 1.3 mg a.s./L_{im}**). As the acute toxicity endpoint is either close to or below 1 mg a.s./L, it cannot be excluded that the criteria for classifying as category 1 Acute in **Commission Regulation (EC) No 1272/2008 Annex I: table 4.1.0** is fulfilled. In a conservative approach, RMS would thus propose that penconazole should be classified as **Aquatic hazard: Category Acute 1.** However, RMS acknowledges that this approach is conservative, and this may be further considered by ECHA.

M-factor
The supportive LC_{50} used to set the acute aquatic hazard (96h, *Oncorhynchus mykiss*, LC50 ≤ 1.13 mg a.s./L_{im}) may indicate a toxicity between ≤ 1 and > 0.1. Thus, according to **Commission Regulation (EC) No 1272/2008 Annex I: Table 4.1.3**, the relevant M-factor is 1.

2.9.2.4.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Table 111: Summary of information on long-term aquatic toxicity relevant for classification

Method	Species	Test material	Results[1]	Key or supportive study	Remarks	Reference
Test was conducted to an internal protocol [a] GLP	Fathead minnow (*Pimephales promelas*)	**Penconazole tech.** Purity: 87.3% Batch: FL 830634	35 d (flow-through) **NOEC = 0.36 mg a.s./L (mm)** $EC_{10;\ weight}$=0.43 mg a.s./L_{mm} $EC_{20;weight}$=0.603 mg a.s./L_{mm}	Key study	Expiry date of technical penconazole not reported Age of embryos at test start: <48 hours. According to the TG the test should start as soon as possible after the eggs have been fertilized and no later than 12 h post fertilisation to ensure exposure during early embryonic development.	[redacted] 1984c; CGA71818/0074 & [redacted] 2016; CGA071818_10494[b]
Internal method US EPA-660/3-75-009 GLP	*Daphnia magna*	**Penconazole tech.** Purity: 87.3% Batch: FL-830634	21 d (flow-through) **NOEC ≤ 0.069 mg a.s./L (mm)**	Key study	As there are some uncertainties regarding the applied statistics, the lowest dose tested (0.069 mg a.s./L) may actually be the LOEP, rather than the NOEC. The study has thus been regarded supportive for use in risk assessment. The study is still considered relevant for hazard classification purposes. The applicant intends to provide new data to clarify the correct endpoint.	Surprenant, 1984d; CGA71818/0080
OECD 202 (1984) [c] GLP	*Daphnia magna*	**A6209G** (Topas 100 EC) Purity: 100 g/L penconazole (nom) Batch: Op 211	21 d (semi-static) **NOEC = 0.32 mg/L (nom)** Equivalent to: **NOEC = 0.032**	Supportive	Expiry date of technical penconazole not reported	Memmert & Knoch, 1994a; CGA71818/1235

Method	Species	Test material	Results[1]	Key or supportive study	Remarks	Reference
		052	**mg a.s./L** **EC_{10} = 0.49 mg prod./L** Equivalent to: **EC_{10} = 0.049 mg a.s./L** EC_{20} = 0.81 **mg prod./L** Equivalent to: **EC_{20} = 0.081 mg a.s./L**			
OECD, Proposal for Toxicity Test with Chironomidae (May 1998) [d]	*Chironomus riparius*	**Penconazole tech.** Purity: 97.4% Batch: EN 603012	28 d (static) <u>Water-spiked:</u> NOEC = 0.8 mg/L (im) <u>Sediment-spiked:</u> NOEC = 25.2 mg/kg sed dw (nom) EC_{10} = 41.8 mg /kg sed dw (nom) EC_{20} = 50.2 mg /kg sed dw (nom)	Supportive	All validity criteria not fulfilled, but regarded reliable. 60 individuals used, whereas 80 should be used to determine the NOEC according to the guideline. Deviations in regard to emergence (more emerged than introduced). Using a WoE approach the study has still been considered acceptable (see RAR Volume 3CA, B.9.)	Grade, 1999; CGA71818/1390 & Kümmich, 2016b; CGA071818_10483 [b]
OECD 201 (2006) [c] GLP	Green algae *(Pseudokirchneriella subcapitata)*	**Penconazole tech.** Purity:99.86% Batch: 0701	72 h (static) **NOEC = 0.234 mg/L (mm)** E_rC_{20} = 0.62 mg/L (mm) E_rC_{10} = 0.26 mg/L (mm)	Key study		Kley & Wydra, 2009: CGA071818_10633 & Lührs & Wydra, 2018: CGA071818_10633 [d]

[a] Evaluated according to OECD 210 (2013)
[b] Statistical re-analysis to determine EC_{10}- and/or EC_{20}-estimates.
[c] Evaluated according to OECD 211 (2012)
[d] Evaluated according to OECD 218 and OECD 219 (2004)
[e] Evaluated according to OECD 305 (2012)
mm: mean measured, nom: nominal. **Bold** provides lowest endpoint.

Degradation
Penconazole is considered “not readily biodegradable”, as no degradation was observed over a 29-day test period,

following OECD guideline 301/B (Grade, 1999). Penconazole is considered hydrolytically stable under environmentally relevant pH conditions (van der Gaauw, 2002 and Spare, 1987a).

In natural water system penconazole was stable to aerobic mineralisation as mean levels of penconazole remained similar throughout the study period (Hurst and Sutcliffe, 2015). In water/sediment systems penconazole dissipated rapidly from the water phase to the sediment, where degradation was slow. Penconazole is stable in water/sediment systems with half-lives for the whole system ranging from 563 to >10,000 days (n=4) (Mamouni, 1998, Brands, 2009 and Hardy and Agostini, 2019e). For more detailed study summaries refer to section 2.8.2.

Penconazole is therefore considered to be not rapidly degradable for the purpose of classification according to the CLP criteria (2017).

Bioaccumulation
In the Guidance on the Application of the CLP Criteria (2017)[18], it is stated that in order to assess the bioaccumulation potential, experimentally derived "BCF values of high quality" are ultimately preferred for classification purposes. According to **Commission Regulation (EC) No 1272/2008 (CLP-regulation), Annex I: 4.1.2.8.1** *A experimental derived BCF in fish of ≥ 500 is indicative of the potential to bioconcentrate for classification purposes*.

As described in **section 2.9.2.1.2** above, one bioaccumulation study with the bluegill sunfish, *Lepomis macrochirus*, has been submitted. In this study, a maximum whole fish **bioconcentration factor (BCF) of 320** was derived. However, the study had deficiencies e.g., lack of measurement of TOC, as well as growth and lipid content of fish. These are parameters which may have a direct effect on the calculated BCF and may have contributed to an underestimation of the BCF in the available study. The study was thus regarded as not reliable, and do not fulfil the requirement of «high quality data ».

In the CLP-guidance, it is further noted that BCF derived from studies with poor or questionable quality should not be used for classification purposes, if high quality data on log K_{ow} are available. According to **Commission Regulation (EC) No 1272/2008**, Annex I : 4.1.2.8.1 . *Using a cut-off value of log K_{ow} ≥ 4 is intended to identify only those substances with a real potential to bioconcentrate*. The measured logarithmic n-octanol/water partition coefficient of penconazole is 3.8 (log K_{ow} = 3.8 at 20 °C).

Therefore, in according to **Commission Regulation (EC) No 1272/2008 Annex I :4.1.2.8.1** and considering that the log K_{ow} = 3.8, the available data *does not give evidence* that penconazole has the potential to bioaccumulate.

RMS notes that there are uncertainties with regard to experimental derived BCF, and that the BCF may be underestimated in the available study. Thus, a new study investigating the BCF may provide a different conclusion.

Chronic hazard
According to the Guidance on the Application of the CLP Criteria (2017)[19] fish, crustacea and algae/aquatic plants represents the 'base-set' in most hazard profiles and represent a minimum dataset for a fully valid description of hazard. The lowest of the available toxicity values will normally be used to define the hazard category. Valid studies with fish, aquatic invertebrates and green algae are available for penconazole technical. Studies conducted with penconazole metabolites provide higher toxicity endpoints than studies with penconazole technical and have thus not been considered further.

Algae/aquatic plants:
For a discussion regarding the relevance of *Lemna gibba* study, please see the section presenting the comparison with the CLP-criteria for the acute hazard (2.9.2.4.1), above. Of the valid studies with penconazole technical, the by Kley & Wydra, 2009 provided the lowest chronic endpoint: *P. subcapitata* 72h (static) **E_rC_{10} = 0.26 mg/L (mm),** and is regarded the key study for this organism group.

Fish:
Of the available chronic fish studies, the early life stage (ELS) toxicity test Surprenant (1984c) provides the lowest endpoint 35 d, *P. promelas*, **$EC_{10;\ weight}$=0.43 mg a.s./L_{mm}**, and is regarded the key study for this organism group.

[18] ECHA 2017. Guidance on the Application of the CLP Criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures Version 5.0. July 2017. Section 4.1.3.2.3.3. Bioaccumulation p. 500-501.

[19] ECHA 2017. Guidance on the Application of the CLP Criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures Version 5.0. July 2017.

RMS notes that a fish-full-life-cycle study which is already initiated, will probably be requested by EFSA during EFSA-stop-the-clock.

Aquatic invertebrates:
Of the available chronic studies with aquatic invertebrates and penconazole technical, the 21-day (flow-through) study with *D. magna* (**NOEC ≤ 0.069 mg a.s./L)** by Suprenant (1984d) provides the lowest endpoint. An attempt was done to calculate the EC_{10} from this study, and the EC_{10} was estimated to be 0.1 mg a.s./L. However, the EC_{10} was regarded as not reliable, as the lower limit confidence interval could not be determined. Due to some uncertainties raised by coRMS, as a conservative approach the NOEC is established to be either **equal to or lower** than 0.069 mg a.s./L. As the study provides the lowest endpoint of the available studies with aquatic invertebrates and penconazole technical (see table above) and this "lower-than"-endpoint in any case can be established to be below the CLP trigger of 0.1 mg/L RMS consider the study as reliable for hazard classification purposes, and also the key study. RMS are aware that it is preferred to use reliable EC_{10}-values for classification purposes and only the NOEC is available here. We further note that the available EC_{10} from the study with the representative formulation A6209G (*D. Magna*, 21 d (semi-static) EC_{10} = 0.49 mg prod./L, equivalent to: **EC_{10} = 0.049 mg a.s./L**) may be regarded as supportive evidence, even though there are some uncertainties in using an endpoint where additional co-formulants are present.

RMS notes that the applicant has also informed that a new chronic study with *D. magna* is being generated, and will be ready to be delivered Q2 2022, and thus may be requested by ECHA and/or EFSA.

According to **Commission Regulation (EC) No 1272/2008 Annex I: table 4.1.0** and considering that the lowest chronic effect concentration is < 0.1 mg/L (NOEC ≤ 0.069 mg a.s./L_{mm}) and that penconazole is not rapidly degradable, penconazole is proposed to be classified as **Aquatic hazard: Category Chronic 1**.

M-factor
The NOEC used to set the chronic hazard (≤ 0.069 mg a.s./L_{mm}) is ≤ 0.1 and > 0.01. Thus, according to **Commission Regulation (EC) No 1272/2008 Annex I: Table 4.1.3**, the relevant M-factor is 1.

NB. New data may become available during EFSA-stop-the-clock (fish full life cycle study and chronic toxicity study with *D. magna*), which may influence the M-factor.

2.9.2.5 Conclusion on classification and labelling for environmental hazards

Table 112: Summary of proposed classification for penconazole technical

Aquatic acute hazard		Aquatic chronic hazard	
Classification	**M-factor**	**Classification**	**M-factor**
Hazardous to the aquatic environment — Acute Hazard, Category 1 H400: Very toxic to aquatic life GHS09	1	Hazardous to the aquatic environment — Chronic Hazard, Category 1 H410: Very toxic to aquatic life with long lasting effects GHS09	1

The classification proposed above, is in line with the harmonised classification for penconazole provided in the RAC opinion for penconazole (2012)[20].

2.9.3 Summary of effects on arthropods

2.9.3.1 Summary of effects on bees

Table 113: Summary of acceptable toxicity endpoints for bees exposed to penconazole and the

[20] Committee for Risk Assessment Opinion proposing harmonised classification and labelling at EU level of Penconazole. ECHA/RAC/CLH-O-0000002679-61-01/F

representative formulation A62069G. Endpoints in **bold** are used in the risk assessment.

Organism	Test item	Test type	Endpoints[a]		Reference (author, date, document No.)
Honey bee	A6209G	Acute oral 48 hours	New study	**48 h $LD_{50, oral}$** >864 µg product /bee (equivalent to **>88.1µg a.s./bee**)[b]	***Franke, 2019; VV-725130***
		Acute contact 96 hours		48 h $LD_{50,contact}$ =1000 µg product/bee (equivalent to 102 µg a.s./bee) **96 h $LD_{50,contact}$** = 841 µg product/bee (equivalent to **85.8 µg a.s./bee**)	
Honey bee	A6209G	Chronic adult 10 days	New study	10 d LDD_{50} >19.5 µg product/bee/day **10 d NOEDD** = 19.5 µg product/bee/day (equivalent to **1.94 µg a.s./bee/day**)	***Kling, 2015; A6209G_11060***
Honey bee	A6209G	Chronic larva 8 days, repeated exposure	New study	8-day LD_{50} = 377.9 µg product /larva/development period **8-day NOED** = 173.3 µg product /larva/development period **(**equivalent to **17.2 µg a.s./larva/ development period**)	***Eckert, 2016; A6209G_11082***
Bumble bee (*Bombus terrestris*)	Penconazole technical (purity: 97.4%)	Acute oral, 48 hours	New study	**48 h LD_{50} = 157.1 µg a.s./bumble bee** 48 h NOED = 47.8.0 µg a.s./bumble bee	***Schmidt, 2019 ; VV-733640***
		Acute contact, 48 hours		**48 h LD_{50} > 400 µg a.s./bumblebee** 48 h NOED ≥ 400 µg a.s./bumblebee	

[a]New study: study not previously submitted
[b] Highest dose tested. 43.3% mortality observed.

Acute and chronic studies on honey bees have been performed with the representative formulation A6209G instead of technical penconazole. A justification from the applicant has been provided in **Volume 3 - B.9 (AS)**, section B.9.4.1. There are no studies on the residue levels of metabolites in nectar or pollen, nor any effect studies on honey bees and relevant metabolites available. Therefore, the data requirement regarding metabolites might be considered as not to be fulfilled. EFSA should considered if this constitutes a data gap and if additional data is required, or if the approach suggested for addressing the risk of metabolites according to the EFSA Bee GD (2013) as presented in **Volume 3 - B.9 (PPP)**, **section B.9.6.1.3** is sufficient.

Acute toxicity to bees

Four acute oral and contact toxicity studies with the representative formulation (A6209G) and honey bees are available. The study summaries have been included in **Volume 3 - B.9 (PPP).** Three of the studies (**Kleiner, 1993: CGA71818/1230** ; **Tornier, 1993: CGA71818/1236; Petto, 1994; CGA71818/1233)** have previously been evaluated and accepted in the EU in the Penconazole B9: Ecotoxicology, June 2007, Volume 3 DAR and DAR addendum (April 2008). These studies were, however, performed before the current test guidelines for testing acute contact (OECD 214) and acute oral (OECD 213) toxicity to honey bees were adopted and have several shortcomings. The current validity criteria with respect to the response of the toxic standard were considered not to be completely fulfilled, and in the direct contact tests the exposure doses were not well defined as the bees were sprayed with the test solution. Furthermore, the studies were not designed to determine LD_{50} values as the bees were exposed to one low dose, only. RMS therefore consider that these studies are not acceptable for use in the risk assessment. In addition, a new acute oral and contact toxicity study with A6209G and honeybees (**Franke, 2019; VV-725130)**, which are in accordance with the current testing guidelines, have been submitted. The study is considered acceptable and endpoints from this study are therefore used in the acute risk assessment for honey bees.

In addition, an acute toxicity study with technical penconazole and bumblebees (*Bombus terrestris*) **(Schmidt, 2019 ; VV-733640)** has been submitted and is considered acceptable by RMS. The study summary have been included in **Volume 3 - B.9 (AS).** The endpoints from the study is used in the acute risk assessment for bumble bees. No studies with solitary bees are available.

The information provided is considered sufficient to address the **Commission regulation (EU) 283/2013** data requirement for active substances (*8.3.1.1. Acute toxicity to bees*) and and the **Commission regulation (EU) 284/2013** data requirement for the representative formulation (*10.3.1.1. Acute toxicity to bees*).

Chronic toxicity to honey bees
A new study investigasting the chronic toxicity of A6209G to adult honey bees **(Kling, 2015; A6209G_11060)** have been submitted. The study summary have been included in **Volume 3 - B.9 (PPP).** No mortality was observed up to and including 1000 mg A6209G /kg feeding solution, the highest concentration tested. All validity criteria were met, but the exposure concentrations were not verified as no samples of the stock or feeding solutions were analysed for determination of the actual content of penconazole. In the study report it was stated that 1000 mg A6209G/kg sucrose solution was the highest possible concentration according to the results of a non-GLP solubility test. Analytical verification is a requirement according to OECD guideline No. 245 (2017). However, as the study was performed before OECD 245 came into force, the feeding solutions were prepared daily (identical test concentrations each day), the highest possible concentration was tested with regard to the solubility problems and no mortality was observed during the study at any of the tested concentrations, the study is considered as acceptable. The endpoint is used in the chronic risk assessment for honey bees.

The information provided is considered sufficient to address the **Commission regulation (EU) 283/2013** data requirement for active substances (*8.3.1.2. Chronic toxicity to bees*) and and the **Commission regulation (EU) 284/2013** data requirement for the representative formulation (*10.3.1.2. Chronic toxicity to bees*).

Effects on honey bee development and other honey bee life stages
A new chronic study with the representative formulation and honey bee larvae (**Eckert, 2016; A6209G_11082**) are available, in which the protocol of the single dose study (OECD TG 237, 2013) was followed except dosing the larvae repeatedly (from day 3 until day 6). The study was terminated at day 8, and a 8-day NOED was determined. A 7/8 day- NOED was considered acceptable as the endpoint to be used in the chronic risk assessment scheme for larvae described in the **EFSA Bee guidance document (2013)**. However, since then the OECD TG 239 (2016) has been finalised, in which larvae are dosed repeatedly (from day 3 until day 6) and followed until adult emergence on day 22. Preferably, a 22-day NOED should be used in the chronic larvae risk assessment. No brood damaging properties (IGR) are, however known for the active substance penconazole and accordingly no significant increase in mortality is expected during the pupation and emergence phase of the larval study. The 8-day NOED from the study by **Eckert (2016)** is therefore used in the risk assessment.

The information provided is considered sufficient to address the **Commission regulation (EU) 283/2013** data requirement for active substances (8.3.1.3. *Effects on honeybee development and other honeybee life stages*) and and the **Commission regulation (EU) 284/2013** data requirement for the representative formulation (*10.3.1.3. Effects on honeybee development and other honeybee life stages*).

The endpoints relevant for the risk assessment on bees are summarised in the table above.

2.9.3.2 Other non-target arthropods

Several standard and extended lab studies with the representative formulation A6209G have been evaluated by the RMS. Most of these are still considered reliable and acceptable for the risk assessment. Additional new extended laboratory studies with *Typhlodromus pyri* and *Aphidius rhopalosiphi* have been submitted**.** These studies have been commissioned to provide more detailed toxicity data (LD_{50} and ED_{50} values) to further support the risk assessment. Furthermore, the previously evaluated semi-field and field studies with *Aphidius rhopalosiphi* and *Typhlodromus pyri* are still considered acceptable for the risk assessment.

The endpoints relevant for the risk assessment for arthropods other than bees are summarised in the table below.

Table 114: Summary of acceptable and supportive endpoints for non-target arthropods exposed to A6209G.

Endpoints in **bold** are used in the risk assessment.

Test species	Test Item	Exposed life stage	Test type	Endpoint	Reference (author, date, Document No.)
Standard laboratory studies					
Aphidius rhopalosiphi	Penconazole in A6209G	Adult	Tier I	**LR_{50} >50 <100 g a.s./ha; $NOER_{repro}$ <10 g a.s./ha**	***Aldershof, 1999; CGA71818/1389***
Typhlodromus pyri	Penconazole in A6209G	Proto-nymphs	Tier I	**LR_{50} >10 <50 g a.s./ha; $NOER_{repro}$ <10 g a.s./ha**	***Calis, 1999; CGA71818/1386***
Poecilus cupreus	A6209G	Adult	Tier I	**LR_{50} >100 g a.s./ha; $NOER_{feeding}$ = 100 g a.s./ha**	***Hoogendoorn, 1999; CGA71818/1387***
Extended laboratory studies					
Aphidius rhopalosiphi	Penconazole in A6209G	Adult	Tier II (3-dimensional test design)	**LR_{50} and ER_{50} >400 g a.s./ha); $NOER_{repro}$ = 400 g a.s./ha)**	***Stevens, 2019; VV-471932***
Typhlodromus pyri	Penconazole in A6209G	Proto-nymphs	Tier II (2-dimensional test design)	**LR_{50} = 138 g a.s./ha; $NOER_{mortality}$ = 50 g a.s/ha; ER_{50} >100 g a.s./ha; $NOER_{repro}$ = 100 g a.s./ha**	***Fallowfield, 2019; VV-619272***
Typhlodromus pyri	A6209G	Proto-nymphs	Tier II	**LR50 >9.6 g a.s./ha; $NOER_{repro}$ <9.6 g a.s./ha**	**Kleiner, 1993a; CGA71818/1228**
Chrysoperla carnea	A6209G	Larvae	Tier II	**LR_{50} >200 g a.s./ha; $NOER_{repro}$ = 200 g a.s./ha**	***Manley, 2001; CGA71818/4377***
Coccinella septempunctata	A6209G	Larvae	Tier II	**LR_{50} >200 g a.s./ha; $NOER_{repro}$ = 200 g a.s./ha**	***Halsall, 2002; CGA71818/4384***
Orius laevigatus	A6209G	Nymphs	Tier II (3-D)	LR50 >200 g a.s./ha; NOERrepro = 200 g a.s./ha	Vinall, 2002; CGA71818/4383[a]
Semi-field studies					
Aphidius rhopalosiphi	A6209G	Adult	Semi field	**$NOER_{repro}$ = 135 g a.s./ha**	***Reber, 2002; CGA71818/4380***
Field studies					
Predatory mites (*Acari: Phytoseiidae*)	A6209G	Adult	Field	**No statistically significant effects on mite populations following 5 applications at 10 and 50 g a.s./ha with 11-13 day spray intervals.**	***Aldershof, 1999; CGA71818/1385***

[a] Study only considered supportive due to deviations from the test guideline

2.9.4 Summary of effects on non-target soil meso- and macrofauna

Table 115: Summary of acceptable and supportive endpoints for non-target soil meso- and macrofauna exposed to penconazole, the representative formulation A6209G and relevant metabolites. Endpoints in

bold are used in the risk assessment.

Organism	Test item	Applic. method of test a.s./OM	Test type	Endpoints		Reference (author, date: document No.)
Earthworm *Eisenia fetida*	Penconazole		Acute[a]	EU[c]	LC_{50corr} >500 mg a.s./kg soil dw (331.5 mg as/kg, adjusted to 100 % a.s)	*Schlaepfer, 1984; CGA71818/ 0085*
	Penconazole in A6209G		Acute[a]	EU[c]	LC_{50corr} >500 mg a.s./kg soil dw	*Lang, 1993; CGA71818/ 1231*
	CGA71019		Acute[a]	EU[c]	LC_{50} >1000 mg /kg soil dw	*Heimbach, 1986; CGA71019/ 0021*
	CGA179944		Acute[a]	EU[c]	LC_{50} >1000 mg/kg soil dw	*Baetscher, 2002; CGA179944 /0012*
			Acute[ab]	Conf. data	LC_{50} >1000 mg/kg soil dw	*Lührs, 2009; CGA179944 _10030*
	CGA142856		Acute[ab]	Conf. data	LC_{50} >1000 mg/kg soil dw	*Lührs, 2002; CGA142856 /0024*
Earthworm *Eisenia fetida*	Penconazole in A6209G	Mixed into the soil / 10% peat	56 day Sublethal reproduction test	EU[c]	NOEC ≥ 100 mg A6209G/kg soil dw (≥ 10 mg a.s./kg soil dw) **$NOEC_{corr}$ ≥5 mg a.s./kg soil dw[h]**	***Gillham, 2002; CGA71818/ 4381***
	CGA71019 (1,2,4-triazole)	Mixed into the soil/ 10% peat	56 day Sublethal reproduction test	EU[c]	NOEC > 0.0708 mg/kg soil dw	***Ehlers, 2000; CGA64250/ 4385***
		Mixed into the soil/ 10% peat	56 day Sublethal reproduction test	EU[ec]	**NOEC = 1.0 mg/kg soil dw[e]**	***Moser & Scheffczyk 2004; CGA64250/ 4683***
	CGA179944	Mixed into the soil/ 10% peat	56 day Sublethal reproduction test	New study	**NOEC ≥ 1000 mg/kg soil dw**	***Friedrich, 2016; CGA179944 _10010***
	CGA142856 (triazole acetic acid)	Mixed into the soil/ 10% peat	56 day Sublethal reproduction test	New study	**NOEC ≥ 1000 mg/kg soil dw**	***Friedrich, 2017; CGA142856 _10038***
	CGA91305	Mixed into the soil/	56 day Sublethal	EU[f]	NOEC = 309 mg/kg soil dw EC_{10} = 239 mg/kg soil dw **$EC_{10, corr}$ =120 mg/kg soil dw[h]**	***Friedrich, 2013;***

Organism	Test item	Applic. method of test a.s./OM	Test type	Endpoints		Reference (author, date: document No.)
		5% peat	reproduction test		EC_{20} = 343 mg/kg soil dw	***CGA091305 _10001***
Folsomia candida	Penconazole in A6209G	Mixed into the soil/ 10% peat	28 day Reproduction test	EU[c]	NOEC= 973 mg A6209G/kg soil dw (98.8 mg a.s./kg soil dw) EC_{10} = 97.6 mg a.s./kg soil dw **EC_{10corr}= 48.8 mg a.s./kg soil dw[h]** EC_{20} = 112.7 mg a.s./kg soil dw	***Barth, 2001; CGA71818/ 4376***
	CGA71019 (1,2,4-triazole)	Mixed into the soil/ 10% peat	28 day Reproduction test	EU[c]	**NOEC = 1.8 mg/kg soil dw**	***Moser & Scheffczyk, 2002; CGA71019/ 0053***
		Mixed into the soil/ 10% peat	28 day Reproduction test	New study	NOEC = 4.0 mg/kg soil dw	***Lührs, 2009c; CA469_100 78***
	CGA179944	Mixed into the soil/ 5% peat	28 day Reproduction test	New study	**NOEC ≥ 1000 mg/kg soil dw**	***Friedrich, 2016a; CGA179944 _10009***
	CGA142856 (triazole acetic acid)	Mixed into the soil/ 10% peat	28 day Reproduction test	Conf. data	**NOEC = 15.6 mg/kg soil dw**	***Klein & Rosenkranz , 2002; CGA142856 /0022***
	CGA91305	Mixed into the soil/ 5% peat	28 day Reproduction test	EU[f]	NOEC = 309 mg /kg soil dw **$NOEC_{corr}$ = 155 mg/kg soil dw[h]**	***Friedrich, 2013a; CGA091305 _10000***
Hypoaspis aculeifer	Penconazole in A6209G	Mixed into the soil/ 5% peat	14 day Reproduction test	New study	NOEC ≥ 1000 mg A6209G /kg soil dw (≥ 101.4 mg a.s./kg soil dw) **$NOEC_{corr}$ ≥ 50.7 mg a.s./kg soil dw[h]**	***Schulz, 2016; A6209G_11 122***
	CGA71019 (1,2,4-triazole)	Mixed into the soil/ 5% peat	14 day Reproduction test	EU[g]	**NOEC = 171 mg/kg soil dw** EC_{10} = 190 mg a.s./kg soil dw EC_{20} = 241 mg a.s./kg soil dw	***Schulz, 2014; CGA071019 _10008***
	CGA179944	Mixed into the soil/ 5% peat	14 day Reproduction test	New study	**NOEC ≥ 1000 mg/kg soil dw**	***Schulz, 2016a; CGA179944 _10007***
	CGA142856 (triazole acetic acid)	Mixed into the soil/ 5% peat	14 day Reproduction test	New study	**NOEC ≥ 1000 mg/kg soil dw**	***Schulz, 2017; CGA142856 _10040***

Organism	Test item	Applic. method of test a.s./OM	Test type	Endpoints		Reference (author, date: document No.)
	CGA91305	Mixed into the soil/ 5% peat	14 day Reproductio n test	EU[f]	NOEC ≥ 1000 mg /kg dw soil **$NOEC_{corr}$ ≥ 500 mg/kg soil dw[h]**	***Schulz, 2014a; CGA091305 _10002***

[a] Supporting information. Studies submitted and evaluated for the first EU approval review of penconazole but no longer a data requirement under Commission Regulation (EU) No 283/2013 and 284/2013.
[b] Supporting information. Confirmatory data, but no longer a data requirement under Commission Regulation (EU) No 283/2013.
[c] Study listed in the EFSA Journal (2008) 175, 1-104 and in the Draft Assessment Report for Penconazole (2007) Volume 3 Annex B.9,
[d] Values estimated in accordance with **Commission Regulation (EU) No 283/2013**. EC_{10} and/or EC_{20} values only shown for endpoints where estimation was possible and accepted by RMS
[e] Reviewed in triazole derivative metabolite assessment (COP no. 2011.00502)
[f] Previously evaluated in the EU: Volume 3, B.9 of the DRAR for Propiconazole (April 2017; RMS Finland)
[g] Previously evaluated in the EU: Volume 3, B.9 of the DRAR for metconazole (August 2019; RMS Belgium).
[h] Penconazole and its metabolite CGA91305 have log P_{OW} values of 3.8 and 2.1, respectively (*i.e.* greater than 2), and therefore it is necessary to correct the endpoints that should be used in the risk assessment by a factor of 2 regardless of the organic matter content in the test soil, as was agreed in EFSA Supporting publication 2015:EN-924)

No sub-lethal toxicity studies on earthworms, collembolans (*folsomia candida*) or predatory mites (*Hypoaspis aculeifer*) and technical penconazole have been submitted. Instead, the chronic studies on these soil organisms were carried out with the representative formulation A6209G. A justification from the applicant has been provided in **Volume 3 - B.9 (CA)**, section B.9.4.1. The study summaries have been included in **Volume 3 - B.9 (PPP).**

Two studies on earthworms and the representative formulation A6209G (**Nienstedt, 2000; CGA71818/4328**; **Gillham, 2002; CGA71818/4381**) have been submitted. The study by **Nienstedt (2000; CGA71818/4328) i**s considered as not acceptable by RMS**,** since one of the validity criteria was not met (coefficient of variation for reproduction in the controls >30%), and since A6209G was sprayed onto the soil surface, whereas according **to Commission Regulation (EU) 283/2013** 8.4.1 *" The test substance shall be incorporated into the soil to obtain a homogenous soil concentration".* Furthermore, the study design was limited by few and low test concentrations. The study by **Gillham (2002; CGA71818/4381**) is considered acceptable by RMS and only the endpoint from this study is is included in the table above.

One study on *Folsomia candida* and the representative formulation A6209G (**Barth, 2001; CGA71818/4376**) has been submitted. This study has previously been evaluated and accepted in the EU. In addition, a new study on *Hypoaspis aculeifer* and A6209G (**Schulz, 2016; A6209G_11122**). Both studies are considered acceptable by RMS.

Totally five Sub-lethal toxicity studies on earthworms, five on collembolans (*folsomia candida*) and four on predatory mites (*Hypoaspis aculeifer*) and the relevant soil metabolites CGA71019, CGA179944, CGA142856 and CGA91305 have been provided. The study summaries have been included in **Volume 3 - B.9 (AS).** All the 14 studies are considered acceptable by RMS and endpoints from the studies are included in the table above.

The information provided is considered sufficient to address the **Commission regulation (EU) 283/2013** data requirement for active substances (*8.4.1 Earthworm – sub-lethal effects* and *8.4.2.1. Species level testing.*) and the **Commission regulation (EU) 284/2013** data requirement for the representative formulation (*10.4.1.1 Earthworms - sub-lethal effects* and *10.4.2. Effects on non-target soil meso- and macrofauna (other than earthworms***).**

2.9.5 Summary of effects on soil nitrogen transformation

Table 116: Summary of acceptable and supportive endpoints for nitrogen transformation. Endpoints in **bold** are considered relevant for the risk assessment.

Organism	Test item	Test type	Endpoints		Reference (author, date, document no.)
Nitrogen transformation	Penconazole in A6209G	Nitrate formation	New study	**< 25% deviation from control after 28 days of exposure at 13.13 mg A6209G/kg soil d.w. (1.34 mg a.s./kg d.w. soil)**	***Persdorf, 2019; VV-716611***
Nitrogen transformation	Penconazole in A6209G	Nitrate formation	EU	< 25% deviation from control after 28 days of exposure at 0.32 mg a.s./kg d.w. soil (240 g a.s./ha) [a]	***Lang, 1993; CGA71818/1232***
Nitrogen transformation	CGA71019 (1,2,4-Triazole)	Nitrate formation	EU	**<25 % deviation from control after 28 days of exposure at 0.35 mg/kg d.w. soil**	***Völkel, 2000; CGA71019/0042***
Nitrogen transformation	CGA179944	Nitrate formation	EU	**< 25% deviation from control after 28 days of exposure at 0.20 mg/kg d.w. soil**	***Völkel, 2001; CGA179944/0008***
Nitrogen transformation		Nitrate formation	New study	< 25% deviation from control after 28 days of exposure at 0.067 mg/kg d.w. soil	***Feil, 2009; CGA179944_10036***
Nitrogen transformation	CGA142856 (triazole acetic acid)	Nitrate formation	Confirmatory data	**< 25% deviation from control after 28 days of exposure at at 0.08043 mg/kg d.w. soil**	***Reis, 2002; CGA142856_0023***
Nitrogen transformation	CGA91305 (R116857)	Nitrate formation	New study	**< 25% deviation from control after 28 days of exposure at 0.377 mg/kg d.w. soil**	***Völkel, 2002; CGA77502/0006***

[a] Study considered supportive only, as the validity criteria could not be properly assessed.
d.w. : dry weight

Five studies with penconazole metabolites have been submitted and are summarised in **Volume 3 – B.9 (AS).** No studies with penconazole technical are available. However, studies with the representative formulation have been provided and are included in **Volume 3 – B.9 (PPP).**

According to **Commission regulation (EU) 283/2013** data requirements *8.5 Effects on soil nitrogen transformation: A test shall provide sufficient data to evaluate the impact of active substances on soil microbial activity, in terms of nitrogen transformation.* (...) *Soils used shall be freshly sampled agricultural soils. The sites from which soil is taken shall not have been treated during the previous two years with any substance that could substantially alter the diversity and levels of microbial populations present, other than in a transitory manner.* As no studies on nitrogen transformation and technical penconazole was available, RMS accepts to use the studies with the representative formulation A6209G to address the **Commission regulation (EU) 283/2013** data requirement 8.5 *Effects on soil nitrogen transformation* for the active substance. The available studies fulfil the validity criteria of the respective OECD guideline (except the study by Lang (1993), which is considered supportive), and for all metabolites and the representative formulation <25% effects on soil nitrogen transformation were observed after 28 days of exposure. The studies also meet the test conditions specified in the data requirements. Thus, the **Commission regulation (EU) 283/2013** data requirement 8.5 *Effects on soil nitrogen transformation* is considered addressed for the penconazole, A6209G and the metabolites.

2.9.6 Summary of effects on terrestrial non-target higher plants

Table 117: Summary of acceptable and supportive endpoints for Non-target terrestrial plants with the A6209G. Endpoints in bold are considered relevant for the risk assessment.

Organism	Test item	Test type	Endpoints		Reference (author, date, File No.)
Non-target terrestrial plants (6 plant species from 5 plant families)	A6209G (Topas 100 EC)	Screening data on vegetative vigour & seedling emergence	EU	Seedling emergence & vegetative vigour <50% effect = 300 g/ha (30 g a.s./ha) [a]	*Wälder, 2000 CGA71818/4342*
Non-target terrestrial plants (6 plant species from 5 plant families)	A6209G (Topas 100 EC)	Screening data on vegetative vigour & seedling emergence	New study	**No effects observed on seedling emergence & vegetative vigour ≥200 g a.s./ha**	*Tomoroga, 2011 A6209G/10023*

[a] Supportive endpoint. The doses used in the current study are not sufficiently high to cover the worst-case GAP.
Endpoints in **bold** used in the risk assessment

Two screening studies with the representative formulation A6209G (Topas 100 EC) and higher plants have been submitted. Study summaries are presented below, and the studies have been evaluated according to recent guidelines and standards.

According to **European commission (EU) 284/2013** data requirements <u>*10.6.1. Summary of screening data:*</u> *(…) Screening data shall be required for plant protection products other than those exhibiting herbicidal or plant growth regulator activity, and if the toxicity cannot be established from data on the active substance (point 8.6.1 of Part A of the Annex to Regulation (EU) No 283/2013). The data shall include testing from at least six plant species from six different families including both mono- and dicotyledons. The tested concentrations/rates shall be equal or higher than the maximum recommended application rate. If screening studies do not cover the specified range of species or the concentrations/rates necessary, then tests in accordance with point 10.6.2 shall be carried out.*

In the data requirements it is stated that the tested concentrations/rates shall be equal or higher than the maximum recommended application rate. In the study by Wälder (2000), the doses were too low to cover the worst-case GAP of the representative uses. The new study by Tomoroga (2011) meets the data requirement with regard to the doses tested. RMS further notes that two of the tested species (*Avena fatua* (wild oats) and *Zea mays* (maize)) are in the same plant family (Poaceae) and thus only 5 plant families are represented, as opposed to 6 stated in the data requirements.

Further, the studies either do not fully comply with the validity criteria and/or exhibit other deviations from the OECD test guidelines. For example, no analytical verification of the dose rates has been performed in the two available studies which is considered a major deviation. In addition, the provided studies have not been conducted according to GLP (**non-GLP study**), which is a requirement according to **Commission Regulation (EU) No 284/2013.** The studies have thus been regarded as supportive only.

Even though no effects were reported at up to 200 g a.s./ha in the newest study by Tomoroga (2011), RMS notes that some phytotoxic effects were observed at the two highest doses tested (15 and 30 g a.s./ha) in the study by Wälder (2000). Information on the number of plants exhibiting these effects per concentration, or the type of phytotoxic effects is however not reported. RMS also notes that a study with technical penconazole and the aquatic plants are available (***L. gibba*, 14-d (static) EC_{50} = 0.11 mg a.s./L_{nom}**). This study is not considered acceptable, due to lack of analytical verification of the test substance at test-end. However, it is reasonable to assume that the endpoint will either be equal to or lower 0.11 mg a.s./L, and thus indicate that penconazole may be toxic to higher plants.

As the two available studies have been regarded as "Supportive only" by RMS, RMS have informed the applicant that we consider a new valid study complying with the GLP-criteria should be provided to finalise the risk assessment. We have thus asked them (22nd of September 2021) to consider conducting a new valid study on terrestrial plants. To take into account the slight effects observed in Wälder (2000), and the effects observed in the study with aquatic plants, we have recommended a full study rather than a screening test. The 13th of October 2021, we received the following comment by the applicant:

> *The applicants acknowledge the deficiencies in the existing non-target plant screening studies (Tomoroga, 2011; Wälder, 2000) as stated by the RMS (non-GLP and no analytical dose verification).*
>
> *In addition to the submitted data, two additional studies according to OECD TG 208 and 227 are available to the Penconazole Task Force for the penconazole 10% EC formulation, DOURO (carried out in lieu of the technical active substance), which the notifier now has the right of access to:*
>
> 1. **Bramby-Gunary J. (2009a). Evaluation of the Phytotoxicity of "DOURO" (Penconazole 100 g a.s./l) GLP Vegetative Vigour Test, Terrestrial Non-Target Plants (Based on OECD Guideline 227). Document No. ACE-08-159.**
>
> 2. **Bramby-Gunary J. (2009b). Evaluation of the Phytotoxicity of "DOURO" (Penconazole 100 g a.s./l) GLP Seedling Emergence and Seedling Growth Test Terrestrial Non-Target Plants (Based on OECD Guideline 208). Document No. ACE-08-158**
>
> *Both studies are available for submission during the EFSA-stop-clock if requested by EFSA during peer review. They both meet the validity criteria according to the current guidance and were carried out in compliance with GLP. Analytical dose verification of the test substance confirms that the test item concentrations were within acceptable limits (88% to 90% of nominal values).*
>
> *Treatments were applied to two monocotyledon and four dicotyledon plant species from six different families (Avena sativa, Allium cepa, Cucumis sativus, Glycine max, Brassica napus and Beta vulgaris), using a dose range of 0.78 to 50 g a.s./ha in both studies. Following both pre- and post-emergence applications on 7 species, the NOER was confirmed as 50 g a.s./ha, and the ER50 values were >50 g a.s./ha.*
>
> *Syngenta also intends to conduct two new studies with the formulated product (A6209G; penconazole 100 g/L EC) in full accordance with current guidance (OECD TG 208 and 227). However, these data are unlikely to be available before Q3 2022.*

Requesting a new GLP-study on non-target terrestrial plants should be considered by EFSA.

2.9.7 Summary of effects on other terrestrial organisms (flora and fauna)

2.9.8 Summary of effects on biological methods for sewage treatment

Table 118: Summary of acceptable and supportive endpoints for activated sludge with the penconazole

technical. Endpoints in bold are considered relevant for the risk assessment.

Organism	Test item	Test type	Endpoints		Reference (author, date, document no)
Activated Sludge	Penconazole	Activated sludge respiration Inhibition test	EU	EC_{50} >100 mg/L_{nom} **EC_{20} = 82.1 mg/L_{nom}** NOEC = 32 mg/L_{nom}	***Grade, 1999a; CGA71818/4323***

According to **Commission Regulation (EU) No 283/2013** data requirement 8.8. *Effects on biological methods for sewage treatment : A test shall provide an indication as to the potential of the active substance on biological sewage treatment systems. (...) Effects on biological methods for sewage treatment shall be reported where the use of plant protection products containing the active substance can give rise to adverse effects on sewage treatment plants*. One study with penconazole on activated sludge has been provided and is considered valid for the risk assessment (see the table, above). The data requirement is thus considered fulfilled.

The EC20 of 82.1 mg a.s./L_{nom} is 5335 times greater than the worst-case FOCUS step 1 initial PEC_{sw} of 0.01537 mg/l (cucumber, BBCH 51-89, 3 x 50 g a.s./ha). Dilution prior to reaching sewage treatment works may also be expected to reduce the risk further. These results suggest limited risk to sewage treatment facilities.

2.9.9 Summary of product exposure and risk assessment

2.9.9.1 Risk assessment for birds and other terrestrial vertebrates

Birds

The risk assessment for birds has been performed according to the latest **EFSA Guidance Document on Risk Assessment for Birds and Mammals (2009)**[21].

Table 119: Summary of endpoints used in the risk assessment for birds

Organism	Test item	Test type	Endpoints[a]	Reference (author, date, File No.)
Mallard duck (*Anas platyrhynchos*)	Penconazole	Acute oral	**LD_{50} >1590 mg/kg bw[a]**	[redacted] ***1984; CGA71818/0067***
Bobwhite quail (*Colinus virginianus*)	Penconazole	Acute oral	**LD_{50} >2510 mg/kg bw[a]**	[redacted] ***1984a; CGA71818/0066***
Mallard duck (*Anas platyrhynchos*)	Penconazole	Sub-chronic toxicity and reproductive	**NOEL = 28.9 mg/kg bw/d**	[redacted] ***1985; CGA71818/0068***

[a] Used in the geomean calculation of the acute endpoint: LD_{50}(geomean) =1998 mg/kg bw

Table 120: Screening step – acute risk assessment for birds

GAP crop	Indicator species	Shortcut value	Rate (kg a.s/ha)	MAF_{90}	DDD (mg a.s/kg bw/day)	LD_{50} (geomean) (mg a.s/kg bw)	TER_A

[21] European Food Safety Authority; Guidance Document on Risk Assessment for Birds & Mammals on request from EFSA. EFSA Journal 2009; 7(12):1438. doi:10.2903/j.efsa.2009.1438. Available online: www.efsa.europa.eu

Pome fruit	Small insectivorous bird	46.8	0.04	1.3	2.43	1998	822
Vines	Small omnivorous bird	95.3	0.03	1.4	4.0		500
Cucumber		158.8	0.05	1.6	12.70		157
Cucumber			0.035	1.0	5.56		359

The TER_A values for penconazole are greater than the relevant trigger value of 10, indicating **acceptable acute risk to birds** following the use of A6209G, according to the proposed use pattern.

Table 121: Screening step – long-term risk assessment for birds

GAP crop	Indicator species	Shortcut value	Rate (kg a.s/ha)	MAF_m	f_{twa}	DDD (mg a.s/kg bw/day)	NOAEL (mg a.s/kg bw/day)	TER_{LT}
Pome fruit	Small insectivorous bird	18.2	0.04	1.5	0.53	0.58	28.9	50
Vines	Small omnivorous bird	38.9	0.03	1.6		0.99		29
Cucumber		64.8	0.05	2.0		3.43		8
Cucumber			0.035	1.0		1.20		24

The TER_{LT} values for penconazole are greater than the trigger value of 5, indicating **acceptable long-term risk to birds** following the use of A6209G, according to the proposed use pattern.

Risk for birds through drinking water

Table 122: Ratios of effective application rate (AR_{eff}) to acute and long-term endpoints for penconazole following the use of A6209G - puddle scenario

Exposure scenario	AR_{eff} (g a.s/ha)[a]	K_{oc} (mL/g)	Relevant endpoint (mg/kg bw)	Ratio of effective application rate to endpoint	Ratio trigger
Acute	145	2123	LD_{50} >1998	<0.072	3000
Long-term			NOEL = 28.9	5	

The resulting ratios are less than the trigger of 3000 indicating that **further assessment of the acute and long-term risk to birds, from drinking water from puddles, is not required for penconazole.**

Secondary poisoning

Risk to earthworm-eating birds

Table 123: Long-term risk from secondary poisoning to earthworm-eating birds

Test item	Maximum $PEC_{Saccumulation}$ (mg/kg)	K_{OW}	f_{oc}	K_{oc}	BCF	PEC_{worm} (mg/kg)	DDD (mg a.s./kg bw/day)	NOEL (mg a.s./kg bw/day)	TER_{LT}
Penconazole	0.0421	5248	0.02	2123	1.25	0.053	0.055	28.9	526

The TER value for penconazole is greater than the long-term trigger value of 5, indicating **acceptable risk to earthworm eating birds** following use of penconazole in A6209G, according to the proposed use pattern. The RMS notes that at the current stage of the evaluation, the input for the PEC_{soil} modelling may be changed during peer review, and new modelling may be necessary. The values presented are thus regarded as preliminary values. However, as the margins of safety are large, the outcome of the risk assessment is not expected to change following new modelling.

Risk to fish-eating birds

Table 124: Long-term risk from secondary poisoning to fish-eating birds

Test item	Maximum Step 3 PEC_{SW} (mg a.s./L)	BCF	PEC_{fish} (mg a.s./kg)	DDD (mg a.s./kg/bw/day)	Long-term NOEL (mg a.s./kg bw/day)	TER_{LT}
Penconazole	0.00159	320	0.509	0.081	28.9	357

The TER value for penconazole is greater than the long-term trigger value of 5, indicating **acceptable risk to fish-eating birds** following use of penconazole in A6209G, according to the proposed use pattern. The RMS notes that at the current stage of the evaluation, the input for the PEC_{SW} modelling may be changed during peer review, and new modelling may be necessary. Likewise, the bioconcentration study with fish has not been accepted by the RMS and no reliable BCF is available. The values presented are thus regarded as preliminary values. However, as the margins of safety are large, the outcome of the risk assessment is not expected to change following new input values.

Metabolites

Eight metabolites are found in relevant concentrations as residues in plant material and should be considered for the avian risk assessment:

CGA71019 (1,2,4-triazole): Maximum Total Radioactive Residues (TRR) of 6.1 % in plants
CGA179944: TRR of 12.6 % in plants
CGA131013 (triazolyl alanine): TRR of 86.7 % in plants
CGA205369 (triazolyl lactic acid): TRR of 76.1 % in plants
CGA142856 (triazolyl acetic acid): TRR of 33.2 % in plants
CGA132465: TRR of 66.9 % in plants
CGA190503: TRR of 4.3 % in plants, later detected at maximum concentrations of 0.02 mg/kg in fruits
CGA127841: TRR of 3.2 % in plants, later detected at maximum concentrations of 0.02 mg/kg in fruits

Based on the available mammalian and avian toxicity data – and that the risk assessment for birds with the active substance is acceptable already at the screening level – it is considered that **the risk to birds is acceptable following exposure to the relevant metabolites.** Please refer to **Volume 3 (PPP) - B.9.2.1.2** for details on the risk assessment.

Mammals

The risk assessment for mammals has been performed according to the latest **EFSA Guidance Document on Risk Assessment for Birds and Mammals (2009)**[22].

[22] European Food Safety Authority; Guidance Document on Risk Assessment for Birds & Mammals on request from EFSA. EFSA Journal 2009; 7(12):1438. doi:10.2903/j.efsa.2009.1438. Available online: www.efsa.europa.eu

Table 125: Summary of the endpoints used in the risk assessment for mammals

Organism	Test item	Test type	Endpoints[a]	Reference (author, date, File No.)
Rabbit	Penconazole	Acute oral	**LD_{50} = 971 mg a.s./kg bw**	[redacted] ***1981; CGA71818/0764***
Rat	A6209G (Topas 100 EC)	Acute oral	**LD_{50} = 2574 mg A6209G/kg bw, corresponding to 257 mg as/kg bw**	[redacted] ***1996; CGA71818/1239 TOX 96-50626***
Rat	Penconazole	2-generation reproduction study	**NOAEL= 21.2 (males)** and 22.7 (females) mg/kg bw/day	[redacted] ***1987; CGA71818/0756***

Table 126: Screening step – acute risk assessment for mammals with penconazole

GAP crop	Indicator species	Shortcut value	Rate (kg a.s/ha)	MAF_{90}	DDD (mg a.s/kg bw/day)	LD_{50} (mg a.s/kg bw)	TER_A
Pome fruit	Small herbivorous mammal	136.4	0.04	1.3	7.09	971	137
Vines			0.03	1.4	5.73		170
Cucumber			0.05	1.6	10.91		89
Cucumber			0.035	1.0	4.77		204

The TER_A values for penconazole are greater than the relevant trigger value of 10, indicating **acceptable acute risk to mammals** following use of A6209G, according to the proposed use pattern.

Table 127: Screening step – acute risk assessment for mammals with the representative formulation A6209G

GAP crop	Indicator species	Shortcut value	Rate (kg a.s/ha)	MAF_{90}	DDD (mg a.s/kg bw/day)	LD_{50} (mg a.s/kg bw)	TER_A
Pome fruit	Small herbivorous mammal	136.4	0.04	1.3	7.09	257	36
Vines			0.03	1.4	5.73		45
Cucumber			0.05	1.6	10.91		24
Cucumber			0.035	1.0	4.77		54

The TER_A values for A6209G (Topas 100 EC) are greater than the relevant trigger value of 10, indicating **acceptable acute risk to mammals** following use of A6209G, according to the proposed use pattern.

Table 128: Screening step – long-term risk assessment for mammals with penconazole

GAP crop	Indicator species	Shortcut value	Rate (kg a.s/ha)	MAF_m	f_{twa}	DDD (mg a.s/kg bw/day)	NOAEL (mg a.s/kg bw/day)	TER_{LT}
Pome fruit	Small herbivorous mammal	72.3	0.04	1.5	0.53	2.30	21.2	9.2
Vines			0.03	1.6		1.84		12
Cucumber			0.05	2.0		3.83		5.5
Cucumber			0.035	1.0		1.34		16

The TER_{LT} values for penconazole are greater than the trigger value of 5, indicating **acceptable long-term risk to mammals** following use of A6209G, according to the proposed use pattern.

Risk for mammals through drinking water

Table 129: Ratios of effective application rate (AR_{eff}) to acute and long-term endpoints for penconazole following the use of A6209G - puddle scenario

Exposure scenario	AR_{eff} (g a.s/ha)[a]	K_{oc} (mL/g)	Relevant endpoint (mg/kg bw)	Ratio of effective application rate to endpoint	Ratio trigger
Acute	145	2123	LD_{50} 971	0.15	3000
Long-term			NOEL = 21.2	6.8	

The resulting ratios are less than the trigger of 3000 indicating that **further assessment of the acute and long-term risk to mammals, from drinking water from puddles, is not required for penconazole.**

Secondary poisoning

Risk to earthworm-eating mammals

Table 130: Long-term risk from secondary poisoning to earthworm-eating mammals

Test item	21d TWA PEC_{soil} (mg/kg)	K_{OW}	f_{oc}	K_{oc}	BCF	PEC_{worm} (mg/kg)	DDD (mg a.s./kg bw/day)	NOAEL (mg a.s./kg bw/day)	TER_{LT}
Penconazole	0.0421	5248	0.02	2123	1.25	0.055	0.070	21.2	303

The TER value for penconazole is greater than the long-term trigger value of 5, indicating **acceptable risk to earthworm eating mammals** following use of penconazole in A6209G, according to the proposed use pattern. The RMS notes that at the current stage of the evaluation, the input for the PEC_{soil} modelling may be changed during peer review, and new modelling may be necessary. The values presented are thus regarded as preliminary values. However, as the margins of safety are large, the outcome of the risk assessment is not expected to change following new modelling.

Risk to fish-eating mammals

Table 131: Long-term risk from secondary poisoning to fish-eating mammals

Test item	Maximum Step 3 PEC_{SW} (mg a.s./L)	BCF	PEC_{fish} (mg a.s./kg)	DDD (mg a.s./kg/bw/day)	Long-term NOAEL (mg a.s./kg bw/day)	TER_{LT}
Penconazole	0.00159	320	0.509	0.072	21.2	294

The TER value for penconazole is greater than the long-term trigger value of 5, indicating **acceptable risk to fish-eating mammals** following use of penconazole in A6209G, according to the proposed use pattern. The RMS notes that at the current stage of the evaluation, the input for the PEC_{SW} modelling may be changed during peer review, and new modelling may be necessary. Likewise, the bioconcentration study with fish has not been accepted by the RMS and no reliable BCF is available. The values presented are thus regarded as preliminary values. However, as the margins of safety are large, the outcome of the risk assessment is not expected to change following new input values.

Metabolites

Eight metabolites are found in relevant concentrations as residues in plant material and should be considered for the mammalian risk assessment:

CGA71019 (1,2,4-triazole): Maximum Total Radioactive Residues (TRR) of 6.1 % in plants
CGA179944: TRR of 12.6 % in plants
CGA131013 (triazolyl alanine): TRR of 86.7 % in plants
CGA205369 (triazolyl lactic acid): TRR of 76.1 % in plants
CGA142856 (triazolyl acetic acid): TRR of 33.2 % in plants
CGA132465: TRR of 66.9 % in plants
CGA190503: TRR of 4.3 % in plants, later detected at maximum concentrations of 0.02 mg/kg in fruits
CGA127841: TRR of 3.2 % in plants, later detected at maximum concentrations of 0.02 mg/kg in fruits

Based on the available mammalian toxicity data – and that the risk assessment for mammals with the active substance is acceptable already at the screening level – it is considered that **the risk to mammals is acceptable following exposure to the relevant metabolites.** Please refer to **Volume 3 (PPP) - B.9.2.2.2** for details on the risk assessment.

2.9.9.2 Risk assessment for aquatic organisms

The risk assessment for aquatic organisms has been conducted according to **EFSA Aquatic Guidance (2013)[23].** The assessment is a tiered procedure which derives Regulatory Acceptable Concentrations (RACs) from the effects data by applying assessment factors appropriate to the taxon and tier assessed. The RAC is compared to the appropriate PEC_{SW} value. If the RAC is >PEC, then the risk is acceptable, otherwise the assessment should be refined with higher tiers. RMS notes that at the input for the FOCUS-modelling may change and that new modelling may be necessary. The FOCUS PEC_{SW} and PEC_{SED} values presented are thus regarded as preliminary values.

Risk assessment for penconazole

The risk assessment for the most sensitive species (worst-case RACs) are compared to the PEC_{sw} and PEC_{SED} for all the applied uses (representative uses). A complete risk assessment for all species is presented in Volume 3 - B.9 (PPP).

Acute effects: The lowest Tier 1 $RAC_{SW, ac}$ is >5.6 µg a.s./L, based on the toxicity to rainbow trout.
Chronic effects: The lowest Tier 1 $RAC_{SW, ch}$ is 3.2 µg a.s./L, based on the toxicity to *Daphnia magna*. The lowest tier 1 $RAC_{SED, ch}$ is 2520 µg a.s./kg, based on the toxicity to *Chironomus riparius*.

Following the EFSA Aquatic Guidance Document (2013), these Tier 1 RACs are compared to the exposure values to determine if the risk is acceptable. The risk assessment is presented in the tables, below.

Table 132: Risk assessment for acute effects in aquatic organisms and the representative uses for

[23] EFSA Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters (EFSA Journal 2013;11(7):3290)

penconazole.

Crop	FOCUS Step	Maximum PEC_{SW} (µg/L) [a]	Acute Tier 1 RAC_{SW} (µg/L)	PEC/RAC	Trigger
Pome fruit 2 x 40 g a.s./ha BBCH 71-89	1	**11.653**	>5.6 [b]	**<2.1**	<1
	2	2.208		<0.4	
Vines (early) 2 x 30 g a.s./ha BBCH 13	1	**6.135**		**<1.1**	
	2	1.268		<0.2	
Vines (late) 2 x 30 g a.s./ha BBCH 85	1	**7.201**		**<1.3**	
	2	1.174		<0.2	
Cucumber 3 x 50 g a.s./ha BBCH 51-89	1	**15.367**		**<2.7**	
	2	1.973		<0.4	
Cucumber 35 g a.s./ha BBCH 51-89	1	**3.586**		<0.6	
	2	0.505		<0.1	

[a] Worst-case FOCUS Step 2-value has been used
[b] Lowest acute RAC-value (based on acute data for *O. mykiss*)
PEC/RAC values in **bold** are above the trigger of 1

Table 133: Risk assessment for chronic effects in aquatic organisms and the representative uses for penconazole.

Crop	FOCUS Step	Maximum PEC_{SW} (µg/L) [a]	Chronic Tier 1 RAC_{SW} (µg/L)	PEC/RAC	Trigger
Pome fruit 2 x 40 g a.s./ha BBCH 71-89	1	11.653	3.2[b]	**3.6**	<1
	2	2.208		0.7	
Vines (early) 2 x 30 g a.s./ha BBCH 13	1	6.135		**1.9**	
	2	1.268		0.4	
Vines (late) 2 x 30 g a.s./ha BBCH 85	1	7.201		**2.3**	
	2	1.174		0.4	
Cucumber 3 x 50 g a.s./ha BBCH 51-89	1	15.367		**4.8**	
	2	1.973		0.6	
Cucumber 35 g a.s./ha BBCH 51-89	1	3.586		**1.1**	
	2	0.505		0.2	

[a] Worst-case FOCUS Step 2-value has been used
[b] Lowest acute RAC-value (based on chronic data for *D. magna*)
PEC/RAC values in **bold** are above the trigger of 1

Table 134: Risk assessment for sediment dwelling organisms and the representative uses for penconazole

Crop	FOCUS Step*	Maximum PEC_{SED} (µg/kg)[a]	Chronic Tier 1 RAC_{SED} (µg/L)	PEC/RAC	Trigger
Pome fruit 2 x 40 g a.s./ha BBCH 71-89	1	166.6	2520 [b]	0.066	<1
	2	32.0		0.013	
	1	110.9		0.044	

Vines (early) 2 x 30 g a.s./ha BBCH 13	2	23.6		0.009	
Vines (late) 2 x 30 g a.s./ha BBCH 85	1	116.6		0.046	
	2	20.2		0.008	
Cucumber 3 x 50 g a.s./ha BBCH 51-89	1	277.4		0.110	
	2	36.3		0.014	
Cucumber 35 g a.s./ha BBCH 51-89	1	64.7		0.026	
	2	9.2		0.004	

[a] Worst-case FOCUS Step 2-value has been used
[b] Chronic RAC-value (based on chronic data for sediment dwelling *C. riparius*)
PEC/RAC values in **bold** are above the trigger of 1

The Tier 1 $RAC_{SW,\ acute}$ of 5.6 µg a.s./L is lower than the FOCUS Step 1 PEC_{SW}-values (which ranged from 3.6 to 15.4 µg a.s./L), for three of four representative use scenarios indicating an unacceptable risk at these three representative uses at FOCUS step 1. The Tier 1 $RAC_{SW,\ chronic}$ of 3.2 µg a.s./L are lower than the FOCUS Step 1 PEC_{SW}-values (which ranged from 3.6 to 15.4 µg a.s./L), indicating an unacceptable risk at FOCUS step 1 for all four representative use scenarios. However, both the chronic and acute Tier 1 RACs are greater than the FOCUS Step 2 PEC_{SW}-values (which ranged from 0.3 to 2.2 µg a.s./L) thereby **indicating an acceptable risk to aquatic (free-swimming) organisms from penconazole following all proposed uses of A6209G.** No higher tier refinements are required.

For all proposed use patterns, the Tier 1 $RAC_{SED,\ chronic}$ of 2520 µg a.s./kg is above the Step 1 PEC_{SED} values (which ranged from 65 to 277 µg a.s./kg), **indicating an acceptable risk to sediment dwelling organisms following the proposed uses of A6209G.**

Risk assessment for metabolites

The relevant aquatic metabolites were CGA71019, CGA179944, CGA142856 and CGA91305. Studies to assess the toxicity of these metabolites to fish (96 h acute), daphnia (48 h acute) and algae (96 h chronic) was provided, and valid endpoints could be derived. All of the metabolites are less toxic than penconazole to aquatic species. The exception was the toxicity to algae and the metabolite CGA142856, where no valid study was available. As a worst-case assumption, the metabolite is assumed to be 10x more toxic than the a.s.

The risk assessment with the metabolites for all the applied uses (representative uses) were acceptable at FOCUS Step 1. Full details can be found in **Volume 3 - B.9.4.3 (PPP).** Below, the risk assessment for the worst-case RACs out of all the metabolites RACs, are compared to the PEC_{sw} for all the applied uses (representative uses).

Acute effects: The lowest Tier 1 $RAC_{SW,ac}$ is 237 µg CGA91305/L based on the toxicity to rainbow trout (*Oncorhynchus mykiss* 96 h, LC_{50}).
Chronic effects: The lowest Tier 1 $RAC_{SW,ch}$ is 34 µg CGA142856/L, based on the endpoint for penconazole and *Desmodesmus subspicatus* divided by 10.

Table 135: Risk assessment for the lowest of the metabolite acute RACs, and FOCUS Step 1 PECsw for the representative uses for penconazol.

Use	FOCUS Step	Maximum PEC_{SW} (µg/L)	Acute Tier 1 RAC_{SW} (µg CGA91305/L)	PEC/RAC
Pome fruit, BBCH 71-89 2 x 40 g a.s./ha	1	1.465	237	0.006
Vines (early), BBCH 13 2 x 30 g a.s./ha	1	1.092		0.005
Vines (late), BBCH 85 2 x 30 g a.s./ha	1	1.092		0.005
Cucumber, BBCH 51-89	1	2.729		0.012

3 x 50 g a.s./ha				
Cucumber, BBCH 51-89 35 g a.s./ha	1	0.637		0.003

Table 136: Risk assessment for the lowest of the metabolite chronic RACs, and FOCUS Step 1 PECsw for the representative uses for penconazol.

Use	FOCUS Step	Maximum PECsw (µg/L)	Chronic Tier 1 RACsw (µg CGA142856/L)	PEC/RAC
Pome fruit, BBCH 71-89 2 x 40 g a.s./ha	1	1.492	34	0.044
Vines (early), BBCH 13 2 x 30 g a.s./ha	1	1.119		0.033
Vines (late), BBCH 85 2 x 30 g a.s./ha	1	1.119		0.033
Cucumber, BBCH 51-89 3 x 50 g a.s./ha	1	2.797		0.082
Cucumber, BBCH 51-89 35 g a.s./ha	1	0.653		0.019

The risk assessment for aquatic species and the metabolites for all the applied uses (representative uses) were acceptable at FOCUS Step 1.

2.9.9.3 Risk assessment for bees and non-target arthropods

2.9.9.1.1 Risk assessment for bees

In the currently notified **Guidance Document on Terrestrial Ecotoxicology** under Council Directive 91/414/EEC **(SANCO/10329/2002)**, only data on acute oral and contact toxicity to adult honey bees are considered in the first tier risk assessment scheme. Thus, the risk assessment scheme is not sufficient as it does not cover the data requirements according to **Commission Regulation (EU) No. 283/2013** on the chronic risk to adult honey bees and honey bee larvae. A new guidance document on the risk assessment of plant protection products on bees (*Apis mellifera*, *Bombus* spp. and solitary bees) has been published in 2013 by **EFSA**[24], in which risk assessment schemes for the chronic risk to adult honeybees and honey bee larvae, and for the risk to bumblebees are described. This Guidance Document is however not yet noted by the Standing Committee on Plants, Animals, Food and Feed. Nevertheless, during the pesticide peer review meeting on general occurring issues in ecotoxicology **(EFSA Supporting publication 2015:EN-924)**, it was agreed that the tier 1 risk assessment to honey bees should be performed according to the **EFSA Guidance document (2013)**. Furthermore, for bumblebees and solitary bees, it was agreed that if any data are submitted, they should be evaluated.

Therefore, the screening and tier 1 risk assessment for honey bees are performed according to the **EFSA guidance document (2013)**. A refined chronic adult risk assessment according to ECPA (2017)[25] is also included for some of the GAP uses/scenarios. Since acute toxicity data for bumblebees are available, an acute risk assessment for bumble bees according to the EFSA guidance document (2013) is also performed, as this is the only risk assessment scheme for bumble bees currently available. By doing so, all available data on bees is taken into account in a risk assessment.

A complete risk assessment for honey bees and bumble bees is presented in **Volume 3 - B.9 (PPP), section B.9.6.1.**

[24] European Food Safety Authority, 2013 (***updated 04 July 2014***). EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera*, *Bombus* spp. and solitary bees). EFSA Journal 2013;11(7):3295, 268 pp., doi:10.2903/j.efsa.2013.3295

[25] ECPA (2017). Proposal for a protective and workable regulatory European bee risk assessment scheme based on the EFSA bee guidance and other new data and available approaches. Available at https://croplifeeurope.eu/wp-content/uploads/2020/12/28028_ECPA-Proposal-for-a-protective-and-workable-EU-Bee-Risk-Assessment-Version-09-June-17.pdf

Risk assessment for penconazole and A6209G

The acute risk to adult honey bees and bumble bees, and the chronic risk to honey bee larvae from penconazole and the representative formulation A6209G are acceptable at the screening level for all proposed uses of A6209G. The chronic risk to adult honey bees for the proposed post flowering uses (BBCH ≥ 70) in pome, vines and cucumber from penconazole and A6209G is acceptable at tier 1. The chronic risk to adult honey bees from penconazole for the proposed uses in vines (BBCH 10-69) and cucumber (BBCH 50-69) is considered acceptable according to a refined risk assessment. Also, the acute and chronic risk to honey bees from exposure to contaminated water are acceptable. The screening assessment for acute and chronic exposure of honey bees, as well as the first tier and refined risk assessment for the adult chronic exposure from pollen and nectar for the worst-case use and scenario (i.e. cucumber BBCH 50-69 at 3 x 50 g a.s./ha), are shown below.

Table 137: Screening step - Risk assessment of acute adult contact exposure to penconazole

Test substance	Application Category	Crop Group	Species	App. rate (g a.s./ha)	LD_{50} contact (µg a.s./bee)	$HQ_{contact}$	Trigger
A6209G	Sideward/upward (SUW) spray applications	Pome fruit	Honey bee	40	85.8	0.5	>85
		Vines		30		0.3	
	Downward spray applications	Fruiting vegetables (cucumber)		50		0.6	>42
		Fruiting vegetables (cucumber)		35		0.4	

HQ (Hazard Quotient) for adult contact exposure. HQ values shown in **bold** are above the relevant trigger and require further refinement.

Table 138: Screening step - Risk assessment of acute adult oral exposure to penconazole from contaminated pollen and nectar

Test substance	Application Category	Crop Group	Species	App. rate (kg a.s./ha)	SV	LD_{50} oral (µg a.s./ bee)	$ETR_{acute\ adult\ oral}$	Trigger
A6209G	Sideward/ upward (SUW) spray applications	Pome fruit	Honey bee	0.040	10.6	>88.1*	<0.005	> 0.2
		Vines		0.030			<0.004	
	Downward spray applications	Fruiting vegetables (cucumber)		0.050	7.6		<0.004	
		Fruiting vegetables (cucumber)		0.035			<0.003	

SV = shortcut value for sideward/upward spray applications and downward spray applications
* Highest dose tested. 43.3% mortality observed.
ETR = Exposure Toxicity Ratio
ETRs in **bold** are above the relevant trigger and require further refinement

Table 139: Screening step - Risk assessment of chronic larva exposure to penconazole

Test substance	Application Category	Crop Group	Species	App. rate (kg a.s./ha)	SV	8 D $NOED_{oral}$ (µg a.s./larva/ development period)	ETR_{larvae}	Trigger
A6209G	Sideward/ upward (SUW) spray applications	Pome fruit	Honey bee	0.040	6.1	17.2*	0.014	>0.2
		Vines		0.030			0.011	
	Downward spray applications	Fruiting vegetables (cucumber)		0.050	4.4		0.013	
		Fruiting vegetables (cucumber)		0.035			0.009	

SV = shortcut value for sideward/upward spray applications and downward spray applications
ETR = Exposure Toxicity Ratio
ETRs in **bold** are above the relevant trigger and require further refinement
*8-day NOED from a repeated larva exposure study, terminated at day 8.

The $\mathbf{ETR_{larvae}}$ values for penconazole were from 14.1 to 22.3 times lower than the trigger value of 0.2. Although an uncertainty still remains concerning whether the use of the 8D NOED is protective enough, the results indicates that the **risk to honeybee larvae is acceptable at the screening level** following use of A6209G according to the proposed use pattern. This is also supported by the aspect, that for the active substance no brood damaging properties (IGR) are known and accordingly no significant increase in mortality is expected during the pupation and emergence phase of the larval study.

Table 140: Screening step - Risk assessment of chronic adult oral exposure to penconazole from contaminated pollen and nectar

Test substance	Application Category	Crop Group	Species	App. rate (kg a.s./ha)	SV	LDD_{50} oral (µg a.s./bee /day)	$ETR_{chronic\ adult\ oral}$	Trigger
A6209G	Sideward/up ward (SUW) spray applications	Pome fruit	Honey bee	0.040	10.6	>1.94*	**<0.219**	>0.03
		Vines		0.030			**<0.164**	
	Downward spray applications	Fruiting vegetables (cucumber)		0.050	7.6		**<0.196**	
		Fruiting vegetables (cucumber)		0.035			**<0.137**	

SV = shortcut value for sideward/upward spray applications and downward spray applications
ETR = Exposure Toxicity Ratio
ETRs in **bold** are above the relevant trigger and require further refinement
* Highest possible concentration according to the results of a non-GLP solubility test; this concentration resulted in no mortality

All the $\mathbf{ETR_{chronic\ adult\ oral}}$ values for penconazole are greater than the trigger of 0.03 for sideward/upward and downward sprays, indicating that the **chronic risk to honeybees following exposure to penconazole requires further assessment at Tier 1** following use of A6209G according to the proposed use pattern.

Tier 1 assessment - Chronic adult exposure

The worst-case tier 1 scenario is considered to be "foraging on the treated crop" when application takes place during flowering in cucumber (BBCH 50-69), at 50 g a.s./ha. The worst-case risk assessment shown below (**Table 134**) is considered to cover all other proposed use patterns.

Table 141: Tier 1 - Risk to adult honeybees following chronic oral exposure to penconazole from foraging on the treated crop

Application Category	BBCH	Species	App. rate (kg a.s./ha)	SV	LDD_{50} oral (µg a.s./bee/ day)	Ef	TWA[a]	$ETR_{chronic\ adult\ oral}$	Trigger
Fruiting vegetables (cucumber)									
DW	50-69	Honey bee	0.050	5.8	>1.94*	1	0.72	**<0.108**	>0.03

[a] The twa value of 0.72 is based on a default DT_{50} of 10 days and a 10-day time window.
SV = shortcut value for sideward/upward spray applications and downward spray applications
ETR = Exposure Toxicity Ratio
ETRs in **bold** are above the relevant trigger and require further refinement
SUW: Sidewards/upwards spray application
DW: Downwards spray application
* Highest possible concentration according to the results of a non-GLP solubility test; this concentration resulted in no mortality

The **$ETR_{chronic\ adult\ oral}$** value for the worst-case scenario "foraging on the treated crop" when application takes place during flowering in cucumber (BBCH 50-69) at 50 g a.s./ha are greater than the trigger of 0.03. Thus, **the chronic risk to honey bees requires further evaluation.**

Refined assessment- Chronic adult exposure

According to the ECPA approach (2017)[26] a NOEDD or LDD_{10} could be used together with an appropriate adjustment in the EFSA 2013 trigger in a refined risk assessment in cases where it is not possible to achieve an experimentally measured LDD_{50}. No LDD50 could be derived from the study by **Kling (2015; A6209G_11060)** as no mortality was observed at the highest dose tested (1.94 µg a.s./bee/day). The NOEDD was therefore determined to be ≥ 1.94 µg a.s./bee/day.

The appropriate trigger can be calculated using the same method as presented by EFSA (2013). If it is assumed that the observed NOEDD is equivalent to the LDD_{10} then the trigger can be calculated as:

10%/1.43% = 6.99, which is equivalent to ETR 1.43/ 10 = 0.143

The **$ETR_{chronic\ adult\ oral}$** value within the treated crop for the worst-case use of A6209G in **cucumber (BBCH 50-69) at 50 g a.s./ha**, are compared to the refined trigger in the table below.

Table 142: Refined Tier 1 - Risk to adult honeybees following chronic oral exposure to penconazole from foraging on the treated crop

Crop	App. method	App. rate (kg a.s./ha)	Shortcut Value (SUW / downward spray)	Ef	TWA	NOEDD (µg a.s./bee/ day)	ETR	Trigger
Fruiting vegetables (cucumber)	DW	0.050	5.8	1	0.72	≥1.94*	≤0.1076	>0.143

ETRs in **bold** are above the relevant trigger and require further refinement

[26] ECPA (2017). Proposal for a protective and workable regulatory European bee risk assessment scheme based on the EFSA bee guidance and other new data and available approaches. Available at https://croplifeeurope.eu/wp-content/uploads/2020/12/28028_ECPA-Proposal-for-a-protective-and-workable-EU-Bee-Risk-Assessment-Version-09-June-17.pdf

The **$ETR_{chronic\ adult\ oral}$** value for penconazole/A6209G for **the worst-case use in cucumber (BBCH 50-69) at 50 g a.s./ha** is less than the refined trigger of 0.143, indicating that the **chronic oral risk to adult honey bees is considered acceptable** following use of A6209G according to the proposed use pattern. No further evaluation is considered necessary.

Risk to honey bees from exposure to contaminated water

For the assessment of risk from exposure to surface water, the worst case FOCUS Step 1 PEC_{SW} values are used. The risk assessment (ETR values) for the worst-case use in cucumber (BBCH 50-69) at 3 x 50 g a.s./ha (shown in the table below) is considered to cover all other proposed use patterns.

Table 143: Risk to adult honey bees and honey bee larvae following the consumption of surface water contaminated with penconazole following the proposed uses of A6209G

Type of assessment	Water consumption (µl)[1]	Max. PEC_{SW} (µg/µL)[2]	Endpoint	ETR	Trigger
Cucumber (3 x 50 g a.s./ha, BBCH 51-89)					
Acute oral exposure adult bees	11.4	1.54×10^{-5}	>88.1 µg/bee	1.99×10^{-6}	>0.2
Chronic oral exposure adult bees	11.4		>1.94 µg/bee/day	9.03×10^{-5}	>0.03
Chronic oral exposure larvae	111		17.2 µg/larva/development period	9.92×10^{-5}	>0.2

[1]water consumption per adult bee per day, or per larva per development period (i.e. 5 days)
[2] The PEC_{SW} -values are derived from FOCUS step 1 modelling
ETRs in **bold** are above the relevant trigger and require further refinement

All the ETR values are well below the relevant triggers, indicating that the acute and chronic risk to adult honey bees and honey bee larvae from exposure to surface water is acceptable following the proposed use pattern of A6209G.

As the Step 1 PEC_{SW} values used in the assessment for surface water are worst case compared to the concentrations calculated for the runoff scenarios (at FOCUS Step 3), the risk assessment for surface water covers the assessment for water in puddles.

Risk assessment for metabolites

There are no studies on the residues of metabolites in pollen or nectar. The risk assessment scheme for metabolites provided in the **EFSA Bee Guidance Document (2013)** was followed. The metabolites considered to be relevant (CGA71019 and CGA132465) were identified based on plant metabolisms and rotational crop studies, and toxicity reported for other organism groups/QSAR (for details see **Volume 3 - B.9 (PPP), section B.9.6.1)**. CGA132465 was detected over the limits (**>10% TRR** or **> 0.01 mg/kg**) in both plant metabolism studies and rotational crops studies, whereas CGA71019 was only detected over the limit in a rotational crop study. The risk for the relevant metabolites is assessed, assuming 10 times higher toxicity of the metabolites compared to penconazole.

The acute risk to adult honey bees and the chronic risk to honey bee larvae from the relevant metabolites are acceptable at the screening level for all proposed uses of A6209G. For CGA71019 the chronic risk to adult honey bees for all the proposed uses of A6209G is considered acceptable at tier 1. For CGA132465, the chronic risk to adult honey bees for the proposed post flowering uses (BBCH ≥ 70) uses in cucumber is considered acceptable at tier 1. The chronic risk to adult honey bees from CGA132465 for the proposed post flowering uses (BBCH ≥ 70) uses in pome and wine is considered acceptable according to the refined risk assessment. The chronic risk to adult honey bees from CGA132465 for the proposed uses in vine (BBCH 10-69) and cucumber (BBCH 50-69) is considered acceptable based on a weight of evidence approach.

Table 144: Screening assessment - Acute oral risk to adult honey bees from metabolites in the treated crop following the proposed use of A6209G. A molecular weight of 284.2 g/mol for penconazole (parent) was

used in the calculations.

Metabolite	Applic. Category	Crop Group	App. rate (kg a.s /ha)	SV	Mwmet (g/mol)	Ftrr	LD_{50} oral (µg a.s./bee)	ETR	Trigger
CGA71019	SUW	Pome fruit	0.040	10.6	69	0.061	8.81[a]	0.001	>0.2
		Vines	0.030					0.001	
	DW	Cucumber	0.050	7.6				0.001	
		Cucumber	0.035					0.0004	
CGA132465	SUW	Pome fruit	0.040	10.6	300	0.669	8.81[a]	0.03	>0.2
		Vines	0.030					0.03	
	DW	Cucumber	0.050	7.6				0.03	
		Cucumber	0.035					0.02	

[a]Assuming 10 times higher toxicity than the parent compound.
SUW: Sidewards/upwards spray supplication
DW: Downwards spray application
SV = shortcut value for the parent molecule for SUW and DW spray applications
Mwmet: molecular mass of the metabolite
Ftrr: fraction of metabolite formed (%TRR/100)
ETR values in **bold** are above the relevant trigger and require further refinement.

For both CGA71019 and CGA132465 all the $ETR_{acute\ adult\ oral}$ values are below the trigger of 0.2 indicating an acceptable acute oral risk to adult honey bees at the screening following the proposed uses of A6209G.

Table 145: Screening assessment - Chronic risk to honey bee larvae from metabolites in the treated crop following the proposed use of A6209G. A molecular weight of 284.2 g/mol for penconazole (parent) was used in the calculations.

Metabolite	Applic. Category	Crop Group	App. rate (kg a.s /ha)	SV	Mw_{met} (g/mol)	Ftrr	NOED larva (µg a.s./larva/ develop. period)	ETR	Trigger
CGA71019	SUW	Pome fruit	0.040	6.1	69	0.061	1.72[a]	0.0021	>0.2
		Vines	0.030					0.0016	
	DW	Cucumber	0.050	4.4				0.0019	
		Cucumber	0.035					0.0013	
CGA132465	SUW	Pome fruit	0.040	6.1	300	0.669	1.72[a]	0.100	>0.2
		Vines	0.030					0.075	
	DW	Cucumber	0.050	4.4				0.090	
		Cucumber	0.035					0.063	

[a] 8-day NOED, assuming 10 times higher toxicity than the parent compound.
SUW: Sidewards/upwards spray supplication
DW: Downwards spray application
SV = shortcut value for the parent molecule for SUW and DW spray applications
Mwmet: molecular mass of the metabolite
Ftrr: fraction of metabolite formed (%TRR/100)
ETR values in **bold** are above the relevant trigger and require further refinement

For both CGA71019 and CGA132465 all the **ETR_{larvae}** values were lower than the trigger value of 0.2 indicating an acceptable chronic risk to honey bee larvae at the screening level following the proposed uses of A6209G.

Tier 1 assessment - Chronic adult exposure

As all ETR values at the screening assessment for **adult chronic oral exposure** for the parent compound was above the trigger, the risk assessment for the metabolites is started directly at tier 1.

Of the two metabolites (CGA71019 and CGA132465) identified as relevant for the risk assessment, only CGA132465 was detected above the limit (TRR 66.9 %) in a plant metabolite study following foliar application of penconazole. Therefore, the assessment of risk from "foraging on the treated crop", "weeds in the treated field", "the field margin" and "an adjacent crop" are performed for CGA132465 using the TRR from this study.

Risk from **foraging on the treated crop** is considered worst-case when application takes place during flowering in vines and cucumber. As the tier 1 ETR values for the parent was above the trigger of 0.03 for these uses, a refined tier 1 assessment according to ECPA (2017) for CGA132465 is shown further below (See **Table 141**).

For **post-flowering (i.e., from BBCH 70 onwards) uses in pome fruit and vines**, risk from **foraging on weeds in the treated crop** can be considered worst-case and are shown in **Table 139**.

Both CGA71019 and CGA132465 were detected over the limits in **rotational crop studies** following application of penconazole to bare soil. The maximum TRR for CGA71019 (6.1%) and CGA132465 (20.2%) from these studies are therefore used in the assessment of risk from "foraging on a succeeding crop for annual crops". RMS consider that there are not sufficient/appropriate data available for the metabolite residues for the "permanent crop the following year", and therefore this scenario is not included in the risk assessment. The risk from **"foraging the following year on a succeeding crop for annual crops**", for the worst-case use of A6209G in **cucumber** (3 x 50 g a.s./ha) are shown in **Table 140**.

Table 146: Tier 1 **- Risk to adult honey bees following chronic oral exposure to the metabolite** CGA132465 **from <u>foraging on weeds in the treated crop.</u>** A molecular weight of 284.2 g/mol for penconazole (parent) was used in the calculations.

Metabolite	App. rate (kg a.s./ha)	SV	fDep/Ef	TWA[a]	Mw_{met} (g/mol)	Ftrr	LDD_{50} oral[b] (µg a.s./bee/ day)	$ETR_{chronic\ adult\ oral}$	Trigger
Pome fruit: BBCH ≥70									
CGA132465	0.04	2.9	0.3	0.72	300	0.669[c]	>0.194[*]	**<0.091**	0.03
Vine: BBCH ≥70									
CGA132465	0.03	2.9	0.3	0.72	300	0.669[c]	>0.194[*]	**<0.068**	0.03

[a] The twa value of 0.72 is based on a default DT_{50} of 10 days and a 10-day time window.
[b] Assuming 10 times higher toxicity than the parent compound.
[c] The maximum TRR in a plant metabolism study following foliar treatment
SV = shortcut value
ETR = Exposure Toxicity Ratio
ETRs in **bold** are above the relevant trigger and require further refinement
[*] Highest possible concentration according to the results of a non-GLP solubility test; this concentration resulted in no mortality

Table 147: Tier 1 - Risk to adult honey bees following chronic oral exposure to metabolites from foraging <u>on a succeeding crop for annual crops</u> for the worst-case use in cucumber. A molecular weight of 284.2

g/mol for penconazole (parent) was used in the calculations.

Metabolite	App. rate (kg a.s./ha)	SV	fDep/Ef	TWA[a]	Mw_{met} (g/mol)	Ftrr	LDD_{50} oral[b] (µg a.s./bee/ day)	$ETR_{chronic\ adult\ oral}$	Trigger
Fruiting vegetables (cucumber): BBCH 50-69 and BBCH ≥70									
CGA71019	0.05	0.54	1	0.72	69	0.061[c]	>0.194*	<0.002	0.03
CGA132465					300	0.202[c]		<0.021	

[a] The twa value of 0.72 is based on a default DT_{50} of 10 days and a 10-day time window.
[b] Assuming 10 times higher toxicity than the parent compound.
[c] The maximum TRR in rotational crop study following application of penconazole to bare soil
SV = shortcut value for downward spray applications
ETRs in **bold** are above the relevant trigger and require further refinement
* Highest possible concentration according to the results of a non-GLP solubility test; this concentration resulted in no mortality

The **$ETR_{chronic\ adult\ oral}$** values for the scenario "foraging on a succeeding crop" for annual crops are below the trigger of 0.03 for both CGA71019 and CGA132465 for the **worst-case use in cucumber (3 x 50 g a.s./ha, BBCH 50-69 and ≥70),** indicating an acceptable chronic risk to adult honey bees following the proposed uses of A6209G.

For the proposed **post-flowering use in pome fruit (BBCH ≥70) and vines (BBCH ≥70)** the **$ETR_{chronic\ adult\ oral}$** values for the worst-case scenario "weeds in the treated field" are above the trigger for the metabolite CGA132465. Thus, **the chronic risk to honey bees requires further evaluation for CGA132465** for these proposed uses of A6209G.

Refined assessment- Chronic adult exposure

According to the ECPA approach (2017)[27] a NOEDD or LDD_{10} could be used together with an appropriate adjustment in the EFSA 2013 trigger in a refined risk assessment in cases where it is not possible to achieve an experimentally measured LDD_{50}. The calculated $ETR_{chronic\ adult\ oral}$ values calculated at tier 1, are compared to the refined trigger (0.143) in the tables below.

The **$ETR_{chronic\ adult\ oral}$** values for chronic oral exposure to CGA132465 from foraging on the treated crop following applications of A6209G in vines (BBCH 10-69) and cucumber (BBCH 50-69) are shown in **Table 132**. The **$ETR_{chronic\ adult\ oral}$** values for chronic oral exposure to CGA132465 from foraging on the weeds in the treated field following post-flowering applications of A6209G in pome fruit and vine (BBCH ≥70) are shown in **Table 133.**

Table 148: Refined tier 1 assessment - Risk to adult honeybees following chronic oral exposure to CGA132465 from foraging on the treated crop

Metabolite	App. rate (kg a.s./ha)	SV	fDep/Ef	TWA[a]	Mw_{met} (g/mol)	Ftrr	NOEDD[b] (µg a.s./bee/ day)	$ETR_{chronic\ adult\ oral}$	Refined Trigger
Vines: BBCH 10-69									
CGA132465	0.030	8.2	1	0.72	300	0.669[c]	≥ 0.194*	**≤0.6447**	0.143
Cucumber: BBCH 50-69									
CGA132465	0.050	5.8	1	0.72	300	0.669[c]	≥ 0.194*	**≤0.7601**	0.143
Cucumber: BBCH 50-69									
CGA132465	0.035	5.8	1	0.72	300	0.669[c]	≥ 0.194*	**≤0.5320**	0.143

[a] The twa value of 0.72 is based on a default DT_{50} of 10 days and a 10-day time window.

[27] ECPA (2017). Proposal for a protective and workable regulatory European bee risk assessment scheme based on the EFSA bee guidance and other new data and available approaches. Available at https://croplifeeurope.eu/wp-content/uploads/2020/12/28028_ECPA-Proposal-for-a-protective-and-workable-EU-Bee-Risk-Assessment-Version-09-June-17.pdf

[b] Assuming 10 times higher toxicity than the parent compound.
[c] The maximum TRR in a plant metabolism study following foliar treatment
SV = shortcut value
ETR = Exposure Toxicity Ratio
ETRs in **bold** are above the relevant trigger and require further refinement
[*] Highest possible concentration according to the results of a non-GLP solubility test; this concentration resulted in no mortality

Table 149: Refined Tier 1 assessment- Risk **to adult honey bees following chronic oral exposure to the metabolite** CGA132465 **from foraging on weeds in the treated field**

Metabolite	App. rate (kg a.s./ha)	SV	fDep/Ef	TWA[a]	Mw_{met} (g/mol)	Ftrr	NOEDD[b] (µg /bee/ day)	$ETR_{chronic\ adult\ oral}$	Refined Trigger
Pome fruit: BBCH ≥70									
CGA132465	0.04	2.9	0.3	0.72	300	0.669[c]	≥ 0.194[*]	≤0.091	0.143
Vine: BBCH ≥70									
CGA132465	0.03	2.9	0.3	0.72	300	0.669[c]	≥0.194[*]	≤0.068	0.143

[a] The twa value of 0.72 is based on a default DT_{50} of 10 days and a 10-day time window.
[b] Assuminng 10 times higher toxicity than the parent compound.
[c] The maximum TRR in a plant metabolism study following foliar treatment
SV = shortcut value
ETR = Exposure Toxicity Ratio
ETRs in **bold** are above the relevant trigger and require further refinement
[*] Highest possible concentration according to the results of a non-GLP solubility test; this concentration resulted in no mortality

For the **post-flowering uses in pome fruit and vine (BBCH ≥70)** the **$ETR_{chronic\ adult\ oral}$** values for CGA132465 are below the refined trigger of 0.143 for the worst-case scenario (foraging on weeds in the treated field), indicating an **acceptable chronic risk to adult honey bees following these proposed uses of A6209G**.

For the proposed uses of A6209G in **vines (BBCH 10-69)** and **cucumber (BBCH 50-69)** the **$ETR_{chronic\ adult\ oral}$** values for CGA132465 for the worst-case scenario (foraging on the treated crop), **exceeds the refined trigger of 0.143** with a factor ranging from 3.7 to 5.3. The trigger of 0.143 is still conservative as it suggests that the SPG defined in the **EFSA Bee Guidance Document (2013)** is met at a dose which is 7x (i.e. 6.99x) lower than the endpoint which gave no effect. In addition, the NOEDD used for CGA132465 in the risk assessment above is conservative at it was derived by dividing the NOEDD for penconazole (≥1.94 µg a.s./bee/ day, the highest concentration tested) by 10, assuming 10 times higher toxicity of the metabolite. It is therefore likely that the **chronic risk of** CGA132465 **to adult honey bees from foraging on the treated crop is acceptable following these proposed uses of A6209G vines (BBCH 10-69)** and **cucumber (BBCH 50-69)**.

2.9.9.1.2 Risk assessment for arthropods other than bees

The risk assessment for non-target arthropods other than bees has been performed according to ESCORT 2 document (**Candolfi *et al.*, 2001**)[28] and the **Guidance Document on Terrestrial Ecotoxicology**.

Risk assessment for in-field exposure

First tier risk assessment

Table 150: In-field risk assessment for non-target arthropods other than bees. HQ values in **bold** are above

[28] Candolfi, M.P., Barrett, K.L., Campbell, P.J., Forster, R., Grandy, N., Huet, M-C., Lewis, G., Oomen, P.A., Schmuck, R., Vogt, H. (2000). 'Guidance Document on regulatory testing procedures for plant protection products with non-target arthropods' From the workshop, European Standard Characteristics of Non-target Arthropod Regulatory Testing (ESCORT 2) 21-23 March 2000.

the trigger value of 2.

Test item	Crop	Test species	LR_{50} (g a.s./ha)	PER (g a.s./ha)	HQ	Trigger
Penconazole (as A6209G)	Pome fruit	*A. rhopalosiphi*	>50	68	<1.36	2
		T. pyri	>10		**<6.8**	2
		P. cupreus	>100		<0.68	2
	Vines	*A. rhopalosiphi*	>50	51	<1.02	2
		T. pyri	>10		**<5.1**	2
		P. cupreus	>100		<0.51	2
	Cucumber	*A. rhopalosiphi*	>50	115	**<2.3**	2
		T. pyri	>10		**<11.5**	2
		P. cupreus	>100		<1.15	2
	Cucumber	*A. rhopalosiphi*	>50	35	<0.70	2
		T. pyri	>10		**<3.50**	2
		P. cupreus	>100		<0.35	2

The first tier risk assessment shows that most of the hazard quotients for *A. rhopalosiphi* are lower than the trigger value of 2, except from the use with multiple applications in cucumber. In the case of *T. pyri* all the hazard quotients are greater than 2. ESCORT 2 recommend the use of more realistic higher tier testing procedures for the species failing at Tier 1 of the risk assessment. Consequently, both *A. rhopalosiphi* and *T. pyri* have been tested in higher tier tests. Furthermore, two fully reliable extended laboratory studies have been conducted with the additional species *C. septempunctata* and *C. carnea*.

Tier 2 risk assessment

Table 151: In-field risk assessment for non-target arthropods other than bees. Unacceptable risk is indicated in **bold**.

Species	Endpoint (g a.s./ha)	GAP Crop	In-field PER_{foliar} (g a.s./ha)	Acceptable risk
Aphidius rhopalosiphi (semi-field)	$NOER_{repro}$ = 135	Pome fruit	68	Yes
		Vines	51	Yes
		Cucumber	115	Yes
		Cucumber	35	Yes
Aphidius rhopalosiphi (Tier 2; 3-D study)	LR_{50} >400	Pome fruit	68	Yes
		Vines	51	Yes
		Cucumber	115	Yes
		Cucumber	35	Yes
	ER_{50} > 400	Pome fruit	68	Yes
		Vines	51	Yes
		Cucumber	115	Yes

Species	Endpoint (g a.s./ha)	GAP Crop	In-field PER_{foliar} (g a.s./ha)	Acceptable risk
		Cucumber	35	Yes
=*Typhlodromus pyri* (Tier 2; 2-D study)	LR_{50}=138	Pome fruit	68	Yes
		Vines	51	Yes
		Cucumber	115	Yes
		Cucumber	35	Yes
	ER_{50} >100	Pome fruit	68	Yes
		Vines	51	Yes
		Cucumber	115	**No**[a]
		Cucumber	35	Yes
=*Typhlodromus pyri* (Tier 2; 2-D study)	LR_{50} >9.6	Pome fruit	68	**No**[b]
		Vines	51	**No**[b]
		Cucumber	115	**No**[b]
		Cucumber	35	**No**[b]
	ER_{50} <9.6	Pome fruit	68	**No**[b]
		Vines	51	**No**[b]
		Cucumber	115	**No**[b]
		Cucumber	35	**No**[b]
Coccinella septempunctata (Tier 2)	LR_{50} >200	Pome fruit	68	Yes
		Vines	51	Yes
		Cucumber	115	Yes
		Cucumber	35	Yes
	ER_{50} >200	Pome fruit	68	Yes
		Vines	51	Yes
		Cucumber	115	Yes
		Cucumber	35	Yes
Chrysoperla carnea (Tier 2)	LR_{50} >200	Pome fruit	68	Yes
		Vines	51	Yes
		Cucumber	115	Yes
		Cucumber	35	Yes
	ER_{50} >200	Pome fruit	68	Yes
		Vines	51	Yes
		Cucumber	115	Yes
		Cucumber	35	Yes

[a] 9 % effect on fecundity at the highest tested dose in the fecundity assessment (100 g a.s./ha - lower than PER)
[b] New rate-response study with *T. Pyri* exposed to severral dose rates has been submitted (Fallowfield, 2019; VV-619272)

It is considered that the in-field risk for *T.Pyri* **still is unresolved for the highest dose in cucumber.** The new study (**Fallowfield, 2019; VV-619272**) indicates acceptable risk for all other uses. Overall, the RMS considers this study to be more reliable than the old study. It is noted that the study, as opposed to the old study, provides rate-response

endpoints (LR_{50}, ER_{50}), which is in accordance with the requirements in **Commission regulation (EU) No 283/2013.** Furthermore, the field study conducted in apple orchards in the Netherlands (**Aldershof, 1999; CGA71818/1385**) indicates acceptable in-field risk for the use in pome fruits. Since no significant effects were observed and no recovery was necessary it is considered that the results from this study may be attributed to the whole EU. Some uncertainties still remain regarding the relevance of the old study (Kleiner, 1993a; CGA71818/1228) for the risk assessment.

Risk assessment for off-field exposure

First tier risk assessment

Off-field risk assessment for non-target arthropods other than bees

Test item	Crop	Test species	LR_{50} (g a.s./ha)	Off-field PER x 10 (CF) (g a.s./ha)	HQ	Trigger
Penconazole (as A6209G)	Pome fruit	*A. rhopalosiphi*	>50	16.5	<0.33	2
		T. pyri	>10		<1.65	2
		P. cupreus	>100		<0.17	2
	Vines	*A. rhopalosiphi*	>50	7.3	<0.15	2
		T. pyri	>10		<0.73	2
		P. cupreus	>100		<0.07	2
	Cucumber	*A. rhopalosiphi*	>50	4.6.	<0.92	2
		T. pyri	>10		<0.46	2
		P. cupreus	>100		<0.05	2
	Cucumber	*A. rhopalosiphi*	>50	1.9	<0.04	2
		T. pyri	>10		<0.19	2
		P. cupreus	>100		<0.02	2

Based on Tier 1 data, the hazard quotients for the species *T. pyri*, *A. rhopalosiphi* and *P. cupreus* are less than the trigger value of 2, indicating **acceptable off-field risk to non-target arthropods** following the proposed uses of A6209G.

2.9.9.2 Risk assessment for non-target soil meso- and macrofauna

The risk assessment on non-target soil meso- and macrofauna has been performed according to the **Guidance Document on Terrestrial Ecotoxicology (2002)**[29]. As an acute risk assessment on earthworms is no longer required in accordance with **Commission Regulation (EU) No 283/2013 and 284/2013,** only the risk assessment including chronic effects have been performed. Also the outcome of the pesticides peer review meetings on recurring issues in ecotoxicology (**EFSA Supporting publication 2015:EN-924**[30] and **EFSA Supporting publication 2019:EN-1673**[31]) were considered. Based on these publications the EC_{10} should be considered instead of the NOEC if it is available, reliable, and lower than the NOEC value. Furthermore, it was concluded that the relevant endpoint from all first tier studies should be divided by a factor of 2 for all substances with a logPOW > 2 regardless of the percentage of organic matter used in the standard test, i.e. even if the test was performed with 5% organic matter (**EFSA Supporting publication 2015:EN-924[11]**).

The exposure to soil organisms was estimated by calculating the maximum initial predicted environmental concentrations in soil (PEC_{SOIL}) or, where relevant, the peak accumulative PEC_{SOIL} ($PEC_{SOIL,\ ACCUMULATION}$) for the proposed use pattern of A6209G. The PEC_{SOIL} value was calculated for each of the proposed crops assuming 65%, 50% and 85% crop interception for Pome fruit, Grapes and cucumber, respectively. The $PEC_{SOIL,ACCUMULATION}$ values were calculated following yearly application to the various crops using a mixing depth of 5 cm for each application and tillage depths of 5 and 20 cm for permanent and annual crops, respectively. For full details on PEC_{SOIL} calculations see **Volume 3 - B.8 (PPP)**, Section B.8.1.3. RMS notes that the input for the PEC_{SOIL} and $PEC_{SOIL,\ ACCUMULATION}$ modelling may change, and new modelling may be necessary. The values presented are thus regarded as preliminary values.

The worst-case risk assessment for penconazole and the most toxic metabolite are shown for the most sensitive organism (earthworms) below. The risk assessment concluded that the chronic risk to non-target soil meso- and macrofauna is acceptable at tier 1 for all proposed uses of the representative formulation A6209G. A complete risk assessment for earthworms, *folsomia candida* and *Hypoaspis aculeifer* is presented in **Volume 3 - B.9 (PPP), section B.9.8**.

Risk assessment for penconazole and A6209G

All the studies on soil meso- and macro fauna have been performed with the representative formulation A6209G. The long-term risk assessment presented below will therefore cover the risk assessment for both the active substance and the representative formulation.

The most sensitive organism was earthworms with the lowest NOEC of ≥ 5 mg a.s./kg soil dw. The worst case $PEC_{soil,accumulation}$ values and correponding long-term TER values for all proposed uses of A6209G are shown for earthworms in the table below. A complete risk assessment for *folsomia candida* and *Hypoaspis aculeifer* is presented in **Volume 3 - B.9 (PPP), section B.9.8.4**.

Table 152: Worst-case chronic risk (TER_{LT}) of **penconazole** to the most sensitive soil meso- and macorfauna (earthworms) following the proposed uses of A6209G.

Use	NOEC (mg a.s./kg soil dw)	Maximum PEC_S accumulation (mg/kg soil)	TER_{LT}[d]	Trigger value
Pome fruit (2 x 40 g a.s./ha)	≥5[ab]	0.0390	≥130	5
Vines (2 x 30 g a.s./ha)		0.0421	≥120	
Cucumber (3 x 50 g a.s./ha)		0.0303	≥170	
Cucumber (1 x 35 g a.s./ha)		0.0100	≥500	

[a] The log POW of penconazole is greater than 2 (i.e. 3.8), and therefore, NOEC has been divided by a factor of 2 (as was agreed in EFSA Supporting publication 2015:EN-924)[32]

[29] Guidance Document on Terrestrial Ecotoxicology in the context of the Directive 91/414/EEC. SANCO/10329/2002 rev. 2 (final). 17 October 2002.

[30] EFSA (European Food Safety Authority), 2015. Technical report on the outcome of the pesticides peer review meeting on general recurring issues in ecotoxicology. EFSA supporting publication 2015:EN-924. 62 pp.

[31] EFSA (European Food Safety Authority), 2019. Technical report on the outcome of the Pesticides Peer Review Meeting on general recurring issues in ecotoxicology. EFSA supporting publication 2019:EN-1673. 117 pp. doi:10.2903/sp.efsa.2019.EN-1673

[32] EFSA (European Food Safety Authority), 2015. Technical report on the outcome of the pesticides peer review meeting on general recurring issues in ecotoxicology. EFSA supporting publication 2015:EN-924. 62 pp.

[b] The endpoint is derived from a study with the representative formulation A6209G
[d] Rounded TER values are shown
Values in **bold** are below the trigger of 5

Risk assessment for metabolites

Based on the available studies on route and rate of degradation in soil, CGA71019, CGA179944, CGA142856 and CGA91305 are considered to be the relevant metabolites that have to be addressed in the risk assessment for non-target soil Meso- and Macrofauna (For details, see **Volume 3 - B.8 (AS).** Acceptable endpoints for earthworms, *folsomia candida* and *hypoaspis aceulifer* and all the relevant metabolites are available**.**

The most toxic of the metabolites is CGA71019, with earthworms and *folsomia candida* showing comparable sensitivity (NOEC of 1.0 and 1.8 mg/kg soil dw, respectively). The results indicates that this metabolite is slightly more toxic than penconazole. The worst case $PEC_{soil,accumulation}$ values and correponding long-term TER values for CGA71019 following all proposed uses of A6209G are shown for earthworms in the table below.

Table 153: Worst-case chronic risk (TER_{LT}) of the metabolite **CGA71019** to the most sensitive soil meso- and macrofauna (earthworms) following the proposed uses of A6209G.

Test item	NOEC (mg/kg soil dw)	Maximum $PEC_{S\ accumulation}$ (mg/kg soil)	TER_{LT}[d]	Trigger value
Pome fruit (2 x 40 g a.s./ha)	1.0	0.0022	460	5
Vines (2 x 30 g a.s./ha)		0.0024	420	
Cucumber (3 x 50 g a.s./ha)		0.0017	590	
Cucumber (1 x 35 g a.s./ha)		0.0006	1700	

The worst case long-term TER values for penconazole and the most toxic metabolite CGA71019 are all greater than the trigger value of 5, indicating that the long-term risk to non-target soil meso- and macrofauna is acceptable following the proposed uses of A6209G.

2.9.9.4 Risk assessment for soil nitrogen transformation

Soil organisms may be exposed to penconazole and its major metabolites. Based on the available studies on route and rate of degradation in soil, CGA71019, CGA179944, CGA142856 and CGA91305 are considered to be the relevant metabolites that have to be addressed in the risk assessment (For details, see **Volume 3 - B.8 (AS).**

The exposure to soil organisms was estimated by calculating the maximum initial predicted environmental concentrations in soil (PEC_{SOIL}) or, where relevant, the peak accumulative PEC_{SOIL} ($PEC_{SOIL,\ ACCUMULATION}$) for the Use pattern of A6209G in Table 9.10-2. The PEC_{SOIL} value was calculated for each of the proposed crops assuming 65%, 50% and 85% crop interception for Pome fruit, Grapes and cucumber, respectively. The $PEC_{SOIL,ACCUMULATION}$ values were calculated following yearly application to the various crops using a mixing depth of 5 cm for each application and tillage depths of 5 and 20 cm for permanent and annual crops, respectively. For full details on PEC_{SOIL} calculations see **Volume 3 - B.8 (PPP)**, Section B.8.1.3. RMS notes that the input for the PEC_{SOIL} and $PEC_{SOIL,\ ACCUMULATION}$ modelling may change, and new modelling may be necessary. The values presented are thus regarded as preliminary values.

Table 154: Risk assessment for effects on soil micro-organisms

Use pattern	Test item	Endpoint (< 25% deviation from control) mg/kg d.w. soil	PECS, accumulation (mg/kg)	Acceptable risk? Y/N
Pome fruit 2 x 40 g a.s./ha	Penconazole	1.34	0.0390	Y
	CGA179944	0.20	0.0074	Y
	CGA71019	0.35	0.0022	Y
	CGA142856	0.08043	0.0037	Y
	CGA91305	0.377	0.0027	Y
Vines 2 x 30 g a.s./ha	Penconazole	1.34	0.0421	Y
	CGA179944	0.20	0.0080	Y
	CGA71019	0.35	0.0024	Y
	CGA142856	0.08043	0.0040	Y
	CGA91305	0.377	0.0029	Y
Cucumber 3 x 50 g a.s./ha	Penconazole	1.34	0.0303	Y
	CGA179944	0.20	0.0058	Y
	CGA71019	0.35	0.0017	Y
	CGA142856	0.08043	0.0028	Y
	CGA91305	0.377	0.0021	Y
Cucumber 1 x 35 g a.s./ha	Penconazole	1.34	0.0100	Y
	CGA179944	0.20	0.0019	Y
	CGA71019	0.35	0.0006	Y
	CGA142856	0.08043	0.0009	Y
	CGA91305	0.377	0.0007	Y

Aacceptable risk on soil nitrogen transformation is expected after exposure of penconazole or the penconazole metabolites.

2.9.9.5 Risk assessment for terrestrial non-target plants

The risk assessment for terrestrial non-target plants has been conducted according to **Terrestrial guidance document**[33].

Spray drift reaching the off- field environment is considered the key exposure route for non-target terrestrial plants located in the vicinity of the treated area. The amount of spray drift reaching off-crop habitats is calculated using the 90th percentile estimates derived by the BBA (2000) [34] from the spray-drift predictions of Ganzelmeier & Rautmann (2000) [35]. This procedure is further described in Terrestrial guidance document. During the pesticides peer review meeting on general recurring issues in ecotoxicology[36] it was agreed that, from a scientific point of view, there is a logical reason to account for multiple applications in the risk assessment for NTTP. However, the experts could not agree which approach should be applied to the risk assessment and it was agreed that for the risk

[33] Anonymous (2002b). Guidance Document on terrestrial ecotoxicology under Council Directive 91/414/EEC. SANCO/10329/2002. 17 October 2002.

[34] BBA (2000). Bundesanzeiger Jg. 52 (Official Gazette), Nr 100, S. 9879-9880 (25.05.2000) Bekanntmachung über die Abtrifteckwerte, die bei der Prüfung und Zulassung von Pflanzenschutzmitteln herangezogen werden. Public domain.

[35] Ganzelmeier H., Rautmann D. (2000). Drift, drift-reducing sprayers and sprayer testing. Aspects of Applied Biology 57, 2000, Pesticide Application. Public domain.

[36] Arena *et al.* (2019). Outcome of the Pesticides Peer Review Meeting on general recurring issues in ecotoxicology. EFSA Supporting publication 2019:EN-1673. doi:10.2903/sp.efsa.2019.EN-1673

assessment of active substances, no MAF-values should be used by default, until a guidance document has been developed. Thus, multiple applications are not accounted for when calculating the PER-values, below.

Table 155: Off-field PER values for application of A6209G

Test item	Crop	BBCH	Application rate (g a.s./ha)	No. of applications (max)	Basic drift values for one application (%)	PER (g a.s./ha)
A6209G	Pome Fruit	71–89	40	2	15.73[a]	**6.29**
	Vines	13-85	30	2	8.02[b]	2.41
	Cucumber	51-89	50	3	8.02[c]	4.01
	Cucumber	51-89	35	1	8.02[c]	2.81

PER: Predicted Environmental Residue. The worst-case PER-value is given in **bold**.
[a]Worst case drift value for fruite crops (late)
[b]Worst case drift value for vines (grapevine late)
[c]Worst case drift value for vegetables/ornamentals/small friute (hight > 50 cm)

Risk assessment for A6209G

According to the Terrestrial guidance document, endpoints measured in most screening studies cannot be interpreted as a NOEC-value covering germination and biomass production. However, it is assumed that the available information usually allows the use of a conservative approach, assuming, for example, that when an untreated control has been run in parallel, any effect accounting for at least 50 % reduction in biomass production could be identified in a visual inspection. In the current screening study, no phytotoxic effects above 50% was detected at an application rate of 200 g a.s./ha covering the worst-case GAP (including accumulation). According to these data, acceptable risk may be anticipated. **However, this study is regarded as « supportive only », due to e.g. non-GLP and lack of analytical verification of the test substance. RMS is of the opinion that a new valid study should be provided in order to conclude on the risk for terrestrial plants.**

A quantitative risk assessment, as described in the Terrestrial guidance document, with the **supportive endpoint** is also presented for completeness:

The potential risk to non-target plants associated with the application of A6209G was assessed considering the available screening endpoint (Table 9.12-1) and the worst-case off-field PER for application in pome fruit (see Table 9.12-2), according to the following formula:

$$TER = \frac{ER_{50}\ (g/ha)}{PER_{off-field}\ (g/ha)}$$

Table 156: Worst case TER values for A6209G

Test item	Most sensitive species and endpoint (g a.s./ha)	ER_{50} (g a.s./ha)	PER (g a.s./ha)	TER
A6209G (seedling emergence)	All tested species	>200	6.29	>32
A6209G (vegetative vigour)	All tested species	>200	6.29	>32

The TER values exceed the trigger value of 5, indicating that the risk to terrestrial non-target plants in off-crop areas is acceptable following the proposed uses of A6209G. **However, a new valid study should be provided in order to finalise the risk assessment.**

2.10 ENDOCRINE DISRUPTING PROPERTIES

According to the ED criteria a substance shall be considered as having ED properties if it meets all of the following criteria:

> a) it shows an adverse effect in [an intact organism or its progeny]/[non-target organisms], which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;
>
> b) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;
>
> c) the adverse effect is a consequence of the endocrine mode of action.

An assessment of the ED-criteria in accordance with **Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009** (EFSA, 2018) have been performed by RMS and is presented below.

2.10.1 Gather all relevant information

Regarding the mammalian toxicology area, data were gathered from all repeated dose toxicity studies in mammals including *in vivo* mechanistic data and *in vitro* mechanistic assays included in the RAR, as well as ToxCast data from the US EPA CompTox Chemicals Dashboard (http://comptox.epa.gov/dashboard).

For non-target organisms, in the dossier for penconazole, 2 reproductive studies on birds (internal protocol similar to OECD TG 206). One of the reproductive studies with birds ([redacted] 1985a) was considered not acceptable by RMS, and has not been included further in the overview of the data or in the excel-spreadsheet (see **Volume 3 – B.9 (AS)**, K-CA 8.1.1.3/02 for further details). In addition, a fish early life stage toxicity test (OECD TG 210; Surprenant 1984c) and a fish sexual development test (draft OECD TG 234; [redacted] 2012) is available in the dossier. A study from open literature on the developmental toxicity of Zebrafish embryos (Aksakal and Ciltas, 2018) is also available. Even though the study is not fully reliable, due to e.g. no analytical verification of the exposure concentrations, the study is still considered supportive for the ED-assessment. A fish full life cycle test (OECD Draft Proposal for Fish Two-Generation Test Guideline (2002) and Draft OPPTS 850.1500 Test Guideline) has been initiated to further assess effects on endocrine activity and especially adversity. Currently only preliminary results have been presented by the applicant. The study has not been evaluated by the RMS as a full study report is not available (for the applicant's summary of the preliminary results, see **Volume 3 – B.9.2.2.2. (AS)).**

An extensive literature search has been performed, using specific endocrine disruption search terms and an extended duration to ensure that all available literature have been located (**Charlton A, Pickford D. (2019)**, document no. CGA071818_10703). This additional search was carried out to identify *in vitro* and *in vivo* studies designed to assess the effects of penconazole on the endocrine system. The literature search process has been sufficiently documented according to the EFSA Journal 2011; 9(2):2092 (EFSA, 2011), however, RMS is of the opinion that the relevance criteria and the rapid and detailed evaluation for ED-specific search could have been better described by the applicant, in order to fully determine whether the search strategy is appropriate. Please see **Volume 3 – B.9 (AS) Appendix** where the search has been summarised by RMS (both tox and ecotox). Toxicology: The search identified 5 relevant and reliable toxicology publications which are summarised in **Volume 3 - B.6.8.3 (AS)**. A further 5 publications were discarded following detailed assessment. Full details are provided in **Volume 3 - B.6 (AS) Appendix** and **Volume 3- B.6.8.3 (AS)**. Ecotoxicology: In addition, the search identified 3 possibly ED relevant ecotox publications (two of these were also identified relevant for mammalian tox), where all were discarded. One study on the developmental toxicity of Zebrafish embryos (Aksakal and Ciltas, 2018), was identified in the general ecotox literature search, and has by RMS also been considered relevant for the assessment of the ED criteria.

Data were populated in the Excel template provided as Appendix E to the EFSA/ECHA guidance for the identification of endocrine disruptors by the applicant, and updated by RMS (EDGD_Appendix-E1_2021-06-11). According to this template each study was given a unique identification number (Study ID Matrix) that is important for its identification in the data-matrix and Lines of Evidence (LoE) spreadsheets of the Excel.

A summary of all studies considered for the mammalian toxicology and non-target organism evaluation, including the Study ID Matrix is outlined in the table below.

Table 157: Outline of dataset considered for mammalian toxicology and non-target organism assessment

Type of toxicity	Study type	Study ID Matrix
Repeated dose toxicity studies in mammals	Subacute oral in rodent (open literature) Volume 3 (AS) B.6 AP1.5. KCA 9/16. El-Sharkawy et al (2013)	1*
	Repeated dose 28-day oral toxicity study in rat Volume 3 (AS) B.6.3.1/01 KCA 5.3.1/01. [redacted] (1984)	28
	Repeated dose 28-day oral toxicity study in rat Volume 3 (AS) B.6.3.1/02 KCA 5.3.1/02. [redacted] (1991)	29a, 29b
	Repeated dose 90-day oral toxicity study in rat Volume 3 (AS) B.6.3.2/01 K-CA 5.3.2/01. [redacted] (1982)	30
	Repeated dose 90-day oral toxicity study in rat Volume 3 (AS) B.6.3.2/02 K-CA 5.3.2/02. [redacted] (1983)	31
	Repeated dose 90-day oral toxicity study in rat Volume 3 (AS) B.6.3.2/03 K-CA 5.3.2/03. [redacted] (1987b)	32
	Repeated dose 90-day oral toxicity study in mouse Volume 3 (AS) B.6.3.2/05 K-CA 5.3.2/05. [redacted] (1987)	33
	Repeated dose 90-day oral toxicity study in dog Volume 3 (AS) B.6.3.2/04 K-CA 5.3.2/04. [redacted] (1984)	34a
	1-year dog toxicity study Volume 3 (AS) B.6.3.2/04 K-CA 5.3.2/04. [redacted] (1984)	34b
	Repeated dose 90-day oral toxicity study in rat Volume 3 (AS) B.6.3.2/06 K-CA 5.3.2/06. [redacted] (2002)	35
	Repeated dose 21-day dermal toxicity study in rabbit Volume 3 (AS) B.6.3.3/01 K-CA 5.3.3/0.1. [redacted] (1983)	36
	Combined chronic toxicity/carcinogenicity studies in mouse Volume 3 (AS) B.6.5.5.1/01 K-CA 5.5/01. [redacted] (1985)	37
	Carcinogenicity study in mouse Volume 3 (AS) B.6.5.5.1/02 K-CA 5.5/02. [redacted] (2004)	38
	Carcinogenicity study in rat Volume 3 (AS) B.6.5.5.2/01 K-CA 5.5/03. [redacted] (1985a)	39
	Two-generation reproduction toxicity test in rat Volume 3 (AS) B.6.6.1 K-CA 5.6.1/01. [redacted] (1983)	40a
	Two-generation reproduction toxicity test in rat Volume 3 (AS) B.6.6.1 K-CA 5.6.1/04. [redacted] (1987)	40b
	Prenatal developmental toxicity study in rat Volume 3 (AS) B.6.6.2 K-CA 5.6.2/01. [redacted] (1981)	41a, 41b
	Prenatal developmental toxicity study in rat Volume 3 (AS) B.6.6.2 K-CA 5.6.2/03. [redacted] [redacted] (1985)	42
	Prenatal developmental toxicity study in rabbit Volume 3 (AS) B.6.6.2 K-CA 5.6.2/04. [redacted] (1982)	43
	Prenatal developmental toxicity study in rabbit Volume 3 (AS) B.6.6.2 K-CA 5.6.2/06. [redacted] (1985)	44
Non-target organisms other than mammals	Avian reproduction test (OECD 206, CF 4) Volume 3 (AS) B.9.1.1.3. K-CA 8.1.1.3/01. [redacted] (1985)	46
	Fish early life stage test (OECD 210, CF 4) Volume 3 (AS) B.9.2.2.1 K-CA 8.2.2.1/01. [redacted] (1984c)	47
	Developmental toxicity in Zebrafish embryos (Open literature) Volume 3 (AS) B.9.2.2.1 K-CA 8.2.2.1/03. Aksakal and Ciltas (2018)	50
	Fish sexual development test (OECD 234, CF 4) Volume 3 (AS) B.9.2.3 K-CA 8.2.3/03. [redacted] (2012)	48
	Fish life cycle toxicity test (OPPTS 850.1500, CF 5) Volume 3 (AS) B.9.2.2.2 Preliminary results as provided by applicant (not validated by RMS	Study (reporting) ongoing, thus not included in current evaluation
***In vivo* mechanistic**	Subacute oral in rodent (open literature)	49

	Volume 3 (AS) B.6.8.2 K-CA 5.8.2/02. Waechter F, Bentley P, Staeubli W (1985)	
***In vitro* mechanistic**	In vitro AR binding assay (open literature) Volume 3 (AS) B.6.8.3 K-CA 5.8.3/04. Roelofs et al (2014)	2
	In vitro AR binding assay (open literature) Volume 3 (AS) B6 Appendix1, Table AP1-5. Lv et al. (2017)	7*
	In vitro method (general) (open literature) Volume 3 B.6.8.2 KCA 9/41. Perdichizzi S. et al (2014)	3
	In vitro aromatase assay (open literature) Volume 3 B.6.8.3 K-CA 5.8.3/07. Sanderson et al (2002)	4
	In vitro aromatase assay (open literature) Volume 3 (AS) B.6.8.3 K-CA 5.8.3/05. Trösken et al (2004)	5
	In vitro aromatase assay (open literature) Volume 3 (AS) B.6.8.3 K-CA 5.8.3/06. Trösken et al (2006)	6
	In vitro ER binding assay (open literature) Volume 3 (AS) B.6.8.3 K-CA 5.8.3/08. Schlotz et al (2017)	8
	In vitro ToxCast ER prediction model (receptor binding assay) Volume 3 (AS) B.6.8.3	9
	In vitro ToxCast ER prediction model (receptor binding assay) Volume 3 (AS) B.6.8.3	10
	In vitro ToxCast ER prediction model (receptor binding assay) Volume 3 (AS) B.6.8.3	11
	In vitro ToxCast ER prediction model (agonism) Volume 3 (AS) B.6.8.3	12
	In vitro ToxCast ER prediction model (antagonism) Volume 3 (AS) B.6.8.3	13
	In vitro ToxCast ER prediction model (agonism) Volume 3 (AS) B.6.8.3	14
	In vitro ToxCast ER prediction model (antagonism)	15
	In vitro ToxCast ER prediction model (agonism) Volume 3 (AS) B.6.8.3	16
	In vitro ToxCast AR prediction model (antagonism) Volume 3 (AS) B.6.8.3	17
	In vitro ToxCast AR prediction model (agonism) Volume 3 (AS) B.6.8.3	18
	In vitro ToxCast AR prediction model (antagonism) Volume 3 (AS) B.6.8.3	19
	In vitro ToxCast AR prediction model (antagonism) Volume 3 (AS) B.6.8.3	20
	In vitro ToxCast TR transactivation assay (agonism) Volume 3 (AS) B.6.8.3	21
	In vitro ToxCast TR transactivation assay (antagonism) Volume 3 (AS) B.6.8.3	22
	In vitro ToxCast TR (cellular proliferation) Volume 3 (AS) B.6.8.3	23
	In vitro ToxCast TSHR transactivation assay (agonism) Volume 3 (AS) B.6.8.3	24
	In vitro ToxCast TSHR transactivation assay (antagonism) Volume 3 (AS) B.6.8.3	25
	In vitro ToxCast TSHR transactivation assay Volume 3 (AS) B.6.8.3	26
	In vitro ToxCast Steroidogenesis (aromatase assay) Volume 3 (AS) B.6.8.3	27
	In vitro steroidogenesis assay (H295R assay) Volume 3 (AS) B.6.8.3 K-CA 5.8.3/03. Venkaart S. (2019)	45

*study considered relevant, but not reliable.

2.10.2 ED assessment for humans

2.10.2.1 ED assessment for T-modality

2.10.2.1.1 Have T-mediated parameters been sufficiently investigated?

Table 158: Have T-mediated parameters been sufficiently investigated?

	Sufficiently investigated
T-mediated parameters	No (to consider the T modality as 'sufficiently investigated' for mammals, the thyroid parameters foreseen to be investigated in the following studies OECD test guidelines 407, 408, 409 (and/or the one-year dog study, if available), 416 (or 443 if available) and 451-3 should have been measured and the results included in the dossier. Studies following the recommended TG or similar design have been performed, but due to several deviations from current guidelines, a number of parameters indicative of T have not been investigated (see Table 161: for details). However, according to the EFSA "Technical report on the outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology" (EFSA supporting publication 2020:EN-1837, page 7, doi:10.2903/sp.efsa.2020.EN-1837), the dataset for thyroid can be considered complete on a case-by-case basis, pending whether the duration and doses selection allow a proper assessment of the thyroid histology (thyroid histopathology is generally considered more sensitive and informative than thyroid weight). RMS is of the opinion that sufficiency may be discussed. The dosing was not optimal in the short term 28-day studies following the OECD TG 407 (study ID 28, 29a, 29b), the 110 days study following the OECD TG 416 (study ID 40a) or in the 2-year study the OECD TG 451-3 (study ID 39) (see Table 103 for details).

2.10.2.1.2 Lines of evidence for adverse effects and endocrine activity related to T-modality

Table 159: Lines of evidence for adverse effects and endocrine activity related to T-modality

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
21	*In vitro* mechanistic	Thyroid receptor	rat, pituitary gland, cell line	28	Hr	Uptake from the medium (*in vitro*)	0	µM	No effect	ToxCast TR model: No TR-mediated agonistic activity	Evidence for TR mediated antagonistic activity *in vitro*, (Penconazole was active in one of these assays (TOX21_TR_LUC_GH3_Antagonist); however, the viability readout was also active and interference with cytotoxicity cannot be excluded.)	Overall, indication of endocrine activity, based on *in vivo* mechanistic data (study ID 49a and 49b) showing marked liver enlargement in rats and mice at 80 mg/kg bw/day and higher (dose-dependent) and a pronounced induction in the activity of several hepatic xenobiotic metabolising enzymes (uridine diphosphate [UDP]-glucuronyl transferase).	Thyroid
22		Thyroid receptor	rat, pituitary gland, cell line	28	Hr	Uptake from the medium (*in vitro*)	56.89	µM	Change	ToxCast TR model: TR-mediated antagonistic activity			
24		TSH receptor (*in vitro*)	human, kidney, cell line	0,5	Hr	Uptake from the medium (*in vitro*)	0	µM	No effect	ToxCast TSHR: No TSHR-mediated activity	Negative, no effect on TSHR *in vitro*		
25		TSH receptor (*in vitro*)	human, kidney, cell line	0,5	Hr	Uptake from the medium (*in vitro*)	111.95	µM	No effect	ToxCast TSHR: No TSHR-mediated activity			
26		TSH receptor (*in vitro*)	human, kidney, cell line	0,5	Hr	Uptake from the medium (*in vitro*)	0	µM	No effect	ToxCast TSHR: No TSHR-mediated activity			

28	EATS-mediated	Thyroid histopathology	rat	28	Days	Oral		mg/kg bw/day	No effect	No effect on thyroid histopathology at the highest dose of 1000 mg/kg bw.	No consistent treatment-related effects on thyroid, but not sufficiently investigated. Increased thyroid weight in female rats treated at 500/1000 mg/kg/day is not considered adverse: The observed variations in thyroid weight were within the range of the limited HCD. Increased thyroid weight and incidences of minimal hypertrophy of the follicle epithelium was seen in low dose (100 mg/kg bw/day) and high dose (500 mg/kg bw/day) rats and were considered adverse. Effects in dogs were not	No consistent EATS-mediated adverse effects, but not sufficiently investigated.	Thyroid
29a			rat	28	Days	Oral	100	mg/kg bw/day	Change	Increased incidences of minimal hypertrophy of the follicle epithelium were seen in male from 100 mg/kg bw/day (5/10 low dose, 10/10 high dose) and female top dose animals (8/10). Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD, however, effects observed are still considered adverse. Effect on thyroid is observed at the same dose level as liver effects (100 mg/kg bw/day).			

29b			rat	28	Days	Oral	500	mg/kg bw/day	Change	Increased incidences of minimal hypertrophy of the follicle epithelium were seen in males (with higher incidences) at 500 mg/kg bw (7/10 animals) and in females (2/10). Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD, however, effects observed are still considered adverse. Effect on thyroid is observed at the same dose level as liver effects (100 mg/kg bw/day).	considered adverse: 90 days exposure - Thyroid *C-cell* hyperplasia were seen in 2/4 top dose males (control dog incidence 1/4) at 132 mg/kg bw/day and in 3/4 top dose females (control dog incidence 2/4) at 137 mg/kg/bw/day: However, C-cell hyperplasia is not considered adverse for T3/T4 activity). 12 months exposure - no effects observed.		
30			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on thyroid histopathology up to top dose (208.6 mg/kg bw/day) in F.				
30			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on thyroid histopathology up to top dose (202.3 mg/kg bw/day) in M.				
31			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on thyroid histopathology up to highest dose tested (7.07 mg/kg bw/day) in M.				
31			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on thyroid histopathology up to highest dose tested (7.27 mg/kg bw/day) in F.				
34a			Dog	90	Days	Oral	132	mg/kg bw/day	Change	Thyroid C-cell hyperplasia were seen in 2/4 top dose males (control dog incidence 1/4). Observed in the presence of significant systemic toxicity; decreased body weight and body weight gain associated with drastically reduced food intake.				
34a			Dog	90	Days	Oral	137	mg/kg bw/day	Change	Thyroid C-cell hyperplasia were seen in 3/4 top dose females (control dog incidence 2/4). Observed in the presence of significant systemic toxicity; decreased body weight and body weight gain associated with drastically reduced food intake.				

34b			Dog	12	Months	Oral	108	mg/kg bw/day	No effect	Thyroid C-cell hyperplasia in 1/4 top dose males, same incidence as in control dogs 1/4) up to highest dose tested (108 mg/kg bw/day).			
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on thyroid histopathology up to highest dose tested (110 mg/kg bw/day) in F.			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on thyroid histopathology up to highest dose tested (177.7 mg/kg bw/day) in M. Thyroid gland was not weighed			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on thyroid histopathology up to highest dose tested (221.5 mg/kg bw/day) in F. Thyroid gland was not weighed			
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on thyroid histopathology (examined together with parathyroid) up to highest dose tested (10.4 mg/kg bw/day) in M.			
39			rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on thyroid histopathology (examined together with parathyroid) up to highest dose tested (11.9 mg/kg bw/day) in F. 1-year interim sacrifice: Hyperplasia of C-cells was found more frequently in the thyroid of females treated with 5.7 mg/kg bw/day (14/80). As the incidence of both these changes showed no dose-relationship, these changes are not considered to be a result of treatment with penconazole.			
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on thyroid histopathology up to highest dose tested (156 mg/kg bw/day in M and 153 mg/kg bw/day in F).			
28		Thyroid weight	rat	28	Days	Oral	500	mg/kg bw/day	Increase	Increased thyroid weight in females only treated at 500/1000 mg/kg/day (the observed variations in thyroid weight were within the range of the limited HCD - concurrent control was lower than the available HCD).			

29a			rat	28	Days	Oral	100	mg/kg bw/day	Increase	Increase in thyroid weight in treated males (abs + rel) up to 500 mg/kg bw/day. Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD, however, effects observed are still considered adverse. Effect on thyroid is observed at the same dose level as liver effects (100 mg/kg bw/day).			
29b			rat	28	Days	Oral	100	mg/kg bw/day	Increase	Increase in thyroid weight in treated males (abs + rel) up to 500 mg/kg bw. Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD, however, effects observed are still considered adverse. Effect on thyroid is observed at the same dose level as liver effects (100 mg/kg bw/day).			
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on thyroid weight. It is unclear whether parathyroids were weighed together with thyroids.			
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on thyroid weight. It is unclear whether parathyroids were weighed together with thyroids.			
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on thyroid weight. It is unclear whether parathyroids were weighed together with thyroids.			

34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on thyroid weight. It is unclear whether parathyroids were weighed together with thyroids.				
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on thyroid weight were observed in males. Thyroid gland was weighed together with parathyroid.				
39			rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on thyroid weight were observed in females. Thyroid gland was weighed together with parathyroid.				
29a	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	rat	28	Days	Oral	500	mg/kg bw/day	Change	Cortical atrophy was noted in most top dose females (8/10*) *two females were sacrificed in moribund condition on day 3 (500 mg/kg bw/day). Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD; however, the observed effects are still considered treatment related	Indications of treatment-related adverse effects on adrenal, based on observed effects in rats (atrophy and increased weight at 500 mg/kg/bw/day) and dogs (increased weight at 110 mg/kg bw/day). Increased adrenals weight in mouse (signficant trend at 75, 150 and 300 ppm) was in absence of a dose relationship and not associated with relevant histopathological changes.	Overall, evidence of adverse effects sensitive to but not diagnostic of EATS (based on effects on adrenal and anomalies in rat and rabbit)	Thyroid
29b			rat	28	Days	Oral	500	mg/kg bw/day	Change	Cortical atrophy was noted in most top dose females (9/10*) *one female was sacrificed in moribund condition on day 2 (500 mg/kg bw/day). Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD; however, the observed effects are still considered treatment related			

31			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology up to highest dose tested (7.07 mg/kg bw/day) in M.		
31			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology up to highest dose tested (7.27 mg/kg bw/day) in F.		
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology in male dogs up to highest dose tested 132 mg/kg bw/day		
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology in female dogs up to highest dose tested 137 mg/kg bw/day		
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology in male dogs up to highest dose tested 108 mg/kg bw/day		
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology in female dogs up to highest dose tested 110 mg/kg bw/day		
35			mouse	90	Days	Oral		ppm	No effect	No effect on adrenals histopathology in F (examined in control and high dose groups only).		
35			mouse	90	Days	Oral		ppm	No effect	No effect on adrenals histopathology in M (examined in control and high dose groups only).		
37			mouse	106	Weeks	Oral		ppm	No effect	No effect on adrenals histopathology up to highest dose tested (300 ppm).		
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology up to highest dose tested (177.7 mg/kg bw/day) in M.		
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology up to highest dose tested (221.5 mg/kg bw/day) in F.		
39			rat	117	Weeks	Oral		mg/kg	No effect	No effect on adrenals histopathology. 1-year interim sacrifice: nodular hyperplasia was observed in the adrenal cortex of females treated with 2.9 mg/kg		

							bw/day		bw/day (19/79) and 5.7 mg/kg bw/day (12/80). However, in the absence of a dose-response relationship this was not attributed to treatment with penconazole.			
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology up to highest dose tested (10.4 mg/kg bw/day) in males.		
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology up to highest dose tested (156 mg/kg bw/day in M and 153 mg/kg/bw/day in F).		
28		Adrenals weight	rat	28	Days	Oral	500	mg/kg bw/day	Increase	Increased adrenal weights in males and females treated at 100/500 mg/kg/day and above.		
29a			rat	28	Days	Oral	500	mg/kg bw/day	Increase	Increase in absolute adrenal weight at 500 mg/kg bw/day. Relative adrenal weights – while higher than concurrent controls - were within the range of HCD in females and in males. Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD.		
29b			rat	28	Days	Oral	500	mg/kg bw/day	Increase	Increase in absolute adrenal weight at 500 mg/kg bw. Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD.		
31			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested (7.07 mg/kg bw/day) in F.		

31			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested (7.27 mg/kg bw/day) in M.			
32			rat	90	Days	Oral	2400	ppm	Increase	Significant increase in relative adrenals weight (15%) at top dose only (absence of a dose relationship).			
33			mouse	90	Days	Oral		ppm	No effect	No effect on adrenals weight up to highest dose tested (2400 ppm).			
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	Slight increase in relative adrenals weight at 132 mg/kg bw/day (top dose) due to low BW in top dose males at termination			
34a			Dog	90	Days	Oral	137	mg/kg bw/day	Increase	Increase in relative adrenals weight at 137 mg/kg bw/day (35%), but not absolute weight, due to low BW in top dose females at termination (-25%)			
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on adrenals weight up to highest dose tested 108 mg/kg bw/day; however, slight increase in top dose males mainly was noted due to lower body weights			
34b			Dog	12	Months	Oral	110	mg/kg bw/day	Increase	Absolute and relative adrenal weights were increased (abs: 34%, rel: 54%) in top dose females (in absence of histopathological changes) and in presence of lower BW			
35			mouse	90	Days	Oral	3000	ppm	Increase	Adrenal weights adjusted for bodyweight were higher than control in females receiving 3000 ppm.			
35			mouse	90	Days	Oral		ppm	No effect	No effect on adrenal weight up to highest dose tested (5000 ppm).			
37			mouse	106	Weeks	Oral	150	ppm	Increase	A statistically significant trend was noted for increased absolute and adrenal weights at the terminal sacrifice in males, this was in absence of a dose relationship, not associated with relevant histopathological changes and the values were within the range of available HCD (relative increases; 75 ppm +10%, 150 ppm +13%, 300 ppm +3%).			
37			mouse	107	Weeks	Oral		ppm	No effect	Variations in adrenal weights achieving statistical significance (absolute changes only at 75 and 150 ppm) in females (decrease at terminal sacrifice) were in absence of a dose relationship. Relative change: 5 ppm -38%, 75 ppm -28%, 150 ppm -35%, 300 ppm -36%.			

38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	Adrenal weight was unaffected by treatment up to highest dose tested (177.7 mg/kg bw/day) in M.			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	Adrenal weight was unaffected by treatment up to highest dose tested (221.5 mg/kg bw/day) in F.			
39			rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on adrenal weight were observed up to highest dose tested (11.9 mg/kg bw/day) in females.			
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on adrenal weight were observed up to highest dose tested (10.4 mg/kg bw/day) in males.			
43		Foetal development	rabbit	14	days	Oral		mg/kg bw/day	No effect	No effect on foetal development up to highest dose tested 150 mg/kg bw/day, except foetal visceral findings were observed, three cases of bilateral microphthalmia, two in combination of internal hydrocephalus at the top dose (2/125 foetus with internal hydrocephalus at 75 ppm). Developmental NOAEL is based on this effect. Test chemical only administered from GD 6-18 only (prenatal developmental toxicity study)	Negative, no effect on foetal development		
40a		Litter size	rat	110	days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 153 mg/kg bw/day: while initial litter sizes were slightly smaller than controls at the top dose level in both generations, the litter sizes in all treated groups are well within the range of limited HCD	Negative, no consistent effect on litter size		
40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect in litter size up to highest dose tested 225 mg/kg bw/day in F0 adults: Litter size (all pups and live-born pups) was comparable to controls			
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect in litter size up to highest dose tested 225 mg/kg bw/day in F1 adults: Litter size (all pups and live-born pups) was comparable to controls			
41a			rat	10	Days	Oral		mg/kg bw/day	No effect	No effect in litter size up to highest dose tested 300 mg/kg bw/day. Penconazole technical were given GD 6-15 only			

30		Pituitary histopathology	rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to top-dose 202.3 mg/kg bw/day in M.	Negative, no consistent treatment-related effects on pituitary. Observed effects on histopathology in rat were in absence of a dose relationship and within the HCD range, and the decrease in weight was transient.		
30			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to top-dose 206.6 mg/kg bw/dayin F.			
31			rat	90	Days	Oral	0.77	mg/kg bw/day	Change	Slightly increased incidence of developmental cysts in the adenohypophysis in males in all treated groups; however, with no dose-relationship (males). Control animals (0/20 animals), low dose (2/20 animals), mid dose (3/20 animals) and top dose (2/20 animals). The incidences were within the range of the available limited HCD.			
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to highest dose tested 132 mg/kg bw/day (M) in the presence of systemic toxicity (> MDT)			
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to highest dose tested 137 mg/kg bw/day (F) in the presence of systemic toxicity (> MDT)			
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to highest dose tested 108 mg/kg bw/day (M)			
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to highest dose tested 110 mg/kg bw/day (M)			
37			mouse	106	Weeks	Oral		ppm	No effect	No effect on pituitary histopathology up to highest dose tested (300 ppm) in M.			
37			mouse	107	Weeks	Oral		ppm	No effect	No effect on pituitary histopathology up to highest dose tested (300 ppm) in F.			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology was observed up to highest dose tested (177.7 mg/kg bw/day) in M.			
38			mouse	80	Weeks	Oral		mg/kg	No effect	No effect on pituitary histopathology was observed up to highest dose tested (221.5 mg/kg bw/day) in F.			

								bw/day					
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology was observed up to highest dose tested (10.4 mg/kg bw/day) in M.			
39			rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology was observed up to highest dose tested (11.9 mg/kg bw/day) in F.			
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to highest dose tested (156 mg/kg bw/day in M and 153 mg/kg/bw/day in F).			
40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology was observed up to highest dose tested (225 mg/kg bw/day) in F0.			
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology was observed up to highest dose tested (225 mg/kg bw/day) in F1.			
40b			rat	21	Days	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology was observed up to highest dose tested (221 mg/kg bw/day) in offspring (F1+F2).			
37		Pituitary weight	mouse	107	Weeks	Oral		ppm	No effect	No effect on pituitary weight was observed up to highest dose tested (300 ppm) in F.			
37			mouse	106	Weeks	Oral		ppm	No effect	No effect on pituitary weight was observed up to highest dose tested (300 ppm) in M.			
39			rat	116	Weeks	Oral	10.4	mg/kg bw/day	Decrease	Pituitary weights were decreased in high dose males (treated with 10.4 mg/kg bw/day) at the 1-year interim sacrifice (-29%), but not after the 2-year or terminal sacrifice.			
39			rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on pituitary weight was observed up to highest dose tested (11.9 mg/kg bw/day) in F.			
41a		Presence of anomalie	rat	10	Days	Oral	300	mg/kg	Increase	The overall number of skeletal anomalies was increased at 300 mg/kg bw/day (main study only) and 450 mg/kg bw/day (supplementary study).	Positive, presence of anomalies in rat and rabbit		

		s (external, visceral, skeletal						bw/day					
41b			rat	5	Days	Oral	450	mg/kg bw/day	Increase	The overall number of skeletal anomalies was increased at 450 mg/kg bw/day (supplementary study).			
42			rat	10	days	Oral	500	mg/kg bw/day	Increase	Incidences of skeletal anomalies were increased and in runt foetuses were seen at 500 mg/kg bw/day			
43			rabbit	14	days	Oral	150	mg/kg bw/day	Increase	Increase in internal hydrocephalus and bilateral microphthalmia (within range, but exceeded mean ±SD) at the top dose (150 ppm)			
44			rabbit	13	days	Oral	200	mg/kg bw/day	Increase	Increase in skeletal variations: The % of foetuses with hyoid body and/or arches unossified and reduced ossification of the skull exceeded the range of HCD at the top dose level (200 mg/kg bw/day) while the litter incidences of both findings were well within the range of HCD			
40a		Pup development	rat	35	days	Oral		mg/kg bw/day	No effect	No effect on pup development up to highest dose tested 156 mg/kg bw/day (F1 offspring, M)	Negative, no consistent treatment-related effects on pup development		
40a			rat	35	days	Oral		mg/kg bw/day	No effect	No effect on pup development up to highest dose tested 153 mg/kg bw/day (F1 offspring, F)			
40a			rat	35	days	Oral		mg/kg bw/day	No effect	No effect on pup development up to highest dose tested 153 mg/kg bw/day (F2 offspring)			
28	Target organ toxicity	Kidney weight	rat	28	Days	Oral	500	mg/kg bw/day	Increase	Increase in kidney weight at 500/1000 mg/kg bw. The relative kidney weights at 1000 mg/kg bw/day exceeded the range of the limited HCD for both sexes.	Nephrotoxicity (rat and dog). Kidney weight (abs/rel) was increased.	Overall evidence of target organ systemic toxicity: Kidney and liver are considered target organs. Spleen and thymus are	Overall evidence of systemic toxicity
29a			rat	28	Days	Oral	500	mg/kg bw/day	Increase	Increase in kidney weight (abs + rel) at 500 mg/kg bw/day. Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with			

									500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD.		not sufficiently investigated	
29b			rat	28	Days	Oral	500	mg/kg bw/day	Increase	Increase in kidney weight (abs + rel) at 500 mg/kg bw. Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD.			
30			rat	90	Days	Oral	208.6	mg/kg bw/day	Increase	Increase in relative kidney weight (17%) at 208.6 mg/kg bw/day, the increase co-incided with a lower body weight in that group.			
31			rat	90	Days	Oral	0.78	mg/kg bw/day	Decrease	Relative (but not absolute) kidney weights were slightly lower in all treated groups in absence of a dose-relationship (weights were within the range of available limited HCD).			
32			rat	90	Days	Oral	2400	ppm	Increase	Significant increase in relative kidney weight (17%) at top dose only.			
33			mouse	90	Days	Oral	2400	ppm	Decrease	Reduction in absolute kidney weight (left kidney only) at 2400 ppm only.			
34a			Dog	90	Days	Oral	132	mg/kg bw/day	Increase	Significant increase in relative kidney weight (60%) in top dose males only (absolute increase 16%). Observed in the presence of significant systemic toxicity; decreased body weight and body weight gain associated with drastically reduced food intake.			
34a			Dog	90	Days	Oral	137	mg/kg bw/day	Increase	Absolute (18%) and relative (55%) kidney weights were increased in top dose females. Observed in the presence of significant systemic toxicity; decreased body weight and body weight gain associated with drastically reduced food intake.			
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect.			

34b			Dog	12	Months	Oral	110	mg/kg bw/day	Increase	Increase observed at the top dose level in the presence of significant systemic toxicity; decreased body weight and body weight gain associated with drastically reduced food intake.			
28		Liver histopathology	rat	28	Days	Oral	500	mg/kg bw/day	Change	Enlarged livers and slight hypertrophy of the hepatocytes in some animals at 500 mg/kg bw (M: 8/10, F: 3/10), and in all rats in the high dose group.	Hepatotoxicity (rat, dog). Consistent treatment-related effects on liver weight (increased) and liver histopathology.		
29a			rat	28	Days	Oral	100	mg/kg bw/day	Change	Increased incidences of minimal hypertrophy of centrilobular hepatocytes; in all treated male groups* (2/10 and 9/10 animals at low dose and high dose, respectively) and at 500 mg/kg bw/day in females* (8/10), minimal to moderate hepatocellular necrosis (3/10 top dose males), and an increase in inflammatory cell infiltrations at the top dose level (minimal to moderate severity in males (8/10 animals), and minimal degree in females (6/10). *It should be noted that minimal to moderate increase in the mitotic activity of hepatocytes was reported in the animals (one male and two females), which were sacrificed in moribund condition on day 3 (500 mg/kg bw/day). A dose of 500 mg/kg/day exceeded the MTD.			
29b			rat	28	Days	Oral	100	mg/kg bw/day	Change	Increased incidences of minimal hypertrophy of the follicle epithelium was seen in male from 100 mg/kg bw/day (5/10 low dose, 10/10 high dose) and female top dose animals (8/10). A dose of 500 mg/kg/day exceeded the MTD.			
30			rat	90	Days	Oral	208.6	mg/kg bw/day	Change	Minimal hepatocyte hypertrophy at top-dose (9/20 animals) in F.			
30			rat	90	Days	Oral	202.3	mg/kg bw/day	Change	Minimal hepatocyte hypertrophy at top-dose (20/20 animals) in M.			
32			rat	90	Days	Oral	500	ppm	Change	Centrilobular hepatocyte hypertrophy at ≥1000 ppm, and some degeneration of the hepatocytes around the central vein in the 2400 ppm group in M. Higher incidences of hepatocytic vacuolisation was observed from ≥500 ppm.			
32			rat	90	Days	Oral	1000	ppm	Change	Centrilobular hepatocyte hypertrophy at ≥1000 ppm, and some degeneration of the hepatocytes around the central vein in the 2400 ppm group in F.			

33			mouse	90	Days	Oral	500	ppm	Change	Centrilobular hepatocyte hypertrophy was observed at ≥500 ppm in males (14/15 males at top dose). Focal coagulative necrosis was found in some males at ≥1000 ppm (4/15 males at top dose). Degeneration of the hepatocytes around the central vein (7/15 males) and hepatocytic vacuolisation (10/15 males) were observed at 2400 ppm in males only.			
33			mouse	90	Days	Oral	2400	ppm	Change	Centrilobular hepatocyte hypertrophy was observed at 2400 ppm in females (7/15 females).			
34a			Dog	90	Days	Oral	132	mg/kg bw/day	Change	At the highest dose, cytoplasmic vacuolisation was noted in 2/4 males, inflammatory cell infiltration in 4/4 males and hepatocyte necrosis in 4/4 males. In mid dose males, 1/4 was noted with inflammatory cell infiltration and 1/4 males with hepatocyte necrosis.			
34a			Dog	90	Days	Oral	137	mg/kg bw/day	Change	Inflammatory cell infiltration was noted in 4/4 and hepatocyte necrosis in 4/4 top dose females.			
34b			Dog	12	Months	Oral	108	mg/kg bw/day	Change	At the highest dose, cytoplasmic vacuolisation was noted in 2/4 males, inflammation with fibrosis in 4/4 males and hepatocyte necrosis in 1/4 males. In mid dose males, 2/4 was noted with inflammatory cell infiltration and 2/4 males with inflammation with fibrosis.			
34b			Dog	12	Months	Oral	110	mg/kg bw/day	Change	Inflammation with fibrosis was noted in 4/4 females and hepatocyte necrosis in 2/4 animals.			
35			mouse	90	Days	Oral	1500	ppm	Change	No effect on liver histopathology. Hepatocyte hypertrophy and increased nuclear pleomorphism was present in all males at ≥1500 ppm.			
35			mouse	90	Days	Oral	3000	ppm	Change	No effect on liver histopathology. Hepatocyte hypertrophy was observed in 4/10 females at 3000 ppm.			
37			mouse	106	Weeks	Oral		ppm	No effect	No effect on liver histopathology up to the highest dose level tested (300 ppm).			
37			mouse	107	Weeks	Oral		ppm	No effect	No effect on liver histopathology up to the highest dose level tested (300 ppm).			
38			mouse	80	Weeks	Oral	177.7	mg/kg bw/day	Change	There was an increase in the incidence and severity of hepatocyte vacuolation of the liver in the high dose males (control 13/50, top dose 37/50).			

38			mouse	80	Weeks	Oral	221.5	mg/kg bw/day	Change	There was an increase in the incidence and severity of hepatocyte vacuolation of the liver in the high dose females (control 1/50, top dose 16/50).			
40a			rat	110	days	Oral	29.9	mg/kg bw/day	Change	Increases in slight (mainly centrilobular) hepatocyte hypertrophy was observed at the mid (14/16 females) and high dose level (16/16 females) and slight recent necrosis (2/16) was seen in top dose females.			
40a			rat	110	days	Oral	29.7	mg/kg bw/day	Change	Increases in slight (mainly centrilobular) hepatocyte hypertrophy was observed at the mid (5/19 males) and high dose level (17/20 males).			
49a			Rat	14	Days	Oral	320	mg/kg bw/day	Increase	Increased proliferation of smooth endoplasmic reticulum membranes at 320 mg/kg bw/day			
49b			Mouse	14	Days	Oral	320	mg/kg bw/day	Increase	Increased proliferation of smooth endoplasmic reticulum membranes at 320 mg/kg bw/day			
28		Liver weight	rat	28	Days	Oral	100	mg/kg bw/day	Increase	Liver weight (abs + rel) increase in both sexes, increase in F from 100 mg/kg bw and in M from 500 mg/kg bw.			
29a			rat	28	Days	Oral	100	mg/kg bw/day	Increase	Increase in liver weight (abs + rel) from 100 mg/kg bw/day.			
29b			rat	28	Days	Oral	100	mg/kg bw/day	Increase	Increase in liver weight (abs + rel) from 100 mg/kg bw and above (M) and increase at 500 mg/kg bw (F).			
30			rat	90	Days	Oral	2.1	mg/kg bw/day	Increase	Increase in F in relative liver weight from 2.1 mg/kg (3.7%) onwards (40% top dose) and in absolute at 208.6 mg/kg bw.			
30			rat	90	Days	Oral	2	mg/kg bw/day	Increase	Increase in M in relative liver weight from 2 mg/kg (5%) and onwards (28% top dose) and in absolute at 2 and 202.3 mg/kg bw			
31			rat	90	Days	Oral	0.77	mg/kg	Increase	Increase in liver weight (abs +rel) at low-dose (rel 11%) and mid-dose (rel 15%); however, no weight change in the top dose males.			

							bw/day					
31			rat	90	Days	Oral	2.14	mg/kg bw/day	Decrease	Marginally reduced liver weight (-9.6%) only in the mid dose females.		
32			rat	90	Days	Oral	1000	ppm	Increase	Increase in relative liver weight (13%) at 1000 ppm and increase (re + abs) at top dose (31%).		
32			rat	90	Days	Oral	500	ppm	Increase	Increase in relative liver weight (10.2%) at 500 ppm and further increase in abs+rel liver weight at the two highest doses (20 and 29% relative increase).		
33			mouse	90	Days	Oral	500	ppm	Increase	Absolute and relative liver weights were significantly increased at ≥500 ppm in males (relative weights: 10% at 500 ppm, 17% at 1000 ppm and 42% at 2400 ppm).		
33			mouse	90	Days	Oral	2400	ppm	Increase	Absolute (24%) and relative (32%) liver weights were significantly increased at 2400 ppm in females. Relative liver weight was also slightly increased significantly at ≥500 ppm (≤10%).		
34a			Dog	90	Days	Oral	18.2	mg/kg bw/day	Increase	Absolute and relative liver weights were increased at the top dose level (abs: 30%, rel: 75%) and mid dose males (abs: 20%, rel: 15%).		
34a			Dog	90	Days	Oral	19.4	mg/kg bw/day	Increase	Absolute and relative liver weights were increased at the top dose level (abs: 22%, rel: 88%) and for mid dose females (abs: 15%, rel: 24%).		
34b			Dog	12	Months	Oral	108	mg/kg bw/day	Increase	Absolute and relative liver weights were increased at the top dose level (abs: 27%, rel: 35%).		
34b			Dog	12	Months	Oral	16.5	mg/kg bw/day	Increase	Absolute and relative liver weights were increased at the top dose level (abs: 46%, rel: 63%) and for mid dose females (abs: 27%, rel: 28%).		
35			mouse	90	Days	Oral	500	ppm	Increase	Relative liver weights were increased in males at 500 ppm. Increase in adjusted weights: 12%, 33% and 48% at 500, 1500 and 300 pmm, respectively.		
35			mouse	90	Days	Oral	1500	ppm	Increase	Relative liver weights were increased in females at ≥1500 ppm. Increase in adjusted weights: 10% and 28% at 1500 and 300 pmm, respectively.		

37			mouse	106	Weeks	Oral	150	ppm	Increase	Relative liver weight was increased in M in 300 ppm dose group (10%) at the 1-year sacrifice and at 150 ppm (but not 300 ppm) 53 weeks sacrifice (23%). No dose-related trend or corresponding histopathological correlate were seen.			
37			mouse	107	Weeks	Oral	300	ppm	Increase	Relative liver weight was increased in F in 300 ppm dose group (15%). No dose-related trend or corresponding histopathological correlate were seen.			
38			mouse	80	Weeks	Oral	177.7	mg/kg bw/day	Increase	Liver weights were increased in top dose males (adjusted weight +27%, relative weight +28%).			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	Slightly higher liver weights (approximately 5% higher than control) in females receiving the top dose (221.5 mg/kg bw/day), but the value did not reach statistical significance.			
39			rat	117	Weeks	Oral	5.7	mg/kg bw/day	Increase	Increase in F in absolute (+20%) in top dose group and in relative liver weight (+13 and 15% at 5.7 and 11.9 mg/kg bw/day, respectively) at week 52. The increase at week 52 was associated with an increase in γ-GT. There was also a statistically significant trend in relative weight at week 104 (+15%) for the top dose group.			
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on liver weight were observed in males up to the highest dose level tested (10.4 mg/kg bw/day).			
40a			rat	35	days	Oral	156	mg/kg bw/day	Increase	Relative liver weights were increased significantly in high dose group (+31%), absolute increase non-significantly (+11%). Offspring (F1) Male.			
40a			rat	35	days	Oral	153	mg/kg bw/day	Increase	Relative liver weights were increased significantly in high dose group (+28%), absolute increase non-significantly (+8.2%). Offspring (F1) female.			
40a			rat	110	days	Oral	153	mg/kg bw/day	Increase	Relative liver weights were significantly increased in F1 adults F (+37%), absolute weight was increased non-significantly (+20%).			
40a			rat	110	days	Oral	156	mg/kg bw/day	Increase	Relative liver weights were significantly increased in F1 adults M (+11%), absolute weight was slightly increased (+4%).			

40a			rat	35	days	Oral	153	mg/kg bw/day	Increase	Relative liver weights were significantly increased in F2 weanlings (+22%), absolute liver weight non-significantly incrased (+16%). It should be noted that only five/sex/group F1 and F2 weanlings were necropsied.			
40a			rat	35	days	Oral	156	mg/kg bw/day	Increase	Relative liver weights were significantly increased in F2 weanlings (+28%), absolute liver weight non-significantly incrased (+21%). It should be noted that only five/sex/group F1 and F2 weanlings were necropsied.			
49a			Rat	14	Days	Oral	80	mg/kg bw/day	Increase	Significantly increased at 80 mg/kg bw/day			
49b			Mouse	14	Days	Oral	160	mg/kg bw/day	Increase	Significantly increased at 80 mg/kg bw/day			
29a		Spleen histopathology	rat	28	Days	Oral	500	mg/kg bw/day	Change	Minimal extramedullary haematopoiesis was found in high-dosed females (3/10).	Effects on spleen are not sufficiently investigated		
29b			rat	28	Days	Oral	100	mg/kg bw/day	Change	Minimal extramedullary haematopoiesis was found in low-dosed males (2/10), in high-dosed males (2/10) and in high-dosed females (2/10).			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on spleen histopathology in M up to the highest dose level tested (177.7 mg/kg bw/day).			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on spleen histopathology in F up to the highest dose level tested (221.5 mg/kg bw/day).			
38		Spleen weight	mouse	80	Weeks	Oral	177.7	mg/kg bw/day	Decrease	Reduced spleen weight in top dose males (adjusted weight -40%).			
38			mouse	80	Weeks	Oral	221.5	mg/kg bw/day	Decrease	Reduced spleen weight in top dose females (adjusted weight -38%).			

29a		Thymus histopathology	rat	28	Days	Oral	500	mg/kg bw/day	Change	Occurrence of tangible body macrophages (phagocytic cells exhibiting condensed nuclear material in their cytoplasm and being responsible for lymphophagocytosis) in thymus cortex was recorded in all moribund-sacrificed animals as well as in one female of the 500 mg/kg bw/day dose level at study termination. Total N=10	Effects on thymus are not sufficiently investigated		
29b			rat	28	Days	Oral	500	mg/kg bw/day	Change	Occurrence of tangible body macrophages (phagocytic cells exhibiting condensed nuclear material in their cytoplasm and being responsible for lymphophagocytosis) in thymus cortex was recorded in one female, which was sacrificed in moribund condition on day 2 (500 mg/kg bw/day). Variations in absolute or relative organ weights occasionally reached statistical significance in the thymus but were in absence of a dose-relationship. They were also not associated with any relevant histopathological changes. Total N=10, effect observed at the top dose			
30		Thymus weight	rat	90	Days	Oral	2.1	mg/kg bw/day	Increase	Increase in relative thymus weight at 2.10 and 208.6 mg/kg bw/day (10% and 12%), the increase co-incided with a lower body weight in that group at the top dose. Study considered supportive only (due to deviations from the test guideline currently in place). Variations in absolute or relative organ weights occasionally reached statistical significance in the thymus but were in absence of a dose-relationship. They were also not associated with any relevant histopathological changes. Total N=10, effect observed at the top dose			
1	Systemic toxicity	Body weight	rat	9	Months	Oral	50	mg/kg bw/day	Decrease	Significant decrease compared to the control group. Reporting deficiencies, unclear test item and dosing scheme, inadequate reporting of body weight development, and no reporting of clinical signs or food consumption. Serious methodological deficiencies, flawed/unsuitable histopathological methodology, no consideration of circadian variation in testosterone measurement.	Sufficient evidence of systemic toxicity based on reduced Bw, food consumpiton, alteration in clinical chemistry and haematology and/or clinical signs. MTD was exceeded at 500 mg/kg bw/day in males and 500 mg/kg bw/day in	Overall evidence of systemic toxicity. MTD ≥500 mg/kg bw (M), ≥500 mg/kg bw (F)	
28			rat	28	Days	Oral	500	mg/kg bw/day	Decrease	Decreased BW (M: ↓13%) week 4 and BW gain (M: ↓ 28% and F: ↓ 14%) for weeks 0-4.			
30			rat	90	Days	Oral	208.6	mg/kg	Decrease	Decrease in BW and a marked effect in BW gain (average reduction 16%) from week 4 onwards at the top dose. Reduced BW (-14%) at termination.			

							bw/day				females (28 days rat) (three female and one male rat dosed with 500 mg/kg/day were sacrificed in moribund condition at experimental days 2-3, and in surviving animals, symptoms such as hunch-backed posture, piloerection and laboured breathing were observed that were more pronounced in female than in male animals).		
31			rat	90	Days	Oral	2.14	mg/kg bw/day	Increase	Increased bodyweights (9.8%) and BW gain (16%) in F only at 2.14 mg/kg bw/d, not confirmed at top-dose.			
32			rat	90	Days	Oral	500	ppm	Decrease	Bodyweights were significantly lower throughout the study in the 2400 ppm (-10% week 13), and in the 1000 ppm treated group at weeks 6, 7, 9, 12, and 13 (-6.2%). BW gain significantly reduced in the 1000 (-8.9%) and 2400 ppm (-15%) treated females. Overall mean food consumption in females was slightly reduced at 1000 and 2400 ppm reaching statistical significance at a few weeks during the dosing period.			
33			mouse	90	Days	Oral	2400	ppm	Increase	Lower BW gain for the 13 weeks period was seen in the 2400 ppm group (-13% vs. control in males and –17% in females).			
34a			Dog	90	Days	Oral	132	mg/kg bw/day	Decrease	In the male high dose group, the dogs lost weight mostly during the first month of the study associated with drastically reduced food intake; the weight loss reached 12% (males) of the initial weights during the first 13 weeks of the study. Animals gained weight in the lowest doses; however, BW gain was lower in the low (-18%) and mid dose males (-25%) compared to control animals. Group mean terminal body weights were reduced (26%) at the top dose level at the interim (13 weeks)			
34a			Dog	90	Days	Oral	137	mg/kg bw/day	Decrease	In the female high dose group, the dogs lost weight mostly during the first month of the study associated with drastically reduced food intake; the weight loss reached 9% (females) of the initial weights during the first 13 weeks of the study. Animals gained weight in the lowest doses; however, BW gain was lower in mid dose females (-22%) compared to control animals. Group mean terminal body weights were reduced (25%) at the top dose level at the interim (13 weeks).			
34b			Dog	12	Months	Oral	108	mg/kg bw/day	Decrease	The top dose level was reduced from 132 mg/kg bw/day to 108 mg/kg bw/day in week 20, but overall BW gain was markedly below controls for the top dose group (M ↓44%). The overall weight gain was also slightly lower in mid dose dogs (M↓14%), whereas there were no differences at the low dose level. Group mean terminal			

									body weights were reduced (8.2%) at the top dose level at terminal sacrifice (53 weeks).			
34b			Dog	12	Months	Oral	16.5	mg/kg bw/day	Decrease	The top dose level was reduced from 137 mg/kg bw/day to 110 mg/kg bw/day in week 20, but overall BW gain was markedly below controls for the top dose group (F ↓58%). The overall weight gain was also lower in mid dose dogs (F↓33%), whereas there were no differences at the low dose level. Group mean terminal body weights were reduced (11%) at the top dose level at terminal sacrifice (53 weeks).			
35			mouse	90	Days	Oral	1500	ppm	Decrease	Slighty reduced BW compared to control day 92 (↓5.6%) while adjusted body weight loss during the study (days 2-92) was ↓19% on day 92 in the 1500 ppm dose group. In the 3000-ppm group, reduced BW compared to control was ↓15% and adjusted body weight loss (days 2-92) during the study was ↓52%. Animals in the 5000-ppm group lost weight throughout the first week of the study (10-17% of initial body weights) and were terminated in the second week.			
35			mouse	90	Days	Oral	3000	ppm	Decrease	Animals in the 5000-ppm group lost weight throughout the first week of the study (8-11% of initial body weights) and were terminated in the second week. Animals in the 1500 and 3000 ppm group had reduced bodyweights with most BW reduction in the 3000-ppm group: ↓11% at day 92 and adjusted BW loss during the study (days 2-92) was ↓38%.			
38			mouse	80	Weeks	Oral	221.5	mg/kg bw/day	Decrease	Marked effect on bodyweight development in females at 221.5 mg/kg bw/day. Week 1-33 (-19%), week 1-51 (-17%) week 1-81 (-16%). The maximum difference from control of adjusted body weights were at weeks 33/37 (-9.6%).			
38			mouse	80	Weeks	Oral	177.7	mg/kg bw/day	Decrease	Marked effect on bodyweight development in males at 177.7 mg/kg bw /day. Week 1-33 (-27%), week 1-51 (-29%), week 1-81 (-26%). The maximum difference from control of adjusted body weights were at week 73 (-15%).			
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	Body weight development in all treated animals was similar to controls up to highest dose tested (10.4 mg/kg bw/day) in M.			
39			rat	117	Weeks	Oral		mg/kg	No effect	No effect on body weight development in all treated animals was similar to controls up to highest dose tested (11.7 mg/kg bw/day) in F.			

								bw/day					
40a			rat	110	days	Oral	153	mg/kg bw/day	Decrease	The markedly lower body weight (-12%) of high dose F0 females on lactation day 1 indicates that the net body weight of dams (without gravid uterus, not measured) during gestation would have been more markedly affected than measured body weights. Body weight development was slightly decreased in high dose females during premating (day 1-60, -8.3%). During gestation, a slight reduction in body weight gain was also noted for high dose F0 dams (day 0-21, -7.7%). During lactation, high dose females of both generations gained slightly more weight than controls.			
40a			rat	110	days	Oral	153	mg/kg bw/day	Decrease	The markedly lower body weight (-11%) of high F1 females on lactation day 1 indicates that the net body weight of dams (without gravid uterus, not measured) during gestation would have been more markedly affected than measured body weights. Body weight development was slightly decreased in high dose females during premating (day 1-60, -6.9%). During gestation, a more marked decrease (day 0-21, -16%) was seen in F1 dams at this dose level. During lactation, high dose females of both generations gained slightly more weight than controls.			
40a			rat	110	days	Oral	156	mg/kg bw/day	Decrease	A slightly lower body weight gain was seen during pre-mating (-2.7%) in F1 high dose males with a more marked reduction after mating (-10.6%). Due to lower body weights at start of the pre-mating period, absolute bodyweights of F1 males were consistently lower than controls over the whole treatment period. Significantly reduced BW at termination (-7.5%).			
40b			rat	19	Weeks	Oral	225	mg/kg bw/day	Decrease	Body weight development of high dose females during pre-mating were reduced at 225 mg/kg bw/day in both generations (premating; F0 9 weeks exposure: -21%, F1 age weeks 4-16: -7.1%). Absolute body weights of high dose F0 and F1 females remained below control values, while body weight gain during gestation was comparable with controls. During lactation, high dose females gained more weight than controls.			
40b			rat	25	Weeks	Oral	225	mg/kg bw/day	Decrease	Body weight development of high dose females during pre-mating were reduced at 225 mg/kg bw/day in both generations (premating; F0 9 weeks exposure: -21%, F1 age weeks 4-16: -7.1%). Absolute body weights of high			

									dose F0 and F1 females remained below control values, while body weight gain during gestation was comparable with controls. During lactation, high dose females gained more weight than controls.				
40b			rat	25	Weeks	Oral	211	mg/kg bw/day	Decrease	Body weight gain of high dose F1 males was decreased during pre-mating and during the complete treatment period (-10.5% w 0-28).			
41a			rat	10	Days	Oral	300	mg/kg bw/day	Decrease	At 300 mg/kg bw/day, body weight gain was decreased during treatment (by 8% on GD 6-16) and the corrected body weight gain (minus gravid uterus weight) on GD day 6-21 (by 12%).			
41b			rat	5	Days	Oral	300	mg/kg bw/day	Decrease	At 300 mg/kg bw/day, body weight gain was markedly decreased during treatment (by 20% on GD 6-16) and GD 6-21 corrected body weight gain (by 55%). During the more limited treatment period (GD 10-14), body weight gain at 450 mg/kg bw/day was reduced by 28% and also GD 6-21 corrected body weight gain was 28% lower than controls.			
42			rat	10	days	Oral	500	mg/kg bw/day	Decrease	Maternal body weight development: corrected bw gain on GD 6-20 was reduced by 41%. BW at GD 20 was significantly reduced (-4.2%: corrected for gravid uterus weight: -2.2%)			
43			rabbit	14	days	Oral	150	mg/kg bw/day	Decrease	Reduced body weight development in high dose females; BW gain GD 0-28; -7.4%, BW gain during GD 6-19; -11% (test chemical was administrated GD 6-18)			
44			rabbit	13	days	Oral	200	mg/kg bw/day	Decrease	Reduced BW gain in high dose females, most markedly in the first week of treatment* (GD 7-10: -104%, GD 10-14; -19%). *The test chemical was administrated from GD 7-19 only.			
49a			Rat	14	Days	Oral	No effect	mg/kg bw/day	No effect	No effect on body weight up to the highest dose tested (320 mg/kg bw/day)			
49b			Mouse	14	Days	Oral	No effect	mg/kg bw/day	No effect	No effect on body weight up to the highest dose tested (320 mg/kg bw/day)			
28		Clinical chemistry and	rat	28	Days	Oral	500	mg/kg bw/day	Decrease	A trend to slightly decreased haemoglobin (↓4.2% to↓6.3%) and haematocrit values (↓4.7% to ↓7%) in female groups from 500 to 1000 mg/kg/ bw.			

28		haematology	rat	28	Days	Oral	500	mg/kg bw/day	Change	A series of parameters were affected in one or both sexes, including products of the metabolism, increased cholesterol and proteins, and increased activity of enzymes related to the hepatic function *(ALAT og ALP*). Sodium, calcium and inorganic phosphate levels were increased, whereas potassium and chloride were decreased. A slight, but statistically significant increase in calcium, creatinine and potassium levels, and decrease in sodium levels was noted at 100 mg/kg bw in M, but the levels of these parameters did not appear to be dose-dependent.			
29a			rat	28	Days	Oral	100	mg/kg bw/day	Change	A dose-related increase in platelets and decrease in prothrombin time was observed in male and female groups reaching statistical significance mostly at 500 mg/kg bw/day (exceeding HCD). Clinical biochemistry: A series of parameters were affected by treatment, dose-related increase of plasma protein concentrations, associated with higher globulin levels and minimally lower albumin-to-globulin (A/G) ratios in both sexes (A/G ratios and albumin levels were within the range of available HCD). Elevated alanine aminotransferase and cholesterol levels were also noted at the top dose level. Total bilirubin was somewhat lower in treated groups as compared to concurrent controls (but well within the range of available HCD). Reductions in plasma chloride levels were within the range of available HCD. Changes in ASAT and ALP (mostly reductions) were within the range of the available HCD. A dose of 500 mg/kg/day exceeded the MTD.			
29b			rat	28	Days	Oral	100	mg/kg bw/day	Change	A dose-related increase in platelets and decrease in prothrombin time was observed in male and female groups reaching statistical significance mostly at 500 mg/kg bw/day (exceeding HCD). Clinical biochemistry: A series of parameters were affected by treatment, dose-related increase of plasma protein concentrations, associated with higher globulin levels and minimally lower albumin-to-globulin (A/G) ratios in both sexes (A/G ratios and albumin levels were within the range of available HCD). Urea levels were slightly increased at 500 mg/kg bw/day in both sexes. Elevated alanine aminotransferase and cholesterol levels were also noted at the top dose level. Total bilirubin was somewhat lower in treated groups as			

									compared to concurrent controls (but well within the range of available HCD). Reductions in plasma chloride levels were within the range of available HCD. Changes in ASAT and ALP (mostly reductions) were within the range of the available HCD. A dose of 500 mg/kg/day exceeded the MTD.			
30			rat	90	Days	Oral	20.7	mg/kg bw/day	Change	Haematology: statistically significant effects on RBC parameters: ↓segmented neutrophils (208.6 mg/kg bw/day), ↑ moncytes and nucleated RBC-normoblasts (from 20.7 mg/kg bw). Blood chemistry: statistically significant changes in: ↑cholesterol and albumin, ↓potassium, chloride. Note that the most findings reflected the normal physiological variation of the respective parameters and were within a limited available HCD.			
30			rat	90	Days	Oral	19.4	mg/kg bw/day	Change	Haematology: statistically significant effects on RBC parameters: ↓ leukocytes (at 2 and 202.3 mg/kg bw/day only) ↑segmented neutrophils (at 19.4 mg/kg bw only), ↓ lymphocytes (from 19.4 mg/kg bw/day). Blood chemistry: statistically significant changes in: ↓ glucose (from 19.4 mg/kg bw/day), ↑ureas-N values (from 19.4 mg/kg bw/day), ↑ cholesterol (202.3 mg/kg bw/day), ↑ total proteins and albumin (from 2 mg/kg bw), ↑total globulin and A/G ratio (increasing trend, significant at 202.3 mg/kg bw/day), ↓ lactate dehydrogenase (decreasing trend from 19.4 mg/kg bw/day), ↑ potassium (at 2 and 202.3 mg/kg bw only), ↑chloride (at 2 and 19.4 mg/kg bw/day only). Note that the most findings reflected the normal physiological variation of the respective parameters and were within a limited available HCD. Only the marginally increased cholesterol in high dose males slightly exceeded the range of the available limited HCD.			
31			rat	90	Days	Oral	0.78	mg/kg bw/day	Change	Haematology: reduced reticulocyte count at all doses (no clear dose-relationship). Clinical chemistry: ↑GGT from mid-dose and globulin and total proteins at top-dose. Most findings reflected the normal physiological variation of the respective parameters and in the absence of clear dose-relationship.			
31			rat	90	Days	Oral	0.77	mg/kg bw/day	Change	Haematology: inceased reticulocyte count at all doses (no clear dose-relationship). Clinical chemistry: ↑ in total proteins from mid-dose and in albumin at top-dose, ↓ inorganic phosphate and a slight increase in sodium. Most findings reflected the normal			

									physiological variation of the respective parameters and in the absence of clear dose-relationship.				
32			rat	90	Days	Oral	2400	ppm	Decrease	↑slightly increase in protein (males only), ↓ albumin (females only), and slighty reduced A/G ratio in both sexes in top dose animals.			
32			rat	90	Days	Oral	10	ppm	Increase	Increased urea nitrogen in treated males (11% at 10 ppm to 35% at 1000 ppm and 22% at 2400 ppm). It should be noted that the value of control males appears to be rather low (139 mg/L) as compared to control females (151 g/L).			
33			mouse	90	Days	Oral	1000	ppm	Change	Lower total protein (↓8.3% and 6.7% at 1000 ppm and 2400 ppm, respectively) and cholesterol (↓31% and 61% at 1000 ppm and 2400 ppm, respectively). ALT at 2400 ppm (↑170%) whereas gamma-GT was significantly reduced at ≥500 ppm.			
33			mouse	90	Days	Oral	1000	ppm	Change	Reduced albumin (↓14%) and A/G ratio (↓13%) in top dose females, wheras cholesterol was decreased at ≥1000 ppm (↓36% to ↓40% in top dose females). Total protein was reduced in top dose females (↓10%).			
34b			Dog	12	Months	Oral	110	mg/kg bw/day	Change	Increased platelet counts were recorded among female dogs of the high-dose group already from the pre-test. Haematological parameters of which reaching increased statistical significance were noted in monocytes in mid dose and high dose females. Red cell parameters (Hb, RBC) among female dogs of the high dose group were slightly lower as compared to controls from week 13. After reduction of the top dose level to 110 mg/kg bw/day in week 20, red blood cell parameters recovered within the range of availble limited HCD in week 52. Clinical biochemistry: mainly change at the high dose level: OCT, AST, ALT, ALP, and γ-GT were markedly increased during the complete treatment period, indicating the liver as a clear target organ. Further effects were most marked at week 13 (↓glucose and urea-nitrogen, ↑inorganic phosphate), but normalised when dose level was reduced.			
34b			Dog	12	Months	Oral	108	mg/kg bw/day	Change	Red cell parameters (Hb, RBC) in high dose M were slightly lower at week 13. After reduction of the top dose level to 108 mg/kg in week 20, red blood cell parameters recovered within the range of HCD in week 52. Variations in haematological parameters (some statistically significant) were noted in eosinophils, lymphocytes and monocytes in absence of a dose-			

									relationship, and within the range of HCD. Platelets increased over time (statistical significance at week 52). The proportion of lymphocytes was increased, and eosinophils were reduced in high dose M. Clinical biochemistry: mainly change at the high dose level; OCT, AST, ALT, ALP, and γ-GT were markedly increased during the complete treatment period, indicating the liver as a clear target organ. Globulin was slightly but consistently increased in high dose males. Further effects were most marked at week 13 (↓glucose and chloride, ↑inorganic phosphate), but normalised when dose level was reduced. ↑inorganic phosphate seen up to the end of treatment.			
35			mouse	90	Days	Oral	500	ppm	Change	Treatment and dose related reduction in cholesterol in all dose group, significant from ≥500 ppm (↓54% at 3000 ppm). Plasma ALP was increased at ≥1500 ppm (13% and 22% increase).			
35			mouse	90	Days	Oral	3000	ppm	Decrease	Treatment and dose related reduction in cholesterol in all dose group, significant from ≥100 ppm (↓54% at 3000 ppm). Plasma ALP was increased at ≥1500 ppm (↑ 25% at 3000 ppm). Plasma albumin (↓ 2.2-6.5%) and total protein (↓2.6-8.1%) were lower in all female groups, and plasma calcium was lower in females at 3000 ppm (↓4.4%).			
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	Observed variations in blood biochemistry parameters were considered unrelated to treatment tested up to the highest dose level (10.4 mg/kg bw/day) in M.			
39			rat	117	Weeks	Oral	0.2	mg/kg bw/day	Change	Slightly higher γ-GT values in high dose females at weeks 27 (top dose only) and 52 (increase at 0.2, 2.9 and 11.9 mg/kg bw/day).			
49a			Rat	14	Days	Oral	10	mg/kg bw/day	Increase	a strong dose-dependent increase of microsomal protein (up to about 60% vs. control) and phospholipid contents (practically doubled at 320 mg/kg bw/day vs. controls). Activities of xenobiotic-metabolising liver enzymes were drastically increased (UDP-glucuronosyltransferase was increased from 80 mg/kg bw/day and up to the top dose).			
49b			Mouse	14	Days	Oral	80	mg/kg bw/day	Increase	a strong dose-dependent increase of microsomal protein (up to about 60% vs. control) and phospholipid contents (practically doubled at 320 mg/kg bw/day vs. controls). Activities of xenobiotic-metabolising liver enzymes			

									were drastically increased (UDP-glucuronosyltransferase was increased from 80 mg/kg bw/day and up to the top dose).				
29a		Clinical signs	rat	28	Days	Oral	500	mg/kg bw/day	Change	Due to marked clinical signs of acute toxicity, one male and two females dosed with 500 mg/kg/ bw/day (Batch B, 96.1% purity) were sacrificed in moribund condition at experimental day 3. In surviving animals, symptoms such as hunch-backed posture, piloerection and laboured breathing were observed that were more pronounced in female than in male animals.			
29b			rat	28	Days	Oral	500	mg/kg bw/day	Change	Due to marked clinical signs of acute toxicity, one female dosed with 500 mg/kg/day (Batch A, 96.2% purity) was sacrificed in moribund condition at experimental day 2. In surviving animals, some females had symptoms such as hunch-backed posture, piloerection and laboured breathing.			
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	Diarrhoea was observed in treatment groups as well as in the control group (there were no differences between the groups). At the high dose, diarrhoea was seen less frequently during the 1st 20 weeks, which was considered due to reduced diet intake.			
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	Diarrhoea was observed in treatment groups as well as in the control group (there were no differences between the groups). At the high dose, diarrhoea was seen less frequently during the 1st 20 weeks, which was considered due to reduced diet intake.			
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	Increased incidence of vomiting was seen in dogs receiving the top dose (132 mg/kg bw/day) diet during the first 13 weeks. No vomiting was seen in males after the dose level had been reduced to 108 mg/kg bw/day. Diarrhoea was observed in treatment groups as well as in the control group (there were no differences between the groups).			
34b			Dog	12	Months	Oral	110	mg/kg bw/day	Decrease	Increased incidence of vomiting was seen in dogs receiving the top dose (137 mg/kg bw/day) diet during the first 13 weeks. Vomiting still continued in the females during the whole study dose level even after the dose had been reduced to 110 mg/kg bw/day. Diarrhoea was observed in treatment groups as well as in the control group (there were noe differences between the groups) but was observed less frequently in all groups during the second half of the study.			

38			mouse	80	Weeks	Oral	177.7	mg/kg bw/day	Change	Increased number of males appeared to be thin in top dose group (6/50 animals).			
42			rat	10	days	Oral	500	mg/kg bw/day	Increase	Crusty eye(s), crusty nose and/or muzzle, damp and yellow/brown-stained fur in perianal and/or abdominal region were noted in several high dose females. Additionally, staggered gait, emaciation, loose stool, weakness, and/or lethargy were noted for 4 high dose dams			
28		Food consumption	rat	28	Days	Oral	500	mg/kg bw/day	Decrease	Dose-dependent trend to lower food intake in treated male and female at 500 and 1000 mg/kg bw (Overall M: ↓18% and F: ↓12%) for weeks 1-4, especially during the first two weeks following the dose changes (F:↓12 to M: 19% vs. control weeks 2-4).			
29a			rat	28	Days	Oral	500	mg/kg bw/day	Decrease	In high-dosed animals, the mean food consumption was decreased during week 1 in both males and females (-10 to -13% vs. control) and to a lesser extent in females during the 2nd week also (-5 to -7%). The overall food consumption during the study was similar in all male groups but remained slightly decreased in high-dosed females (-3 to -4%). Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD.			
29b			rat	28	Days	Oral	500	mg/kg bw/day	Decrease	In high-dosed animals, the mean food consumption was decreased during week 1 in both males and females (-10 to -13% vs. control) and to a lesser extent in females during the 2nd week also (-5 to -7%). The overall food consumption during the study was similar in all male groups but remained slightly decreased in high-dosed females (-3 to -4%). Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were			

									sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD.			
30			rat	90	Days	Oral	208.6	mg/kg bw/day	Decrease	Food consumption of the high-dosed animals was generally lower, but not significantly lower than in other groups (average reduction of 10% vs. control)		
34a			Dog	90	Days	Oral	132	mg/kg bw/day	Decrease	Reduced food intake week 1-13 was noted in males (34%)		
34a			Dog	90	Days	Oral	137	mg/kg bw/day	Decrease	Reduced food intake week 1-13 was noted in females (36%).		
34b			Dog	12	Months	Oral	16.8	mg/kg bw/day	Decrease	Food consumption at the top dose level was drastically reduced during the first weeks 1-19 (M↓29%) of the study and improved slowly during the following weeks. Food consumption returned to normal when top dose was reduced from 5000 to 2500 ppm.		
34b			Dog	12	Months	Oral	16.5	mg/kg bw/day	Decrease	Food consumption at the top dose level was drastically reduced during the first weeks 1-19 (F↓32%) of the study and improved slowly during the following weeks. Food consumption returned to normal when top dose was reduced from 5000 to 2500 ppm.		
35			mouse	90	Days	Oral		ppm	No effect	Food consumption was reduced in both sexes receiving 3000 and 5000 ppm on day 1, but there were no consistent effects as the study progressed.		
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No consistent evidence of an effect of treatment on food consumption but food utilisation was less efficient than that of controls in females in the top dose group.		
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No consistent evidence of an effect of treatment on food consumption but food utilisation was less efficient than that of controls in males in the top dose group		
40a			rat	110	days	Oral	153	mg/kg bw/day	Decrease	FC was slightly reduced during pre-mating (-4.5%) and gestation (-5.1%) in adult F0 female.		
40a			rat	110	days	Oral	153	mg/kg	Decrease	FC was slightly reduced during premating (-4.2%) and gestation (-8.8%, days 0-6) in adult F1 female.		

							bw/day					
40a			rat	110	days	Oral	156	mg/kg bw/day	Decrease	FC was slightly reduced (-7.1%) after mating in F1 adult M.		
40b			rat	19	Weeks	Oral	225	mg/kg bw/day	Decrease	A slight reduction was seen during premating for high dose females of both generations (F0: -7.1%, F1 -7.6%). FC during gestation was also significantly lower than controls for high dose F0 females (-7%), slight reduction seen for F1 females (-3.7%). During lactation, high dose females of both generations also consumed slightly less (not significant) food than controls (F0: -4.5%, F1: -4.2%).		
40b			rat	25	Weeks	Oral	225	mg/kg bw/day	Decrease	A slight reduction was seen during premating for high dose females of both generations (F0: -7.1%, F1 -7.6%). FC during gestation was also significantly lower than controls for high dose F0 females (-7%), slight reduction seen for F1 females (-3.7%). During lactation, high dose females of both generations also consumed slightly less (not significant) food than controls (F0: -4.5%, F1: -4.2%).		
41a			rat	10	Days	Oral	300	mg/kg bw/day	Decrease	Reduced FC at 300 mg/kg bw/day (by 16% for GD 6-11), FC during complete treatment period was reduced by 9%. FC reductions were slight at the low and mid dose group for GD 6-11 (low dose -7.3%, mid dose -9.4%)		
41b			rat	5	Days	Oral	300	mg/kg bw/day	Decrease	At 300 mg/kg bw/day, food consumption gain was markedly decreased during the first days of treatment (by 17% on GD 6-11) and overall by 13% during the complete treatment period (GD 6-16). Food consumption was also still decreased during GD 16-21. FC at 450 mg/kg bw/day was somewhat decreased (treatment for gestation days 10-14 only).		
42			rat	10	days	Oral	500	mg/kg bw/day	Decrease	FC was transiently reduced for high (-42%) dose animals on GD 6 following the first dosing while it was comparable to controls at GD 13 and 19. A slightly lower food consumption on GD 6 for mid-dose animals was reported but is not considered adverse.		
43			rabbit	14	days	Oral	150	mg/kg bw/day	Decrease	Reduced FC in high dose females during GD 6-19; -13%. (test chemical was administrated GD 6-18)		

44			rabbit	13	days	Oral	200	mg/kg bw/day	Decrease	Reduced FC in high dose females, most markedly in the first week of treatment* (GD 7-10: -43%, GD 10-14; -54%, GD 7-20: -37%). *The test chemical was administrated from GD 7-19 only.			
32		Mortality	rat	90	Days	Oral		ppm	No effect	No effect on mortality up to the highest dose level tested (2400 ppm).			
33			mouse	90	Days	Oral	500	ppm	Increase	One female in each of the 2400- and the 1000-ppm dose groups and one male in the 500-ppm dose group died during study week 8. No clinical observations were reported for these animals before death.			
35			mouse	90	Days	Oral	5000	ppm	Increase	Killed for humane reasons due to BW loss during the first week.			
40a			rat	110	days	Oral	153	mg/kg bw/day	Increase	Three dams died post partum in Adult (F0): one dam died day 4, one dam died day 11 and one dam died shortly after delivery. No observations on possibly impaired parturition were recorded for any of these dams and all of these dams completed parturition and delivered all pups. Dam mortalities after parturition may be related to maternal toxicity; however, RMS cannot exclude a link to dystocia.			
40a			rat	110	days	Oral	153	mg/kg bw/day	Increase	Three dams died post partum in Adult (F1): one dam died day 4, and two dams died day 2. No observations on possibly impaired parturition were recorded for any of these dams and all of these dams completed parturition and delivered all pups. Dam mortalities after parturition may be related to maternal toxicity; however, RMS cannot exclude a link to dystocia.			
41a			rat	10	Days	Oral	300	mg/kg bw/day	Increase	At 300 mg/kg bw/day, 2 dams died shortly before the autopsy on gestation day 21. Autopsy did not reveal any obvious pathological condition.			
41b			rat	5	Days	Oral	300	mg/kg bw/day	Increase	Four and 2 dams died at 300 and 450 mg/kg bw/day, respectively, shortly before the autopsy on gestation day 21. Autopsy did not reveal any obvious pathological condition.			
42			rat	10	days	Oral	500	mg/kg bw/day	Increase	Two gravid and one non-gravid females at 500 mg/kg bw/day (on day 10, 11 and 12, respectively; clinical signs were observed ante mortem and occurrence of stomach and intestinal lesions).			
46			Mallard duck	23	weeks	Oral	No effect	ppm	No effect	No effects on survival in the parental generation up to the highest dose level tested (1000 ppm).			

49a			Rat	14	Days	Oral	No effect	mg/kg bw/day	No effect	No effect up to the highest dose level tested 320 mg/kg bw/day			
49b			Mouse	14	Days	Oral	No effect	mg/kg bw/day	No effect	No effect up to the highest dose level tested 320 mg/kg bw/day			
3	[Not in list]	[Not in list]	human, breast, cell line	4	Hr	Uptake from the medium (*in vitro*)		µM	Change	changes in RNA of T-47D cells treated with PNZ or extract from PNZ-treated grapes			
36	No relevant effect observed	No relevant effect observed	rabbit	21	days	Dermal		mg/kg bw/day	No effect	No relevant effect observed up to the highest dose level (2000 ppm)			
37	No relevant effect observed	No relevant effect observed	mouse	107	Weeks	Oral		ppm	No effect	No differences in the tumour incidences up to highest dose tested (300 ppm)			
37	No relevant effect observed	No relevant effect observed	mouse	106	Weeks	Oral		ppm	No effect	No differences in the tumour incidences up to highest dose tested (300 ppm)			
38	No relevant effect observed	No relevant effect observed	mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No increase in malignant or benign tumours up to the highest dose tested (177.7 mg/kg bw/day)			
38	No relevant effect observed	No relevant effect observed	mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No increase in malignant or benign tumours up to the highest dose tested (221.5 mg/kg bw/day)			

39	No relevant effect observed	No relevant effect observed	rat	117	Weeks	Oral		mg/kg bw/day	No effect	no differences in the tumour incidences up to the highest dose tested (10.4 mg/kg bw/day)			
39	No relevant effect observed	No relevant effect observed	rat	116	Weeks	Oral		mg/kg bw/day	No effect	no differences in the tumour incidences up to the highest dose tested (11.9 mg/kg bw/day)			

2.10.2.1.2.1 Assessment of the integrated lines of evidence and weight of evidence for T-mediated adversity and endocrine activity

Table 160: WoE for T-mediated adversity

- **Overall conclusion: No consistent T-mediated adversity, but not sufficiently investigated.**
- **Increased thyroid weight and incidences of minimal hypertrophy of the follicle epithelium was observed in one species (rat) in a short term 28 days study and considered adverse (study ID 29 a and b, 1991). The effect was observed at the two dose levels tested: low dose (100 mg/kg bw/day) and high dose (500 mg/kg bw/day). Three female and one male rat dosed with 500 mg/kg/day were sacrificed in moribund condition at experimental days 2-3. This indicates that a dose of 500 mg/kg/day exceeded the MTD; however, effects observed in thyroid are still considered adverse.**
- **The effects were not confirmed in longer term studies or in other species (mice and dogs).**
- **Target organ toxicity was observed in the adrenal and kidney at the high dose level (500 mg/kg/bw/day) and in the liver at both low dose (100 mg/kg bw/day) and high dose (500 mg/kg bw/day) (study ID 29 a and b, 1991).**
- **For the liver, target organ toxicity was mainly characterized by hypertrophy; however, necrosis and fibrosis in dogs (500 ppm) and hepatic degeneration in rats (1000 ppm) could be considered adverse.**

Although the available dataset for T-mediated adversity is negative, this dataset is not considered sufficient. To consider the T modality as 'sufficiently investigated' for mammals the thyroid parameters foreseen to be investigated in the following studies OECD test guidelines 407, 408, 409 (and/or the one-year dog study, if available), 416 (or 443 if available) and 451-3 should have been measured and the results included in the dossier. Studies following the recommended TG or similar design have been performed, but due to the age of these studies they do not assess all parameters which are required by the EFSA-ECHA ED guidance document to conclude that all parameters indicative of T-mediated adversity have been sufficiently investigated. The major deviations from current guideline are summarized in Table 161: . However, according to the EFSA "Technical report on the outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology" (EFSA supporting publication 2020:EN-1837, page 7, doi:10.2903/sp.efsa.2020.EN-1837), the dataset for thyroid can be considered complete on a case-by-case basis, pending whether the duration and doses selection allow a proper assessment of the thyroid histology (thyroid histopathology is generally considered more sensitive and informative than thyroid weight).

Dose-levels were not optimal in a number of the included studies. Of significant importance, the rat 28 days study (study ID 29) only had two dose levels, whereas an intermediate dose would have been preferred. Dose-levels were considered to be too low in some of the long-term studies following TG 451-3 (Combined chronic toxicity/carcinogenicity study in mice, study ID 37 and rat, study ID 39) and 416 (Two-generation reproduction toxicity test in rats, study ID 40a and b).

Consequently, RMS is in the opinion that sufficiency may be discussed. See Table 106 for details on the studies included to assess T-adversity (based on thyroid histopathology).

Table 161: Overview over selected parameters investigated and missing parameters in the studies recommended.

Test guideline	OECD TG 407 study ID 28 and 29	OECD TG 408 study ID 30, 31, 32 and 33	OECD TG 409 and/or the one-year dog study study ID 34b	OECD TG 451-3 study ID 37, 38, 39	OECD TG 416 (a) study ID 40a and 40b
Parameter Indicative of T-mediated adversity	X: recommended investigated in TG Investigated in studies				
Colloid area (thyroid histopathology)	X Not measured				
Follicular cell height (thyroid histopathology)	X Not measured				X Not measured
HDL/LDL ratio(c)		X Not measured	X Not measured		
Liver weight(c)	X Yes	X Yes	X Yes	X Not measured	X Measured only in F1 and F2 in study ID 40a, not measured in in study ID 40b.
Thyroid histopathology	X Yes	X Only in study ID 30 and 31, not in study ID 32, 33, 35	X Yes	X Yes	x (optional) Only F1 in study ID 40a, not measured in in study ID 40b.
Thyroid weight	x (optional) Not measured	X Not measured	X Yes, but unclear whether parathyroids were weighed together with thyroids	X Yes	X Not measured

While there was no consistent observable T-mediated adversity in the included studies, some parameters sensitive to, but not diagnostic of, EATS were observed on adrenal in rats (atrophy and increased weight at 500 mg/kg/bw/day) and dogs (increased weight at 110 mg/kg bw/day, as well as anomalies in rat and rabbit. The data also showed an overall evidence of target organ systemic toxicity for kidney and liver whereas spleen and thymus were considered not sufficiently investigated. There was overall evidence of systemic toxicity. MTD ≥500 mg/kg bw (M), ≥500 mg/kg bw (F).

Table 162: Overview studies included to assess T-adversity (based on thyroid histopathology)

Study principle	Study ID Matrix	Species	Doses tested in mg/kg bw/day	Duration of exposure	Acceptance for the ED assessment

Repeated dose 28-days	28	Rat	0; 20/100; 100/500; 500/1000	28 days	Study considered supportive only (as dose levels were increased on day 8 of treatment)
Repeated dose 28-days	29a and 29b	Rat	0; 100; 500	28 days	Study considered as supportive only, due to the fact that only two dose levels were tested, and because of the deficiencies in dose level selection (toxicity already at the low dose, excessive toxicity at the high dose)
Repeated dose 90-days	30	Rat	In F : 0; 2.1; 20.7; 208.6 In M : 0; 2; 19.4; 202.3	90 days	Study accepted
Repeated dose 90-days	31	Rat	In F : 0; 0.78; 2.14; 7.27 In M : 0; 0.77; 2.12; 7.07	90 days	Study accepted
Repeated dose 90-days	34a	Dog	In F : 0; 3.8; 19.4; 137 In M : 0; 3.4; 18.2; 132	90 days	Study accepted
Carcinogenicity	38	Mouse	In F : 0; 3.5; 28.2; 221.5 In M : 0; 2.7; 21.7; 177.7	80 weeks	Study accepted
Carcinogenicity	39	Rat	In F : 0; 0.2; 2.9; 5.7; 11.9 In M : 0; 0.2; 2.7; 5; 10.4	116/117 weeks	Study concidered supportive only (as the selected dose levels were too low to produce significant toxicological effects
Two-generation reproduction toxicity test	40a	Rat	In F : 0; 5.9; 29.9; 153 In M : 0; 6; 29.7; 156	110 days	Study considered supportive only, as dose levels were considered too low (based on weight loss in the rats not consistently exceeding 10% of their body weight)

Table 163: WoE for T-mediated endocrine activity

- **Overall conclusion: Indication of endocrine activity (based on increased UDP-GT), but not sufficiently investigated.**

- **In one *in vivo* mechanistic study (open literature study, ID 49, 1985) marked liver enlargement in rats and mice at 80 mg/kg bw/day and higher (dose-dependent) and a pronounced induction in the activity of several hepatic xenobiotic metabolizing enzymes (uridine diphosphate [UDP]-glucuronyl transferase) was observed. Increased UDP-GT may be indicative of T-mediated endocrine activity.**

- **Evidence for TR-mediated antagonistic activity *in vitro*, (Penconazole was active in one of these assays (TOX21_TR_LUC_GH3_Antagonist); however, the viability readout was also active and interference with cytotoxicity cannot be excluded) (study ID 22). As only one single assay was tested to determine the potential of penconazole to interact with the TR as an antagonist, the result should be interpreted with caution.**

- **ToxCast TSHR showed no TSHR-mediated activity (study ID 24, 25, 26).**

The overall dataset is considered limited with regard to investigation of T-mediated endocrine activity. As described in the previous section, the included mammalian studies have several limitations, and they do not follow current guidelines. There is no measurement of T3, T4 or TSH levels in the studies included. These hormone levels are recommended investigated in TG 407 (relevant for study ID 28,29), 408 (relevant for study ID 30,31,32,33) and 409 and/or the one-year dog study (relevant for study ID 34b). However, according to the" Technical report on the outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology" (EFSA supporting publication 2020:EN-1837, page 7, doi:10.2903/sp.efsa.2020.EN-1837), EFSA clarified that in the old versions of the OECD TGs the measurement of thyroid hormones was optional. Therefore, in these cases, the lack of THs measurement cannot be used to conclude that the dataset for adversity is not complete. A level 3 *in vivo* mechanistic study (Study ID 49, [redacted] (1985), K-CA 5.8.2/02) is considered by RMS to provide information indicative of T-mediated endocrine activity.

2.10.2.1.3 Initial analysis of the evidence and identification of relevant scenario for the ED assessment of T-modality

Table 164: Selection of relevant scenario

Adversity based on T-mediated parameters	Positive mechanistic OECD CF level 2/3 Test	Scenario	Next step of the assessment	Scenario selected
No (sufficiently investigated)	Yes/No	1a	Conclude: ED criteria not met because there is not "**T-mediated**" adversity	
Yes (sufficiently investigated)	Yes/No	1b	Perform MoA analysis	
No (not sufficiently investigated)	Yes	2a (i)	Perform MoA analysis (additional information may be needed for the analysis)	**X**
No (not sufficiently investigated)	No (sufficiently investigated)	2a (ii)	Conclude: ED criteria not met because no **T-mediated endocrine activity** observed	
No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	
Yes (not sufficiently investigated)	Yes/No	2b	Perform MoA analysis	

2.10.2.1.4 MoA analysis for T-modality

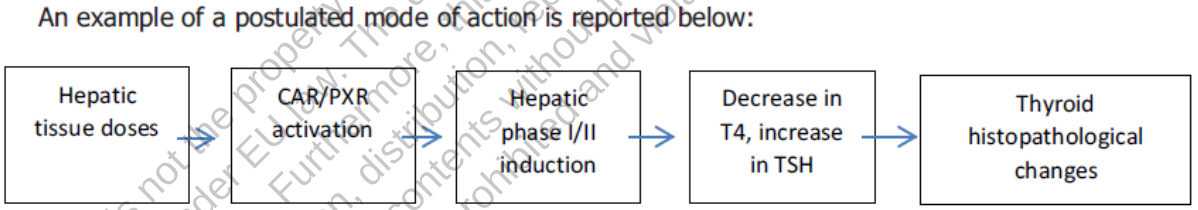
2.10.2.1.4.1 Postulate MoA

Table 165: Description of the postulated MoA

	Description	Supporting Evidence
MIE	CAR-PXR activation	Not investigated
KE1	Phase I /Phase II catabolic activation	Uridine diphosphate [UDP]-glucuronyl transferase (Phase II) was investigated in **one study** (short term 14 day) and was increased in **rat and mouse** hepatocytes (study ID 49 a and b, 1985).
KE2	Decrease serum concentration of T4	Not investigated
KE3	Increase in TSH	Not investigated
KE4	Increase in follicular cells proliferation	Not investigated
AO	Increased thyroid weight and incidences of minimal hypertrophy of the follicle epithelium	No consistent T-mediated adverse effects, but not sufficiently investigated. Increased thyroid weight and incidences of minimal hypertrophy of the follicle epithelium was observed in **one study** (short term 28 day) in **one species** (rat) and were considered adverse (study ID 29 a and b, 1991); however, these findings were not confirmed in other studies.

2.10.2.1.4.2 Further information to be generated to postulate MoA

The MoA suggested by RMS for penconazole follows the example in the EFSA-ECHA ED guidance document:



However, the empirical support of the postulated MoA is limited. No consistent endocrine adversity was observed, but as highlighted in section 2.10.2.1.2.1 relevant ED parameters are missing from the available studies. Although there were no consistent effects on thyroid, RMS is of the opinion that the dose levels in many of these studies are not optimal to address the examined endpoints and that higher dose levels may be needed to remove the concern arising from the available *in vivo* mechanistic data. Furthermore, no data are available on hormone levels, which is a KE in the postulated MoA.

In RMS's opinion, it is therefore recommended to investigate these parameters as described in Table 154 in a new study following the latest version of TG 407/408 and 416.

According to the ED guidance, three pieces of information are needed to investigate whether liver enzyme induction is responsible for the effects seen on thyroid histopathology and weight, as well as to determine whether the effect is likely to be human relevant or not:
1) A specifically designed *in vivo* toxicity study should be considered to measure TSH, T3 and T4 and, where possible, additional data on liver enzyme induction (e.g. measurement of UDPGT) should be included.
2) Comparative studies of enzyme activity induced by the test substance in liver *in vitro* systems should be measured in both the relevant test species (e.g. rat, mouse and dog) and humans.

3) The presence of other possible thyroid-disrupting modes of action such as interference with TH synthesis should also be excluded, e.g. by evaluating *in vitro* the potential for inhibition of the sodium–iodide symporter (NIS) and thyroid peroxidase (TPO).

RMS suggests that these pieces of information is investigated if adversity or activity is confirmed in a new study and if liver enzyme induction is found potentially responsible for the effects.

If changes in circulating THs is observed and human relevance cannot be clearly excluded as a result of these assays, a thyroid assessment study conducted in the foetus and pups in line with the US EPA, Office of Pesticide Programs, Health Effects Division, Washington (DC) is recommended. Available online: https://www.epa.gov/sites/production/files/2015-06/documents/thyroid_guidance_assay.pdf .

According to the ECHA/EFSA-ED GD, to appropriately investigate thyroid concerns, existing test protocols need to be modified. When considering such modifications, the recommendations on how to investigate thyroid effects in rodent models from the American Thyroid Association should be considered ([redacted] et al., 2014).

In addition, the following points should be considered and reported in the study report:
- The methodology for sampling and the analytical method to evaluate the thyroid hormones and TSH.
- Laboratory documentation of the method validation with inclusion of the LOD for foetus and pups.
- Considering the inclusion of a positive control.
- Control of iodine content in diet (should not be exceeding 5 µg/kg food, which is the rodent daily need).
- Select appropriate dose range (e.g. highest dose from the rat studies with thyroid follicular hyperplasia and/or above the MTD of 500 mg/kg bw/day).

2.10.2.1.4.3 Empirical support of the postulated MoA

Not applicable considering the limited data available (see Table 165:).

2.10.2.1.4.4 Empirical support of the postulated MoA

Not applicable considering the limited data available (see Table 165:).

2.10.2.1.5 Conclusion of the assessment of T-modality

Overall, the WoE indicates that T-mediated adversity was not observed for penconazole. However, the dataset for the assessment of T-mediated adversity is not considered sufficient, and the available dataset for endocrine activity was positive for the T-modality. Consequently, a complete dataset is needed to investigate adversity e.g., that OECD TG 416 (latest version) and 407/408 should be conducted. A complete dataset from these studies would address the concern arising from the positive outcome of the *in vivo* mechanistic study. Furthermore, the execution of the endpoints in a single experimental set is expected to minimize the uncertainties associated with comparing endpoints between different study designs and uncertainties associated with the study design. The proposed MoA also needs further investigations if adversity or activity is confirmed in a new study and if liver enzyme induction is found potentially responsible for the effects. Also, if changes in circulating THs is observed and human relevance cannot be clearly excluded as a result of these assays, a thyroid assessment study conducted in the foetus and pups is recommended (as described above).

2.10.2.2 ED assessment for EAS-modalities

2.10.2.2.1 Have EAS-mediated parameters been sufficiently investigated?

Table 166: Have EAS-mediated parameters been sufficiently investigated?

	Sufficiently investigated
EAS-mediated parameters	No (to have the EAS-mediated adversity with regard to humans and mammals (as non-target organisms) sufficiently investigated, all the data requirements of the specific

	Regulations, must be fulfilled. This should include all the 'EAS-mediated' parameters foreseen to be investigated in an extended one-generation reproductive toxicity study (EOGRTS; OECD TG 443; with cohort 1a/1b including the mating of cohort 1b to produce the F2 generation (OECD, 2012b)) or a two-generation reproductive toxicity study (OECD TG 416; test protocol according to latest version of January 2001 (OECD, 2001) Studies following the recommended TG or similar design have been performed, but due to several deviations from current guidelines, a number of parameters indicative of EAS have not been investigated (see Table 162 for details).

2.10.2.2.2 Lines of evidence for adverse effects and endocrine activity related to EAS-modalities

Table 167: Lines of evidence for adverse effects and endocrine activity related to EAS-modalities

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
8	*In vitro* mechanistic	Estrogen receptor	human, breast, cell line	24	Hr	Uptake from the medium (*in vitro*)	32.1	µM	No effect	Non-GLP literature study acceptable as supplementary. Inactive ER binding assay: weak inducer of ER activation in T47Dluc cells (EC_{50} = 32.1 µM), but cytotoxic effect in T47D cells was evident in the same concentration range as the derived EC_{50} in T47Dluc cells	Positive, evidence for ER-mediated antagonistic activity *in vitro*	Overall evidence of AR and ER-mediated activity (antagonism), and effects (inhibition) on steroidogenesis activity *in vitro*.	**E**
9			bovine, uterus, tissue-based cell-free	18	Hr	Uptake from the medium (*in vitro*)	0	µM	No effect	ToxCast ER model: no ER binding			
10			human, cell-free	18	Hr	Uptake from the medium (*in vitro*)	0.21	µM	No effect	ToxCast ER model: no ER binding			
11			mouse, cell-free	18	Hr	Uptake from the medium (*in vitro*)	0	µM	No effect	ToxCast ER model: no ER binding			
12			human, kidney, cell line	24	Hr	Uptake from the medium (*in vitro*)	90.36	µM	No effect	ToxCast ER model: No ER-mediated agonistic activity			
13			human, kidney, cell line	24	Hr	Uptake from the medium (*in vitro*)	38.17	µM	Change	ToxCast ER model: ER-mediated antagonistic activity (only highest conc. above baseline, active)			
14			human, breast, cell line	22	Hr	Uptake from the medium (*in vitro*)	0	µM	No effect	ToxCast ER model: No ER-mediated agonistic activity			

15			human, breast, cell line	22	Hr	Uptake from the medium (*in vitro*)	66.37	µM	Change	ToxCast ER model: ER-mediated antagonistic activity (less than 50% efficacy)		
2		Androgen receptor	human, breast, cell line	24	Hr	Uptake from the medium (*in vitro*)	17.1	µM	Decrease	Non-GLP literature study acceptable as supplementary. Inhibition of testosterone-induced AR activation in a concentration-dependent manner (IC_{50} = 17.1 µM)	Positive, evidence for AR-mediated antagonistic activity *in vitro*	**A**
7			yeast	2	Hr	Uptake from the medium (*in vitro*)	18.28	µM	Change	AR-mediated antagonistic effects: IC_{50} = 18.3 µM (literature study not reliable as the publication has several deficiencies)		
16			human, kidney, cell line	24	Hr	Uptake from the medium (*in vitro*)	0	µM	No effect	ToxCast AR model: No AR-mediated agonistic activity		
17			human, kidney, cell line	24	Hr	Uptake from the medium (*in vitro*)	38.35	µM	Change	ToxCast AR model: AR-mediated antagonistic activity (assay was near or in the cytotoxicity range)		
18			human, breast, cell line	24	Hr	Uptake from the medium (*in vitro*)	0	µM	No effect	ToxCast AR model: No AR-mediated agonistic activity		
19			human, breast, cell line	24	Hr	Uptake from the medium (*in vitro*)	39	µM	Change	ToxCast AR model: AR-mediated antagonistic activity		
20			human, breast, cell line	24	Hr	Uptake from the medium (*in vitro*)	58.77	µM	Change	ToxCast AR model: AR-mediated antagonistic activity		
45		Estradiol synthesis	human, adrenal corticocarcinoma, cell line	48	Hours	Uptake from the medium (*in vitro*)	0.1	other	Decrease	Inhibition of estradiol synthesis (H295R steroidogenesis assay)	Positive, evidence of effects on steroidogenesis *in vitro* (decreased estradiol synthesis)	**S**

45			human, adrenal corticocarcinoma, cell line	48	Hours	Uptake from the medium (*in vitro*)	3160	other	Decrease	Inhibition of estradiol synthesis (H295R steroidogenesis assay)				
2		Testosterone level (*in vitro*)	mouse, leydig, cell line	48	Hr	Uptake from the medium (*in vitro*)		µM	No effect	Non-GLP literature study acceptable as supplementary. No inhibition of Leydig cell testosterone excretion in MA-10 cells	Positive, evidence of effects on steroidogenesis *in vitro* (decreased testosteronel synthesis)			
45		Testosterone synthesis	human, adrenal corticocarcinoma, cell line	48	Hours	Uptake from the medium (*in vitro*)	0.1	other	Decrease	Inhibition of testosterone synthesis (H295R steroidogenesis assay)				
45			human, adrenal corticocarcinoma, cell line	48	Hours	Uptake from the medium (*in vitro*)	3160	other	Decrease	Inhibition of testosterone synthesis (H295R steroidogenesis assay)				
4		CYP19	human, adrenal corticocarcinoma, cell line	24	Hr	Uptake from the medium (*in vitro*)	20	µM	Change	Non-GLP literature study acceptable as supplementary. Inhibition of CYP19: *in vitro* weak competitive aromatase inhibition in H295R cells (IC_{50} = 20 µM)	Positive, evidence for aromatase inhibition *in vitro*			
5			n/a			[Not in list]	0.85	µM	Change	Non-GLP literature study acceptable as supplementary. Inhibition of CYP19: *in vitro* aromatase inhibition using dibenzylfluorescein as substrate (IC_{50} = 0.85 µM)				
6			n/a			[Not in list]	47	µM	Change	Non-GLP literature study acceptable as supplementary. Inhibition of CYP19: *in vitro* weak aromatase inhibition, LC-MS/MS method using testosterone as substrate (IC_{50} = 47 µM)				
27			human, breast, cell line	24	Hr	Uptake from the medium (*in vitro*)	12.32	µM	Change	ToxCast Steroidogenesis model: inhibition of CYP19				
38	EATS-mediated	Cervix histopathology	mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on cervix histopathology up to highest dose tested 221.5 mg/kg bw (carcinogenicity study)	Negative, no effect on oviduct histopathology	Overall negative, no evidence for a consistent		**E, A, S**

40b		Coagulating gland histopathology	rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect on coagulating gland histopathology up to highest dose tested 211 mg/kg bw/day in F0 adults	Negative, no effect on coagulating gland histopathology	pattern of endocrine adversity. However, the EAS-modality is not sufficiently investigated
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect on coagulating gland histopathology up to highest dose tested 211 mg/kg bw/day in F1 adults		
40b			rat	21	Days	Oral		mg/kg bw/day	No effect	No effect on coagulating gland histopathology up to highest dose tested 211 mg/kg bw/ day in 10 randomly selected F1 and F2 weanlings		
28		Epididymis histopathology	rat	28	Days	Oral		mg/kg bw/day	No effect	No effect on epididymides histopathology up to highest dose tested 1000 mg/kg bw/day. Study acceptable as supplementary as dose levels were increased on day 8 of treatment. Does not fulfil requirements of OECD TG 407	Negative, no consistent effects on epididymides. Effects in dogs were not considered adverse: 90 days exposure - Change in the epididymis (4/4 animals) at 132 mg/kg bw/day, in the presence of severe systemic toxicity (> MTD: extreme body weight loss and liver toxicity). 12 months exposure - no effects observed at 108 mg/kg bw/day (top dose >MTD, 132 mg/kg bw/day, was reduced during week 20; top dose animals then	
31			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on epididymides histopathology up to highest dose tested 7.07 mg/kg bw/day; considered supportive only as several ED parameters are missing including; epididymis, prostate + seminal vesicles with coagulating glands as a whole complex were not weighed and no histopathological examination was conducted on the coagulating glands. Does not fulfil requirements of OECD TG 408		
34a			Dog	90	Days	Oral	132	mg/kg bw/day	Change	Cellular debris in 4/4 top-dose males. Absence of spermatozoa in the epididymis containing cellular debris were related to the testis findings. Observed in the presence of significant systemic toxicity; decreased body weight and body weight gain associated with drastically reduced food intake. Study not conducted under GLP/Officially recognised testing facilities (no formal GLP statement provided, but a quality assurance statement)		
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on epididymis histopathology up to highest dose tested 108 mg/kg bw/day. Study not conducted under GLP/Officially recognised testing facilities (no formal GLP statement provided, but a quality assurance statement)		

35			mouse	90	Days	Oral		ppm	No effect	No effect on epididymis histopathology (only examined in control and high dose groups, 5000 ppm); study considered supportive due to deviations from the test guideline. The study was conducted as a preliminary carcinogenicity study and was not intended to comply with any regulatory guidelines.	gained more weight for the remainder of the treatment period as the other groups, including controls, while overall BW gain was reduced (44%). Decrease in epididymis weight in mouse not considered adverse (no effect observed in top dose males)		
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on epididymis histopathology up to highest dose tested 10.4 mg/kg bw/day. Study acceptable as supplementary as selected dose levels were too low to produce significant toxicological effects. Does not fulfil OECD TG 453			
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect in F0 males on epididymis histopathology up to highest dose tested 156 mg/kg bw/day. Study acceptable as supplementary as dose levels were considered too low and due to major deviations from current guideline OECD TG 416. Epididymis histopathology was only examined in F0 males.			
40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect in F0 males on epididymis histopathology up to highest dose tested 211 mg/kg bw/day. Study acceptable as supplementary due to low dosing and major deviations from guideline OECD TG 416; dosing was continued for 9 weeks only for both sexes in F0 (it should be continued for at least 10 weeks before the mating period), and was continued in both sexes for 20 days during mating period (it should have been 14 days only)			
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect in F1 adults on epididymis histopathology up to highest dose tested 211 mg/kg bw/day. Study acceptable as supplementary due to low dosing and major deviations from guideline OECD TG 416; dosing was continued for 9 weeks only for both sexes in F0 (it should be continued for at least 10 weeks before the mating period), and was continued in both sexes for 20 days during mating period (it should have been 14 days only)			
35		Epididymis weight	mouse	90	Days	Oral	3000	ppm	Decrease	Decrease in absolute weight (21%) and adjusted epididymis weight (22%) in the 3000 ppm group. No effect in the top dose group (5000 ppm); The lower epididymis weights in the study are considered to reflect the marked BW effects in the animals. Study considered supportive due to deviations from the test guideline. The study was conducted as a preliminary			

									carcinogenicity study and was not intended to comply with any regulatory guidelines			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on epididymes weight up to highest dose tested 177.7 mg/kg bw/day		
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on epididymis weight up to highest dose tested 156 mg/kg bw/day, measured in F0 males only		
28		Mammary gland histopathology (female)	rat	28	Days	Oral		mg/kg bw/day	No effect	No effect on mammary area histopathology up to highest dose tested 1000 mg/kg bw/day	Negative, no consistent effects on mammary gland histopathology	
31			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on mammary area histopathology up to highest dose tested 7.27 mg/kg bw/day. Study acceptable as supplementary. Does not fulfil requirements of OECD TG 408		
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on mammary area histopathology up to highest dose tested 137 mg/kg bw/day		
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on mammary area histopathology up to highest dose tested 110 mg/kg bw/day		
37			mouse	107	Weeks	Oral		ppm	No effect	No effect on mammary gland histopathology up to highest dose tested 300 ppm, corresponding to 35.7 mg/kg bw/day for females. Study acceptable as supplementary due to the selected doses that were too low to reveal any adverse effect on the examined endpoints. Does not fulfil OECD TG 453		
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on mammary gland histopathology up to highest dose tested 221.5 mg/kg bw/day		

39			rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on mammary gland histopathology up to highest dose tested 11.9 mg/kg bw/day. Study acceptable as supplementary as the selected dose levels were too low to produce significant toxicological effects. Does not fulfil OECD TG 453			
31		Mammary gland histopathology (male)	rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on mammary area histopathology up to highest dose tested 7.07 mg/kg bw/day. Study acceptable as supplementary. Does not fulfil requirements of OECD TG 408			
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on mammary area histopathology up to highest dose tested 132 mg/kg bw/day			
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on mammary area histopathology up to highest dose tested 108 mg/kg bw/day			
37			mouse	106	Weeks	Oral		ppm	No effect	No effect on mammary gland histopathology up to highest dose tested 300 ppm, corresponding to 40.8 mg/kg bw/day for males. Study acceptable as supplementary due to the selected doses that were too low to reveal any adverse effect on the examined endpoints. Does not fulfil OECD TG 453.			
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on mammary gland histopathology up to highest dose tested 10.4 mg/kg bw/day. Study acceptable as supplementary as the selected dose levels were too low to produce significant toxicological effects. Does not fulfil OECD TG 453			
28		Ovary histopathology	rat	28	Days	Oral		mg/kg bw/day	No effect	No effect on ovary histopathology up to highest dose tested 1000 mg/kg bw/day	Negative, no consistent effects on ovaries		
31			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on ovary histopathology up to highest dose tested 7.27 mg/kg bw/day. Study acceptable as supplementary. Does not fulfil requirements of OECD TG 408			
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on ovary histopathology up to highest dose tested 137 mg/kg bw/day			

34b		Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on ovary histopathology up to highest dose tested 110 mg/kg bw/day		
35		mouse	90	Days	Oral		ppm	No effect	No effect on ovary histopathology (examined in control and high dose group at 5000 ppm only). Study considered supportive due to deviations from the test guideline. The study was conducted as a preliminary carcinogenicity study and was not intended to comply with any regulatory guidelines.		
37		mouse	107	Weeks	Oral		ppm	No effect	No effect on ovary histopathology up to highest dose tested 300 ppm, corresponding to 35.7 mg/kg bw/day for females. Study acceptable as supplementary due to the selected doses that were too low to reveal any adverse effect on the examined endpoints. Does not fulfil OECD TG 453		
38		mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on ovary histopathology up to highest dose tested 221.5 mg/kg bw/day		
39		rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on ovary histopathology up to highest dose tested 11.9 mg/kg bw/day. Study acceptable as supplementary as the selected dose levels were too low to produce significant toxicological effects. Does not fulfil OECD TG 453		
40a		rat	110	days	Oral		mg/kg bw/day	No effect	No effect on ovary histopathology up to highest dose tested 153 mg/kg bw/day in F1 adults		
40b		rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect on ovary histopathology up to highest dose tested 225 mg/kg bw/day in F0 adults. Study acceptable as supplementary due to low dosing and major deviations from guideline OECD TG 416; dosing was continued for 9 weeks only for both sexes in F0 (it should be continued for at least 10 weeks before the mating period), and was continued in both sexes for 20 days during mating period (it should have been 14 days only)		
40b		rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect on ovary histopathology up to highest dose tested 225 mg/kg bw/day in F1 adults. Study acceptable as supplementary due to low dosing and major deviations from guideline OECD TG 416;		

									dosing was continued for 9 weeks only for both sexes in F0 (it should be continued for at least 10 weeks before the mating period), and was continued in both sexes for 20 days during mating period (it should have been 14 days only)	
40b			rat	21	Days	Oral		mg/kg bw/day	No effect	No effect on ovary histopathology up to highest dose tested 225 mg/kg bw/day in 10 randomly selected F1 and F2 weanlings
31		Ovary weight	rat	90	Days	Oral	0.78	mg/kg bw/day	Decrease	Decrease at 0.78 mg/kg bw (Relative ovary weights were significantly lower in low dose and mid dose females (-13%), while the top dose at 7.27 mg/kg bw/day was not significantly reduced (-11%). The reduced weights were within the range in the available limited HCD.)
32			rat	90	Days	Oral	2400	ppm	Increase	Significant increase in relative ovary weight (17%) in top dose group only at 2400 ppm observed in the presence of reduced BW (10%), BW gain (15%) and FC (9%), increased liver weight (29%) and hypertrophy and hepatocellular degeneration (NOAEL is 300 ppm corresponding to 28.3 (females) mg/kg bw/day)
33			mouse	90	Days	Oral		ppm	No effect	No effect on ovary weight up to highest dose tested 2400 ppm
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on ovary weight up to highest dose tested 137 mg/kg bw/day; variations in ovary weight are considered unrelated to treatment and mostly due to high (week 13) concurrent control
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on ovary weight highest dose tested 110 mg/kg bw/day. Variations in ovary weight could be attributed to low concurrent control values and therefore not considered treatment related (increase abs weight low dose: 13%, mid dose 85%, high dose 50%; increase relative weight low dose 11%, mid dose 86%, high dose 68%)
37			mouse	107	Weeks	Oral		ppm	No effect	No effect on ovary weight up to highest dose tested 300 ppm

38		mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on ovary weight up to highest dose tested 221.5 mg/kg bw/day		
39		rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on ovary weight were observed in females up to highest dose tested 11.9 mg/kg bw/day		
40a		rat	35	days	Oral		mg/kg bw/day	No effect	Highest dose tested 153 mg/kg bw/day. Absolute ovary weights were non-significantly increased (+17%) and relative ovary weights were significantly increased (+38%) in F1 offspring. It should be noted that only five/sex/group F1 and F2 weanlings were necropsied and that pup weight development in top dose F1 weanlings was lower compared to control. In mid dose F1 weanlings, absolute and relative ovary weights increased non-significantly +17% and +25%, respectively, while pup weight development was not affected		
40a		rat	110	days	Oral		mg/kg bw/day	No effect	No effect on ovary weight up to highest dose tested 153 mg/kg bw/day. Increase in relative ovary weight in F1 adults (relative +16%, absolute +9.1%); however, the body weight was lower in top dose adults (-6% at termination, non-significant reduction)		
40a		rat	35	days	Oral		mg/kg bw/day	No effect	No effect on ovary weight up to highest dose tested 153 mg/kg bw/day in five/sex/group randomly selected F2 weanlings		
40b		rat	19	Weeks	Oral		mg/kg bw/day	No effect	In parent F0 (exposure 19 weeks) and F1 animals (exposure 25 weeks) statistically significant decreases in mean body weights in high dose females (225 mg/kg bw/day) led to a corresponding increase in relative ovary weights, but absolute ovary weights were not affected.		
40b		rat	25	Weeks	Oral		mg/kg bw/day	No effect	In parent F0 (exposure 19 weeks) and F1 animals (exposure 25 weeks) statistically significant decreases in mean body weights in high dose females (225 mg/kg bw/day) led to a corresponding increase in relative ovary weights, but absolute ovary weights were not affected.		

40b			rat	21	Days	Oral		mg/kg bw/day	No effect	No effect on ovary weight up to highest dose tested 225 mg/kg bw/day in 10 randomly selected F1 and F2 weanlings			
31		Oviduct histopathology	rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on oviduct histopathology up to highest dose tested 7.27 mg/kg bw/day	Negative, no effect on oviduct histopathology		
28		Prostate histopathology (with seminal vesicles and coagulating glands) Prostate weight	rat	28	Days	Oral		mg/kg bw/day	No effect	No effect on prostate histopathology (with seminal vesicles and coagulating glands) at the highest dose of 1000 mg/kg bw/day. Epididymis, prostate + seminal vesicles with coagulating glands and heart were not weighed in the study	Negative, no consistent treatment-related effect on prostate histopathology and prostate weight		
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on prostate histopathology up to highest dose tested 132 mg/kg bw/day (not stated if it included seminal vesicles and coagulating glands)			
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on prostate histopathology up to highest dose tested 108 mg/kg bw/day (not stated if it included seminal vesicles and coagulating glands)			
37			mouse	106	Weeks	Oral		ppm	No effect	No effect on prostate histopathology up to highest dose tested 300 ppm			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on prostate histopathology up to highest dose tested 177.7 mg/kg bw/day; histopathology did not incl. coagulating glands			
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on prostate histopathology up to highest dose tested 10.4 mg/kg bw/day; histopathology did not incl. coagulating glands (the selected dose levels in the study were too low to produce significant toxicological effects)			
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on prostate histopathology up to highest dose tested 156 mg/kg bw/day (only examined in F1 adults, seminal vesicles and coagulating glands not included)			

40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect on prostate histopathology up to highest dose tested 211 mg/kg bw/day in F0 adults		
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect on prostate histopathology up to highest dose tested 211 mg/kg bw/day in F1 adults		
40b			rat	21	Days	Oral		mg/kg bw/day	No effect	No effect on prostate histopathology up to highest dose tested 211 mg/kg bw/day in 10 randomly selected F1 and F2 weanlings		
37			mouse	106	Weeks	Oral	75	ppm	Increase	At terminal sacrifice (wk 106), prostate weights were dose-dependently increased in males at 75, 150, and 300 ppm (relative increase +23%, 26% and 39% at 75, 150 and 300 ppm, respectively). However, the NOAEL is considered to be 300 ppm, corresponding to 40.8 mg/kg bw/day for males and the study is acceptable as supplementary due to the selected doses that were too low to reveal any adverse effect on the examined endpoints.		
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on prostate weight up to highest dose tested 177.7 mg/kg bw/day		
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on prostate weight up to highest dose tested 10.4 mg/kg bw/day		
37		Seminal vesicles histopathology	mouse	106	Weeks	Oral		ppm	No effect	No effect on seminal vesicles histopathology up to highest dose tested 300 ppm	No effect on seminal vesicles histopathology	
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on seminal vesicles histopathology up to highest dose tested 177.7 mg/kg bw/day		
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on seminal vesicles histopathology up to highest dose tested 10.4 mg/kg bw/day		

40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect on seminal vesicles histopathology up to highest dose tested 211 mg/kg bw/day in F0 adults		
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect on seminal vesicles histopathology up to highest dose tested 211 mg/kg bw/day in F1 adults		
40b			rat	21	Days	Oral		mg/kg bw/day	No effect	No effect on seminal vesicles histopathology up to highest dose tested 211 mg/kg bw/day in 10 randomly selected F1 and F2 weanlings		
1		Testis histopathology	rat	9	Months	Oral	50	mg/kg bw/day	Change	Necrobiotic changes of seminiferous tubules. NOTE: Literature study considered not acceptable and not reliable	Indications of testicular toxicity in dogs at the highest dose tested; however, these effects may be considered to be secondary to systemic toxicity; reduced spermatogenesis, reduced testis weight (90 days and 12 months exposure) and tubular atrophy (12 months exposure) observed at the highest dose levels. No consistent treatment-related effects on testis in rats and mice.	
28			rat	28	Days	Oral		mg/kg bw/day	No effect	No effect on testis histopathology up to highest dose tested 1000 mg/kg bw/day		
31			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on testis histopathology up to 7.27 mg/kg bw/day		
34a			Dog	90	Days	Oral	132	mg/kg bw/day	Change	Reduced spermatogenesis in 4/4 top dose males at 132 mg/kg bw/day (unilateral in one dog). Observed in the presence of significant systemic toxicity; decreased body weight and body weight gain associated with drastically reduced food intake. Non-GLP study (no formal GLP statement provided, but a quality assurance statement)		
34b			Dog	12	Months	Oral	108	mg/kg bw/day	Change	Reduced spermatogenesis in 2/4 top dose males (unilateral in one dog) characterised by tubular atrophy of the seminiferous epithelium associated with formation of giant cells. Tubular atrophy was also noted in recovery animals (2/2) sacrificed week 57, while spermatogenesis was not affected after the recovery period (four weeks). Animals were fed diets containing 0; 3.4; 18.2; 132 mg/kg bw/day of test material for 19 weeks. During week 20, the highest dose level was reduced to 108 mg/kg bw/day due to		

									excessive reduction in food consumption and body weight gain (body weight loss) of the animals in that group. After dose reduction, top dose animals then gained more weight for the remainder of the treatment period as the other groups, including controls, while overall BW gain was reduced (-44%). Non-GLP study (no formal GLP statement provided, but a quality assurance statement)			
35			mouse	90	Days	Oral		ppm	No effect	No effect on testis histopathology, examined in control and high dose groups (5000 ppm) only		
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on testis histopathology up to highest dose tested 177.7 mg/kg bw/day		
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on testis histopathology up to highest dose tested 10.4 mg/kg bw/day		
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on testis histopathology in F0 adult up to highest dose tested 156 mg/kg bw/day		
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on testis histopathology in F1 adult up to highest dose tested 156 mg/kg bw/day		
40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect on testis histopathology in F0 adult up to highest dose tested 211 mg/kg bw/day		
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect on testis histopathology in F1 adult up to highest dose tested 211 mg/kg bw/day		
40b			rat	21	Days	Oral		mg/kg bw/day	No effect	No effect on testis histopathology up to highest dose tested 211 mg/kg bw/day in 10 randomly selected F1 and F2 weanlings		

1		Testis weight	rat	9	Months	Oral	50	mg/kg bw/day	Decrease	Significant decrease compared to the control group at dose levels 50 and 100 mg/kg bw/day. NOTE: Literature study considered not acceptable and not reliable			
30			rat	90	Days	Oral	202.3	mg/kg bw/day	Increase	Increase in relative (+10%) and absolute (+5.3g) testis weight at top-dose only at 202 mg/kg bw/day. Changes in absolute organ weight were within a limited historical control range and no histopathological alterations were observed, while increase in relative testis weight exceeded the limited HCD. Study acceptable as supplementary due to deviations from the test guideline currently in place			
31			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect; however absolute weight significantly increased in the top dose males 7.07 mg/kg bw/day (relative increase 5% both in low dose and high dose males)			
33			mouse	90	Days	Oral		ppm	No effect	No effect on testis weight up to highest dose tested 2400 ppm			
34a			Dog	90	Days	Oral	132	mg/kg bw/day	Decrease	Testis weights were reduced at the top dose level 132 mg/kg bw/day (abs: -47%, rel: -27%). Observed in the presence of significant systemic toxicity; decreased body weight and body weight gain associated with drastically reduced food intake. Non-GLP study (no formal GLP statement provided, but a quality assurance statement)			
34b			Dog	12	Months	Oral	108	mg/kg bw/day	Decrease	Testis weights were reduced at the top dose level 108 mg/kg bw/day (abs: -15%, rel: -9%). Testis weights were still low after a four-week recovery period (abs: -42%, rel -49%: 2 animals sacrificed week 57). Animals were fed diets containing 0; 3.4; 18.2; 132 mg/kg bw/day of test material for 19 weeks. During week 20, the highest dose level was reduced to 108 mg/kg bw/day due to excessive reduction in food consumption and body weight gain (body weight loss) of the animals in that group. Non-GLP study (no formal GLP statement provided, but a quality assurance statement)			

35			mouse	90	Days	Oral		ppm	No effect	No effect on testis weight up to highest dose tested 5000 ppm		
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on testis weight up to highest dose tested 177.7 mg/kg bw/day		
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on testis weight were observed in males up to highest dose tested 10.4 mg/kg bw/day		
40a			rat	110	days	Oral	156	mg/kg bw/day	Increase	A slightly higher testes weight was recorded in high dose F0 males (156 mg/kg bw/day; absolute increase +10.9%, relative increase +7.2%), but the weights were well within the range of available limited HCD ranges. The relative testes weights were not significantly affected		
40a			rat	110	days	Oral		mg/kg bw/day	No effect	Increase in relative testis weight in high dose adult F1 males was observed (156 mg/kg bw/day; absolute +2.6%, relative +12%), but lower body weight was also recorded in this group		
40a			rat	35	days	Oral		mg/kg bw/day	No effect	No effect on testis weight up to highest dose tested 156 mg/kg bw/day in five/sex/group randomly selected F1 and F2 weanlings		
40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect on testis weight up to highest dose tested 211 mg/kg bw/day in F0 adults		
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect on testis weight up to highest dose tested 211 mg/kg bw/day in F1 adults		
40b			rat	21	Days	Oral		mg/kg bw/day	No effect	No effect on testis weight up to highest dose tested 211 mg/kg bw/day in 10 randomly selected F1 and F2 weanlings		

28		Uterus histopathology (with cervix)	rat	28	Days	Oral		mg/kg bw/day	No effect	No effect on uterus histopathology with cervix up to highest dose tested 1000 mg/kg bw/day	Negative, no consistent treatment-related effects on uterus		
31			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on uterus histopathology (cervix was not examined) up to highest dose tested 7.07 mg/kg bw/day			
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on uterus histopathology (cervix was not examined) up to highest dose tested 137 mg/kg bw/day			
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on uterus histopathology (cervix was not examined) up to highest dose tested 110 mg/kg bw/day			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on uterus histopathology up to highest dose tested 221.5 mg/kg bw/day			
39			rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on uterus histopathology up to highest dose tested (cervix was not examined) up to 11.9 mg/kg bw/day			
40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect on uterus histopathology up to highest dose tested 225 mg/kg bw/day in F0 adults			
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect on uterus histopathology up to highest dose tested 225 mg/kg bw/day in F1 adults			
40b			rat	21	Days	Oral		mg/kg bw/day	No effect	No effect on uterus histopathology up to highest dose tested 225 mg/kg bw/day in 10 randomly selected F1 and F2 weanlings			
35		Uterus weight (with cervix)	mouse	90	Days	Oral		ppm	No effect	No effect on uterus weight up to highest dose tested 5000 ppm			

38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on uterus weight up to highest dose tested 221.5 mg/kg bw/day			
41a			rat	10	Days	Oral		mg/kg bw/day	No effect	No effect: Gravid uterus weights were recorded (it is not stated if it included the cervix) up to highest dose tested 300 mg/kg bw/day. Prenatal developmental toxicity study: it should be noted that the test chemical was administered from GD 6-15 only			
41b			rat	5	Days	Oral		mg/kg bw/day	No effect	No effect: Gravid uterus weights were recorded (it is not stated if it included the cervix) at any dose levels. Supplementary study to Prenatal developmental toxicity study 41a: treatment at 0 and 300 mg/kg bw/day (GD 6-15), and with 450 mg/kg bw/day (GD 10-14)			
42			rat	10	days	Oral	500	mg/kg bw/day	Decrease	Gravid uterus weights were 12% lower than concurrent controls in high dose females at 500 mg/kg bw/day (it is not stated if it included the cervix). Prenatal developmental toxicity study: it should be noted that the test chemical was administered from GD 6-15 only			
43			rabbit	14	days	Oral		mg/kg bw/day	No effect	No effect: Gravid uterus weights were weighted (it is not stated if it included the cervix) up to highest dose tested 150 mg/kg bw/day. Prenatal developmental toxicity study: it should be noted that the test chemical was administered from GD 6-18 only			
44			rabbit	13	days	Oral		mg/kg bw/day	No effect	No effect: Gravid uterus weights were weighted (it is not stated if it included the cervix) up to highest dose tested 200 mg/kg bw/day. Prenatal developmental toxicity study: it should be noted that the test chemical was administered from GD 7-19 only			
38		Vagina histopathology	mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on vagina histopathology up to highest dose tested 221.5 mg/kg bw/day	Negative, no consistent treatment-related effect on vagina		
39			rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on vagina histopathology up to highest dose tested at 11.9 mg/kg bw/day			

40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect on vagina histopathology up to highest dose tested at 225 mg/kg bw/day in F0 adults			
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect on vagina histopathology up to highest dose tested at 225 mg/kg bw/day in F1 adults			
40b			rat	21	Days	Oral		mg/kg bw/day	No effect	No effect on vagina histopathology up to highest dose tested at 225 mg/kg bw/day in 10 randomly selected F1 and F2 weanlings			
29a	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	rat	28	Days	Oral	500	mg/kg bw/day	Change	Cortical atrophy was noted in most top dose females (8/10*) *two females were sacrificed in moribund condition on day 3 (500 mg/kg bw/day). Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD; however, the observed effects are still considered treatment related	Indications of treatment-related adverse effects on adrenal, based on observed effects in rats (atrophy and increased weight at 500 mg/kg/bw/day) and dogs (increased weight at 110 mg/kg bw/day). Increased adrenals weight in mouse (significant trend at 75, 150 and 300 ppm) was in absence of a dose relationship and not associated with relevant histopathological changes.	Overall evidence of adverse effects sensitive to but not diagnostic of EATS based on effects on adrenal and anomalies in rat and rabbit, evidence of decreased litter/pup weight during development in rats (both 2-generation studies) and slightly reduced birth weights in rats (developmental toxicity studies), decreased number of	**E, A, S**
29b			rat	28	Days	Oral	500	mg/kg bw/day	Change	Cortical atrophy was noted in most top dose females (9/10*) *one female was sacrificed in moribund condition on day 2 (500 mg/kg bw/day). Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD; however, the observed effects are still considered treatment related			

31		rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology up to highest dose tested (7.07 mg/kg bw/day) in M.	live births in rats (in 2-generation study at 225 mg/kg bw/day and prenatal developmental toxicity study at 450 mg/kg bw/day) and effects on numbers of embryonic or foetal deaths and post implantation loss in rats and rabbits viable foetuses in rat and rabbit.	
31		rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology up to highest dose tested (7.27 mg/kg bw/day) in F.		
34a		Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology in male dogs up to highest dose tested 132 mg/kg bw/day		
34a		Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology in female dogs up to highest dose tested 137 mg/kg bw/day		
34b		Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology in male dogs up to highest dose tested 108 mg/kg bw/day		
34b		Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology in female dogs up to highest dose tested 110 mg/kg bw/day		
35		mouse	90	Days	Oral		ppm	No effect	No effect on adrenals histopathology in F (examined in control and high dose groups only).		
35		mouse	90	Days	Oral		ppm	No effect	No effect on adrenals histopathology in M (examined in control and high dose groups only).		
37		mouse	106	Weeks	Oral		ppm	No effect	No effect on adrenals histopathology up to highest dose tested (300 ppm).		
38		mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology up to highest dose tested (177.7 mg/kg bw/day) in M.		

38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology up to highest dose tested (221.5 mg/kg bw/day) in F.			
39			rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology. 1-year interim sacrifice: nodular hyperplasia was observed in the adrenal cortex of females treated with 2.9 mg/kg bw/day (19/79) and 5.7 mg/kg bw/day (12/80). However, in the absence of a dose-response relationship this was not attributed to treatment with penconazole.			
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology up to highest dose tested (10.4 mg/kg bw/day) in males.			
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on adrenals histopathology up to highest dose tested (156 mg/kg bw/day in M and 153 mg/kg/bw/day in F).			
28		Adrenals weight	rat	28	Days	Oral	500	mg/kg bw/day	Increase	Increased adrenal weights in males and females treated at 100/500 mg/kg/day and above.			
29a			rat	28	Days	Oral	500	mg/kg bw/day	Increase	Increase in absolute adrenal weight at 500 mg/kg bw/day. Relative adrenal weights – while higher than concurrent controls - were within the range of HCD in females and in males. Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD.			
29b			rat	28	Days	Oral	500	mg/kg bw/day	Increase	Increase in absolute adrenal weight at 500 mg/kg bw. Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500			

								mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD.			
31		rat	90	Days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested (7.07 mg/kg bw/day) in F.			
31		rat	90	Days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested (7.27 mg/kg bw/day) in M.			
32		rat	90	Days	Oral	2400	ppm	Increase	Significant increase in relative adrenals weight (15%) at top dose only (absence of a dose relationship).			
33		mouse	90	Days	Oral		ppm	No effect	No effect on adrenals weight up to highest dose tested (2400 ppm).			
34a		Dog	90	Days	Oral		mg/kg bw/day	No effect	Slight increase in relative adrenals weight at 132 mg/kg bw/day (top dose) due to low BW in top dose males at termination			
34a		Dog	90	Days	Oral	137	mg/kg bw/day	Increase	Increase in relative adrenals weight at 137 mg/kg bw/day (35%), but not absolute weight, due to low BW in top dose females at termination (-25%)			
34b		Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on adrenals weight up to highest dose tested 108 mg/kg bw/day; however, slight increase in top dose males mainly was noted due to lower body weights			
34b		Dog	12	Months	Oral	110	mg/kg bw/day	Increase	Absolute and relative adrenal weights were increased (abs:34%, rel: 54%) in top dose females (in absence of histopathological changes) and in presence of lower BW			

35			mouse	90	Days	Oral	3000	ppm	Increase	Adrenal weights adjusted for bodyweight were higher than control in females receiving 3000 ppm.				
35			mouse	90	Days	Oral		ppm	No effect	No effect on adrenal weight up to highest dose tested (5000 ppm).				
37			mouse	106	Weeks	Oral	150	ppm	Increase	A statistically significant trend was noted for increased absolute and adrenal weights at the terminal sacrifice in males, this was in absence of a dose relationship, not associated with relevant histopathological changes and the values were within the range of available HCD (relative increases; 75 ppm +10%, 150 ppm +13%, 300 ppm +3%).				
37			mouse	107	Weeks	Oral		ppm	No effect	Variations in adrenal weights achieving statistical significance (absolute changes only at 75 and 150 ppm) in females (decrease at terminal sacrifice) were in absence of a dose relationship. Relative change: 5 ppm -38%, 75 ppm -28%, 150 ppm -35%, 300 ppm -36%.				
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	Adrenal weight was unaffected by treatment up to highest dose tested (177.7 mg/kg bw/day) in M.				
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	Adrenal weight was unaffected by treatment up to highest dose tested (221.5 mg/kg bw/day) in F.				
39			rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on adrenals weight were observed up to highest dose tested (11.9 mg/kg bw/day) in females.				
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on adrenals weight were observed up to highest dose tested (10.4 mg/kg bw/day) in males.				
28		Brain weight	rat	28	Days	Oral		mg/kg bw/day	No effect	No effect on brain weight up to highest dose tested 1000 mg/kg bw/day	Negative, no consistent treatment-related			

29a			rat	28	Days	Oral		mg/kg bw/day	No effect	No effect on brain weight up to highest dose tested 500 mg/kg bw/day	effects on brain weight		
29b			rat	28	Days	Oral		mg/kg bw/day	No effect	No effect on brain weight up to highest dose tested 500 mg/kg bw/day			
35			mouse	90	Days	Oral	3000	ppm	Increase	Increase in adjusted brain weight in males (4.7%)			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on brain weight up to highest dose tested 177.7 mg/kg bw/day (males)			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on brain weight up to highest dose tested 221.5 mg/kg bw/day (females)			
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on brain weight were observed in males up to highest dose tested 10.4 mg/kg bw/day			
39			rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on brain weight were observed in females up to highest dose tested 11.9 mg/kg bw/day			
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on brain weight up to highest dose tested 153 mg/kg bw/day in F1 adults (F)			
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on brain weight up to highest dose tested 156 mg/kg bw/day in F1 adults (M)			
1		Fertility (mammals)	rat	9	Months	Oral	50	mg/kg bw/day	Decrease	Leydig cells were significantly decreased: NOTE: literature study considered not reliable	Negative, no consistent treatment-related effects on fertility		

1			rat	9	Months	Oral	50	mg/kg bw/day	Change	Ultrastructural investigation showed Sertoli; NOTE: literature study considered not reliable			
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on fertility in F0 adults up to highest dose tested 153 mg/kg bw/day			
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on fertility in F1 adults up to highest dose tested 153 mg/kg bw/day			
40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect on fertility in F0 adults up to highest dose tested 225 mg/kg bw/day			
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect on fertility in F1 adults up to highest dose tested 225 mg/kg bw/day			
43		Foetal development	rabbit	14	days	Oral		mg/kg bw/day	No effect	No effect on foetal development up to highest dose tested 150 mg/kg bw/day, except foetal visceral findings were observed; three cases of bilateral microphthalmia, two in combination of internal hydrocephalus at the top dose (2/125 foetus with internal hydrocephalus at 75 ppm). Developmental NOAEL is based on this effect. Test chemical only administered from GD 6-18 only (prenatal developmental toxicity study)	Negative, no effect on foetal development		
40a		Gestation length	rat	110	days	Oral	153	mg/kg bw/day	Increase	Gestation length was slightly, but significantly increased in top dose F0 females (Control: 21.1 days, 153 mg/kg bw/day: 21.8 days)	Negative (no effect was observed in study 40b, although the dose level was higher than in study 40a)		
40a			rat	110	days	Oral	153	mg/kg bw/day	Increase	The mean duration of pregnancy appeared to be slightly increased in high dose F1 females and exceeds the available limited HCD (control: 21.4 days, 153 mg/kg bw/day: 22.2 days) but variation of gestation length in individual animals did not exceed the concurrent control range in any treated group			

40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect, gestation length was similar to controls in all treated groups (F0 adults), highest dose 225 mg/kg bw/day		
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect, gestation length was similar to controls in all treated groups (F1 adults), highest dose 225 mg/kg bw/day		
40a		Litter size	rat	110	days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 153 mg/kg bw/day: while initial litter sizes were slightly smaller than controls at the top dose level in both generations, the litter sizes in all treated groups are well within the range of limited HCD	Negative, no consistent effect on litter size	
40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect in litter size up to highest dose tested 225 mg/kg bw/day in F0 adults: Litter size (all pups and live-born pups) was comparable to controls		
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect in litter size up to highest dose tested 225 mg/kg bw/day in F1 adults: Litter size (all pups and live-born pups) was comparable to controls		
41a			rat	10	Days	Oral		mg/kg bw/day	No effect	No effect in litter size up to highest dose tested 300 mg/kg bw/day. Penconazole technical were given GD 6-15 only		
40a		Litter/pup weight	rat	35	days	Oral	153	mg/kg bw/day	Decrease	Offspring F1 (females): Pup weight development was significantly reduced in top dose pups day 4-21 (-22.6%)	Evidence of decreased litter/pup weight during development in rats (both 2-generation studies) and slightly reduced birth weights in rats (developmental toxicity studies).	
40a			rat	35	days	Oral	156	mg/kg bw/day	Decrease	Offspring F1 (males): Pup weight development was reduced non-significantly in top dose pups day 4-21 (-15.9%)		
40b			rat	21	Days	Oral	211	mg/kg bw/day	Decrease	Pup body weight gain during lactation was reduced (statistically significant at day 21 pp) for both sexes in both F1 and F2 generations for the high dose group (Day 0-21 pp; F1 -8%, F2 -9%). Pup body weights at birth were similar to control for all treatment groups		

41a			rat	10	Days	Oral		mg/kg bw/day	No effect	No effect on litter/pup weight up to highest dose tested 300 mg/kg bw/day. Test chemical administered from GD 6-15 only		
41b			rat	5	Days	Oral	300	mg/kg bw/day	Decrease	Foetal body weight was slightly, but significantly reduced in both treatment groups (300 mg/kg bw/day: -4.5%, 450 mg/kg bw/day: -5.8%). Treatment at 0 and 300 mg/kg bw/day (GD 6-15), and with 450 mg/kg bw/day (GD 10-14)		
42			rat	10	days	Oral	500	mg/kg bw/day	Decrease	Foetal body weights were slightly reduced at 500 mg/kg bw/day (males -5.9%, females -3.1%). Exposure from GD 6-15 only		
44			rabbit	13	days	Oral		mg/kg bw/day	No effect	No effect on litter/pup weight up to highest dose tested 200 mg/kg bw/day. Test chemical administered from GD 7-19 only		
40a		Number of implantations, corpora lutea	rat	110	days	Oral		mg/kg bw/day	No effect	No effect on number of implantations up to highest dose tested 153 mg/kg bw/day in F0 adults. Corpora lutea was not recorded	Negative, no effect on number of implantations, corpora lutea	
40a			rat	110	days	Oral	153	mg/kg bw/day	Decrease	The number of implantation sites was slightly, but significantly lower in F1 high dose females (mean implantation sites per dam: control 15.9 and high dose 15.1), values of all treated groups were well within the range of available limited HCD. Corpora lutea was not recorded		
40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect on number of implantations up to highest dose tested 225 mg/kg bw/day in F0 adults. Corpora lutea was not recorded		
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect on number of implantations up to highest dose tested 225 mg/kg bw/day in F1 adults. Corpora lutea was not recorded		
41a			rat	10	Days	Oral		mg/kg bw/day	No effect	No effect on number of implantations up to highest dose tested 300 mg/kg bw/day. Test chemical administered from GD 6-15 only		

41b			rat	5	Days	Oral		mg/kg bw/day	No effect	No effect on number of implantations up to highest dose tested 450 mg/kg bw/day. Treatment at 0 and 300 mg/kg bw/day (GD 6-15), and with 450 mg/kg bw/day (GD 10-14)			
42			rat	10	days	Oral		mg/kg bw/day	No effect	No effect on number of implantations up to highest dose tested 500 mg/kg bw/day. Test chemical administered from GD 6-15 only			
43			rabbit	14	days	Oral		mg/kg bw/day	No effect	No effect on number of implantations up to highest dose tested 150 mg/kg bw/day. Test chemical administered from GD 6-18 only			
44			rabbit	13	days	Oral		mg/kg bw/day	No effect	No effect on number of implantations up to highest dose tested 200 mg/kg bw/day. Test chemical administered from GD 7-19 only			
40a		Number of live births	rat	35	days	Oral		mg/kg bw/day	No effect	No effect in F1 offspring up to highest dose tested 156 mg/kg bw/day, but for a number of litters, it was unclear whether the pups were born alive (e.g. died on lactation day 0), the % of (confirmed) liveborn pups were lower at the mid (F1, 43 pups uncertain) and high dose group (F1, 66 pups uncertain)	Evidence of decreased number of live births in rats (in 2-generation study at 225 mg/kg bw/day and prenatal developmental toxicity study at 450 mg/kg bw/day) and evidence of treatment-related effects on numbers of embryonic or foetal deaths and viable foetuses in rat and rabbit		
40a			rat	35	days	Oral		mg/kg bw/day	No effect	No effect in F2 offspring, but for a number of litters, it was unclear whether the pups were born alive (e.g. died on lactation day 0), the % of (confirmed) liveborn pups were lower at the high dose group (F2, 44 pups uncertain)			
40b			rat	25	Weeks	Oral	225	mg/kg bw/day	Decrease	In both generations, the mean number of dead pups at birth/pups that died until day 4 was slightly but not statistically higher at 225 mg/kg bw/day when compared with control. Mean number of stillborn pups was higher in high dose group in both generations (F1 control, 1 vs 11 stillborn in high dose; F2 control, 11 vs 24 stillborn in high dose)			
41b			rat	5	Days	Oral	450	mg/kg bw/day	Decrease	The number of dead foetuses was increased at 450 mg/kg bw/day (control group 1 dead foetus, 450 mg/kg bw/day 5 dead foetuses). Treatment at 0 and 300 mg/kg bw/day (GD 6-15), and with 450 mg/kg bw/day (GD 10-14)			

43			rabbit	14	days	Oral		mg/kg bw/day	No effect	No effect on number of live births up to highest dose tested 150 mg/kg bw/day. Test chemical administered from GD 6-18 only		
41a		Numbers of embryonic or foetal deaths and viable foetuses	rat	10	Days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 300 mg/kg bw/day. Test chemical administered from GD 6-15 only		
41b			rat	5	Days	Oral	450	mg/kg bw/day	Change	The number of dead foetuses was increased at 450 mg/kg bw/day (control group 1 dead foetus, 450 mg/kg bw/day 5 dead foetuses) while live births were comparable to respective control group. Treatment at 0 and 300 mg/kg bw/day (GD 6-15), and with 450 mg/kg bw/day (GD 10-14)		
42			rat	10	days	Oral	500	mg/kg bw/day	Change	A slightly lower number of life foetuses per dam (-16%) were reported at 500 mg/kg bw/day (below limited available HCD). Exposure from GD 6-15 only		
44			rabbit	13	days	Oral	200	mg/kg bw/day	Change	Live foetuses/litters were reduced compared to control (live foetuses/dam control: 6.9, live foetuses/dam high dose: 4.8). The numbers were within the range of HCD but exceeded the mean +/- SD and may be related to treatment. In addition, two dead foetuses were recorded in high dose females only. Test chemical administered from GD 7-19 only		
30		Pituitary histopathology	rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to top-dose 202.3 mg/kg bw/day in M.	Negative, no consistent treatment-related effects on pituitary. Observed effects on histopathology in rat were in absence of a dose relationship and within the HCD range, and the decrease in weight was transient.	
30			rat	90	Days	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to top-dose 206.6 mg/kg bw/day in F.		
31			rat	90	Days	Oral	0.77	mg/kg bw/day	Change	Slightly increased incidence of developmental cysts in the adenohypophysis in males in all treated groups; however, with no dose-relationship (males). Control animals (0/20 animals), low dose (2/20 animals), mid dose (3/20 animals) and top dose (2/20 animals). The incidences were within the range of the available limited HCD.		

34a		Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to highest dose tested 132 mg/kg bw/day (M) in the presence of systemic toxicity (> MDT)		
34a		Dog	90	Days	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to highest dose tested 137 mg/kg bw/day (F) in the presence of systemic toxicity (> MDT)		
34b		Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to highest dose tested 108 mg/kg bw/day (M)		
34b		Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to highest dose tested 110 mg/kg bw/day (M)		
37		mouse	106	Weeks	Oral		ppm	No effect	No effect on pituitary histopathology up to highest dose tested (300 ppm) in M.		
37		mouse	107	Weeks	Oral		ppm	No effect	No effect on pituitary histopathology up to highest dose tested (300 ppm) in F.		
38		mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology was observed up to highest dose tested (177.7 mg/kg bw/day) in M.		
38		mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology was observed up to highest dose tested (221.5 mg/kg bw/day) in F.		
39		rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology was observed up to highest dose tested (10.4 mg/kg bw/day) in M.		
39		rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology was observed up to highest dose tested (11.9 mg/kg bw/day) in F.		

40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology up to highest dose tested (156 mg/kg bw/day in M and 153 mg/kg/bw/day in F).		
40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology was observed up to highest dose tested (225 mg/kg bw/day) in F0.		
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology was observed up to highest dose tested (225 mg/kg bw/day) in F1.		
40b			rat	21	Days	Oral		mg/kg bw/day	No effect	No effect on pituitary histopathology was observed up to highest dose tested (221 mg/kg bw/day) in offspring (F1+F2).		
37		Pituitary weight	mouse	107	Weeks	Oral		ppm	No effect	No effect on pituitary weight was observed up to highest dose tested (300 ppm) in F.		
37			mouse	106	Weeks	Oral		ppm	No effect	No effect on pituitary weight was observed up to highest dose tested (300 ppm) in M.		
39			rat	116	Weeks	Oral	10,4	mg/kg bw/day	Decrease	Pituitary weights were decreased in high dose males (treated with 10.4 mg/kg bw/day) at the 1-year interim sacrifice (-29%), but not after the 2-year or terminal sacrifice.		
39			rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on pituitary weight was observed up to highest dose tested (11.9 mg/kg bw/day) in F.		
40a		Post implantation loss	rat	110	days	Oral		mg/kg bw/day	No effect	No effect on post implantation loss up to highest dose tested 153 mg/kg bw/day in F0 adults	Positive, evidence of post implantation loss in rats and rabbits	
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect on prenatal loss: pups delivered vs implantation sites (F1 adults)		

40b			rat	25	Weeks	Oral	225	mg/kg bw/day	Increase	A slightly higher post-implantation loss was seen in F1 dams (control F1 dams 10.2% loss, high dose F1 dams: 16.7% loss) while litter size (all pups and live-born pups) was comparable to controls in F1 dams (F2 pups)		
41a			rat	10	Days	Oral	300	mg/kg bw/day	Increase	Slightly higher post-implantation loss was seen at ≥300 mg/kg bw/day in all studies (preliminary, main and supplementary study), due to an increase in early resorptions. Post-implantation loss exceeded limited HCD in preliminary study only		
41b			rat	5	Days	Oral	300	mg/kg bw/day	Increase	Slightly higher post-implantation loss was seen at ≥300 mg/kg bw/day due to an increase in early resorptions (control 5.4%, mid dose 12.5%, top dose 10.4%)		
42			rat	10	days	Oral	500	mg/kg bw/day	Increase	Increase in post-implantation loss was seen at 500 mg/kg bw/day due to increases in early and late resorptions (control dams; 2.2% vs high dose dams; 18.9%)		
43			rabbit	14	days	Oral		mg/kg bw/day	No effect	No effect on post-implantation loss up to highest dose tested 150 mg/kg bw/day		
44			rabbit	13	days	Oral	200	mg/kg bw/day	Increase	Increased post-implantation loss in high dose females: control dams 9.2% and high dose dams 21.4 %; however, within the range of available HCD		
42		Pre-implantation loss	rat	10	days	Oral		mg/kg bw/day	No effect	No effect on pre-implantation loss up to highest dose tested 500 mg/kg bw/day	Negative, no effect on pre-implantation loss	
43			rabbit	14	days	Oral		mg/kg bw/day	No effect	No effect on pre-implantation loss up to highest dose tested 150 mg/kg bw/day		
44			rabbit	13	days	Oral		mg/kg bw/day	No effect	No effect on pre-implantation loss up to highest dose tested 200 mg/kg bw/day		

41a		Presence of anomalies (external, visceral, skeletal	rat	10	Days	Oral	300	mg/kg bw/day	Increase	The overall number of skeletal anomalies was increased at 300 mg/kg bw/day (main study only) and 450 mg/kg bw/day (supplementary study).	Positive, presence of anomalies in rat and rabbit		
41b			rat	5	Days	Oral	450	mg/kg bw/day	Increase	The overall number of skeletal anomalies was increased at 450 mg/kg bw/day (supplementary study).			
42			rat	10	days	Oral	500	mg/kg bw/day	Increase	Incidences of skeletal anomalies were increased and in runt foetuses were seen at 500 mg/kg bw/day			
43			rabbit	14	days	Oral	150	mg/kg bw/day	Increase	Increase in internal hydrocephalus and bilateral microphthalmia (within range, but exceeded mean+-SD) at the top dose (150 ppm)			
44			rabbit	13	days	Oral	200	mg/kg bw/day	Increase	Increase in skeletal variations; The % of foetuses with hyoid body and/or arches unossified and reduced ossification of the skull exceeded the range of HCD at the top dose level (200 mg/kg bw/day) while the litter incidences of both findings were well within the range of HCD			
40a		Pup development	rat	35	days	Oral		mg/kg bw/day	No effect	No effect on pup development up to highest dose tested 156 mg/kg bw/day (F1 offspring, M)	Negative, no consistent treatment-related effects on pup development		
40a			rat	35	days	Oral		mg/kg bw/day	No effect	No effect on pup development up to highest dose tested 153 mg/kg bw/day (F1 offspring, F)			
40a			rat	35	days	Oral		mg/kg bw/day	No effect	No effect on pup development up to highest dose tested 153 mg/kg bw/day (F2 offspring)			
40a		Pup survival index	rat	35	days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 156 mg/kg bw/day. Survival during lactation (day 1-4 viability and day 4-21 lactation index) was higher in mid dose (F1 pups) and high dose pups (F1+F2) vs controls	Negative, no consistent treatment-related effects		

40b			rat	21	Days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 225 mg/kg bw/day in F1 and F2 offsprings		
40a		Reproduction	rat	110	days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 153 mg/kg bw/day in F0 adults (F)	Negative, no consistent treatment-related effects	
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 156 mg/kg bw/day in F0 adults (M)		
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 153 mg/kg bw/day in F1 adults (F)		
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 156 mg/kg bw/day in F1 adults (M)		
40a		Sex ratio	rat	35	days	Oral		mg/kg bw/day	No effect	No effect on sex ratio in F1 offspring up to highest dose tested 156 mg/kg bw/day	Negative, no consistent treatment-related effects	
40b			rat	21	Days	Oral		mg/kg bw/day	No effect	No effect on sex ratio in F1+F2 offspring up to highest dose tested 225 mg/kg bw/day		
41a			rat	10	Days	Oral		mg/kg bw/day	No effect	No effect on sex ratio up to highest dose tested 300 mg/kg bw/day		
41b			rat	5	Days	Oral		mg/kg bw/day	No effect	No effect on sex ratio up to highest dose tested 450 mg/kg bw/day		
42			rat	10	days	Oral		mg/kg bw/day	No effect	No effect on sex ratio up to highest dose tested 500 mg/kg bw/day		

43			rabbit	14	days	Oral		mg/kg bw/day	No effect	No effect on sex ratio up to highest dose tested 150 mg/kg bw/day			
44			rabbit	13	days	Oral		mg/kg bw/day	No effect	No effect on sex ratio up to highest dose tested 200 mg/kg bw/day			
40a		Time to mating	rat	110	days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 153 mg/kg bw/day, F0 adults (F)	Negative, no consistent treatment-related effects		
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 156 mg/kg bw/day, F0 adults (M)			
40a			rat	110	days	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 153 mg/kg bw/day, F1 adults			
40b			rat	19	Weeks	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 225 mg/kg bw/day, F0 adults: The % of pairings resulting in positive evidence of mating was slightly reduced in both generations in high dose females vs. controls. However, for 2-3 pairings without evidence of mating in the high dose groups, dams were pregnant after all			
40b			rat	25	Weeks	Oral		mg/kg bw/day	No effect	No effect up to highest dose tested 225 mg/kg bw/day, F1 adults: The % of pairings resulting in positive evidence of mating was slightly reduced in both generations in high dose females vs. controls. However, for 2-3 pairings without evidence of mating in the high dose groups, dams were pregnant after all			
28	Target organ toxicity	Kidney weight	rat	28	Days	Oral	500	mg/kg bw/day	Increase	Increase in kidney weight at 500/1000 mg/kg bw. The relative kidney weights at 1000 mg/kg bw/day exceeded the range of the limited HCD for both sexes.	Nephrotoxicity (rat and dog). Kidney weight (abs/rel) was increased.	Overall evidence of target organ systemic toxicity: Kidney and liver are considered target organs.	Overall evidence of systemic toxicity
29a			rat	28	Days	Oral	500	mg/kg bw/day	Increase	Increase in kidney weight (abs + rel) at 500 mg/kg bw/day. Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and			

								mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD.	Spleen and thymus are not sufficiently investigated	
29b		rat	28	Days	Oral	500	mg/kg bw/day	Increase	Increase in kidney weight (abs + rel) at 500 mg/kg bw. Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%) only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD.		
30		rat	90	Days	Oral	208.6	mg/kg bw/day	Increase	Increase in relative kidney weight (17%) at 208.6 mg/kg bw/day, the increase co-incided with a lower body weight in that group.		
31		rat	90	Days	Oral	0.78	mg/kg bw/day	Decrease	Relative (but not absolute) kidney weights were slightly lower in all treated groups in absence of a dose-relationship (weights were within the range of available limited HCD).		
32		rat	90	Days	Oral	2400	ppm	Increase	Significant increase in relative kidney weight (17%) at top dose only.		
33		mouse	90	Days	Oral	2400	ppm	Decrease	Reduction in absolute kidney weight (left kidney only) at 2400 ppm only.		
34a		Dog	90	Days	Oral	132	mg/kg bw/day	Increase	Significant increase in relative kidney weight (60%) in top dose males only (absolute increase 16%). Observed in the presence of significant systemic toxicity; decreased body weight and body weight gain associated with drastically reduced food intake.		
34a		Dog	90	Days	Oral	137	mg/kg bw/day	Increase	Absolute (18%) and relative (55%) kidney weights were increased in top dose females. Observed in the presence of significant systemic toxicity; decreased		

										body weight and body weight gain associated with drastically reduced food intake.		
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	No effect.		
34b			Dog	12	Months	Oral	110	mg/kg bw/day	Increase	Increase observed at the top dose level in the presence of significant systemic toxicity; decreased body weight and body weight gain associated with drastically reduced food intake.		
28		Liver histopathology	rat	28	Days	Oral	500	mg/kg bw/day	Change	Enlarged livers and slight hypertrophy of the hepatocytes in some animals at 500 mg/kg bw (M: 8/10, F: 3/10), and in all rats in the high dose group.	Hepatotoxicity (rat, dog). Consistent treatment-related effects on liver weight (increased) and liver histopathology.	
29a			rat	28	Days	Oral	100	mg/kg bw/day	Change	Increased incidences of minimal hypertrophy of centrilobular hepatocytes; in all treated male groups* (2/10 and 9/10 animals at low dose and high dose, respectively) and at 500 mg/kg bw/day in females* (8/10), minimal to moderate hepatocellular necrosis (3/10 top dose males), and an increase in inflammatory cell infiltrations at the top dose level (minimal to moderate severity in males (8/10 animals), and minimal degree in females (6/10). *It should be noted that minimal to moderate increase in the mitotic activity of hepatocytes was reported in the animals (one male and two females), which were sacrificed in moribund condition on day 3 (500 mg/kg bw/day). A dose of 500 mg/kg/day exceeded the MTD.		
29b			rat	28	Days	Oral	100	mg/kg bw/day	Change	Increased incidences of minimal hypertrophy of the follicle epithelium were seen in male from 100 mg/kg bw/day (5/10 low dose, 10/10 high dose) and female top dose animals (8/10). A dose of 500 mg/kg/day exceeded the MTD.		
30			rat	90	Days	Oral	208.6	mg/kg bw/day	Change	Minimal hepatocyte hypertrophy at top-dose (9/20 animals) in F.		

30			rat	90	Days	Oral	202.3	mg/kg bw/day	Change	Minimal hepatocyte hypertrophy at top-dose (20/20 animals) in M.		
32			rat	90	Days	Oral	500	ppm	Change	Centrilobular hepatocyte hypertrophy at ≥1000 ppm, and some degeneration of the hepatocytes around the central vein in the 2400 ppm group in M. Higher incidences of hepatocytic vacuolisation was observed from ≥500 ppm.		
32			rat	90	Days	Oral	1000	ppm	Change	Centrilobular hepatocyte hypertrophy at ≥1000 ppm, and some degeneration of the hepatocytes around the central vein in the 2400 ppm group in F.		
33			mouse	90	Days	Oral	500	ppm	Change	Centrilobular hepatocyte hypertrophy was observed at ≥500 ppm in males (14/15 males at top dose). Focal coagulative necrosis was found in some males at ≥1000 ppm (4/15 males at top dose). Degeneration of the hepatocytes around the central vein (7/15 males) and hepatocytic vacuolisation (10/15 males) were observed at 2400 ppm in males only.		
33			mouse	90	Days	Oral	2400	ppm	Change	Centrilobular hepatocyte hypertrophy was observed at 2400 ppm in females (7/15 females).		
34a			Dog	90	Days	Oral	132	mg/kg bw/day	Change	At the highest dose, cytoplasmic vacuolisation was noted in 2/4 males, inflammatory cell infiltration in 4/4 males and hepatocyte necrosis in 4/4 males. In mid dose males, 1/4 was noted with inflammatory cell infiltration and 1/4 males with hepatocyte necrosis.		
34a			Dog	90	Days	Oral	137	mg/kg bw/day	Change	Inflammatory cell infiltration was noted in 4/4 and hepatocyte necrosis in 4/4 top dose females.		
34b			Dog	12	Months	Oral	108	mg/kg bw/day	Change	At the highest dose, cytoplasmic vacuolisation was noted in 2/4 males, inflammation with fibrosis in 4/4 males and hepatocyte necrosis in 1/4 males. In mid dose males, 2/4 was noted with inflammatory cell infiltration and 2/4 males with inflammation with fibrosis.		

34b		Dog	12	Months	Oral	110	mg/kg bw/day	Change	Inflammation with fibrosis was noted in 4/4 females and hepatocyte necrosis in 2/4 animals.			
35		mouse	90	Days	Oral	1500	ppm	Change	No effect on liver histopathology. Hepatocyte hypertrophy and increased nuclear pleomorphism was present in all males at ≥1500 ppm.			
35		mouse	90	Days	Oral	3000	ppm	Change	No effect on liver histopathology. Hepatocyte hypertrophy was observed in 4/10 females at 3000 ppm.			
37		mouse	106	Weeks	Oral		ppm	No effect	No effect on liver histopathology up to the highest dose level tested (300ppm).			
37		mouse	107	Weeks	Oral		ppm	No effect	No effect on liver histopathology up to the highest dose level tested (300ppm).			
38		mouse	80	Weeks	Oral	177.7	mg/kg bw/day	Change	There was an increase in the incidence and severity of hepatocyte vacuolation of the liver in the high dose males (control 13/50, top dose 37/50).			
38		mouse	80	Weeks	Oral	221.5	mg/kg bw/day	Change	There was an increase in the incidence and severity of hepatocyte vacuolation of the liver in the high dose females (control 1/50, top dose 16/50).			
40a		rat	110	days	Oral	29.9	mg/kg bw/day	Change	Increases in slight (mainly centrilobular) hepatocyte hypertrophy was observed at the mid (14/16 females) and high dose level (16/16 females) and slight recent necrosis (2/16) was seen in top dose females.			
40a		rat	110	days	Oral	29.7	mg/kg bw/day	Change	Increases in slight (mainly centrilobular) hepatocyte hypertrophy was observed at the mid (5/19 males) and high dose level (17/20 males).			
49a		Rat	14	Days	Oral	320	mg/kg bw/day	Increase	Increased proliferation of smooth endoplasmic reticulum membranes at 320 mg/kg bw/day			

49b			Mouse	14	Days	Oral	320	mg/kg bw/day	Increase	Increased proliferation of smooth endoplasmic reticulum membranes at 320 mg/kg bw/day		
28		Liver weight	rat	28	Days	Oral	100	mg/kg bw/day	Increase	Liver weight (abs + rel) increase in both sexes, increase in F from 100 mg/kg bw and in M from 500 mg/kg bw.		
29a			rat	28	Days	Oral	100	mg/kg bw/day	Increase	Increase in liver weight (abs + rel) from 100 mg/kg bw/day.		
29b			rat	28	Days	Oral	100	mg/kg bw/day	Increase	Increase in liver weight (abs + rel) from 100 mg/kg bw and above (M) and increase at 500 mg/kg bw (F).		
30			rat	90	Days	Oral	2.1	mg/kg bw/day	Increase	Increase in F in relative liver weight from 2.1 mg/kg (3.7%) onwards (40% top dose) and in absolute at 208.6 mg/kg bw.		
30			rat	90	Days	Oral	2	mg/kg bw/day	Increase	Increase in M in relative liver weight from 2 mg/kg (5%) and onwards (28% top dose) and in absolute at 2 and 202.3 mg/kg bw		
31			rat	90	Days	Oral	0.77	mg/kg bw/day	Increase	Increase in liver weight (abs +rel) at low-dose (rel 11%) and mid-dose (rel 15%), however no weight change in the top dose males.		
31			rat	90	Days	Oral	2.14	mg/kg bw/day	Decrease	Marginally reduced liver weight (-9.6%) only in the mid dose females.		
32			rat	90	Days	Oral	1000	ppm	Increase	Increase in relative liver weight (13%) at 1000 ppm and increase (rel + abs) at top dose (31%).		
32			rat	90	Days	Oral	500	ppm	Increase	Increase in relative liver weight (10.2%) at 500 ppm and further increase in abs+rel liver weight at the two highest doses (20 and 29% relative increase).		

33		mouse	90	Days	Oral	500	ppm	Increase	Absolute and relative liver weights were significantly increased at ≥500 ppm in males (relative weights: 10% at 500 ppm, 17 % at 1000 ppm and 42% at 2400 ppm).
33		mouse	90	Days	Oral	2400	ppm	Increase	Absolute (24%) and relative (32%) liver weights were significantly increased at 2400 ppm in females. Relative liver weight was also slightly increased significantly at ≥500 ppm (≤10%).
34a		Dog	90	Days	Oral	18.2	mg/kg bw/day	Increase	Absolute and relative liver weights were increased at the top dose level (abs: 30%, rel: 75%) and mid dose males (abs: 20%, rel: 15%).
34a		Dog	90	Days	Oral	19.4	mg/kg bw/day	Increase	Absolute and relative liver weights were increased at the top dose level (abs: 22%, rel: 88%) and for mid dose females (abs: 15%, rel: 24%).
34b		Dog	12	Months	Oral	108	mg/kg bw/day	Increase	Absolute and relative liver weights were increased at the top dose level (abs: 27%, rel: 35%).
34b		Dog	12	Months	Oral	16.5	mg/kg bw/day	Increase	Absolute and relative liver weights were increased at the top dose level (abs: 46%, rel: 63%) and for mid dose females (abs: 27%, rel: 28%).
35		mouse	90	Days	Oral	500	ppm	Increase	Relative liver weights were increased in males at 500 ppm. Increase in adjusted weights: 12%, 33% and 48% at 500, 1500 and 300 ppm, respectively.
35		mouse	90	Days	Oral	1500	ppm	Increase	Relative liver weights were increased in females at ≥ 1500 ppm. Increase in adjusted weights: 10% and 28% at 1500 and 300 ppm, respectively.
37		mouse	106	Weeks	Oral	150	ppm	Increase	Relative liver weight was increased in M in 300 ppm dose group (10%) at the 1-year sacrifice and at 150 ppm (but not 300 ppm) 53-week sacrifice (23%). No dose-related trend or corresponding histopathological correlate were seen.

37		mouse	107	Weeks	Oral	300	ppm	Increase	Relative liver weight was increased in F in 300 ppm dose group (15%). No dose-related trend or corresponding histopathological correlate were seen.		
38		mouse	80	Weeks	Oral	177.7	mg/kg bw/day	Increase	Liver weights were increased in top dose males (adjusted weight +27%, relative weight +28%).		
38		mouse	80	Weeks	Oral		mg/kg bw/day	No effect	Slightly higher liver weights (approximately 5% higher than control) in females receiving the top dose (221.5 mg/kg bw/day), but the value did not reach statistical significance.		
39		rat	117	Weeks	Oral	5.7	mg/kg bw/day	Increase	Increase in F in absolute (+20%) in top dose group and in relative liver weight (+13 and 15% at 5.7 and 11.9 mg/kg bw/day, respectively) at week 52. The increase at week 52 was associated with an increase in γ-GT. There was also a statistically significant trend in relative weight at week 104 (+15%) for the top dose group.		
39		rat	116	Weeks	Oral		mg/kg bw/day	No effect	No effect on liver weight were observed in males up to the highest dose level tested (10.4 mg/kg bw/day).		
40a		rat	35	days	Oral	156	mg/kg bw/day	Increase	Relative liver weights were increased significantly in high dose group (+31%), absolute increase non-significantly (+11%). Offspring (F1) Male.		
40a		rat	35	days	Oral	153	mg/kg bw/day	Increase	Relative liver weights were increased significantly in high dose group (+28%), absolute increase non-significantly (+8.2%). Offspring (F1) female.		
40a		rat	110	days	Oral	153	mg/kg bw/day	Increase	Relative liver weights were significantly increased in F1 adults F (+37%), absolute weight was increased non-significantly (+20%).		
40a		rat	110	days	Oral	156	mg/kg bw/day	Increase	Relative liver weights were significantly increased in F1 adults M (+11%), absolute weight was slightly increased (+4%).		

40a			rat	35	days	Oral	153	mg/kg bw/day	Increase	Relative liver weights were significantly increased in F2 weanlings (+22%), absolute liver weight non-significantly increased (+16%). It should be noted that only five/sex/group F1 and F2 weanlings were necropsied.			
40a			rat	35	days	Oral	156	mg/kg bw/day	Increase	Relative liver weights were significantly increased in F2 weanlings (+28%), absolute liver weight non-significantly increased (+21%). It should be noted that only five/sex/group F1 and F2 weanlings were necropsied.			
49a			Rat	14	Days	Oral	80	mg/kg bw/day	Increase	Significantly increased at 80 mg/kg bw/day			
49b			Mouse	14	Days	Oral	160	mg/kg bw/day	Increase	Significantly increased at 80 mg/kg bw/day			
29a		Spleen histopathology	rat	28	Days	Oral	500	mg/kg bw/day	Change	Minimal extramedullary haematopoiesis was found in high-dosed females (3/10).	Effects on spleen are not sufficiently investigated		
29b			rat	28	Days	Oral	100	mg/kg bw/day	Change	Minimal extramedullary haematopoiesis was found in low-dosed males (2/10), in high-dosed males (2/10) and in high-dosed females (2/10).			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on spleen histopathology in M up to the highest dose level tested (177.7 mg/kg bw/day).			
38			mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No effect on spleen histopathology in F up to the highest dose level tested (221.5 mg/kg bw/day).			
38		Spleen weight	mouse	80	Weeks	Oral	177.7	mg/kg bw/day	Decrease	Reduced spleen weight in top dose males (adjusted weight -40%).			

38			mouse	80	Weeks	Oral	221.5	mg/kg bw/day	Decrease	Reduced spleen weight in top dose females (adjusted weight -38%).		
29a		Thymus histopathology	rat	28	Days	Oral	500	mg/kg bw/day	Change	Occurrence of tangible body macrophages (phagocytic cells exhibiting condensed nuclear material in their cytoplasm and being responsible for lymphophagocytosis) in thymus cortex was recorded in all moribund-sacrificed animals as well as in one female of the 500 mg/kg bw/day dose level at study termination. Total N=10	Effects on thymus are not sufficiently investigated	
29b			rat	28	Days	Oral	500	mg/kg bw/day	Change	Occurrence of tangible body macrophages (phagocytic cells exhibiting condensed nuclear material in their cytoplasm and being responsible for lymphophagocytosis) in thymus cortex was recorded in one female, which was sacrificed in moribund condition on day 2 (500 mg/kg bw/day). Variations in absolute or relative organ weights occasionally reached statistical significance in the thymus but were in absence of a dose-relationship. They were also not associated with any relevant histopathological changes. Total N=10, effect observed at the top dose		
30		Thymus weight	rat	90	Days	Oral	2.1	mg/kg bw/day	Increase	Increase in relative thymus weight at 2.10 and 208.6 mg/kg bw/day (10% and 12%), the increase co-incided with a lower body weight in that group at the top dose. Study considered supportive only (due to deviations from the test guideline currently in place). Variations in absolute or relative organ weights occasionally reached statistical significance in the thymus but were in absence of a dose-relationship. They were also not associated with any relevant histopathological changes. Total N=10, effect observed at the top dose		
1	Systemic toxicity	Body weight	rat	9	Months	Oral	50	mg/kg bw/day	Decrease	Significant decrease compared to the control group. Reporting deficiencies, unclear test item and dosing scheme, inadequate reporting of body weight development, and no reporting of clinical signs or food consumption. Serious methodological deficiencies, flawed/unsuitable histopathological methodology, no consideration of circadian variation in testosterone measurement.	Sufficient evidence of systemic toxicity based on reduced Bw, food consumpiton, alteration in clinical chemistry and haematology and/or clinical signs. MTD was	Overall evidence of systemic toxicity. MTD ≥500 mg/kg bw (M), ≥500 mg/kg bw (F)

											exceeded at 500 mg/kg bw/day in males and 500 mg/kg bw/day in females (28 day rat) (three female and one male rat dosed with 500 mg/kg/day were sacrificed in moribund condition at experimental days 2-3 and in surviving animals symptoms such as hunch-backed posture, piloerection and laboured breathing were observed that were more pronounced in female than in male animals).	
28			rat	28	Days	Oral	500	mg/kg bw/day	Decrease	Decreased BW (M:↓13%) week 4 and BW gain (M:↓ 28% and F:↓ 14%) for weeks 0-4.		
30			rat	90	Days	Oral	208.6	mg/kg bw/day	Decrease	Decrease in BW and a marked effect in BW gain (average reduction 16%) from week 4 onwards at the top dose. Reduced BW (-14%) at termination.		
31			rat	90	Days	Oral	2.14	mg/kg bw/day	Increase	Increased bodyweights (9.8%) and BW gain (16%) in F only at 2.14 mg/kg bw/d, not confirmed at top-dose.		
32			rat	90	Days	Oral	500	ppm	Decrease	Bodyweights were significantly lower throughout the study in the 2400 ppm (-10% week 13), and in the 1000 ppm treated group at weeks 6, 7, 9, 12, and 13 (-6.2%). BW gain significantly reduced in the 1000 (-8.9%) and 2400 ppm (-15%) treated females. Overall		

								mean food consumption in females was slightly reduced at 1000 and 2400 ppm reaching statistical significance at a few weeks during the dosing period.			
33		mouse	90	Days	Oral	2400	ppm	Increase	Lower BW gain for the 13-week period was seen in the 2400 ppm group (-13% vs. control in males and –17% in females).		
34a		Dog	90	Days	Oral	132	mg/kg bw/day	Decrease	In the male high dose group, the dogs lost weight mostly during the first month of the study associated with drastically reduced food intake; the weight loss reached 12% (males) of the initial weights during the first 13 weeks of the study. Animals gained weight in the lowest doses; however, BW gain was lower in the low (-18%) and mid dose males (-25%) compared to control animals. Group mean terminal body weights were reduced (26%) at the top dose level at the interim (13 weeks)		
34a		Dog	90	Days	Oral	137	mg/kg bw/day	Decrease	In the female high dose group, the dogs lost weight mostly during the first month of the study associated with drastically reduced food intake; the weight loss reached 9% (females) of the initial weights during the first 13 weeks of the study. Animals gained weight in the lowest doses; however, BW gain was lower in mid dose females (-22%) compared to control animals. Group mean terminal body weights were reduced (25%) at the top dose level at the interim (13 weeks).		
34b		Dog	12	Months	Oral	108	mg/kg bw/day	Decrease	The top dose level was reduced from 132 mg/kg bw/day to 108 mg/kg bw/day in week 20, but overall BW gain was markedly below controls for the top dose group (M ↓44%). The overall weight gain was also slightly lower in mid dose dogs (M↓14%), whereas there were no differences at the low dose level. Group mean terminal body weights were reduced (8.2%) at the top dose level at terminal sacrifice (53 weeks).		
34b		Dog	12	Months	Oral	16.5	mg/kg bw/day	Decrease	The top dose level was reduced from 137 mg/kg bw/day to 110 mg/kg bw/day in week 20, but overall BW gain was markedly below controls for the top dose group (F ↓58%). The overall weight gain was also lower in mid dose dogs (F↓33%), whereas there were no differences at the low dose level. Group mean		

								terminal body weights were reduced (11%) at the top dose level at terminal sacrifice (53 weeks).			
35		mouse	90	Days	Oral	1500	ppm	Decrease	Slightly reduced BW compared to control day 92 (↓5.6%) while adjusted body weight loss during the study (days 2-92) was ↓19% on day 92 in the 1500 ppm dose group. In the 3000 ppm group, reduced BW compared to control was ↓15% and adjusted body weight loss (days 2-92) during the study was ↓52%. Animals in the 5000 ppm group lost weight throughout the first week of the study (10-17% of initial body weights) and were terminated in the second week.		
35		mouse	90	Days	Oral	3000	ppm	Decrease	Animals in the 5000 ppm group lost weight throughout the first week of the study (8-11% of initial body weights) and were terminated in the second week. Animals in the 1500 and 3000 ppm group had reduced bodyweights with most BW reduction in the 3000 ppm group: ↓11% at day 92 and adjusted BW loss during the study (days 2-92) was ↓38%.		
38		mouse	80	Weeks	Oral	221.5	mg/kg bw/day	Decrease	Marked effect on bodyweight development in females at 221.5 mg/kg bw/day. Week 1-33 (-19%), week 1-51 (-17%) week 1-81 (-16%). The maximum difference from control of adjusted body weights were at weeks 33/37 (-9.6%).		
38		mouse	80	Weeks	Oral	177.7	mg/kg bw/day	Decrease	Marked effect on bodyweight development in males at 177.7 mg/kg bw /day. Week 1-33 (-27%), week 1-51 (-29%), week 1-81 (-26%). The maximum difference from control of adjusted body weights were at week 73 (-15%).		
39		rat	116	Weeks	Oral		mg/kg bw/day	No effect	Body weight development in all treated animals was similar to controls up to highest dose tested (10.4 mg/kg bw/day) in M.		
39		rat	117	Weeks	Oral		mg/kg bw/day	No effect	No effect on body weight development in all treated animals was similar to controls up to highest dose tested (11.7 mg/kg bw/day) in F.		
40a		rat	110	days	Oral	153	mg/kg bw/day	Decrease	The markedly lower body weight (-12%) of high dose F0 females on lactation day 1 indicates that the net body weight of dams (without gravid uterus, not measured) during gestation would have been more		

								markedly affected than measured body weights. Body weight development was slightly decreased in high dose females during premating (day 1-60, -8.3%). During gestation, a slight reduction in body weight gain was also noted for high dose F0 dams (day 0-21, -7.7%). During lactation, high dose females of both generations gained slightly more weight than controls.		
40a		rat	110	days	Oral	153	mg/kg bw/day	Decrease	The markedly lower body weight (-11%) of high F1 females on lactation day 1 indicates that the net body weight of dams (without gravid uterus, not measured) during gestation would have been more markedly affected than measured body weights. Body weight development was slightly decreased in high dose females during premating (day 1-60, -6.9%). During gestation, a more marked decrease (day 0-21, -16%) was seen in F1 dams at this dose level. During lactation, high dose females of both generations gained slightly more weight than controls.		
40a		rat	110	days	Oral	156	mg/kg bw/day	Decrease	A slightly lower body weight gain was seen during pre-mating (-2.7%) in F1 high dose males with a more marked reduction after mating (-10.6%). Due to lower body weights at start of the pre-mating period, absolute bodyweights of F1 males were consistently lower than controls over the whole treatment period. Significantly reduced BW at termination (-7.5%).		
40b		rat	19	Weeks	Oral	225	mg/kg bw/day	Decrease	Body weight development of high dose females during pre-mating were reduced at 225 mg/kg bw/day in both generations (premating; F0 9 weeks exposure: -21%, F1 age weeks 4-16: -7.1%). Absolute body weights of high dose F0 and F1 females remained below control values, while body weight gain during gestation was comparable with controls. During lactation, high dose females gained more weight than controls.		
40b		rat	25	Weeks	Oral	225	mg/kg bw/day	Decrease	Body weight development of high dose females during pre-mating were reduced at 225 mg/kg bw/day in both generations (premating; F0 9 weeks exposure: -21%, F1 age weeks 4-16: -7.1%). Absolute body weights of high dose F0 and F1 females remained below control values, while body weight gain during gestation was comparable with controls. During lactation, high dose females gained more weight than controls.		

40b			rat	25	Weeks	Oral	211	mg/kg bw/day	Decrease	Body weight gain of high dose F1 males was decreased during pre-mating and during the complete treatment period (-10.5% w 0-28).		
41a			rat	10	Days	Oral	300	mg/kg bw/day	Decrease	At 300 mg/kg bw/day, body weight gain was decreased during treatment (by 8% on GD 6-16) and the corrected body weight gain (minus gravid uterus weight) on GD day 6-21 (by 12%).		
41b			rat	5	Days	Oral	300	mg/kg bw/day	Decrease	At 300 mg/kg bw/day, body weight gain was markedly decreased during treatment (by 20% on GD 6-16) and GD 6-21 corrected body weight gain (by 55%). During the more limited treatment period (GD 10-14), body weight gain at 450 mg/kg bw/day was reduced by 28% and also GD 6-21 corrected body weight gain was 28% lower than controls.		
42			rat	10	days	Oral	500	mg/kg bw/day	Decrease	Maternal body weight development: corrected bw gain on GD 6-20 was reduced by 41%. BW at GD 20 was significantly reduced (-4,2%: corrected for gravid uterus weight: -2.2%)		
43			rabbit	14	days	Oral	150	mg/kg bw/day	Decrease	Reduced body weight development in high dose females; BW gain GD 0-28; -7.4%, BW gain during GD 6-19; -11% (test chemical was administrated GD 6-18)		
44			rabbit	13	days	Oral	200	mg/kg bw/day	Decrease	Reduced BW gain in high dose females, most markedly in the first week of treatment* (GD 7-10: -104%, GD 10-14; -19%). *The test chemical was administrated from GD 7-19 only.		
49a			Rat	14	Days	Oral	No effect	mg/kg bw/day	No effect	No effect on body weight up to the highest dose tested (320 mg/kg bw/day)		
49b			Mouse	14	Days	Oral	No effect	mg/kg bw/day	No effect	No effect on body weight up to the highest dose tested (320 mg/kg bw/day)		
28		Clinical chemistry and	rat	28	Days	Oral	500	mg/kg bw/day	Decrease	A trend to slightly decreased haemoglobin (↓4.2% to↓6.3%) and haematocrit values (↓4.7% to ↓7%) in female groups from 500 to 1000 mg/kg/ bw.		

28		haematology	rat	28	Days	Oral	500	mg/kg bw/day	Change	A series of parameters were affected in one or both sexes, including products of the metabolism, increased cholesterol and proteins, and increased activity of enzymes related to the hepatic function (*ALAT og ALP*). Sodium, calcium and inorganic phosphate levels were increased, whereas potassium and chloride were decreased. A slight, but statistically significant increase in calcium, creatinine and potassium levels, and decrease in sodium levels was noted at 100 mg/kg bw in M, but the levels of these parameters did not appear to be dose-dependent.		
29a			rat	28	Days	Oral	100	mg/kg bw/day	Change	A dose-related increase in platelets and decrease in prothrombin time was observed in male and female groups reaching statistical significance mostly at 500 mg/kg bw/day (exceeding HCD). Clinical biochemistry: A series of parameters were affected by treatment, dose-related increase of plasma protein concentrations, associated with higher globulin levels and minimally lower albumin-to-globulin (A/G) ratios in both sexes (A/G ratios and albumin levels were within the range of available HCD). Elevated alanine aminotransferase and cholesterol levels were also noted at the top dose level. Total bilirubin was somewhat lower in treated groups as compared to concurrent controls (but well within the range of available HCD). Reductions in plasma chloride levels were within the range of available HCD. Changes in ASAT and ALP (mostly reductions) were within the range of the available HCD. A dose of 500 mg/kg/day exceeded the MTD.		
29b			rat	28	Days	Oral	100	mg/kg bw/day	Change	A dose-related increase in platelets and decrease in prothrombin time was observed in male and female groups reaching statistical significance mostly at 500 mg/kg bw/day (exceeding HCD). Clinical biochemistry: A series of parameters were affected by treatment, dose-related increase of plasma protein concentrations, associated with higher globulin levels and minimally lower albumin-to-globulin (A/G) ratios in both sexes (A/G ratios and albumin levels were within the range of available HCD). Urea levels were slightly increased at 500 mg/kg bw/day in both sexes. Elevated alanine aminotransferase and cholesterol levels were also noted at the top dose level. Total bilirubin was somewhat lower in treated groups as		

								compared to concurrent controls (but well within the range of available HCD). Reductions in plasma chloride levels were within the range of available HCD. Changes in ASAT and ALP (mostly reductions) were within the range of the available HCD. A dose of 500 mg/kg/day exceeded the MTD.		
30		rat	90	Days	Oral	20.7	mg/kg bw/day	Change	Haematology: statistically significant effects on RBC parameters: ↓segmented neutrophils (208.6 mg/kg bw/day), ↑ moncytes and nucleated RBC-normoblasts (from 20.7 mg/kg bw). Blood chemistry: statistically significant changes in: ↑cholesterol and albumin, ↓potassium, chloride. Note that most findings reflected the normal physiological variation of the respective parameters and were within a limited available HCD.		
30		rat	90	Days	Oral	19.4	mg/kg bw/day	Change	Haematology: statistically significant effects on RBC parameters: ↓ leukocytes (at 2 and 202.3 mg/kg bw/day only) ↑segmented neutrophils (at 19.4 mg/kg bw only), ↓ lymphocytes (from 19.4 mg/kg bw/day). Blood chemistry: statistically significant changes in: ↓ glucose (from 19.4 mg/kg bw/day), ↑ureas-N values (from 19.4 mg/kg bw/day), ↑ cholesterol (202.3 mg/kg bw/day), ↑ total proteins and albumin (from 2 mg/kg bw), ↑total globulin and A/G ratio (increasing trend, significant at 202.3 mg/kg bw/day), ↓ lactate dehydrogenase (decreasing trend from 19.4 mg/kg bw/day), ↑ potassium (at 2 and 202.3 mg/kg bw only), ↑chloride (at 2 and 19.4 mg/kg bw/day only). Note that most findings reflected the normal physiological variation of the respective parameters and were within a limited available HCD. Only the marginally increased cholesterol in high dose males slightly exceeded the range of the available limited HCD.		
31		rat	90	Days	Oral	0.78	mg/kg bw/day	Change	Haematology: reduced reticulocyte count at all doses (no clear dose-relationship). Clinical chemistry: ↑GGT from mid-dose and globulin and total proteins at top-dose. Most findings reflected the normal physiological variation of the respective parameters and in the absence of clear dose-relationship.		
31		rat	90	Days	Oral	0.77	mg/kg bw/day	Change	Haematology: increased reticulocyte count at all doses (no clear dose-relationship). Clinical chemistry: ↑ in total proteins from mid-dose and in albumin at top-dose, ↓ inorganic phosphate and a slight increase in sodium. Most findings reflected the normal		

								physiological variation of the respective parameters and in the absence of clear dose-relationship.		
32		rat	90	Days	Oral	2400	ppm	Decrease	↑slightly increase in protein (males only), ↓ albumin (females only), and slightly reduced A/G ratio in both sexes in top dose animals.		
32		rat	90	Days	Oral	10	ppm	Increase	Increased urea nitrogen in treated males (11% at 10 ppm to 35% at 1000 ppm and 22% at 2400 ppm). It should be noted that the value of control males appears to be rather low (139 mg/L) as compared to control females (151 g/L).		
33		mouse	90	Days	Oral	1000	ppm	Change	Lower total protein (↓8.3% and 6.7% at 1000 ppm and 2400 ppm, respectively) and cholesterol (↓31% and 61% at 1000 ppm and 2400 ppm, respectively). ALT at 2400 ppm (↑170%) whereas gamma-GT was significantly reduced at ≥500 ppm.		
33		mouse	90	Days	Oral	1000	ppm	Change	Reduced albumin (↓14%) and A/G ratio (↓13%) in top dose females, whereas cholesterol was decreased at ≥1000 ppm (↓36% to ↓40% in top dose females). Total protein was reduced in top dose females (↓10%).		
34b		Dog	12	Months	Oral	110	mg/kg bw/day	Change	Increased platelet counts were recorded among female dogs of the high-dose group already from the pre-test. Haematological parameters of which reaching increased statistical significance were noted in monocytes in mid dose and high dose females. Red cell parameters (Hb, RBC) among female dogs of the high dose group were slightly lower as compared to controls from week 13. After reduction of the top dose level to 110 mg/kg bw/day in week 20, red blood cell parameters recovered within the range of available limited HCD in week 52. Clinical biochemistry: mainly change at the high dose level: OCT, AST, ALT, ALP, and γ-GT were markedly increased during the complete treatment period, indicating the liver as a clear target organ. Further effects were most marked at week 13 (↓glucose and urea-nitrogen, ↑inorganic phosphate), but normalised when dose level was reduced.		

34b			Dog	12	Months	Oral	108	mg/kg bw/day	Change	Red cell parameters (Hb, RBC) in high dose M were slightly lower at week 13. After reduction of the top dose level to 108 mg/kg in week 20, red blood cell parameters recovered within the range of HCD in week 52. Variations in haematological parameters (some statistically significant) were noted in eosinophils, lymphocytes and monocytes in absence of a dose-relationship, and within the range of HCD. Platelets increased over time (statistical significance at week 52). The proportion of lymphocytes was increased and eosinophils were reduced in high dose M. Clinical biochemistry: mainly change at the high dose level: OCT, AST, ALT, ALP and γ-GT were markedly increased during the complete treatment period, indicating the liver as a clear target organ. Globulin was slightly but consistently increased in high dose males. Further effects were most marked at week 13 (↓glucose and chloride, ↑inorganic phosphate), but normalised when dose level was reduced. ↑inorganic phosphate seen up to the end of treatment.		
35			mouse	90	Days	Oral	500	ppm	Change	Treatment and dose related reduction in cholesterol in all dose group, significant from ≥500 ppm (↓54% at 3000 ppm). Plasma ALP was increased at ≥1500 ppm (13% and 22% increase).		
35			mouse	90	Days	Oral	3000	ppm	Decrease	Treatment and dose related reduction in cholesterol in all dose group, significant from ≥100 ppm (↓54% at 3000 ppm). Plasma ALP was increased at ≥1500 ppm (↑ 25% at 3000 ppm). Plasma albumin (↓ 2.2-6.5%) and total protein (↓2.6-8.1%) were lower in all female groups, and plasma calcium was lower in females at 3000 ppm (↓4.4%).		
39			rat	116	Weeks	Oral		mg/kg bw/day	No effect	Observed variations in blood biochemistry parameters were considered unrelated to treatment tested up to the highest dose level (10.4 mg/kg bw/day) in M.		
39			rat	117	Weeks	Oral	0.2	mg/kg bw/day	Change	Slightly higher γ-GT values in high dose females at weeks 27 (top dose only) and 52 (increase at 0.2, 2.9 and 11.9 mg/kg bw/day).		

49a			Rat	14	Days	Oral	10	mg/kg bw/day	Increase	A strong dose-dependent increase of microsomal protein (up to about 60% vs. control) and phospholipid contents (practically doubled at 320 mg/kg bw/day vs. controls). Activities of xenobiotic-metabolising liver enzymes were drastically increased (UDP-glucuronosyltransferase was increased from 80 mg/kg bw/day and up to the top dose).		
49b			Mouse	14	Days	Oral	80	mg/kg bw/day	Increase	A strong dose-dependent increase of microsomal protein (up to about 60% vs. control) and phospholipid contents (practically doubled at 320 mg/kg bw/day vs. controls). Activities of xenobiotic-metabolising liver enzymes were drastically increased (UDP-glucuronosyltransferase was increased from 80 mg/kg bw/day and up to the top dose).		
29a		Clinical signs	rat	28	Days	Oral	500	mg/kg bw/day	Change	Due to marked clinical signs of acute toxicity, one male and two females dosed with 500 mg/kg/ bw/day (Batch B, 96.1% purity) were sacrificed in moribund condition at experimental day 3. In surviving animals, symptoms such as hunch-backed posture, piloerection and laboured breathing were observed that were more pronounced in female than in male animals.		
29b			rat	28	Days	Oral	500	mg/kg bw/day	Change	Due to marked clinical signs of acute toxicity, one female dosed with 500 mg/kg/day (Batch A, 96.2% purity) was sacrificed in moribund condition at experimental day 2. In surviving animals, some females had symptoms such as hunch-backed posture, piloerection and laboured breathing.		
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	Diarrhoea was observed in treatment groups as well as in the control group (there were no differences between the groups). At the high dose, diarrhoea was seen less frequently during the 1st 20 weeks, which was considered due to reduced diet intake.		
34a			Dog	90	Days	Oral		mg/kg bw/day	No effect	Diarrhoea was observed in treatment groups as well as in the control group (there were no differences between the groups). At the high dose, diarrhoea was seen less frequently during the 1st 20 weeks, which was considered due to reduced diet intake.		
34b			Dog	12	Months	Oral		mg/kg bw/day	No effect	Increased incidence of vomiting was seen in dogs receiving the top dose (132 mg/kg bw/day) diet during the first 13 weeks. No vomiting was seen in males after the dose level had been reduced to 108 mg/kg bw/day. Diarrhoea was observed in treatment groups		

									as well as in the control group (there were no differences between the groups).			
34b			Dog	12	Months	Oral	110	mg/kg bw/day	Decrease	Increased incidence of vomiting was seen in dogs receiving the top dose (137 mg/kg bw/day) diet during the first 13 weeks. Vomiting still continued in the females during the whole study even after the dose had been reduced to 110 mg/kg bw/day. Diarrhoea was observed in treatment groups as well as in the control group (there were no differences between the groups), but was observed less frequently in all groups during the second half of the study.		
38			mouse	80	Weeks	Oral	177.7	mg/kg bw/day	Change	Increased number of males appeared to be thin in top dose group (6/50 animals).		
42			rat	10	days	Oral	500	mg/kg bw/day	Increase	Crusty eye (s), crusty nose and/or muzzle, damp and yellow/brown-stained fur in perianal and/or abdominal region were noted in several high dose females. Additionally, staggered gait, emaciation, loose stool, weakness, and/or lethargy were noted for 4 high dose dams		
28		Food consumption	rat	28	Days	Oral	500	mg/kg bw/day	Decrease	Dose-dependent trend to lower food intake in treated male and female at 500 and 1000 mg/kg bw (Overall M: ↓18% and F: ↓12%) for weeks 1-4, especially during the first two weeks following the dose changes (F:↓12 to M: 19% vs. control weeks 2-4).		
29a			rat	28	Days	Oral	500	mg/kg bw/day	Decrease	In high-dosed animals, the mean food consumption was decreased during week 1 in both males and females (-10 to -13% vs. control) and to a lesser extent in females during the 2nd week also (-5 to -7%). The overall food consumption during the study was similar in all male groups but remained slightly decreased in high-dosed females (-3 to -4%). Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%), only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively.		

									This indicates that a dose of 500 mg/kg/day exceeded the MTD.		
29b		rat	28	Days	Oral	500	mg/kg bw/day	Decrease	In high-dosed animals, the mean food consumption was decreased during week 1 in both males and females (-10 to -13% vs. control) and to a lesser extent in females during the 2nd week also (-5 to -7%). The overall food consumption during the study was similar in all male groups but remained slightly decreased in high-dosed females (-3 to -4%). Study considered supportive only; for each batch of test material (Batch A 96.2% and Batch B 96.1%), only two dose levels were tested (100 and 500 mg/kg) with toxicity already at the low dose-level and mortality at the high dose-level. One female dosed with 500 mg/kg/day (Batch A) and one male and two females dosed with 500 mg/kg/day (Batch B) were sacrificed in moribund condition at experimental days 2 and 3, respectively. This indicates that a dose of 500 mg/kg/day exceeded the MTD.		
30		rat	90	Days	Oral	208.6	mg/kg bw/day	Decrease	Food consumption of the high-dosed animals was generally lower, but not significantly lower than in other groups (average reduction of 10% vs. control)		
34a		Dog	90	Days	Oral	132	mg/kg bw/day	Decrease	Reduced food intake week 1-13 was noted in males (34%)		
34a		Dog	90	Days	Oral	137	mg/kg bw/day	Decrease	Reduced food intake week 1-13 was noted in females (36%).		
34b		Dog	12	Months	Oral	16.8	mg/kg bw/day	Decrease	Food consumption at the top dose level was drastically reduced during the first weeks 1-19 (M↓29%) of the study and improved slowly during the following weeks. Food consumption returned to normal when top dose was reduced from 5000 to 2500 ppm.		
34b		Dog	12	Months	Oral	16.5	mg/kg bw/day	Decrease	Food consumption at the top dose level was drastically reduced during the first weeks 1-19 (F↓32%) of the study and improved slowly during the following		

								weeks. Food consumption returned to normal when top dose was reduced from 5000 to 2500 ppm.		
35	mouse	90	Days	Oral		ppm	No effect	Food consumption was reduced in both sexes receiving 3000 and 5000 ppm on day 1, but there were no consistent effects as the study progressed.		
38	mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No consistent evidence of an effect of treatment on food consumption but food utilisation was less efficient than that of controls in females in the top dose group.		
38	mouse	80	Weeks	Oral		mg/kg bw/day	No effect	No consistent evidence of an effect of treatment on food consumption but food utilisation was less efficient than that of controls in males in the top dose group		
40a	rat	110	days	Oral	153	mg/kg bw/day	Decrease	FC was slightly reduced during pre-mating (-4.5%) and gestation (-5.1%) in adult F0 female.		
40a	rat	110	days	Oral	153	mg/kg bw/day	Decrease	FC was slightly reduced during premating (-4.2%) and gestation (-8.8%, days 0-6) in adult F1 female.		
40a	rat	110	days	Oral	156	mg/kg bw/day	Decrease	FC was slightly reduced (-7.1%) after mating in F1 adult M.		
40b	rat	19	Weeks	Oral	225	mg/kg bw/day	Decrease	A slight reduction was seen during premating for high dose females of both generations (F0: -7.1%, F1 -7.6%). FC during gestation was also significantly lower than controls for high dose F0 females (-7%), slight reduction seen for F1 females (-3.7%). During lactation, high dose females of both generations also consumed slightly less (not significant) food than controls (F0: -4.5%, F1: -4.2%).		
40b	rat	25	Weeks	Oral	225	mg/kg bw/day	Decrease	A slight reduction was seen during premating for high dose females of both generations (F0: -7.1%, F1 -7.6%). FC during gestation was also significantly lower than controls for high dose F0 females (-7%), slight reduction seen for F1 females (-3.7%). During		

										lactation, high dose females of both generations also consumed slightly less (not significant) food than controls (F0: -4.5%, F1: -4.2%).		
41a			rat	10	Days	Oral	300	mg/kg bw/day	Decrease	Reduced FC at 300 mg/kg bw/day (by 16% for GD 6-11), FC during complete treatment period was reduced by 9%. FC reductions were slight at the low and mid dose group for GD 6-11 (low dose -7.3%, mid dose -9.4%)		
41b			rat	5	Days	Oral	300	mg/kg bw/day	Decrease	At 300 mg/kg bw/day, food consumption gain was markedly decreased during the first days of treatment (by 17% on GD 6-11) and overall by 13% during the complete treatment period (GD 6-16). Food consumption was also still decreased during GD 16-21. FC at 450 mg/kg bw/day was somewhat decreased (treatment for gestation days 10-14 only).		
42			rat	10	days	Oral	500	mg/kg bw/day	Decrease	FC was transiently reduced for high (-42%) dose animals on GD 6 following the first dosing while it was comparable to controls at GD 13 and 19. A slightly lower food consumption on GD 6 for mid-dose animals was reported but is not considered adverse.		
43			rabbit	14	days	Oral	150	mg/kg bw/day	Decrease	Reduced FC in high dose females during GD 6-19; -13% (test chemical was administrated GD 6-18)		
44			rabbit	13	days	Oral	200	mg/kg bw/day	Decrease	Reduced FC in high dose females, most markedly in the first week of treatment* (GD 7-10: -43%, GD 10-14; -54%, GD 7-20: -37%). *The test chemical was administrated from GD 7-19 only.		
32		Mortality	rat	90	Days	Oral		ppm	No effect	No effect on mortality up to the highest dose level tested (2400 ppm).		
33			mouse	90	Days	Oral	500	ppm	Increase	One female in each of the 2400- and the 1000-ppm dose groups and one male in the 500-ppm dose group died during study week 8. No clinical observations were reported for these animals before death.		

35		mouse	90	Days	Oral	5000	ppm	Increase	Killed for humane reasons due to BW loss during the first week.		
40a		rat	110	days	Oral	153	mg/kg bw/day	Increase	Three dams died post partum in Adult (F0): one dam died day 4, one dam died day 11 and one dam died shortly after delivery. No observations on possibly impaired parturition were recorded for any of these dams and all of these dams completed parturition and delivered all pups. Dam mortalities after parturition may be related to maternal toxicity; however, RMS cannot exclude a link to dystocia.		
40a		rat	110	days	Oral	153	mg/kg bw/day	Increase	Three dams died post partum in Adult (F1): one dam died day 4, and two dams died day 2. No observations on possibly impaired parturition were recorded for any of these dams and all of these dams completed parturition and delivered all pups. Dam mortalities after parturition may be related to maternal toxicity; however, RMS cannot exclude a link to dystocia.		
41a		rat	10	Days	Oral	300	mg/kg bw/day	Increase	At 300 mg/kg bw/day, 2 dams died shortly before the autopsy on gestation day 21. Autopsy did not reveal any obvious pathological condition.		
41b		rat	5	Days	Oral	300	mg/kg bw/day	Increase	Four and 2 dams died at 300 and 450 mg/kg bw/day, respectively, shortly before the autopsy on gestation day 21. Autopsy did not reveal any obvious pathological condition.		
42		rat	10	days	Oral	500	mg/kg bw/day	Increase	Two gravid and one non-gravid females at 500 mg/kg bw/day (on day 10, 11 and 12, respectively; clinical signs were observed ante mortem and occurrence of stomach and intestinal lesions).		
46		Mallard duck	23	weeks	Oral	No effect	ppm	No effect	No effects on survival in the parental generation up to the highest dose level tested (1000 ppm).		
49a		Rat	14	Days	Oral	No effect	mg/kg bw/day	No effect	No effect up to the highest dose level tested 320 mg/kg bw/day		

49b			Mouse	14	Days	Oral	No effect	mg/kg bw/day	No effect	No effect up to the highest dose level tested 320 mg/kg bw/day			
36	No relevant effect observed	No relevant effect observed	rabbit	21	days	Dermal		mg/kg bw/day	No effect				
37	No relevant effect observed	No relevant effect observed	mouse	107	Weeks	Oral		ppm	No effect				
37	No relevant effect observed	No relevant effect observed	mouse	106	Weeks	Oral		ppm	No effect				
38	No relevant effect observed	No relevant effect observed	mouse	80	Weeks	Oral		mg/kg bw/day	No effect				
38	No relevant effect observed	No relevant effect observed	mouse	80	Weeks	Oral		mg/kg bw/day	No effect				
39	No relevant effect observed	No relevant effect observed	rat	117	Weeks	Oral		mg/kg bw/day	No effect				

39	No relevant effect observed	No relevant effect observed	rat	116	Weeks	Oral		mg/kg bw/day	No effect				

2.10.2.2.2.1 Assessment of the integrated lines of evidence and weight of evidence for EAS-mediated adversity and endocrine activity

Table 168: WoE for EAS-mediated adversity

- **Overall conclusion: No evidence for a consistent pattern of endocrine adversity. However, the EAS-modality is not sufficiently investigated.**
- **The most relevant studies for adversity are two 2-generations rat studies which did not show any ED effects; however, several relevant ED parameters are missing. In both studies, the doses chosen were too low (based on weight loss in the rats not consistently exceeding 10% of their body weight).**
- **Testicular toxicity observed in the 90-day study and in the 1-year dog study receiving top dose: Cellular debris in epididymis (90 days), reduced spermatogenesis and reduced testis weight (90 days and 1-year) and tubular atrophy (1-year). Effects observed above the MTD (90 days) and around the MTD (1-year).**
- **EAS parameters were also examined in other studies at different dose levels and of different durations in rats and mice by oral administration of the substance and no adversity was observed. However, in several studies, dose levels were not optimal. Three available carcinogenic long-term studies are available (two in mice and one in rats). The selected dose levels in the first mouse study and in rats were conducted below the MTD (too low to reveal any adverse effect on the examined endpoints).**
- Target organ toxicity was observed in the adrenal and kidney
- For the liver, target organ toxicity was mainly characterized by hypertrophy; however, necrosis and fibrosis in dogs (500 ppm) and hepatic degeneration in rats (1000 ppm) could be considered adverse.

Although the available dataset for EAS-mediated adversity is negative this dataset is not considered sufficient based on two old OECD TG 416 studies conducted prior to 2001. The two studies are considered supportive only as dose levels were considered too low (based on weight loss in the rats not consistently exceeding 10% of their body weight) and due to the age of these studies that they do not assess all parameters which are required by the EFSA-ECHA ED guidance document to conclude that all "EATS-mediated" parameters have been sufficiently investigated. The major deviations from current guideline are summarized in the table below:

Table 169: Overview over selected parameters investigated and missing parameters in the two-generation studies according to OECD TG 416.

Parameter	Assessed in two-generation study (study ID 40a)	Assessed in two-generation study (study ID 40b)
Gross necropsy	Yes	Yes
Time to mating		

Gestation length Number of implantations Litter size Fertility Post-implantation loss	Yes	Yes
Number of live births	Yes (but for some litters it was uncertain whether the pups were born alive or dead)	Yes
Number of corpora lutea	No	No
Sex ratio	Yes	Yes
Oestrus cyclicity	No	No
Sperm analysis (morphology, motility, numbers)	No	No
Ano-genital distance*	No *(should be measured at postnatal day 0 in F2 pups if triggered by alterations in F1 sex ratio or timing of sexual maturation)	No *(should be measured at postnatal day 0 in F2 pups if triggered by alterations in F1 sex ratio or timing of sexual maturation)
Age of vaginal opening and preputial separation	No (incidences of vaginal opening and whether testes had descended recorded at predefined ages considered reasonable substitute for measuring age when sexual developmental landmarks were reached (however suboptimal reporting)	No
Organ weights: uterus, ovaries, testes, epididymis (total and cauda), prostate, seminal vesicles with coagulating glands and their fluids (as one unit), pituitary, thyroid, and adrenal glands	Only testes/epididymis weighed in P (F0) adults, coagulating gland, epididymis, uterus, prostate, seminal vesicles, pituitary, and thyroid not weighed in F1 adults, 5 weanlings/sex/group used for organ weights	Testes and ovaries were weighed in P (F0) and F1 adults, and selected F1 and F2 pups (10 sex/group), uterus, epididymis, prostate, seminal vesicles with coagulating glands, brain, liver, kidneys, spleen, pituitary, thyroid, adrenals not weighed in adults, and brain, spleen and thymus not weighed in pups
Histopathological examination: vagina, uterus (with cervix), ovaries, testis, epididymis, seminal vesicles, prostate (and coagulating gland)	Several tissues not examined in adults (uterus, vagina, seminal vesicle, coagulating gland; epididymis only in F0), 5 weanlings/sex/group used for histopathological examinations	Yes 10 weanlings/sex/group used for histopathological examinations

While there was no observable EAS-mediated adversity in the two 2-generation studies, some parameters sensitive to, but not diagnostic of, EATS occurred in the 2-generation studies and in the developmental toxicity studies. There were no consistent effects on sexual function and fertility throughout the studies. Although some effects, like for instance increased gestation length was seen in the 2-generation study 40a, there was no effect on gestation length in 2-generation study 40b conducted with a slightly higher top dose. Several effects indicative of developmental toxicity was however observed in the available studies in accordance with penconazole being classified as H361d (Suspected of damaging the unborn child):

- Post-implementation loss in the form of early resorptions was seen in all developmental studies except one study in rabbits (study ID 43; the higher number of resorptions was considered unrelated to treatment).
- Litter/pup weight was decreased postnatally in both 2-generation studies at the top dose.
- Presence of anomalies were seen in the developmental toxicity studies; however, the effects are not pronounced and consistent in the different studies: the most severe malformations were seen in one study in rabbit (study ID 43) with increase in internal hydrocephalus and bilateral microphthalmia (within range but exceeded mean +-SD) at the top dose (150 ppm). Variations or delays in development were otherwise seen throughout the other studies; incomplete/absent ossification occurred in rats (study ID 41 and 42) and in rabbits (study ID 44) in addition to supernumerary cervical ribs (study ID 42), all in the presence of maternal toxicity.
- A slightly change occurred in the numbers of embryonic or foetal deaths and viable foetuses in the developmental toxicity studies; number of dead foetuses slightly increased in two rat studies at the top dose (study ID 41 and 42) and reduced live foetuses/litters in addition to two dead foetuses were recorded in rabbits (study ID 44).

EAS-mediated adversity (anti-androgenic activity) was observed in male dogs only (study ID 34a and 34b; 90-day study and 1-year study), but these effects were observed largely above the MTD at 5000 ppm (132 mg/kg bw/day) in the 90-day study and around the MTD at 2500 ppm (108 mg/kg bw/day) in the 1-year study. Cellular debris in epididymis (90 days), reduced spermatogenesis and reduced testis weight (90 days and 1-year) and tubular atrophy of the seminiferous epithelium associated with formation of giant cells (1-year) were observed. Reduced spermatogenesis was however not observed in the 2 dogs sacrificed after a four-week recovery period. The relative decreases in gonad weights in the 90-day study were not consistent compared to control, low to high dose (+23%, -4%, -27%) but both absolute weight (-47%) and relative testis weight (-27%) were markedly decreased at the top-dose.

In the 90-day study, body weight gain was reduced -12% and food consumption was reduced -34%, week 1-13 in males. Dogs (90 days) received only the highest dose level (132 mg/kg bw/day), while this dose level was reduced to 108 mg/kg bw/day (1-year study) during week 20 due to excessive reduction in food consumption -19% and body weight gain, -29% of the animals in that group. After dose reduction, top dose animals then gained more weight for the remainder of the treatment period as the other groups, including controls, while overall BW gain was reduced (-44%). Notably, the two males sacrificed after the recovery period also gained weight during the recovery weeks (body weight at termination was increased +11% compared to control).

A dose-dependent increase in relative liver weight was also observed in the 90-days study: +2, +15, +75% for males while there was no dose-dependent increase in liver weight for males in the 1-year study with increase at the top dose only, +21%. In addition, hepatocyte necrosis was observed in 4/4 males in the 90-day study compared to 1/4 males in the 1-year study.

Taking the body weight effects in the 90-days study and in the 1-year study into consideration (week 1-19), the reduced testis weight and associated histopathological findings can be considered secondary to systemic toxicity. Further, these anti-androgenic effects were not observed in rats or mice. However, it should be noted that in the 2-generation studies, the carcinogenicity study (rats) and in several of the 90-day studies in rats, the doses chosen were not considered to be high enough to reveal adverse effects on the examined endpoints. In addition, several of the studies are considered supportive due to deviations from their respective current guideline.

The dataset available shows positive S-modality activity based on the inhibition of testosterone and estradiol synthesis at the OECD TG 456. As an endocrine gland, producing also steroid hormones and cortisol, the adrenal can be directly linked to steroidogenesis. Effects on adrenals are addressed in the EFSA-ECHA ED GD (EFSA Journal 2018;16(6):5311) as a "*sensitive to, but not diagnostic of ED*" parameter. Although the effects on the adrenal

cannot be considered diagnostic on their own the effects might contribute to the evaluation of adversity and provide indications of an endocrine MoA that might warrant further investigation. There were indications of treatment-related adverse effects on adrenal based on findings in rats and dogs. In rats treated with a top dose of 500 mg/kg/bw/day for 28 days, absolute adrenal weight was increased (male 18% and female 24% in study ID 29a and male 14% and female 22% in study ID 29b) and cortical atrophy was observed in 8/10 females and 9/10 females (study ID 29a and ID 29b, respectively). In female dogs treated with a top dose of 110 mg/kg/bw/day for 12 months, absolute and relative adrenal weights were increased (abs:34%, rel: 54%) in absence of histopathological changes and in presence of lower BW (study ID 34b). Adrenal histopathology and weight were investigated in rats, dogs and mice, in totally 8 (histopathology) and 10 (weight) studies. Although there were no consistent adverse effects on adrenal, dosing was not optimal in several of the studies, as described in the previous sections.

Table 170: WoE for EAS-mediated endocrine activity

- **Overall conclusion: Evidence of AR and ER-mediated activity (antagonism) and effects (inhibition) on steroidogenesis activity *in vitro***

- **Several *in vitro* assays were positive, providing evidence of ER and AR-mediated antagonistic activity:**

- ToxCast ER bioactivity (agonism: neg- and antagonism: pos+)
- ToxCast AR bioactivity (agonism: neg- and antagonism: pos+)
- Open literature study: Inhibition of testosterone-induced AR activation

- **Several *in vitro* assays were positive, providing evidence of inhibition of steroidogenic activity:**

- ToxCast Steroidogenesis activity (inhibition of aromatase)
- Open literature studies (inhibition of aromatase)
- OECD 456 (inhibition of testosterone and estradiol synthesis)

Penconazole is examined in the United States Environmental Protection Agency's ToxCast™ programme, which includes binding, transactivation and steroidogenic assays equivalent to OECD Conceptual Framework Level 2. In addition, open literature studies are available. For penconazole, the EAS-mediated endocrine activity is not sufficiently investigated e.g., studies are missing for E-modality (ToxCast ER Bioactivity Model and OECD TG 455 not available) and A-modality (AR Bioactivity Model and OECD TG 458 not available). However, the available *in vitro* dataset from ToxCast and open literature is positive for ER and AR-mediated antagonism as well as for inhibition of steroidogenic activity; both inhibition of CYP19 and of inhibition of testosterone and estradiol synthesis (OECD TG 456.) Taken together, these results provide evidence indicative of endocrine activity for the E, A and S-modality, which is sufficient to start a MoA analysis.

2.10.2.2.3 Initial analysis of the evidence and identification of relevant scenario for the ED assessment of EAS-modalities

Table 171: Selection of relevant scenario

Adversity based on EAS-mediated parameters	**Positive mechanistic OECD CF level 2/3 Test**	**Scenario**	**Next step of the assessment**	**Scenario selected**
No (sufficiently investigated)	Yes/No	1a	Conclude: ED criteria not met because there is not "**EAS-mediated**" adversity	
Yes (sufficiently investigated)	Yes/No	1b	Perform MoA analysis	
No (not sufficiently investigated)	Yes	2a (i)	Perform MoA analysis (additional information may be needed for the analysis)	X

Adversity based on EAS-mediated parameters	**Positive mechanistic OECD CF level 2/3 Test**	**Scenario**	**Next step of the assessment**	**Scenario selected**
No (not sufficiently investigated)	No (sufficiently investigated)	2a (ii)	Conclude: ED criteria not met because no **EAS-mediated endocrine activity** observed	
No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	
Yes (not sufficiently investigated)	Yes/No	2b	Perform MoA analysis	

2.10.2.2.4 MoA analysis for EAS-modalities

2.10.2.2.4.1 Postulate MoA

Table 172: Description of the postulated MoA (androgen receptor antagonist)

	Description	**Supporting Evidence**
MIE	Androgen receptor antagonist	*In vitro* assays using human cell lines (ToxCast) and one open literature using human cell line showing inhibition of testosterone-induced AR activation. Concordance between assays. (supporting evidence of anti-androgenic activity) (study ID 2, 17, 19, 20)
KE1	Decrease in transcription of genes by the androgen receptor.	No data/studies available for penconazole
KE2	Reduced testis weights	Shown in 90-days and 1 year dog study (study ID 34a, b)
KE3	Reduced spermatogenesis	Shown in 90-days and 1 year dog study (study ID 34a, b)
KE4	Tubular atrophy of the seminiferous epithelium associated with formation of giant cells	Shown in 1-year dog study (Study ID 34b)
AO	Impairment of male reproductive capacity	Shown in 90-days and 1 year dog study (study ID 34a ,b)

Table 173: Description of the postulated MoA (inhibition of steroidogenesis)

	Description	**Supporting Evidence**
MIE	Inhibition of steroidogenic enzymes (testicular steroidogenesis) in Leydig cells	No data available on inhibition of steroidogenic enzymes catalysing the steps from cholesterol to testosterone while *in vitro* studies, both open literature and ToxCast, show inhibition of CYP19 (enzyme responsible of catalysing the aromatization of androgens to estrogens) (study ID 4, 5, 6, 27)
KE1	Inhibition of testosterone synthesis	Measured in H295R steroidogenesis assay (study ID 45)
	Decreased testicular testosterone	No data/studies available for penconazole
KE2	Decrease in transcription of genes by the androgen receptor.	No data/studies available for penconazole
KE3	Reduced testis weights	Shown in 90-days and 1 year dog study (study ID 34a, b)

	Description	Supporting Evidence
KE4	Reduced spermatogenesis	Shown in 90-days and 1 year dog study (study ID 34a, b)
KE5	Tubular atrophy of the seminiferous epithelium associated with formation of giant cells	Shown in 1-year dog study (Study ID 34b)
AO	Impairment of male reproductive capacity	Shown in 90-days and 1 year dog study (study ID 34a, b)

The postulated Mode of Actions include three KE (reduced testis weights, reduced spermatogenesis and tubular atrophy) observed above the **MTD** (90 days dog) and/or around the **MTD** (1-year dog). These effects may be considered secondary to systemic toxicity. There were no consistent treatment related effects on testis in rats and mice; however, dosing was not optimal in several of these studies.

2.10.2.2.4.2 Further information to be generated to postulate MoA

No endocrine adversity was observed in rats and mice, but as highlighted in section 2.2.2.1, relevant ED parameters are missing from the two available 2-generation studies. It is therefore not possible to postulate a MoA in rats to address the positive Level 2 outcome for endocrine activity for the EAS-modalities. A MoA analysis for anti-androgenic activity is therefore postulated here to address the adversity observed in male dogs; however, the reduced testis weights associated with histopathological changes can be considered secondary to systemic toxicity. Although there were no consistent effects on testis weights or testis histopathology in rats or mice, RMS is of the opinion that the dose levels chosen in many of these studies are not high enough to address the examined endpoints and that higher dose levels may be needed to remove the concern arising from the available *in vitro* mechanistic data. The MoA presented here is therefore a theoretical explanation that the findings in dogs could arise from penconazole acting as an androgen receptor antagonist action and/or inhibition testosterone synthesis, but a biological plausible link between endocrine activity and EAS-mediated adversity is not possible to establish as the adversity is observed together with excessive systemic toxicity, in addition, there are no *in vivo* mechanistic data available for penconazole to support the postulated MoA.

RMS proposes that a complete dataset is needed to investigate adversity e.g., that OECD TG 416 (latest version) should be conducted, with investigation of the following parameters in line with the EFSA "Technical report on the outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology" (EFSA supporting publication 2020:EN-1837, page 6-7, doi:10.2903/sp.efsa.2020.EN-1837)): anogenital distance (AGD), nipple retention, mammary gland histopathology and hormone measurements. A complete dataset from a Level 5 study would fully address the concern arising from the positive outcome of the Level 2 studies, which would be sufficient to conclude whether the ED criteria are met or not.

2.10.2.2.4.3 Empirical support of the postulated MoA

Not applicable considering the limited data available.

2.10.2.2.4.4 Empirical support of the postulated MoA

Not applicable considering the limited data available.

2.10.2.2.5 Conclusion of the assessment of EAS-modality

Overall, the WoE indicates that EAS-mediated adversity was not observed for penconazole. However, the dataset for the assessment of EAS-mediated adversity was not considered sufficient. According to the ECHA/EFSA ED GD, the available dataset for endocrine activity is short of Level 2 studies in line with OECD TG 455 (ER transactivation assays) and OECD TG 458 (AR STTA assays). However, as also literature and *in vitro* mechanistic ToxCast data were collected, the overall results are considered sufficient as evidence indicative of endocrine activity for the E, A and S- modality which triggers a MoA analysis. In RMS's opinion, a complete dataset is needed to investigate adversity e.g., that OECD TG 416 (latest version) should be conducted, with investigation of the following parameters: anogenital distance (AGD), nipple retention, mammary gland histopathology and hormone measurements. A complete dataset from a Level 5 study would fully address the concern arising from the positive outcome of the Level 2 studies. Further, the execution of the endpoints in a single experimental set is expected to

minimize all the uncertainties associated with comparing endpoints between different study designs uncertainties associated with the study design.

2.10.2.2.6 Overall conclusion on the ED assessment for humans

The available dataset was indicative of T-mediated activity: Uridine diphosphate [UDP]-glucuronyl transferase was increased in rat and mouse hepatocytes. There was no consistent evidence of T-mediated adversity: Increased thyroid weight and incidences of minimal hypertrophy of the follicle epithelium was observed in one study (short term 28 day) in one species (rat) and were considered adverse. However, these findings were not confirmed in other studies. Although there were no consistent effects on T-mediated adversity and activity, RMS is of the opinion that these parameters may not have been sufficiently investigated.

The available dataset was positive for EAS-mediated activity. There was evidence of AR and ER-mediated activity (antagonism) and effects (inhibition) on steroidogenesis activity *in vitro*. There was no consistent evidence of EAS-mediated adversity: Testicular toxicity was observed in the 90-day study and in the 1-year dog study receiving top dose (cellular debris in epididymis (90 days), reduced spermatogenesis and reduced testis weight (90 days and 1-year) and tubular atrophy (1-year)). These effects were observed above the MTD (90 days) and around the MTD (1-year). EAS parameters were also examined in other studies at different dose levels and of different durations in rats and mice by oral administration of the substance and no adversity was observed. However, RMS is of the opinion that EAS-adversity has not been sufficiently investigated.

In summary, as the endocrine disrupting properties of penconazole have not been sufficiently investigated, a firm conclusion regarding the endocrine disruption potential of penconazole cannot be drawn.

2.10.3 ED assessment for non-target organisms

2.10.3.1 ED assessment for T-modality

2.10.3.1.1 Have T-mediated parameters been sufficiently investigated?

Table 174: Have T-mediated parameters been sufficiently investigated?

	Sufficiently investigated
T-mediated parameters	*Non-target organisms other than mammals* No, as none of the following studies, measuring T-mediated adversity and/or activity, in non-target organisms other than mammals are available: - LAGDA (OECD 241) - AMA (OECD 231) - XETA (OECD 248) *Mammals as non-target organisms* T-mediated parameters for mammals as non-target organisms have not been sufficiently investigated, please see Section 2.10.2.1.

2.10.3.1.2 Lines of evidence for adverse effects and endocrine activity related to T-modality

Table 175: Lines of evidence for adverse effects and endocrine activity related to T-modality

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
21	In vitro mechanistic	Thyroid receptor	rat, pituitary gland, cell line	28	Hr	Uptake from the medium (in vitro)	0	µM	No effect	ToxCast TR model: No TR mediated agonistic activity	Evidence for TR mediated antagonistic activity *in vitro*, (Penconazole was active in one of these assays (TOX21_TR_LUC_GH3_Antagonist); however, the viability readout was also active and interference with cytotoxicity cannot be excluded.)	Overall, indication of endocrine activity, based on *in vivo* mechanistic data (study ID 49a and 49b) showing marked liver enlargement in rats and mice at 80 mg/kg bw/day and higher (dose-dependent) and a pronounced induction in the activity of several hepatic xenobiotic metabolising enzymes (uridine diphosphate [UDP]-glucuronyl transferase).	**T**
22		Thyroid receptor	rat, pituitary gland, cell line	28	Hr	Uptake from the medium (in vitro)	56.89	µM	Change	ToxCast TR model: TR mediated antagonistic activity			
24		TSH receptor (in vitro)	human, kidney, cell line	0,5	Hr	Uptake from the medium (in vitro)	0	µM	No effect	ToxCast TSHR: No TSHR mediated activity	Negative, no effect on TSHR *in vitro*		
25		TSH receptor (in vitro)	human, kidney, cell line	0,5	Hr	Uptake from the medium (in vitro)	111.95	µM	No effect	ToxCast TSHR: No TSHR mediated activity			
26		TSH receptor (in vitro)	human, kidney, cell line	0,5	Hr	Uptake from the medium (in vitro)	0	µM	No effect	ToxCast TSHR: No TSHR mediated activity			
48	Sensitive to, but not diagnostic of,	Behaviour (fish)	Fathead minnow	94 (post hatch)	Days	Uptake from water		mg/L water	No effect	No effects on behaviour	No effects on behaviour or appearance.	Parameters investigated are sensitive to but not diagnostic of EATS and cannot be assigned to a specific modality. These data cannot by themselves provide (or support) evidence of adversity.	May indicate a specific modality, but not
48		Appearance [Not in list]		94 (post hatch)	Days	Uptake from water	No effect	mg/L water	No effect	In the study report it is stated that "No abnormal appearance" was observed. No further information is provided.			

46	EATS	Behaviour [Not in list]	Mallard duck	23	weeks	Oral	No effect	ppm	No effect	No abnormal behavioural reactions noted which could be attributed to the treatment		diagnostic of EATS
47		Body weight (fish)	Fathead minnow	30 (post hatch)	Days	Uptake from water	0.68	mg/L water	Decrease	Dose dependent effect	Decreased fish length and weight observed at doses of 0.68 mg a.s./L and above in one study. Decrease embryo length observed at 0.8 mg a.s./L and above. In neither of the fish studies effects on growth was statistically significant at 0.6 mg a.s./L or below. No effects in Mallards.	
48				94 (post hatch)	Days	Uptake from water		mg/L water	No effect*	No effects in males, females or combined. The highest dose tested was 0.6 mg a.s./L . *12.7% reduction in males was observed at the top dose of 0.6 mg a.s./L however not statistically significant).		
46		Body weight (bird)	Mallard duck	23	weeks	Oral		ppm	No effect	No effects on bird weight.		
47		Length (fish)	Fathead minnow	30 (post hatch)	Days	Uptake from water	0.68	mg/L water	Decrease	Dose dependent effect		
48				94 (post hatch)	Days	Uptake from water		mg/L water	No effect	No effects in males, females or combined. The highest dose tested was 0.6 mg/L .		
50[1]		Larval length	Zebrafish (*Danio rerio*)[1]	4	Days	Uptake from water	0.6	mg/L water	Decrease	Significantly ($p < 0.05$) decreased body length at 1.6 mg a.s./L and above (dose dependent response).		
50[1]		Morphological abnormalities	Zebrafish (*Danio rerio*)[1]	4	Days	Uptake from water	0.8	mg/L water	Increase	Significantly ($p < 0.05$) increased malformations (including pericardial edema, yolk-sac edema, axial malformation, tail malformation and spinal curvature) in embryos at		

									concentrations of 0.8 mg/L and above (dose dependent response).				
47		Hatching success	Fathead minnow	4 to 5 (11)	Days	Uptake from water	3.3	mg/L water	Decrease	Impaired hatching at highest dose	Impaired (0%) hatching at the highest dose (3.3 mg a.s./L) in the ELS. In neither of the fish studies effects on hatching was observed at lower doses. Effects on hatchability also observed for Mallards at the top dose.		
48				4	Days	Uptake from water		mg/L water	No effect	No effect (the highest dose tested was 0.6 mg a.s./L.)			
50[1]			Zebrafish (Danio rerio) [1]	4	Days	Uptake from water	0.8	mg/L water	Decrease	Significantly reduced hatching rate at 0.8 mg/L and above, in a dose-dependent manner.			
46		Hatchability	Mallard duck	23	weeks	Oral	1000	ppm	Decrease	73 % of the eggs hatched at top dose compared to 86% in the control.			
46		Cracked eggs	Mallards	23	weeks	Oral		ppm	No effect	No effect	No effects were observed on eggs (other than hatchability, see above) or embryos of Mallards up to the top dose (1000 ppm).		
46		Egg production								No effect			
46		Eggshell thickness								No effect			
46		Viable embryos								No effect			
46		Viability ducklings [Not in list]								No effect on % viability of 14-day old ducklings at any test concentration			

46		Eggs set [Not in list]							no effects on eggs set at any test concentration			
46		Embryos [Not in list]							No effect on no. of or % live 17-day embryos at any test concentration			
50[1]		survival of embryos	Zebrafish (Danio rerio) [1]	4	Days	Uptake from water	0.8	mg/L water	Decrease	In the study, survival of embryos and larvae have been merged, and is significantly decreased at the lowest dose tested in a dose dependent manner. Absolute decrease is not reported but seem from the figure to be >10%.		
50[1]	unknown	Heartbeat rate [Not in list]	Zebrafish (Danio rerio) [1]	4	Days	Uptake from water	1.6	mg/L water	Decrease	Significantly reduced embryo heartbeat rate at 1.6 mg/L and above in a dose dependent manner.		
47	Systemic toxicity	Survival (fish)	Fathead minnow	30 (post hatch)	Days	Uptake from water	3.3	mg/L water	Decrease	Post-hatch survival could not be assessed at the top dose (3.3. mg a.s./L), as none of the eggs hatched. Post-hatch survival was not significantly reduced at the second highest dose (1.5 mg a.s./L).	In the ELS hatchability was 0% at the top dose (3.3. mg a.s./L), and thus survival was also 0%. 3.3 mg a.s./L is thus above the MTC (at least for eggs/embryos).	The dose 3.3 mg a.s./L is probably above the MTC for fish (at least for fish eggs). No other effects on systemic toxicity were observed at the tested doses in fish or in mammals.	Systemic toxicity

[1] This is an open literature study regarded as supportive by RMS. The main reasons why it is considered supportive is the lack of analytical verification of the test substance and uncertainty on whether the study fulfils the validity criteria. RMS is still of the opinion that the results of the study may provide valuable information to be included in a WoE the ED-criteria. For further details, see Volume 3 – B.9.2.2.1, K-CA 8.2.2.1/03.

2.10.3.1.2.1 Assessment of the integrated lines of evidence and weight of evidence for T-mediated adversity and endocrine activity

Table 176: WoE for T-mediated adversity

- **Overall conclusion: No indication of endocrine adversity, however not sufficiently investigated.**

- **No specific endpoints for T-mediated adversity were examined as neither the LAGDA (OECD TG 241) nor the AMA (OECD TG 231) are available.**

- **Sensitive to, but not diagnostic of EATS parameters have been investigated in the Fish sexual development test (FSDT; Study ID 48) and a fish early life stage toxicity test (ELS; study ID 47) with Fathead minnow (98 and 30 days of exposure, respectively), and in an open literature study (Study ID 50) on embryonic development of Zebrafish (4 days of exposure). The open literature study is regarded as supportive, please see Volume 3 – B.9.2.2.1 for further details.**

- **In zebrafish (*Danio rerio*) embryos/larvae, malformations such as pericardial edema, yolk-sac edema, axial malformation, tail malformation and spinal curvature was observed at all doses (0.8, 1.6 mg a.s./L and 2.4 mg a.s./L) in a dose dependent manner. Pericardial edema and yolk sac edema were common malformations in zebrafish embryos exposed to penconazole as compared to other malformations.**

- **Reduced Zebrafish larval length was observed at 1.6 mg/L and above, whereas reduced weight and length in 30-day old Fathead minnow larvae were observed at 0.68 mg a.s./L and above. No statistically significant effects on weight/length of adult fish were observed up to the top dose of 0.6 mg a.s./L in the FSTD. However, RMS notes that a non-statistically significant weight reduction (-12.7%) in male fish was observed at the top dose of 0.6 mg a.s./L in the FSDT.**

Table 177: WoE for T-mediated endocrine activity

- **Overall conclusion: Indication of endocrine activity (based on increased UDP-GT in mice and rats), however not sufficiently investigated.**

- **In one in vivo mechanistic study (open literature study, ID 49, 1985) marked liver enlargement in rats and mice at 80 mg/kg bw/day and higher (dose-dependent) and a pronounced induction in the activity of several hepatic xenobiotic metabolising enzymes (uridine diphosphate [UDP]-glucuronyl transferase) was observed. Increased UDP-GT may be indicative of T-mediated endocrine activity.**

- **Evidence for TR mediated antagonistic activity in vitro, (Penconazole was active in one of these assays (TOX21_TR_LUC_GH3_Antagonist); however, the viability readout was also active and interference with cytotoxicity cannot be excluded) (study ID 22).**

- **ToxCast TSHR showed no TSHR mediated activity (study ID 24, 25, 26).**

- **No studies investigating T-mediated activity in amphibians are available.**

The overall dataset is considered limited with regard to investigation of T-mediated endocrine activity. Please see **Section 2.10.2.1.2.1** for further details. Even though induction of UDP-GT were observed in mammals (mice, rat), the phase II enzyme UDP-GT superfamily is present in all kingdoms of life and is thus also considered relevant for non-mammalian vertebrates such as amphibians and fish ([redacted] **2016.** *The UDP-glycosyltransferase (UGT) superfamily expressed in humans, insects and plants: Animal-plant arms-race and co-evolution.* Biochem Pharmacol. 2016 Jan 1;99:11-7. doi: 10.1016/j.bcp.2015.10.001).

2.10.3.1.3 Initial analysis of the evidence and identification of relevant scenario for the ED assessment of T-modality

Table 178: Selection of relevant scenario

Adversity based on T-mediated parameters	**Positive mechanistic OECD CF level 2/3 Test**	**Scenario**	**Next step of the assessment**	**Scenario selected**
No (sufficiently investigated)	Yes/No	1a	Conclude: ED criteria not met because there is not "**T-mediated**" adversity	
Yes (sufficiently investigated)	Yes/No	1b	Perform MoA analysis	
No (not sufficiently investigated)	Yes	2a (i)	Perform MoA analysis (additional information may be needed for the analysis)	**X**
No (not sufficiently investigated)	No (sufficiently investigated)	2a (ii)	Conclude: ED criteria not met because no **T-mediated endocrine activity** observed	
No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	
Yes (not sufficiently investigated)	Yes/No	2b	Perform MoA analysis	

2.10.3.1.4 MoA analysis for T-modality

Mammals as non-target organisms

Please see **Section 2.10.2.1.4.** Mammals as non-target organisms will be further assessed when a conclusion has been reached in the assessment of the T-modality for humans.

Non-target organisms other than mammals

Even though UDP-GT may also be relevant for non-target organisms other than mammals, the ecotoxicology data-base only included parameters 'sensitive to, but not diagnostic of, EATS'. In addition, no specific evidence investigating endocrine activity in amphibians are available. Therefore, a MoA analysis for the T-modality is not currently possible.

2.10.3.1.4.1 Further information to be generated to postulate MoA

According to the ECHA/EFSA Guidance and in line with the general principle of reduction of unnecessary animal testing, it is recommended to first conclude on the ED properties with regard to humans and in parallel, using the same data package, on mammals as non-target organisms. Only if the criteria are not met for mammals as non-target organisms, the assessment should proceed considering other taxonomic groups, in particular fish and amphibians. As concluded in **Section 2.10.2.1.4.2**, T-mediated adversity has not been sufficiently investigated, and data should first be generated for mammals. Anyhow, RMS would like to propose a testing strategy for non-target organisms other than mammals regarding the T-modality if the outcome of the assessment based on mammalian data indicates that either:

- The ED criteria are not met for humans and mammals as non-target organisms.
- The ED criteria are met for humans but not for mammals as not-target organisms as the adverse effects, based on the same data package, are not considered relevant at population level for mammals as non-target organisms

Testing strategy for non-target organisms other than mammals:
As no evidence is available for amphibians, further Level 2 and 3 information may need to be generated. EFSA has recently published a guideline on when to choose either the AMA or the XETA in the test strategy[37]. As highlighted in the figure below, RMS propose to await the data from the mammalian tox section before proposing the next step in the testing strategy for non-target organisms other than mammals. The testing scheme below should be followed when a conclusion has been reached for humans and mammals as non-target organisms.

[37] Annex A – Use of the XETA in the assessment strategy of the ECHA/EFSA Guidance https://efsa.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.2903%2Fj.efsa.2018.5311&file=efs25311-sup-0002-Annex.pdf

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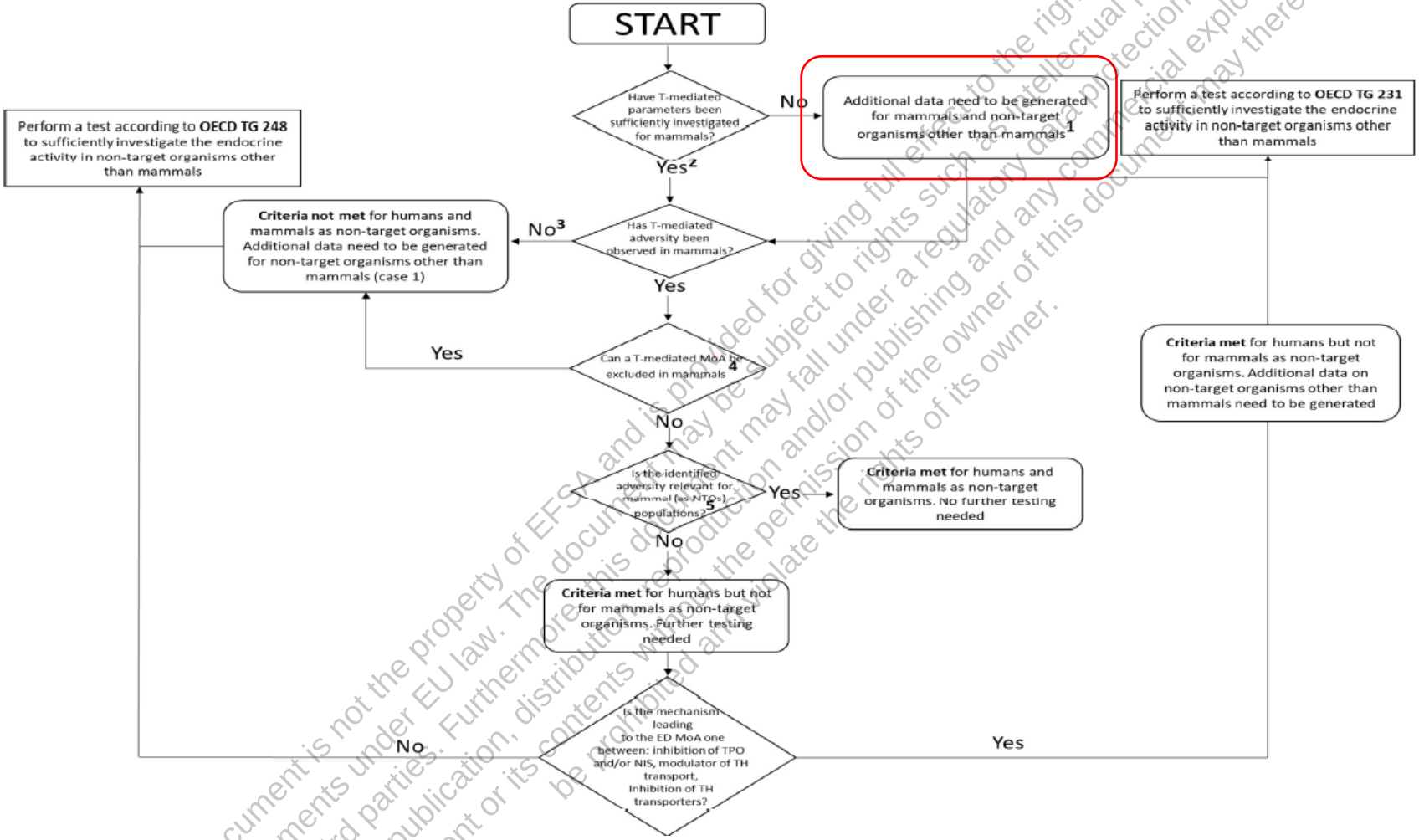


Figure 1. Flowchart illustrating the testing strategy for investigating endocrine activity in amphibians. Red square illustrating the current stage of the test strategy. Source: Annex A – Use of the XETA in the assessment strategy of the ECHA/EFSA Guidance

2.10.3.1.5 Conclusion of the assessment of T-modality

There is evidence of endocrine activity, however, endocrine adversity has not been sufficiently investigated (Scenario 2a (i)). According to **Commission Implementing Regulation (EU) 2018/1659** Penconazole is considered a pending application (submission of the application for renewal (Art. 1 of the Reg. 844/2012) before 10th of November 2018, more specifically the administrative application was 31st of December 2016).

Commission implementing Regulation (EU) 2018/1659 further states: *For such pending applications, it is possible that the information submitted by the applicant does not allow to conclude the assessment as regards whether the scientific criteria for the determination of endocrine disrupting properties set out in point 3.6.5 and point 3.8.2 of Annex II to Regulation (EC) No 1107/2009 are met or not and to conclude whether the ap-proval criteria set out in those points are met or not. Therefore, the European Food Safety Authority ('the Authority') should be able to request additional information from the applicant in order to conclude whether the approval criteria set out in those points are met or not.*

The T-modality has not been sufficiently investigated for mammals as non-target organisms, nor for amphibians. A testing strategy have been presented for mammals in in **Section 2.10.2.1.4.2** and for amphibians in **Section 2.10.3.1.4.1**. According to the flow chart (Figure 1) for AMA and XETA, further data should be generated for mammals prior to deciding on the next step in the test strategy for amphibians.

2.10.3.2 ED assessment for EAS-modalities

2.10.3.2.1 Have EAS-mediated parameters been sufficiently investigated?

Table 179: Have EAS-mediated parameters been sufficiently investigated?

	Sufficiently investigated
EAS-mediated parameters	*Non-target organisms other than mammals* No, based on non-availability[1] of (a final) study measuring EAS-mediated adversity, such as: - **MEOGRT (OECD 240) or FLCTT measuring all endpoints foreseen to be measured in OECD 240 Studies measuring EAS-mediated activity.** [1]A FLCTT have been initiated. As the final results and study report is currently not available, these data have not been included in the current evaluation. *Mammals as non-target organisms* EAS-mediated parameters for mammals as none-target organisms have not been sufficiently investigated, please see **Section 2.10.2.2**.

2.10.3.2.2 Lines of evidence for adverse effects and endocrine activity related to EAS-modalities

Table 180: Lines of evidence for adverse effects and endocrine activity related to EAS-modalities

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
8	In vitro mechanistic	Estrogen receptor	human, breast, cell line	24	Hr	Uptake from the medium (in vitro)	32.1	µM	No effect	Non GLP literature study acceptable as supplementary. Inactive ER binding assay: weak inducer of ER activation in T47Dluc cells (EC50 = 32.1 µM), but cytotoxic effect in T47D cells was evident in the same concentration range as the derived EC50 in T47Dluc cells	Positive, evidence for ER mediated antagonistic activity *in vitro*	Overall evidence of AR and ER mediated activity (antagonism), and effects (inhibition) on steroidogenesis activity *in vitro*, as well as decreased VTG *in vivo.*	**EAS**
9			bovine, uterus, tissue-based cell-free	18	Hr	Uptake from the medium (in vitro)	0	µM	No effect	ToxCast ER model: no ER binding			
10			human, cell-free	18	Hr	Uptake from the medium (in vitro)	0.21	µM	No effect	ToxCast ER model: no ER binding			
11			mouse, cell-free	18	Hr	Uptake from the medium (in vitro)	0	µM	No effect	ToxCast ER model: no ER binding			
12			human, kidney, cell line	24	Hr	Uptake from the medium (in vitro)	90.36	µM	No effect	ToxCast ER model: No ER mediated agonistic activity			
13			human, kidney, cell line	24	Hr	Uptake from the medium (in vitro)	38.17	µM	Change	ToxCast ER model: ER mediated antagonistic activity (only highest conc. above baseline, active)			

14			human, breast, cell line	22	Hr	Uptake from the medium (in vitro)	0	µM	No effect	ToxCast ER model: No ER mediated agonistic activity	
15			human, breast, cell line	22	Hr	Uptake from the medium (in vitro)	66.37	µM	Change	ToxCast ER model: ER mediated antagonistic activity (less than 50% efficacy)	
2		Androgen receptor	human, breast, cell line	24	Hr	Uptake from the medium (in vitro)	17.1	µM	Decrease	Non GLP literature study acceptable as supplementary. Inhibition of testosterone-induced AR activation in a concentration-dependent manner (IC50 = 17.1 µM)	Positive, evidence for AR mediated antagonistic activity *in vitro*
7			yeast	2	Hr	Uptake from the medium (in vitro)	18.28	µM	Change	Non GLP literature study acceptable as supplementary. AR mediated antagonistic effects: IC50 = 18.3 µM (literature study not reliable as the publication has several deficiencies)	
16			human, kidney, cell line	24	Hr	Uptake from the medium (in vitro)	0	µM	No effect	ToxCast AR model: No AR mediated agonistic activity	
17			human, kidney, cell line	24	Hr	Uptake from the medium (in vitro)	38.35	µM	Change	ToxCast AR model: AR mediated antagonistic activity (assay was near or in the cytotoxicity range)	
18			human, breast, cell line	24	Hr	Uptake from the medium (in vitro)	0	µM	No effect	ToxCast AR model: No AR mediated agonistic activity	
19			human, breast, cell line	24	Hr	Uptake from the medium (in vitro)	39	µM	Change	ToxCast AR model: AR mediated antagonistic activity	
20			human, breast, cell line	24	Hr	Uptake from the medium (in vitro)	58.77	µM	Change	ToxCast AR model: AR mediated antagonistic activity	

45		Estradiol synthesis	human, adrenal corticocarcinoma, cell line	48	Hr	Uptake from the medium (in vitro)	0.1	other	Decrease	Inhibition of estradiol synthesis (H295R steroidogenesis assay)	Positive, evidence of effects on steroidogenesis *in vitro* (decreased estradiol synthesis)		
45			human, adrenal corticocarcinoma, cell line	48	Hr	Uptake from the medium (in vitro)	3160	other	Decrease	Inhibition of estradiol synthesis (H295R steroidogenesis assay)			
2		Testosterone level (in vitro)	mouse, leydig, cell line	48	Hr	Uptake from the medium (in vitro)		µM	No effect	Non GLP literature study acceptable as supplementary. No inhibition of Leydig cell testosterone excretion in MA-10 cells	Positive, evidence of effects on steroidogenesis *in vitro* (decreased testosteronel synthesis)		
45		Testosterone synthesis	human, adrenal corticocarcinoma, cell line	48	Hr	Uptake from the medium (in vitro)	0.1	other	Decrease	Inhibition of testosterone synthesis (H295R steroidogenesis assay)			
45			human, adrenal corticocarcinoma, cell line	48	Hr	Uptake from the medium (in vitro)	3160	other	Decrease	Inhibition of testosterone synthesis (H295R steroidogenesis assay)			
4		CYP19	human, adrenal corticocarcinoma, cell line	24	Hr	Uptake from the medium (in vitro)	20	µM	Change	Non GLP literature study acceptable as supplementary. Inhibition of CYP19: *in vitro* weak competitive aromatase inhibition in H295R cells (IC50 = 20 µM)	Positive, evidence for aromatase inhibition in vitro		
5			n/a			[Not in list]	0.85	µM	Change	Non GLP literature study acceptable as supplementary. Inhibition of CYP19: *in vitro* aromatase inhibition using dibenzylfluorescein as substrate (IC50 = 0.85 µM)			
6			n/a			[Not in list]	47	µM	Change	Non GLP literature study acceptable as supplementary. Inhibition of CYP19: *in vitro* weak aromatase inhibition, LC-MS/MS method using testosterone as substrate (IC50 = 47 µM)			

27			human, breast, cell line	24	Hr	Uptake from the medium (in vitro)	12.32	µM	Change	ToxCast Steroidogenesis model: inhibition of CYP19			
48	In vivo mechanistic	Vitellogenin (VTG) in females	Fathead minnow	94 (post hatch)	Days	Uptake from water	0.6	mg/L water	Decrease	Decrease in VTG at top dose	Decreased VTG may be indicative of endocrine activity		
48		Vitellogenin (VTG) in males	Fathead minnow	94 (post hatch)	Days	Uptake from water	0.6	mg/L water	Decrease	Decrease in VTG at top dose			
48	EATS-mediated	Sex ratio (Female biased)	Fathead minnow	94 (post hatch)	Days	Uptake from water		mg/L water	No effect	No effects on sex-ratio	There is no evidence of adversity (sex ratio) during the developmental part of the life cycle, however, effects on reproduction (fecundity and fertility) have not been investigated.	Overall, no evidence of EAS-mediated adversity, but not sufficiently investigated.	
48		Specific gonad histopathology	Fathead minnow	94 (post hatch)	Days	Uptake from water		mg/L water	No effect	No effect on specific gonad histopathology reported. However, not all criteria listed in the respective OECD Guidance on fish gonad histopathology (2010) were assessed (such as proportion of spermatogonial alterations in interstitial cells and perifollicular cells, gonadal staging, etc.). RMS has thus concluded that the gonad histopathological examination conducted in the current study cannot be considered fully reliable, and the conclusion on the gonad histopathology from the current study should be interpreted with caution in the ED assessment.			
48	Sensitive to, but not diagnostic of,	Behaviour (fish)	Fathead minnow	94 (post hatch)	Days	Uptake from water		mg/L water	No effect	No effects on behaviour	No effects on behaviour or appearance.	Parameters investigated are sensitive to but not diagnostic of EATS, and cannot be assigned to a	May indicate a specific modality, but
48		Appearance [Not in list]		94 (post hatch)	Days	Uptake from water	No effect	mg/L water	No effect	In the study report it is stated that "No abnormal appearance" was observed. No further information is provided.			

46	EATS	Behaviour [Not in list]	Mallard duck	23	weeks	Oral	No effect	ppm	No effect	No abnormal behavioural reactions noted which could be attributed to the treatment	Decreased fish length and weight observed at doses of 0.68 mg a.s./L and above in one study. Decrease embryo length observed at 0.8 mg a.s./L and above. In neither of the fish studies effects on growth was statistically significant at 0.6 mg a.s./L or below. No effects in Mallards.	specific modality. These data cannot by themselves provide (or support) evidence of adversity.	not diagnostic of EATS
47		Body weight (fish)	Fathead minnow	30 (post hatch)	Days	Uptake from water	0.68	mg/L water	Decrease	Dose dependent effect			
48				94 (post hatch)	Days	Uptake from water		mg/L water	No effect*	No effects in males, females or combined. The highest dose tested was 0.6 mg a.s./L . *12.7% reduction in males was observed at the top dose of 0.6 mg a.s./L however not statistically significant).			
46		Body weight (bird)	Mallard duck	23	weeks	Oral		ppm	No effect	No effects on bird weight.			
47		Length (fish)	Fathead minnow	30 (post hatch)	Days	Uptake from water	0.68	mg/L water	Decrease	Dose dependent effect			
48				94 (post hatch)	Days	Uptake from water		mg/L water	No effect	No effects in males, females or combined. The highest dose tested was 0.6 mg/L .			
50[1]		Larval length	Zebrafish (*Danio rerio*) [1]	4	Days	Uptake from water	1.6	mg/L water	Decrease	Significantly ($p < 0.05$) decreased body length at 1.6 mg a.s./L and above (dose dependent response).			
50[1]		Morphological abnormalities	Zebrafish (*Danio rerio*) [1]	4	Days	Uptake from water	0.8	mg/L water	Increase	Significantly ($p < 0.05$) increased malformations (including pericardial edema, yolk-sac edema, axial malformation, tail malformation and spinal curvature) in embryos at concentrations of 0.8 mg/L and above (dose dependent response).			

47		Hatching success	Fathead minnow	4 to 5 (11)	Days	Uptake from water	3.3	mg/L water	Decrease	Impaired hatching at highest dose	Impaired (0%) hatching at the highest dose (3.3 mg a.s./L) in the ELS. In neither of the fish studies effects on hatching was observed at lower doses. Effects on hatchability also observed for Mallards at the top dose.	
48				4	Days	Uptake from water		mg/L water	No effect	No effect (the highest dose tested was 0.6 mg a.s./L.)		
50[1]			Zebrafish (Danio rerio) [1]	4	Days	Uptake from water	0.8	mg/L water	Decrease	Significantly reduced hatching rate at 0.8 mg/L and above, in a dose-dependent manner.		
46		Hatchability	Mallard duck	23	weeks	Oral	1000	ppm	Decrease	73 % of the eggs hatched at top dose compared to 86% in the control.		
46		Cracked eggs	Mallard duck	23	weeks	Oral	1000	ppm	No effect	No effect	No effects were observed on eggs, embryos or ducklings of Mallard duck (other than hatchability, see above) or embryos of Mallards up to the top dose (1000 ppm).	
46		Egg production								No effect		
46		Eggshell thickness								No effect		
46		Viable embryos								No effect		
46		Viability ducklings [Not in list]								No effect on % viability of 14-day old ducklings at any test concentration		
46		Eggs set [Not in list]								no effects on eggs set at any test concentration		

46		Embryos [Not in list]							No effect on no. of or % live 17-day embryos at any test concentration				
50[1]		survival of embryos	Zebrafish (Danio rerio)[1]	4	Days	Uptake from water	0.8	mg/L water	Decrease	In the study, survival of embryos and larvae have been merged, and is significantly decreased at the lowest dose tested in a dose dependent manner. Absolute decrease is not reported but seem from the figure to be >10%.	Decreased survival of Zebra fish embryos/larvae at the lowest dose tested (0.8 mg a.s./L)		
50[1]	unknown	[Not in list]	Zebrafish (Danio rerio) [1]	4	Days	Uptake from water	1.6	mg/L water	Decrease	Significantly reduced embryo heartbeat rate at 1.6 mg/L and above in a dose dependent manner.			
47	Systemic toxicity	Survival (fish)	Fathead minnow	30 (post hatch)	Days	Uptake from water	3.3	mg/L water	Decrease	Post-hatch survival could not be assessed at the top dose (3.3. mg a.s./L), as none of the eggs hatched. Post-hatch survival was not significantly reduced at the second highest dose (1.5 mg a.s./L).	In the ELS hatchability was 0% at the top dose (3.3. mg a.s./L), and thus survival was also 0%. 3.3 mg a.s./L is thus above the MTC (at least for eggs/embryos).	The dose 3.3 mg a.s./L is probably above the MTC for fish (at least for fish eggs). No other effects on systemic toxicity were observed at the tested doses in fish or in mammals.	Systemic toxicity
48		Survival (fish)	Fathead minnow	30 (post hatch)	Days	Uptake from water		mg/L water	No effect	No effects on survival up to the top dose (0.6 mg a.s./L)	No effects on survival (top-dose thus below MTC).		
48		Survival (fish)	Fathead minnow	60 (post hatch)	Days	Uptake from water		mg/L water	No effect				
48		Survival (fish)	Fathead minnow	94 (post hatch)	Days	Uptake from water		mg/L water	No effect				
46		Mortality	Mallard duck	23	weeks	Oral		ppm	No effect		No effects on mortality or food consumption.		

46		[Not in list]	Mallard duck	23	weeks	Oral		ppm	No effect	No effects on food consumption in any test treatment.			

[1] This is an open literature study regarded as supportive by RMS. The main reasons why it is considered supportive is the lack of analytical verification of the test substance and uncertainty on whether the study fulfils the validity criteria. RMS is still of the opinion that the results of the study may provide valuable information to be included in a WoE the ED-criteria. For further details, see Volume 3 – B.9.2.2.1, K-CA 8.2.2.1/03.

2.10.3.2.2.1 Assessment of the integrated lines of evidence and weight of evidence for T-mediated adversity and endocrine activity

Table 181: WoE for EAS-mediated adversity

- **Overall conclusion: No consistent EAS-mediated adversity, but not sufficiently investigated.**

- **The most relevant study is the fish sexual development study (FSDT; study ID 48), investigating effects during the developmental part of the fish life cycle. EAS-mediated parameter (sex-ratio) were investigated and gave no evidence of adversity up to the top dose of 0.6 mg a.s./L.**

- **Sensitive to, but not diagnostic of EATS parameters have been investigated in the FSDT and also in a fish early life stage toxicity test (ELS; study ID 47) with Fathead minnow (30 days) and an open literature study (Study ID 50) on embryonic development og Zebrafish (4 days), summarised below.**

- **Survival of Zebrafish embryos/larvae were decreased at 0.8 mg a.s./L and above. Whereas no effects on survival was observed in Fathead minnows, except at the top dose of 3.3 mg a.s./L (0% hatched, see below)**

- In Zebrafish hatching was significantly reduced at 0.8 mg a.s./L and above, whereas no effects on hatching success was observed up to 1.5 mg a.s./L in Fathead minnows. However, 0 % hatching was observed in Fathead minnows (in the ELS) at the top dose (3.3 mg a.s./L).

- Reduced Zebrafish larval length was observed at 1.6 mg/L and above, whereas reduced weight and length in 30-day old Fathead minnow larvae were observed at 0.68 mg a.s./L and above. No statistically significant effects on weight/length were observed up to the top dose of 0.6 mg a.s./L in the FSTD, however, a non-statistically significant weight reduction (-12.7%) in male fish was observed at the top dose of 0.6 mg a.s./L.

- From the available data, Zebrafish embryos seem to be more sensitive than Fathead minnows, with regard to survival and hatching success. Also, male fish may be more sensitive than female fish with regard to effects on length (observed in Fathead minnows).

- The FSDT (study ID 48) only provides data on endocrine activity and adversity during the developmental part of the fish life cycle. More evidence is needed to investigate adverse effects on reproduction (fertility/fecundity) and on gonad histopathology, which has not been (sufficiently) investigated in the available studies. A FLCTT have been initiated but the final report is not yet finalised.

Table 182: WoE for EAS-mediated endocrine activity

- **Overall conclusion: Indication of endocrine activity – in vitro evidence of inhibition of steroidogenesis, ER- and AR-antagonism, as well as in vivo reduction in plasme VTG.**

- **Several *in vitro* assays were positive, providing evidence of ER and AR mediated antagonistic activity:**

  - ToxCast ER bioactivity (agonism: neg- and antagonism: pos+)

- ToxCast AR bioactivity (agonism: neg- and antagonism: pos+)
- Open literature study: Inhibition of testosterone-induced AR activation

- **Several *in vitro* assays were positive, providing evidence of inhibition of steroidogenic activity:**

  - ToxCast Steroidogenesis activity (inhibition of aromatase)
  - Open literature studies (inhibition of aromatase)
  - OECD 456 (inhibition of testosterone and estradiol synthesis)

- **In vivo data with fathead minnow (Study ID 48) indicates a dose dependent reduction in VTG (males and females), however, only statistically significant at the top dose of 0.6 mg a.s./L.**

In vitro mechanistic data provides evidence of effects on steroidogenesis (aromatase inhibition). As well as AR and ER mediated antagonistic activity. Further, the FSDT (study ID 48) provide evidence of endocrine activity *in vivo* indicating that that penconazole has potential endocrine disruptive properties *in vivo*. Plasma vitellogenin (VTG) levels in fathead minnow were significantly reduced in a dose-dependent manner, however, only statistically significant at the highest dose tested (0.60 mg a.s./L). The effects were observed in both male and female fish.

2.10.3.2.3 Initial analysis of the evidence and identification of relevant scenario for the ED assessment of EAS-modalities

Table 183: Selection of relevant scenario

Adversity based on EAS-mediated parameters	**Positive mechanistic OECD CF level 2/3 Test**	**Scenario**	**Next step of the assessment**	**Scenario selected**
No (sufficiently investigated)	Yes/No	1a	Conclude: ED criteria not met because there is not "**EAS-mediated**" adversity	
Yes (sufficiently investigated)	Yes/No	1b	Perform MoA analysis	
No (not sufficiently investigated)	Yes	2a (i)	Perform MoA analysis (additional information may be needed for the analysis)	X
No (not sufficiently investigated)	No (sufficiently investigated)	2a (ii)	Conclude: ED criteria not met because no **EAS-mediated endocrine activity** observed	
No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	
Yes (not sufficiently investigated)	Yes/No	2b	Perform MoA analysis	

2.10.3.2.4 MoA analysis for EAS-modalities

2.10.3.2.4.1 Postulate MoA

Mammals as non-target organisms

Mammals as non-target organisms will but further assessed when a conclusion has been reached in the assessment of the EAS-modality for humans, please see **Section 2.10.2.2.**

Non-target organisms other than mammals

The MoA suggested by RMS for penconazole follows the AOP25 (included at the AOP-wiki). A graphical presentation is given below (Figure 2), and a description of the KE and supporting evidence for penconazole is presented in the table below.

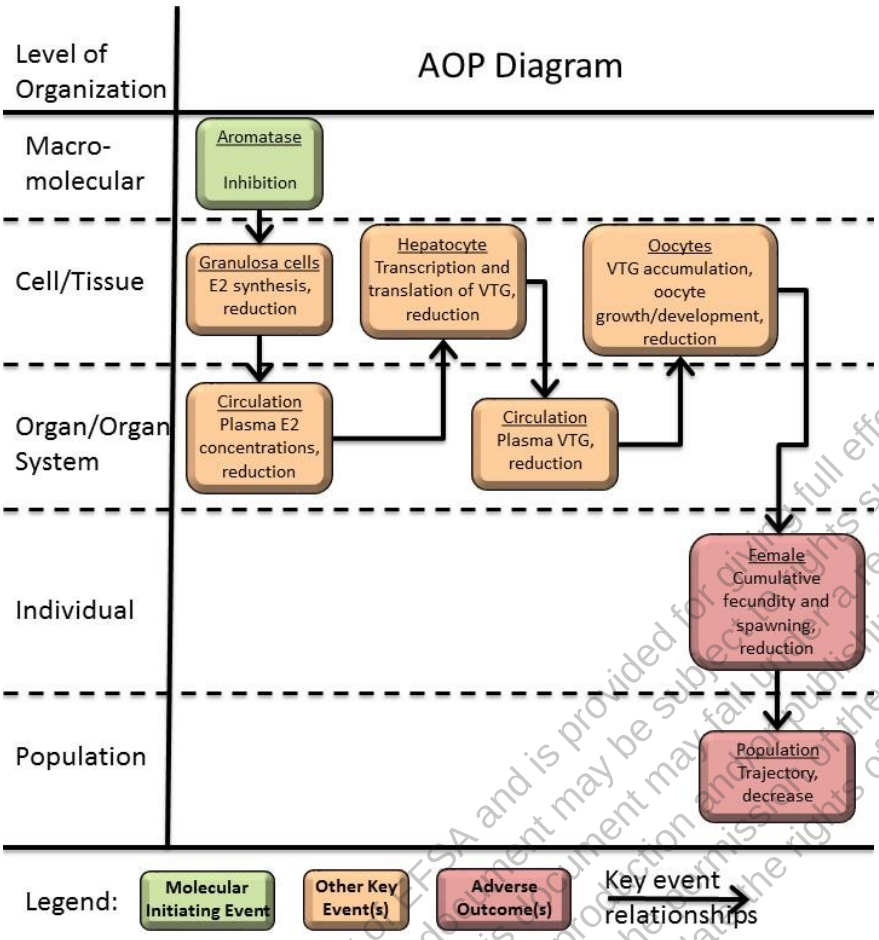


Figure 2. Graphical presentation of AOP25. Source: https://aopwiki.org/aops/25

Table 184: Description of the postulated MoA (Aromatase inhibition leading to reproductive dysfunction)

	Description[ab]	Supporting Evidence
MIE	Aromatase inhibitor	Overall positive evidence for aromatase (CYP19) inhibition, based on ToxCast and open literature studies. This is also supported by *in vitro* mechanistic data (steroidogenesis assay) which indicates that penconazole inhibits the production of estradiol and testosterone.
KE1	Reduced E2 synthesis in Granulosa cells	*In vitro* mechanistic data (steroidogenesis assay) indicates that penconazole can inhibit the production of estradiol (and testosterone) *in vitro*.
KE2	Reduction in circulation plasma E2 concentration	No direct evidence of reduced circulating E2 concentrations
KE3	Reduced VTG syntheses (transcription and translation) in liver	No direct evidence (see below)
KE4	Reduced circulation of plasma VTG	Reduction of blood plasma vitellogenin levels (determined with an ELISA) was observed in a dose dependent manner in the FSDT (study

	Description[ab]	Supporting Evidence
		ID 48), however, only statistically significant at the top dose of 0.6 mg a.s./L.
KE5	Reduced oocyte growth/development due to reduced VTG accumulation in oocytes	No available evidence
AO (individual)	Reduced female cumulative fecundity and spawning	No available evidence. Effects on reproduction (fecundity/fertility) need to be further investigated to assess adversity in fish exposed to penconazole.
AO (population)	Decreased population trajectory	

[a] For further details see the APO-wiki: https://aopwiki.org/aops/25
[b] NB! The KER as in the graphical presentation at the AOPwiki have been used, as far as we can see the figure is not coherent with the "Summary of the AOP" on the AOP-wiki (sequence of KEs).

2.10.3.2.4.2 Further information to be generated to postulate MoA

The available data is not sufficient to support the postulated MoA (AOP25) and generation of further information is needed, especially to further investigate adversity. A FSDT (Level 4 study) was available investigating EAS-mediated parameters for activity (VTG) and adversity (sex ratio and gonad histopathology) *in vivo*. However, the study only provides data on endocrine activity and adversity during the *developmental part of the fish life cycle*. According to the AOP-wiki, AOP25 are relevant for reproductively mature adults (and applies to females only). As toxicity to reproductive mature adults were not investigated in the FSDT, further data should be generated to assess the postulated AOP further. The OECD conceptual framework (OECD 150) provides guidance on how and when further data should be generated (Table C.3.4 Fish Sexual Development Test (FSDT)). RMS has identified Scenario C as the relevant scenario as:

- ***In vitro* mechanistic data provides evidence of effects on steroidogenesis (aromatase inhibition). As well as AR and ER mediated antagonistic activity.**
- **The FSDT (study ID 48) gave evidence of endocrine activity *in vivo* indicating that that penconazole has potential endocrine disruptive properties *in vivo.* Plasma vitellogenin (VTG) levels in fathead minnow were significantly reduced in a dose-dependent manner, however, only statistically significant at the highest dose tested (0.60 mg a.s./L). The effects were observed in both male and female fish.**
- **No effects on apical endpoints in the FSDT**

According to Scenario C one should consider performing a fish life cycle toxicity test (Level 5 in the OECD conceptual framework), to provide further data on reproduction. It is noted that for substances which are expected to be more toxic to reproduction than sexual development, such a test may be more responsive than a FSDT. Thus, a Level 5 study is needed to conclude on EAS-mediated adversity.

In vitro mechanistic data providing evidence for effects on endocrine activity (inhibition of steroidogenesis) and the FSDT (study ID 48) were available when RMS and the applicant discussed the ED-testing strategy (during the pre-submission period of penconazole). As aromatase inhibition leading to reproductive dysfunction is a proposed AOP for some triazoles, RMS strongly recommended the applicant to also investigate the reproductive effects of penconazole and to proceed to Level 5 in the OECD conceptual framework, such as a Medaka Extended One Generation Reproductive Study (OECD 240) or a fish life cycle toxicity test (FLCTT). RMS also sought guidance and advice from coRMS DE and EFSA during the pre-submission period and took their advice into account.

The applicant proposed doing a FLCTT with Fathead minnow following the OECD Draft Proposal for Fish Two-Generation Test Guideline (2002) and Draft OPPTS 850.1500 Test Guideline. As the previously conducted Fish Sexual Development Test (FSDT) was conducted with Fathead minnows, the test concentrations which were already set in the FSDT could be used, and a new range finding test would not be necessary (which would be needed for Medaka).

RMS provided the following recommendations to the applicant:

- **If the FLCTT is performed, preferably, the same parameters as for the MEOGRT should be**

measured.

- **Also, liver histopathology should be evaluated, as it is known that the liver is one of the target organs for penconazole. If altered VTG levels are apparent it should be possible to exclude, or in the opposite case, to demonstrate if histopathological alterations in the liver caused the changed VTG concentrations.**
- **As the reproductive performance of Fathead minnow can vary considerably it is considered crucial to ensure that the statistical power is sufficient to detect possible reproductive effects.**

The following is stated by the applicant (in *italics*) on the expected outcome of the study, the choice of test-species and study protocol:

This study will provide data on potential population relevant effects (e.g., survival, development, growth and reproduction) for the determination of a No-Observed-Effect Concentration (NOEC); however, the main aims of the study are to establish:

*a) The reproducibility of the apparent effect on plasma VTG concentrations of exposure to 0.6 mg/L penconazole, from embryo up to sexual maturation, observed in the existing FSDT (**York 2012; File No. CGA071818_10278**).*

b) Whether such an effect correlates with adverse effects (relevant at population level), namely sexual differentiation (i.e. change in sex ratio, not observed in the FSDT), and reproduction (i.e. fecundity, fertility, not measured in the FSDT)

Fathead minnow are an ideal test species due to their ease of handling and their ability to be reared and bred under laboratory conditions. They are also a recommended test species due to their known sensitivity to a variety of toxicants and the extensive existing data for this common fish species.

The protocol was developed using the following guidance documents: "User's Guide for Conducting Chronic Toxicity Tests with Fathead Minnows" (Benoit, 1981[38]); the "Standard Evaluation Procedure for Fish Life-Cycle Toxicity Tests" issued by the Hazard Evaluation Division of EPA's Office of Pesticide Programs (Rexrode and Armitage, 1986[39]) and "Biological Field and Laboratory Methods for Measuring the Quality of Surface Waters and Effluents" (EPA-670/4-73-001[40]). The latter document is cited as an acceptable protocol in the Office of Chemical Safety and Pollution Prevention (OCSPP) 850.1500 draft guideline for fish life-cycle tests. Additional endpoints to evaluate potential endocrine activity will be based on the Organization for Economic Co-operation and Development (OECD) 229[41] and 234[42] guidance documents, with further reference to the ECHA-EFSA Guidance for the Identification of endocrine disrupters in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009.

The protocol describes an in vivo bioassay where newly fertilized embryos (first generation, F_0) will be exposed to penconazole technical (purity: 97.4%). These embryos will be hatched and reared to adulthood, with endpoints reported for hatching success, time to hatch, larval survival and growth. Once the F_0 generation is sexually mature, spawning groups will be formed where the impacts of the test chemical on expression of secondary sexual characteristics, plasma vitellogenin levels, reproduction and tissue histopathology will be assessed. During the F_0 reproductive phase, embryos will be collected and reared to approximately 28-days post hatch to assess embryonic and larval/juvenile development of the F_1 (second) generation.

To investigate the effects of endocrine disrupting properties, a **fish life-cycle toxicity test** has been initiated. Whilst this study is still in progress, the applicant has provided a brief evaluation of the biological results obtained so far

[38] Benoit, D.A. 1981. User's Guide for Conducting Chronic Toxicity Tests with Fathead Minnows (*Pimephales promelas*). EPA-600/8-81/011.

[39] Rexrode, M. and T.M. Armitage. 1986. Standard Evaluation Procedure; Fish Life-Cycle Toxicity Tests. Hazard Evaluation Division, Office of Pesticide Programs. Washington, D.C. 20460. EPA 540/9-86-137. July, 1986.

[40] U.S. EPA. 1973. Biological Field and Laboratory Methods for Measuring the Quality of Surface Waters and Effluents. EPA-670/4-73-001. U.S. Environmental Protection Agency, Washington, D.C.

[41] OECD. 2009. Fish Short Term Reproduction Assay. OECD Guideline for the Testing of Chemicals: Test No. 229. Paris, France. 40 pp.

[42] OECD, 2011. Fish Sexual Development Test. Guideline #234. OECD Guidelines for the Testing of Chemicals. OECD, Paris, France.

(see **Volume 3 - B.9.2.2.2 (AS)**). As the study report is not yet available, RMS has not been able to verify the accuracy of the information provided and has thus not evaluated the results or included them in the current assessment of whether penconazole fulfils the ED-criteria. As penconazole is a pending application (according to **Commission Implementing Regulation (EU) 2018/1659)**, RMS would propose that EFSA request the full study report during a Stop-Clock, in order to conclude on adversity of EAS-modalities.

2.10.3.2.4.3 Empirical support of the postulated MoA

Not applicable considering the limited data available.

2.10.3.2.4.4 Empirical support of the postulated MoA

Not applicable considering the limited data available.

2.10.3.2.4.5 Alternative MoA analysis

Decrease in VTG may also be caused by overt or systemic toxicity and non-endocrine (MoAs), such as hepatotoxicity. As penconazole is known to target the liver, this hypothesis also needs to be investigated in light of the results of the FLCTT.

2.10.3.2.5 Conclusion of the assessment of EAS-modality

There is evidence of endocrine activity, however, endocrine adversity has not been sufficiently investigated (Scenario 2a (i)). According to **Commission Implementing Regulation (EU) 2018/1659** Penconazole is considered a pending application (submission of the application for renewal (Art. 1 of the Reg. 844/2012) before 10th of November 2018, more specifically the administrative application for penconazole was recieved 31st of December 2016).

Commission implementing Regulation (EU) 2018/1659 further states: *For such pending applications, it is possible that the information submitted by the applicant does not allow to conclude the assessment as regards whether the scientific criteria for the determination of endocrine disrupting properties set out in point 3.6.5 and point 3.8.2 of Annex II to Regulation (EC) No 1107/2009 are met or not and to conclude whether the ap-proval criteria set out in those points are met or not. Therefore, the European Food Safety Authority ('the Authority') should be able to request additional information from the applicant in order to conclude whether the approval criteria set out in those points are met or not.*

As the FLCTT was not finalised during the submission of the Supplemental Dossier (30/06-2019), or the Top-Up submission in December 2019, RMS would propose that EFSA request the full study report during a Stop-Clock, in order to conclude on adversity of the EAS-modalities.

2.10.4 Conclusion on the ED assessment

Overall, there are evidence for penconazole inducing endocrine mediated activity for both the T- and the EAS-modalities. There is no consistent evidence of EATS-mediated adversity, however in the opinion of RMS, this may not have been sufficiently investigated. Further data is thus needed in order to conclude on whether penconazole fulfils the ED-criteria, and RMS propose the following studies to be generated:

Table 185: RMS proposal for further testing

Modality	Proposal for further testing	Timeline
Humans and mammals as non-target organisms		
T-modality	First priority is to perform a study to following 407/408 and 416. Further investigations on the proposed MoA may be necessary. Please see section 2.10.2.1.4.2 for details.	Studies should be initiated if it is concluded by EFSA that adversity is not sufficiently investigated.
EAS-modality	As recommended for investigation of the T-modality a study following the OECD 416 is recommended to investigate the EAS modality. Please see section 2.10.2.2.4.2 for details.	Studies should be initiated if it is concluded by EFSA that adversity is not sufficiently investigated.
Non-target organisms other than mammals		

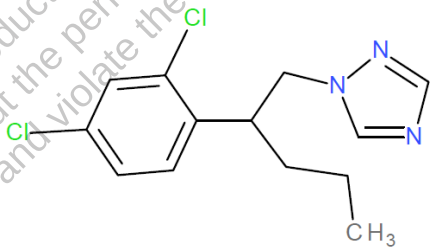
T-modality	AMA (OECD 231) or XETA (OECD 248) depending on the outcome of the assessment for humans and mammals as non-target organisms.	Preferably, to be initiated when a conclusion has been reached for the T-modality for mammals as non-target organisms. However, as the available maximal time frame for stop-the-clock may not be enough to first conclude on the ED assessment of humans and mammals as non-target organisms, datasets may be complemented in parallel. This should be left open for the applicant to decide.
EAS-modality	Fish life cycle toxicity test (study has been initiated, but reporting was not finalised before delivery of the Top-up submission in December 2019).	Final report to be requested by EFSA during stop-the-clock

2.11 PROPOSED HARMONISED CLASSIFICATION AND LABELLING ACCORDING TO THE CLP CRITERIA *[SECTIONS 1-6 OF THE CLH REPORT]*

2.11.1 Identity of the substance [section 1 of the CLH report]

2.11.1.1 Name and other identifiers of the substance

Table 186: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Penconazole (ISO); 1-[2-(2,4-dichlorophenyl)pentyl]-1H-1,2,4-triazole
Other names (usual name, trade name, abbreviation)	CGA71818
ISO common name (if available and appropriate)	Penconazole
EC number (if available and appropriate)	266-275-6
EC name (if available and appropriate)	1-[2-(2,4-dichlorophenyl)pentyl]-1 *H* -1,2,4-triazole
CAS number (if available)	66246-88-6
Other identity code (if available)	446
Molecular formula	$C_{13}H_{15}Cl_2N_3$
Structural formula	
SMILES notation (if available)	Clc2ccc(C(CCC)Cn1cncn1)c(Cl)c2
Molecular weight or molecular weight range	284.2 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Racemate comprising equal amounts of (R)- and (S)-penconazole.
Degree of purity (%) (if relevant for the entry in Annex VI)	≥ 95%

2.11.1.2 Composition of the substance

Table 187: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
Penconazole, CAS no. 66246-88-6	Min. 95%	Acute tox. 4 – H302 Repr. 2 – H361d Aquatic Acute 1 – H400 Aquatic chronic 1 – H410	See ECHA C&L Inventory[1]

[1] https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/105155

Table 188: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
Not relevant				

Table 189: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**
Not relevant					

Test substances (non-confidential information)**Identification of test substance**	**Purity**	**Impurities and additives (identity, %, classification if available)**	**Other information**	**The study(ies) in which the test substance is used**
Penconazole technical Batch : FL-840833	98.7%			K-CA 5.1.1/05 K-CA 5.1.1/06 K-CA 5.1.1/07 K-CA 5.2.5/01 K-CA 5.3.2/03 K-CA 5.3.2/05 K-CA 5.6.1/04 K-CA 5.6.2/03 K-CA 5.6.2/06
Penconazole technical Batch : FL 830634	87.3%			K-CA 8.1.1.1/01 K-CA 8.1.1.1/02 K-CA 8.1.1.2/01 K-CA 8.1.1.3/01 K-CA 8.2.5.1/01 K-CA 8.2.5.1/01 K-CA 8.2.2.1/01
Penconazole technical Batch : P2	>99%			K-CA 5.1.1/08
Penconazole technical Batch : AMS 204/102	99.5%			K-CA 5.1.1/09
Penconazole technical Batch : AMS 204/3	99.3%			K-CA 5.1.2/01 K-CA 5.2.7/01
Penconazole technical Batch : P.2+3	88.4%			K-CA 5.2.1/01 K-CA 5.2.1/02 K-CA 5.2.1/03 K-CA 5.2.1/04 K-CA 5.2.2/01 K-CA 5.2.4/01 K-CA 5.6.2/01 K-CA 8.1.1.1/04 K-CA 8.1.1.2/03 K-CA 8.1.1.2/04
Penconazole technical Batch : EN 603012	96.1%			K-CA 5.2.3/01 K-CA 5.2.6/01 K-CA 5.3.1/02 K-CA 5.4.1/02 K-CA 5.4.1/05 K-CA 5.4.1/06 K-CA 5.4.2/01 K-CA 8.2.5.3/01 K-CA 8.8/01

Penconazole technical Batch : P. 11-14	91.7%			K-CA 5.3.1/01 K-CA 5.3.2/01 K-CA 5.3.2/02 K-CA 5.3.2/04 K-CA 5.3.3/01 K-CA 5.4.1/01 K-CA 5.4.1/07 K-CA 5.5/01 K-CA 5.5/03 K-CA 5.6.1/01 K-CA 5.6.2/04
Penconazole technical Batch : op. 3-23.01.90	96.2%			K-CA 5.3.1/02 K-CA 8.2.4.1/01
Penconazole technical Batch : WS007001	97.7%			K-CA 5.3.2/06 K-CA 5.5/02 K-CA 8.2.6.1/01
Penconazole technical Batch : 0704	100.15 %			K-CA 5.4.1/03 K-CA 5.4.1/04
Penconazole technical Batch : 0701	99.86%			K-CA 8.2.6.1/03a
Penconazole technical Batch : SSH4D030	97.4%			K-CA 5.8.3/03 KCA 8.2.3/03 K-CA 8.3.1.1 /01
Penconazole technical Batch : WRS 1270/1	97.6%			KCA 6.1/04
Penconazole technical Batch : P 401013	99			K-CA 8.2.1/05
Penconazole technical Batch : NV-X111-58	specific activity 0.26 µCi/mg			K-CA 8.2.2.3/01

2.11.2 Proposed harmonized classification and labelling

2.11.2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 190: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	613-317-00-X	Penconazole (ISO); 1-[2-(2,4-dichlorophenyl)pentyl]-1*H*-1,2,4-triazole	266-275-6	66246-88-6	Acute tox. 4 Repr. 2 Aquatic acute 1 Aquatic chronic 1	H302 H361d H400 H410	GHS07 GHS08 GHS09 Wng	H302 H361d H410		 M = 1 M = 1	
Dossier submitters proposal	613-317-00-X	Penconazole (ISO); 1-[2-(2,4-dichlorophenyl)pentyl]-1*H*-1,2,4-triazole	266-275-6	66246-88-6	**Retain:** Acute tox. 4 Repr. 2 Aquatic acute 1 Aquatic chronic 1 **Add:** STOT RE 2	**Retain:** H302 H361d H400 H410 **Add:** H373 (liver)	**Retain:** GHS07 GHS08 GHS09 Wng	**Retain:** H302 H361d H410 **Add:** H373 (liver)		Oral ATE: 971 mg/kg bw M = 1 M = 1	
Resulting Annex VI entry if agreed by	613-317-00-X	Penconazole (ISO);	266-275-6	66246-88-6	Acute tox. 4 Repr. 2	H302 H361d	GHS07 GHS08	H302 H361d		Oral ATE: 971 mg/kg bw	

RAC and COM		1-[2-(2,4-dichlorophenyl)pentyl]-1*H*-1,2,4-triazole			STOT RE 2 Aquatic acute 1 Aquatic chronic 1	H373 (liver) H400 H410	GHS09 Wng	H373 (liver) H410		M = 1 M = 1	

2.11.2.2 Additional hazard statements / labelling

Table 191: Reason for not proposing harmonised classification and status under CLH public consultation

Hazard class	Reason for no classification	Within the scope of CLH public consultation
Explosives	Data conclusive but not sufficient for classification	Yes
Flammable gases (including chemically unstable gases)	Hazard class not applicable	No
Oxidising gases	Hazard class not applicable	No
Gases under pressure	Hazard class not applicable	No
Flammable liquids	Hazard class not applicable	No
Flammable solids	Data conclusive but not sufficient for classification	Yes
Self-reactive substances	Data conclusive but not sufficient for classification	Yes
Pyrophoric liquids	Hazard class not applicable	No
Pyrophoric solids	Data conclusive but not sufficient for classification	Yes
Self-heating substances	Data conclusive but not sufficient for classification	Yes
Substances which in contact with water emit flammable gases	Data conclusive but not sufficient for classification	Yes
Oxidising liquids	Hazard class not applicable	No
Oxidising solids	Data conclusive but not sufficient for classification	Yes
Organic peroxides	Hazard class not applicable	No
Corrosive to metals	Data conclusive but not sufficient for classification	Yes
Acute toxicity via oral route	Harmonised classification proposed	Yes
Acute toxicity via dermal route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via inhalation route	Data conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	Data conclusive but not sufficient for classification	Yes
Serious eye damage/eye irritation	Data conclusive but not sufficient for classification	Yes
Respiratory sensitisation	Data lacking	No
Skin sensitisation	Data conclusive but not sufficient for classification	Yes
Germ cell mutagenicity	Data conclusive but not sufficient for classification	Yes
Carcinogenicity	Data inconclusive	Yes
Reproductive toxicity	Harmonised classification proposed	Yes
Specific target organ toxicity-single exposure	Data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-repeated exposure	Harmonised classification proposed	Yes
Aspiration hazard	Hazard class not applicable	No

Hazard class	Reason for no classification	Within the scope of CLH public consultation
Hazardous to the aquatic environment	Harmonised classification proposed	Yes
Hazardous to the ozone layer	Data conclusive but not sufficient for classification	Yes

2.11.3 History of the previous classification and labelling

A harmonised classification and labelling for penconazole has been adopted by the ECHA Committee for Risk Assessment (RAC) on 11th of July 2012 (ECHA/RAC/CLH-O-0000002679-61-01/F). All the human health hazard classes (except respiratory sensitisation, aspiration hazard and adverse effects on or via lactation as well as endocrine disruption properties) were reviewed by the ECHA RAC. The classification for health and environmental hazard are as follows:
Repr. 2, H361d
Acute Tox., 4 H302
Aquatic Acute 1, H400, M=1
Aquatic Chronic 1, H410, M=1

Penconazole was approved for use as an agricultural fungicide under Council Directive 91/414/EEC in 2010, with Germany as Rapporteur Member State. It is approved for use under Regulation (EC) 1107/2009 and is being reviewed for the renewal of approval under the AIR(IV) renewal programme with Norway as the RMS.

Physical hazards
Previous human health hazard assessment of physicochemical properties of penconazole concluded: "*Penconazole (technical): is not explosive in the sense of EEC method A14; is not highly flammable in the sense of EEC method A10; has no oxidising properties in the sense of EEC method A17"* (CLH Report; November 2010).

Health hazards
From the previous assessment and conclusion on penconazole: Based on the results of the acute oral LD_{50} in rabbits and rats, Penconazole is considered 'harmful if swallowed' and should be classified as Acute tox. 4 – H302 according to the Regulation (EC) 1272/2008 (CLP Regulation) and Xn; R22 according to the Directive 91/414/EEC (DSD).

Regarding developmental toxicity, effects were seen on several variables. Post-implementation loss in the form of early resorptions was seen in all developmental studies at the top dose. In one study, the effect was clear and statistically significant, but associated with considerable maternal toxicity. In the other studies, the effect was about two-fold and neither consistently above historical controls nor statistically significant, and also here slight to more marked maternal toxicity was observed. However, as the effects were consistently seen in all the studies they could not be disregarded as chance findings. Pup weight was decreased postnatally in both rat multigeneration studies at the high dose. Incomplete/absent ossification occurred in two rat and one rabbit studies, and supernumerary cervical ribs in one rat study, all in the presence of slight to considerable maternal toxicity. These variations or delays in development may not warrant classification on their own, especially when associated with maternal toxicity, but here they are regarded to add to the WoE. Finally, and most important, severe malformations were seen in one study in rabbits: these were three cases of microphtalmia, two in combination with internal hydrocephalus. This effect cannot be disregarded. Other severe malformations seen in the rat and rabbit studies were single cases, not consistent and within historical controls, and do thus not contribute to the WoE. Overall, there are several effects on development seen and although these may each not all warrant classification on their own, the WoE of all the effects combined makes classification warranted. Overall, adverse effects on development are seen in the studies. The effects are not pronounced and consistent in the different studies. However, it would be inappropriate to not classify, as there are effects seen in several studies and it has not been shown that these are irrelevant for humans. It should be noted that this is a borderline case for classification. As no evidence from humans is available, classification in Repr. 1A is not possible. The data are not sufficiently conclusive to place the substance in Repr. 1B. Classification for developmental toxicity as Repr. 2 - H361d according to the Regulation (EC) 1272/2008 (CLP Regulation) and Repr. Cat. 3; R63 according to the Directive 91/414/EEC (DSD) is therefore warranted.
Regarding repeated dose toxicity, the reported liver changes can be considered as only adaptive responses to the increased metabolic load. Although some liver changes at 16.9/16.7 (M/F) mg/kg bw/day (500 ppm) in dog studies could be considered as severe, they appear as isolated cases: necrosis in 1 male out of 4 in the 90-day study and also fibrosis in 1 male out of 4 when the study was prolonged to 1-year. A similar interpretation can be made for the hepatic degeneration observed in one rat 90-day study at 72 mg/kg bw/d (1000 ppm). Although the effective dose

levels in both dogs and rats are within the $10 < C \leq 100$ mg/kg body weight/day range, RAC's conclusion was that a classification for specific target organ toxicity is not required under the CLP Regulation or DSD.

Regarding carcinogenicity, three carcinogenicity bioassays have been performed with Penconazole. In two of these studies, one in rats and one in mice, the highest dose was 300 ppm (equals 15.3 mg/kg bw/d (M) and 16.6 mg/kg bw/d (F) and 40.8 mg/kg bw/d (M) and 35.7 mg/kg bw/d (F) for rats and mice, respectively). No adverse findings, including tumours, were seen in these studies. However, as no toxicity was seen at the top dose, it was concluded that the doses were too low and the studies can only be considered supportive. In the third study in mice, a top dose of 1500 ppm, equal to 178 mg/kg bw/d (M) and 222 mg/kg bw/d (F), was used. This dose caused clear toxic effects but no tumours. The negative result of the latter study together with the supportive studies in mice and rats indicates no carcinogenic potential of Penconazole. Therefore, classification for carcinogenicity is not required.

Environmental hazards

For the environmental classification there was general agreement during the previous review that penconazole should be classified as Acute Category 1 (M-factor 1) and Chronic Category 1 (M-factor 1) (ECHA, 2012).

Degradability

In the RAC opinion for penconazole (2012) penconazole was not found to be readily biodegradable, according to the OECD Guideline No. 301B, because no degradation occurred during 28 days whereas >70% degradation within 28 days is required to achieve this criterion.

In the RAC opinion for penconazole (2012) penconazolewas found to dissipated primarily by partitioning to the sediment in water/sediment systems, with single first order DT50 of 1.9-3.4 days where it subsequently degraded (whole system pseudo first order DT50 505 up to >706 days) forming the major metabolite CGA 179944 that was present in the water phase (max. 17.3 % of AR after 365 days) and only accounted for a maximum of 4.8% of AR in the sediment. In aerobic laboratory soil degradation studies the overall geometric mean DT50 value of Penconazole was 117 days (SFO, 20 °C, pF2). In field soil dissipation studies DT50 values of Penconazole were in the between 67 d – 115 days (SFO). In the field, Penconazole can exhibit slow primary degradation but not ultimate mineralisation. As a result of the field and laboratory studies, Penconazole is considered as not rapidly degradable.

In the current evaluation additional studies have been submitted assessing degradability in water/sediment and soil. New kinetic assessment, resulting in different DT50-values, have been provided for the sake of renewal.

Bioaccumulation

In the RAC opinion for penconazole (2012)[43], the BCF was established to be 320, based on the available bioaccumulation study by [redacted] (1984d). RMS has re-evaluated the study and have regarded the study as not reliable (See Volume 3 (AS) B.9.2.2.3), due to several deficiencies. In the current evaluation against the CLP-criteria, the logPow have thus been when evaluating the potential for bioaccumulation. (See Volume 1, Section 2.9.2.1).

Ecotoxicity

In the RAC opinion for penconazole (2012), the endpoint derived from a study with *Lemna gibba* (14-day EC_{50} = 0.19 mg/l based on frond numbers) provided the lowest acute endpoint and was thus the endpoint used to support the harmonised classification: Acute category 1. RMS has re-evaluated the Lemna-study and have regarded the study as not reliable (See Volume 3 (AS) B.9.2.7), due to several deficiencies.

In the RAC opinion for penconazole (2012), the endpoint derived from a study with *Daphnia magna* (21-day NOEC = 0.069 mg/l) provided the lowest chronic endpoint and was thus the endpoint used to support the harmonised classification: Chronic category 1. After the current review, this study is still regarded reliable for hazard classification, however, the endpoint has been set to *Daphnia magna* 21-day NOEC ≤ 0.069 mg/l, as there are some uncertainties in the applied statistics.

Please see Section **2.9.2** for an overview of the available data and Section **2.9.2.4** for RMS comparison with the CLP-criteria.

[43] Committee for Risk Assessment Opinion proposing harmonised classification and labelling at EU level of Penconazole. ECHA/RAC/CLH-O-0000002679-61-01/F

2.11.4 Identified uses

Penconazole is an agricultural fungicide which is used by foliar application to control a wide range of diseases in fruits and vegetables.

Please see 1.5 for the full details on identified uses.

2.11.5 Data sources

The data was submitted in the context of renewal of pesticide active substances under Regulation no. 1107/2009 concerning the placing of plant protection products on the market. The data was evaluated in the Renewal Assessment Report (RAR) Vol. 1-4.

2.12 RELEVANCE OF METABOLITES IN GROUNDWATER

The potential relevance of metabolites of penconazole has been assessed with respect to the current guidance for relevance in groundwater (Sanco/221/2000-rev.10, 25 February 2003).

2.12.1 STEP 1: Exclusion of degradation products of no concern

2.12.2 STEP 2: Quantification of potential groundwater contamination

Preliminary evaluation shows that metabolites CGA179944 and CGA142856 exceed the concentration of 0.1 µg/L, except for use in cucmber with application rate of 35 g penconazole/ha x 1. CGA142856 is also predicted to exceed the concentration of 0.75 µg/L. However, new groundwater modelling should be provided using updated endpoints. For current modelling and estimated concentrations in groundwater see Volume 3 CP B.8 of the dRAR.

2.12.3 STEP 3: Hazard assessment – identification of relevant metabolites

2.12.3.1 STEP 3, Stage 1: screening for biological activity

The available biological screening data for CGA179944 and CGA142856 demonstrate that when compared to parent penconazole the biological (fungicidal) activity is greatly reduced. Therefore, it can be concluded that these metabolites do not retain the fungicidal activity of parent penconazole and can be considered non-relevant from the perspective of biological activity.

2.12.3.2 STEP 3, Stage 2: screening for genotoxicity

CGA179944

CGA179944 was not mutagenic in the gene mutation assays (Ames test and mouse lymphoma cell L5178Y assay). It gave a positive result in the chromosome aberration test; but in the confirmatory *in vivo* micronucleus test the outcome was negative, see Table 3.3.2-1 below.

Clinical signs within the mouse micronucleus test reveal systemic exposure to CGA179944.

Table 3.3.2-1: Summary of Genotoxicity data on CGA179944

Study	Test Object	Concentration	Results
Ames test Sokolowski 2015, CGA1749944_10005	*S.typhimurium* TA1535, TA1537, TA98 TA100 and *E.coli* WP2, WP2 uvrA	3-5000 µg/plate (+/-S9)	Negative (+/-S9)
Chromosome aberration test Pritchard 2002, CGA179944_10040	Human lymphocytes	-S9: 5-8 mM (3 h) +S9: 7-9 mM (3 h)	Positive (+/-S9)

Gene mutation in mammalian cells [redacted] 2002, CGA179944_10041	Mouse lymphoma cells L5178Y	-S9: 0.1-1.5 mM (3 h) -S9: 0.1-1.0 mM (24 h) +S9: 0.1-2.5 mM (3 h)	Negative (+/-S9)
***In vivo* micronucleus test** [redacted] 2003, CGA179944_10042	Mouse bone marrow	375, 750 and 1500 mg/kg bw	Negative

CGA179944 is therefore considered not to be genotoxic *in vivo*.

CGA142856 (triazole acetic acid, TAA)

CGA142856 was negative in the available *in vitro* gene mutation and chromosome aberration assays, see Table 3.3.2-2 below.

Table 3.3.2-2: Summary of Genotoxicity data on CGA142856

Study	Test Object	Concentration	Results
Ames test Deparade 1984, CGA142856/0003	*S.typhimurium* TA1535, TA1537, TA98 TA100	20-5120 µg/plate (+/-S9)	Negative (+/-S9)
Chromosome aberration test Pritchard 2002, CGA142856/0017	Human lymphocytes	+/-S9: 2.5-10 mM (3 h) -S9: 2.5-10 mM (20 h)	Negative (+/-S9)
Gene mutation in mammalian cells [redacted] CGA142856/0018	Mouse lymphoma cells L5178Y	+/-S9: 0.63-10 mM (3 h) -S9: 0.63-10 mM (24 h)	Negative (+/-S9)

CGA142856 is therefore considered not to be genotoxic.

2.12.3.3 STEP 3, Stage 3: screening for toxicity

CGA179944

The parent penconazole is classified as Cat 2 for developmental toxicity (H361d) based on a weight of evidence approach using information from available rat and rabbit reproductive and developmental toxicity studies. To investigate whether CGA179944 would result in similar developmental effects or not, the metabolite was tested in developmental toxicity studies in rat and rabbits.

Table 3.3.3-1: Toxicity data on CGA179944

Study	Species	Dose level	Result
Developmental toxicity (feeding) – range finder [redacted] 2017a, CGA179944_10020	rat	0, 1000, 3000, 10000 ppm corresponding to 0, 85, 258, 813 mg/kg bw/day	Maternal: transiently ↓ bw gain and food consumption at 10000 ppm Developmental: no treatment-related findings
Developmental toxicity (feeding) [redacted] 2017b, CGA179944_10021	rat	0, 1000, 3000, 10000 ppm corresponding to 84, 250, 796 mg/kg bw/day	Maternal: transiently ↓ bw gain at 10000 ppm, marked ↓ bw gain during GD 6-20 when corrected for gravid uterus Developmental: Number of intrauterine deaths and post-implantation loss ↑ at 3000 and 10000, minor abnormalities and variant finding ↑ at 3000 and 10000 Maternal/developmental NOAEL 84 mg/kg bw/day

Developmental toxicity (gavage) – range finder [redacted] 2017c, CGA179944_10024	rabbit	0, 100, 300, 600 mg/kg bw/day	Maternal: ↓ bw gain and food consumption at 600 mg/kg Developmental: no treatment-related findings
Developmental toxicity (gavage) [redacted] 2018, CGA179944_10027	rabbit	0, 100, 300, 600 mg/kg bw/day	Maternal: mortality and ↓ bw gain and food consumption at 600 mg/kg Developmental: Slight ↑ in intra-uterine deaths and ↓ mean foetal weight at 600 mg/kg. ↑ incomplete interventricular septum and different variations (also at 300 mg/kg) at 600 mg/kg Maternal NOAEL: 300 mg/kg bw/day Developmental NOAEL: 100 mg/kg bw/day

CGA179944 did reveal relevant developmental findings and a classification for developmental toxicity is considered required. Comparison of the maternal findings seen in the studies with CGA179944 to the respective studies with the parent indicate a comparable toxic potential of CGA179944 as compared to penconazole.

CGA179944 is therefore considered 'relevant'.

Table 3.3.3-2: Comparison of the toxicity profile of CGA179944 with penconazole

Study	CGA179944	Penconazole°
Rat developmental toxicity	Maternal NOAEL: 84 mg/kg bw/day Developmental NOAEL: 84 mg/kg bw/day	Maternal NOAEL: 100 mg/kg bw/day Developmental NOAEL: 100 mg/kg bw/day
Rabbit developmental toxicity	Maternal NOAEL: 300 mg/kg bw/day Developmental NOAEL: 100 mg/kg bw/day	Maternal NOAEL: 75 mg/kg bw/day Developmental NOAEL: 50 mg/kg bw/day
Point mutation assay	Negative	Negative
Chromosome aberration assay	Positive	Negative
Mammalian cell gene mutation	Negative	Negative
***In vivo* rodent micronucleus assay**	Negative	Negative

° relevant NOAELs based on two available studies each in rats and rabbits

CGA142856

The recent EU evaluation resulted in an ADI and ARfD of 1 mg/kg bw/day for CGA142856 (TAA) based on the NOAELs of 100 mg/kg bw/day of the available reproductive toxicity (rat) and developmental toxicity (rabbit) study.

2.12.4 STEP 4: Exposure assessment – threshold of concern approach

Exposure assessment is not necessary for CGA179944 as this metabolite is proposed to be considered as a relevant.

2.12.5 STEP 5: Refined risk assessment

Refined risk assessment is not necessary for CGA179944 as this metabolite is proposed to be considered as a relevant.

2.12.6 Overall conclusion

Based on the above evaluation, it can be concluded that the metabolite CGA142856 is not relevant according to the "Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC. (SANCO/221/2000 –rev.10- final. 25 February 2003)". CGA179944 is however proposed to be considered as relevant.

2.13 CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

2.13.1 Identity and physical chemical properties

Penconazole technical material is a racemate comprising equal amounts of the (R)- and (S)- enantiomer.

2.13.2 Methods of analysis

Not differentiated in the analytical methods

2.13.3 Mammalian toxicity

Not differentiated in the assessment.

2.13.4 Operator, Worker, Bystander and Resident exposure

Not differentiated in the assessment.

2.13.5 Residues and Consumer risk assessment

Not differentiated in the assessment

Published literature Wang et al, 2014 (CGA0718181_10706), found no change in the stereoisomer ratio for parent in crops belonging to the fruit and fruiting veg metabolism group (cucumbers and tomatoes). A similar pattern was seen in published literature Zhang et al, 2019 (CGA071818_10694) for grapes produced in the Tianjin region of China. Whereas Zhang et al, 2019 (CGA071818_10694) indicated that (-)-penconazole dissipated/degraded slightly faster in grapes produced than (+)-penconazole in the Jinhua region of China.

Based on the published literature Zhang, 2019 (CGA071818_10694), which analysed the rate loss of penconazole enantiomers in two soils, it can be concluded that in a system demonstrating a high level of biotic mediated loss of penconazole, which was assumed to be via degradation, there was no significant change in the ratio of the two enantiomers of penconazole in one of the soils. In the other soil, a very moderate change in the ratio was observed, although it should be noted that the isomeric ratio at zero time was not 1:1 which casts doubt on any change in ratio over time.

2.13.6 Environmental fate

2.13.7 Ecotoxicology

2.14 RESIDUE DEFINITIONS

2.14.1 Definition of residues for exposure/risk assessment

Food of plant origin: Sum of penconazole and free and conjugated CGA132465, CGA190503 and CGA127841, expressed as penconazole

Food of animal origin: Not required.

Soil: Penconazole, CGA179944, CGA142856, CGA71019 and CGA91305

Groundwater: Penconazole, CGA179944, CGA142856, CGA71019 and CGA91305

Surface water: Penconazole, CGA179944, CGA142856, CGA71019 and CGA91305

Sediment: Penconazole

Air: Penconazole

2.14.2 Definition of residues for monitoring

Food of plant origin: Penconazole (sum of all constituent isomers)

Food of animal origin: Not required.

Soil: Penconazole and CGA71019 (1,2,4-Triazole)

Groundwater: Penconazole, CGA179944 and CGA71019 (1,2,4-Triazole)

Surface water: Penconazole

Sediment: Penconazole

Air: Penconazole

Body fluids and tissues: Penconazole and penconazole-OH

Level 3

Penconazole

3. PROPOSED DECISION WITH RESPECT TO THE APPLICATION

3.1 BACKGROUND TO THE PROPOSED DECISION

3.1.1 Proposal on acceptability against the decision making criteria – Article 4 and annex II of regulation (EC) No 1107/2009

3.1.1.1 Article 4				
		Yes	No	
i)	It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with. Specifically the RMS considers that authorisation in at least one Member State is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.			For the areas where it is possible to conclude (see exceptions below), it is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with for penconazole for at least one representative use (see point 3.1.1.3, Restrictions on approval, below). A final decision regarding Article 4 is currently not possible, as more data are needed to reach a conclusion on the ED-assessment. Thus, a conclusion has not yet been reached for criteria 3.6.5 and 3.8.2 in Annex II (to Regulation (EC) 1107/2009). See further information under point 3.1.1.2, below.
3.1.1.2 Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted		X	See ii), immediately below.
ii)	It is considered that in the absence of a full dossier the active substance may be approved even though certain information is still to be submitted because: (a) the data requirements have been amended or refined after the submission of the dossier; or (b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.			The dossier is **not** considered complete, and a regulatory decision can currently not be made as: In the ED-assessment (see Section 2.10 Endocrine disrupting properties) RMS have concluded that endocrine activity has been observed and that further information is needed to conclude on the endocrine disrupting properties of penconazole. The missing data is regarded critical for the decision of approval, as it is needed to complete the ED-assessment and to

				decide whether the approval criteria (point 3.6.5 and 3.8.2 in Annex II to Regulation (EC) 1107/2009) is fulfilled or not. The ED criteria were implemented after the application for renewal was received. According to Commission Implementing Regulation (EU) 2018/1659 Penconazole is considered a pending application, as the application for renewal (according to Art. 1 of the Reg. 844/2012) was received before 10th of November 2018. More specifically the administrative application for penconazole was received the 31st of December 2016. For pending applications, information may be requested by EFSA during EFSA stop-clock. When information needed to finalise the ED-assessment have been provided, the dossier may be regarded as complete. RMS proposal for which studies should be requested is listed under point 3.1.4. Point 3.1.4 also lists other data gaps identified by RMS
	3.1.1.3 Restrictions on approval			
		Yes	No	
	It is considered that in line with Article 6 of Regulation (EC) No 1107/2009 approval should be subject to conditions and restrictions.	X		The purity of the active substance shall be minimum 950 g/kg The nature and maximum content of certain impurities are confidential information – data are provided separately (Vol. 4) by the Penconazole Task force members. Based on the evaluation of the available data, RMS has identified a relevant metabolite, CGA179944, considered to exceed the permitted level in groundwater (>0.1 µg/L) for all uses in the GAP except the 1 x 35 g a.s./ha in cucmber. CGA179944 shows similar developmental toxicity compared with penconazole, and RMS proposes the same classification, as "Suspected of damaging the unborn child», H361d.
	3.1.1.4 Criteria for the approval of an active substance			
Dossier				
		Yes	No	
	It is considered the dossier contains the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).	X		

	It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes (relevant for substances for which one or more representative uses includes use on feed or food crops or leads indirectly to residues in food or feed). In particular it is considered that the dossier: (a) permits any residue of concern to be defined; (b) reliably predicts the residues in food and feed, including succeeding crops (c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing; (d) permits a maximum residue level to be defined and to be determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.	X		The residue definition for monitoring in plants is proposed to be parent penconazole, only. The residue definition for risk assessment in plants is proposed to be the sum of penconazole + CGA132465 + CGA190503 + CGA127841, and the conjugates of the metabolites, expressed as penconazole (fruit and fruiting vegetables, only). The residue definition for risk assessment in processed plant commodities (fruit and fruiting vegetables, only) is proposed to be the same as for unprocessed plant commodities. The qualitative nature of the residues in rotated crops is similar to and consistent with the pathways found in the representative primary crops. The dietary burden triggering the submission of livestock metabolism studies is >0.004 mg/kg bw/d for the active substances falling under Regulation (EU) No 283/2013. Calculated dietary burden calculations for feed-related representative crops (apple, only) are below the trigger in Regulation (EU) No 283/2013 (>0.004 mg/kg bw/d) for ruminants, and zero for poultry, pigs and fish. Therefore, residue definitions for monitoring and risk assessment in animal commodities are not required. The study on residue levels in honey did not provide enough data to determine a maximum residue level for penconazole. The results of the TMDI and IEDI calculations indicate that there is no unacceptable chronic risk to human health from the consumption of commodities treated with penconazole according to the uses considered. The results of the IESTI calculation indicate that there is no unacceptable acute risk to human health from the consumption of commodities treated with penconazole according to the uses considered.
	It is considered that the dossier submitted is sufficient to permit, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.	X		All intended uses
Efficacy				
		Yes	No	
	It is considered that it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use is sufficiently effective.	X		See level 2 (section 2.3).
Relevance of metabolites				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.	X		All intended uses

Composition				
		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.		X	**Specification for Syngenta sources:** The (eco)toxicological relevance of one impurity remains open/are not finalised. **Specification for Ascenzas source:** RMS has not received the necessary information in this AIR submission to evaluate (eco)toxicological relevance of eventual impurities in the technical material, nor to perform an equivalence assessment against the current and proposed reference specifications. The technical specification for Ascenza's source remains unconcluded.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.			Not relevant; Such FAO specification for penconazole does not exist.
	It is considered for reasons of protection of human or animal health or the environment, stricter specifications than that provided for by the FAO specification should be adopted			Not relevant; Such FAO specification for penconazole does not exist.
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently specific, correctly calibrated, accurate and precise.	X		**Syngenta and Ascenza sources:** Validated analytical methods in line with data requirements and guidelines have been used in the generation of data used in the risk assessment.
	It is considered that the methods of residue analysis for the active substance and relevant metabolites in plant, animal and environmental matrices and drinking water, as appropriate, shall have been validated and shown to be sufficiently sensitive with respect to the levels of concern.	X		Validation of the analytical method in line with current data requirements and guidelines have not been provided for all methods used for the generation of data to be used in the risk assessment. Sufficient information and/or data are, however, available to conclude on the acceptability of the analytical method and/or reliability of the generated data used in the risk assessment. Please refer to Level 2 – 2.5.1.
	It is confirmed that the evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		
Impact on human health				

Impact on human health - ADI, AOEL, ARfD				
		Yes	No	
	It is confirmed that (where relevant) an ADI, AOEL and ARfD can be established with an appropriate safety margin of at least 100 taking into account the type and severity of effects and the vulnerability of specific groups of the population.	X		In line with the previous evaluation (DAR, 2007), the ADI is based on the NOAEL (3 mg/kg bw/day) from the 90 days/1 year toxicity study in dogs. From a comparison of NOAELS/LOAELs potentially relevant for setting an ADI, i.e. those from short-term, long-term and reproduction toxicity studies, it was concluded that the species most sensitive to repeated administration of penconazole was the dog, with the most relevant NOAEL of ca. 3 mg/kg bw/day, being derived from the combined 90-day/1-year oral gavage study on the basis of reduced body weight development and hepatotoxicity at about 17 mg/kg bw/day and above. With respect to safety factors, it was previously (DAR, 2007) decided to use a default value of 100 (accounting for potential interspecies as well as for intraspecies variation), resulting in an ADI of 0.03 mg/kg bw/day. During this re-assessment, an extra safety factor of 2 is proposed to be applied, to account for the extrapolation from sub-chronic to chronic studies. Notably, the histopathological findings in the combined 90-day/1-year oral gavage study indicate a time-dependent increase in the number of animals with inflammation with fibrosis in the liver. In addition, more severe effects in the liver are seen at lower penconazole levels after 1 year compared with 90 days. In total, three chronic/long term studies were conducted (two in mice and one in rats). However, in line with the previous evaluation (DAR, 2007), it was concluded that the tested doses in two of these studies were too low and that the studies could only be considered supportive, as no toxicity was seen at the top dose. In the third long-term study in mice, a NOAEL of 21.7 mg/kg bw/day was derived, based on reduced body weight development and an increase in liver weight associated with an increase in hepatocyte vacuolisation at the highest dose tested. Notably, a NOAEL of 69 mg/kg bw/day was derived for a 90-Day Preliminary Carcinogenicity Study In Mice, based on reduced body weight development and an increase in liver weight associated with an increase in hepatocellular hypertrophy at increasing dose. The proposed ADI was calculated as follows:

				ADI = NOAEL 90-day/1-year, dog/ SF = (3 mg/kg bw/day)/200 = 0.015 mg/kg bw/day. During the previous evaluation (DAR, 2007), the setting of an ARfD for penconazole was considered unnecessary, based on an evaluation in accordance with recommendations of the WHO published in 2004 (JMPR, 2004. Guidance for the derivation of an acute reference dose, pesticide residues in food-2004, Report of the JMPR, FAO Plant Production and Protection Paper, 178). During the current evaluation, an ARfD of 50 mg/kg bw/day is proposed, based on the NOAEL from a developmental toxicity study in rabbit. With respect to uncertainty factors, it is proposed to use a default value of 100, accounting for potential interspecies as well as for intraspecies variation. Based on the comparative intravenous (iv) vs. oral data, the oral absorption of penconazole can be assumed to be practically complete, and no additional correction factor is proposed. The proposed ARfD was calculated as follows: **ARfD = NOAEL dev. Tox rabbit /SF = (50 mg/kg bw/day)/100 = 0.5 mg/kg bw/day** In line with the previous evaluation (DAR, 2007), the AOEL is based on the NOAEL (3 mg/kg bw/d) from the 90 days/1 year toxicity study in dogs. From a comparison of potentially relevant NOAELs/LOAELs for short-term and reproduction toxicity, the combined 90-d/1-yr study in dogs was chosen as being the most relevant one for the setting of the systemic AOEL (AOEL-S). With respect to safety factors, it is, in line with the previous evaluation (DAR, 2007), decided to use a default value of 100, accounting for potential interspecies as well as for intraspecies variation. Based on the comparative intravenous (iv) vs. oral data, the oral absorption of penconazole can be assumed to be practically complete, and no additional correction factor is proposed. The proposed AOEL was calculated as follows: **AOEL-S = NOAEL 90-day/1-year, dog /SF = (3 mg/kg bw/day)/100 = 0.03 mg/kg bw/day** An EU-wide harmonised approach for the derivation of the AAOEL is still pending. However, based on the Commission Guidance Document

				SANTE-108322015 rev. 1.7, 24 January 2017, the ARfD is suggested as a value for the AAOEL. The proposed AAOEL was calculated as follows: **AAOEL = NOAEL dev. Tox rabbit /SF = (50 mg/kg bw/day)/100 = 0.5 mg/kg bw/day**
Impact on human health – proposed genotoxicity classification				
		Yes	No	
	It is considered that, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as mutagen category 1A or 1B.**		X	Penconazole did not reveal any genotoxic potential in all available *in vitro* studies. All tests were considered acceptable by RMS except for one out of four Ames tests, the chromosome aberration assay and an unscheduled DNA synthesis test, which were considered supplementary. The negative Ames tests and the *in vitro* HPRT mammalian cell gene mutation test confirm that penconazole does not induce gene mutations in bacterial cells and in mammalian cells. An *in vitro* micronucleus test was not available during the completeness check, but was later done with technical penconazole spiked for several impurities. In addition to the *in vitro* micronucleus test, an Ames test and an *in vitro* HPRT mammalian cell gene mutation test were done with the same spiked batch of penconazole: the Ames test was negative, while the *in vitro* HPRT test was considered to be equivocal (more details are provided in Volume 4). The *in vitro* micronucleus test confirms the absence of both aneugenic and clastogenic potential for penconazole and the negative result for clastogenicity in the supplementary chromosomal aberration assay. The *in vivo* micronucleus study is supportive only due to too few cells analysed; thus, it is not possible to conclude that penconazole is clearly negative regarding structural or numerical chromosome aberrations *in vivo*. As the phototoxicity test revealed no phototoxic potential of penconazole, a photomutagenicity test is not required, in accordance with EFSA technical report 2016 (Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology, EFSA Supporting publication 2016:EN-1074). Taken together, it is not possible to conclude whether Penconazole is considered not genotoxic, due to the supplementary *in vivo* micronucleus study provided. A re-analysis of the *in vivo* study would provide a better basis to draw a conclusion.
Impact on human health – proposed carcinogenicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the carcinogenicity testing carried out in accordance with the data		X	Three carcinogenicity bioassays have been performed with Penconazole.

	requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as carcinogen category 1A or 1B.**			In two of these studies, one in mice and one in rats, no adverse findings, including tumours, were seen. However, as no toxicity was seen at the top dose, it was previously concluded (DAR, 2007) that the tested doses were too low and that the studies could only be considered supportive. In rats, the only dose-related finding of potential toxicological relevance that attained statistical significance was a slight increase in absolute and relative liver weight in females of the mid- and high-dose groups. However, these findings lacked a biochemical or histopathological correlate and were therefore not considered adverse. In the third study in mice, a higher top dose was used. This dose caused toxic effects but no tumours. The body weight development was reduced and an increase in liver weight was associated with an increase in hepatocyte vacuolisation. In RMS's opinion, it should be rediscussed to what extent these three available long-term studies are sufficient to exclude a carcinogenic potential of penconazole, and whether additional testing of long-term toxicity and carcinogenesis at higher doses in rats may be needed.
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as toxic for reproduction category 1A or 1B.**	X		Several findings from all four studies were related to developmental effects. Increases in post-implantation loss were seen in both rat studies and in the second rabbit study. In the first rat study, an increase in dead foetuses were seen at 450 mg/kg bw/day. Reduced foetal weights were reported in both rat studies. In the second rabbit study, two foetuses were dead, and the number of live foetuses per litter were reduced. An increase in runt foetuses were reported in the second rat study. Skeletal findings were reported in both rat studies, mainly increases in incomplete ossification and occurrence of extra ribs. However, the individual skeletal findings contributing to these increases were not reproducible within the

				same study nor between the two studies except for some indications for delayed ossification. In the first rabbit study, the incidences of internal hydrocephalus slightly exceeded available HCD. This was not seen in the second study. In addition, three foetuses in the first study had microphtalmia (within the range of HCD), including two which also had hydrocephalus. In the second rabbit study, foetuses with hyoid body and/or arches unossified and reduced ossification of the skull were observed and exceeded available HCD ranges. Taken together, several of these findings contribute to the need for classification. Since the data are from animal studies only and are not sufficiently convincing to classify in category 1b, classification in category 2 is warranted. For further details, see Section 2.6.6.2
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.		X	
Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that the substance SHOULD BE identified as having endocrine disrupting properties in accordance with the provisions of point 3.6.5 in Annex II of Regulation (EC) No 1107/2009			The available dataset was indicative of T-mediated activity: Uridine diphosphate [UDP]-glucuronyl transferase was increased in rat and mouse hepatocytes. There was no consistent evidence of T-mediated adversity: Increased thyroid weight and incidences of minimal hypertrophy of the follicle epithelium was observed in one study (short term 28 day) in one species (rat) and were considered adverse. However, these findings were not confirmed in other studies. Although there were no consistent effects on T-mediated adversity and activity, RMS is of the opinion that these parameters have not been sufficiently investigated. The available dataset was positive for EAS-mediated activity. There was evidence of AR and ER mediated activity (antagonism) and effects (inhibition) on steroidogenesis activity in vitro. There was no consistent evidence of EAS-mediated adversity: Testicular toxicity was observed in

				the 90-day study and in the 1-year dog study receiving top dose (cellular debris in epididymis (90 days), reduced spermatogenesis and reduced testis weight (90 days and 1-year) and tubular atrophy (1-year)). These effects were observed above the MTD (90 days) and around the MTD (1-year). EAS parameters were also examined in other studies at different dose levels and of different durations in rats and mice by oral administration of the substance and no adversity was observed. However, RMS is of the opinion that EAS-adversity has not been sufficiently investigated. In summary, as the endocrine disrupting properties of penconazole have not been sufficiently investigated, a firm conclusion regarding the endocrine disruption potential of penconazole cannot be drawn.
ii)	Linked to above identification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Fate and behaviour in the environment				
Persistent organic pollutant (POP)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1.		X	*Persistence* Penconazole is considered to be persistent as it fulfils the persistence criteria in Regulation 1107/2009 Annex II Section 3.7.1. See discussion in Vol. 1 Level 2, section 2.8.1 and 2.8.2 and Vol. 3 CA B.8, section B.8.5. *Bioaccumulative* The available study on bioaccumulation is not regarded reliable by RMS. A decision regarding the bioaccumulative potential can thus not be reached. See further information in Level 2, Section 2.9.2.1. *Potential for long-range transport* The potential for long-range transport is not fulfilled. See further information in Level 2, section 2.8.3.

				Reliable data to conclude on bioaccumulation is currently not available, however, the potential for long-range transport is not fulfilled. Penconazole does thus not fulfil the criteria for a POP-substance.
Persistent, bioaccumulative and toxic substance (PBT)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2.		(X)*	*Persistence* Penconazole is considered to be persistent as it fulfils the persistence criteria in Regulation 1107/2009 Annex II Section 3.7.1. See discussion in Vol. 1 Level 2, section 2.8.1 and 2.8.2 and Vol. 3 CA B.8, section B.8.5. *Bioaccumulative* The available study on bioaccumulation is not regarded reliable by RMS. **A decision regarding the bioaccumulative potential can thus not be reached**. See further information in Level 2, Section 2.9.2.1. *Toxic* - **the long-term no-observed effect concentration for marine or freshwater organisms is (currently) not less than 0.01 mg/l. From laboratory studies on the toxicity of penconazole to aquatic organisms the preliminary long-term NOEC for daphnia is ≤ 0.069 mg a.s./L. However, the study is regarded as supportive, due to uncertainty regarding the applied statistics. The applicant has informed RMS that the Penconazole Task Force intend to conduct a new study according to OECD TG 211, which fully complies with current guidance, with the data ready to be delivered on request by Q2 2022. See further information in Level 2, Section 2.9.2.3.5.** - **the substance is not classified as carcinogenic (category 1A or 1B) or mutagenic (category 1A or 1B); however, the substance is toxic for reproduction (category 2) pursuant to Regulation (EC) No 1272/2008** - **There is also evidence of chronic toxicity, as identified by the**

				classification as STOT RE 2 pursuant to Regulation (EC) No 1272/2008. Thus, penconazole fulfils the criteria of a toxic substance. As two of the PBT-criteria (P and T) are considered fulfilled for penconazole, the substance may be regarded as a candidate-of-substitution. *Penconazole does not fulfil the criteria for a PBT-substance, however, reliable data to conclude on bioaccumulation is currently not available.
Very persistent and very bioaccumulative substance (vPvB).				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		(X)*	*Very persistent* Penconazole is considered to be very persistent as it fulfils the persistence criteria in Regulation 1107/2009 Annex II Section 3.7.1. See discussion in Vol. 1 Level 2, section 2.8.1 and 2.8.2 and Vol. 3 CA B.8, section B.8.5. *Very bioaccumulative* The available study on bioaccumulation is not regarded reliable by RMS. A decision regarding the bioaccumulative potential can thus not be reached. See further information in Level 2, Section 2.9.2.1. *Penconazole does not fulfil the criteria for a vPvB-substance, however, reliable data to conclude on bioaccumulation is currently not available.
Ecotoxicology				
		Yes	No	
i	It is considered that the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or synergist. The RMS is content that the assessment takes into account the severity of effects, the uncertainty of the data, and the number of organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.	X		The surface water and soil modelling presented in volume 3CP is the original modelling submitted by the applicant, and it has not been updated with the new endpoints/other issues that have been decided by RMS/co-RMS (please refer to table XX for a comparison of original and new endpoints relevant for modelling). In the opinion of the RMS the modelling needs an update, but we will leave the final decision up to the MS and EFSA during/after the peer review. The acute and long-term risk to birds and mammals is acceptable at the screening level for all proposed uses. Likewise, the available data indicate

				acceptable risk via the consumption of drinking water and through secondary poisoning for both birds and mammals. For aquatic organisms, the Tier 1 $RAC_{SW,acute}$ of 5.6 µg a.s./L is lower than the FOCUS Step 1 PEC_{SW}-values (which ranged from 3.6 to 15.4 µg a.s./L), for three of four representative use scenarios indicating an unacceptable risk at these three representative uses at FOCUS step 1. The Tier 1 $RAC_{SW,chronic}$ of 3.2 µg a.s./L are lower than the FOCUS Step 1 PEC_{SW}-values (which ranged from 3.6 to 15.4 µg a.s./L), indicating an unacceptable risk at FOCUS step 1 for all four representative use scenarios. However, both the chronic and acute Tier 1 RACs are greater than the FOCUS Step 2 PEC_{SW}-values (which ranged from 0.3 to 2.2 µg a.s./L) thereby indicating an acceptable risk to aquatic organisms from penconazole following all proposed uses of A6209G. For all proposed use patterns, the Tier 1 $RAC_{SED,\,ch}$ of 2520 µg a.s./kg is above the Step 1 PEC_{SED} values (which ranged from 65 to 277 µg a.s./kg), indicating an acceptable risk to sediment dwelling organisms following the proposed uses of A6209G. The risk assessment for aquatic species and the metabolites were acceptable at FOCUS Step 1 for all the applied representative uses. Thus, an acceptable risk to aquatic organisms following the proposed uses of A6209G have been identified. No higher tier refinements are required. The risk for bees is considered to be acceptable following all the representative uses of A6209G. For details, see *iv* further down. The off-field risk to non-target arthropods other than bees is acceptable at the first tier. The in-field risk to *T.Pyri* is unacceptable for alle proposed uses at the first tier and a tier 2 risk assessment has been conducted. The tier 2 risk assessment shows acceptable risk for all uses, except from the highest dose rate in cucumbers. With this dose the reproductive risk is considered unresolved. For earthworms and soil macro-organisms, all the TER values for penconazole and the relevant metabolites are well above the relevant triggers, indicating acceptable long-term risk for all the representative uses of A6209G. For soil nitrogen transformation, < 25% deviation from control after 28 days was observed for penconazole (in A6209G) and relevant soil

				metabolites, at doses relevant for the representative uses. Thus, acceptable risk on soil nitrogen transformation is expected after exposure of penconazole or the penconazole metabolites. Two screening studies with the representative formulation A6209G (Topas 100 EC) and higher plants have been submitted, these are both regarded as supportive. According to the Terrestrial guidance document, endpoints measured in most screening studies cannot be interpreted as a NOEC-value covering germination and biomass production. However, it is assumed that the available information usually allows the use of a conservative approach, assuming, for example, that when an untreated control has been run in parallel, any effect accounting for at least 50 % reduction in biomass production could be identified in a visual inspection. In the current screening study, no phytotoxic effects above 50% was detected at an application rate of 200 g a.s./ha covering the worst-case GAP (including accumulation). According to these data, acceptable risk may be anticipated for the representative uses. However, this study is regarded as « supportive only », due to e.g. non-GLP and lack of analytical verification of the test substance. RMS is of the opinion that a new valid study should be provided in order to conclude on the risk for terrestrial plants. The applicant has indicated that studies with the formulation Duoro (10% EC formulation) can be submitted during EFSA-stop-clock, and that syngent intend to conduct two new studies with A6209G and NTTP, which may be available Q3 2022. In the risk assessment for biological methods for sewage treatment the EC_{20} of 82.1 mg a.s./L_{nom} is 5335 times greater than the worst-case FOCUS step 1 initial PEC_{sw} of 0.01537 mg/l (cucumber, bbch 51-89, 3 x 50 g a.s./ha). Dilution prior to reaching sewage treatment facilities may also be expected to reduce the risk further. These results suggest limited risk to sewage treatment facilities.
ii	It is considered that the substance **SHOULD BE identified as having endocrine disrupting properties** that may cause adverse effects on non-target organisms in accordance with the provisions of point 3.8.2 in Annex II of Regulation (EC) No 1107/2009.			There is evidence of endocrine activity (E, A, S and T) however, endocrine adversity has not been sufficiently investigated (Scenario 2a (i) in EFSA/ECHA guidance). Therefore, further data should be generated before a conclusion could be drawn. According to **Commission Implementing Regulation (EU) 2018/1659** Penconazole is considered a pending application (submission of the application for renewal (Art. 1 of the Reg.

				844/2012) before 10th of November 2018, more specifically the administrative application was 31st of December 2016). To conclude on adversity, further information is needed: - **Fish life cycle toxicity test has been initiated by the applicant, but reporting was not finalised before delivery of the Top-up submission in December 2019. Study will address potential adverse effects on the EAS-modality for non-target organisms other than mammals.** - **AMA (OECD 231) or XETA (OECD 248) is needed to finalise the assessment of the T-modality for non-target organisms other than mammals.** For mammals as non-target organisms: please see Level 3 Impact on human health – proposed endocrine disrupting properties classification i), above. Please see Volume 1, Level 2.10, for further details.
iii	Linked to the consideration of the endocrine properties immediately above. It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic proposed conditions of use is negligible.			Not applicable
iv	It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist: — will result in a negligible exposure of honeybees, or — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.	X		Studies have been submitted and evaluated, investigating the chronic toxicity of Penconazole (in preparation A6209G) to adult honeybees and honeybee larvae, in line with the data requirements. Further, acute toxicity studies with bumble bees and penconazole have been submitted and evaluated. The risk assessment for honey bees and bumble bees has been performed according to the EFSA Bee guidance (EFSA Journal 2013;11(7):3295). The acute risk to adult honey bees and bumble bees, and the chronic risk to honey bee larvae from penconazole are acceptable at the screening level for all proposed uses of A6209G. The chronic risk to adult honey bees for the proposed post flowering uses (BBCH ≥ 70) in pome, vines and cucumber from penconazole and the formulation A6209G is acceptable at tier 1. The chronic risk to adult honey bees from penconazole for the proposed uses in

				vines (BBCH 10-69) and cucumber (BBCH 50-69) is considered acceptable according to a refined risk assessment. There are no studies on the residues of metabolites in pollen or nectar. The metabolites considered to be relevant (CGA71019 and CGA132465) were identified based on plant metabolisms and rotational crop studies, and toxicity reported for other organism groups/QSAR. The risk for the relevant metabolites is assessed, assuming 10 times higher toxicity of the metabolites compared to penconazole. The acute risk to adult honey bees and the chronic risk to honey bee larvae from the relevant metabolites are acceptable at the screening level for all proposed uses of A6209G. For CGA71019 the chronic risk to adult honey bees for all the proposed uses of A6209G is considered acceptable at tier 1. For CGA132465, the chronic risk to adult honey bees for the proposed post flowering uses (BBCH ≥ 70) uses in cucumber is considered acceptable at tier 1. The chronic risk to adult honey bees from CGA132465 for the proposed post flowering uses (BBCH ≥ 70) uses in pome and wine is considered acceptable according to the refined risk assessment. The chronic risk to adult honey bees for the proposed uses in vine (BBCH 10-69) and cucumber (BBCH 50-69) is considered acceptable based on a weight of evidence approach.
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.	X		For monitoring: Penconazole only For risk assessment: Sum of penconazole and free and conjugated CGA132465, CGA190503 and CGA127841, expressed as penconazole
Fate and behaviour concerning groundwater				
		Yes	No	
	It is considered that it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites, degradation or reaction products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.			To be completed with updated calculations, for current calculations see Volume 3 CP B.8 of the dRAR The groundwater modelling presented in volume 3CP is the original modelling submitted by the applicant, and it has not been updated with the new endpoints/other issues that have been decided by RMS/co-RMS (please refer to table 96 for a comparison of original and new endpoints relevant for modelling). In the opinion of the RMS the groundwater modelling needs an update, but we will leave the final decision up to the MS and EFSA during/after the peer review.

				Preliminary evaluation shows that metabolites CGA179944 and CGA142856 exceed the concentration of 0.1 µg/L, except for use in cucmber with application rate of 35 g penconazole/ha x 1. CGA142856 is also predicted to exceed the concentration of 0.75 µg/L

3.1.2 Proposal – Candidate for substitution

Candidate for substitution				
		Yes	No	
	It is considered that the active substance shall be approved as a candidate for substitution	X		Yes, penconazole should be approved as a candidate for substitution as it meets two of the criteria to be considered as a PBT substance (P and T).

3.1.3 Proposal – Low risk active substance

Low-risk active substances				
		Yes	No	
	It is considered that the active substance **shall be considered of low risk.** If the active substance is not a micro-organism, in particular it is considered that: (a) the substance **should NOT be classified or proposed for classification** in accordance to Regulation (EC) No 1272/2008 as any of the following: — carcinogenic category 1A, 1B or 2, — mutagenic category 1A, 1B or 2, — toxic to reproduction category 1A, 1B or 2, — skin sensitiser category 1, — serious damage to eye category 1, — respiratory sensitiser category 1, — acute toxicity category 1, 2 or 3, — specific Target Organ Toxicant, category 1 or 2, — toxic to aquatic life of acute and chronic category 1 on the basis of appropriate standard tests, — explosive, — skin corrosive, category 1A, 1B or 1C; (b) it has **not been identified as priority substance under Directive 2000/60/EC**; (c) it is **not deemed to be an endocrine disruptor** in accordance to Annex II of Regulation (EC) No 1107/2009; (d) it **has no neurotoxic or immunotoxic effects**; (e) it **is not persistent** (half-life in soil is more than 60 days) or its **bio-concentration factor is lower than 100**. (f) it is a **semiochemical** and verifies points (a) to (d).		X	

	Paragraph (e) doesn't apply to naturally occurring active substances. If the active substance is a micro-organism, in particular it is considered that at strain level the micro-organism has not demonstrated multiple resistance to anti-microbials used in human or veterinary medicine. If the active substance is a baculovirus, in particular it has not demonstrated adverse effects on non-target insects.			

3.1.4 List of studies to be generated, still ongoing or available but not peer reviewed

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	**Study on-going and anticipated date of completion**	**Study available but not peer-reviewed**
3.1.4.1 Identity of the active substance or formulation				
Ascenza's source for TM: The submitted 5-batch analysis are not within the timeframe required by the regulation (5 years from the time of submission).	No relevance		Anticipated completion May 2022	
Ascenza's source for TM: Insufficient information is provided for the evaluation of (eco)toxicological relevance of eventual impurities in this AIR submission, nor to perform an equivalence assessment against the current and proposed reference		X		
3.1.4.2 Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
CA B.2.7: Study reports for the determination of the partition coefficient (n-octanol/water) for three of the metabolites included in the residue definition are either lacking information on the batches used for studies (CGA179944 and CGA71019), or the study report entirely (CGA91305).		X		
3.1.4.3 Data on uses and efficacy				

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	**Study on-going and anticipated date of completion**	**Study available but not peer-reviewed**
3.1.4.4 Data on handling, storage, transport, packaging and labelling				
3.1.4.5 Methods of analysis				
Methods for post control and monitoring purposes: The Task Force has not provided analytical methods for metabolites CGA71019 (1,2,4-Triazole), included in the residue definitions for soil and groundwater, as well as penconazole-OH, included in the residue definition for bodily fluids and tissues.		X		
3.1.4.6 Toxicology and metabolism				
Genotoxicity study with metabolite CGA179944: *In vitro* mammalian cell gene mutation (OECD 490). Due to lack of colony sizing, and the equivocal result of the existing study, a novel study should be provided.		X		
To investigate EAS-adversity a study following the OECD TG 416 (latest version) should be		x		

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	**Study on-going and anticipated date of completion**	**Study available but not peer-reviewed**
conducted, with investigation of the following parameters: anogenital distance (AGD), nipple retention, mammary gland histopathology and hormone measurements. A complete dataset from a Level 5 study would fully address the concern arising from the positive outcome of the Level 2 studies, which would be sufficient to conclude whether the ED criteria are met or not.				
The first step should be to investigate T-adversity in a study following the OECD TG 407/408 and OECD TG 416 (latest version). To investigate whether liver enzyme induction is responsible for the effects seen on thyroid histopathology and weight and to determine whether the effect is likely to be human relevant or not, studies on the following will be needed: 1) A specifically designed in vivo toxicity study should be considered to measure TSH, T3 and T4 and, where possible, additional data on liver enzyme induction (e.g. measurement of UDPGT) should be included. 2) Comparative studies of enzyme activity induced by the test substance in liver in vitro systems should be measured in both the relevant test species (e.g. rat, mouse and dog) and humans.		x		

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	**Study on-going and anticipated date of completion**	**Study available but not peer-reviewed**
3) The presence of other possible thyroid-disrupting modes of action such as interference with TH synthesis should also be excluded, e.g. by evaluating in vitro the potential for inhibition of the sodium–iodide symporter (NIS) and thyroid peroxidase (TPO). If changes in circulating THs are observed and human relevance cannot be clearly excluded as a result of these assays, a thyroid assessment study conducted in the foetus and pup.				
3.1.4.7 Residue data				
Effect on the residue level in pollen and bee products – setting of MRL		X		
3.1.4.8 Environmental fate and behaviour				
No acceptable field dissipation studies on the active substance. As the soil DT50 values for penconazole are greater than 60 days in laboratory studies, field studies are considered required in accordance with Commission Regulation (EU) No 283/2013.		X		
According to the data requirements of the commission regulation (EU) No 283/2013, soil accumulation studies shall provide estimates of the		X		

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	**Study on-going and anticipated date of completion**	**Study available but not peer-reviewed**
time required for dissipation of 50 % and 90 % (DisT50 field and DisT90 field). It is not possible to fulfil this data requirement by model calculations. Single yearly residue analysis at various times does not allow for kinetic evaluations. This data requirement is not filled.				
The modelling presented in volume 3CP and LoEP is the original modelling submitted by the applicant, and it has not been updated with the new endpoints (degradation and sorption) that have been suggested by RMS/co-RMS (please refer to table 96 for a comparison of original and new endpoints relevant for modelling). In the opinion of the RMS the modelling needs an update, but we will leave the final decision up to the MS and EFSA during/after the peer review If deemed necessary by MS/EFSA the following adjustments should also be made for the new modelling: - PECsoil using geometric mean DT50 - PECgw using "spring cereals" as a surrogate crop for cucumber (based on co-RMS commenting table, comment 59) - PECsw Steps 1-2 calculations covering the entire application period. See RMS's grey commenting box in Vol. 3CP B.8, under section B.8.5 for an overview of	Relevant for all representative uses	X		

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	**Study on-going and anticipated date of completion**	**Study available but not peer-reviewed**
the additional modelling that should be provided. - Any new calculations provided for metabolite CGA91305 should be conducted using the correct molecular weight of 258.1 g/mol.				
The potential effects of water treatment processes should be considered a data gap if deemed necessary.		X		
3.1.4.9 Ecotoxicology				
A Fish full life cycle study to address the ED-criteria for adversity.			X (Study has been initiated, but reporting was not finalised before delivery of the Top-up submission in December 2019. Final report can be requested by EFSA during stop-the-clock.)	
A valid GLP study to address data requirement 8.2.2.3 Bioconcentration in fish, in European commission (EU) 283/2013.		X		
A valid GLP study with technical penconazole and *D. magna* to address data requirement 8.2.4.1 Acute		X		

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	**Study on-going and anticipated date of completion**	**Study available but not peer-reviewed**
toxicity to *Daphnia magna*, in European commission (EU) 283/2013		(Not to RMS knowledge).		
The applicant acknowledges that the existing Daphnia chronic exposure study (CGA71818/0080) addressing data requirement 9.2.5.1 Long-term and chronic toxicity to aquatic invertebrates, has some limitations according to today's standards.			X (The Penconazole Task Force intend to conduct a new study according to OECD TG 211, which fully complies with current guidance, with the data ready to be delivered on request by Q2 2022.)	
A valid GLP study with CGA142856 (triazole acetic acid) and green algae to address data requirement 8.2.6.1 Effects on growth of green algae, in European commission (EU) 283/2013.		X (Unknown. However, during the completeness check RMS requested that the applicant provided a study to derive the missing EC_{20}-value, in order to address the data requirement. RMS received the following response: *The Task Force are therefore proposing to conduct a new study to fulfil the current validity criteria for the study and*		

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	**Study on-going and anticipated date of completion**	**Study available but not peer-reviewed**
		provide all required ECx values where possible. RMS do not know whether the study have been or are planned to be initiated.)		
Even though data requirement 8.2.7 Effects on aquatic macrophytes in European commission (EU) 283/2013 do not apply to fungicides, the available data indicates that technical penconazole may be toxic to *Lemna gibba*. EFSA should therefore consider whether a study should be provided		X		
A valid GLP study(ies) on non-target terrestrial plants and technical penconazole/the representative formulation is needed to address the data requirements 8.6. Effects on terrestrial non-target higher plants and 10.6. Effects on terrestrial non-target higher plants, in European commission (EU) 283/2013 and European commission (EU) 284/2013, respectively			X (Two studies according to OECD TG 208 and 227 are available to the Penconazole Task Force for the penconazole 10% EC formulation, DOURO. Both studies are available for submission during the EFSA-stop-clock if requested by EFSA during peer review. Syngenta also intends to conduct two new	

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	**Study on-going and anticipated date of completion**	**Study available but not peer-reviewed**
			studies with the formulated product (A6209G; penconazole 100 g/L EC) in full accordance with current guidance (OECD TG 208 and 227). However, these data are unlikely to be available before Q3 2022.)	
There are no studies on the residue levels of metabolites in nectar or pollen, nor any effect studies on honey bees and relevant metabolites available. Therefore, the data requirement regarding metabolites might be considered as not fulfilled. EFSA should considered if this constitutes a data gap and if additional data is required, or if the approach suggested for addressing the risk of metabolites according to the EFSA Bee GD (2013) as presented in **Volume 3 - B.9 (PPP)**, **section B.9.6.1.3** is sufficient		x		

3.1.5 Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) No 546/2011, and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

Area of the risk assessment that could not be finalised on the basis of the available data	**Relevance in relation to representative use(s)**
Genotoxic potential of penconazole: The *in vivo* micronucleus study is supportive only due to too few cells analysed; thus, it is not possible to conclude that penconazole is clearly negative regarding structural or numerical chromosome aberrations *in vivo*. A re-analysis of the *in vivo* study would provide a better basis to draw a conclusion.	Relevant for all representative uses
The endocrine disrupting potential of penconazole could not be finalised due to lack of sufficient information.	Relevant for all representative uses
The bioconcentration factor (BCF) for penconazole could not be determined, as the available study is regarded as not reliable by RMS. Thus, the assessment of the approval criteria in Annex II (3.7.1 – POP, 3.7.2 -PBT, 3.7.3 vPvB) could not be finalised.	Relevant for all representative uses
The risk assessment to non-target terrestrial plants, as no valid GLP study/studies fulfilling the data requirements is/are available.	Relevant for all representative uses

3.1.6 Critical areas of concern

An issue is listed as a critical area of concern:
(a) where the substance does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II of Regulation (EC) No 1107/2009 and the applicant has not provided detailed evidence that the active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, taking into account risk mitigation measures to ensure that exposure of humans and the environment is minimised, or
(b) where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) 546/2011, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

Critical area of concern identified	Relevance in relation to representative use(s)
Based on the evaluation of the available data, RMS has identified a relevant metabolite, CGA179944, considered to exceed the permitted level in groundwater (>0.1 µg/L). CGA179944 shows similar developmental toxicity compared with penconazole, and RMS proposes the same classification, as "Suspected of damaging the unborn child», H361d.	Relevant for all representative uses except 1x 35 g a.s./ha in cucumber
The endocrine disrupting potential of penconazole could not be finalised due to lack of sufficient information	Relevant for all representative uses

3.1.7 Overview table of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in 3.3.1, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)

Representative use		Pome fruit BBCH 71–89 2 x 40 g a.s./ha	Grapes, table and wine BBCH 13-85 2 x 30 g a.s./ha	Cucumber BBCH 51-89 3 x 50 g a.s./ha	Cucumber BBCH 51-89 1 x 35 g a.s./ha
Operator risk	Risk identified	None	None	None	None
	Assessment not finalised				
Worker risk	Risk identified	None	None	None	None
	Assessment not finalised				
Bystander risk	Risk identified	None	None	None	None
	Assessment not finalised				
Consumer risk	Risk identified	None*	None*	None*	None
	Assessment not finalised				
Risk to wild non target terrestrial vertebrates	Risk identified	None	None	None	None
	Assessment not finalised				
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified	None	None	None	None
	Assessment not finalised	X[1]	X[1]	X[1, 2]	X[1]
Risk to aquatic organisms	Risk identified	None	None	None	None
	Assessment not finalised				
Groundwater exposure active substance	Legal parametric value breached				
	Assessment not finalised	X[3]	X[3]	X[3]	X[3]
Groundwater exposure metabolites	Legal parametric value breached				

	Parametric value of 10µg/L[(a)] breached				
	Assessment not finalised	X[3]	X[3]	X[3]	X[3]
Comments/Remarks					

The superscript numbers in this table relate to the numbered points indicated within chapter 3.1.5 and 3.1.6. Where there is no superscript number, see level 2 for more explanation.
(a): Value for non relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003
[1] Non-target-terrestrial plants
[2] Non-target arthropods other than bees
[3] Updated modelling required
* As the metabolite CGA179944 is proposed to be classified with H361d and exceeds the permitted level of 0.1 µg/ml in groundwater, consumer risk has been identified in relation to drinking water

3.1.8 Area(s) where expert consultation is considered necessary

It is recommended to organise a consultation of experts on the following parts of the assessment report:

Area(s) where expert consultation is considered necessary	**Justification**
Long-term carcinogenicity studies	EFSA previously concluded (EFSA, 2008) that penconazole had no carcinogenic potential and did not need to be tested at higher doses in rats. Furthermore, the Committee for Risk Assessment (RAC) previously (RAC, 2012) concluded that classification for carcinogenicity after exposure to penconazole is considered not required according to Classification Regulation (EC) No 1272/2008. According to RAC, the negative result of the study in mice ([redacted] (2004), K-CA 5.5/02), together with the supportive studies in mice ([redacted] (1985), K-CA 5.5/01) and rats ([redacted] (1985a), K-CA 5.5/03) indicates no carcinogenic potential of penconazole. In RMS' opinion, it should be re-discussed to what extent these three available long term studies are sufficient to exclude a carcinogenic potential of penconazole, and whether additional testing of long-term toxicity and carcinogenesis at higher doses in rats may be needed.
Bioconcentration factor	One bioaccumulation study with the bluegill sunfish, *Lepomis macrochirus*, is available, and a maximum whole fish bioconcentration factor (BCF) of 320 was derived. In the study TOC was not measured during the test. Organic matter content, quantified as total organic carbon (TOC) and dissolved organic carbon (DOC) can have a significant effect on the amount of freely dissolved test substance during flow-through fish tests, especially for highly lipophilic substances. A metabolism study with a 7-day semi static exposure was available, and during this part of the study partitioning of penconazole between the aqueous and organic phase in water was investigated. The results show that 85-98% of ^{14}C-residues were extracted from the organic phase. Sorption of the test substance to organic matter may reduce its bioavailability and therewith result in an underestimation of the BCF[44]. In total, this brings uncertainty about the accuracy of calculated BCF.

[44] OECD (2017). Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation. ENV/JM/MONO(2017)16

	In addition, there was a lack of lipid and growth measurements which prevented normalisation of the BCF, and the calculation of the BCF was not done according to the guideline. The BCF was instead calculated based on the mean maximum concentration in fish and the concentration in fish was highest at the start of the exposure period. RMS asked coRMS DE for their opinion regarding the validity of the study, and received the following comment (excerpt): *(...) In our opinion, this study should not be considered valid. The relation of the BCF to the high concentration at the beginning might be conservative, but might also be due to the fact that the test substance was not completely bioavailable in the further course of the study. Consequently, there is a high uncertainty attributed to the BCF. (…).* RMS thus consider the study not valid, and recommend a new valid study is conducted to conclude on the BCF. As this is a vertebrate study involving a large number of fish, the reliability of the study and the need to conduct a new study should be discussed during peer review.
pH dependent sorption	There are indications that the soil adsorption of penconazole and metabolites is pH dependent. This issue was not concluded.
Harsh extraction	A method described as "harsh" extraction was used in some of the studies assessing the rout and rate of degradation in soil. The residues of penconazole and its metabolites that were detected in the harsh extracts were included when performing the kinetic fitting. RMS consulted the co-RMS regarding the definition of a harsh extraction and whether to include the harsh extracts in the overall data who suggested that including the values from harsh extraction is more conservative and can be considered as acceptable in this case, but that this issue should be discussed in an expert meeting. Please refer to RMS's evaluation in 3CA B.8 of: - Glänzel, 1999 - Scacchi and Pizzingrilli, 2000 - Scacchi and Pizzingrilli, 2003 - Mainolfi and Colombini, 2019
Version of AppDate	Different versions of AppDate can give very different application dates/window. Based on suggestion from co-RMS, which version of AppDate is valid for EU risk assessment at present should be discussed in an expert meeting. Refer to discussion in 3CP B.8, section B.8.5.
Risk assessment for non-target arthropods other than bees	It is considered that the in-field risk for *T.Pyri* still is unresolved for the highest dose in cucumber. The new study with *T.Pyri* indicates acceptable risk for all other uses when assuming that this rate-response study supersede the old study with only one dose level. Both studies are considered acceptable by the RMS. The relevance of the old study for the risk assessment should be discussed during peer review.
Ecotoxicological endpoints from metabolites that are common for several active substances.	For some of the metabolites (e.g., CGA71019 and CGA91305) that are common for several active substances, "new" studies have been submitted that have not previously been evaluated in the DAR/RAR of the active substance under re-evaluation, but have previously been evaluated in the DAR/RAR of another active substance (e.g., Metconazole and propiconazole). We have noticed that different endpoints from the same metabolite studies have been used in the DAR/RAR of other active substances. In the current

	evaluation RMS also suggest other endpoints for some of the metabolites than previously agreed in LoEP's for other active substances. RMS suggest that the final selection of the agreed endpoint from these studies should be further considered by EFSA, and/or discussed with other MS at an expert meeting since it might lead to discrepancy with endpoints previously listed for these metabolites in the LoEP for other active substances. Please see RMS's evaluation of the following studies in Volume 3 B.9 (CA): - **K-CA 8.2.1/06** - **K-CA 8.4.2.1/02** - **K-CA 8.4.2.1/07**

3.1.9 Critical issues on which the Co RMS did not agree with the assessment by the RMS

Points on which the co-rapporteur Member State did not agree with the assessment by the rapporteur member state. Only the points relevant for the decision making process should be listed.

Issue on which Co-RMS disagrees with RMS	**Opinion of Co-RMS**	**Opinion of RMS**

3.2 PROPOSED DECISION

[redacted]

3.3 RATIONAL FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH THE APPROVAL OR AUTHORISATION(S), AS APPROPRIATE

3.4 APPENDICES

3.4.1 GUIDANCE DOCUMENTS USED IN THIS ASSESSEMENT

General

Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market.

Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market

Section identity, physical chemical and analytical methods

Commission working document SANCO/825/00 rev. 8.1 (November 2010). Guidance document on pesticide residue analytical methods.

Commission working document SANCO/3029/99 rev. 4 (July 2000). Residues: Guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414.

Commission working document SANCO/3030/99 rev. 4 (July 2000). Technical Material and Preparations: Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414.

Commission working document SANCO/10597/2003 rev. 10.1 (July 2012). Guidance document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009.

Section Data on application and efficacy

Section Toxicology

EFSA (2014), Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, EFSA Journal 2014;12(10):3874

EFSA (2017) Guidance on dermal absorption, EFSA Journal 2017;15(6):4873

ECHA/EFSA ED guidance document, EFSA Journal 2018;16(6):5311

EFSA "Technical report on the outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology" (EFSA supporting publication 2020:EN-1837, doi:10.2903/sp.efsa.2020.EN-1837)

Section Residue and consumer risk assessment

OECD MRL CALCULATOR: STATISTICAL WHITE PAPER ENV/JM/MONO(2011)3

Guidelines - Maximum Residue levels page of the Europa.eu website in 2017 (pesticides_mrl_guidelines_animal_model_2017.xls)

SANCO 7525/VI/95 Rev. 10.3 GUIDANCE DOCUMENT Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs (2017)

OECD (2016) GUIDANCE DOCUMENT ON CROP FIELD TRIALS SECOND EDITION Series on Pesticides - No. 66 Series on Testing & Assessment - No. 164

Guidance on the establishment of the residue definition for dietary risk assessment EFSA Panel on Plant Protection Products and their Residues (PPR) EFSA Journal 2016;14(12):4549

OECD (2008). Guidance document on magnitude of pesticide residues in processed commodities. Environment, Health and Safety Publications. Series on Testing and Assessment No. 96.

OECD (2018) GUIDANCE DOCUMENT ON RESIDUES IN ROTATIONAL CROPS Series on Pesticides No. 97 Series on Testing & Assessment No. 279

SANTE/11956/2016 rev. 9 (2018) Technical guidelines for determining the magnitude of pesticide residues in honey and setting Maximum Residue Levels in honey

Section fate and behaviour in environment

DG SANCO (2012) Working Document on «Evidence Needed to Identify POP, PBT and vPvB Properties for Pesticides », Brussels 25.09.2012 – rev. 3

ECHA (2017) Guidance on the Application of the CLP Criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures Version 5.0. July 2017.

EFSA (2014) Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil. EFSA Journal 2014; 12(5):3662.

EFSA (2017) Guidance Document for predicting environmental concentrations of active substances of plant protection products and transformation products of these active substances in soil. EFSA Journal 2017;15(10):4982

EFSA (2017) Outcome of the pesticides peer review meeting on the OECD 106 evaluators checklist. EFSA Supporting publication 2017:EN-1326

European Commission (2003) Guidance Document on Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated under Council Directive 91/414/EEC. SANCO/221/2000-rev. 10 - final, 25 February 2003

FOCUS (2008) Pesticides in Air, SANCO/10553/2006 Rev. 2 June 2008

FOCUS (2014) Generic guidance for Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration; FOCUS, version 1.1, 18 December 2014

FOCUS (2014) Generic Guidance for Tier 1 FOCUS Ground Water Assessments; FOCUS, Version 2.2, May 2014

FOCUS (2015) Generic guidance for FOCUS surface water Scenarios; FOCUS, Version 1.4, May 2015

Section ecotoxicology

Candolfi, M.P., Barrett, K.L., Campbell, P.J., Forster, R., Grandy, N., Huet, M-C., Lewis, G., Oomen, P.A., Schmuck, R., Vogt, H. (2000). 'Guidance Document on regulatory testing procedures for plant protection products with non-target arthropods' From the workshop, European Standard Characteristics of Non-target Arthropod Regulatory Testing (ESCORT 2) 21-23 March 2000.

EFSA (2009). Guidance Document on Risk Assessment for Birds and Mammals. EFSA Journal 2009; 7(12):1438

EFSA (2013). Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013;11(7):3290

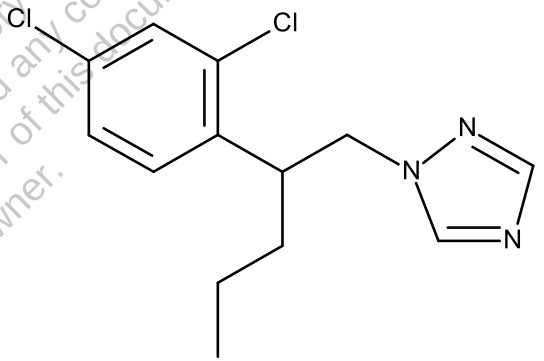
EFSA (2013, ***updated 04 July 2014***).). Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera*, Bombus spp. and solitary bees). EFSA Journal 2013;11(7):3295, 268 pp., doi: 10.2903/j.efsa.2013.3295

EU (2002). Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC. SANCO/10329/2002 rev 2 final. 17 October 2002.

EFSA (2018) Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. DOI: https://doi.org/10.2903/j.efsa.2018.5311

ECHA (2017) Guidance on the Application of the CLP Criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures Version 5.0. July 2017.

3.4.2 METABOLITES OVERVIEW TABLE

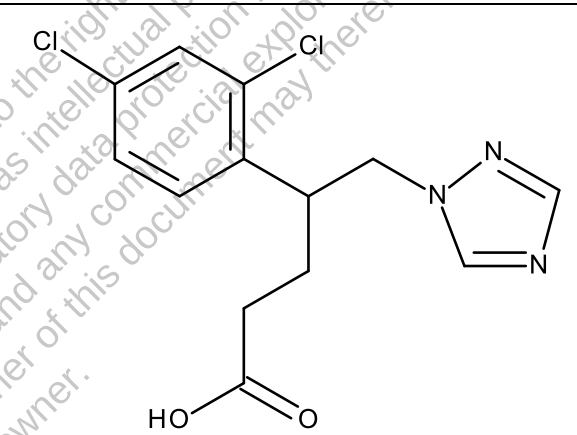
<table>
<tr><th>Code Number (Synonyms)</th><th colspan="2">(IUPAC name /SMILES notation /InChiKey)</th><th colspan="3">Compound found in xxx (level):
(For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)</th><th>Structural formula</th></tr>
<tr><td rowspan="11">Penconazole
CGA071818
CGA71818
CSAA061668
CAS: 66246-88-6
(- isomer): CSAC037637
(+ isomer): CSAC037638</td><td>Mol. Formula:</td><td>$C_{13}H_{15}Cl_2N_3$</td><td colspan="3">Dietary Metabolism Studies[1]</td><td rowspan="11">  </td></tr>
<tr><td>SMILES</td><td>CCCC(Cn1cncn1)c2ccc(Cl)cc2Cl</td><td>Commodity</td><td>%TRR</td><td>mg/kg</td></tr>
<tr><td>IUPAC Name:</td><td>1-[2-(2,4-dichlorophenyl)pentyl]-1,2,4-triazole</td><td colspan="3">Primary Plant Metabolism</td></tr>
<tr><td>InChiKey</td><td>WKBPZYKAUNRMKP-UHFFFAOYSA-N</td><td colspan="3">^{14}C-Triazole label studies</td></tr>
<tr><td rowspan="7" colspan="2"></td><td>Tomato Fruit (7-day PHI)</td><td>18.6</td><td>0.013</td></tr>
<tr><td>Tomato Leaves (7-day PHI)</td><td>9.7</td><td>0.383</td></tr>
<tr><td>Tomato Fruit (40-day PHI)</td><td>12.6</td><td>0.004</td></tr>
<tr><td>Tomato Leaves (40-day PHI)</td><td>4.1</td><td>0.028</td></tr>
<tr><td>Tomato Fruit (40-day PHI, 5x rate)</td><td>6.6</td><td>0.024</td></tr>
<tr><td>Tomato Foliage (40-day PHI, 5x rate)</td><td>9.9</td><td>0.029</td></tr>
<tr><td>Apple Peel</td><td>21.9</td><td>0.080</td></tr>
<tr><td rowspan="4"></td><td>Apple Pulp</td><td>5.2</td><td>0.003</td></tr>
<tr><td>Apple Whole Fruit</td><td>11.6</td><td>0.012</td></tr>
<tr><td>Apple Tree Leaves</td><td>6.8</td><td>0.261</td></tr>
<tr><td colspan="3">^{14}C-Phenyl label study</td></tr>
</table>

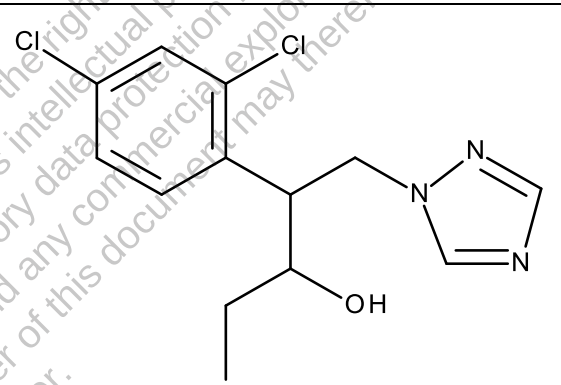
Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)	Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
		Tomato Fruit (7-day PHI)	15.1	0.005	
		Tomato Leaves (7-day PHI)	8.1	0.220	
		Tomato Fruit (40-day PHI)	7.2	0.001	
		Tomato Leaves (40-day PHI)	0.3	0.001	
		Confined Rotational Crops			
		^{14}C-Triazole label study			
		Wheat Tops, 50% mature (32-day PBI)	0.9	0.001	
		Wheat Fodder (32-day PBI)	1.9	0.008	
		Wheat Fodder (126-day PBI)	0.3	0.005	
		Winter Wheat Fodder (179-day PBI)	3.3	0.011	
		Wheat Grain (32-day PBI)	0.1	<0.001	
		Wheat Grain (126-day PBI)	<0.1	0.001	
		Lettuce (32-day PBI)	2.8	<0.001	
		Radish Tops (32-day PBI)	7.1	0.005	
		Radish Tops (358-day PBI)	2.0	0.002	

Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)	Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
		Radish Roots (32-day PBI)	6.9	0.006	
		Radish Roots (358-day PBI)	3.8	0.002	
		^{14}C-Phenyl label study			
		Wheat Tops, 50% mature (32-day PBI)	6.1	0.002	
		Wheat Fodder (32-day PBI)	3.0	0.003	
		Wheat Fodder (126-day PBI)	0.3	<0.001	
		Lettuce (32-day PBI)	2.6	0.002	
		Radish Tops (32-day PBI)	11.7	0.004	
		Radish Tops (126-day PBI)	3.0	<0.001	
		Radish Roots (32-day PBI)	27.2	0.004	
		Hen Metabolism			
		^{14}C-Phenyl label studies			
		Excreta	3.7	NR	
		^{14}C-Triazole label study			
		Excreta	0.78	NR	
		Goat Metabolism			
		^{14}C-Phenyl label studies			
		Faeces	24.3	NR	
		Urine	2.1	NR	
		Muscle	4.6	0.007	

Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)	Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
		Fat	15.5	0.115	
		Liver	49.4	2.62	
		Kidney	17.4	0.916	
		Milk	0.7	<0.001	
		^{14}C-Triazole label study			
		Faeces	21	1.70	
		Environmental Fate Studies[2]			
		Substrate	**%AR**	**DAT**	
		NA (100% AR by definition at study initiation)			
		Rat Metabolism			
		Substrate	**% dose**	**Dose (mg/kg)**	
		Faeces	0.8	25	

CGA177279	**Mol. Formula:**	$C_{13}H_{13}Cl_2N_3O_2$	**Dietary Metabolism Studies[1]**		
	SMILES	OC(=O)CCC(Cn1cncn1)c2ccc(Cl)cc2Cl	**Commodity**	**%TRR***	**mg/kg**
	IUPAC Name:	4-(2,4-dichlorophenyl)-5-(1,2,4-triazol-1-yl)pentanoic acid	**Hen Metabolism**		
	InChiKey	CDHPJFRPRRPCJK-UHFFFAOYSA-N	^{14}C-Phenyl label study		
			Excreta	21.6	NR
			^{14}C-Triazole label study		
			Excreta	20.6	NR
			Goat Metabolism		
			^{14}C-Phenyl label study		
			Urine	32.2	NR
			Faeces	13.5	NR
			Muscle	23.8	0.039
			Fat	24.3	0.179
			Liver	4.0	0.212
			Kidney	22.9	1.21
			Milk	7.9	0.008
			Rat Metabolism		
			Substrate	**% dose**	**Dose (mg/kg)**
			Urine	16	22.8



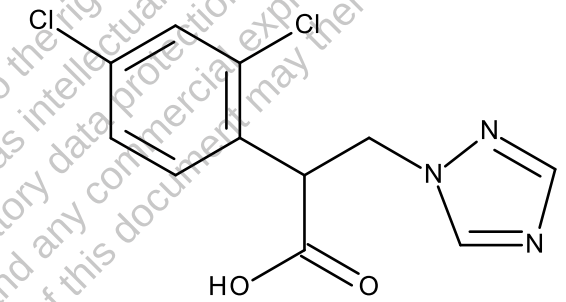
CGA190503	**Mol. Formula:**	$C_{13}H_{15}Cl_2N_3O$	**Dietary Metabolism Studies[1]**			
	SMILES	CCC(O)C(Cn1cncn1)c2ccc(Cl)cc2Cl	**Commodity**	**%TRR***	mg/kg	
	IUPAC Name:	2-(2,4-dichlorophenyl)-1-(1,2,4-triazol-1-yl)pentan-3-ol	**Primary Plant Metabolism**			
	InChiKey	ZJVGPMQNGDMHFS-UHFFFAOYSA-N	^{14}C-Triazole label studies			
			Tomato Fruit (7-day PHI)	4.3	0.003	
			Tomato Leaves (7-day PHI)	15.4	0.605	
			Tomato Fruit (40-day PHI)	3.3	0.001	
			Tomato Leaves (40-day PHI)	14.0	0.094	
			Apple Peel	<8.8	<0.032	
			Apple Pulp	1.3	0.001	
			Apple whole Fruit	0.8	0.001	
			Apple Leaves	1.9	0.073	
			^{14}C-Phenyl label study			
			Tomato Fruit (7-day PHI)	3.2	0.001	
			Tomato Leaves (7-day PHI)	16.4	0.444	
			Tomato Fruit (40-day PHI)	3.5	<0.001	
			Tomato Leaves (40-day PHI)	10.8	0.046	

CGA179944
CSAA168010
(M14360-acid)

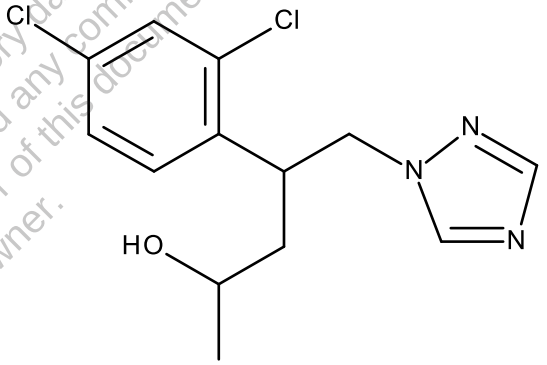
Mol. Formula:	$C_{11}H_9Cl_2N_3O_2$
SMILES	OC(=O)C(Cn1cncn1)c2ccc(Cl)cc2Cl
IUPAC Name:	2-(2,4-dichlorophenyl)-3-(1,2,4-triazol-1-yl)propanoic acid
InChiKey	MFGQUIFCNUUDBI-UHFFFAOYSA-N

Dietary Metabolism Studies[1]

Commodity	**%TRR***	mg/kg
Plant Metabolism		
^{14}C-Triazole label study		
Apple Peel	0.5	0.002
Apple Whole Fruit	0.2	<0.001
Apple Leaves	3.8	0.146
Confined Rotational Crop		
^{14}C-Phenyl label study		
Wheat Tops, 50% mature (32-day PBI)	2.8	<0.001
Wheat fodder (32-day PBI)	12.4	0.016
Wheat fodder (126-day PBI)	6.6	0.019
Winter Wheat fodder (179-day PBI)	1.4	0.001
Wheat fodder (358-day PBI)	3.7	0.002
Lettuce (32-day PBI)	1.3	<0.001
Radish tops (32-day PBI)	6.4	0.002
Radish tops (126-day PBI)	6.7	<0.001
Radish roots (32-day PBI)	12.6	0.002
Lettuce (32-day PBI)	1.3	<0.001

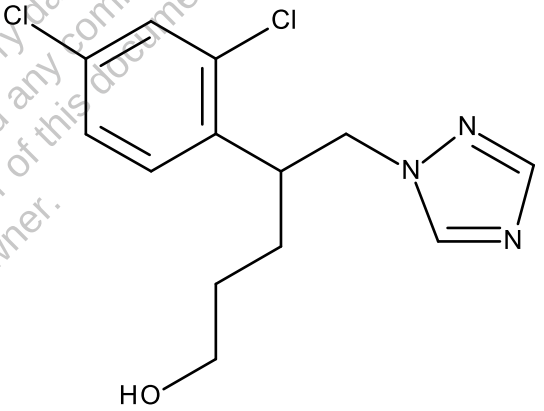


		Environmental Fate Studies[2]			
		Substrate	**%AR**	**DAT**	
		Aerobic soil	≤18.9	various	
		Anaerobic	<0.5	various	
		Water sediment	<22.1	various	
		Rat Metabolism			
		Substrate	**% dose**	**Dose (mg/kg)**	
		Urine	6.2	25	

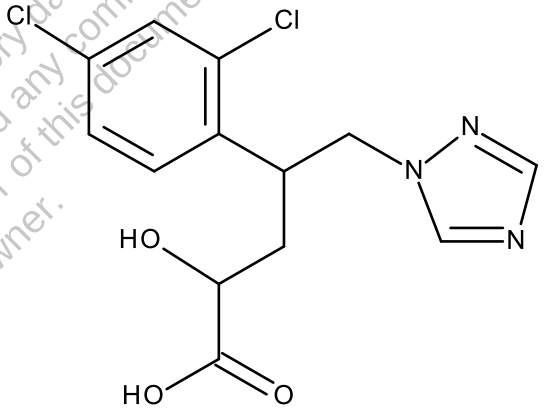
Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)		Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
CGA132465	**Mol. Formula:**	$C_{13}H_{15}Cl_2N_3O$	**Dietary Metabolism Studies[1]**			
	SMILES	CC(O)CC(Cn1cncn1)c2ccc(Cl)cc2Cl	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	4-(2,4-dichlorophenyl)-5-(1,2,4-triazol-1-yl)pentan-2-ol	**Primary Plant Metabolism**			
	InChiKey	PKABSUBVGQGJHT-UHFFFAOYSA-N	^{14}C-Triazole label studies			
			Tomato Fruit (7-day PHI)	66.9	0.047	
			Tomato Leaves (7-day PHI)	67.4	2.66	
			Tomato Fruit (40-day PHI)	55.2	0.016	
			Tomato Leaves (40-day PHI)	70.1	0.471	
			Tomato Fruit (40-day PHI, 5x rate[3])	0.8	0.003	
			Tomato Leaves (40-day PHI, 5x rate[3])	0.8	0.048	
			Apple Peel	17.6	0.064	
			Apple Pulp	12.3	0.008	
			Apple whole Fruit	14.3	0.014	
			Apple Leaves	37.9	1.46	
			^{14}C-Phenyl label study			
			Tomato Fruit (7-day PHI)	61.6	0.021	

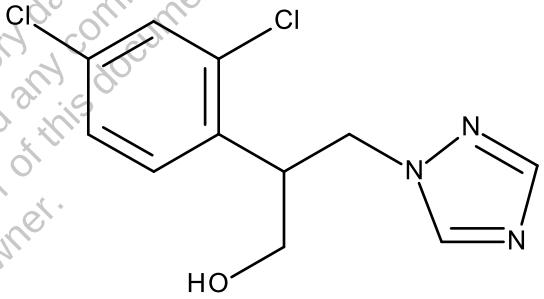
Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)	Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
		Tomato Leaves (7-day PHI)	64.0	1.73	
		Tomato Fruit (40-day PHI)	63.0	0.009	
		Tomato Leaves (40-day PHI)	59.9	0.254	
		Confined Rotational Crops			
		^{14}C-Phenyl label study			
		Wheat Tops, 50% mature (32-day PBI)	20.2	0.005	
		Wheat fodder (32-day PBI)	14.6	0.020	
		Wheat fodder (126-day PBI)	16.8	0.048	
		Winter Wheat fodder (179-day PBI)	3.2	0.003	
		Lettuce (32-day PBI)	2.1	0.002	
		Radish Tops (32-day PBI)	17.7	0.006	
		Goat Metabolism			
		^{14}C-Phenyl label study			
		Urine	62.0	NR	
		Faeces	61.4	NR	
		Muscle	63.9	0.104	
		Fat	44.5	0.328	
		Liver	34.4	1.83	
		Kidney	55.5	2.93	

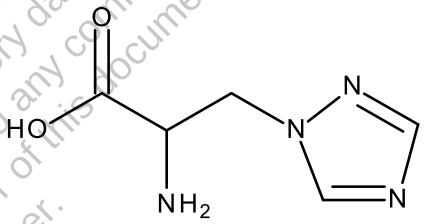
Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)	Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
		Milk	83.2	0.087	
		Rat Metabolism			
		Substrate	**% dose**	**Dose (mg/kg)**	
		urine	<2.5[4]	22.8	

Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)		Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
CGA127841	**Mol. Formula:**	$C_{13}H_{15}Cl_2N_3O$	**Dietary Metabolism Studies[1]**			
	SMILES	OCCCC(Cn1cncn1)c2ccc(Cl)cc2Cl	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	4-(2,4-dichlorophenyl)-5-(1,2,4-triazol-1-yl)pentan-1-ol	**Primary Plant Metabolism**			
	InChiKey	MJKJNWXUOARBPS-UHFFFAOYSA-N	^{14}C-Triazole label studies			
			Tomato Fruit (40-day PHI)	2.2	0.001	
			Tomato Leaves (40-day PHI)	2.4	0.012	
			Apple Peel	0.3	0.001	
			Apple Pulp	0.6	<0.001	
			Apple whole Fruit	0.5	0.001	
			Apple Leaves	2.0	0.077	
			^{14}C-Phenyl label study			
			Tomato Fruit (7-day PHI)	1.7	0.001	
			Tomato Leaves (7-day PHI)	1.9	0.052	
			Tomato Fruit (40-day PHI)	2.3	<0.001	
			Tomato Leaves (40-day PHI)	1.6	0.007	
			Hen Metabolism			
			^{14}C-Triazole label study			
			Excreta	0.93	NR	
			^{14}C-Phenyl label study			

Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)	Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
		Excreta	1.9	NR	
		Rat Metabolism			
		Substrate	**% dose**	**Dose (mg/kg)**	
		urine	26.7	0.47	
		faeces	7.4	50.7	

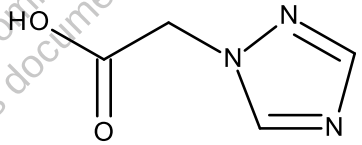
Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)		Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
CGA177281	**Mol. Formula:**	$C_{13}H_{13}Cl_2N_3O_3$	**Dietary Metabolism Studies[1]**			
	SMILES	OC(CC(Cn1cncn1)c2ccc(Cl)cc2Cl)C(=O)O	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	4-(2,4-dichlorophenyl)-2-hydroxy-5-(1,2,4-triazol-1-yl)pentanoic acid	**Goat Metabolism**			
	InChiKey	RWKKUBFWJSWIKO-UHFFFAOYSA-N	^{14}C-Phenyl label study			
			Urine	0.9	NR	
			Fat	4.0	0.030	
			Liver	1.5	0.082	
			Rat Metabolism			
			Substrate	**% dose**	**Dose (mg/kg)**	
			urine	4.4	22.8	

Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)		Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
CGA189659	**Mol. Formula:**	$C_{11}H_{11}Cl_2N_3O$	**Dietary Metabolism Studies[1]**			
	SMILES	OCC(Cn1cncn1)c2ccc(Cl)cc2Cl	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	2-(2,4-dichlorophenyl)-3-(1,2,4-triazol-1-yl)propan-1-ol	**Primary Plant Metabolism**			
	InChiKey	QMUIPLNEIWEBJS-UHFFFAOYSA-N	^{14}C-Triazole label study			
			Apple Peel	6.1	0.022	
			Apple Pulp	1.2	0.001	
			Apple Whole Fruit	3.0	0.003	
			Apple Leaves	13.8	0.530	
			Rat Metabolism			
			Substrate	**% dose**	**Dose (mg/kg)**	
			Faeces	4.8	51.6	

Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)		Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
CGA131013 (triazole alanine, TA)	**Mol. Formula:**	$C_5H_8N_4O_2$	**Dietary Metabolism Studies[1]**			
	SMILES	NC(Cn1cncn1)C(=O)O	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	2-amino-3-(1,2,4-triazol-1-yl)propanoic acid	**Primary Plant Metabolism**			
	InChiKey	XVWFTOJHOHJIMQ-UHFFFAOYSA-N	^{14}C-Triazole label studies			
			Tomato Fruit (40-day PHI)	15.4	0.004	
			Tomato Leaves (40-day PHI)	0.1	0.001	
			Apple Peel	2.5	0.009	
			Apple Pulp	36.6	0.024	
			Apple Whole Fruit	23.0	0.023	
			Confined Rotational Crops			
			^{14}C-Triazole label study			
			Wheat Grain (32-day PBI)	34.5	0.337	
			Wheat Grain (126-day PBI)	57.4	1.888	
			Wheat Grain (358-day PBI)	59.1	0.636	
			Winter Wheat Grain (179-day PBI)	61.3	0.256	
			Wheat Tops, 50% mature (32-day PBI)	38.9	0.052	

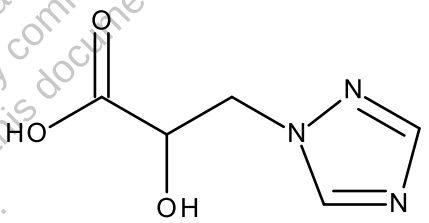
Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)	Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
		Wheat Tops, 50% mature (126-day PBI)	58.1	0.120	
		Wheat Tops, 50% mature (358-day PBI)	37.0	0.070	
		Winter Wheat Tops, 50% mature (179-day PBI)	42.0	0.035	
		Wheat Fodder (32-day PBI)	3.5	0.015	
		Wheat Fodder (126-day PBI)	8.3	0.116	
		Wheat Fodder (358-day PBI)	8.8	0.037	
		Winter Wheat Fodder (179-day PBI)	4.1	0.014	
		Lettuce (32-day PBI)	22.7	0.004	
		Lettuce (126-day PBI)	9.1	0.007	
		Lettuce (358-day PBI)	20.1	0.013	
		Radish Tops (32-day PBI)	45.0	0.034	
		Radish Tops (126-day PBI)	43.8	0.015	
		Radish Tops (358-day PBI)	68.3	0.057	

Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)	Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
		Radish Roots (32-day PBI)	66.7	0.056	
		Radish Roots (126-day PBI)	86.7	0.027	
		Radish Roots (358-day PBI)	76.0	0.036	
		Environmental Fate Studies[2]			
		Substrate	**%AR**	**DAT**	
		Aerobic soil	0.2	60	

Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)		Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
CGA142856 (triazole acetic acid, triazolyl acetic acid, TAA)	**Mol. Formula:**	$C_4H_5N_3O_2$	**Dietary Metabolism Studies[1]**			
	SMILES	OC(=O)Cn1cncn1	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	2-(1,2,4-triazol-1-yl)acetic acid	**Primary Plant Metabolism**			
	InChiKey	RXDBSQXFIWBJSR-UHFFFAOYSA-N	^{14}C-Triazole label studies			
			Tomato Fruit (40-day PHI)	1.0	<0.001	
			Tomato Leaves (40-day PHI)	<0.1	<0.001	
			Apple Peel	0,1	<0.001	
			Apple Pulp	1.4	0.001	
			Apple Fruit	0.8	0.008	
			Apple Leaves	3.2	0.123	
			Confined Rotational Crops			
			^{14}C-Triazole label study			
			Wheat Grain (32-day PBI)	22.7	0.222	
			Wheat Grain (126-day PBI)	26.4	0.868	
			Wheat Grain (358-day PBI)	33.1	0.357	
			Winter Wheat Grain (179-day PBI)	33.2	0.139	
			Wheat Tops, 50% mature (32-day PBI)	15.6	0.021	

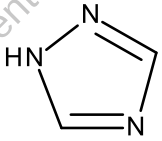
Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)	Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
		Wheat Tops, 50% mature (126-day PBI)	6.6	0.015	
		Wheat Tops, 50% mature (358-day PBI)	30.0	0.057	
		Winter Wheat Tops, 25% mature (358-day PBI)	2.2	0.004	
		Winter Wheat Tops, 50% mature (179-day PBI)	8.7	0.007	
		Wheat Fodder (32-day PBI)	19.7	0.084	
		Wheat Fodder (126-day PBI)	20.8	0.290	
		Wheat Fodder (358-day PBI)	21.3	0.091	
		Winter Wheat Fodder (179-day PBI)	9.1	0.030	
		Radish Tops (32-day PBI)	0.5	<0.001	
		Radish Tops (358-day PBI)	0.8	<0.001	
		Radish Roots (32-day PBI)	1.7	0.001	
		Environmental Fate Studies[2]			
		Substrate	**%AR**	**DAT**	
		Aerobic soil	≤12.5	various	

Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)	Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
		Anaerobic soil	≤5.5	various	

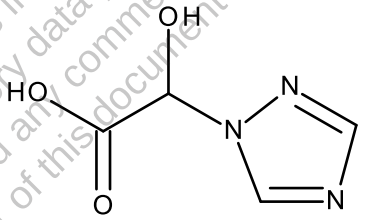
Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)		Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
CGA205369 (triazole lactic acid, TLA)	**Mol. Formula:**	$C_5H_7N_3O_3$	**Dietary Metabolism Studies[1]**			
	SMILES	OC(Cn1cncn1)C(=O)O	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	2-hydroxy-3-(1,2,4-triazol-1-yl)propanoic acid	**Primary Plant Metabolism**			
	InChiKey	KJRGHGWETVMENC-UHFFFAOYSA-N	^{14}C-Triazole label studies			
			Tomato Fruit (40-day PHI)	2.3	0.001	
			Tomato Leaves (40-day PHI)	0.2	0.001	
			Apple Peel	5.0	0.018	
			Apple Pulp	7.7	0.005	
			Apple Fruit	6.7	0.007	
			Apple Leaves	2.4	0.092	
			Confined Rotational Crops			
			^{14}C-Triazole label study			
			Wheat Grain (32-day PBI)	0.6	0.006	
			Wheat Grain (126-day PBI)	<0.1	<0.001	
			Wheat Tops, 50% mature (32-day PBI)	21.8	0.029	
			Wheat Tops, 50% mature (126-day PBI)	25.6	0.059	
			Wheat Tops, 50% mature (358-day PBI)	21.9	0.042	

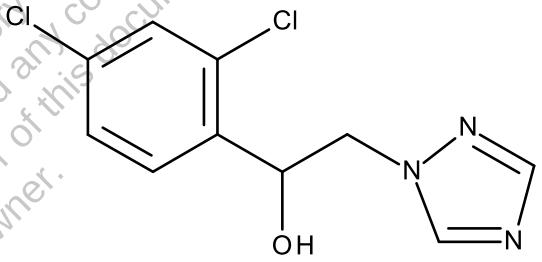
Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)	Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
		Winter Wheat Tops, 25% mature (179-day PBI)	33.7	0.058	
		Winter Wheat Tops, 50% mature (179-day PBI)	33.0	0.028	
		Wheat Fodder (32-day PBI)	34.4	0.146	
		Wheat Fodder (126-day PBI)	38.3	0.532	
		Wheat Fodder (358-day PBI)	51.9	0.222	
		Winter Wheat Fodder (179-day PBI)	62.5	0.210	
		Lettuce (32-day PBI)	37.3	0.006	
		Lettuce (126-day PBI)	76.1	0.055	
		Lettuce (358-day PBI)	67.7	0.042	
		Radish Tops (32-day PBI)	7.0	0.005	
		Radish Tops (126-day PBI)	16.9	0.006	
		Radish Tops (358-day PBI)	6.4	0.005	
		Radish Roots (32-day PBI)	7.9	0.007	

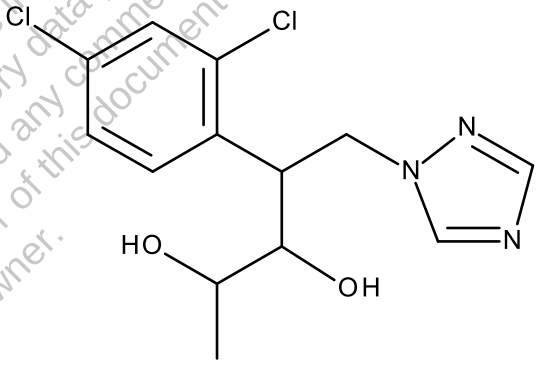
Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)	Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
		Radish Roots (358-day PBI)	5.7	0.003	

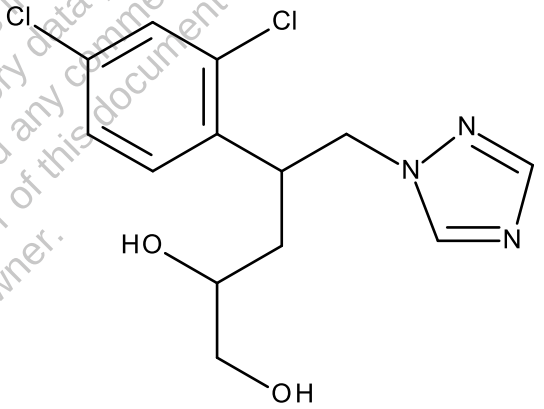
Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)		Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
CGA071019 CGA71019 (1,2,4-triazole, 124-T, 1,2,4-T)	**Mol. Formula:**	$C_2H_3N_3$	**Dietary Metabolism Studies[1]**			
	SMILES	c1nc[nH]n1	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	1H-1,2,4-triazole	**Confined Rotational Crops**			
	InChiKey	NSPMIYGKQJPBQR-UHFFFAOYSA-N	^{14}C-Triazole label study			
			Wheat Grain (32-day PBI)	2.7	0.026	
			Wheat Grain (126-day PBI)	0.9	0.029	
			Wheat Grain (358-day PBI)	1.2	0.013	
			Winter Wheat Grain (179-day PBI)	1.7	0.007	
			Wheat Tops, 50% mature (32-day PBI)	4.4	0.006	
			Wheat Tops, 50% mature (126-day PBI)	1.7	0.004	
			Winter Wheat Tops, 25% mature (179-day PBI)	2.9	0.005	
			Wheat Fodder (32-day PBI)	6.1	0.026	
			Wheat Fodder (126-day PBI)	4.1	0.057	
			Wheat Fodder (358-day PBI)	1.9	0.008	

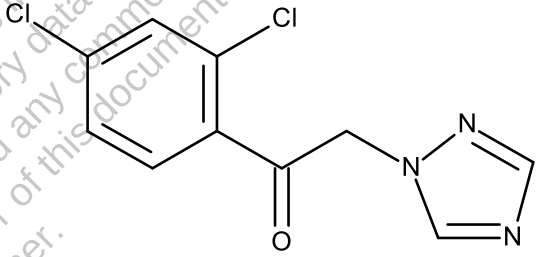
Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)	Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
		Winter Wheat Fodder (179-day PBI)	2.7	0.009	
		Radish Tops (358-day PBI)	2.0	0.002	
		Radish Roots (32-day PBI)	1.3	0.001	
		Environmental Fate Studies[2]			
		Substrate	**%AR**	**DAT**	
		Aerobic soil	≤38.6	various	
		Anaerobic soil	≤27.2	various	
		Rat Metabolism			
		Substrate	**% dose**	**Dose (mg/kg)**	
		Faeces	1	22.8	
		urine	14.7	25	

Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)		Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
CGA205373 Triazolyl glycolic acid	**Mol. Formula:**	$C_4H_5N_3O_3$	**Dietary Metabolism Studies[1]**			
	SMILES	OC(C(=O)O)n1cncn1	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	2-hydroxy-2-(1,2,4-triazol-1-yl)acetic acid	**Primary Plant Metabolism**			
	InChiKey	AHMGWEOLNJUSQD-UHFFFAOYSA-N	^{14}C-Triazole label study			
			Apple Peel	0.7	0.003	
			Apple Fruit	0.3	<0.001	
			Apple Leaves	0.3	0.012	

Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)		Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
CGA091305 CGA91305	**Mol. Formula:**	$C_{10}H_9Cl_2N_3O$	**Primary Plant Metabolism[1]**			
	SMILES	OC(Cn1cncn1)c2ccc(Cl)cc2Cl	^{14}C-Triazole label study			
	IUPAC Name:	1-(2,4-dichlorophenyl)-2-(1,2,4-triazol-1-yl)ethanol	Apple Leaves	0.04	0.002	
	InChiKey	XCWJBJOPHSVLGU-UHFFFAOYSA-N	**Environmental Fate Studies[2]**			
			Substrate	**%AR**	**DAT**	
			Aerobic soil	7.5	120	

Code Number (Synonyms)	**(IUPAC name /SMILES notation /InChiKey)**		**Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)**			**Structural formula**
α, β-dihydroxy CGA071818 α, β-dihydroxy CGA71818	**Mol. Formula:**	$C_{13}H_{15}Cl_2N_3O_2$	**Primary Plant Metabolism[1]**			
	SMILES	CC(O)C(O)C(Cn1cncn1)c2ccc(Cl)cc2Cl	^{14}C-Triazole label study			
	IUPAC Name:	4-(2,4-dichlorophenyl)-5-(1,2,4-triazol-1-yl)pentane-2,3-diol	Apple Peel	NQ	NQ	
	InChiKey	NGQJXEKOEFWFHG-UHFFFAOYSA-N	Apple Pulp	0.9	0.001	
			Apple Whole Fruit	0.5	0.001	
			Apples Leaves	3.3	0.127	

Code Number (Synonyms)	**(IUPAC name /SMILES notation /InChiKey)**		**Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)**			**Structural formula**
β,γ -dihydroxy CGA071818 β,γ -dihydroxy CGA71818	**Mol. Formula:**	$C_{13}H_{15}Cl_2N_3O_2$	**Primary Plant Metabolism[1]**			
	SMILES	OCC(O)CC(Cn1cncn1)c2ccc(Cl)cc2Cl	^{14}C-Triazole label study			
	IUPAC Name:	4-(2,4-dichlorophenyl)-5-(1,2,4-triazol-1-yl)pentane-1,2-diol	Apple Peel	NQ	NQ	
	InChiKey	HEFAECYMSJUPOE-UHFFFAOYSA-N	Apple Pulp	NQ	NQ	
			Apple Whole Fruit	NQ	NQ	
			Apples Leaves	0.4	0.015	

Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)		Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets)			Structural formula
CGA091304 CGA91304	**Mol. Formula:**	$C_{10}H_7Cl_2N_3O$	**Primary Plant Metabolism[1]**			
	SMILES	Clc1ccc(C(=O)Cn2cncn2)c(Cl)c1	^{14}C-Triazole label study			
	IUPAC Name:	1-(2,4-dichlorophenyl)-2-(1,2,4-triazol-1-yl)ethanone	Apple Leaves	0.03	0.001	
	InChiKey	XOHMICFWUQPTNP-UHFFFAOYSA-N				

* no need to include all metabolites found in rat in case not found in the other matrices.
** levels should be expressed as % of applied radioactivity (AR) or total radioactive residue (TRR) for environmental compartments and plant/animal residues, respectively
NQ - detected but not quantified
NR – not reported
NA - not applicable
PHI - post harvest interval (days after last application)
PBI - plant back interval (days after bare ground application)

1. **Highest residue reported for the cited residue in the specified commodity. Sum of conjugated and unconjugated residues.**
2. **Highest level in %AR observed for the identified degradate from all studies.**
3. **5x crop samples were not subjected to hydrolysis. As such the presented values only represent the unconjugated metabolites.**
4. **Measured as an unresolved mixture of CGA132465, SYN502203, SYN502204 and SYN502205 glucuronides (2.5% in total for all four glucuronides).**

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