European Commission

Draft Renewal Assessment Report prepared according to the Commission Regulation (EU) N° 1107/2009

TRITICONAZOLE

Volume 1

Rapporteur Member State: Austria
Co-Rapporteur Member State: United Kingdom

Version History

When	What
2003/ September	Initial DAR
2018/July	Draft Renewal Assessment Report (DRAR)

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Level 1

TRITICONAZOLE

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

Triticonazole was originally included in Annex I of the EU Council Directive 91/414/EEC with Commission Directive 2006/39/EC (entry into force on 12 April 2006). The active substance was subsequently approved under Regulation (EC) 1107/2009 via Implementing Regulation (EU) 540/2011. In accordance with Commission Regulation (EU) 844/2012 of 18 September 2012, BASF submitted a dossier to support the renewal of the approval of Triticonazole. Austria acting as the Rapporteur Member State (RMS) evaluated all aspects of the renewal dossiers via a Draft Renewal Assessment Report (DRAR). The DRAR was the subject of a peer review by the Co-RMS United Kingdom.

This DRAR provides a discussion of relevant new studies and information submitted and evaluated since the first approval of Triticonazole in 2006. Regarding studies submitted for the original approval mostly re-wording was conducted and additional information was included in DRAR where considered necessary for better overview. Finally, the validity of studies in view of updated OECD guidelines was proven.

No proposal for MRL setting is included in the DRAR.

The RMS also paid special attention to new criteria for classification and labelling according to Regulation (EC) 1272/2008. The outcome of the Meeting of the Commission Working Group on the Classification and Labelling of Dangerous Substances Pesticides, ECB Ispra, 22 August 2007 (ECBI/90/06 Rev. 8), that no classification and labelling for triticonazole is necessary for human health, could be partially supported. During the renewal of triticonazole RMS concluded that STOT RE 2 should additionally be considered for triticonazole.

Regarding ecotoxicity, new proposal for classification and labelling has been established (H400 and H410 instead of current H411), based on the new data included in the supplementary dossier for the renewal and on changes in the classification criteria according to CLP.

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

According to an agreement reached by the respective designated authorities, the RMS Austria conducted the full evaluation and prepared the DRAR. The Co-RMS United Kingdom reviewed the DRAR for commenting. After further evaluation taking into account the received comments from United Kingdom and the notifiers the first official version of the DRAR was submitted to the Commission and EFSA at the beginning of July 2018.

1.1.3. EU Regulatory history for use in Plant Protection Products

Triticonazole was one of the substances covered by the Commission Regulation (EEC) No 451/2000 from 28 February 2000 laying down the detailed rules for the implementation of the second stage of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC.

In accordance with the provisions of Article 5 of Regulation (EEC) No 451/2000, the Commission designated Austria as rapporteur Member State to carry out the assessment of Triticonazole on the basis of the dossiers submitted by the notifier.

Aventis Crop Science (and by 2003 BASF since the notification and the property rights of the European dossier on triticonazole have been transferred to BASF) submitted by the deadline a dossier to the rapporteur Member

State which did not contain substantial data gaps, taking into account the supported uses. Therefore BASF was considered to be the main data submitter.

In accordance with the provisions of Article 8(1) of Regulation (EC) No 451/2000, Austria submitted on 29 September 2003 to the EFSA the report of their examination, hereafter referred to as the draft assessment report, including, as required, a recommendation concerning the possible inclusion of triticonazole in Annex I to the Directive. Moreover, in accordance with the provisions of Article 8(2) of Regulation (EC) 451/2000, the Commission and the Member States received also the summary dossier on triticonazole from BASF, on 24 November 2003.

In accordance with the provisions of Article 8 of Regulation (EC) No 451/2000, the EFSA organised the consultation on the draft assessment report by all the Member States as well as by BASF being the main data submitters, on 4 December 2003 by making it available.

The EFSA organised an intensive consultation of technical experts from a certain number of Member States, to review the draft assessment report and the comments received thereon (peer review).

In accordance with the provisions of Article 8 (7) of Regulation 451/2000 the EFSA sent to the Commission its conclusion on the risk assessment [Conclusions regarding the peer review of the pesticide risk assessment of the active substance triticonazole (finalised: 22 June 2005)5]. This conclusion refers to background document A (draft assessment report) and background document B (EFSA peer review report).

In accordance with the provisions of Article 8 (7) of Regulation (EC) No 451/2000, the Commission referred on 23 September 2005 a draft review report to the Standing Committee on the Food Chain and Animal Health, for final examination. The draft review report was finalised in the meeting of the Standing Committee on 18 November 2005.

The overall conclusions of the evaluation of triticonazole, as finalised by the Standing Committee on Plant Health on 27 January 2006, were provided in the Review Report (Triticonazole, SANCO/10442/2005-final).

On 12 March 2010 the Standing Committee on the Food Chain and Animal Health has taken note of the revision of the review report after the assessment of the above confirmatory data. This assessment has been carried out in line with the Guidance document on the procedures for submission and assessment of confirmatory data following inclusion of an active substance in Annex I of Council Directive 91/414/EEC6. The Committee agrees that, on the basis of the current outcome, the risk for the exposed species is acceptable. No further review by EFSA has been considered necessary.

In agreement with Article 3 of Regulation (EC) No 844/2012 BASF (BASf Agro B.V. Arnhem (NL), Wädenswil Branch, Im Tiergarten 7, 8055 Zürich, Switzerland) submitted application for renewal to Austria as RMS and UK as Co-RMS by the deadline of 31 January 2014. The application was considered complete.

BASF submitted the supplementary dossier by the deadline for submission (28 October 2015). As required by Article 8 of Regulation (EC) No 844/2012 RMS checked the supplementary dossier for its completeness. It was concluded that the supplementary dossiers completely fulfil the requirements set out in Article 7 of the Regulation (EC) No 844/2012. .

From the first approval of Triticonazole (2006) EFSA conclusion exists: EFSA Scientific Report (2005) 33, 1-69, Conclusion on the peer review of triticonazole

Reasoned opinion on the review of the existing maximum residue levels (MRLs) for triticonazole according to Article 12 of Regulation (EC) No 396/2005 from 2009 is available (EFSA Scientific Report (2009) 277, 2-23).

1.1.4. Evaluations carried out under other regulatory contexts

Triticonazole is used only as fungicide and not regulated by other EU legislations ((e.g. biocides, flavourings, food additives, cosmetics).

No evaluation of the US EPA can be found under

https://archive.epa.gov/pesticides/reregistration/web/html/status_page_t.html

No evaluation of the PMRA was found.

Triticonazole has not been considered by the JMPR.

No FAO specification exists for Triticonazole.

Triticonazole is currently included in Annex VI of Regulation (EC) No 1272/2008 with Index No 613-282-00-0 (CAS No: 131983-72-7, new CAS No: 138182-18-0) and new EC Number 603-543-7, as Aquatic Chronic 2, H411.

1.2. APPLICANT INFORMATION

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

BASF Agro B.V. Arnhem (NL) Freienbach Branch
Huobstrasse 3
CH-8808 Pfäffikon SZ
Switzerland

Contact person: [redacted]
Telephone n°: [redacted]
Telefax n°: [redacted]
Email : [redacted]

Alternativ:
Contact person: [redacted]
Telephone n°: [redacted]
Telefax n°: [redacted]
Email : [redacted]

1.2.2. Producer or producers of the active substance

Manufacturer of triticonazole (legal entity):

BASF Agro B.V., Arnhem (NL) - Zuerich (Wädenswil) Branch
Im Tiergarten 7
8055 Zuerich
Switzerland

Contact person: [redacted]
Telephone n°: [redacted]
Telefax n°: [redacted]
Email : [redacted]

Alternativ:
Contact person: [redacted]
Telephone n°: [redacted]
Telefax n°: [redacted]
Email : [redacted]

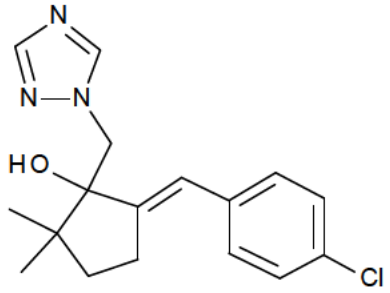
Location of the manufacturing site of triticonazole:

Confidential information - data provided in Volume 4.

1.2.3. Information relating to the collective provision of dossiers

There is only one notifier for the renewal of Triticonazole:

1.3. IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1. Common name proposed or ISO-accepted and synonyms	Triticonazole (ISO)
1.3.2. Chemical name (IUPAC and CA nomenclature)	
IUPAC	(*RS*)-(*E*)-5-(4-chlorobenzylidene)-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol
CA	(5*E*)-5-[(4-chlorophenyl)methylene]-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol
1.3.3. Manufacturer's development code number	BAS 595 F, Reg. No. 4378513 former Reg. No. RPA400727
1.3.4. CAS, EEC and CIPAC numbers	
CAS	131983-72-7 138182-18-0
EEC	603-543-7
CIPAC	652
1.3.5. Molecular and structural formula, molecular mass	
Molecular formula	$C_{17}H_{20}ClN_3O$
Structural formula	
Molecular mass	317.82 u
1.3.6. Method of manufacture (synthesis pathway) of the active substance	Confidential information - data provided separately in Volume 4
1.3.7. Specification of purity of the active substance in g/kg	Minimum purity (TC): 950 g/kg Minimum purity (TK): 890 g/kg (Commercial plant)
1.3.8. Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1. Additives	Confidential information - data provided separately in Volume 4
1.3.8.2. Significant impurities	Confidential information - data provided separately in Volume 4
1.3.8.3. Relevant impurities	Methanol ≤ 3 g/kg
1.3.9. Analytical profile of batches	Confidential information - data provided in Volume 4

1.4. INFORMATION ON THE PLANT PROTECTION PRODUCT

<table>
<tr><td>1.4.1. Applicant</td><td>BASF Agro B.V., Arnhem (NL) - Zuerich (Wädenswil) Branch
Im Tiergarten 7
8055 Zuerich
Switzerland</td></tr>
<tr><td>1.4.2. Manufacturer of the plant protection product</td><td>BASF Agro B.V., Arnhem (NL) - Zuerich (Wädenswil) Branch
Im Tiergarten 7
8055 Zuerich
Switzerland</td></tr>
<tr><td>1.4.3. Trade name or proposed trade name and producer's development code number of the plant protection product</td><td>Trade names: Premis, Premis 25 FS
Code number: BAS 595 01 F
(former code EXP 80472 B</td></tr>
<tr><td colspan="2">1.4.4. Detailed quantitative and qualitative information on the composition of the plant protection product</td></tr>
<tr><td>1.4.4.1. Composition of the plant protection product</td><td>25 g/L Triticonazole
Co-formulants: CONFIDENTIAL information - data provided in Volume 4.</td></tr>
<tr><td>1.4.4.2. Information on the active substances</td><td>
<table>
<tr><th>Type</th><th>Name/Code Number</th></tr>
<tr><td>ISO common name</td><td>Triticonazole</td></tr>
<tr><td>CAS No</td><td>131983-72-7
138182-18-0</td></tr>
<tr><td>EC No</td><td>603-543-7</td></tr>
<tr><td>CIPAC No</td><td>652</td></tr>
<tr><td>Salt, ester anion or cation present</td><td>None</td></tr>
</table>
</td></tr>
<tr><td>1.4.4.3. Information on safeners, synergists and co-formulants</td><td>CONFIDENTIAL information - data provided in Volume 4.</td></tr>
<tr><td>1.4.5. Type and code of the plant protection product</td><td>Flowable concentrate for seed treatment [Code: FS]</td></tr>
<tr><td>1.4.6. Function</td><td>Fungicide</td></tr>
<tr><td>1.4.7. Field of use envisaged</td><td>Seed treatment</td></tr>
<tr><td>1.4.8. Effects on harmful organisms</td><td>Contact and systemic fungicide for seed treatment; target fungal pathogens are killed or suppressed. It shows an apoplastic (upwards) distribution inside the plant after penetration.</td></tr>
</table>

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	F G I (b)	Pests or group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					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)	Water l/ha min max	g a.i./ha min max (*) (g/ha)		
winter wheat TRZAW spring wheat TRZAS winter barley HORVX spring barley HORVS rye SECCW triticale TTLWI oats AVESA	BE, BG, CZ, EE, ES, FR, HU, IE, IT, LT, LV, PL, RO, UK	BAS 595 01 F	F	*Fusarium* spp (FUSASP), *Tilletia caries/Tilletia tritici* (TILLCA), *Ustilago nuda tritici* (USTINT), *Ustilago nuda* (USTINH), *Ustilago hordei* (USTIHO), *Ustilago avenae* (USTIAV), *Urocystis occulta* (UROCOC)	FS	25 g/L	Seed treatment (slurry), seed treatment machinery	BBCH 00/ Spring and autumn	a) 1 b) 1	N/A	N/A	Used undiluted or diluted with water at a max ratio of 1:5 (prod : water)	a) 12.5 g/ha (based on 5 g ai/100 kg seed, 250 kg seed/ha) b) 12.5 g/ha (based on 5 g ai/100 kg seed, 250 kg seed/ha)	N/A	Maximum seedling rate is 250 kg/ha

* For uses where the column „Remarks“ in marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s).

(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)

(c) *e.g.* biting and suckling 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

(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. 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

Please refer to section 1.5.1

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

No other uses applied for to support the setting of MRLs beyond the representative uses.

1.5.4. Overview on authorisations in EU Member States

The currently authorized uses of the triticonazole formulations are provided in the following:

BAS 591 01 F (Kinto, Kinto Duo, etc.):

- Triticonazole (20 g/L) + Prochloraz copper chloride complex (60 g/L), FS

BAS 595 01 F (Premis, etc.):

- Triticonazole (25 g/L), FS

BAS 595 02 F (Alios, Diadem, etc.):

- Triticonazole (300 g/L), FS

BAS 604 00 F (Rubin TT):

- Triticonazole (25 g/L) + Prochloraz copper chloride complex (42 g/L) + Pyrimethanil (42 g/L), FS

BAS 604 01 F (Rubin TT):

- Triticonazole (25 g/L) + Prochloraz copper chloride complex (42 g/L) + Pyrimethanil (42 g/L), FS

Level 2

TRITICONAZOLE

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

2.1. IDENTITY

All points of the date requirements regarding Section 1 have been addressed and the information supplied is acceptable. The technical specification for inclusion in Annex I (DAR 2003) based on a pilot plant. Equivalence of commercial production was assessed in Volume 4. There was no change in the minimum purity TC 950 g/kg. and TK 890 g/kg. In addition to previous specification a relevant impurity was identified in the TK–Methanol max. content 3 g/kg.

2.2. PHYSICAL AND CHEMICAL PROPERTIES

2.2.1. Summary of physical and chemical properties of the active substance

Triticonazole is a white powder with a melting point of 137 to 141°C. It has a very low vapour pressure and is very slightly volatile. It has low solubility in water (8-9 mg/L) but is soluble in organic solvents. It does not dissociate in water and has a partition coefficient (log Pow) of 3.3, indicating a potential for bioaccumulation. Triticonazole does not possess explosive or oxidising properties and is neither flammable nor auto-flammable, indicating that it does not present problems during transport or storage. There are no implications for classification.

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

BAS 595 01 F is a flowable / suspension concentrate for seed treatment (FS) formulation containing 25 g/L triticonazole as active substance. It is a bright orange/red opaque liquid, with a density of 1.07 g/mL and a pH of 7.5. The product is not highly flammable, has an auto ignition temperature of 440°C and does not possess oxidising or explosive properties. BAS 595 01 F has good suspensibility and pourability characteristics, and does not produce excessive amounts of foam. The product has been demonstrated to be stable in studies at 54°C for 2 weeks, 0°C for 7 days and room temperature for 2 years, with no significant loss of active substance content. The packaging of the product remained free from any corrosion or degradation for the duration of the stability studies and the shelf life of the product is 24 months. A new accelerated storage study (54°C for 2 weeks) and a new low temperature study (7 days at 0°C) have been provided to support changes in the in-use concentrations. It was not deemed necessary to repeat the 2-year study, as there have been no changes to the product and the accelerated study adequately demonstrates that the in-use concentration changes do not affect the technical properties of the product. The technical properties of BAS 595 01 F indicate that no particular problems are expected when it is used as recommended and there are no implications for classification.

2.2.3. Data on application and efficacy

Triticonazole is active as a contact and systemic fungicide and belongs to the chemical group of triazoles. Triticonazole is applied as a seed treatment. Applications is done prior to planting of the seeds (pre-sowing). The application rate of Triticonazole is 12.5 g a.i./ha (based on 5 g ai/100 kg seed, max. 250 kg cereal seed/ha).

The representative formulation is a FS-formulation “Premis” (BAS 595 01 F) containing 25 g Triticonazole/L. The intended maximum application rate is 0.5 L product/ha, based on 2 L/t seed and 250 kg seed/ha.

Triticonazol is used to control a range of seed and soil borne diseases such as *Tilletia* spp, *Ustilago* spp, *Fusarium* spp in cereals. Seed treatments are applied preventatively, and as such control disease at an early stage, by disinfecting infected seeds or protecting the germinating seed from pathogen attack from the soil. Seed treatment is the only effective method of controlling most seed and soil borne pathogens. Only one application per crop/season is relevant for seed treatment.

Method of application:

The product is applied to seed by specialist seed treatment application equipment which varies from Member State to Member State in scale and manufacturer. Most seed treatment products applied to cereals in the European Union are either on-farm or in usually larger-scale industrial plants or stations.

The product is applied to the seed usually in an enclosed space by means of equipment which ensures (after calibration) product is applied at the correct dose and evenly over the entire sample of seed. Application efficiency can usually be verified visually because of the use of a colorant in the formulation. Product does not need to be diluted, although water can be co-applied with the product without the need for pre-mixing. If dilution is required then up to 10 litres of water/t of treated seed are recommended (e.g. in Spain). In certain countries, dilution is not required and product is applied to the seed directly in its formulated concentration.

2.2.4. Summary of effectiveness

Premis 25 FS (BAS 595 01 F) is used at rates of 5 g a.i./ha to control seed and soil borne diseases such as *Fusarium* sp., *Tilletia caries* and *Ustilago*. The tables below are a brief summary of results against three key diseases. Celest (Fludioxinil), which is widely authorized as cereal seed treatment in the EU, was used as reference product.

Premis 25 FS delivers nearly complete control of TILLCA and USTINH, and a mean of approx. 80% efficacy on *Fusarium* spp, which is similar to Celest.

Table 2.2.4.a: Efficacy of Premis 25 FS againts *Tilletia caries* (TILLCA) on winter wheat (n = 13). Data from 2017.

Trial	EPPO Zone	Crop	Variety	Disease	Untreated % infection	Premis25, 5g %efficacy	Celest, 5g %efficacy
DEV-S-2017-DE-C02-A-06.0-DE-D11-C02	Central Maritime	TRZAW	JB ASANO	TILLCA	6.2	100.0	100.0
DEV-S-2017-DE-C14-A-05.0-DE-D04-S14	Central Maritime	TRZAW	JB ASANO 97%KF	TILLCA	45.0	100.0	100.0
DEV-S-2017-EX-C02-V-04.0-DE-VTF-518	Central Maritime	TRZAW	JB ASANO	TILLCA	9.8	100.0	99.6
DEV-S-2017-EX-C14-V-04.0-DE-VTF-516	Central Maritime	TRZAW	PATRAS	TILLCA	16.7	100.0	100.0
DEV-S-2017-EX-C14-V-04.0-DE-VTF-517	Central Maritime	TRZAW	PATRAS	TILLCA	17.7	100.0	100.0
DEV-S-2017-FR-C02-A-01.0-FR-FR4-417	South Maritime	TRZAW	JB ASANO	TILLCA	6.1	100.0	100.0
DEV-S-2017-FR-C02-A-01.0-FR-FRE-E08	South Maritime	TRZAW	PATRAS	TILLCA	29.2	100.0	100.0
DEV-S-2017-FR-C14-A-02.0-FR-FR7-701	South Maritime	TRZAW	PATRAS	TILLCA	41.3	100.0	100.0
DEV-S-2017-HU-C14-A-05.0-HU-HU0-AG1	Central South east	TRZAW	PATRAS	TILLCA	51.4	100.0	100.0
DEV-S-2017-HU-C14-A-05.0-HU-HU0-AG2	Central South east	TRZAW	PATRAS	TILLCA	45.0	100.0	100.0
DEV-S-2017-PL-C02-A-06.0-PL-PLC-025	Central North east	TRZAW	PATRAS	TILLCA	25.0	100.0	100.0
DEV-S-2017-PL-C14-A-05.0-PL-PLC-024	Central North east	TRZAW	JB ASANO	TILLCA	32.1	100.0	100.0
DEV-S-2017-PL-C14-A-05.0-PL-PLF-002	Central North east	TRZAW	JB ASANO	TILLCA	46.2	100.0	100.0
			Range	TILLCA	6,1 - 91,5	100 - 100	99,6 - 100
			Mean	TILLCA	**28.6**	**100.0**	**100.0**

Table 2.2.4.b: Efficacy of Premis 25 FS againts *Ustilago nuda* (USTINH) on winter and spring barley (n = 9). Data from 2013-2017.

Trial	EPPO Zone	Crop	Variety	Disease	Untreated % infection	Premis25, 5g %efficacy	Celest, 5g %efficacy
DEV-S-2013-PL-C25-X-01.0-PL-PLC-080	Central North east	HORVS	BEATRIX	USTINH	26.3	83.5	-36.7
DEV-S-2013-PL-C25-X-01.0-PL-PLF-009	Central North east	HORVS	NADEK	USTINH	90.6	100.0	100.0
DEV-S-2013-UK-C25-A-01.0-UK-UK4-C38	Central Maritime	HORVS	CHALICE	USTINH	27.7	83.0	-28.9
DEV-S-2014-DE-C25-A-03.0-DE-D01-011	Central Maritime	HORVS	RIVIERA 91% KF	USTINH	15.0	100.0	6.7
DEV-S-2014-PL-C25-A-03.0-PL-PLF-002	Central North east	HORVS	NADEK	USTINH	5.0	100.0	95.8
DEV-S-2015-EX-C24-V-04.0-DE-VTF-519	Central Maritime	HORVS	STREIFERL	USTINH	11.8	100.0	89.9
DEV-S-2015-FR-C23-A-01.0-FR-FR3-317	South Mediterranean	HORVS	07KF335	USTINH	17.6	98.0	99.5
DEV-S-2017-ES-C50-A-06.0-ES-ESH-501	South Mediterranean	HORVW	SAFFRON	USTINH	21.6	100.0	9.2
DEV-S-2017-ES-C50-A-06.0-ES-ESH-502	South Mediterranean	HORVW	IGRI	USTINH	17.8	99.9	24.4
			Range	USTINH	5,0 - 90,6	83,5 - 100,0	-36,7 - 100
			Mean	USTINH	**25.9**	**96.0**	**40.0**

Table 2.2.4.c: Efficacy of Premis 25 FS againts *Fusarium* spp. (FUSASP) on winter and spring wheat (n = 12). Data from 2013-2017.

Trial	EPPO Zone	Crop	Variety	Disease	Untreated % infection	Premis25, 5g %efficacy	Celest, 5g %efficacy
DEV-S-2013-FR-C21-A-02.0-FR-FR3-303	South Mediterranean	TRZAW	ALIXAN	FUSASP	96.1	71.7	71.5
DEV-S-2013-PL-811-X-02.0-PL-PLC-060	Central North east	TRZAS	HEWILLA	FUSASP	12.5	84.0	76.0
DEV-S-2013-PL-811-X-02.0-PL-PLC-061	Central North east	TRZAS	ZURA	FUSASP	10.5	81.0	85.7
DEV-S-2013-PL-811-X-02.0-PL-PLD-001	Central North east	TRZAS	BOMBONA	FUSASP	35.5	83.1	81.7
DEV-S-2013-PL-811-X-02.0-PL-PLD-002	Central North east	TRZAS	KATODA	FUSASP	12.0	83.3	75.0
DEV-S-2013-PL-811-X-02.0-PL-PLF-001	Central North east	TRZAS	VINJETT	FUSASP	79.5	69.8	73.6
DEV-S-2013-PL-811-X-02.0-PL-PLF-002	Central North east	TRZAS	BOMBONA	FUSASP	79.5	73.6	73.6
DEV-S-2014-PL-C21-X-03.0-PL-PLC-014	Central North east	TRZAW	TURNIA	FUSASP	16.8	84.5	93.6
DEV-S-2017-IT-C13-A-06.0-IT-IT2-350	South Mediterranean	TRZAW	JULIE	FUSACU	15.0	77.8	100.0
DEV-S-2017-IT-C13-A-06.0-IT-IT2-351	South Mediterranean	TRZAW	JULIE	FUSACU	51.1	75.1	81.3
DEV-S-2017-PL-C13-A-06.0-PL-PLC-015	Central North east	TRZAW	JULIE	FUSACU	57.0	80.5	68.6
DEV-S-2017-PL-C13-A-06.0-PL-PLF-001	Central North east	TRZAW	TOBAK	FUSASP	79.5	90.6	96.9
			Range	FUSASP	10,5 - 96,1	69,8 - 90,6	68,6 - 100
			Mean	FUSASP	**45.4**	**79.6**	**81.5**

2.2.5. Summary of information on the development of resistance

Triticonazole is active as a contact and systemic fungicide seed treatment; target fungal pathogens are killed or supressed. It shows an apoplastic (upwards) distribution inside the plant after penetration.

As with most of the methyl-triazol derivatives, triticonazole acts as a C-14 demethylation inhibitor in the sterol biosynthesis pathway found in most of the fungi except Oomycetes. When applied onto plants, triticonazole is effective against a broad range of fungi belonging to several groups of plant pathogens (Ascomycetes, Adelomycetes, Basidiomycetes) It is active as a contact and systemic fungicide. It shows an apoplastic (upward) distribution inside the plant after penetration. When applied as a seed treatment, the product is slowly absorbed by the seedlings through the seed, teguments and the root.

Information on Occurrence or Possible Occurrence of the Development of Resistance and Appropriate Management Strategies

Triticonazole should present the same cross-resistance patterns as other sterol demethylation inhibitor (DMI) fungicides. A resistance risk analysis was conducted in 2013. No reports on a reduced sensitivity to demethylation inhibitors (DMIs) for the target pathogens exist at the current time. There is no cross-resistance within the SBI-group, i.e. between morpholines and DMI fungicides. Likewise there is no cross resistance or a correlation in the

sensitivity to SBI fungicides and other modes of action. Baseline data are not available. No monitoring data and no reports on field failure are available for the target pathogens. The FRAC (Fungicide resistance action committee) working group described the DMI-fungicides in general as medium-risk compounds. The pathogen risk is assessed as follows:

- Low risk pathogens: *Tilletia caries, Ustilago nuda, Pyrenophora graminea*
- Medium risk pathogens: *Microdochium* spp., *Fusarium* spp..

The combined resistance risk of *Pyrenophora graminea*, *Tilletia caries*, *Ustilago nuda* and DMIs is concluded to be low and that of *Microdochium* spp. and *Fusarium* spp. and DMIs to be medium. For common bunt (*Tilletia caries*) and loose smut (*Ustilago nuda*) resistance development would only have consequences if it developed in a crop destined for seed production. Development of resistant isolates in a food crop would be inconsequential because the resistant propagules would be removed from the population at harvest. This further lowers the chances of resistance becoming a problem.

The objective of anti-resistance management strategies is the reduction of selection pressure to avoid or delay the occurrence of resistance. This can be achieved by good agricultural practice, which leads to less infection pressure (e.g. phytosanitary measurements, cultivation of less susceptible varieties, appropriate crop cultivation unfavorable for the target pathogens). Another important resistance management strategy is the restriction of use. By their very nature, cereal seed treatments are only applied once per season.

Since population size of pathogens is lower at disease onset than when already established in the field, selection pressure is less when using preventive applications rather than curative or eradicative spray schemes. A seed treatment is the most preventive application that can be made. This is - from a resistance management point of view - an optimal timing that is also an effective resistance management (van den Berg et al. 2013).

The applicant BASF is a member of the FRAC SBI Working Group and will promote effective anti-resistance management strategies.

Summary information on triticonazole

Triticonazole	
IUPAC name:	rac-(5*E*)-5-(4-chlorobenzylidene)-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol
Chemical group:	Triazole
Mode of action:	Blocking of ergosterol biosynthesis leading to inhibition of growth and cell membrane disruption
Plant translocation:	Systemic, shows an apoplastic (upwards) distribution inside the plant after penetration.
Biological action: Harmful organism, plant growth regulator, etc.	Acts as a contact and systemic fungicide against seed and soil-borne diseases of cereals

2.2.6. Summary of adverse effects on treated crops

Triticonazole is very safe to treated seeds, as can be seen from the data on relative emergence and phytotoxicity to emerged plants presented below. Additional more than 20 years of commercial use have demonstrated that Triticonazole is save to treated crops when used according to the label recommendation.

Table 2.2.6.a: Relative emergence (based on plant counts) of treated seeds compared to untreated control (n = 83).

Trial	EPPO Zone	Crop	Variety	Disease	Untreated Emergence in %	Premis25, 5g Emergence in %	Celest, 5g Emergence in %
Various	Various	n = 83	Range	AUFLPF		78 - 193	76 - 195
			Mean	AUFLPF	100.0	106.5	109.2

Table 2.2.6.b: Phytotoxicity to emerged plants of treated seeds compared to untreated control (n = 53).

Trial	EPPO Zone	Crop	Variety	Disease	Untreated % PHYTOX	Premis25, 5g % PHYTOX	Celest, 5g % PHYTOX
Various	Various	n = 53	Mean	PHYTOX	0.0	0.0	0.1

2.2.7. Summary of observations on other undesirable or unintended side-effects

No reports of unintended effects have been reported.

2.3. FURTHER INFORMATION

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

For information on active substance please see Volume 3CA, B4.

For information on representative formulations please see Volume 3CP, B4.

2.3.2. Summary of procedures for destruction or decontamination

For information on active substance please see Volume 3CA, B4.

For information on representative formulations please see Volume 3CP, B4.

2.3.3. Summary of emergency measures in case of an accident

For information on active substance please see Volume 3CA, B4.

For information on representative formulations please see Volume 3CP, B4.

2.4. METHODS OF ANALYSIS

2.4.1. Methods used for the generation of pre-authorisation data

Adequate methods are available for the analysis of the technical compound and risk assessment analysis.

2.4.2. Methods for post control and monitoring purposes

Adequate methods are available to monitor the respective current residue definition in plant material, soil, drinking water, surface water, air, and body fluids. A summary of adequate enforcement methods are given in the tables below:

Matrix group / crop group	Analyte	LOQ	Methods		
			Primary method	**Confirmatory method**	**Independent lab validation**
Wheat grain = Dry commodity (high protein/high starch content)	Triticonazole	0.01 mg/kg	**Stanislowski T., 2014c** 2014/1031578 LC-MS/MS using two transitions	**Not necessary**	**Jarrett H., 2014a** 2014/1031576 LC-MS/MS using two transitions covering all crop groups
Tomato = Commodity with high water content		0.01 mg/kg			
Rape seed = Commodity with high oil content		0.01 mg/kg			
Orange fruit = Commodity with high acid content		0.01 mg/kg			
Bovine Meat	Triticonazole	0.01 mg/kg	**Stanislowski T., 2014d** 2014/1031579 LC-MS/MS using two transitions	**not necessary**	**Chambers J.G. et al., 2014a** 2014/1031577 LC-MS/MS using two transitions covering all matrices
Bovine Liver		0.01 mg/kg			
Whole Milk		0.01 mg/kg			
Eggs		0.01 mg/kg			
Fat		0.01 mg/kg			
Soil LUFA 2.2 LUFA 2.4	Triticonazole M595F001 M595F002 M595F014	0.002 mg/kg each	**Obermann M., Langenbach S., 2016** 2016/1190727	**not necessary**	**not necessary**
Water (drinking and surface)	Triticonazole	0.05 µg/L	**Class T., 2014d** 2014/1036831 **Class T., 2015b** 2015/1173435 LC-MS/MS using two transitions	**not necessary**	drinking water**: Chambers J. et al., 2014b** 2014/1036832 **Chambers J., 2015a** 2015/1177041 LC-MS/MS

Matrix group / crop group	Analyte	LOQ	Methods		
			Primary method	**Confirmatory method**	**Independent lab validation**
					using two transitions
Air	Triticonazole	7.5 µg/m^3	**Stanislowski T., 2014b** LC-MS/MS using two transitions	**not necessary**	**not necessary**
Body fluids Urine, blood	Triticonazole	0.01 mg/kg	**Richter S., 2016** LC-MS/MS using two transitions	**not necessary**	**not necessary**
Body tissues	Triticonazole	0.01 mg/kg	refer to animal matrices above	refer to animal matrices above	**not necessary**

2.5. EFFECTS ON HUMAN AND ANIMAL HEALTH

2.5.1. Summary of absorption, distribution and excretion in mammals

Absorption: Triticonazole, universally radiolabelled with [^{14}C] at the phenylring, is almost completely and rapidly absorbed following a single low dose (5 mg/kg bw). Based on the recoveries of radioactivity obtained in urine (plus cage wash), bile and tissue, the absorption rate from the gastrointestinal tract for both sexes can be estimated at > 98 % of the total dose given. Absorption of a single high dose (500 mg/kg bw) was not so extensive (32 % – 36 %, based on radioactivity recoveries in urine, bile and tissues), implying that saturation of absorption from the gastro-intestinal tract was occurring at this high dose level. This hypothesis is also supported by the fact that a greater percentage of parent material was found in the faeces within 24 hours after dosing from the high dose group (70 – 80 % of the total dose) compared with 1 – 1.4 % found in the low dose group.

Pharmacokinetic parameters were investigated following single oral doses of 5 or 500 mg/kg bw. There were no sex differences in either dose groups. In both dose groups, a rapid peak in blood radioactivity concentration (0.5 to 1 hour post-dose at the low dose level, 1 – 2 hours after dosing at the high dose level) was followed by a rapid decline over 24 – 48 hours and then a slow elimination thereafter with terminal elimination half-lives of 116.4 - 119.4 hours at the low dose level and 95.62 - 106.3 hours at the high dose level, resp. Plasma results were very similar to the results obtained with whole blood.

Distribution: Following oral administration to rats, radioactivity was widely distributed into the tissues. However, the levels of radioactivity remaining in the tissues after 168 hours were low in the high dose group (0.08 [♂] and 0.04 % [♀] of the dose) and very low in both low dose groups (0.41 – 0.57 [♂] and 0.12 – 0.22 % [♀] of the dose). After high dose administration the highest tissue concentrations were observed in the skin & fur and liver for both sexes. After single oral low application, mean tissue concentrations in males ranged between non-detected and 0.07 µg/g (plasma) in males and between non-detected and 0.04 µg/g (adrenals) in females, resp. After repeated low dose, mean tissue concentrations ranged from 0.01 µg/g to 0.18 µg/g (blood) in males and between non-detected to 0.07 µg/g (adrenals) in females. In all experiments, the levels of radioactivity in male tissues tended to be slightly higher than female. There was no evidence of a potential for bioaccumulation.

Excretion: In rats [^{14}C] triticonazole was almost completely excreted with more than 98 % of the administered dose following single high dose and > 95 % within 72 hours after single low dose administration. Animals in the multiple low dose experiment excreted > 89 % of the administered dose in urine and faeces within 72 hours after 14 consecutive days of dosing. Rates and routes of excretion in the single and repeated low dose experiments were similar indicating no effects on pharmacokinetics resulting from repeated administration.

The major route of elimination in the rat was via faeces and the remainders of the doses were found in the urine. There was a significant sex difference in the amounts of radioactivity eliminated via urine and faeces in the two low dose groups only. In a biliary excretion study in rats, significant excretion of radioactivity via bile was demonstrated. No significant levels of radiolabelled carbon dioxide were detected in the trap fluids collected up to 24 hours after dosing for either male or female rats.

Metabolism of triticonazole was found to be rapid and extensive at the low dose level (single and repeated application), with no parent material excreted via urine and only low amounts (< 1.5 % of the dose) found in the faeces 24 hours after dosing only. At the high dose level, triticonazole was identified the major compound in the faecal extracts after 24 hours indicating limited absorption. However, these initially high levels decreased rapidly thereafter. Analysis by HPLC revealed a total of 10 and 12 components in faecal and urinary extracts, resp. The metabolite profiles obtained for males and females were qualitatively very similar and differed rather in quantitative terms. Based on the identified metabolites

in urine and faeces by LC/MS, a metabolic pathway was proposed which involved hydroxylation at different positions of the molecule.

It was stated that the rat ADME study was performed following the US EPA guideline which required labelling of the molecule on that part that was thought to be most stable. In a preliminary ADME rat study, no significant release of [^{14}C] CO_2 following oral administration of phenyl-labelled material was demonstrated, confirming the relative stability of the phenyl group. In the main study, the majority of the administered radioactivity was eliminated via faeces and urine within 72 hours and the proportion of the administered dose identified was high, especially for the high dose group where ca. 98 % of the administered radioactivity was assigned a structure. The pattern of all metabolites identified in urine and faeces of the rat were molecules in which the triazole and phenylrings remained linked and the possibility of cleavage of the phenylring from the remainder of the molecule during metabolism was very low. Therefore, it can be concluded that the studies performed are sufficient to characterise the metabolites of triticonazole and no further study investigating ADME with triticonazole radiolabelled at the triazole ring is necessary.

No ADME study by a route other than oral has been submitted. The study by intravenous exposure route is not considered necessary since the information on oral absorption and bioavailability is gained from bile cannulation study.

Based on the comparative in vitro metabolism study and literature data, no unique human metabolite of triticonazole is expected.

Since the absorption of triticonazole was extensive (> 98% after single and repeated low dose administration), no adjustment of the AOEL is necessary.

2.5.2. Summary of acute toxicity

Acute toxicity tests with triticonazole demonstrated that this compound is of low acute toxicity to CD (Sprague dawley) rats by the oral, dermal and also respiratory routes.

Triticonazole is non-irritating to the skin and to the eyes of the New Zealand White rabbit, and is a non-sensitizer in the Buehler test (3 and 9 inductions) and in the Magnusson and Kligman dermal maximization study conducted in Dunkin-Hartley guinea pig as well. A summary of the results from the acute toxicity studies is presented in table 2.6.2 -1.

Based on the experimental results, triticonazole has not to be classified for acute oral/dermal/inhalative toxicity, eye/skin irritation and skin sensitization according to Regulation (EC) 1272/2008. At the time it is concluded that based on the negative results of 3T3 NRU-PT, which is currently the only listed test for addressing phototoxicity (Commission Communications 2013/C 95/01), triticonazole is not considered to be phototoxic.

No non-lethal effects in acute oral toxicity studies were observed which would warrant the classification as STOT SE (specific target organ toxicity - single exposure) for triticonazole.

Table 2.6.2 -1: Overview of results of the acute toxicity studies, studies for skin and eye irritation, skin sensitisation and phototoxicity

Type of study	Species	Vehicle	Results	Reference
Acute oral toxicity	CD-Rat (Sprague Dawley)	Water/CMC*	♂/♀ > 2000 mg/kg bw	[redacted], *1990*
Acute dermal toxicity	CD-Rat (Sprague Dawley)	moistened with water	♂/♀ > 2000 mg/kg bw	[redacted] *1991*
Acute inhalative toxicity	CD-Rat (Sprague Dawley)	-	♂/♀ > 1.4 mg/l air (4h, nose only)	[redacted] *1991*

Type of study	Species	Vehicle	Results	Reference
Acute inhalative toxicity	Rat (Sprague Dawley)	-	♂/♀ > 2.63 mg/l air (4h, nose only)	[redacted] *1998*
Acute inhalative toxicity	Rat (Sprague Dawley)	-	♂/♀ > 5.61 mg/l air (4h, nose only)	[redacted] *1998*
Dermal irritation study	Rabbit (NZW; ♂)	moistened with water	no dermal irritation	[redacted] *1991*
Eye irritation study	Rabbit (NZW; ♂)	-	no eye irritation	[redacted] *1991*
Eye irritation study	Rabbit (NZW; ♀)	-		[redacted] *1997*
Dermal sensitization M & K-test	Guinea pig (♂/♀) (Dunkin-Hartley)	Propylene glycol	not sensitizing	[redacted] *1993*
Dermal sensitization Buehler-test (9 inductions)	Guinea pig (♂/♀) (Dunkin-Hartley)	Propylene glycol	not sensitizing	[redacted] *1992*
Dermal sensitization Buehler-test (3 inductions)	Guinea pig (♀) (Dunkin-Hartley)	Propylene glycol	not sensitizing	[redacted] [redacted] *2006*
Phototoxicity (*in vitro*)	Neutral red (NR) test with BALB/c 3T3 cells	DMSO	not phototoxic	*Cetto V., Landsiedel R., 2013*

* CMC = Carboxymethylcellulose

2.5.3. Summary of short-term toxicity

The short term toxicity of triticonazole has been investigated in rats and mice following a 90 day exposure period and in dogs following a 1-year treatment period. The dosages of these studies were selected based on the results of 4 to 6-week preliminary studies (except for mice where the dosages used were higher compared to the suggested dosages as the outcome of the range finding study). In addition, a 21-day dermal study was conducted in rats.

In a 90 day dietary study in the rat, there was clear evidence of systemic toxicity at the two top dose groups (12500 and 25000 ppm). Treatment-related findings included reductions in body weight gain and food consumption, haematological and clinical chemistry changes, organ weight effects and histopathological findings. The liver and the adrenals were identified as the major target organs. Vacuolation of the adrenal cortex was noted in all groups but, based on severity grade and microscopic appearance, the findings at the dose levels of 25 and 250 ppm were considered to be typical of spontaneous changes commonly found in untreated animals. The short term NOAEL for triticonazole in the rat can be set at 250 ppm (equivalent to 19.8 (m) and 22.3 (f) mg/kg bw per day).

Also in mice, continuous dietary treatment during 90 days produced severe systemic toxicity at all dose levels with the liver being identified as the major target organ showing organ weight changes associated with histopathological alterations (hypertrophy, fatty vacuolation, necrosis, and increased mitotic activity). No short-term (90 days study) NOAEL could be determined in mice.

In the 52-week dog-study, clear systemic toxicity was evident at the high dose (150 mg/kg) including cataractogenic effects, decreased body weight gains, haematological and clinical chemistry findings and increased liver and adrenal weights. In adrenals also marked histopathological changes were observed. Clinical chemistry findings together with organ weight effects suggested toxicological effects on the liver, but there were no histopathological alterations seen in the liver. Based on decreased terminal body weight gain and also clinical chemistry effects in females at 25 mg/kg bw per

day, and histological alterations in adrenals in males and females the NOAEL for this study is considered to be 2.5 mg/kg bw per day.

Dermal application of triticonazole at dose levels up to 1000 mg/kg bw per day to rats for 21 days did produce neither local effects nor systemic toxicity. The NOAEL for this study was 1000 mg/kg bw per day (the highest dose tested).

Table 2.6.3-1 Summarised results of subacute/subchronic toxicity studies

Study; Reference	Dose levels	NOAEL	Relevant effects at LOAEL
F-344 rat 4 weeks oral [redacted] *1991 (a)*	0, 500, 1500, 5000, 15000 and 50000 ppm/diet (equivalent to 0, 50.1, 152.3, 513.2, 1494 and 4802 mg/kg bw per day in males; 0, 52.4, 151.3, 489.4, 1476 and 4945 mg/kg bw per day in females)	152.3 mg/kg bw per day (m) 52.4 mg/kg bw per day (f)	– ↓ body weight gain (m) - ↓ uterus weight
CD rat 13 weeks oral [redacted] *1991 (c)*	0, 25, 250, 12500 and 25000 ppm/diet (equivalent to 0, 2.0, 19.8, 1117.0 and 2309.3 mg/kg bw per day in males 0, 2.2, 22.3, 1183.5 and 2368.8 mg/kg bw per day in females)	19.8 (m) / 22.3 (f) mg/kg bw per day	– ↓ body weight gain (m/f) – ↓ food consumption and food utilisation ratio (m/f) – ↓ RBC (m), ↓haemoglobin, MCV and MCH (f), ↑ cholesterol (m/f) – ↑ liver weight (m/f), – ↑ ovaries weight – histological alterations in liver and adrenals
CD-1 mouse 6 weeks oral [redacted] *1991 (b)*	0, 500, 1500, 5000, 15000 and 50000 ppm/diet (equivalent to 0, 77, 233, 851 and 3270 mg/kg bw per day in males; 0, 98.8, 286, 982 and 4091 mg/kg bw per day in females)	cannot be determined	– decreased body weight gain (f) – ↑ liver weight (m/f) – histological alterations in the liver (m)
CD-1 mouse 13 weeks oral [redacted] *1991*	0, 2500, 5000 and 8000 ppm/diet (equivalent to 0, 382.8, 807.6 and 1426.2 mg/kg bw per day in males; 0, 503.8, 969.2 and 1657.6 mg/kg bw per day in females)	cannot be determined	– ↓ body weight and body weight gain – ↑ liver weight (m/f) – histological alterations in the liver
Beagle dogs 4 weeks oral [redacted] *; 1991*	0, 10, 30, 100 and 300 mg/kg bw per day via capsule	30 mg/kg bw per day	– ↑ ALP (m) – ↑ liver weight (f) – ↓ relative and absolute thymus weight (m/f)
Beagle dogs 52 weeks oral [redacted] *; 1993*	0, 2.5, 25 and 150 mg/kg bw per day via capsule	2.5 mg/kg bw per day	– decreased terminal body weight (f) – ↑ ALP (f) – histological alterations in adrenals (m/f)
CD-rat 3 weeks dermal [redacted] *1997*	0, 100, 300 and 1000 mg/kg bw per day	1000 mg/kg bw per day	– no effects observed at any dose level

Considerations for STOR RE classification

Liver and adrenals were target organs of triticonazole. In order to estimate if triticonazole produces significant toxicity following repeated exposure at or below the guidance values a comparison with STOT RE criteria has been conducted for liver and adrenals. In the comparison also the long-term studies in rats and mice have been included, as well as results from the ACTH assay (study itself is inserted under the chapter on endocrine disruption). Additionally, maternal mortality, attributed to exposure to triticonazole, was observed in rabbit developmental study at 75 and 50 mg/kg bw per day.

According to the Guidance Document on the application of the CLP criteria (version 4.1, June 2015), specific target organ toxicity (repeated exposure) means specific, target organ toxicity arising from a repeated exposure to a substance or mixture. All significant health effects that can impair function, reversible and irreversible, immediate and/or delayed are included. STOT RE 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 which significantly impact on health. Both factors have to be evaluated by weight of evidence and expert judgement. If no human data are available a classification for STOT RE shall be based on non-human (animal) data. The decision to classify at all can be influenced by reference to the dose/concentration guidance values at or below which a significant toxic effect has been observed.

In the context of a weight of evidence decision some guidance is given, which effects might qualify for a classification with STOT RE. These are:

a) morbidity or death resulting from repeated dose or long-term exposure

b) significant functional changes in the central or peripheral nervous systems

c) any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters

d) significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination

e) multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity

f) morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g., severe fatty change in the liver)

g) evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

Table 2.6.3-2: Summarised results of subacute/subchronic toxicity studies - Specific target organ toxicity (STOT RE) - summary of toxicologically relevant effects and comparison to cut-off values

Effect / Dose		Study duration	Cut-off value for STOT RE 2 [mg/kg bw per day]	Reference
Adrenals	No effects on adrenals up to the highest tested dose (4802 mg/kg bw per day in males and 4945 mg/kg bw per day in females)	28 days rat oral	300	[redacted] *1991*
	No effects on adrenals up to the highest tested dose of 1000 mg/kg bw per day	21 days rat dermal	450	[redacted]*; 1997*
	No effects on adrenals up to the highest tolerated dose (851 mg/kg bw per day in males and 982 mg/kg bw per day in females)	6 weeks mouse oral	450	[redacted] *1991*
	No effects on adrenals up to the highest tested dose of 300 mg/kg bw per day	28 days dog oral (capsule)	300	[redacted] *1991*

	Females at 1183.5 mg/kg bw per day: • Degeneration of *zona reticularis* (9/10) • Cortical droplet vacuolation in *zona fascicularis (4/10)* *Males* at 1117.0 mg/kg bw per day: • Cortical droplet vacuolation in *zona fascicularis (10/10)* No effects on adrenals observed at the next lower dose of 19.8 and 22.3 mg/kg bw per day (250 ppm) in males and females, respectively	90 days rat oral	100	[redacted] *1991*
	No effects on adrenals in females up to 479 mg/kg bw per day (5000 ppm), highest dose tested In males, at 412 mg/kg bw per day (5000 ppm) degeneration / regeneration (*zona fasciculate/reticularis*) of grade 1 and two in all 6 animals No effects on adrenals observed at next dose of 59 and 68 mg/kg bw per day (750 ppm) in males and females, respectively	90 days rat oral – ACTH challenge assay	100	[redacted] *2016*
	Adrenals not investigated	90 days mouse oral	100	[redacted] *1991*
	At 25 mg/kg bw per day: • slight vacuolation of *zona fasciculata* in males (3 out of 4 animals) • moderate vacuolation of *zona fasciculata* in females (1 out of 3 animals)	1 year dog oral	25	[redacted] *1993*
	No effects on adrenals up to 750 ppm (29.4 and 38.3 mg/kg bw per day in males and females, respectively)	2 years rat oral	12.5	[redacted] *1994*
	No effects on adrenals up to 150 ppm (17.4 and 20.1 mg/kg bw per day in males and females, respectively)	1.5 years mouse oral	17	[redacted] *1994*
Liver	Females at 489.4 mg/kg bw per day (5000 ppm): • increased relative liver weight (+38.3%), no histopathological findings No effects on liver of males at 5000 ppm No effects at 152.3 and 151.3 mg/kg bw per day (1500 ppm)in males and females, respectively	28 days rat oral	300	[redacted] *1991*
	No effects on liver up to the highest tested dose of 1000 mg/kg bw per day	21 days rat dermal	450	[redacted] *1997*
	Males at 77 mg/kg bw per day (500 ppm): • increased relative liver weight (+13.8%), increased incidence of inflammatory cells (2/12) Males at 233 mg/kg bw per day (1500 ppm): • increased relative liver weight (+51%), increased incidence of inflammatory cells (4/12) Males at 851 mg/kg bw per day (5000 ppm) • increased relative liver weight (+143.1%), increased incidence of enlarged liver (5/12), hepatocytic hypertrophy (12/12), fatty vacuolation (2/12) and increased ploïdy (2/12)	6 weeks mouse oral	450	[redacted] *1991*

	Females at 286 mg/kg w/d (1500 ppm): • increased relative liver weight (+26.4%), increased incidence of hepatocyte hypertrophy (2/12) Females at 982 mg/kg w/d (5000 ppm): • increased relative liver weight (+105.5%), increased incidence of enlarged liver (4/12), hepatocyte hypertrophy (10/12), fatty vacuolation (6/12) and increased ploïdy (9/12)			
	Males at 300 mg/kg bw per day: • increased relative liver weight (+18.9%) and periacinar hypertrophy of hepatocytes with associated fatty vacuolation (2/2) Females at 100 mg/kg bw per day: • increased relative liver weight (+9.7%) Females at 300 mg/kg bw per day: • increased relative liver weight (+8.5%)	28 days dog oral (capsule)	300	[redacted] *1991*
	Males at 1117.0 mg/kg bw per day (12500 ppm): • increased cholesterol (+142.6%) • increased relative liver weight (132.6%) • increased peracinar hepatocyte hypertrophy (6/10) Females at 1183.5 mg/kg bw per day (12500 ppm): • increased cholesterol (+184.4%) • increased relative liver weight (167.5%) • increased peracinar hepatocyte hypertrophy (6/10) • increased centriacinar fatty vacuolation (7/10) No effects on liver observed at the next lower dose of 19.8 and 22.3 mg/kg bw per day (250 ppm) in males and females, respectively	90 days rat oral	100	[redacted] *1991*
	Males at 412 mg/kg bw per day (5000 ppm): • no effects on liver weight Females at 479 mg/kg bw per day (5000 ppm): • increased relative liver weight (+26.3%) No histopathology performed. No effects on liver weight observed < 5000 ppm	90 days rat oral – ACTH challenge assay	100	[redacted] [redacted] *2016*
	Males at 328.8 mg/kg bw per day: • increased relative liver weight (+191.2%) • increased incidence at pericinar vacuolation (7/12), increased panacinar vacuolation (12/12), increased	90 days mouse oral	100	[redacted] *1991*

	hepatocyte hypertrophy (8/12), coagulative necrosis (4/12) and hepatocyte necrosis (7/12) Females at 503.8 mg/kg bw per day: • increased relative liver weight (+163.8%) • increased incidence at pericinar vacuolation (10/12), increased panacinar vacuolation (12/12), increased hepatocyte hypertrophy (12/12), coagulative necrosis (1/12) and hepatocyte necrosis (1/12) This (2500 ppm) was the lowest dose tested therefore no information on potential effects at the cut-off value of 100 mg/kg bw per day is available			
	No effects on liver were observed at the cut-off value of 25 mg/kg bw per day	1 year dog oral	25	[redacted] *1993*
	No effects on liver up to 750 ppm (29.4 and 38.3 mg/kg bw per day in males and females, respectively)	2 years rat oral	12.5	[redacted] *1994*
	No effects on liver up to 150 ppm (17.4 and 20.1 mg/kg bw per day in males and females, respectively)	1.5 years mouse oral	17	[redacted] *1994*
Mortality	No mortality	28 days rat oral	300	[redacted] *1991*
	No treatment related mortality	21 days rat dermal	450	[redacted] *1997*
	50000 ppm (no information on mg/kg bw per day): • all animals (12 males, 12 females) died or were killed in extremis within the first week of treatment 15000 ppm (3270 and 4091 mg/kg bw per day in males and females, respectively): • one male and ten females (out of 12 per sex) died or were killed in extremis within the first week of treatment 5000 ppm (851 and 982 mg/kg bw per day in males and females, respectively) and below: • no mortality	6 weeks mouse oral	450	[redacted] *1991*
	No treatment related mortality	28 days dog oral (capsule)	300	[redacted] *1991*
	No treatment related mortality	90 days rat oral	100	[redacted] *1991*
	No treatment related mortality	90 days rat oral – ACTH challenge assay	100	[redacted] *2016*
	No treatment related mortality	90 days mouse oral	100	[redacted]; *1991*
	No treatment related mortality	1 year dog oral	25	[redacted] *1993*
	No treatment related mortality	2 years rat oral	12.5	[redacted] *1994*
	No treatment related mortality	1.5 years mouse oral	17	[redacted], *1994*
	No treatment related mortality	Preliminary teratology study in the rat	300	[redacted] *1990*
	No treatment related mortality	Teratology study in the rat	300	[redacted] *1991*
	500 mg/kg bw per day: • 2 of 2 animals sacrificed in extremis on Day 3 following marked toxic response, characterized by bodyweight loss and reduced food intake and	Tolerance study in the rabbit	300	[redacted] *1990*

	faecal output No mortalities observed in animals treated with 100, 50 and 25 mg/kg bw per day No OECD GD conform study, terminated at day 13 of gestation			
	150 mg/kg bw per day: • All 8 animals sacrificed in extremis between day 8 and 9 of insemination following weight losses, reduced food and water intakes and reduced faecal output No mortalities observed in animals treated with 75, 50, 15 and 5 mg/kg bw per day	Range finding study in the rabbit	300	[redacted] *1990*
	75 mg/kg bw per day: • 6 from 20 dams sacrificed in extremis between day 13 to 18 following marked weight loss, reduced food intake and reduced faecal output, reduced body temperature and red staining in the cage undertray 50 mg/kg bw per day • 1 from 20 dams sacrificed in extremis following marked weight loss, reduced food intake and reduced faecal output, reduced body temperature and red staining in the cage undertray No treatment related mortality at 25 and 5 mg/kg bw per day observed	Teratology study in the rabbit	300	[redacted] *1991*

Studies where effects were observed below the cut-off values are coloured in grey

Adrenals:

Although adrenal is a target organ of triticonazole, only in 1 year dog study some histopathological effects (slight vacuolation of *zona fasciculata* in 3 out of 4 males and moderate vacuolation in 1 out of 3 females) were observed at the corresponding cut-off value (25 mg//kg bw/d) for STOR RE 2 classification. By balancing the data the RMS is of the opinion that the severity and nature of effects in adrenals after sub-acute exposure to triticonazole in dogs at respective cut-off value of 25 mg/kg bw per day do not reflect significant organ damage which might provide clear evidence of marked organ dysfunction. Therefore, proposal for STOT RE for adrenal effects is not considered justified.

Liver:

No effects on liver below the cut-off values were observed in the short and long-term studies in rats, mice and dogs. The only two studies where effects on liver were observed below the cut-off values were 6 weeks study in mouse and 28-days study in dog. The observed effects below the threshold were increased liver weight (male and female mice, male dog), increased incidence of inflammatory cells (male mice), increased incidence of hepatocyte hypertrophy (female mice) and increased incidence of periacinar hypertrophy of hepatocytes with associated fatty vacuolation (male dogs). None of these effects were observed below the cut-off values in the studies of longer duration. By balancing the data the RMS is of the opinion that the severity and nature of effects in liver after sub-acute exposure to triticonazole at respective cut-off values do not reflect significant organ damage which might provide clear evidence of marked organ dysfunction. Therefore, proposal for STOT RE for liver effects is not considered justified.

Mortality:

The only studies where treatment related mortality was observed were rabbit developmental toxicity studies. In the preliminary study, all 8 animals at 150 mg/kg bw per day were sacrificed in extremis between day 8 and 9 of insemination following weight losses, reduced food and water intakes and reduced faecal output. No mortalities were observed at 5, 15, 50 and 75 mg/kg bw per day.

In the main rabbit study at 75 mg/kg bw per day 6 from 20 dams were sacrificed in extremis between day 13 to 18 following marked weight loss, reduced food intake and reduced faecal output, reduced body temperature and red staining in the cage undertray. The same was the case for one female treated with 50 mg/kg bw per day.

Some of the explanations for rabbit mortality can be excluded:

- There were no indication of any mis-gavage or mis-dosing
- There was no indication for infections or diarrhoea based on irritation by triticonazole
- Triticonazole is well absorbed and metabolised (please see ADME studies) so it can be excluded that by cecotrophy there was a recycling of triticonazole and therefore a higher exposure

Notifier provided an explanation why mortality observed in rabbits is not relevant for humans:

"With regard to effect cluster a) "morbidity or death resulting from repeated dose or long-term exposure", the results from the rabbit teratogenicity study (C018959) and the range finder study (C019984) are looked at in more detail in the following section and assessed with regard to the justification to classify triticonazole with STOT RE.

Doses of 5, 15, 50, 75 and 150 mg/kg bw were given to groups of pregnant rabbits. The does treated with 150 mg/kg bw had to be sacrificed in extremis due to poor general condition. No mortalities were seen at 75 mg/kg bw in this range finding study. In the main study also one animals from the 50 and 6 animals from the 75 mg/kg bw group had to be sacrificed after treatment-related body weight losses. Other clinical signs were reduced food and water consumption and reduced fecal output. Necropsy of the prematurely sacrificed animals revealed the following macroscopic findings: Compacted and/or gaseous stomach or GI tract contents and reduced GI-tract or caecum contents were seen at necropsy. A tabulated summary of the clinical and necropsy findings is given in the table below:

Table 2.5.3-1: Summary of clinical and necropsy findings of rabbits prematurely sacrificed

	50 mg/kg bw	*75 mg/kg bw*	*150 mg/kg bw*
Compacted/dark cecal content		*3/6*	
Stomach / GI tract content compacted		*4/6*	*2/8*
Reduced GI-tract/caecum content	*1/1*	*3/6*	*3/8*
GI tract / stomach gaseous		*1/6*	*1/8*
Soft pellets in rectum			*1/8*
Yellow mucoid material in small intestine	*1/1*		

These findings and the related mortalities are considered to be irrelevant to humans, as the digestive tract of rabbits is different from humans.

Rabbits produce two types of excreta, one nutrient-low, poorly digested fiber and a more readily digested soluble proteins, carbohydrates, dissolved nutrients, and fluid. Separation of large fiber particles from small particles and fluid occurs mechanically by muscular contractions of the cecum. The cecum of the rabbit is – in contrast to rodents or humans - large and may contain 40% of intestinal content, it has 10 times the capacity of the stomach [redacted] *2006). The denser small particles and fluids accumulate at the outer edge of the colon, in the haustrae, whereas the large,*

less dense fiber particles segregate out in the lumen. Peristaltic action moves the fiber through the colon, while reverse peristalsis moves the fluids and small particles in a retrograde manner into the cecum. The fiber forms the hard fecal pellets. The fluid and small particles support fermentation in the cecum. The material is formed into pellets referred to as cecotropes, surrounded by a layer of mucus. The cecotropes are consumed directly from the anus by the animal. This process is known as "cecotrophy" (Cheeke), is specific to rabbits, and is an integral part of digestion in rabbits. Proper fiber-containing diet is essential for rabbits to also maintain the hindgut motility [redacted], 2006, [redacted], 2003). If feed intake is decreased, the growth rate is reduced and animals are predisposed to enteritis. Hindgut hypomotility is a contributing factor to the development of enterotoxemia in rabbits. The essential cecotroph fermentation process depends heavily on an appropriate diet and the action of resident bacteria and protozoa, which are vital to the GI health of the rabbit. Dysbiosis is a common sequela of gastrointestinal disease occurring secondary to dietary or environmental factors (Kohles et al., 2014)

The consequence of disturbances in rabbit digestion and cecotrophy might be a so-called "digestive syndrome" or "mucoid enteropathy" which is frequently observed in experimental rabbit studies. If the intestinal transit of nutrient is disturbed in rabbits (via decreased food consumption, or low-fibre diet), potentially harmful opportunistic bacteria can proliferate in the GI tract of rabbits and consequently cause severe health consequences (Kohles 2014, Percy D.H., Barthold S.W., Pathology of Laboratory Rodents and Rabbits, 3rd edition (2007) Whiley-Blackwell). An epizootic rabbit enteropathy, which was artificially induced in specific pathogenic-free rabbits and studied and described by Licois et al., 2005. No specific histologic lesions are seen, as well as no inflammatory or congestive lesions. Rambling noise and distended abdomen were frequent, mucus excretion and cecal impaction were frequent but not constant, as well as the presence of a stomach and/or duodenum dilated by liquid and gas. 30 – 40% mortality in a few days are observed and about 100% morbidity.

The clinical and necropsy findings seen in rabbits after dosage of triticonazole (see table above) give no indication for inflammation or specific histological lesions, but indicate some disturbances in the digestive process. The presence of each one animal with gaseous contents in stomach or GI tract (in the range finder and in the main study) and the observation of compacted and dark cecal contents in 3/6 animals gives some evidence for the early occurrence of a rabbit specific mucous enteropathy. Overall, the systemic toxicity of triticonazole is much lower, when dosed to rats, mice or dogs in repeated dose toxicity via diet or via gavage. The necropsy observations and the increased mortality rates seen in the rabbits dosed with triticonazole are similar to the findings being seen as indicative for the "digestive syndrome" and are thus considered to display a rabbit-specific toxic effect without relevance to humans. No classification with STOT RE is justified for triticonazole."

RMS considered every single sacrificed animal and listed individually the observed necropsy findings in gastro-intestinal tract in the sacrificed rabbits (please see Vol 3, B6 CA, two rabbit developmental studies).

According to the literature data and knowledge on rabbit physiology, the most common symptoms of gastrointestinal disorders, among others mucous enteropathy, in rabbits are: anorexia, lethargy, crouched stance, diarrhoea, teeth grinding, cecal impaction, accumulation of large quantities of clear gelatinous mucous in the colon. At necropsy, the stomach may be distended with fluid and gas. The jejunum is frequently distended with translucent, watery fluid. Most of the gastro-intestinal disorders in rabbits come from wrong nutrition, causing dysbiosis in the very fragile rabbit digestive system.

RMS acknowledges that most of rabbit gastro-intestinal disorders can hardly be extrapolated to humans, based on very specific gastro-intestinal properties of rabbits.

The most prominent symptom in sacrificed rabbits in the preliminary and the main study was loss of weight. Necropsy findings in thoracic cavity of sacrificed rabbits were inconsistent. Some sacrificed rabbits did not show signs of gastro-intestinal disorder.

By balancing the available data RMS cannot conclude that rabbit mortality at doses below the cut-off values for STOT RE 2 was solely due to disorder in gastro-intestinal tract of rabbits. The animals were sacrificed based on their bad health conditions. The most prominent effect of higher doses of triticonazole on rabbits was that they either stopped or markedly reduce their food and water consumption and finally lost weight remerkably.

The reason for reducing food and water consumption cannot be clarified. It cannot be disregarded that this could be a result of toxicity of triticonazole to rabbits. Systemic toxicity in developmental studies is measured in very limited set of parameters. While for other species (rat) also other studies with much more extensive data set are available, this is not the case for rabbits. Therefore, rabbit developmental studies have to be taken for themselves alone.

Based on the results of the rabbit studies it is assumed that the rabbit mortality can be explained by a very high sensitivity of this species. Considering the limited effects on the rabbit pups (mostly skeletal variations), there is no reason to believe that the mortality is specific for pregnant rabbits, but rather is a general effect of triticonazole on rabbits. For a short study (28 days), the guidance value is 30-300 mg/kg/day for STOT RE 2. The **rabbit mortality/morbidity** is clearly severe and occurs at doses below the relevant guidance value. RMS concluded that this is **warranting classification with STOT RE 2 (H373).**

2.5.4. Summary of genotoxicity

Triticonazole was tested in an acceptable range of *in vitro* and *in vivo* mutagenicity assays measuring different end points of potential mutagenicity such as gene mutation in bacteria and in mammalian cells, and chromosomal aberration and UDS in somatic cells.

Results from these studies showed that triticonazole did not induce gene mutation in two AMES tests, or gene mutation in mammalian cells in culture (*CH-V79 assay*). No potential for clastogenicity was observed in the *in vitro chromosome aberration assay in human lymphocytes* (2 studies) or in the *in-vitro UDS assay in rat hepatocytes* as well.

The only suggestion of a genotoxic response was an increase in the incidence of polyploid cells in one of the *in vitro* assays with human lymphocytes in the presence of exogenous metabolic activation. However, there was no clear dose response in the absence of any effect on the mitotic index seen in this study. Moreover, no such effect on numerical aberrations was evident in the second more recent *chromosomal aberration study in human lymphocytes* with a comparable concentration range tested. In addition, no indications of numerical aberrations were evident in the in vivo mouse micronucleus assay.

In the *in vivo mouse micronucleus assay*, a clear negative result was obtained. Based on ADME studies with triticonazole and observed toxicity in the MN assay it can be concluded that triticonazole reached the bone marrow. Therefore, it can be concluded that triticonazole has no genotoxic potential of relevance to human risk assessment.

In three non-standard *in vitro* genotoxicity assays (GreenScreen HC GADD45a-GFP, CellCiphr p53, CellSensor p53 RE-bla) triticonazole showed throughout negative results (literature data).

Table 2.6.4 -1 Summary of mutagenicity studies with triticonazole

Type of study	Dose range	Results	Reference
In vitro-studies			
Reverse mutation assay (*S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100)	0, 25, 79, 250, 790 and 2500 µg/plate (dissolved in DMSO)	negative (+/- S-9 mix)	*May K.; 1991*

Type of study	Dose range	Results	Reference
Reverse mutation assay (*S. typhimurium* TA 1535, TA 1537, TA 98, TA 100 and *E. coli* WP2 uvrA)	0, 33, 100, 333, 1000, 2750 and 5500 µg/plate (dissolved in DMSO)	negative (+/- S-9 mix)	*Woitkowiak C., 2014*
Chinese Hamster V79 cell/HGPRT locus gene mutation assay	0, 62.5, 125, 250, 500 and 1000 µg/ml (dissolved in DMSO)	negative (+/- S-9 mix)	*Lloyd J. M.; 1991*
Chromosomal aberration assay in cultured human lymphocytes	0, 10, 20, 40, 50 and 60 µg/ml (- S-9) 0, 125, 250 and 500 µg/ml (+ S-9) (dissolved in DMSO)	no structural aberrations (+/- S-9 mix) increased polyploidy at 250 and 500 µg/ml (+ S-9) [questionable signif.]	*Dance C. A.; 1992*
Chromosomal aberration assay in cultured human lymphocytes	0 – 800 µg/l (dissolved in DMSO) evaluation performed at: (I) 274.4, 392, 560 µg/ml (+/- S-9) (II) 253.1, 337.5, 450 µg/ml (- S-9) 337.5, 450, 600 µg/ml (+ S-9)	negative (+/- S-9 mix)	*Marshall R.; 1997*
Unscheduled DNA synthesis assay in rat hepatocytes	0, 7.81, 15.6, 31.3 and 62.5 µg/ml (dissolved in DMSO)	negative	*Foster B.; 1992*
In vivo-studies			
Micronucleus test in CD-1 mice	0, 25, 125 and 625 mg/kg bw (single oral dose [gavage]; dissolved in 0.5 % aqueous methyl cellulose)	negative	*Edwards C. N.; 1992*
Non-standard genotoxicity studies (in vitro)			
GreenScreen HC GADD45a-GFP; CellCiphr p53; CellSensor p53 RE-bla	GreenScreen HC GADD45a-GFP: 50, 100 and 200 µM CellCiphr p53: 0.39 – 200 µM CellSensor p53 RE-bla: 1.2 nM – 92 µM Solvent for all three: DMSO	negative	*Knight, A.W. et al., 2009*

2.5.5. Summary of long-term toxicity and carcinogenicity

The long-term toxicity and carcinogenicity of triticonazole has been investigated in rats and mice.

In a 2-year combined chronic toxicity/carcinogenicity study in rats, continuous dietary administration of triticonazole produced clear evidence of toxicity at 5000 ppm. In addition to reduced body weight gain and reduced efficiency of food conversion, there were some changes in haematology and clinical chemistry in both sexes, and also histopathological non-neoplastic findings in the liver and the adrenal cortex. Changes in the eye lens (evident in males at 5000 ppm after 98 weeks of treatment only) were considered to be normal age-related changes and not an effect of treatment. Although the poor survival rate limits the value of the rat carcinogenicity study, there was no convincing evidence of any treatment-related hyperplastic or oncogenic response. Increased incidences of benign pituitary adenoma and keratoacanthoma of the skin were noted but were considered to be coincidental and not indicative of an oncogenic potential. Further evidence suggesting that triticonazole is not oncogenic is demonstrated by the lack of any oncogenic effect in the valid mouse carcinogenicity study and the negative genotoxicity studies. The NOAEL for this chronic toxicity/carcinogenicity study in the rat was considered to be 750 ppm (equivalent to 29.4 [♂] – 38.3 [♀] mg/kg bw per day).

In the mouse carcinogenicity study, continuous dietary administration of triticonazole for 78 weeks produced clear evidence of toxicity at 1500 ppm. Bodyweight gains were reduced during the majority of the dosing period and increased

liver weight was associated with histopathological non-neoplastic changes (hepatocytic fatty vacuolation).There was no indication of oncogenic potential at any dose level. On the basis of these results, the dose level of 150 ppm (equivalent to 17.4 [♂] and 20.1 [♀] mg/kg bw per day) can be considered a NOAEL of this study.

No effects on rodents were observed below the values of 25 mg/kg bw per day (chronic studies) and 12.5 mg/kg bw per day (carcinogenicity studies) which are considered as guidance values for potential classification of substances as STOT-RE 2 (specific target organ toxicity – repeated exposure). No treatment related neoplastic findings were observed in any of the studies. Therefore, triticonazole is considered not to be potentially carcinogenic substance.

Table 2.5.5.-1: Summarised results of long term toxicity/carcinogenicity studies

Study; Reference	Dose levels	NOAEL	Relevant effects at LOAEL
Chronic toxicity/ oncogenicity study in CD-rats; oral via diet for 99/100 weeks [redacted] *1994*	0, 5, 25, 750 and 5000 ppm (equivalent to 0, 0.2, 1.0, 29.4 and 203.6 mg/kg bw per day [♂] and 0, 0.3, 1.3, 38.3 and 286.6 mg/kg bw per day [♀])	29.4 (♂)/38.3 (♀) mg/kg bw per day	– reduced body weight gain – histological changes in adrenals (degeneration) and liver (fatty vacuolation) no oncogenic potential
Oncogenicity study in CD-1 mice oral via diet for 78 weeks [redacted] *1994*	0, 15, 150 and 1500 ppm (equivalent to 0, 1.8, 17.4 and 202.2 mg/kg bw per day [♂] and 0, 2.1, 20.1 and 209.5 mg/kg bw per day [♀])	17.4 (♂)/20.1 (♀) mg/kg bw per day	– reduced body weight gain – increased liver and adrenal weights – histological changes in liver and lymph nodes no oncogenic potential

2.5.6. Summary of reproductive toxicity

In the 2-generation reproduction study in rats, distinct parental toxicity was produced at the dietary concentration of 5000 ppm. Treatment-related findings in parental animals were recorded as premature deaths (F_0 females only), significant reduction in bodyweight gain and food consumption as well, and necropsy findings in adrenals, liver and ovary. Adverse effects on reproductive parameters at 5000 ppm included decreased mating and fertility index (F_1 generation). These effects were attributed to excessive systemic toxicity rather than to hormonal disturbance. Regarding offspring, increased pup mortality, decreased pup viability and decreased pup bodyweights were observed (F_0 and F_1). Effects observed at 5000 ppm are considered as consequence of distinct maternal toxicity at this very high dose level, exceeding the maximum tolerated dose. There were no significant parental, reproductive of offspring findings at 750 ppm which was considered the NOAEL for parental, reproductive and offspring effects.

In the range finding developmental study in rats (6 dams per dose group) triticonazole was applied up to 1250 mg/kg bw per day. Based on the toxicological response of dams (reduced body weight and body weight gain) and foetuses in utero (bilateral hydronephrosis) to a dosage of 1250 mg/kg bw per dayay, a dosage of 1000 mg/kg bw per dayay was suggested as a suitable top dose to be used in the main prenatal developmental toxicity study in rats. The NOAEL of the range finding study is proposed at 250 mg/kg bw per day (mid dose) for both maternal and developmental toxicity.

In the teratology study in rats, there was evidence of maternal toxicity at 1000 mg/kg bw per day, observed as reductions in body weight gain and food consumption. Foetal survival and growth was not affected in any dose group. However, there was an apparently increase in the incidence of foetuses with an additional 13/14th rib or pair of ribs at all dose

levels, but this was only outside the historical background range at 1000 mg/kg bw per day. This finding was attributed to maternal toxicity. No treatment-related teratogenic effect was observed at any dose level. The NOAEL for both maternal and developmental toxicity was set by RMS (2016) at 200 mg/kg bw per day.

A tolerance study in rabbits (no OECD GD) was conducted by gavage at different dosing regimens and with low number of animals (two per group). It was concluded from this investigation that dosages of triticonazole for use in a preliminary teratology study in the rabbit should not exceed 50 mg/kg bw.

A range finding developmental study in rabbits (7-8 animals per group) was conducted at gavage doses of 5, 15, 50, 75 and 150 mg/kg bw per day. All females at 150 mg/kg bw per dayay were terminated prematurely due to animal welfare reasons. The maternal NOAEL is proposed at 5 mg/kg bw per day, based on dose-related (slight) body weight loss (days 6 to 8) at ≥ 15 mg/kg bw per day. Fetal NOAEL is proposed at 50 mg/kg bw per day, based on increased post-implantation loss, resorptions and increased limb flexures (external examination)at 75 mg/kg bw per day.

A rabbit developmental toxicity study was conducted at gavage doses of 5, 25, 50 and 75 mg/kg bw in New Zealand rabbits. Triticonazole caused body weight losses and decreased food consumption in pregnant rabbits at doses ≥ 25 mg/kg bw per day. Both top doses (50 and 75 mg/kg bw caused excessive maternal toxicity indicated by deaths, abortions, decreased faeces and an increased respiration rate. At the top dose group 30 % maternal mortality was observed. Concerning foetal findings, a slight increase in both pre- and post-implantation losses was observed at 75 mg/kg bw, which is considered to be related to maternal toxicity. Increased incidences of precocious ossification of acromion process (=elongation of acromion process) were seen at ≥ 25 mg/kg bw per day. The precocious ossification of the acromion process is of low severity, as this part of the scapula is ossified during development of the offspring and an earlier ossification has no impact on survival or quality of life. In the top dose increased incidences of variations of the midline anterior cranial bones, rudimentary floating 13th rib, and reduced/incomplete ossification of metacarpals and phalanges (also at 50 mg/kg bw) were seen at excessive maternal toxic doses. As these variations occur only in the presence of excessive maternal toxicity, they are not indicative of a specific teratogenic response of triticonazole. There was no teratogenic effect observed at any dose level. On the basis of these results, the dose level of 5 mg/kg bw per day can be considered the maternal and the foetal NOAEL as well.

Triticonazole showed no effects on mortality, blood vessel development, and blood vessels discoloration in the Chicken Embryotoxicity Screening Test (CHEST) under the conditions reported. Reduced embryo development (incidence of 4% compared to vehicle control) was slightly above the laboratory historical control data (2%) for animals treated with the highest dose.

Results from the literature data show that triticonazole had a toxic potential on the zebra fish embryo/larvae indicated by nonviable larvae or larvae that did not hatch at concentrations >20 µM. However, no malformations were observed in the larvae after exposure to triticonazole. Triticonazole was found to be the least potent triazole with regard to general developmental and to specific teratogenic endpoints in a zebrafish embryotoxicity test, where zebrafish embryos have been evaluated 72 h post fertilization. Triticonazole was considered to be non-embryotoxic, based on very little morphological changes induced in zebra fish embryos. The results of the gene expression data and the concentration-response genes correlated to GMS (general morphology score) suggest that triticonazole has the least unwanted effects – compared to other tested triazoles – with respect to developmental toxicity. In the Embryonic stem cell test (EST) triticonazole was the lowest potent compared to the other tested triazoles. In the Whole embryo culture (WEC)

triticonazole was the second-least potent compound. WEC, EST and ZET assays correctly identified the potency of triticonazole for developmental effects, based on in vivo data, as triticonazole did not induce malformations such as cleft palate, renal malformations and hydrocephaly.

No effects on rodents were observed below MTD which are considered relevant for potential classification of substance as reproductive toxicant. Therefore, triticonazole is considered not to be potentially reprotoxic substance with regard to effects observed in multigeneration studies. Neither in rat nor in rabbit teratogenic/ developmental effects were observed which would justify classification for developmental toxicity.

Table 2.5.6-1 Summarised results of reproductive toxicity/developmental toxicity

Study ***Reference***	**Dose levels**	**NOAEL**	**Relevant effects at LOAEL**
Two-generation study in rats (Sprague Dawley CD) [redacted] *1993*	0, 5, 25, 750 and 5000 ppm equivalent to 0, 0.34 (♂) – 0.32 (♀), 1.64 (♂) – 1.59 (♀), 49.35 (♂) – 48.41 (♀) and 350.8 (♂) – 337.6 (♀) mg/kg bw per day	Parental: 49.35 (♂) – 48.41 (♀) mg/kg bw per day Reproductive: 49.35 (♂) – 48.41 (♀) mg/kg bw per day Offspring: 49.35 (♂) – 48.41 (♀) mg/kg bw per day	Parental effects: – mortalities – decreased weight gain – necropsy findings (histopathology and organ weights) in adrenals, ovaries and liver Fertility effects: – decreased mating and fertility indices Litter data: – decreased pup body weight – decreased livebirth and viability indices
Range finding developmental study in rats (Sprague Dawley CD) [redacted] *1990*	0, 50, 250 and 1250 mg/kg bw per day	Maternal NOAEL 250 mg/kg bw per day Foetal NOAEL 250 mg/kg bw per day	Maternal toxicity: – reduced body weight and body weight gain Foetal toxicity: – bilateral hydronephrosis
Teratogenicity study in rats (Sprague Dawley CD) [redacted] *1991(a)*	0, 40, 200 and 1000 mg/kg bw per day	Maternal NOAEL 200 mg/kg bw per day Foetal NOAEL 200 mg/kg bw per day	Maternal toxicity: – reduced body weight gain Foetal toxicity: – additional 13/14th ribs
Tolerance study in rabbits (New Zealand White) [redacted] *1990*	Group I (500 mg/kg bw, non-pregnant animals) Group II (variable dose, non-pregnant animals) Group III (50 mg/kg bw pregnant animals)	Dosage in a preliminary teratology study in the rabbit should not exceed 50 mg/kg bw	-

Study *Reference*	Dose levels	NOAEL	Relevant effects at LOAEL
Range finding developmental study in rabbits (New Zealand White) [redacted] *1990*	0, 5, 15, 50, 75 and 150 mg/kg bw per day	Maternal: 5 mg/kg bw per day Foetal: 50 mg/kg bw per day	Maternal toxicity: – decreased body weight and food consumption -slight body weight loss (d 6 to 8) Foetal toxicity: – increased skeletal abnormalities
Teratogenicity study in rabbits (New Zealand White) [redacted] *1991(b)*	0, 5, 25, 50 and 75 mg/kg bw per day	Maternal: 5 mg/kg bw per day Foetal: 5 mg/kg bw per day	Maternal toxicity: -slight body weight loss (d 6 to 8) Foetal toxicity: – increased implantation loss

2.5.7. Summary of neurotoxicity

Triticonazole does not belong to a chemical family for which testing for delayed neurotoxicity is required. However, there was indication of neurotoxicity seen at the top dose in the 52-week dog study (tremors, ataxia, convulsions), but no microscopic findings in brain, spinal cord or isciatic nerves were observed.

For further clarification, studies on neurotoxicity after acute and repeated oral exposure to rats have been performed: In the acute oral (by gavage) neurotoxicity study in rats, no evidence for neurotoxicity was seen up to dose levels of 2000 mg/kg bw. Also after repeated dose administration via the diet, no neurobehavioral or neuromorphological effects occurred following 13 weeks of continuous exposure. The NOAEL for neurotoxic effects in 13 week rat study is > 10000 ppm (695.11 mg/kg bw per day for males and 820.3 mg/kg bw per day for females).

2.5.8. Summary of toxicological data on impurities and metabolites

2.5.8.1. Metabolites

Table 2.5.8.1-1: Summary table for prediction of Ames mutagenicity for triticonazole and its metabolites using CASE Ultra models

Substance name	Experimental	Konsolidator Outcome [1]	GT1_A7B Salmonella[2]	GT1_ A7B Salmonella Trained [3]	GT1_Ecoli[2]	GT1_Ecoli Trained[3]	GT Expert[2]
BAS 595 F	negative	Negative[4]	Negative[4]	Known negative	Negative[4]	Known negative	Negative[4]
M595F001 and M595F002	negative	Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]
M595F004-1		Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]
M595F004-2		Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]
M595F005		Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]
M595F006	Covered by parent	Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]
M595F007		Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]
M595F010	Glucuronide of M595F006	Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]
M595F013		Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]	Negative[4]

M595F014	**negative**	**Negative[4]**	**Negative[4]**	**Known negative**	**Negative[4]**	**Known negative**	**Negative[4]**
M595F015-1		**Negative[4]**	**Negative[4]**	**Negative[4]**	**Negative[4]**	**Negative[4]**	**Negative[4]**
M595F015-2		**Negative[4]**	**Negative[4]**	**Negative[4]**	**Negative[4]**	**Negative[4]**	**Negative[4]**
Reg 4710773	**negative**	**Negative[4]**	**Negative[4]**	**Negative[4]**	**Negative[4]**	**Negative[4]**	**Negative[4]**

1 Konsolidator model provided with Case Ultra; combines evaluation from the two basic statistical models GT1_A7B and GT1_E.coli with the results from the rule based model GT_Expert; this is than supplemented with a comparison to experimental data from a structure database of >11.000 chemicals

2 Models as provided with CASE Ultra version 1.6.0.

3 Models were trained with data extracted from EFSA conclusions (period 2006 to 2016) and further expanded by BASF proprietary data to enter the chemical space of plant protection products into the models

4 Negative predictions or experimental values by/in the models are depicted **bold**

Table 2.5.8.1-2: Summary table for prediction of DNA damage for triticonazole metabolites

Substance name	Case Ultra in vivo MNT prediction[1]	Toxtree[2]
BAS 595 F	**Known Negative[3]**	**Negative[3]**
M595F001 and 002	**Negative[3]**	**Negative[3]**
M595F004-1	**Negative[3]**	**Negative[3]**
M595F004-2	**Negative[3]**	**Positive[4,5]**
M595F005	**Negative[3]**	**Negative[3]**
M595F006	**Negative[3]**	**Negative[3]**
M595F007	**Negative[3]**	**Negative[3]**
M595F010	**Negative[3]**	**Negative[3]**
M595F013	**Negative[3]**	**Negative[3]**
M595F014	**Known Negative[3]**	**Negative[3]**
M595F015-1	**Negative[3]**	**Negative[3]**
M595F015-2	**Negative[3]**	**Negative[3]**
Reg.No 4710773	**Negative[3]**	**Negative[3]**

1 CASE Ultra predictions depicted are those performed with the model GTS_MNT_Trained_PPPs plus BASF, as this model is most representative for the chemical space of DMPT and its metabolites; the basic in vivo MNT model was not predictive for triticonazole and/or other azoles

2 Toxtree Version 2.6; Structural alert SA 34: H-acceptor-path3-H-acceptor is disregarded as mentioned in the guidance document for plant residues; chemicals only displaying SA 34 are depicted as negative

3 Negative in domain predictions are depicted in **bold**

4 Positive in domain predictions are depicted underscored

5 Positive alert for Toxtree stems from the structural alert SA10, alpha, beta unsaturated carbonyls; this structural alert is not supported by the information extracted from the trained Case Ultra model; This structural alert is frequently observed in pesticides and larger molecules like unsaturated fatty acids which are not mutagenic and do not have chromosome damaging properties. This alert is largely valid for short molecules where the double bound is not stabilized by mesomeric effects. This is indirectly confirmed by the negative prediction in the Ames Expert module.

Additionally to QSAR analysis for genotoxicity, following studies on metabolites are available:

M595F002 (Reg. 5059144, RPA 406341)

Acute oral LD_{50} of RPA 406341 in male and female rats was above 2000 mg/kg bw. RPA 406341 did not induce gene mutation in bacteria in the AMES test.

M595F014 (Z-isomer, Reg. 5079359, RPA 406203)

Acute oral LD_{50} of RPA 406203 in male and female rats was above 2000 mg/kg bw. RPA 406341 did not induce gene mutation in bacteria in the AMES test. RPA 406203 was also negative in *in vitro* mouse micronucleus assay.

Only metabolite M595F004-2 has shown a positive alert in Toxtree for clastogenic effects (but not in Case Ultra). However, even if calculated against the genotoxicity TTC of 0.0000025 mg/kg bw per day, this threshold was not exceeded.

Neither any single metabolite nor sum of all metabolites exceeded acute and chronic TTC of 5 µg/kg bw/d and 1.5 µg/kg bw/d.

Metabolite M595F006 is considered to be covered by parent triticonazole since it was measured > 10% of absorbed dose. M595F010 is glucuronide of M595F006 and therefore considered to be also covered by triticonazole.

RMS (fate and behaviour section) identified a metabolite fraction called "MET 6 (MWT 333)", which might occur in groundwater < 0.2 µg/l. The potential metabolite(s) belonging to this fraction is/are not yet identified, but based on the molecular weight it is strongly assumed that it is a mono-hydroxylated parent triticonazole.

All currently identified mono-hydroxylated metabolites of triticonazole (M595F001, M595F002, M595F004, M595F007, M595F013), hydroxylated on different part of parent molecule and investigated based on their occurrence in residues of plant and animal origin, were devoid of any genotoxic concern (proven in an extensive QSAR evaluation; for details please see B.6.8.1). Although it is not *a priori* expected that unidentified fraction "MET 6 (MWT 333)", assumed to be a mono-hydroxylated parent, is a fraction of genotoxic concern, this assumption cannot be currently substantiated by data (since no identification has been done yet).

2.5.8.2. Impurities

[redacted]

Acute oral and dermal LD_{50} of [redacted] in male and female rats was above 2000 mg/kg bw. [redacted] did not induce gene mutation in bacteria in two AMES tests and it was negative in *in vitro* micronucleus assay in human lymphocytes. Mouse lymphoma assay was positive (a reproducible and dose-related shift in the ratio of small versus large colonies). TK6 assay in human lymphoblastoid cells was negative.

The NOAEL in the 14 days comparative study [redacted]) was 100 mg/kg bw per day for both [redacted] and triticonazole.

[redacted]

[redacted] did not induce gene mutation in bacteria in two AMES tests (one with technical impurity and one with triticonazole and spiked impurities).

[redacted] did not induce gene mutation in bacteria in one AMES test with triticonazole and spiked impurities.

[redacted] did not induce gene mutation in bacteria in one AMES test with triticonazole and spiked impurities.

Acute oral and dermal LD_{50} of [redacted] in male and female rats was above 2000 mg/kg bw. [redacted] did not cause eye or skin irritation or skin sensitization. In the 5 days range finding study no NOAEL was discussed in the study report. In the 28 days study no NOAEL could be determined since at the lowest tested dose (50 mg/kg bw per day) increase in relative liver weight > 10% in females and centrilobular hypertrophy in 1/6 females was observed. [redacted] did not induce gene mutation in bacteria in the AMES test or chromosomal aberrations in cultured human lymphocytes.

Methanol

Based on its intrinsic toxicological properties in comparison to triticonazole, methanol is considered a toxicologically relevant impurity.

The harmonized classification (CLP regulation EC 1272/2008) regarding toxicological properties of methanol is acutely toxic by oral, dermal and inhalation route (Acute Tox 3, H301, H311 and H331) and specific target organ toxicity by single exposure (STOT SE 1, H370).

A reference value for long-term systemic exposure (DNEL) via dermal route of 6.66 mg/kg bw per dayay is proposed for the general population and a value of 40 mg/kg bw per dayay for worker. The exposure assessment with methanol towards a derived reference value shows the exposure towards zero for all concerned groups.

2.5.9. Summary of supplementary studies on the active substance

2.5.9.1. Immunotoxicity

Triticonazole did not reveal any signs of immunotoxicity when administered via the diet over a period of 4 weeks to female Wistar rats. The NOAEL for the immunotoxicity was determined to be 5000 ppm (462 mg/kg bw per dayay; highest dose tested). The NOAEL for systemic toxicity was set to 1500 ppm (162 mg/kg bw per dayay), based on treatment-related changes (reduced body weight (gain) and increased absolute and relative liver weights) in the next higher dose group (5000 ppm). Although no effects on immune system were observed it is noted that a study of longer duration (no effects on adrenals were observed after oral 28 days range-finding study in rats) with inclusion of parameters for non-specific immune system maybe could have provided more information on the effects of triticonazole on adrenal insufficiency and immune system.

2.5.9.2. Pharmacology

In the general pharmacology study (data requirement for Japan) triticonazole did not affect the general behavior of mice and rats. In the cardiorespiratory system, no effects were noted on the respiratory parameters in rats. Blood pressure was elevated transitory in rats treated with 2000 mg triticonazole/kg bw.

2.5.9.3. Hepatotoxicity

Based on submitted literature data triticonazole was active in 4 assays (CYP1A1/2, CYP3A4, and CYP2B6), indicating that triticonazole may induce expression of mRNA that is mediated by the CAR/PXR or AhR receptors. In the second published study with regard to gene expression, triticonazole induced it only via PXR receptor, no other active signal was seen in other investigated nuclear receptors (among them AhR, AR, ER, CAR, and PPAR). Further triticonazole showed a slight induction of Cyp2B6, inducing mRNA. This is in concordance to the activation of the PXR receptor. Triticonazole was inactive in all Tox21 assays and showed no induction or inhibition of the reporter gene through the nuclear receptors AR, Era, FXR, PPARd and PPARg. Triticonazole was found to bind to the human and the chimpanzee AR receptor although no transactivation through the AR receptor was detected.

As triticonazole did not induce liver tumors, the results on receptor activation and Cyp2B6 induction are of minor relevance for the hazard assessment of triticonazole. Further, the ability of triticonazole to bind to the androgen receptor is of limited relevance as no gene expression via transactivation through the AR receptor was detected.

2.5.10. Summary of studies on endocrine disruption

Table 2.5.10-1 Summarised results of studies on endocrine disruption*

Study *Reference*	Dose levels	Results
ACTH challenge assay in rats *Beerens-Heijnem, C.G.M., 2016*	0, 80, 750 and 5000 ppm equivalent to 0, 6, 59, 412mg/kg bw per day in males 0, 7, 68 and 479 mg/kg bw per day in females	Mechanistic study; no effects on corticosterone excretion after the ACTH challenge up to 5000 ppm
YAS assay *Woitkowiak C., 2012*	10^{-10}, 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5} and 10^{-4} mol/L	No androgenic/antiandrogenic activity
YES assay *Woitkowiak C., 2012*	10^{-10}, 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5} and 10^{-4} mol/L	No estrogenic/antiestrogenic activity
Aromatase inhibition *Mentzel T., 2015*	10^{-11}, 10^{-10}, 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5} and 10^{-4} mol/L	Human aromatase IC50 [M]: 4.40 x 10-5 Rat aromatase IC50 [M]: 1.8 x 10-6

*Results from public data not included in the table of BASF studies but summarized below. The studies are described in Vol 3, B.6.8.3.5.

In order to identify if morphological changes in *zona fasciculata* also lead to functional impairment of adrenals, especially regarding corticosterone production, a 90-days ACTH challenge assay in rats was conducted. In the ACTH assay no impairment of corticosterone excretion after ACTH challenge was measured although morphological changes in adrenals (vacuolation in *zona fasciculata* in males and degeneration/regeneration in *zona fasciculata/regularis* in females) were observed in all animals treated with 5000 ppm. However, these morphological changes were not an evidence of marked ACTH overstimulation as this would inevitably results in adrenal hypertrophy and frank increases in gland size and weight, which was not observed. The lack of large increases in adrenal weight/hypertrophy supports the thesis that an adequate glucocorticoid competency remained. While there is no evidence for blockage of steroidogenesis and glucocorticoid production as a possible mode of action of triticonazole, the most likely explanation for adrenal toxicity is reversible direct cytotoxicity.

Also the steroidogenesis assay conducted under ToxCast program (Karmaus et al., 2016) did not give evidence for a blockage of steroidogenesis or glucocorticoid production. There was some evidence for decreased cortisol levels in the H295R cell line with an AC_{50} of 4.48 µM, however the decreased levels are only seen at and above cytotoxic concentrations of triticonazole (2.27 µM), diminishing the specificity and relevance of this finding. A *decrease* in a hormone signal is plausibly explainable by systemic cell toxicity, especially if an activity is only seen at cytotoxic concentrations. Further no changes are seen for any of the androgenic or estrogenic hormones in this very sensitive steroidogenesis assay.

In the Level 2 ED studies there is no evidence for triticonazole having estrogenic or anti-estrogenic activity, neither in the ToxCast data nor in the YES assay conducted. Also the assays run in the H295R cells under the ToxCAST program, indicative for effects on the steroidogenesis, did not reveal any evidence for decreased testosterone or estrogen levels, although the test itself is considered to be more sensitive compared to an OECD TG 456.

The tests for androgenicity/anti-androgenicity gave some conflicting results. While the ToxCast data indicate binding properties of triticonazole to chimpanzee and human androgen receptor with an IC50 of 0.68 and 0.91 µM respectively, the assays indicative for a protein stabilization were positive only at or above cytotoxic concentrations. Further, there was no indication for an activity of the androgen receptor by triticonazole from the ToxCast data. There are two further androgen receptor reporter gene assays available. One in human breast cancer cell line T47D-ARE transfected with a firefly luciferase reporter gene (Roelofs et al., 2014) and one in yeast strain PGKhAR containing a gene for the human androgen receptor and an androgen responsive element of the reporter gene lacZ (Woitkowiak, 2012). Triticonazole showed a decrease in the androgen receptor activation with an IC_{50} of $1.07E^{-05}$ M in the T47D-ARE and was inactive in the YAS assay, tested up to 10^{-04} M. In a further published test system, a concentration of 10 µM triticonazole led to decreases in testosterone secretion in murine MA-10 cells (tumorigenic Leydig cell line) (Roelofs et al., 2014). No data on cytotoxicity of triticonazole were presented in this publication, while from the ToxCast data a cytotoxicity of 2.27 µM has been determined for triticonazole. Further, the only validated test system is the YAS assay, as the ToxCAST data are neither peer-reviewed, nor were the results finally interpreted, as the ToxCAST database is still under development. Summarizing the evidence for an (anti)-androgenic mode of action of triticonazole, there is an indication in the ToxCAST database that triticonazole has binding properties to the chimpanzee and human androgen receptor. All other assays were either negative or indicated *in vitro* activity only at very high and/or cytotoxic concentrations. Thus there is no evidence that a specific anti-androgenic mode of action has contributed to the

observed reproduction effects in the 2-Generation toxicity study, which can be well explained by general systemic toxicity.

No effects on thyroid hormone receptors and no inhibition of TPO or deiodinase type 1 enzyme activity were observed for triticonazole in the US EPA ToxCast screening programme.

Triticonazole is considered devoid of ED properties, based on available regulatory studies and supplementary data. Detailed interpretation of all results is included in Volume 3, CA, B.6.8.4.6.

2.5.11. Summary of medical data and information

No human cases of intoxication or poisoning deriving from triticonazole are known to BASF SE.

Neither data on exposure of the general public nor epidemiologic studies on triticonazole are available for BASF SE, nor is BASF SE aware on any epidemiologic studies performed by third parties.

2.5.12. Toxicological end point for assessment of risk following long-term dietary exposure - ADI

The estimation of the Acceptable Daily Intake (ADI) is based on the lowest no-observed adverse effect level (NOAEL) observed in subchronic and chronic toxicity, neurotoxicity, carcinogenicity and reproduction studies with triticonazole. Given the results from all relevant studies, the lowest NOAEL of 2.5 mg/kg bw per day was found in the 52-week dog study. This NOAEL was based on decreased terminal body weight in females (87% of control), increased ALP and decreased plasma protein in females and histopathological findings in adrenals (males and females), all effects observed at 25 mg/kg bw per day.

It can be concluded that triticonazole exhibits no mutagenic, teratogenic; neurotoxic or oncogenic potential. In the 2-generation reproductive study in the rat, signs of reproductive toxicity were evident only at the top dose level (5000 ppm; equivalent to 337.6 mg/kg bw per day), which is by far exceeding the maximum tolerated dose. Therefore, in agreement with the conclusion from DAR (2003) and EFSA Conclusion (2005) it is confirmed in DRAR (2016) to apply an uncertainty factor of 100 to the NOAEL of 2.5 mg/kg bw per day from the dog study mentioned, resulting in an **ADI of 0.025 mg/kg bw per day**.

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

For the determination of the Acute Reference Dose (ARfD), results from oral studies that used acute or short term exposure are considered to be the most relevant. Triticonazole is of low acute oral toxicity. There was also no evidence of genotoxicity, neurotoxicity or teratogenicity seen in relevant studies. However, in the rabbit teratology study, dose-related maternal body weight losses were observed at dose levels of 25, 50 and 75 mg/kg bw per day triticonazole during the first two days of treatment. This effect can be considered as a result from an acute oral exposure. Bodyweights of animals receiving 5 mg/kg bw per day were unaffected by treatment. This dose level was also the maternal (and foetal) NOAEL for the study.

An **ARfD of 0.05 mg/kg bw per day** from DAR (2003) and EFSA Conclusion (2005) is confirmed in DRAR (2016) for triticonazole based on applying a 100-fold assessment factor to the NOAEL of 5 mg/kg bw per dayay, determined in the teratology study in rabbits.

2.5.14. Toxicological end point for assessment of occupational, bystander and residents risks – AOEL

The proposed acceptable operator exposure level should be established on the basis of the lowest dose at which no adverse effect is observed in relevant studies in the most sensitive species. The setting of an AOEL is usually based on mid-term studies (i.e. subacute/ subchronic and reproduction or developmental toxicity studies) since these studies in most cases can be considered a more appropriate model for the actual operator exposure to be expected.

As already stated in the proposal for ADI, the lowest NOAEL of all relevant studies was found in the 52-week dog study, which is considered a mid-term study. This NOAEL of 2.5 mg/kg bw per day was based on decreased terminal body weight in females (87% of control), increased ALP and decreased plasma protein in females and histopathological findings in adrenals (males and females), all effects observed at 25 mg/kg bw per day.

Since the oral absorption of triticonazole is considered to be extensive, no correction for oral absorption is required. It is also considered appropriate (DRAR 2016) to confirm the conclusion from DAR (2003) and EFSA Conclusion (2005) to use a 100 fold assessment factor resulting in a systemic **AOEL of 0.025 mg/kg bw per day.**

2.5.15. Toxicological end point for assessment of occupational, bystander and residents risks – AAOEL

According to Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products (EFSA, 2014) AAOEL is a term used to describe a reference value against which acute non-dietary exposures (i.e. those that might be incurred in a single day) could be assessed. This would be relevant only to those plant protection products for which such exposures might produce significant toxicity.

Currently there is no standardised or harmonised procedure and no Guideline for derivation of AAOEL.

Triticonazole is of low acute oral toxicity. There was also no evidence of genotoxicity, neurotoxicity or teratogenicity seen in relevant studies. Only in the rabbit teratology study, dose-related maternal body weight losses were observed at dose levels of 25, 50 and 75 mg/kg bw per day triticonazole during the first two days of treatment. Bodyweights of animals receiving 5 mg/kg bw per day were unaffected by treatment. This dose level was also the maternal (and foetal) NOAEL for the study.

For following reasons RMS is of the opinion that no AAOEL has to be set for triticonazole if applied only in seed treatment products:

- Triticonazole is not acutely toxic substance, nor it produces local effects
- Triticonazole is an active substance used for seed treatment under professional working conditions in seed treatment plants and where exposure to innocent bystanders and residents is not given.
- The exposure during the seed treatment is not calculated according to EFSA Model but according to SeedTropex and its modifications where no AAOEL as reference value is reflected
- The exposure estimation of triticonazole with the AOEL of 0.025 mg/kg bw per day revealed safe use

- Using ARfD (0.05 mg/kg bw per day) as surrogate for AAOEL would only reduce the exposure estimations in SeedTropex
- Effects of triticonazole used to derive ARfD (body weight losses in pregnant rabbits during the first two days of treatment) are considered less relevant to seed treatment plants where no general public is exposed

However, according to several EU national registers, triticonazole is also formulated (by other applicants) in products applied on ornamentals. Therefore it is concluded that beside representative uses and products formulated by BASF, there are other application regimes which might need a comparison of the exposure to the AAOEL.
RMS proposes to derive the **AAOEL same as ARfD (0.05 mg/kg bw per day)**.

2.5.16. Summary of product exposure and risk assessment

2.5.16.1. Operator exposure

According to the UK and French SeedTropex model calculations, it can be concluded that the risk for the operator using BAS 595 01 F to treat cereal seeds is acceptable with the use of personal protective equipment. A higher tier exposure assessment which addresses both static seed treatment plants and on-farm treatments carried out using mobile seed treatment equipment confirms levels of exposure for seed treatment operators are within the AOEL and AAOEL. This higher tier assessment is based on exposure studies which are more representative in terms of application rate to BAS 595 01 F than the SeedTropex studies and is therefore expected to give more realistic estimates of exposure for seed treatment operators using BAS 595 01 F. Protective gloves and coveralls should be worn during mixing/loading, calibration and cleaning operations. Suitable protective clothing (coveralls) should be worn during bagging operations. An impermeable coverall, in addition to work clothing, should be worn during cleaning operations.
The updated estimates based on the revised SeedTropex model (Version 15 of 2014) further substantiate the safe use for seed treatment of cereals with triticonazole when applied in BAS 595 01 F. The estimates considered coveralls worn during mixing/loading, calibration and bagging operations. An impermeable coverall, in addition to work clothing and protective gloves were considered during cleaning operations.
Estimates of exposure for triticonazole for operators sowing BAS 595 01 F treated seed are within the AOEL where protective clothing (coveralls) are worn during the seed sowing operation. This conclusion was confirmed by the updated estimates based on the revised SeedTropex sowing model, additionaly including the safe use after acute exposure (AAOEL).

Table 2.5.16-1: Estimated operator exposure to triticonazole from use of BAS 595 01 F during seed treatment

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of AOEL
Product used undiluted. Application rate = 5 g a.s./100 kg seed.			
UK SeedTropex Model 60 kg operator	Gloves and coveralls worn during mixing/loading, calibration and cleaning. Coveralls worn during bagging.	0.0097	39
Product diluted 1:5 Product:Water. Application rate = 5 g a.s./100 kg seed.			

UK SeedTropex Model 60 kg operator	Gloves and coveralls worn during mixing/loading, calibration and cleaning. Coveralls worn during bagging.	0.0061	24
Product used undiluted. Application rate = 5 g a.s./100 kg seed.			
France SeedTropex Model 70 kg operator	Gloves and coveralls worn during mixing/loading, calibration and cleaning. Coveralls worn during bagging. RPE worn during cleaning.	0.0137	55
Product diluted 1:5 Product:Water. Application rate = 5 g a.s./100 kg seed.			
France SeedTropex Model 70 kg operator	Gloves and coveralls worn during mixing/loading, calibration and cleaning. Coveralls worn during bagging. RPE worn during cleaning.	0.0172	69

Table 2.5.16-2: Estimated operator exposure to triticonazole from use of BAS 595 01 F during seed treatment using higher tier data

Scenario	Level of PPE	Total absorbed dose* (mg/kg/day)	% of AOEL
Static seed treatment	Cotton/polyester work clothing for mixing/loading, calibration and bagging. An impermeable coverall is worn over work clothing with suitable protective gloves during cleaning operations	6.3×10^{-5}	0.25
Mobile seed treatment	Cotton/polyester work clothing and suitable protective gloves for mixing/loading, calibration and bagging.	7.9×10^{-5}	0.32

*Assumes 3% dermal absorption

Table 2.5.16-3: Estimated operator exposure to triticonazole from use of BAS 595 01 F during seed treatment using updated SeedTropex model approach

Long-term exposure assessment			
Scenario	**Level of PPE**	**Total absorbed dose* (mg/kg/day)**	**% of AOEL**
Static seed treatment (75th percentile)	Cotton/polyester work clothing for mixing/loading, calibration and bagging. An impermeable coverall is worn over work clothing with suitable protective gloves during cleaning operations	0.00116	4.7
Mobile seed treatment (75th percentile)	Cotton/polyester work clothing for mixing/loading, calibration and bagging.	0.00078[5]	3.1
Acute exposure assessment			
Scenario	**Level of PPE**	**Total absorbed dose* (mg/kg/day)**	**% of AAOEL**
Static seed treatment (95th percentile)	Cotton/polyester work clothing for mixing/loading, calibration and bagging. An impermeable coverall is worn over work clothing with suitable protective gloves during cleaning operations	0.00394	7.9
Mobile seed treatment (95th percentile)	Cotton/polyester work clothing for mixing/loading, calibration and bagging.	0.00775	15.5

*Assumes 1% dermal absorption mixing/loading and 3% dermal absorption for all other operations

Table 2.5.16-4: Estimated operator exposure to triticonazole from sowing seed treated with BAS 595 01 F

Dermal exposure (mg/day)	**Inhalation exposure (mg/day)**	**Total systemic exposure* (mg/kg bw per dayay)**	**AOEL (mg/kg bw per dayay)**	**% AOEL**
Triticonazole				
7.33	0.2	0.007	0.025	28

*Assumes 3% dermal absorption

Table 2.5.16-5: Estimated operator exposure to triticonazole from sowing seed treated with BAS 595 01 F using updated SeedTropex model approach

Long-term exposure assessment				
Dermal exposure (mg/kg bw per dayay)	**Inhalation exposure (mg/kg bw per dayay)**	**Total systemic exposure* (mg/kg bw per dayay)**	**AOEL (mg/kg bw per dayay)**	**% AOEL**
0.124	0.0014	0.0037	0.025	15
Acute exposure assessment				
Dermal exposure (mg/kg bw per dayay)	**Inhalation exposure (mg/kg bw per dayay)**	**Total systemic exposure* (mg/kg bw per dayay)**	**AAOEL (mg/kg bw per dayay)**	**% AAOEL**
0.256	0.0031	0.0076	0.05	15

*Assumes 3% dermal absorption

2.5.16.2. Bystander and resident exposure

Dressing of seeds with BAS 595 01 F is typically performed in professional plants, where persons whose presence is quite incidental and unrelated to the work (i.e. bystanders) will not be present. However, workers who are not directly involved in the seed treatment process, such as forklift operators, may be present.

During loading/sowing of the seed treated with BAS 595 01 F it is highly unlikely that bystander exposure will occur. However, even in the theoretical case that exposure to dust from the treated seed could occur, e.g. as treated seed is loaded into the seed drill hopper, levels of exposure for bystanders would not be expected to exceed those of operators involved in bagging treated seed, where exposure is predominately from airborne dust. For operators wearing a single layer of clothing and no gloves the predicted exposures for this task (5.58 mg/person dermal exposure and 0.043 mg/person inhalation exposure) were within acceptable levels for triticonazole (14% of the AOEL), using the UK SeedTropex model. Levels of exposure for forklift operators are predicted to be 4% of the AOEL assuming a 10 hour working day and a 60 kg body weight.

Table 2.5.16.2-1: Estimated exposure to triticonazole for forklift operators working in seed treatment plants

Dermal exposure (mg/day)	Inhalation exposure (mg/day)	Total systemic exposure* (mg/kg bw per dayay)	AOEL (mg/kg bw per dayay)	% AOEL
1.4	0.016	0.001	0.025	4

*Assumes 3% dermal absorption for triticonazole

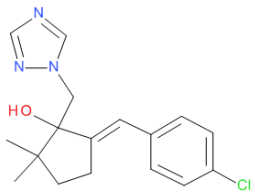
2.5.16.3. Worker exposure

There is no worker re-entry scenario for this product. Estimated operator exposure to triticonazole from sowing seed treated with BAS 595 01 F is maximum 28% of the AOEL for triticonazole. By applying revised SeedTropex, acute and long-term exposure is calculated to be 15% of the AOEL (75^{th} percentiles) and AAOEL (95^{th} percentiles).

2.6. RESIDUE

Triticonazole belongs to the class of conazole fungicides. Triticonazole can be used only as fungicide and it is used for the control a broad range of fungi belonging to several groups of plant pathogens (Ascomycetes, Adelomycetes, Basidiomycetes) in wheat seeds. Triticonazole is taken up slowly by the seedlings via the seed, teguments and roots and act as a C-14 demethylation inhibitor in the sterol biosynthesis pathway. The soil around the roots acts as a reservoir to feed the plant with triticonazole for several months after sowing.

Notations of parent triticonazole

Code Number		Description		Relevant compartments	Structure
Manufacturing code	**Reg No.**	**Chemical name**	**CAS-No.**		
BAS 595 F Triticonazole former BAS 9318 F RPA 400727 M595F000	43785 13	(*RS*)-(*E*)-5-(4-chlorobenzylidene)-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol	131983-72-7	Rat Livestock (goat) Plant Fish Rot Crop Soil Surface water	

Triticonazole is a **racemic mixture** of the two enantiomers (R)-(5E)-5-(4-chlorobenzylidene)-2,2-dimethyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol and (S)-(5E)-5-(4-chlorobenzylidene)-2,2-dimethyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol. The minimum purity of the dry material (racemate) is 950 g/kg.

The ratio of the enantiomers in the technical material and in formulations **(racemic mixture; 1:1 ratio) is deemed to be stable**.

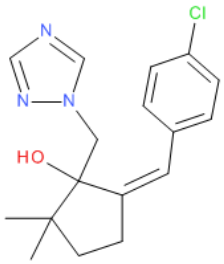
The Z-isomer, which could theoretically exist due to the E/Z-isomerism at the double bond, is not included in the definition of the active substance and is not observed in the technical material.

All studies were done with the racemic mixture of Triticonazole. There are no detectable residues of Triticonazole at harvest, therefore a separation of enantiomers was not necessary.

Due to the planned use as seed treatment, triticonazole is not expected to be exposed to light and therefore, the formation of the Z isomer (photometabolite RPA 406203) is not considered to be relevant for residue studies. The Z-isomer was also not detected in edible matrices in the plant metabolism study.

Further considerations regarding the influence of isomers on the outcome of the residue behaviour and therefore on the consumer risk assessments are not needed.

Notations of the Z isomer (photometabolite RPA 406203)

Code Number		Description		Relevant compartments	Structure
Manufacturing code	Reg No.	Chemical name	CAS-No.		
RPA 406203 Photometabolite Z isomer of parent M595F014	5079359	(1RS, Z)-5-(4-chlorobenzylidene)- 2, 2- dimethyl- 1- ((1H)-1,2,4-triazol-1-ylmethyl)-cyclopentan-1-ol	none	Plant (barley, forage, and straw. <10% TRR) Rot Crop (soil only) Soil surface (from soil photolysis, not relevant for seed treatment uses) Surface water (from aqueous photolysis)	

2.6.1. Summary of storage stability of residues

For the active substance triticonazole, data on the stability of residues were reviewed during the Annex I inclusion process under the 91/414/EEC framework.

Maize (grain) and winter wheat (grain and straw) fortified at a level of 0.1 mg triticonazole/kg (grain) and 0.5 mg triticonazole/kg (straw) were stored under deep freeze conditions of < -20°C. After sampling intervals of about 0, 3, 6, and 12 months samples were analysed for triticonazole. For all sampling intervals, the mean measured residue levels in stored grain (maize, winter wheat) and straw ranged from 71.3 – 119.7 % of the nominal level.

Triticonazole residues in cereals remain stable after storage under deep freeze conditions up to 12 months.

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

Plants:

In context of the previous submission for Annex I inclusion, three plant metabolism studies in cereal crops were evaluated:

The application rate in these studies on wheat and barley ranged between approx. 10.7 and 483 g a.s./ha.

After treatment with triticonazole 14C-labeled in the phenyl ring, only low total radioactive residues were found in grains at harvest (<0.001 – 0.05 mg/kg). Triticonazole formed the majority of the residue in grain, plants, chaff and in straw. Several hydroxylated metabolites of triticonazole exceeded 10% of the recovered radioactivity in one or more matrices: RPA 406780/RPA 404766, RPA 404886 and RPA 406341.

After treatment with triticonazole 14C-labeled in the triazole ring, the pattern of observed metabolism was rather different. The majority of the recovered radioactivity in nearly all plant parts investigated consisted of numerous polar and natural compounds (15 – 88% in plants; 91% in ears; 91 – 93% in grains; 18 – 52% in straw; 51% in chaff). These compounds are derived through the incorporation of fragments of the triazole ring into polar

natural products. Intact 1,2,4-triazole was not identified. Parent triticonazole was also detected, as were three of the hydroxylated metabolites: RPA 406780, RPA 404766 and RPA 404886.

The studies were adequate to conclude that the metabolism of triticonazole occurs by hydroxylation, with separation and destruction of the triazole moiety, leading to incorporation of the triazole-derived material into polar natural products.

However, two of the three older metabolism studies were overdosed and do not reflect the intended use pattern in order to provide a metabolism study matching the current GAP, and to completely address any potential issues arising from the TDMs, a new metabolism study in wheat after seed-treatment with triticonazole was conducted.

After a single application of either [phenyl-14C] or [triazole-3(5)-14C]-(BAS 595 F) on wheat seeds (actual application rate ranging from 11.5 to 11.7 g a.s. / ha), highest amounts of BAS 595 F residues were detected in hay and straw samples (0.191 to 0.225 mg/kg), whereas residues in forage and grain were significantly lower (0.038 to 0.047 mg/kg). The parent compound (BAS 595 F) was the major component identified in forage (62.7 to 65.3 % TRR), whereas in straw, significantly smaller portions of BAS 595 F were detected (14.0 to 20.0 % TRR) and no quantifiable BAS 595 F residues were detected in grain samples. Hence, BAS 595 F was extensively metabolised in mature wheat, particularly wheat grain.

As seed treatment does produce very low total amounts of residue, identification and characterisation of at least 90% of the total radioactive residue (TRR) in each raw agricultural commodity (RAC) of the treated crop was not possible However, presence and levels of the components were presented clearly, and adequate attempts were made to characterise them.

The study is considered acceptable and the metabolic pathway proposed in the other metabolism studies can be confirmed: metabolism of triticonazole occurs by hydroxylation, with separation and destruction of the triazole moiety, leading to incorporation of the triazole-derived material into polar natural products.

Figure 2.6.2-1: Proposed Biotransformation Pathway for [^{14}C]-BAS 595 F in cereals

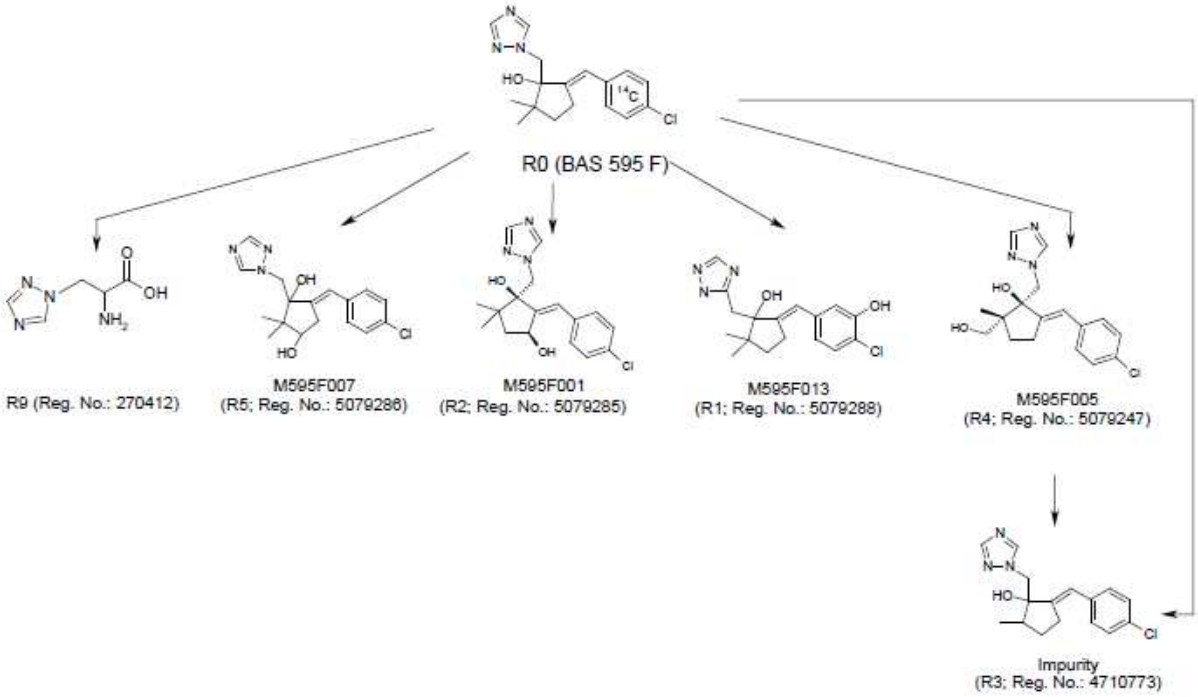


Table 2.6.2-1: Synonyms of plant metabolites of triticonazole mentioned above

Code Number	
Manufacturing code	**Reg No.**
cis-diol **RPA 404766** **M595F001** R2	5079285
trans-diol **RPA 406341** AE 0540093 M595F002	5059144
RPA 404886 **M595F005** R4	5079247
RPA406972 M595F006	5079450
RPA 406780 **M595F007** R5	5079286
RPA 407922 **M595F013** R1	5079288
Triazole-alanine, **R9**	270412

Poultry:

No studies on the metabolism, distribution and expression of residues in livestock were submitted for Annex 1 inclusion of triticonazole. Since at that time no residues above the limit of determination were expected to be found in possible feed items, studies were regarded as not necessary. Dietary burden calculations conducted along this renewal did not result in burdens exceeding 0.004 mg/kg bw per dayay.

Lactating ruminant:

No studies on the metabolism, distribution and expression of residues in livestock were submitted for Annex 1 inclusion of triticonazole. Since at that time no residues above the limit of determination were expected to be found in possible feed items, studies were regarded as not necessary as long as cereal green forage is not used in animal diet. The study was not triggered by dietary burden calculations although cereal green forage is used in the OECD animal diet. However, it is considered valid and adequate for proposing an animal residue definition if needed.

Additionally, some residues are detectable (see B.7.2.1) in early-stage green plant material (BBCH 11-23), which could be grazed. To address the possible occurrence of residues in feed, and because the general potential for TDMs arising from triazole fungicides to occur in animal commodities is a current regulatory concern, a metabolism study was conducted in the lactating goat.

Following administration through **7 days of a mean daily dose of 22.2 mg [Triazole-3(5)-^{14}C]-BAS 595 F per kg food consumed** (dry weight equivalent) to a lactating goat, the **radioactive residues in milk, muscle and fat were very low and accounted for a maximum of 0.026 mg/kg.** Residues in milk had reached steady state within **5 days. The plateau concentration** accounted for approximately **0.019 mg equiv/kg**.

The residues in the other edible matrices accounted for 1.028 mg/kg (liver) and 0.394 mg/kg (kidney).

Approximately 81.5% of the total dose was recovered, the majority of which was present almost equally between feces (36.5%) and urine (29.7%). There was also a large proportion present in the GI tract contents (7.9%) and relatively low proportions recovered in the cage wash (3.4%). Radioactivity associated with edible portions (milk and tissues) accounted for ≤ 1% of the administered dose.

The **extractability** of milk was high (100.0% TRR), equivalent to 0.023 mg/kg. The extractability of the edible tissues was also high, ranging from 98.7% (liver) to 99.9% (muscle) of the TRR.

BAS 595 F (Reg. No. 4378513) was extensively metabolized in the lactating goat. **The unchanged parent was not detected in samples of milk or muscle and was found in portions below 0.8% TRR in kidney**.

There was a greater proportion of BAS 595 F found in the liver which accounted for 14.6% TRR.

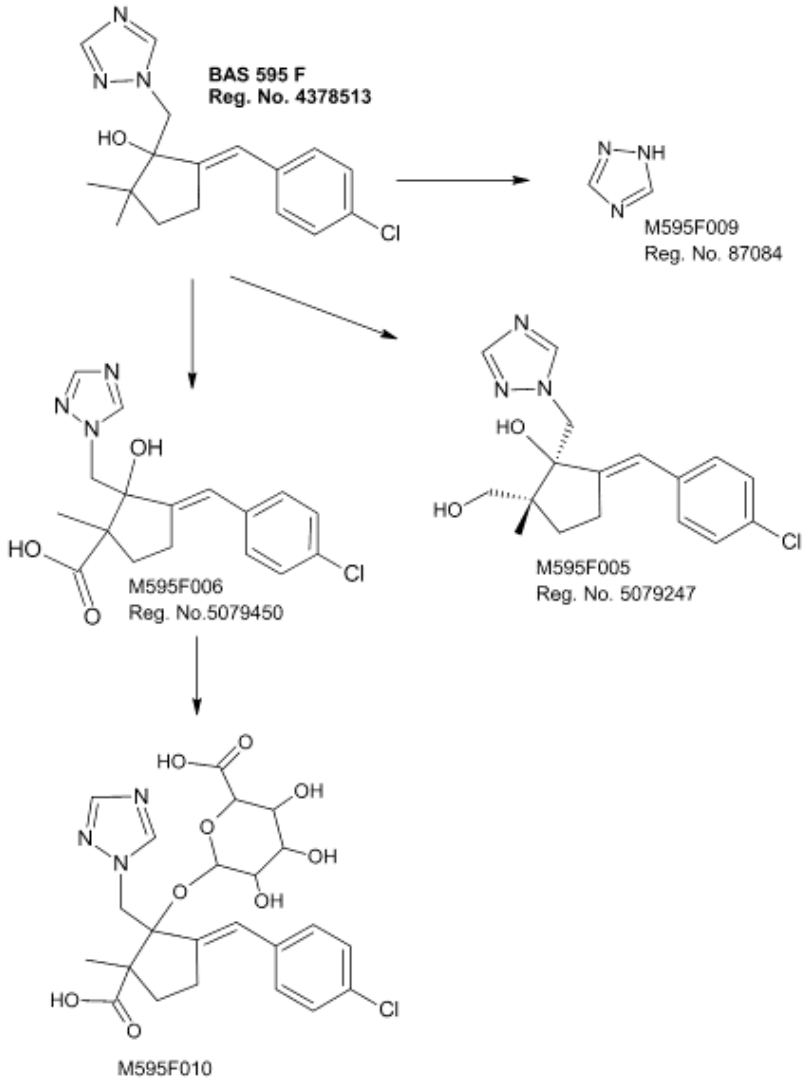
The **main component in extracts of liver and kidney** was **M595F006** (Reg. No. 5079450), formed by oxidation of the cyclopentane alkyl side chain to yield a carboxyl group. This component was also identified in composite muscle at lower proportions (14.6% TRR, 0.004 mg/kg). **M595F010** was also found in the liver in significant proportions.

The **main component in extracts of milk and composite muscle** was **M595F009** (**triazole-alanine**. Reg. No. 87084), formed by the cleavage of the triazole moiety from the parent compound. M595F009 (Reg. No. 87084) was also identified as a minor component in the liver and kidney.

Presence and levels of the components were presented clearly, and adequate attempts were made to characterise them. The study is considered acceptable and the metabolic pathway proposed to occur:

- mainly via oxidation followed by glucuronide conjugation and
- Cleavage of the triazole moiety.

Figure 2.6.2-2: Proposed Biotransformation Pathway for [^{14}C]-BAS 595 F in the Lactating Goat



Pigs

No metabolism study was performed in pigs, since the metabolite patterns in rodents (rats) and ruminants (goats) did not differ significantly.

Fish

According to Commission Regulation 283/2013, metabolism studies in fish may be required where the plant protection product is used in crops whose parts or products, also after processing, are fed to fish and where

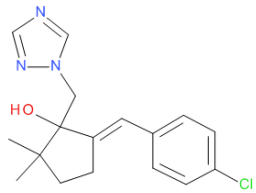
residues in feed may occur from the intended applications. Green forage does not form part of fish diets and since there are no detectable residues in grain or straw, a fish metabolism study is not required.

2.6.3. Definition of the residue

Plant residue definition

The metabolism of triticonazole was studied in barley and wheat after seed treatment using two radiolabelled forms. Triticonazole was metabolised in growing cereal plants via hydroxylation following separation and destruction of the triazole moiety with incorporation of triazole derived material into natural products to form polar residues.

After application of phenyl-labelled triticonazole the major residue in grain and in the other plant parts analysed was triticonazole. Metabolism of triazole-labelled triticonazole shows a different metabolic pattern: The majority of the recovered radioactivity in nearly all plant parts investigated was shown to be a number of polar and natural compounds with a water soluble nature.

Portrait of the active substance	**Residues levels in metabolism studies** (Studies conducted at the **N GAP** are pointed out in **bold**)				**Comments (Dietary Burden calculations,…)**
PARENT **BAS 595 F** **Triticonazole** former BAS 9318 F **RPA 400727** **M595F000**  Rat Livestock (goat) Plant Fish Rotational Crop Soil	**Dose level / label**	**Matrix**	**% TRR**	**[mg equiv/kg]**	Dietary burden calculations according step 15 of the GD for residue definition (sum of parent and major plant metabolites) via animal model 2016 at the 1N rate for cereals including maize do not trigger metabolism studies in ruminant, poultry or pig.
	279 g/ha (22.3 N) phenyl	Wheat plant straw	63 (Z30) / 27 (Z62) 28	0.57/0.19 062	
	454 g/ha (36.3 N) phenyl	Barley grain straw	33 32	0.017 0.54	
	384 g/ha (30.7 N) triazole	Wheat plant straw	94 (Z30) /3 (Z65) 18	5.27 /0.02 0.37	
	483 g/ha (38.6 N) triazole	Barley straw	28	0.66	
	10.65 g/ha (0.9 N) triazole	Barley straw	10	0.0003	
	138.98 g/ha (11 N) phenyl	Barley plant grain straw	28 (Z24) / 15 (Z 65)5 19 35	0.0035 0.0004 0.018	
	109.53 g/ha (8.8 N) triazole	Barley plant straw	20 (Z 24) / 2 (Z 65) 2	0.024 0.0006	
	11.5 g/ha (~N) phenyl	**Wheat forage hay straw**	**65 25 20**	**0.031 0.056 0.044**	
	11.7 g/ha (~N) triazole	**Wheat forage hay straw**	**63 17 16**	**0.03 0.033 0.032**	
	0.32 mg a.i./kg bw/d (22.2 mg/kg DM) not triggered!	Goat liver goat kidney goat muscle *faeces*	15 1 3 2	0.157 0.004 0.001 0.099	
	285.9 g/ha (20 N) triazole Rotational crops	wheat straw 30 d tillering 149 d tillering 366 d tillering lettuce leaves 30 d tillering	 21 20 26 85 49	 0.028 0.034 0.030 0.041 0.012	

Portrait of the active substance	**Residues levels in metabolism studies** (Studies conducted at the **N GAP** are pointed out in **bold**)				**Comments (Dietary Burden calculations,…)**
		radish bulbs 30 d tillering radish leaves 30 d tillering radish roots 30 d tillering	55 31	0.042 0.070	

Based on stepwise assessments following Guidance on the establishment of the residue definition for dietary risk assessment (EFSA Journal 2016;14(12):4549), the residues in of concern is defined as **triticonazole for risk assessment and monitoring purposes** (**limited to seed dressing on cereals);** a residue definition for plants in general cannot be proposed.

Plant residue definition for monitoring (RD-Mo) **limited to seed dressing on cereals**	Triticonazole
Plant residue definition for risk assessment (RD-RA) **limited to seed dressing on cereals**	Triticonazole

Please see also:

Point B.6.8.1 of section toxicology and metabolism, Part B.6

Point 2.6.12. of this document: Assessment following Guidance on the establishment of the residue definition for dietary risk assessment

Animal residue definition

In 2005 EFSA concluded in context of the Conclusion on the peer review of triticonazole (EFSA Scientific Report (2005) 33, 1-69), that after one seed treatment application in cereals at 5 g a.i. per 100 kg seed "no residues of triticonazole were quantified in any of the cereal grain or straw samples from field trials conducted according critical good agricultural practice (GAP)".

In context of this AIR3 submission, additional trials are reported (see CA 6.3) being conducted within ± 25% according to the critical GAP already evaluated by EFSA in 2005. Residues in cereal grain and straw were again always below the respective LOQs (grain: 0.01 mg/kg, straw: 0.05 mg/kg).

EFSA also concluded in 2005: "No quantifiable triticonazole residues were found in cereal grains and straw at the time of harvest and triticonazole and/or its metabolites are not deemed to accumulate in animal tissue. Therefore, metabolism studies in livestock are not necessary as long as cereal green forage is not used in animal diet and a definition of residues in food of animal origin has not to be proposed."

It can be concluded, that furthermore no residues in animal tissues can be expected and **a definition of residues in food of animal origin is not necessary**.

However, the submitted metabolism study in lactating goat is considered valid and adequate for proposing an animal residue definition if needed.

2.6.4. Summary of residue trials in plants and identification of critical GAP

Crop residue data from 23 field studies on wheat, barley and rye (40 trial sites conducted in Germany, Denmark, Italy, Spain and Greece) were submitted for Annex I inclusion of triticonazole. All 40 trials (20 in northern Europe and 20 in southern Europe) match the intended use as a seed treatment for cereals. At harvest, no residues at or above the LOQ (0.01 mg/kg) were detected in any of the grain samples. In context of the existing residue studies only residues of triticonazole were determined. In view of the current concern over possible occurrence of the common TDMs, a new set of residue trials was conducted. Eight trials with triticonazole applied as a seed treatment to wheat at a rate of 6.25 g as/100 kg seed based on a seeding rate of 180 kg/ha were performed in Europe (four in northern Europe and four in Southern Europe) in the growing season 2012/2013. This number of trials is adequate to support use on all cereal crops, since the use is a seed treatment. A second year of residue trials was conducted in 2013/2014 to evaluate possible residues in feed items (plants at different growth stages, fodder, forage).

Table 2.6.4-1: Summary of the critical GAP for the proposed use in cereals for BAS 595 01 F

Crop	Outdoor/ Protected	Growth stage (BBCH)	Maximum number of applications	Minimum application interval (days)	Application Method	Maximum		Minimum PHI (days)
						Rate* (g as/ha)	Water (L/ha)	
Wheat	O	BBCH 00 Spring and autumn	1	-	Seed treatment	12.5 * based on 5 g as/100 kg seed, 250 kg seed/ha	Used undiluted or diluted with water at a max ratio of 1:5 (prod:water)	n.a.

n.a. not applicable

Table 2.6.4-2: Summary of residues data from the supervised residue trials (Regulation (EU) N° 283/2013, Annex Part A, point 6.3)

Crop	Region/ Indoor (a)	**Residue levels** (mg/kg) **observed in the supervised residue trials relevant to the supported GAPs** (b)	**Recommendations/comments** (OECD calculations)	**MRL** proposals (mg/kg)	**HR** (mg/kg) (c)	**STMR** (mg/kg) (d)
Representative use: Wheat (spring and winter), seed treatment						
Wheat grain Barley grain Rye grain	NEU	27 x <0.01 Combined dataset on barley (10), rye (2) and wheat (15) with application rates of 50 g a.s./ton.	Triticonazole (MO and RA)	0.01*	0.01	0.01
	SEU	28 x <0.01 Combined dataset on barley (7) and wheat (21) with application rates of 50 g a.s./ton.				
Livestock feed						
Wheat	NEU	20 x <0.05, 7 x <0.01	Triticonazole (MO and RA)	Not	0.05	0.05

Crop	**Region/ Indoor** (a)	**Residue levels** (mg/kg) **observed in the supervised residue trials relevant to the supported GAPs** (b)	**Recommendations/comments** (OECD calculations)	**MRL** proposals (mg/kg)	**HR** (mg/kg) (c)	**STMR** (mg/kg) (d)
straw Barley grain Rye grain	SEU	20 x <0.05, 8 x <0.01		applicable		
Wheat forage Barley forage Rye forage	NEU	6 x <0.05, 8 x <0.01	Triticonazole (MO and RA) BBCH 49 to BBCH 85 for shoots/whole plant without roots was taken into account.	Not applicable	0.05	0.01
	SEU	8 x <0.01				
Summary of data on residues in pollen and bee products (Regulation (EU) No 283/2013, Annex Part A, point 6.10.1)						
Product(s)	**Region**	**Residue data** (mg/kg)	**Recommendations/comments**			
Wheat		No data available.	Cereal crops are regarded as having no melliferous potential.			

(a): **NEU** or **SEU** for northern or southern **outdoor** trials in EU member states (**N+SEU** if both zones), **Indoor** for glasshouse/protected crops, **Country** if non-EU location.

(b): Residue levels in trials conducted according to GAP reported in ascending order (*e.g.* 3x <0.01, 0.01, 6x 0.02, 0.04, 0.08, 3x 0.10, 2x 0.15, 0.17). When residue definition for monitoring and risk assessment differs, use **Mo/RA** to differentiate data expressed according to the residue definition for **Mo**nitoring and **R**isk **A**ssessment.

(c): **HR**: Highest residue. When residue definition for monitoring and risk assessment differs, HR according to residue definition for monitoring reported in brackets (HR_{Mo}).

(d): **STMR:** Supervised Trials Median Residue. When residue definition for monitoring and risk assessment differs, STMR according to definition for monitoring reported in brackets ($STMR_{Mo}$).

2.6.5. Summary of feeding studies in poultry, ruminants, pigs and fish

No feeding studies have been submitted for Annex I inclusion of triticonazole.
In grain, all residues were below the LOQ (0.01 mg/kg) and also in harvestable forage (whole plant without root) no residues above the LOQ were determined. In the 16 new trials throughout Europe, at BBCH 49 and 59 in specimens of "whole plant without root" the triticonazole residues were always <0.01 mg/kg (see B 7.3).
Based on the calculations, the trigger of 0.004 mg/kg bw per dayay was not exceeded for livestock (dairy ruminants, meat ruminants, poultry and pigs). Therefore, no feeding studies are required.

According to the Commission Regulations (EU) No 283/2013 (active substances) and 284/2013 (plant protection products) as of 1 March 2013, metabolism studies on fish and fish feeding studies might be required in future, if residues occur in crops that are intended as feed items for fish. Green rest of plants do not form part of fish diets and since there are also no detectable residues in cereal grain or straw, a fish feeding study is not required.

2.6.6. Summary of effects of processing

No studies on the effects of industrial processing and/or household preparation have been submitted for Annex I inclusion of triticonazole because of the residue situation: as no residues above the LOD are expected because of the application regime (seed treatment), and based on the results of the residue trials provided, these studies are not regarded as necessary.
However, current guidance requires that a study on the nature of the residue in processed commodities (high-temperature hydrolysis study) is required in any case where residues at or above 0.01 mg/kg may be found. In view of this low threshold, and to provide information on the fate of any possible residues in cereal commodities to be processed, a high-temperature hydrolysis study was conducted. The study is considered acceptable.
14C-triticonazole (BAS 595 F) was hydrolytically stable in sterile buffer solution pH 4 at a temperature simulating pasteurisation (90°C) after 20 minutes, at pH 5 at 100°C after 60 minutes (simulating baking/brewing/boiling) and at pH 6 at 120°C after 20 minutes simulating sterilisation
Hydrolysis products were detected in a range between 2.8 and 3.2 % of applied radioactivity. They were not further investigated, due to their low amount in the test solutions.

Distribution of the residue in peel and pulp is not relevant for the intended uses in cereals.

The residue studies show residues in grain to be < 0.01 mg/kg, and therefore industrial processing studies are not required.

2.6.7. Summary of residues in rotational crops

A metabolism study in rotational crops was evaluated previously for Annex I inclusion of triticonazole.
[Phenyl-14C] radiolabelled triticonazole was applied as a spray rate of 285.9 g a.i./ha (approximately 20 x the intended application rate) and was incorporated into soil since triticonazole is to be applied as a seed dressing. 30, 149 and 366 days after the application, both the treated and the control plots were planted with seeds of radish (root crop), lettuce (leafy crop) and wheat (grain crop).

Edible parts of plants from the first rotation (30 day plant-back) contained total radioactive residues of 0.23 mg/kg (radish roots), 0.048 mg/kg (lettuce leaves) and 0.003 mg/kg (wheat grain). Total radioactive residues declined with the planting interval and the major component of the recovered radioactivity was unchanged triticonazole.
The uptake and metabolism of triticonazole residues in succeeding crops are adequately understood and no further data are required.

However, in the framework of the inclusion into Annex I according to Directive 91/414/EEC, five additional field trials on the magnitude of the residue in rotational crops were evaluated:
Following sowing of seed treated wheat no detectable triticonazole residues in crops planted after harvest of wheat (protein peas, sugar beet root, sunflower seed, oilseed rape and grains of wheat).
Based on the findings, it is concluded that the application of triticonazole to seeds of cereals will not lead to detectable residues in succeeding crops.

2.6.8. Summary of other studies

Review of scientific peer-reviewed open literature for residues of triticonazole
A scientific peer-reviewed open literature search as required by Article 8(5) of Regulation (EC) No 1107/2009 and according to the guidance of EFSA (EFSA Journal 2011;9(2):2092) has been conducted on the active substance Triticonazole and the common product trade names was performed.

The Literature Search Report on Triticonazole describes the general search and evaluation process as well as details on search profiles, search histories and summary tables.

Literature Search was done following the relevance and reliability criteria as set out in the EXTERNAL SCIENTIFIC REPORT “Case studies for the application of the Guidance of EFSA on Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009, using substances for which dossiers are submitted under Regulation (EU) No 1141/2010”:
In this project, the relevance criteria were generally derived from the respective data requirements. However, in specific cases, additional criteria going beyond the data requirements (e.g. cross-contamination for products used in storehouses, mode of action for certain effects, information on sensitivity of some strains) were considered to possibly be relevant and could be included, on a case by case basis, in the literature search in order to allow a possible refinement of the risk assessment. For the reliability criteria the assumption was that non-guideline data (e.g. from academic laboratories) following good scientific principles in design, conduct and reporting as well as employing appropriate statistics, were judged as being of equal quality to the studies conducted according to up-to-date Test Guidelines by a GLP-accredited facility.

The first step of the search result processing based on summary records was done by the Information Center and involved the separation into "hits" and "ballast" (obviously irrelevant records). The “ballast” was not further

processed. The "hits" were further evaluated by the scientific experts and categorized into "not relevant", "not reliable", and "used for dossier".

Results

According to the strategy for scientific literatur research, no literature was identified as relevant for further evaluation.

Conclusion

An extensive search of the published literature did not reveal any studies that would affect the regulatory assessment of triticonazole.

Effect on the residue level in pollen and bee products

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

The representative use of this dossier is wheat. Considering the low TRR levels in the metabolism studies at BBCH 65 (flowering), no residues in pollen are expected and residue studies in honey are therefore not required.

2.6.9. Estimation of the potential and actual exposure through diet and other sources

Estimation of chronic and acute exposure through diet

The long term risk assessment is based on the ADI (0.025 mg/kg bw per dayay). TMDI-calculation was carried out by means of the EFSA PRIMo-rev. 2 (Pesticide Residue Intake Model). The proposed MRLs as given in Table 2.6.10 1 were used for calculation:

Table 2.6.9-1: Triticonazole – Summary of the TMDI calculation with respect to the representative uses (EFSA PRIMo model rev. 2.0)

TMDI (% ADI)	Diet	Highest contributor to the diet (% ADI)	Commodity
0.4	DK child	0.2	Wheat
0.4	WHO Cluster diet B	0.3	Wheat
0.3	WHO cluster diet D	0.3	Wheat
0.3	IT kids/toddler	0.3	Wheat
0.2	WHO cluster diet E	0.2	Wheat

Conclusion:

The estimated Theoretical Maximum Daily Intakes (TMDI) for triticonazole with regard to the representative uses is below 1% of the ADI for all consumer groups. Thus no chronic consumer risk could be identified.

The acute risk assessment is based on the ARfD value of 0.05 mg/kg bw. IESTI-calculation was carried out by means of the EFSA PRIMo-rev. 2 (Pesticide Residue Intake Model). For each commodity the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical

consumption. If no data on the unit weight was available from that MS an average European unit weight was used for the IESTI calculation.

In the IESTI 1 calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002.

In the IESTI 2 calculations, the variability factors of 10 and 7 were replaced by 5..

Table 2.6.9-2: Triticonazole – Summary of the TMDI calculation with respect to the representative uses (EFSA PRIMo model rev. 2.0)

IESTI 1		IESTI 2	
Highest % of ARfD	Commodities	Highest % of ARfD	Commodities
0.3	Wheat	0.3	Wheat
0.1	Rye	0.1	Rye
0.1	Oats	0.1	Oats
0.0	Barley	0.0	Barley

The results of the IESTI calculations (Acute risk assessment /children as worst case) are reported for at least 5 commodities. If the ARfD is exceeded for more than 5 commodities, all IESTI values > 90% of ARfD are reported.

Conclusion:

No exceedance of the ARfD was identified.

A short term intake of residues of triticonazole is unlikely to present a public health risk.

Estimation of the potential and actual exposure through other means

No identified triticonazole residues above 0.1 µg/L are expected to occur in drinking water. Triticonazole residue intake through drinking water can therefore be assessed as not relevant.

2.6.10. Proposed MRLs and compliance with existing MRLs

EU MRLs for triticonazole are listed in Annex II to regulation (EC) No 396/2005 as published in Commission Regulation (EU) No 559/2011 dated June 7, 2011. The published MRLs for the representative uses are listed in the table below.

Table 2.6.10-1: EU MRLs for triticonazole as published in EU Regulation 549/2011

Code number	Groups and examples of individual products to which the MRLs apply (a)	Triticonazole#
0500000	. CEREALS	0.01*
0500010	**. Barley**	**0.01***
0500050	**. Oat**	**0.01***
0500070	**. Rye**	**0.01***
0500090	**. Wheat**	**0.01***

* indicates that the input value is proposed at the limit of analytical quantification

No new MRLs were proposed.

2.6.11. Proposed import tolerances and compliance with existing import tolerances

No import tolerances were intended in the framework of the renewal process.

2.6.12. Assessment following Guidance on the establishment of the residue definition for dietary risk assessment (EFSA Journal 2016;14(12):4549)

Generation of Residue Input Data

the assessment should be initiated (**step 1** of the decision scheme) with the creation of an inventory of all identified metabolites at any level in nature-of-residue studies (i.e. primary and rotational crops, food-producing animals, food processing).

Triticonazole is applied for seed treatment resulting in residues <LOQ. The Guidance Document says: "*Where no adequate field data is available, the metabolite input level for exposure assessments can be derived by normalising the metabolism study values to 1N GAP conditions (if outside ±25% of application rate), thus resulting in a single residue value. This value, derived for one (or more) model crops in metabolism studies, may need to be extrapolated to all intended crops for exposure assessment*."

Therefore, metabolite residue levels from the 4 plant metabolism studies were normalized to the 1N GAP. No distinction between labels and wheat / barley was made. The highest metabolite levels across the studies were selected as input parameters for PRIMO and Dietary Burden.

For plant commodities, input was either for the representative crop wheat or for cereals (wheat, rye, oats, barley, triticale, and also for maize), respectively. The use in maize is intended and was also considered in the Art.12 MRL Review (EFSA Scientific Report (2009) 277, 1-23: *It is noted that for sorghum and maize, the respective application rates of 120 g a.s./ton and 1200 g a.s./ton are significantly higher than the application rate evaluated in the peer review. This is however not considered to be of concern as the amount of sorghum/maize seeds used per hectare is significantly lower than for the other cereal grains*.)

For livestock commodities, dietary burden calculations were performed (Animal Model 2016); the sum of the highest parent and metabolite levels for grain, straw, forage and hay were summed up for the dietary burden calculation. Input was either for the representative crop wheat or for cereals (wheat, rye, oats, barley, triticale, maize), respectively. Feed items relevant in EU animal diets were considered including forage and hay (reflecting GAPs not only for grain production as worst case).

Based on the results of the dietary burden calculation and the goat metabolism study, 1N-dose related metabolite levels for goat/sheep, cattle and swine*.

* EFSA, September 2015: Estimation of animal intakes and HR, STMR and MRL calculations for products of animal origin: *Usually feeding studies are available for dairy cow and laying hen only, and the STMRs, HRs and MRLs for ovine and swine are derived from the feeding study data on dairy cow. This has been taken into account in the Excel calculator where the data from the dairy cow feeding study are automatically reported in the worksheets "Sheep" and "Swine"*.

"EFSA Journal 2011;9(3):2099; Modification of the existing MRLs for chlorantraniliprole in various crops and in products of animal origin." and "EFSA Journal 2012;10(10):2932, Reasoned opinion on the setting of new MRLs for tembotrione in kidney and liver of bovine and swine.": swine MRLs based on the ruminant studies were proposed in absence of further data.

No input was made for equine (extrapolated from ruminant), as they are only low contributors to human intake in the EU.

Table 2.6.12-1: Overview on metabolite residue levels from the 4 plant metabolism studies and normalization to the 1N GAP

Crop	Wheat	Wheat	Barley	Barley	Barley	Wheat	Barley	Wheat	Barley	Wheat	Barley	Barley	Wheat	Wheat	Wheat	Wheat
Rate	**0.9 N**	**0.9 N**	**N**	**11 N**	**8.8 N**	**30.7 N**	**38.6 N**	**22.3 N**	**36.3 N**	**0.9 N**	**11 N**	**36.3 N**	**0.9 N**	**0.9 N**	**0.9 N**	**0.9 N**
Matrix	Straw	Straw	Straw	Straw	Straw	Straw	Straw	Straw	Straw	Grain	Grain	Grain	Forage	Forage	Hay	Hay
Label	phenyl	triazol	triazol	phenyl	triazol	triazol	triazol	phenyl	phenyl	triazol	phenyl	phenyl	phenyl	triazol	phenyl	triazol
g a.s./ha	11.5	11.7	11.96	138.98	109.53	384	483	279	454	11.7 g	138.98	454	11.5 g	11.7	11.5	11.7
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
PARENT	0.044	0.029	0.0001	0.0180	0.0121	0.370	0.660	0.630	0.52		0.0004	0.017	0.031	0.030	0.056	0.033
RPA 406780 (R5. 5079286) **M595F007**	0.007			**0.0014**					0.01		**0.0001**					
RPA 404766 (R2. 5079285) **M595F001**	0.007		0.0003	0.0032		**0.210**	0.170		0.08		**0.0002**				**0.022**	0.010
RPA 404886 (R4. 5079247) **M595F005**		0.020	0.0002	0.0026	0.0013	0.270	0.350	**0.380**			**0.0001**					
RPA 406341 (5059144) **M595F002**			0.0002	0.0045	0.0017			**0.270**	0.11		0.0002	**0.017**				
RPA 406203 (Z isomer of parent. 5079359)				0.0024												
RPA 407922 (R1. 5079288) **M595F013**		0.009			**0.0012**										**0.016**	0.007
R3. 47010773		**0.017**													**0.015**	
R9. 270412. triazole-alanin		**0.009**								**0.015**				**0.004**		**0.021**
M595F004		**0.018**														**0.023**
M595F013		**0.019**														
Rate	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**
PARENT	0.048	0.032	0.0010	0.0016	0.0014	0.012	0.017	0.028	0.01		0.00004	0.00047	0.034	0.033	0.062	0.036
RPA 406780 (R5. 5079286) **M595F007**	**0.008**			0.0001					0.00019		**0.00001**					
RPA 404766 (R2. 5079285) **M595F001**	0.008		0.0003	0.0003		0.007	0.004		**0.00220**		**0.00002**				**0.024**	0.011
RPA 404886 (R4. 5079247) **M595F005**		**0.022**	0.0002	0.0002	0.0001	0.009	0.009	0.017			**0.00001**					
RPA 406341 (5059144) **M595F002**			0.0002	0.0004	0.0002			**0.012**	0.00303		0.00002	**0.00047**				
RPA 406203 (Z isomer of parent. 5079359)				**0.0002**												
RPA 407922 (R1. 5079288) **M595F013**		**0.010**			0.0001										**0.018**	0.008
R3. 47010773		**0.019**													**0.017**	
R9. 270412. triazole-alanin		**0.010**								**0.017**				**0.004**		**0.023**
M595F004		**0.020**														**0.025**
M595F013		**0.020**														

Chronic and acute risk assessment was performed against: the general toxicity TTC reference values

A chronic and acute risk assessment was performed against: the **general toxicity TTC** reference value of 1.5 µg/kg bw/d (chronic) and 5.1 µg/kg bw/d (acute) (for PRIMO: 0.0015 mg/kg bw per day and 0.0051 mg/kg bw per day, respectively).

The risk assessment was performed for each single metabolite, for which no tox reference values are established, and for the sum of the respective metabolites (mg-equiv/kg !)

These are: Identified metabolites, plus 2 proposed (tentative) structures, without triazole-alanin, 1,2,4-triazole, Cereals (wheat, barley, rye, oats, triticale, maize), general toxicity TTC reference value of 1.5 µg/kg bw/d (chronic) and 5.1 µg/kg bw/d (acute)

Table 2.6.12-2: Input values for exposure assessment and dietary burden calculation, Identified **PLANT metabolites** plus 2 proposed structures **without** R9 (270412, triazole-alanin), **without** 1,2,4-triazole but **with** RPA406203 (z-isomer)

Values for RiskAss	Straw mg/kg	Grain mg/kg	Forage mg/kg	Hay mg/kg
Parent for DB	0.048	0.00047	0.034	0.062
Plant Metabolites				
M595F007 (RPA 406780, R5, 5079286)	0.008	0.00001		
M595F001 (RPA 404766, R2, 5079285)	0.0022	0.00002		0.024
M595F005 (RPA 404886, R4, 5079247	0.022	0.00001		
M595F002 (RPA 406341, 5059144)	0.012	0.00047		
M595F013 (RPA 407922, R1, 5079288)	0.010			0.018
R3, 47010773	0.019			
M595F015	0.021			
M595F004	0.020			0.025
Sum of metabolites for PRIMO:		0.00051		
Total for Dietary Burden	0.162	0.00098	0.034	0.129

Please note: Z isomer (found in straw only) has no impact on Dietary burden

Calculations and input values for dietary burden of metabolites found in feed items only along TTC assessment for evaluation of general toxicity (step 11):

Table 2.6.12-3: Input values for dietary burden calculation , Identified **PLANT metabolites** plus 2 proposed structures found in feed items only

Values for RiskAssessment	Straw mg/kg	Grain mg/kg	Forage mg/kg	Hay mg/kg
M595F013 (RPA 407922, R1, 5079288)	0.010			0.018
R3, 47010773	0.019			
M595F015	0.021			
M595F004	0.020			0.025

M 595F013 worst case: straw and hay

Animals	Median burden (mg/kg bw)	Maximum burden (mg/kg bw)	Above 0.004 mg /kg bw	Maximum burden (mg/kg DM)	Highest contributing commodities
Beef cattle	0.000	0.000	No	0.00	Triticale hay
Dairy cattle	0.000	0.000	No	0.00	Triticale hay
Ram/Ewe	0.000	0.000	No	0.01	Triticale hay
Lamb	0.000	0.000	No	0.01	Oat hay
Pig (breeding)	0.000	0.000	No	0.00	Triticale hay
Pig (finishing)					
Poultry broiler					
Poultry layer	0.000	0.000	No	0.00	Wheat hay
Turkey					

R3, 47010773 EU: straw only relevant in EU diet, no residues in hay

Animals	Median burden (mg/kg bw)	Maximum burden (mg/kg bw)	Above 0.004 mg /kg bw	Maximum burden (mg/kg DM)	Highest contributing commodities
Beef cattle	0.000	0.000	No	0.01	Barley straw
Dairy cattle	0.000	0.000	No	0.01	Barley straw
Ram/Ewe	0.000	0.000	No	0.01	Barley straw
Lamb	0.001	0.001	No	0.01	Barley straw
Pig (breeding)					
Pig (finishing)					
Poultry broiler					
Poultry layer	0.000	0.000	No	0.00	Wheat straw
Turkey					

M595F015 EU: straw only relevant in EU diet, no residues in hay

Animals	Median burden (mg/kg bw)	Maximum burden (mg/kg bw)	Above 0.004 mg /kg bw	Maximum burden (mg/kg DM)	Highest contributing commodities
Beef cattle	0.000	0.000	No	0.01	Barley straw
Dairy cattle	0.000	0.000	No	0.01	Barley straw
Ram/Ewe	0.000	0.000	No	0.01	Barley straw
Lamb	0.001	0.001	No	0.01	Barley straw
Pig (breeding)					
Pig (finishing)					
Poultry broiler					
Poultry layer	0.000	0.000	No	0.00	Wheat straw
Turkey					

M 595F004 worst case: straw and hay

Animals	Median burden (mg/kg bw)	Maximum burden (mg/kg bw)	Above 0.004 mg /kg bw	Maximum burden (mg/kg DM)	Highest contributing commodities	
Beef cattle	0.000	0.000	No	0.01	Barley	straw
Dairy cattle	0.000	0.000	No	0.01	Barley	straw
Ram/Ewe	0.000	0.000	No	0.01	Barley	straw
Lamb	0.001	0.001	No	0.01	Barley	straw
Pig (breeding)	0.000	0.000	No	0.01	Triticale	hay
Pig (finishing)						
Poultry broiler						
Poultry layer	0.000	0.000	No	0.00	Wheat	hay
Turkey						

Conclusion: The metabolites present in feed items only do not trigger metabolism studies in livestock.

Step 15: Dietary burden (parent and major metabolites)

Major plant metabolites: ≥10% of the TRR and ≥0.01 mg/kg in food and in feed commodities:

RPA 404766 (R2, 5079285) hay: 10% TRR 0.022 mg/kg

RPA 404886 (R4, 5079247) straw: 10% TRR 0.022 mg/kg

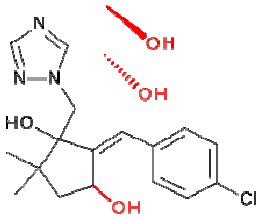
M595F004 (proposed structure) hay: 12% TRR 0.023 mg/kg

Input Values for RiskAssessment	Straw	Grain	Forage	Hay
Parent for DB	0.048	0.00047	0.034	0.062
Metabolites				
RPA 404766 (R2. 5079285)	0.0022	0.00002		0.024
RPA 404886 (R4. 5079247)	0.022	0.00001		
M595F004	0.020			0.025
Total for DB Step 15	0.0922	0.0005	0.034	0.111

Animals	Median burden (mg/kg bw)	Maximum burden (mg/kg bw)	Above 0.004 mg /kg bw	Maximum burden (mg/kg DM)	Highest contributing commodities	
Beef cattle	0.002	0.002	No	0.07	Corn, field	forage/silage
Dairy cattle	0.002	0.002	No	0.05	Corn, field	forage/silage
Ram/Ewe	0.002	0.002	No	0.06	Barley	straw
Lamb	0.003	0.003	No	0.06	Barley	straw
Pig (breeding)	0.001	0.001	No	0.03	Wheat	forage
Pig (finishing)	0.000	0.000	No	0.00	Barley	grain
Poultry broiler	0.000	0.000	No	0.00	Barley	grain
Poultry layer	0.001	0.001	No	0.01	Wheat	forage
Turkey	0.000	0.000	No	0.00	Rye	grain

A summary of the stepwise assessment of all metabolites is given below:

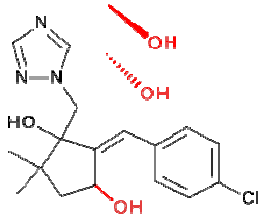
Table 2.6.12-3: Summary of the stepwise assessment of metabolites

<table>
<tr><th>Metabolite</th><th>Residues levels in metabolism studies
(Studies conducted at the N GAP are pointed out in bold)</th><th>Genotoxicity evaluation conclusion:</th><th>General toxicity exposure assessment
general toxicity TTC reference value of 1.5 µg/kg bw/d (chronic) and 5.1 µg/kg bw/d (acute)</th><th>Comments / Conclusion</th></tr>
<tr>
<td>M595F001
RPA 404766 (R2, 5079285)
 

Rat (urine; at levels below the sensitivity of the radioactivity detector used for quantification of metabolites)
Rotational crop (wheat straw)
Cereals (grain, forage, hay and straw)</td>
<td>
<table>
<tr><th>Dose level / label</th><th>Matrix</th><th>% TRR</th><th>[mg equiv/kg]</th></tr>
<tr><td>454 g/ha (36.3 N) phenyl</td><td>Barley straw</td><td>5</td><td>0.085</td></tr>
<tr><td>384 g/ha (30.7 N) triazole</td><td>Wheat
forage
straw</td><td>
0.5
10</td><td>
0.028
0.21</td></tr>
<tr><td>483 g/ha (38.6 N) triazole</td><td>Barley straw</td><td>7</td><td>0.16</td></tr>
<tr><td>10.65 g/ha (0.9 N) triazole</td><td>Barley straw</td><td>3</td><td>0.0003</td></tr>
<tr><td>138.98 g/ha (11 N) phenyl</td><td>Barley
straw
grain
forage</td><td>
6
13
3</td><td>
0.003
0.00026
0.0039</td></tr>
<tr><td>11.5 g/ha (~N) phenyl</td><td>Wheat
straw
hay</td><td>
3
10</td><td>
0.007
0.022</td></tr>
<tr><td>11.7 g/ha (~N) triazole</td><td>Wheat
hay</td><td>
5</td><td>
0.01</td></tr>
<tr><td>285.9 g/ha (20 N) triazole</td><td>Rotational crop
(wheat straw)
30 d tillering
149 d tillering</td><td>
13
10</td><td>
0.018
0.018</td></tr>
</table>
</td>
<td>negative</td>
<td>Based on the sum results of plant and livestock metabolites, the acute and chronic TTC is not exceeded:
Chronic:
Max 0.4% (WHO Cluster diet B. wheat)

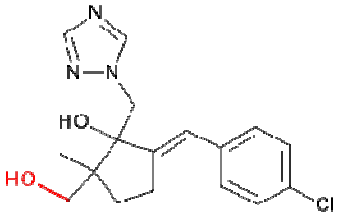
Acute:
Children:
0.5% Bovine: Liver
0.1% Wheat
0.1% Bovine: Kidney
0.1% Maize
0.1% Rye

Adults:
0.2% Bovine: Liver
0.1% Sheep: Liver
0.1% Wheat
0.1% Barley
0.1% Bovine: Kidney</td>
<td>Based on stepwise assessment <u>not included in the residue definition</u>.</td>
</tr>
</table>

<table>
<tr><th>Metabolite</th><th>Residues levels in metabolism studies
(Studies conducted at the N GAP are pointed out in bold)</th><th>Genotoxicity evaluation conclusion:</th><th>General toxicity exposure assessment
general toxicity TTC reference value of 1.5 µg/kg bw/d (chronic) and 5.1 µg/kg bw/d (acute)</th><th>Comments / Conclusion</th></tr>
<tr>
<td>M595F002
RPA 406341 (5059144)
 
Rat (urine; at levels below the sensitivity of the radioactivity detector used for quantification of metabolites)
Rotational crop (wheat straw)
Cereals (grain, forage, and straw)</td>
<td>
<table>
<tr><th>Dose level / label</th><th>Matrix</th><th>% TRR</th><th>[mg equiv/kg]</th></tr>
<tr><td>10.65 g/ha (~N) triazole</td><td>Barley straw</td><td>2</td><td>0.0002</td></tr>
<tr><td>138.98 g/ha (11 N) phenyl</td><td>Barley
straw
grain
green plant</td><td>
9
9
3</td><td>
0.0045
0.0002
0.0039</td></tr>
<tr><td>279 g/ha (22.3 N) phenyl</td><td>Wheat
green plant
straw</td><td>
3
12</td><td>
0.027
0.27</td></tr>
<tr><td>454 g/ha (36.3 N) phenyl</td><td>Barley
grain
straw</td><td>
33
8</td><td>
0.017
0.14</td></tr>
<tr><td>109.53 g/ha (8.8 N) triazole</td><td>Barley
straw
green plant</td><td>
2
2</td><td>
0.0016
0.0024</td></tr>
<tr><td>285.9 g/ha (20 N) triazole</td><td>Rotational crop (wheat straw)
30 d tillering
149 d tillering
366 d tillering</td><td>
20
16
31</td><td>
0.026
0.029
0.036</td></tr>
</table>
</td>
<td>negativ</td>
<td>Based on the sum results of plant and livestock metabolites, the acute and chronic TTC is not exceeded:
Chronic:
Max 0.4% (WHO Cluster diet B. wheat)

Acute:
Children:
0.5% Bovine: Liver
0.1% Wheat
0.1% Bovine: Kidney
0.1% Maize
0.1% Rye

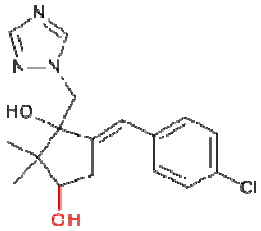
Adults:
0.2% Bovine: Liver
0.1% Sheep: Liver
0.1% Wheat
0.1% Barley
0.1% Bovine: Kidney</td>
<td>Based on stepwise assessment <u>not included in the residue definition</u>.</td>
</tr>
</table>

<table>
<tr><th>Metabolite</th><th>Residues levels in metabolism studies
(Studies conducted at the N GAP are pointed out in bold)</th><th>Genotoxicity evaluation conclusion:</th><th>General toxicity exposure assessment
general toxicity TTC reference value of 1.5 µg/kg bw/d (chronic) and 5.1 µg/kg bw/d (acute)</th><th>Comments / Conclusion</th></tr>
<tr>
<td>M595F005
RPA 404886 (R4, 5079247)
 
Goat (faeces)
Rat (feces; RLD):
M: 15.14%dose
F: 24.12 %dose

Rotational crop (wheat straw)
Cereals (grain, straw)</td>
<td>
<table>
<tr><th>Dose level / label</th><th>Matrix</th><th>% TRR</th><th>[mg equiv/kg]</th></tr>
<tr><td>279 g/ha (22.3 N) phenyl</td><td>Wheat straw</td><td>17</td><td>0.38</td></tr>
<tr><td>384 g/ha (30.7 N) triazole</td><td>Wheat straw</td><td>13</td><td>0.27</td></tr>
<tr><td>483 g/ha (38.6 N) triazole</td><td>Barley straw</td><td>15</td><td>0.35</td></tr>
<tr><td>10.65 g/ha (~N) triazole</td><td>Barley straw</td><td>3</td><td>0.0003</td></tr>
<tr><td>138.98 g/ha (11 N) phenyl</td><td>Barley straw
Barley grain</td><td>5
8</td><td>0.0025
0.00016</td></tr>
<tr><td>109.53 g/ha (8.8 N) triazole</td><td>Barley straw</td><td>6</td><td>0.0048</td></tr>
<tr><td>11.7 g/ha (~N) triazole</td><td>Wheat straw</td><td>6</td><td>0.012</td></tr>
<tr><td>0.32 mg a.i./kg bw/d (22.2 mg/kg DM) not triggered</td><td>Goat faeces</td><td>5</td><td>0.284</td></tr>
<tr><td>285.9 g/ha (20 N) triazole</td><td>Rotational crop (wheat straw)
30 d tillering
149 d tillering</td><td>
14
10</td><td>
0.019
0.018</td></tr>
</table>
</td>
<td>negative</td>
<td>Based on the sum results of plant and livestock metabolites, the acute and chronic TTC is not exceeded:
Chronic:
Max 0.4% (WHO Cluster diet B. wheat)

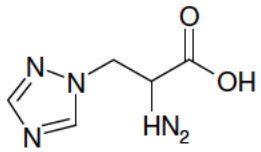
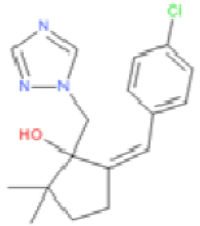
Acute:
Children:
0.5% Bovine: Liver
0.1% Wheat
0.1% Bovine: Kidney
0.1% Maize
0.1% Rye

Adults:
0.2% Bovine: Liver
0.1% Sheep: Liver
0.1% Wheat
0.1% Barley
0.1% Bovine: Kidney</td>
<td>Based on stepwise assessment <u>not included in the residue definition</u>.</td>
</tr>
</table>

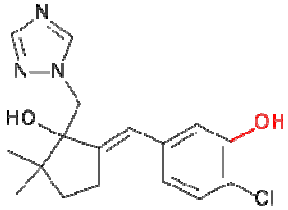
<table>
<tr><th>Metabolite</th><th>Residues levels in metabolism studies
(Studies conducted at the N GAP are pointed out in bold)</th><th>Genotoxicity evaluation conclusion:</th><th>General toxicity exposure assessment
general toxicity TTC reference value of 1.5 µg/kg bw/d (chronic) and 5.1 µg/kg bw/d (acute)</th><th>Comments / Conclusion</th></tr>
<tr>
<td>M595F007
RPA 406780 (R5, 5079286)
 
Rat (urine; at levels below the sensitivity of the radioactivity detector used for quantification of metabolites)
Cereals (grain, forage, straw)</td>
<td>
<table>
<tr><th>Dose level / label</th><th>Matrix</th><th>% TRR</th><th>[mg equiv/kg]</th></tr>
<tr><td>279 g/ha (22.3 N)
phenyl</td><td>Wheat straw</td><td>7</td><td>0.16</td></tr>
<tr><td>454 g/ha (36.3 N)
phenyl</td><td>Barley straw</td><td>1</td><td>0.17</td></tr>
<tr><td>138.98 g/ha (11 N)
phenyl</td><td>Barley straw
grain
forage</td><td>3
5
13</td><td>0.0015
0.0001
0.017</td></tr>
<tr><td>138.98 g/ha (11 N)
triazole</td><td>Barley forage</td><td>11</td><td>0.013</td></tr>
</table>
</td>
<td>negative</td>
<td>Based on the sum results of plant and livestock metabolites, the acute and chronic TTC is not exceeded:
Chronic:
Max 0.4% (WHO Cluster diet B. wheat)

Acute:
Children:
0.5% Bovine: Liver
0.1% Wheat
0.1% Bovine: Kidney
0.1% Maize
0.1% Rye

Adults:
0.2% Bovine: Liver
0.1% Sheep: Liver
0.1% Wheat
0.1% Barley
0.1% Bovine: Kidney</td>
<td>Based on stepwise assessment <u>not included in the residue definition</u>.</td>
</tr>
</table>

<table>
<tr><th>Metabolite</th><th>Residues levels in metabolism studies
(Studies conducted at the N GAP are pointed out in bold)</th><th>Genotoxicity evaluation conclusion:</th><th>General toxicity exposure assessment
general toxicity TTC reference value of 1.5 µg/kg bw/d (chronic) and 5.1 µg/kg bw/d (acute)</th><th>Comments / Conclusion</th></tr>
<tr>
<td>Triazole alanine (R9, 270412)
 
Cereals (grain, forage, hay and straw)</td>
<td>
<table>
<tr><th>Dose level / label</th><th>Matrix</th><th>% TRR</th><th>[mg equiv/kg]</th></tr>
<tr><td>11.7 g/ha (0.9N) triazole</td><td>Wheat
forage
hay
straw
grain</td><td>
9
11
7
38</td><td>
0.004
0.021
0.014
0.015</td></tr>
</table>
</td>
<td>negative</td>
<td>Not included, not necessary (own reference values available).</td>
<td>It is noted that triazole derived compounds are not specific to triticonazole. Therefore they are <u>not included in the residue definition</u> for the active under evaluation. Discussion on triazole common metabolites is not considered in the framework of this evaluation since confirmatory data are ongoing (United Kingdom, 2016) and (EFSA, 2016) leading to an issue that could not be finalized.</td>
</tr>
<tr>
<td>RPA406203 (z-Isomer)
Photometabolite
M595F014
 
Cereals (straw)
FEED ONLY</td>
<td>
<table>
<tr><th>Dose level / label</th><th>Matrix</th><th>% TRR</th><th>[mg equiv/kg]</th></tr>
<tr><td>138.98 g/ha (11 N) phenyl</td><td>Barley straw</td><td>5</td><td>0.0024</td></tr>
</table>
</td>
<td>negative</td>
<td>Based on the sum results of plant and livestock metabolites, the acute and chronic TTC is not exceeded:
Chronic:
Max 0.4% (WHO Cluster diet B. wheat)
Acute:
Children:
0.5% Bovine: Liver
0.1% Wheat
0.1% Bovine: Kidney
0.1% Maize
0.1% Rye
Adults:
0.2% Bovine: Liver
0.1% Sheep: Liver
0.1% Wheat
0.1% Barley
0.1% Bovine: Kidney</td>
<td>Dietary burden calculations by animal model 2016 at the 11N rate for cereals do not trigger metabolism studies in ruminant, poultry or pig.

Based on stepwise assessment <u>not included in the residue definition</u>.</td>
</tr>
</table>

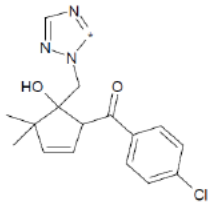
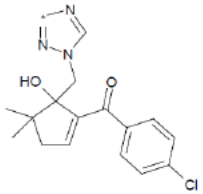
<table>
<tr><th>Metabolite</th><th>Residues levels in metabolism studies
(Studies conducted at the N GAP are pointed out in bold)</th><th>Genotoxicity evaluation conclusion:</th><th>General toxicity exposure assessment
general toxicity TTC reference value of 1.5 µg/kg bw/d (chronic) and 5.1 µg/kg bw/d (acute)</th><th>Comments / Conclusion</th></tr>
<tr>
<td>M595F013
RPA 407922 (R1, 5079288)
 

Cereals (straw, hay)
FEED ONLY</td>
<td>
<table>
<tr><th>Dose level / label</th><th>Matrix</th><th>% TRR</th><th>[mg equiv/kg]</th></tr>
<tr><td>109.53 g/ha (8.8 N) triazole</td><td>Barley straw</td><td>2</td><td>0.0016</td></tr>
<tr><td>11.5 g/ha (~N) phenyl</td><td>Wheat hay straw</td><td>7
4</td><td>0.016
0.008</td></tr>
<tr><td>11.7 g/ha (N) triazole</td><td>Wheat hay</td><td>3</td><td>0.007</td></tr>
</table>
</td>
<td>negative</td>
<td>Based on the sum results of plant and livestock metabolites, the acute and chronic TTC is not exceeded:
Chronic:
Max 0.4% (WHO Cluster diet B. wheat)

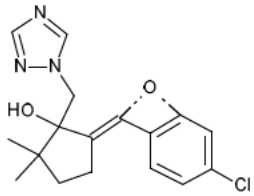
Acute:
Children:
0.5% Bovine: Liver
0.1% Wheat
0.1% Bovine: Kidney
0.1% Maize
0.1% Rye

Adults:
0.2% Bovine: Liver
0.1% Sheep: Liver
0.1% Wheat
0.1% Barley
0.1% Bovine: Kidney</td>
<td>Dietary burden calculations by animal model 2016 at the 1N rate for cereals do not trigger metabolism studies in ruminant, poultry or pig

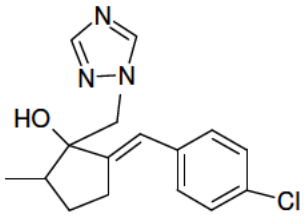
Based on stepwise assessment <u>not included in the residue definition</u>.</td>
</tr>
</table>

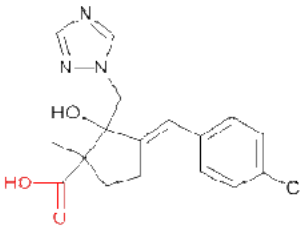
<table>
<tr><th>Metabolite</th><th>Residues levels in metabolism studies
(Studies conducted at the N GAP are pointed out in bold)</th><th>Genotoxicity evaluation conclusion:</th><th>General toxicity exposure assessment
general toxicity TTC reference value of 1.5 µg/kg bw/d (chronic) and 5.1 µg/kg bw/d (acute)</th><th>Comments / Conclusion</th></tr>
<tr>
<td>M595F004 (structure tentative)
 
Or isomer
 
Cereals (straw, hay)
FEED ONLY</td>
<td>
<table>
<tr><th>Dose level / label</th><th>Matrix</th><th>% TRR</th><th>[mg equiv/kg]</th></tr>
<tr><td>11.7 g/ha (~N) triazole</td><td>Wheat hay
straw</td><td>12
9</td><td>0.023
0.018</td></tr>
</table>
</td>
<td>Ames: Negative
CA: Positive SA 10 (alpha, beta unsaturated carbonyls) in Toxtree, CASE Ultra negative

No exposure estimation against genotox TTC done, since the metabolite(s) detected only in feed items (straw) and not in animal tissues.</td>
<td>Metabolite in feed item only, therefore contributing to dietary burden of livestock.
No TTC exceedance via food of animal origin observed, based on the sum results of plant and livestock metabolites.</td>
<td>Dietary burden calculations by animal model 2016 at the 1N rate for cereals do not trigger metabolism studies in ruminant, poultry or pig.

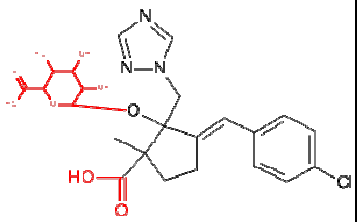
The highest residue was found in cereal hay, which is not fed to livestock in the EU.
Considering that the low levels expected in the feed items (not triggering dosing of livestock) will usually lead to far lower levels of degradation products in animal metabolism, this compound is <u>not included in the residue definition</u>.</td>
</tr>
<tr>
<td>M595F015 (structure tentative)
 
Cereals (straw)
FEED ONLY</td>
<td>
<table>
<tr><th>Dose level / label</th><th>Matrix</th><th>% TRR</th><th>[mg equiv/kg]</th></tr>
<tr><td>11.7 g/ha (~N) triazole</td><td>Wheat straw</td><td>9</td><td>0.019</td></tr>
</table>
</td>
<td>negative</td>
<td>Metabolite in feed item only, therefore contributing to dietary burden of livestock.
No TTC exceedance via food of animal origin observed, based on the sum results of plant and livestock metabolites.</td>
<td>Dietary burden calculations by animal model 2016 at the 1N rate for cereals do not trigger metabolism studies in ruminant, poultry or pig.

Based on stepwise assessment <u>not included in the residue definition</u>.</td>
</tr>
</table>

<table>
<tr><th>Metabolite</th><th>Residues levels in metabolism studies
(Studies conducted at the N GAP are pointed out in bold)</th><th>Genotoxicity evaluation conclusion:</th><th>General toxicity exposure assessment
general toxicity TTC reference value of 1.5 µg/kg bw/d (chronic) and 5.1 µg/kg bw/d (acute)</th><th>Comments / Conclusion</th></tr>
<tr>
<td>R3, 47010773
 
Cereals (straw, hay)
FEED ONLY</td>
<td>
<table>
<tr><th>Dose level / label</th><th>Matrix</th><th>% TRR</th><th>[mg equiv/kg]</th></tr>
<tr><td>11.5 g/ha (~N) phenyl</td><td>Wheat hay</td><td>7</td><td>0.015</td></tr>
<tr><td>11.7 g/ha (~N) triazole</td><td>Wheat hay</td><td>3</td><td>0.006</td></tr>
</table>
</td>
<td>negative</td>
<td>Metabolite in feed item only, therefore contributing to dietary burden of livestock.
No TTC exceedance via food of animal origin observed based on the sum results of plant and livestock metabolites.</td>
<td>Dietary burden calculations by animal model 2016 at the 1N rate for cereals do not trigger metabolism studies in ruminant, poultry or pig.

Based on stepwise assessment <u>not included in the residue definition</u>.</td>
</tr>
<tr>
<td>M595F0006 (RPA406972, 5079450)
 
Goat (liver, kidney, muscle, excreta, bile)
Rat (urine, RLD):
M: 2.18 %dose = 17.9 %absorbed dose
F: 11.23 %dose = 55.9%absorbed dose
Rat (faeces):
M: 34.16 %dose
F: 21.59 %dose
ANIMAL ONLY</td>
<td>
<table>
<tr><th>Dose level / label</th><th>Matrix</th><th>% TRR</th><th>[mg equiv/kg]</th></tr>
<tr><td>0.32 mg a.i./kg bw/d (22.2 mg/kg DM)</td><td>Goat
liver
kidney
muscle
faeces
urine
bile</td><td>
23
57
15
87
82
12</td><td>
0.251
0.244
0.004
4.8
4.6
3</td></tr>
</table>
</td>
<td>negative</td>
<td>Based on the sum results of plant and livestock metabolites, the acute and chronic TTC is not exceeded:
Chronic:
Max 0.4% (WHO Cluster diet B. wheat)
Acute:
Children:
0.5% Bovine: Liver
0.1% Wheat
0.1% Bovine: Kidney
0.1% Maize
0.1% Rye
Adults:
0.2% Bovine: Liver
0.1% Sheep: Liver
0.1% Wheat
0.1% Barley
0.1% Bovine: Kidney</td>
<td>For the time being, a <u>proposal of a residue definition for livestock is not needed since low residues in feed items do not trigger a livestock metabolism study.</u>

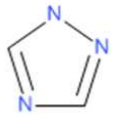
If once needed, this metabolite might be included in the residue definitions for ruminant matrices.
Based on stepwise assessment, toxicological reference values of the parent compound can be applied.</td>
</tr>
</table>

<table>
<tr><th>Metabolite</th><th>Residues levels in metabolism studies
(Studies conducted at the N GAP are pointed out in bold)</th><th>Genotoxicity evaluation conclusion:</th><th>General toxicity exposure assessment
general toxicity TTC reference value of 1.5 µg/kg bw/d (chronic) and 5.1 µg/kg bw/d (acute)</th><th>Comments / Conclusion</th></tr>
<tr>
<td>M595F010
 
Goat (liver and bile)
ANIMAL ONLY</td>
<td>
<table>
<tr><th>Dose level / label</th><th>Matrix</th><th>% TRR</th><th>[mg equiv/kg]</th></tr>
<tr><td>0.32 mg a.i./kg bw/d (22.2 mg/kg DM)
X N</td><td>Goat
liver
bile</td><td>
23
12</td><td>
0.251
3</td></tr>
</table>
</td>
<td>negative</td>
<td>Based on the sum results of plant and livestock metabolites, the acute and chronic TTC is not exceeded:
Chronic:
Max 0.4% (WHO Cluster diet B. wheat)

Acute:
Children:
0.5% Bovine: Liver
0.1% Wheat
0.1% Bovine: Kidney
0.1% Maize
0.1% Rye

Adults:
0.2% Bovine: Liver
0.1% Sheep: Liver
0.1% Wheat
0.1% Barley
0.1% Bovine: Kidney</td>
<td>For the time being, a <u>proposal of a residue definition for livestock is not needed since low residues in feed items do not trigger a livestock metabolism study.</u>

If once needed, this metabolite might be included in the residue definitions for ruminant matrices.
Based on stepwise assessment, toxicological reference values of the parent compound can be applied.</td>
</tr>
</table>

<table>
<tr><th>Metabolite</th><th>Residues levels in metabolism studies
(Studies conducted at the N GAP are pointed out in bold)</th><th>Genotoxicity evaluation conclusion:</th><th>General toxicity exposure assessment
general toxicity TTC reference value of 1.5 µg/kg bw/d (chronic) and 5.1 µg/kg bw/d (acute)</th><th>Comments / Conclusion</th></tr>
<tr>
<td>1,2,4-triazole
M595F009 (87084)
 
Goat (muscle and milk)
ANIMAL ONLY</td>
<td>
<table>
<tr><th>Dose level / label</th><th>Matrix</th><th>% TRR</th><th>[mg equiv/kg]</th></tr>
<tr><td>0.32 mg a.i./kg bw/d (22.2 mg/kg DM)
not triggered</td><td>Goat
muscle
milk</td><td>
57
86</td><td>
0.014
0.020</td></tr>
</table>
</td>
<td>negative</td>
<td>Not included in the assessment, not necessary (own reference values available).</td>
<td>It is noted that triazole derived compounds are not specific to triticonazole. Therefore they are <u>not included in the residue definition</u> for the active under evaluation. Discussion on triazole common metabolites is not considered in the framework of this evaluation since confirmatory data are ongoing (United Kingdom, 2016) and (EFSA, 2016) leading to an issue that could not be finalized.</td>
</tr>
</table>

2.7. FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.7.1. Summary of fate and behaviour in soil

Route of degradation

Legacy studies on the **aerobic degradation** of triticonazole in soil conducted at 22, 25 and 10 °C for one year and two recent degradation study conducted at 20 °C for 120 days and for one year, respectively, showed that the main degradation pathway of triticonazole is hydroxylation releasing the two major mono-hydroxylated transformation products **RPA 406341 (Trans-diol)** (max. 20.2 % AR at 22 °C) and **RPA 404766 (Cis-diol)** (max. 13.9 % AR at 10 °C). These two metabolites were consistently observed in all soils.

Beside these two major degradation products several unknown metabolites, amongst them most probably other mono- and di-hydroxylated as well as oxidized (keto) derivatives of triticonazole, with indicative mol weights (MWT) of 315, 331, 333, 347 and 349 have been detected partly above 5 % AR (and partly > 10 % AR) but could not be unambiguously identified. Notice that in case of the legacy studies (conducted around 1993 - 1996) only metabolites above 10 % AR had to be investigated further. The RMS AT notes that all these unidentified metabolites were observed at late stage of the one-year incubation experiments (above 5 % AR at 140 DAT earliest), with maximum amounts at study termination in several cases. It is also noted that highest amounts of unknown and unidentified metabolite fraction were generally observed in the earliest studies (Ayliffe & Austin, 1993, Ayliffe & McMillan-Staff, 1994, and Ayliffe & Godward, 1993) when HPLC techniques were less advanced in comparison to studies conducted later. In this respect, it cannot be excluded that some of these metabolite fractions actually comprise more than one substance. A summary on unknown metabolite fractions observed above 5 % AR is given in the table below.

Table B.2.7.1-1 Unknown metabolite fractions observed above 5 % AR in aerobic soil degradation experiments with triticonazole

Study temp. (°C)	Metabolite coding	Proposed MWT	Soil	Max. occ. (% AR)	Day of max. occ. (DAT)	1st day > 5 % AR	> 5 % AR at two consecutive sampling points	Ref.
22	'Met 5'[(a)]	349	UK clay loam	6.7	363[(b)]	168	Yes	Ayliffe & Austin (1993)
	'Met 6'	333	UK clay loam	12.8	266	140	Yes	
	'Met 7'	315	UK sandy loam	6.5	266	224	Yes	
	'Met 7'	333	UK loamy sand	6.2	363[(b)]	363[(b)]	No	Ayliffe & Godward (1993)
	'Met 8'	315	UK loamy sand	5.3	245	245	No	
10	'Met 6'[(a)]	349	UK sandy loam	10.5	363[(b)]	363[(b)]	No	Ayliffe & Godward (1993)
			UK clay loam	11.1	363[(b)]	363[(b)]	No	
			UK loamy sand	6.5	363[(b)]	363[(b)]	No	
	'Met 7'	333	UK sandy loam	6.9	245	245	No	
			UK clay loam	5.3	306	168	No	
	'Met 8'	315	UK clay loam	6.1	363[(b)]	363[(b)]	No	
25	Unknown	Unknown	Manningtree sandy loam, standard	5.9	365[(b)]	Un-known[(c)]	No[(d)]	Simmonds et al. (1996)
	Unknown	Unknown	Manningtree sandy loam, red. rate	5.2	365[(b)]	Un-known[(c)]	No[(d)]	

(a) Considered to actually comprise two substances with a MWT of 333 and 349 at more or less equimolar amounts (refer to text below)
(b) Last day of incubation
(c) The study report does not contain tabulated results on individual metabolite fractions
(d) Confirmed by the RMS AT on basis of GLP raw data

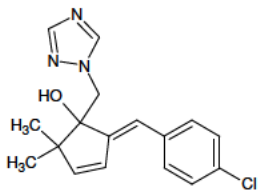
One of these unknown metabolites, called **'Met 6 (MWT 333)'** in Ayliffe & Austin (1993), occurring at max. 12.8 % AR in one soil, was originally claimed being identified as RPA 407922 in Ayliffe & McMillan-Staff (1994). This identification was also accepted for first Annex I approval triggering a number of additional studies with RPA 407922 (amongst them metabolite dosed degradation and sorption studies as well as ecotox studies). However, on basis of information provided by Simmonds & Lowden (2002), applying the same isocratic HPLC

methods as used in Ayliffe & Austin (1993) and Ayliffe & McMillan-Staff (1994), and considering further information given in Doble et al. (1996) and Simmonds et al. (1996), the RMS AT now challenges 'Met 6 (MWT 333)' being RPA 407922 (for more information please refer to Ayliffe & McMillan-Staff, 1994, and Simmonds & Lowden, 2002). For that reasons, the applicant was requested by the RMS AT to further underpin their peak assignment. The applicant performed HPLC analysis of the reference substances RPA 407922 and RPA 406341 (Trans-diol) with the same type of columns and same isocratic and gradient conditions as in Ayliffe & Austin (1993) and Ayliffe & McMillan-Staff (1994). The retention times obtained by the authors could not be reproduced. A complete separation of the two peaks could not be shown unambiguously. Finally, the applicant agreed with the conclusion of the RMS AT that 'Met 6 (MWT 333)' in the chromatogram does not belong to the metabolite RPA 407922 but to an unidentified structure. The RMS AT notes that the supporting additional HPLC runs conducted by the applicant have not been submitted to the RMS AT.

On basis of the proposed MWT in Ayliffe & Austin (1993) the applicant concluded that 'Met 6 (MWT 333)' probably represents another mono-hydroxylated triticonazole derivative. Excluding already known mono-hydroxylated derivatives, the applicant came to the conclusion that there is only one possible structure remaining (refer to Szegedi, 2018). The RMS AT agrees with the study author, that 'Met 6 (MWT 333)' probably comprises another mono-hydroxylated derivative of triticonazole. However, as demonstrated in Ta & Strobush (2012), there are other mono-hydroxylated structures of triticonazole possible (and already identified) beside those ones considered by Szegedi (2018), all having the same mol mass of 333.8 g/mol (refer to Ta & Strobush, 2012). Based on findings in Ta & Strobush (2012) other structures are indeed considered more reliable. Notice that triticonazole derivatives hydroxylated at the chlorophenyl ring (e.g. RPA 407922) have never been unambiguously identified in any of the soil degradation studies. On overall, the RMS AT considers the exact structure of 'Met 6 (MWT 333)' still uncertain.

The applicant further concluded that **'Met 7 (MWT 315)'**, observed above 5 % AR in Ayliffe & Austin (1993) as well, probably represents a triticonazole derivative with an additional unsaturation in the cyclopentane ring (Figure B.8.1.1.4-3). The same structure was observed in a recent study (Ta & Strobush, 2012) in a similar position of the HPLC chromatogram (below 5 % AR). In general, the RMS AT considers the structure proposal for 'Met 7 (MWT 315)', albeit not fully verified by authentic reference material, scientifically valid and reliable. Nevertheless, the applicant is asked to further support this identification by chromatographic studies with authentic reference material.

Figure B.2.7.1-1: Proposed structures of the metabolite fraction 'Met 7 (MWT (315)' observed > 5 % AR at two consecutive sampling points in Ayliffe & Austin (1993)



(*R/S*-isomers)

'Met 7 (MWT 315)'

On basis of additional work done by Simmonds & Lowden (2002) with one additional soil, metabolite fraction 'Met 5 (MWT 349)' observed in Ayliffe & Austin (1993) above 5 % at two consecutive sampling points appears to actually comprise two unidentified compounds at more or less equimolar amounts, one with a mol mass of 333 g/mol and one with a mol mass of 349 g/mol, probably unknown mono- and di-hydroxylated derivatives of triticonazole.

The applicant claims that all unknown degradation products were observed in legacy studies beyond 120 DAT, which would be the study duration according to the respective OECD guidance. Accordingly, considering current guidance documents, no exposure or risk assessment would be necessary for the previously not identified and not reproducible degradation product. The RMS AT notes that OECD guideline 307 indeed recommends continuing the incubation for longer periods (e.g. 6 or 12 months) *where necessary* to characterise the decline of the test substance and the formation and decline of major transformation products. In view of the limited degradation of triticonazole in aerobic laboratory soil incubation experiments accompanied by late formation of degradation products the RMS AT does not agree with the applicant and considers the entire one-year incubation

period representative for triggering additional work on metabolites in line with Regulation (EU) No 283/2013. Notice that on basis of soil microbial biomass measurements at the start and end of incubation none of these soils is considered being microbially exhausted during the incubation. The RMS AT also notes that OECD guideline 307 recommends additional incubation experiments at 10 °C if the chemical is applied or released in colder climates (e.g. in northern countries, during autumn/winter periods). As triticonazole is intended to be used as seed treatment in spring and winter cereals, the RMS AT indeed considers studies conducted at 10 °C equally representative for triggering additional work on metabolites.

The RMS AT considers it worthwhile to notice that the common triazole fungicide metabolites 1,2,4-triazole and 1,2,4-triazole-1-ylacetic acid have been hardly found (< 5 % AR) in any of the soil degradation experiments investigating triazole labelled parent.

Under aerobic conditions mineralisation to CO_2 is rather limited with 0.1 - 8.1 % AR around 120 DAT, formation of non-extractable residues (NER) is limited as well with 4.5 - 27.3 % AR around 120 DAT.

Degradation of triticonazole under **anaerobic conditions** was not significant and did only lead to minor metabolites as well as to the formation of non-extractable residues (max. 25.2 % AR). Formation of CO_2 was insignificant at all. Notice that anaerobic soil incubation was conducted with phenyl labelled parent only. In view of the results obtained, it is unlikely that applying the triazole label would lead to any new results.

Photolysis on soil surface contributes to the dissipation of triticonazole in soil (if exposed to light), resulting mainly in the formation of **RPA 406203**, the Z-isomer of triticonazole. The reaction from triticonazole (E-isomer) to RPA 406203 (Z-isomer) is considered fully reversible, finally leading to equilibrium of both substances with time. Formation of CO_2 (1.3 % AR after 30 days) and NER (4.1 % AR after 30 days) was limited under conditions of soil photolysis. It is noted that soil photolysis was conducted with phenyl labelled parent only. However, in view of the intended use as seed treatment, triticonazole is not expected to be exposed to light and, therefore, soil photolysis is not considered to be relevant in soil at all.

Figure B.2.7.1-2: **Proposed route of degradation of triticonazole in soil (notice that all these structures represent racemic mixtures of two isomers with the isomer underlined indicating the isomer structure actually shown in this figure)**

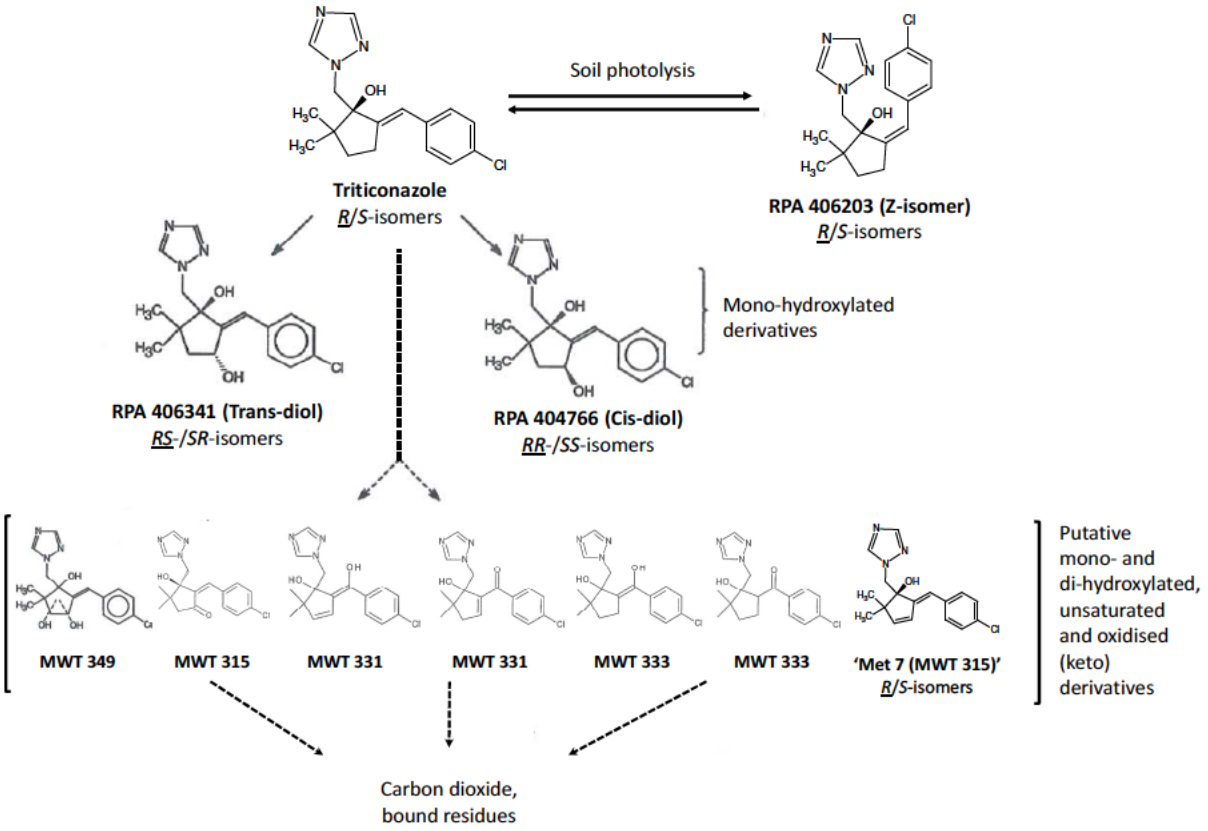


Table B.2.7.1-2 **Summary on maximum occurrence (% AR) of identified and non-identified (unknown) metabolites in laboratory soil route studies conducted with triticonazole (metabolites shaded in grey require an exposure assessment in soil, groundwater and surface water)**

Compound	Aerobic (10 °C)	Aerobic (20 - 25 °C)	Anaerobic	Soil photolysis
RPA 406341 (Trans-diol)	16.1	20.2	1.8[a]	3.5
RPA 404766 (Cis-diol)	13.9	9.9	2.0	3.3
RPA 406203 (Z-isomer)[b]	4.4	4.1	-	11.0
Metabolite fraction 'Met 6 (MWT 333)'[c]	6.9[e]	12.8	-	-
Metabolite fraction 'Met 7 (MWT 315)'[d]	6.1[e]	6.5	-	-

(a) At onset of anaerobic phase (30 DAT)
(b) RPA 406203 (Z-isomer) has to be included in the exposure assessment only in case of spray applications (if there is exposure to irradiation at the soil surface)
(c) 'Met 6' in Ayliffe & Austin (1993), equivalent to 'Met 7' in Ayliffe & Godward (1993)
(d) 'Met 7' in Ayliffe & Austin (1993), equivalent to 'Met 8' in Ayliffe & Godward (1993)
(e) Not above 5 % AR at two consecutive sampling points

Isomeric composition of triticonazole and its metabolites

Triticonazole is a racemic mixture of the two enantiomers (*R*)-(5*E*)-5-(4-chlorobenzylidene)-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol and (*S*)-(5*E*)-5-(4-chlorobenzylidene)-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol. Chiral analysis of representative soil extracts (up to 365 DAT) shows that both the *R* and *S* isomers of the racemic parent are comparably degradable. There is no indication for a significant shift in the *R*/*S* ratio during degradation in aerobic soils.

Metabolites RPA 406341 (Trans-diol) and RPA 404766 (Cis-diol) are diastereomers which are hydroxylated at the same position in the cyclopentane ring. Metabolite RPA 406341 (Trans-diol) includes the two enantiomers for which the hydroxyl group has the opposite orientation as the second hydroxyl group in the cyclopentane ring (*RS*, *RS* isomers). Metabolite RPA 404766 (Cis-diol) includes the two enantiomers for which both hydroxyl groups have the same orientation (*RR*, *SS* isomers). Chiral analysis of RPA 406341 (Trans-diol) in representative soil extracts show that an enantioselective degradation of the metabolites is unlikely to occur.

Sorption and soil metabolism data show different behaviour of the two major soil metabolites. This observation is in line with physicochemical principles and expectations based on different steric forces around these molecules.

Rate of degradation

Studies on rate of degradation in soil with the formulation were not performed, since it is possible to extrapolate from data obtained with the active substance.

The rate of degradation in soil of triticonazole and metabolites has been assessed in laboratory studies and is summarised in the tables below. Notice that the kinetic assessment provided by the RMS AT is based on the entire period of incubation (so one year in most cases). Metabolite RPA 407922 is not considered to occur at significant amounts in soil degradation studies. Therefore degradation data obtained for RPA 407922 in a dedicated soil degradation study are not considered further. Conservative degradation rates and formation fractions for the two metabolite fractions 'Met 6 (MWT 333)' and 'Met 7 (MWT 315)' have been obtained in a separate position paper (Szegedi, 2018).

Table B.2.7.1-3 Summary on aerobic degradation rates of triticonazole in laboratory soil degradation studies conducted at 20 - 25 °C - trigger & modelling endpoints

Soil origin	Soil type (USDA)	Label	*p*H ($CaCl_2$)	T (°C)	Water content	*DegT50* (d)	*DegT90* (d)	*DegT50* (d) 20 °C, *p*F2	χ^2 err. (%)	Kinetic model	Ref.[a]
UK	Sandy loam[b]	Ph	6.4[c]	22	75 % 33 kPa	289	> 1000	280[d]	5.0	HS	1
UK	Clay loam[b]	Ph	6.2[c]	22	75 % 33 kPa	137	455	148	4.4	SFO	
Speyer 2.2	Loamy sand[b]	Ph	6.8[c]	22	75 % 33 kPa	233	986	360[d]	5.0	HS	2
UK	Loamy sand[b]	Ph	6.3[c]	22	75 % 33 kPa	290	> 1000	565[d]	4.2	HS	3
US	Clay	T	5.7	25	75 % 33 kPa	495	> 1000	376	5.7	SFO	4
Manningtree	Sandy loam	Ph	6.1	25	50 % FC	183[c] 221[f]	702 816	312[d] 358[d]	3.3 6.5	HS HS	5
California	Sand	T	8.1[h]	20	50 % MHWC	305	> 1000	262	3.1	SFO	
New Jersey	Loam	Ph & T	6.8[h]	20	50 % MHWC	78.8	661	230[d]	2.4	DFOP	6
Wisconsin	Sandy loam	T	6.0[h]	20	50 % MHWC	128	664	199[d]	3.2	DFOP	
Li 10	Loamy sand	Ph & T	6.3	20	50 % MWHC	148	633	178[d]	1.0	DFOP	7
LUFA 2.2	Loamy sand	-	5.5	20	50 % MWHC	317	> 1000	298	7.3	SFO	
LUFA 2.3	Sandy loam	-	6.9	20	50 % MWHC	115	381	109	5.9	SFO	8
LUFA 5M	Sandy loam	-	7.4	20	50 % MWHC	114	521	161[d]	6.3	HS	
					Maximum (n = 13)	**495**	**> 1000**	-	-	SFO	
					Geometric mean (n = 13)[g]	-	-	**246**	-	SFO	
					pH-dependency: y/n	**n**	-	**-**	-	-	

(a) Reference:
1: Ayliffe & Austin (1993)
2: Ayliffe & McMillan-Staff (1994)
3: Ayliffe & Godward (1993)
4: Doble et al. (1996)
5: Simmonds et al. (1996)
6: Ta & Strobush (2012)
7: Ta & Strobush (2015)
8: Grella et al. (2014)
(b) Soil texture classification not specified
(c) Matrix not specified
(d) On basis of slow phase *DegT50* (DFOP or HS)
(e) Standard conditions
(f) Reduced application rate
(g) Two experiments in Simmonds et al. (1996) averaged (geometric mean) before averaging different soils
(h) In water

Table B.2.7.1-4 Summary on aerobic degradation rates of triticonazole in laboratory soil degradation studies conducted at 10 °C or reduced soil moisture

Soil origin	Soil type (USDA)	Label	*p*H ($CaCl_2$)	T (°C)	Water content	*DegT50* (d)	*DegT90* (d)	*DegT50* (d) 20 °C, *p*F2	χ^2 err. (%)	Kinetic model	Reference
UK	Sandy loam[a]	Ph	6.3[b]	10	75 % 33 kPa	341	> 1000	nc	3.5	DFOP	Ayliffe & Godward (1993)
UK	Clay loam[a]	Ph	6.1[b]	10	75 % 33 kPa	176	892	nc	5.0	HS	
Speyer 2.2	Loamy sand[a]	Ph	6.3 [b]	10	75 % 33 kPa	> 1000	> 1000	nc	2.6	HS	
UK	Loamy sand[a]	Ph	6.2[b]	10	75 % 33 kPa	862	> 1000	nc	3.9	HS	
Manning-tree	Sandy loam	Ph	6.1	10	50 % FC	584	> 1000	nc	4.5	SFO	Simmonds et al. (1996)
				25	20 % FC	259	> 1000	nc	13.1	DFOP	

(a) Soil texture classification not specified
(b) Matrix not specified

Table B.2.7.1-5 Summary on aerobic degradation rates of RPA 406341 (Trans-diol) in laboratory soil degradation studies conducted at 20 - 25 °C - trigger & modelling endpoints

Soil origin	Soil type (USDA)	Label	*p*H ($CaCl_2$)	T (°C)	Water content	*DegT 50* (d)	*DegT 90* (d)	*ff*[i]	*DegT50* (d) 20 °C, *p*F2	χ^2 err. (%)	Kinetic model	Ref.[a]
UK	Sandy loam[b]	Ph	6.4[c]	22	75 % 33 kPa	80.1	266	0.426	56.1	13.2	P_{HS}→M_{SFO}	1
UK	Clay loam[b]	Ph	6.2[c]	22	75 % 33 kPa	68.5	228	0.372	74.0	17.3	P_{SFO}→M_{SFO}	
Speyer 2.2	Loamy sand[b]	Ph	6.8[c]	22	75 % 33 kPa	405	> 1000	0.390	450	7.5	P_{HS}→M_{SFO}	2
UK	Loamy sand[b]	Ph	6.3[c]	22	75 % 33 kPa	105	349	0.473	127	21.3	P_{HS}→M_{SFO}	3
US	Clay	T	5.7	25	75 % 33 kPa	170	566	0.583	139	17.4	P_{SFO}→M_{SFO}	4
Manningtree	Sandy loam	Ph	6.1	25	50 % FC	188[d]	623	0.510	263	7.1	P_{HS}→M_{SFO}	5
						207[e]	686	0.607	290	5.9	P_{HS}→M_{SFO}	
California	Sand	T	8.1[h]	20	50 % MHWC	462	> 1000	0.207	397	10.1	P_{SFO}→M_{SFO}	6
New Jersey	Loam	Ph & T	6.8[h]	20	50 % MHWC	208	692	0.118	185	7.8	P_{DFOP}→M_{SFO}	
Wisconsin	Sandy loam	T	6.0[h]	20	50 % MHWC	176	584	0.160	151	6.3	P_{DFOP}→M_{SFO}	
Li 10	Loamy sand	Ph & T	6.3	20	50 % MWHC	202	670	0.178	172	5.8	P_{DFOP}→M_{SFO}	7
Royston	Clay Loam	Ph	7.0	20	45 % MWHC	165	549	na	102	2.0	SFO	8
Ipswich	Sandy Loam	Ph	5.3	20	45 % MWHC	199	661	na	143	2.3	SFO	
Ongar	Loam	Ph	6.2	20	45 % MWHC	346	> 1000	na	232	3.5	SFO	
					Maximum (n = 13)	**462**	**> 1000**	-	-	-	SFO	
					Geometric mean (n = 13)[f]	-	-	**-**	**163**	-	SFO	
					Arithmetic mean (n = 13)[g]	-	-	**0.347**	**-**	-		
					***p*H-dependency: y/n**	**n**	-	**-**	**-**	-		

(a) Reference:
1: Ayliffe & Austin (1993)
2: Ayliffe & McMillan-Staff (1994)
3: Ayliffe & Godward (1993)
4: Doble et al. (1996)
5: Simmonds et al. (1996)
6: Ta & Strobush (2012)
7: Ta & Strobush (2015)
8: McGhee (2000)
(b) Soil texture classification not specified
(c) Matrix not specified
(d) Standard conditions
(e) Reduced application rate
(f) Two experiments in Simmonds et al. (1996) averaged (geometric mean) before averaging different soils
(g) Two experiments in Simmonds et al. (1996) averaged (arithmetic mean) before averaging different soils
(h) In water
(i) From parent

Table B.2.7.1-6 Summary on aerobic degradation rates of RPA 406341 (Trans-diol) in laboratory soil degradation studies conducted at 10 °C or reduced soil moisture

Soil origin	Soil type (USDA)	Label	*p*H ($CaCl_2$)	T (°C)	Water content	*DegT 50* (d)	*DegT 90* (d)	*ff*[d]	*DegT 50* (d) 20 °C, *p*F2	χ^2 err. (%)	Kinetic model	Ref.[a]
UK	Clay loam[b]	Ph	6.1[c]	10	75 % 33 kPa	309	> 1000	0.370	nc	12.5	P_{HS}→M_{SFO}	1
Manningtree	Sandy loam	Ph	6.1	10	50 % FC	393	> 1000	0.736	nc	18.5	P_{SFO}→M_{SFO}	2

(a) Reference:
1: Ayliffe & Godward (1993)
2: Simmonds et al. (1996)
(b) Soil texture classification not specified
(c) Matrix not specified
(d) From parent

Table B.2.7.1-7 Summary on aerobic degradation rates of RPA 404766 (Cis-diol) in laboratory soil degradation studies conducted at 20 - 25 °C - trigger & modelling endpoints

Soil origin	Soil type (USDA)	Label	*p*H ($CaCl_2$)	T (°C)	Water content	*DegT 50* (d)	*DegT 90* (d)	*ff*[i]	*DegT 50* (d) 20 °C, *p*F2	χ^2 err. (%)	Kinetic model	Ref.[a]
UK	Clay loam[b]	Ph	6.2[c]	22	75 % 33 kPa	22.7	75.5	0.628	24.5	19.1	P_{SFO}→M_{SFO}	1
Speyer 2.2	Loamy sand[b]	Ph	6.8[c]	22	75 % 33 kPa	155	516	0.365	172	9.5	P_{HS}→M_{SFO}	2
UK	Loamy sand[b]	Ph	6.3[c]	22	75 % 33 kPa	42.0	141	0.448	50.8	26.2	P_{HS}→M_{SFO}	3
US	Clay	T	5.7	25	75 % 33 kPa	213	707	0.418	175	22.6	P_{SFO}→M_{SFO}	4
Manningtree	Sandy loam	Ph	6.1	25	50 % FC	95.0[d] 98.2[e]	315 326	0.354 0.393	133 137	12.4 6.2	P_{HS}→M_{SFO} P_{HS}→M_{SFO}	5
California	Sand	T	8.1[h]	20	50 % MHWC	170	566	0.305	146	9 9	P_{SFO}→M_{SFO}	6
New Jersey	Loam	Ph & T	6.8[h]	20	50 % MHWC	139	461	0.181	124	4.2	P_{DFOP}→M_{SFO}	
Wisconsin	Sandy loam	T	6.0[h]	20	50 % MHWC	148	493	0.214	127	4.8	P_{DFOP}→M_{SFO}	
Li 10	Loamy sand	Ph & T	6.3	20	50 % MWHC	93.5	311	0.243	79.5	4.5	P_{DFOP}→M_{SFO}	7
Baylham	Sandy loam	Ph	4.5	20	*p*F2.5 - 2	30.9	103	na	30.9	7.2	SFO	
Royston	Silty clay loam	Ph	7.2	20	*p*F2.5 - 2	20.8	69.0	na	20.8	15.8	SFO	8
Ongar	Clay loam	Ph	6.9	20	*p*F2.5 - 2	56.1	187	na	56.1	9.1	SFO	
					Maximum (n = 12)	**213**	**707**	-	-	-	SFO	
					Geometric mean (n = 12)[f]	-	-	**-**	**75.3**	-	SFO	
					Arithmetic mean (n = 12)[g]	-	-	**0.353**	**-**	-		
					***p*H-dependency: y/n**	**n**	**-**	**-**	**-**	**-**		

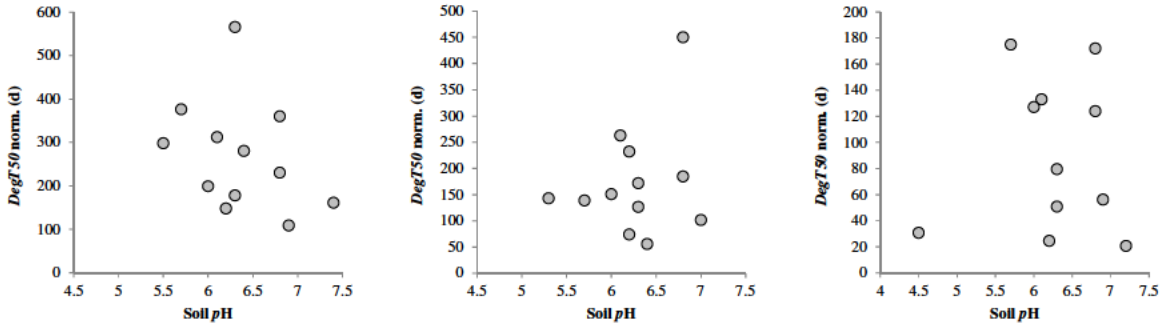
(a) Reference:
1: Ayliffe & Austin (1993)
2: Ayliffe & McMillan-Staff (1994)
3: Ayliffe & Godward (1993)
4: Doble et al. (1996)
5: Simmonds et al. (1996)
6: Ta & Strobush (2012)
7: Ta & Strobush (2015)
8: Crowe (2002)
(b) Soil texture classification not specified
(c) Matrix not specified
(d) Standard conditions
(e) Reduced application rate
(f) Two experiments in Simmonds et al. (1996) averaged (geometric mean)
(g) Two experiments in Simmonds et al. (1996) averaged (arithmetic mean)
(h) In water
(i) From parent

Table B.2.7.1-8 Summary on aerobic degradation rates of RPA 404766 (Cis-diol) in laboratory studies conducted at 10 °C or reduced soil moisture

Soil origin	Soil type (USDA)	Label	*p*H ($CaCl_2$)	T (°C)	Water content	*DegT 50* (d)	*DegT 90* (d)	*ff*[d]	*DegT 50* (d) 20 °C, *p*F2	χ^2 err. (%)	Kinetic model	Ref.[a]
UK	Clay loam[b]	Ph	6.1[c]	10	75 % 33 kPa	140	464	0.405	nc	21.2	P_{HS}→M_{SFO}	1
Manningtree	Sandy loam	Ph	6.1	25	20 % FC	296	983	0.209	nc	7.0	P_{DFOP}→M_{SFO}	2

(a) Reference:
1: Ayliffe & Godward (1993)
2: Simmonds et al. (1996)
(b) Soil texture classification not specified
(c) Matrix not specified
(d) From parent

The RMS AT investigated degradation rates of triticonazole and its metabolites in relation to soil *p*H. No such relationship could be established (see figure below).



Triticonazole **RPA 406341 (Trans-diol)** **RPA 404766 (Cis-diol)**

Figure B.2.7.1-3: Normalized *DegT50* of triticonazole, RPA 406341 (Trans-diol) and RPA 404766 (Cis-diol) in relation to soil *p*H

The RMS AT notes that the metabolite fractions **'Met 6 (MWT 333)'** and **'Met 7 (MWT 315)'** have been observed in four legacy soil degradation experiments (conducted at 22 °C) at maximum amounts of 12.8, 4.2, 1.6 and 6.2 % AR ('Met 6 (MWT 333)') and 6.5, 0.9, 3.6 and 5.3 % AR ('Met 7 (MWT 315)') (Ayliffe & Austin, 1993; Ayliffe & McMillan-Staff, 1994; Ayliffe & Godward, 1993). Maximum residues were generally observed at the end of incubation (~ 365 days) or close to the end of incubation. In analogy to averaging substance properties (*DegT50* and formation fraction) of the parent and metabolites in the exposure assessment, the RMS AT considers it defendable to conduct the groundwater assessment for 'Met 6 (MWT 333)' and 'Met 7 (MWT 315)' also on basis of an average (arithmetic mean) occurrence in soil, which is 6.2 and 4.1 % AR for 'Met 6 (MWT 333)' and 'Met 7 (MWT 315)', respectively. Coupling the geometric mean *DegT50* of 78.7 days for the parent (i.e. the modelling endpoint derived from field studies, refer to Chapter B.8.1.2.3, summary on field dissipation/degradation) with a conservative *DegT50* of 1000 days for the two metabolite fractions, a maximum occurrence in the exposure modelling of 6.2 and 4.1 % for 'Met 6 (MWT 333)' and 'Met 7 (MWT 315)', respectively, is archived if the formation fraction is set to **0.077** and **0.051** for 'Met 6 (MWT 333)' and 'Met 7 (MWT 315)', respectively. On overall, the RMS AT considers residues of these two metabolite fractions observed in legacy studies sufficiently covered by this approach.

Under **anaerobic conditions** triticonazole is considered to be stable.

In comparison to dark conditions, the rate of degradation of triticonazole under conditions of **photolysis on soil surface** is relatively fast (*DissT50* of 65.3 days under environmental conditions, 50 °N). However, as triticonazole is intended to be used as a seed treatment the impact of soil photolysis is negligible.

Field dissipation/degradation

The dissipation/degradation of **triticonazole** under realistic outdoor conditions has been assessed in eight field dissipation trials spread all over Europe (IT, DE, UK, FR, ES). Triticonazole was incorporated into bare soils at a nominal application rate of 240 g/ha immediately before planting of winter cereals (in one field trial triticonazole

was actually applied as a seed treatment). Notice that all these field trials are clearly overdosed in view of an intended application rate of 12.5 g ai/ha only. In principal, cropping in field trials is not in line with EFSA guidance on *DegT50* (EFSA, 2014)[1] recommending the soil to be kept free from vegetation in order to exclude any possible uptake by plants. However, as the intended use is indeed seed treatment in winter & spring cereals, the RMS AT considers the *DegT50* values obtained in these field trials at least sufficiently robust for the intended use. Notice that plant uptake has to be switched off in exposure models in order to avoid double counting of plant uptake. Using *DegT50* values obtained in these field trials for uses other than winter & spring cereals or at significantly deviating crop stages in winter & spring cereals will be subject to some uncertainties.

Table B.2.7.1-9 **Summary on non-normalized field dissipation rates of triticonazole - trigger endpoints**

Field trial	Soil type (USDA)	*p*H ($CaCl_2$)	*DissT50* (d)	*DissT90* (d)	χ^2 err. (%)	Kinetic model	Reference
Bologna (IT)	Loam	8.4[(a)]	169	563	32.5	SFO	Wicks (1996)
Goch (DE)	Sandy loam	6.6[(a)]	183	609	28.5	SFO	
Manningtree (UK) - Spray	Sandy loam	5.3[(a)]	55.0	633	13.5	DFOP	
Manningtree (UK) - Seed treat.	Sandy loam	5.3[(a)]	223	741	38.2	SFO	
Mereville (FR)	Silty clay loam	7.8[(a)]	204	678	17.6	SFO	
Brentwood (UK)	Sandy silt loam	7.3	242	803	27.8	SFO	Duncan et al. (2003)
Saint Trivier sur Moignans (FR)	Sandy silt loam	7.1	118	392	21.1	SFO	
Balaguer (ES)	Clay loam	7.4	99.1	329	31.4	SFO	
Goch (DE)	Sandy silt loam	6.7	36.1	477	8.2	DFOP	
	Maximum (n = 9)		**242**	**803**	**-**	**SFO**	

(a) Measured in water

Table B.2.7.1-10 **Summary on time-step normalized field degradation rates of triticonazole - modelling endpoints**

Field trial	Soil type (USDA)	*p*H ($CaCl_2$)	*DegT50* (d)	*DegT90* (d)	χ^2 err. (%)	Kinetic model	Modelling *DegT50 (d)*	Ref.
Bologna (IT)	Loam	8.4[(a)]	78.9	262	20.7	SFO	78.9	Wicks (1996)
Goch (DE)	Sandy loam	6.6[(a)]	66.9	222	28.7	SFO	66.9	
Manningtree (UK) - Spray	Sandy loam	5.3[(a)]	15.4	281	13.0	DFOP	84.6[(b)]	
Manningtree (UK) - Seed treat.	Sandy loam	5.3[(a)]	90.4	300	33.2	SFO	90.4	
Mereville (FR)	Silty clay loam	7.8[(a)]	35.7	441	13.5	HS	133[(b)]	
Brentwood (UK)	Sandy silt loam	7.3	101	337	30.3	SFO	101	Duncan et al. (2003)
Saint Trivier sur Moignans (FR)	Silty silt loam	7.1	51.2	170	16.9	SFO	51.2	
Balaguer (ES)	Clay loam	7.4	15.2	245	28.5	HS	73.8[(b)]	
Goch (DE)	Sandy silt loam	6.7	12.2	208	9.4	DFOP	62.7[(b)]	
	Geometric mean (n = 8)[(c)]		**-**	**-**	**-**	**SFO**	**78.7**	
	***p*H-dependency: y/n**		**-**	**-**	**-**	**-**	**n[(d)]**	

(a) Measured in water
(b) Pseudo-SFO *DegT50* based on DFOP or HS overall *DegT90* divided by 3.32 (as residues at study end are clearly below 10 % of initial dose)
(c) Different experiments from Manningtree field site (spray and seed treatment) averaged (geometric mean) before averaging results from different field sites
(d) Refer to text below

The RMS AT investigated field degradation rates of triticonazole in relation to soil *p*H. No such relationship could be established (see figure below).

[1] EFSA (2014) EFSA 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

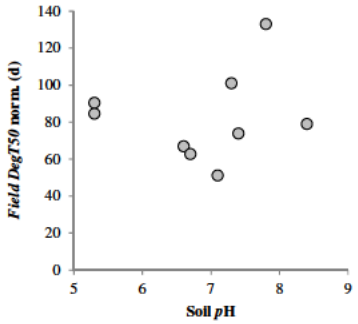


Figure B.2.7.1-4: Time-step normalized field *DegT50* of triticonazole in relation to soil *p*H

The RMS AT notes that in case of the ground water exposure assessment the obtained geometric *DegT50* of 78.7 days, based on a mixture of SFO *DegT50* values and pseudo *DegT50* values from DFOP and HS fits, is of course conservative for the parent triticonazole but not necessarily conservative for its metabolites. In case of biphasic degradation the FOCUS degradation report 2006 (EC, 2014) gives the option to perform the exposure assessment on basis of two separate runs, the first on basis of the slow DFOP/HS degradation rates and the second on basis of the fast phase DFOP/HS degradation rate. The highest concentration of the two sets may then be used in the risk assessment.

In case of this dataset degradation rates from SFO and DFOP/HS models are mixed making the situation more complicated. As already indicated in a draft guidance document, prepared by CRD in view of supporting the current FOCUS degradation kinetics guidance, this situation may be handled assuming the SFO model a special case of the DFOP model with SFO-k = DFOP-k_1 = DFOP-k_2 and g undefined. In analogy, the SFO may also be considered a special case of the HS model with an undefined split point (t_b). If applied to the time-step normalized triticonazole dataset this gives a geometric fast phase *DegT50* of 35.8 days and a geometric slow phase *DegT50* of 98.2 days (see table below). In line with the FOCUS approach mentioned above an additional exposure assessment may therefore be performed on basis of a SFO model with a geometric fast phase *DegT50* of 35.8 days.

Table B.2.7.1-11 Summary on normalized field degradation rates of triticonazole - alternative approach for deriving modelling endpoints for the fast and slow degradation phase

Field trial	Soil type (USDA)	*p*H ($CaCl_2$)	Fast phase *DegT50* (d)	Slow phase *DegT50* (d)	DFOP-*g*	Kinetic model	Ref.
Bologna (IT)	Loam	8.4[a]	78.9[b]	78.9[b]	na	SFO	Wicks (1996)
Goch (DE)	Sandy loam	6.6[a]	66.9[b]	66.9[b]	na	SFO	
Manningtree (UK) - Spray	Sandy loam	5.3[a]	6.9	140	0.60	DFOP	
Manningtree (UK) - Seed treat.	Sandy loam	5.3[a]	90.4[b]	90.4[b]	na	SFO	
Mereville (FR)	Silty clay loam	7.8[a]	35.7	191	na	HS	
Brentwood (UK)	Sandy silt loam	7.3	101[b]	101[b]	na	SFO	Duncan et al. (2003)
Saint Trivier sur Moignans (FR)	Silty silt loam	7.1	51.2[b]	51.2[b]	na	SFO	
Balaguer (ES)	Clay loam	7.4	15.2	111	na	HS	
Goch (DE)	Sandy silt loam	6.7	7.3	133	0.71	DFOP	
	Geometric mean (n = 8)[c]		**35.8**	**98.2**	-		
	***p*H-dependency: y/n**		**n**	-	-		

(a) In water
(b) SFO model considered as a special case of a DFOP or HS model with $k_1 = k_2$ and g and t_b, respectively, undefined
(c) Data from Manningtree soil (spray and seed treatment) averaged (geometric mean) before averaging different soils

The dissipation/degradation of the metabolite **RPA 406341 (Trans-diol)** under realistic outdoor conditions has been assessed in four field dissipation trials spread all over Europe (DE, BE, FR and ES). RPA 406341 (Trans-diol) was sprayed on bare soils at a nominal application rate of 100 g/ha followed by irrigation to satisfy requirements given in EFSA (2014). Obtained dissipation/degradation rates are given in the tables below. It is noted that application of RPA 306341 (Trans-diol) in these field trials was in late August/early September. This application date may not necessarily be considered representative for the intended use in winter cereals. However, as the peak occurrence of metabolite RPA 406431 (Trans-diol) under real field situation is roughly

around late summer / early autumn in case of application in spring cereals and somewhere in spring in case of application in winter cereals dissipation rates obtained in this study are considered sufficiently robust for trigger endpoints as well as PEC soil calculation.

Table B.2.7.1-12 Summary on non-normalized field dissipation rates of RPA 406341 (Trans-diol)

Field trial	Soil type[(a)] (USDA)	*p*H[(a)] ($CaCl_2$)	*DissT50* (d)	*DissT90* (d)	χ^2 error (%)	Kinetic model	Reference
Goch-Nierswalde (DE)	Silt loam	4.7	58.2	193	13.8	SFO	Richter (2009)
Rummen (BE)	Silt loam	5.1	78.9	262	20.7	SFO	
Meauzac (FR)	Loam	5.4	123	407	16.3	SFO	
Alberic/Valencia (ES)	Clay	7.6	25.5	84.7	28.8	SFO	
	Maximum (n = 4)		**123**	**407**	**-**	**SFO**	

(a) Top soil

Table B.2.7.1-13 Summary on time-step normalized (20 °C and *p*F 2) field degradation rates of RPA 406431 (Trans-diol) - modelling endpoints

Field trial	Soil type[(a)] (USDA)	*p*H[(a)] ($CaCl_2$)	*DegT50* (d)	*DegT90* (d)	χ^2 error (%)	Kinetic model	Reference
Goch-Nierswalde (DE)	Silt loam	4.7	34.8	116	10.9	SFO	Richter (2009)
Rummen (BE)	Silt loam	5.1	32.7	109	23.5	SFO	
Meauzac (FR)	Loam	5.4	55.8	186	12.8	SFO	
Alberic/Valencia (ES)	Clay	7.6	42.6	142	18.4	SFO	
	Geometric mean (n = 4)		**40.6**	**135**	**-**	**SFO**	
	***p*H-dependency: y/n**		**n**	**-**	**-**	**-**	

(a) Top soil

The RMS AT notes, that lab *DegT50* values of **RPA 404766 (Cis-diol)** are partly above 60 days thus triggering field dissipation/degradation studies for this metabolite as well. This is currently not the case and considered a data gap from a formal point of view. However, it may be noted that degradation of RPA 404766 (Cis-diol) in laboratory studies was consistently faster than degradation of RPA 406341 (Trans-diol) in all soils (with the exception of the US clay soil in Doble, 1996). Therefore, from a scientific point of view, the RMS AT considers field degradation data available for RPA 406341 (Trans-diol) sufficiently robust to serve as conservative estimates of RPA 404766 (Cis-diol) field degradation.

A comparison of the laboratory and field modelling endpoints on basis of the EXCEL sheet **EFSA *DegT50* selector** revealed that field studies with triticonazole show significantly shorter modelling *DegT50* values than laboratory studies (lab and field studies considered as different populations). The same is true for RPA 406431 (Trans-diol). Following EFSA guidance (EFSA, 2014), these results indicate that field degradation rates for triticonazole and RPA 406431 (Trans-diol) are appropriate modelling endpoints for the exposure assessment.

For triticonazole, a **field accumulation study** conducted in DE and UK at an elevated application rate of 112.5 g ai/ha (sprayed) revealed that after correction for the application rate the plateau concentration for triticonazole was in the range of 0.001 mg/kg with peak concentrations ranging from 0.0017 to 0.0043 mg/kg. Concentrations of the major soil metabolite RPA 406341 (Trans-diol) were below LOQ (0.002 mg/kg) except for five sampling points in DE (0.002 – 0.004 mg/kg, uncorrected).

Adsorption and mobility in soil

Soil adsorption of triticonazole, RPA 406341 (Trans-diol) and RPA 404766 (Cis-diol) in soil has been assessed in OECD guideline 106 batch studies and is summarised in the tables below. The RMS AT notes that the dossier on triticonazole accounts for several studies on sorption of triticonazole and the metabolites which may not be considered fully reliable owing to missing pre-equilibration phases in these experiments. However, as results obtained in studies without pre-equilibration phase are close to results with adequate pre-equilibration phase, results from these studies are considered equally reliable. It is noted that these studies have been repeated some few years later using the same soils (albeit different batches). Unfortunately, there is no guidance on when to assume a soil being 'identical' to another soil. On overall, the soils are considered fairly similar with respect to soil properties. However, in some cases there are quite some differences with respect to soil *p*H or organic matter as well as with respect to the sorption results obtained.

Table B.2.7.1-14 Summary on soil adsorption of triticonazole

Soil name	Soil type (USDA)	OC (%)	*p*H ($CaCl_2$)	K_d (mL/g)	K_{oc} (mL/g)	K_f (mL/g)	K_{foc} (mL/g)	1/*n* (-)	Ref.
Wildacker	Silt loam	1.85	5.7	na	na	11.8	636	0.92	Vasques (2015a)
LUFA 2.3	Sandy loam	0.99	6.7	na	na	3.67	370	0.89	
LUFA 2.1	Sand	0.60	5.6	na	na	5.23	871	0.93	
Li 10	Loamy sand	0.95	6.2	na	na	4.79	504	0.91	
La Gironda	Sandy clay loam	1.22	7.4	na	na	3.97	325	0.94	
Wildacker	Silt loam	2.01	5.8	na	na	13.4	665	0.893	Sim-monds (2017a)
LUFA 2.3	Sandy loam	0.66	5.3	na	na	4.52	685	0.898	
LUFA 2.1	Sand	0.72	5.6	na	na	5.60	778	0.889	
Li 10	Loamy sand	0.89	6.1	na	na	5.11	574	0.888	
La Gironda	Silty clay loam	1.92	7.1	na	na	5.56	290	0.848	
	Arithmetic mean (n = 10)			**-**	**-**	**-**	**-**	**0.90**	
	Geometric mean (n = 10)			**-**	**-**	**5.78**	**537**	**-**	
	Minimum[(b)]					**-**	**307**	**-**	
	Maximum[(c)]					**-**	**823**	**-**	
	pH-dependency: y/n			y[(a)]					

(a) Refer to text below
(b) Geometric mean of the two similar La Gironda soils (both sandy clay loam soils, *p*H 7.1 - 7.4).
(c) Geometric mean of the two similar LUFA 2.1 soils (both sand soils, *p*H 5.6)

Table B.2.7.1-15 Summary on soil adsorption of RPA 406341 (Trans-diol)

Soil name	Soil type (USDA)	OC (%)	*p*H ($CaCl_2$)	K_d (mL/g)	K_{oc} (mL/g)	K_f (mL/g)	K_{foc} (mL/g)	1/*n* (-)	Ref.
Wildacker	Clay silt	1.97	5.8	na	na	2.59	132	0.95	Vasques (2015b)
LUFA 2.3	Loamy sand	0.7	7.1	na	na	0.80	114	0.96	
LUFA 2.1	Sand	0.6	6.0	na	na	0.68	114	0.98	
Li 10	Silty sand	0.6	5.5	na	na	1.94	324	1.00	
La Gironda	Sandy clay loam	1.3	7.7	na	na	1.38	106	0.94	
Wildacker	Silt loam	2.01	5.8	na	na	3.72	185	0.919	Kingman (2017)
LUFA 2.3	Sandy loam	0.66	5.3	na	na	1.02	154	0.945	
LUFA 2.1	Sand	0.72	5.6	na	na	1.35	188	0.937	
Li 10	Loamy sand	0.89	6.1	na	na	1.31	148	0.932	
La Gironda[(a)]	Silty clay loam	1.92	7.1	na	na	1.57	81.6	0.839	
	Arithmetic mean (all soil, n = 10)			**-**	**-**	**-**	**-**	**0.94**	
	Geometric mean (all soil, n = 10)			**-**	**-**	**1.45**	**144**	**-**	
	pH-dependency: y/n			n					

(a) Sorption coefficients have been reassessed by the RMS AT excluding NER in the calculation (refer to Kingman, 2017)

Table B.2.7.1-16 Summary on soil adsorption of RPA 404766 (Cis-diol)

Soil name	Soil type (USDA)	OC (%)	*p*H ($CaCl_2$)	K_d (mL/g)	K_{oc} (mL/g)	K_f (mL/g)	K_{foc} (mL/g)	1/*n* (-)	Ref.
Wildacker	Clay silt	1.97	5.8	na	na	0.68	161	0.95	Vasques (2015b)
LUFA 2.3	Loamy sand	0.7	7.1	na	na	0.83	49.0	0.90	
LUFA 2.1	Sand	0.6	6.0	na	na	0.28	46.1	0.97	
Li 10	Silty sand	0.6	5.5	na	na	0.34	139	0.98	
La Gironda	Sandy clay loam	1.3	7.7	na	na	3.17	52.6	0.99	
Wildacker[(a)]	Silt loam	2.01	5.8	na	na	1.71	85.3	0.889	O'Brien (2017)
LUFA 2.3	Sandy loam	0.66	5.3	na	na	0.48	72.6	0.920	
LUFA 2.1	Sand	0.72	5.6	na	na	0.68	94.0	0.946	
Li 10	Loamy sand	0.89	6.1	na	na	0.67	74.8	0.922	
La Gironda[(a)]	Silty clay loam	1.92	7.1	na	na	1.03	53.6	0.868	
	Arithmetic mean (all soil, n = 10)			**-**	**-**	**-**	**-**	**0.93**	
	Geometric mean (all soil, n = 10)			**-**	**-**	**0.76**	**75.7**	**-**	
	pH-dependency: y/n			n					

(a) Sorption coefficients have been reassessed by the RMS AT excluding NER in the calculation (refer to O'Brian, 2017)

The RMS AT investigated a possible relationship between sorption coefficient (K_{foc}) and soil *p*H for triticonazole, RPA 406341 (Trans-diol) and RPA 404766 (Cis-diol) more in detail (see figure below). It may be noted that there are neither strong structural reasons nor evidence from phys-chem data to expect a strong *p*H effect (no dissociation, no *p*H effect on Log P_{ow} or solubility). The same is probably true for the metabolites RPA 406341 (Trans-diol) and RPA 404766 (Cis-diol), both structurally similar to the parent. Nevertheless, there

appears to be a fairly strong *p*H dependent sorption in case of the parent triticonazole with lower sorption in more alkaline soils with $p = 0.001$ applying Kendall's Tau-b test (two-tailed) on basis of the combined dataset. No such relationship could be found for the 1/*n* value. There is also some indication of *p*H dependent sorption for the two metabolites; however, the relationship is less obvious in these cases (although still significant ($p = 0.01$) in case of RPA 406341 (Trans-diol) applying Kendall's Tau-b test; no significant correlation is given in case of RPA 404766 (Cis-diol)). In order to adequately address these findings in the exposure assessment, the RMS AT recommends accounting for *p*H dependent sorption in case of triticonazole but not necessarily in case of the metabolites as *p*H dependency is much less pronounced for these substances. In case of triticonazole, the RMS AT recommends using the minimum/maximum K_{foc} (307 and 823 mL/g, respectively, both calculated on basis of two similar soils) in combination with the arithmetic mean 1/*n* of 0.90 derived on basis of the entire dataset for the groundwater and surface water exposure assessment.

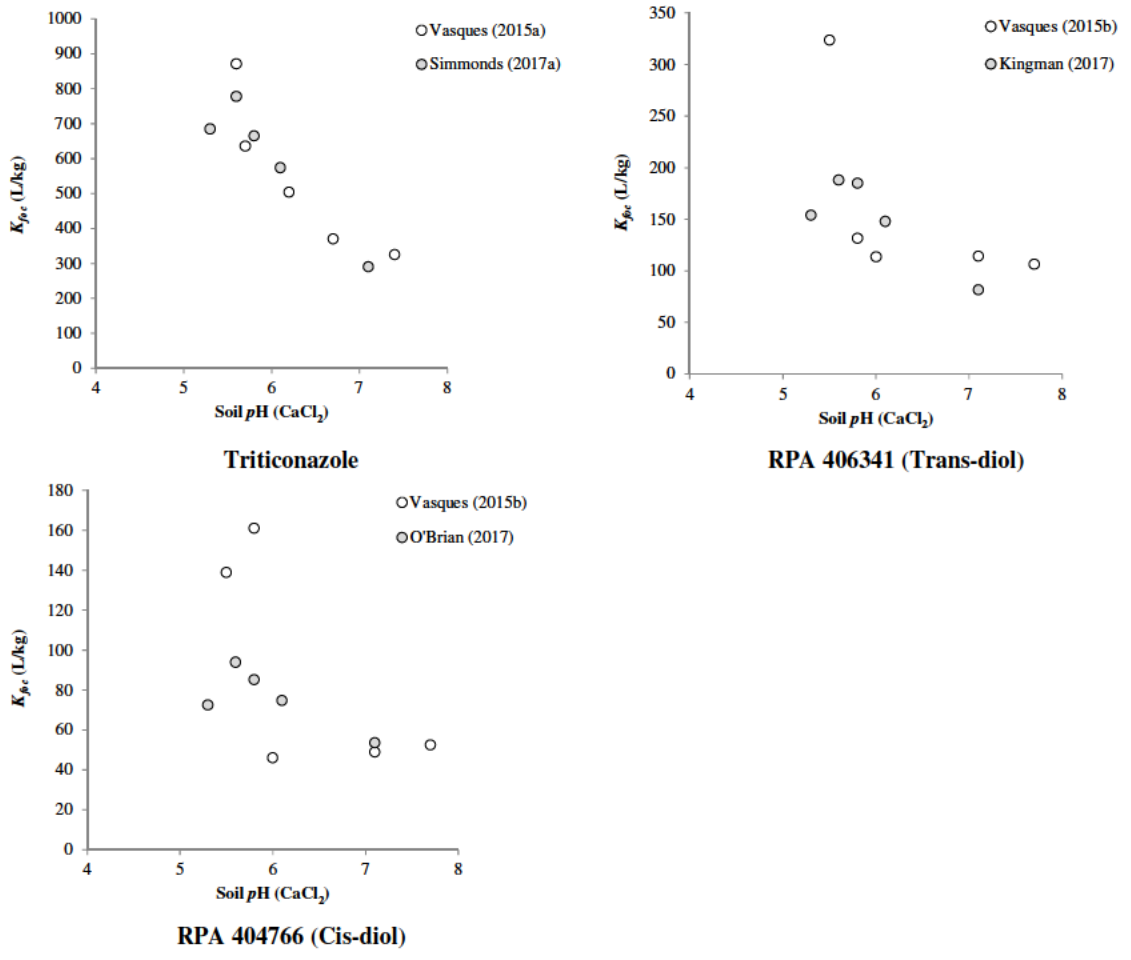


Figure B.2.7.1-5: Soil sorption (Kfoc) of triticonazole and its metabolites vs. soil pH (in CaCl2)

On basis of their relative HPLC retention time (rRT) observed in Ayliffe & Austin (1993), set into context with measured mean adsorption properties and retention times of triticonazole, RPA 406341 (Trans-diol) and RPA 404766 (Cis-diol) observed in this study, K_{foc} values of the two metabolite fractions **'Met 6 (MWT 333)'** (rRT = 0.63) and **'Met 7 (MWT 315)'** (rRT = 0.70) are estimated to be approx. 278 mL/g and 327 mL/g, respectively (on basis of the regression K_{foc} (mL/g) = 697 × rRT - 161, $r^2 = 0.999$).

Results of a **non-aged and aged column study** show that the mobility of triticonazole was dependent on the soil type, having a medium to low mobility in all but a sand soil where up to 71 % AR (non-aged experiment) was found in the leachate. In the experiment on aged residues (with still 95 % of triticonazole present after 30 days) amounts of triticonazole in the leachate of the sand soil have been reduced to 27.1 % AR indicating that triticonazole is prone to aged sorption in soil. This is also evident from the OECD guideline 106 batch experiments with sorption coefficients consistently increasing with the number of desorption cycles. In view of

the RMS AT aged sorption of triticonazole in soil is also most probably responsible for the bi-phasic decline behaviour observed in many laboratory degradation experiments.

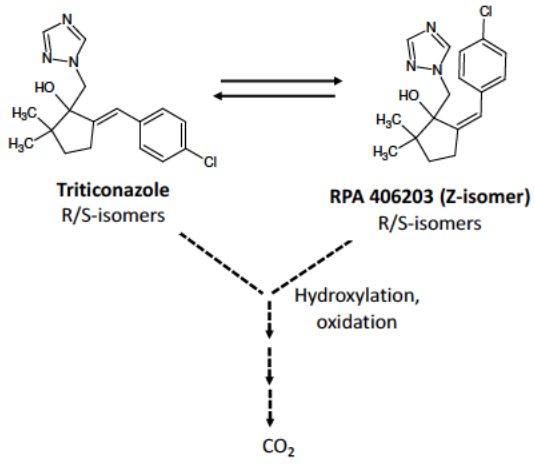
Two **lysimeter studies** have been conducted on a silty sand (1.32 % OC) with either [phenyl-U-^{14}C] or [triazole-3(5)-^{14}C] labelled triticonazole. Triticonazole was applied as a seed treatment in winter cereals with an intended application rate of 12.5 g ai/ha. Application took place in the first year only or in the first and second year with study durations of two years in case of the phenyl label and three years in case of the triazole label. Annual amounts of leachates collected were in the range from 295 - 590 L/m^2. Neither triticonazole nor RPA 406341 (Trans-diol) or RPA 404766 (Cis-diol) have been detected in the leachate samples (LOD = 0.008 - 0.01 µg/L). Unknown radioactivity did not exceed annual mean concentrations of 0.026 µg/L a.i. equivalents for the phenyl label. In case of the triazole label unidentified radioactivity at annual mean concentrations of 0.180 µg/L a.i. equivalents has been detected. The vast majority (0.150 µg/L mean annual concentration) was very polar material considered not to exceed 0.1 µg/L on individual basis. However, as the peak concentration was observed in the last year, the study does not allow concluding on residues in the leachates in subsequent years.

2.7.2. Summary of fate and behaviour in water and sediment

Triticonazole (phenyl and triazole label) is considered stable under conditions of **aquatic hydrolysis**. No isomeric conversation (from the *R* to the *S* enantiomer) could be observed.

Under conditions of **direct photochemical degradation** conducted in sterile buffer solutions at *p*H 5 triticonazole (phenyl and triazole label) is converted into its Z-isomer RPA 406203 (maximum 42.3 % AR after 3 days, without sensitizer). The photolytic conversion from triticonazole (E-isomer) to RPA 406203 (Z-isomer) is considered to be reversible since equilibrium with the parent compound triticonazole was established within 1 to 2 days. No other metabolites were observed > 5 % AR. Under laboratory conditions the *DT50* values for the dissipation of triticonazole obtained in two independent studies were 7.4 and 32.7 days, respectively, once equilibrium has been reached. The *DT50* value for the dissipation of RPA 406203 (Z-isomer) was 27.6 days.

Figure B.2.7.2-1: Proposed route of degradation of triticonazole under conditions of direct photochemical degradation



Triticonazole is considered **not ready biodegradable** under conditions of a CO_2 evolution (Modified Sturm) test.

Triticonazole (phenyl and triazole label) is considered stable under conditions of **aerobic mineralisation studies in surface water** (studied at low and high dose level). No metabolite fraction above 5 % AR was observed. Formation of CO_2 was limited with maximum 3.1 % AR at study end (59 days).

The fate and behaviour of phenyl labelled triticonazole in **aerobic water/sediment** was investigated in two water/sediment systems. The RMS AT notes that these two water/sediment systems are very close with respect to organic carbon as well as water and sediment *p*H. However, as degradation of triticonazole in (dark) aquatic systems is anyhow limited, the impact of more acidic *p*H values or higher organic carbon is not considered to significantly alter the study results. Degradation of triticonazole in the entire system was indeed limited with

transfer to the sediment being representing the mayor dissipation process in the water phase. No individual metabolite fraction exceeded 5 % AR in the total system. Formation of CO_2 was limited with maximum 1.7 % AR at study end (105 days), NER accounted for maximum 25 % AR at study end. The RMS AT notes that water/sediment studies were conducted with phenyl labelled parent only. However, as degradation of triticonazole was limited in the water/sediments systems metabolites from the triazole label are not considered to occur at significant amounts.

Table B.2.7.2-1 Summary on maximum occurrence (% AR) of identified and non-identified (unknown) metabolites in aquatic laboratory studies conducted with triticonazole (metabolites shaded in grey require an exposure assessment in surface water)

Compound	Aquatic hydrolysis (25 °C)	Direct photolytic degradation	Aerobic mineralisation in surface water (low dose)	Water/sediment		
				Water phase	Sediment phase	Entire system
Triticonazole	na	na	na	na	76.0	na
RPA 404766 (Cis-diol)	ni	ns	1.3	ni	ni	ni
RPA 406341 (Trans-diol)	ni	ni	1.8	ni	ni	ni
RPA 406203 (Z-isomer)	2.6	42.3[(a)]	4.2[(b)]	ni	ni	ni
Unknowns	≤ 2	4.3	3.9	0.7	2.5	2.5

na denotes not applicable
ni denotes not investigated
ns denotes not stated
(a) Without sensitizer
(b) Arithmetic mean of phenyl and triazole label

The rate of degradation/dissipation of triticonazole in water/sediment systems is summarized below.

Table B.2.7.2-2 Summary on degradation and dissipation of triticonazole in the total water/sediment system as well as in the water and sediment phase (20 °C) - trigger & modelling endpoints

Water / sediment system	*p*H water / sed.[(a)]	Label	*DegT50* system (d)	*DegT90* system (d)	Kinetic model	*DissT50* water (d)	Kinetic model	*DissT50* sed. (d)	Kinetic model	Reference
Rhine River	7.7 / 6.9	Ph	399	1325	SFO	5.3	FOMC	-	-	Wyss-Benz,
Anwil Pond	8.0 / 6.9	Ph	225	748	SFO	9.5	FOMC	-	-	1995
Geometric mean (n = 2)			**300**	**996**	SFO	**-**		**-**		

(a) Measured in KCl (sediment phase)

2.7.3. Summary of fate and behaviour in air

The vapour pressure of triticonazole was determined as 9×10^{-8} Pa at 25 °C. Therefore, concentrations in air are considered to be negligible. Furthermore, the atmospheric half-life was re-calculated according to Atkinson using the current version of AOPWIN in EPI Suite v4.11. A value of 1.4 hrs (corresponding to 0.114 days) was determined (for a 12 hrs day). Thus, long range transport of triticonazole can be disclosed.

Due to the low vapour pressure and the *DT50* in air being below 2 days, no exposure and long-range transport of triticonazole in air is expected. Furthermore, as triticonazole is applied as seed treatment no relevant atmospheric input is expected. Thus, no calculation of PEC from airborne transport was conducted as this is not a relevant entry pathway.

2.7.4. Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

Publically available groundwater monitoring data for triticonazole shows that, following application according to the label, the leaching of unacceptable amounts of triticonazole is highly unlikely. Additionally entry of unacceptable amounts of triticonazole into surface water is highly unlikely.

2.7.5. Definition of the residues in the environment requiring further assessment

The residue definitions relevant for risk assessment for each compartment are the following:

Compartment	Residue Definition
Soil	Triticonazole, RPA 406341 (Trans-diol), RPA 404766 (Cis-diol), RPA 406203 (Z-isomer)[(a)], 'Met 6 (MWT 333)'[(b)], 'Met 7 (MWT 315)'[(b)]
Groundwater	Triticonazole, RPA 406341 (Trans-diol), RPA 404766 (Cis-diol), RPA 406203 (Z-isomer)[(a)], 'Met 6 (MWT 333)'[(b)], 'Met 7 (MWT 315)'[(b)]
Surface Water	Triticonazole, RPA 406341 (Trans-diol), RPA 404766 (Cis-diol), RPA 406203 (Z-isomer)[(c)], 'Met 6 (MWT 333)'[(b)], 'Met 7 (MWT 315)'[(b)]
Sediment	Triticonazole, RPA 406341 (Trans-diol), RPA 404766 (Cis-diol), RPA 406203 (Z-isomer)[(c)], 'Met 6 (MWT 333)'[(b)], 'Met 7 (MWT 315)'[(b)]
Air	Triticonazole

(a) RPA 406203 (Z-isomer) has to be included in the exposure assessment in case of spray applications only (exposure to irradiation at the soil surface)
(b) Metabolite fraction > 5 % AR at two consecutive sampling points in a legacy soil degradation study (Ayliffe & Austin, 1993)
(c) Above 10 % AR in aquatic photolysis

2.7.6. Summary of exposure calculations and product assessment

The **predicted environmental concentrations in soil (PEC_{soil})** of the active substance triticonazole and its soil metabolites RPA 406341 (Trans-diol) and RPA 404766 (Cis-diol) as well as the two tendatively identified metabolite fractions 'Met 6 (MWT 333)' and 'Met 7 (MWT 315)' (the latter two observed > 5 % AR at two consecutive sampling points in a legacy study, Ayliffe & Austin , 1993) were calculated based on a first tier approach using a Microsoft® Excel spreadsheet, assuming even distribution of the compound in the upper 0 - 5 cm soil layer. A standard soil density of 1.5 g/cm^3 was assumed. The use of triticonazole as seed treatment in winter and spring cereals was assessed according to Good Agricultural Practice (GAP) under European cropping conditions taking into account potential accumulation of triticonazole and its metabolites in soil.

Predicted environmental concentrations in groundwater (PEC_{gw}) for triticonazole and its metabolites RPA 406341 (Trans-diol) and RPA 404766 (Cis-diol) as well as the two metabolite fractions 'Met 6 (MWT 333)' and 'Met 7 (MWT 315)' were calculated for the use as a seed treatment in winter and spring cereals in Europe, using the simulation models FOCUS PEARL 4.4.4, FOCUS PELMO 5.5.3 and FOCUS MACRO 5.5.4. PEC_{gw} were evaluated as the 80th percentile of the mean annual leachate concentration at 1 m soil depth. Model parameters and scenarios consisting of weather, soil, and crop data were used as proposed by FOCUS (2009, 2014). PEC_{gw} values were below the regulatory threshold of 0.1 µg/L for the parent triticonazole, the metabolite RPA 406341 (Trans-diol) and the metabolite fraction 'Met 7 (MWT 315)' for all scenarios and the representative uses as a seed treatment in winter and spring cereals.

The leaching assessment for RPA 404766 (Cis-diol), if based on the laboratory *DegT50*, resulted in exceedance of the 0.1 µg/L threshold in the Hamburg and Okehampton scenario (max. 0.147 µg/L) in spring and winter cereals. From a scientific point of view is appears defendable to use the field degradation rate of RPA 406341 (Trans-diol) as a conservative estimate of the (*per se* unknown) field degradation rate of its isomeric sibling RPA 404766 (Cis-diol) in a modelling refinement step. On basis of this refinement, RPA 404766 (Cis-diol) does not exceed the regulatory threshold of 0.1 µg/L in any of the FOCUS groundwater scenarios.

PEC_{gw} values for the metabolite fraction 'Met 6 (MWT 333)' are above the regulatory threshold of 0.1 µg/L (max. 0.187) in most of the FOCUS groundwater scenarios. The RMS AT notes that modelling results obtained indicate a leaching risk for this metabolite fraction. However, it should be kept in mind that metabolite fraction 'Met 6 (MWT 333)' has only been overserved in legacy studies (Ayliffe & Austin, 1993; Ayliffe & McMillan-Staff, 1994; and Ayliffe & Godward, 1993) applying chromatographic methods which may not have been fully capable to adequately separate all metabolites of triticonazole. In all later studies, applying more sophisticated HPLC separation methods, no metabolites other than RPA 406341 (Trans-diol) and RPA 404766 (Cis-diol) were observed above 5 % AR at two consecutive sampling points.

Predicted environmental concentrations of triticonazole and its metabolites RPA 406341 (Trans-diol), RPA 404766 (Cis-diol) and RPA 406203 (Z-isomer) as well as the two metabolite fractions 'Met 6 (MWT 333)' and 'Met 7 (MWT 315)' **in surface water (PEC_{sw}) and sediment (PEC_{sed})** were calculated for the use as seed

treatment in winter and spring cereals in Europe, using the tiered FOCUS Surface Water (SW) approach (FOCUS 2001, 2015). All relevant entry routes of a compound into surface water (dust drift, runoff/erosion or drain flow in case of seed treatment application) were considered in these calculations. For the use of Premis 25 FS (Triticonazole 25 g/L) as a seed treatment application to winter and spring cereals, FOCUS Steps 1, 2 & 3 calculations were performed for triticonazole and its relevant metabolites.

Exposure via Air
No PEC_{air} calculations were required due to the low volatility and the short half-life in air.

Other routes of exposure
There are no other routes of exposure to be considered if the product is used according to Good Agricultural Practice.

2.8. EFFECTS ON NON-TARGET SPECIES

2.8.1. Summary of effects on birds and other terrestrial vertebrates

The toxicity endpoints for birds and other terrestrial vertebrates are summarised in the following two tables.

Table 2.8-1: Toxicity of triticonazole to birds

Test species	Test design	Ecotoxicological endpoint	Reference
Bobwhite quail *(Colinus virginianus)*	Acute, oral	LD_{50} > 2000 mg ai/kg bw **$LD_{50\ extrapol.}$ = 3776 mg ai/kg bw** [a]	[redacted], 1991a
Mallard duck *(Anas platyrhynchos)*		LD_{50} > 2000 mg ai/kg bw $LD_{50\ extrapol.}$ = 3776 mg ai/kg bw [a]	[redacted], 1991b
Grey partridge *(Perdix perdix)*		LD_{50} > 2000 mg ai/kg bw **$LD_{50\ extrapol.}$ = 3776 mg ai/kg bw** [a]	[redacted], 1992a
Red-legged partridge *(Alectoris rufa)*		LD_{50} > 2000 mg ai/kg bw **$LD_{50\ extrapol.}$ = 3776 mg ai/kg bw** [a]	[redacted], 1992b
Pigeon (*Columba livia*)		LD_{50} > 2000 mg ai/kg bw	[redacted], 1990a
Ring-necked pheasant *(Phasianus colchicus)*		LD_{50} > 2000 mg ai/kg bw	[redacted], 1990b
Bobwhite quail *(Colinus virginianus)*	Short-term, dietary	LC_{50} > 5200 ppm LDD_{50} > 693 mg ai/kg bw/d	[redacted]., 1992a
Mallard duck *(Anas platyrhynchos)*		LC_{50} > 5200 ppm LDD_{50} > 1300 mg ai/kg bw/d	[redacted] 1992b
Bobwhite quail *(Colinus virginianus)*	Reproduction	NOEC = 150 mg/kg diet NOEL = 10.98 mg ai/kg bw/d	[redacted], 2012a
		NOAEL = 12.4 mg/kg bw per day	[redacted], 2007[c]
		NOAEL = 19.5 mg/kg bw per day	[redacted], 1995a
Mallard duck *(Anas platyrhynchos)*		NOEC = 1000 ppm NOAEL = 108.15 mg ai/kg bw[b]	[redacted], 1998b

Bold values were used for the risk assessment

[a] LD_{50} extrapolated according to the EFSA Guidance Document on Birds and Mammals (2009). 10 birds per group were tested without any mortality during the study. An extrapolation factor of 1.888 was used for the calculation of the extrapolated LD_{50}.

[b] conversion based on the mean consumption of 117.98 g/day and an average body weight of 1090, 9 g

[c] reliability of the study is questioned; please refer to Volume 3 – B.9-CA

Table 2.8-2: Toxicity of metabolite RPA 406341 to birds

Test species	Test design	Ecotoxicological endpoint	Reference
Bobwhite quail *(Colinus virginianus)*	Acute, oral	**$LD_{50} \geq 2250$**	[redacted], 2000a

Bold values were used for the risk assessment

Table 2.8-3: Toxicity of triticonazole to mammals

Test design	Test species	Ecotoxicological endpoint	Effects the Endpoint is based on	Reference
Oral acute	Rat	**LD_{50} > 2000 mg ai/kg bw**	decreased motor activity and ataxia	[redacted] 1990
Oral toxicity 28 days		NOAEL = 500 ppm corresponding to 52.4 mg ai/kg bw/d	↓absolute uterus weight	[redacted], 1991
Oral toxicity 90 days		NOAEL = 250 ppm corresponding to 19.8 mg ai/kg bw/d (males) and 22.3 mg ai/kg/bw/d (females)	↓Body weight gain, ↓food consumption, ↑absolute and relative liver weight, ↑absolute and relative ovary weight, necropsy findings in adrenals	[redacted], 1991
2-generation reproduction		NOAEL = 750 ppm corresponding to 48.41 mg ai/ kg bw	<u>Parental:</u> maternal mortality, ↓body weight, necropsy findings in adrenals, liver and ovaries ↓mating and fertility index in F1 generation <u>Offspring:</u> reduced survival and growth consistently observed across both generations	[redacted] 1993
Developmental toxicity		NOAEL = 200 mg ai/kg bw/d	↓maternal body weight gain, <u>Foetal:</u> ↑incidence of additional 13th and 14th rib	[redacted], 1991
	Rabbit	**NOAEL = 25 mg ai/kg bw/d**	<u>Paternal:</u> maternal mortality, abortions, ↓food consumption, ↓body weight gain <u>Foetal:</u> Increased incidences of different skeletal findings	[redacted] 1991

Bold values are used for the risk assessment

The toxicological endpoint identified in Section B6 is the lowest NOAEL of 5 mg ai/kg bw/d from the developmental study in rabbits (Burns, 1991) as at ≥ 25 mg ai/kg bw a slight body weight loss at days 6 to 8 and reduced food intake occurred. Furthermore one precocious ossification of acromiom process was noted at ≥ 25 mg ai/kg/d. However, the body weight loss and the reduced food intake were < 10% and not statistically significant and the precocious ossification is not considered ecotoxicologically relevant. The 2-generation reproduction enpoint with the rat of 48.41 mg ai/kg bw may be more relevant than the developmental endpoint with the rabbit. However, for precautionary reasons the endpoint of 25 mg ai/kg bw/d was used for the risk assessment.

Table 2.8-4: Toxicity of RPA 406341 to mammals

Test design	Test species	Ecotoxicological endpoint	Effects the Endpoint is based on	Reference
Oral acute	Rat	**LD_{50} > 2000 mg/kg bw**	decreased activity, reduced defacation	[redacted] 1999

Bold values were used for the risk assessment

Endocrine disrupting properties:

Wild mammals
All endocrine-related mechanistic studies conducted by the notifier (in vivo and in vitro) or identified in the open literature are included in Section B6. In summary, based on the results of in vivo tests conducted with triticonazole, there is no evidence of a specific effect on the endocrine system or on any endocrine organ, with a demonstrated endocrine MoA. Triticonazole has been shown to inhibit the aromatase enzyme in vitro like other members of the azole class of fungicides, with 20-times lower IC for rat than for human aromatase. However, in vitro activity did not translate into any specific endocrine-related effect in vivo. This observation is supported by the lack of treatment-related carcinogenic effects in two lifetime cancer bioassays conducted in rats and mice, as well as the absence of specific reproductive or developmental toxicity in a 2-generation reproduction study and two developmental toxicity studies. The observed morphological changes in adrenals in all species and almost all studies, always accompanied by marked general toxicity, did not prove to impair the functional capacity of adrenals since corticosterone was successfully excreted after ACTH challenge. It is concluded that no evidence is available that effects observed in studies with triticonazole have an endocrine MoA

Birds
At the date of submission no formally adopted criteria were available in the EU for what constitutes an endocrine disruptor under Regulation 1107/2009. For birds, there was also no internationally validated regulatory testing guideline available. The population relevant effects of triticonazole on birds were studied in reproductive toxicity studies on bobwhite quail and mallard ducks. According to the applicant Many plant protection product actives were among the chemicals screened in the EDSP, including four triazoles, namely myclobutanil, propiconazole, tebuconazole and triadimefon. All these compounds belong to the same chemical group as triticonazole, i.e. the triazoles. For all evaluated triazoles, the US EPA concluded that further bird testing is not recommended and the avian reproduction studies were considered sufficient for the evaluation of potential reproductive effects on birds. However, at the current state, without a noted guidance, a final conclusion on the potential of triticonazole on endocrine disrupting properties is not possible.

Amphibians and Reptiles
Currently no test methods are established to assess the population relevant effects of chemicals to amphibians or reptiles. While an amphibian metamorphosis test exists, this test was developed to evaluate the potential effect on the thyroid system, and not to measure population relevant effects. Therefore no further studies can be suggested at this time for these groups of organisms.
Under consideration of the lack of information it is not possible to draw a final conclusion on the endocrine disrupting potential of triticonazole. However, triticonazole is used as a seed treatment and therefore no contact exposure in terrestrial ecosystems for reptiles and amphibians is expected to occur.

2.8.2. Summary of effects on aquatic organisms

The toxicity endpoints for aquatic organisms are summarised in the following two tables.

Table 2.8-5: Endpoints: Toxicity of triticonazole to aquatic organisms

Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg/L]	EC_x/LC_x [mg/L]	Reference
Fish							
Oncorhynchus mykiss Rainbow trout	Semi-static	96 h	Mortality	n	10	LC_{50} > 10	[redacted] 1990a
Oncorhynchus mykiss Rainbow trout	Flow-through	96 h	Mortality	mm	1.4	**LC_{50} > 3.6**	[redacted] 1998a
Oncorhynchus mykiss Rainbow trout	Static	96 h	Mortality	mm	2.62	LC_{50} > 12.4	[redacted] 2006a
Lepomis macrochirus Bluegill sunfish	Flow-through	96 h	Mortality	mm	8.9	LC_{50} > 8.9	[redacted] 1998b
Lepomis macrochirus Bluegill sunfish	Static	96 h	Mortality	mm	10.1	LC_{50} > 10.1	[redacted] 2006b
Cyprinodon	Flow-	96 h	Mortality	mm	5.7	LC_{50} > 9.1	[redacted]

Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg/L]	EC_x/LC_x [mg/L]	Reference
variegatus Sheepshead minnow	through						1998a
Cyprinus carpio Common carp	Static	96 h	Mortality	mm	9.1	LC_{50} > 18	[redacted] 2014a
Pimephales promelas Fathead minnow	Flow-through	FFLC	Reproduction/Growth	mm	**0.0114**	-	[redacted] 2008a
Pimephales promelas Fathead minnow	Flow-through	FFLC	Reproduction/ Growth	mm	0.0473	-	[redacted] 2012a
Pimephales promelas Fathead minnow	Flow-through	ELS (34 d)	Mortality/ Growth	n	< 0.024	$EC_{10\ length}$ = 0.156 $EC_{20\ length}$ = 0.282 $EC_{50\ length}$ = 0.777 $EC_{10\ dry\ weight}$ = 0.037 $EC_{20\ dry\ weight}$ = 0.077 $EC_{50\ dry\ weight}$ = 0.239	[redacted] 1998b
Pimephales promelas Fathead minnow	Flow-through	ELS (34 d)	Mortality/ Growth	n	0.021	-	[redacted] 1998c
Cyprinodon variegatus Sheepshead minnow	Flow-through	ELS (34 d)	Mortality/ Growth	mm	0.12	-	[redacted] [redacted] 2006a
Aquatic invertebrates							
Daphnia magna Waterflea	Static	48 h	Immobility	n	1.8	**EC_{50} = 7.85**	Douglas, M.T., Halls, R.W.S., Macdonald, I.A. 1990b
Mysidopsis bahia (Americamysis bahia) Mysid shrimp	Flow-through	96 h	Immobility	mm	1	**LC_{50} =1.9**	Sousa, J.V., 1998d
Crassostrea virginica Eastern oyster	Flow-through	96 h	Mortality/ Shell growth	mm	1.4	**LC_{50} = 8.9**	Dionne, E, 1998a
Daphnia magna Waterflea	Semi-static	21 d	Survival Reproduction	mm	NOAEC = 0.19	EC_{50} > 3	Putt, E., 2006a
Daphnia magna Waterflea	Semi-static	21 d	Survival/ Reproduction/Growth	mm	**0.11**	EC_{50} > 3.5	Urann, K, 2012a
Americamysis bahia Mysid shrimp	Flow-through	28 d	Survival Reproductio	mm	**0.041**	LC_{50} > 0.32	Putt, E., 2006b

Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg/L]	EC_x/LC_x [mg/L]	Reference
			n				
Sediment dwelling organisms							
Chironomus riparius Midge	Static	26 d	Emergence/ Development	imm	0.777	EC_{50} > 0.777	Van der Kolk, J., 1998[a]
Algae							
Pseudokirchneriella subcapitata Green algae	Static	72 h	Growth rate Yield	n	NOEC = 1.0	E_rC_{50} > 10 E_yC_{50} > 10	Seeland-Fremer, A., Wydra, V., 2014a
Skeletonema costatum Saltwater diatom	Static	72 h	Growth rate Biomass	n	-	E_rC_{10} = 0.25 E_rC_{20} = 0.31 **E_rC_{50} = 0.46** E_yC_{10} = 0.23 E_yC_{20} = 0.33 E_yC_{50} = 0.22	Hoberg, J.R., 1998e[b]
		120 h	Growth rate Biomass	n	0.031	E_rC_{10} = 0.24 E_rC_{20} = 0.33 E_rC_{50} = 0.58 E_yC_{10} = 0.25 E_yC_{20} = 0.28 E_yC_{50} = 0.34	
Aquatic macrophytes							
No valid studies provided							
Bioconcentration fish[c]							
Lepomis macrochirus Bluegill sunfish	**BCF_{Kwhole} fish**				72.55		
	$BCF_{Kinedible}$ fish				114.86		
	$BCF_{Kedible}$ fish				9.2		

Bold values are used for the risk assessment

n…nominal, mm…mean measured, imm…initially mean measured

[a]validity of the study is questionable, for details please refer to the commenting box of the study summary.

[b]not valid according to OECD 201 as coefficient of variation for section-by-section specific growth rates is 60%, but valid according OCSPP 850.4500.

[c]the results of the study indicate some uncertainties as the bioconcentration factor seems to first decrease and than increase again. Furthermore some information is missing in the study report (lipid content of fish, TOC, testing of a second concentration). However, even if the validity of the study is questionable, the results have been used to be able to do a risk assessment.

Effects to aquatic organisms from exposure to the metabolites RPA 404766, RPA 406341 and RPA 406203 were tested for the aquatic invertebrates. RPA 406203 was also tested for algae. No studies were conducted with fish and aquatic macrophytes.

Table 2.8-6: Toxicity of metabolites to aquatic organisms

Test substance	Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg/L]	EC_x/LC_x [mg/L]	Reference
Aquatic invertebrates								
Metabolite RPA 404766	*Daphnia magna* Waterflea	Semi-static	48 h	Immobility	n	100	**EC_{50} > 100**	Sewell, I.G., Mulle, D.M., 2001b
Metabolite RPA 407922	*Daphnia magna* Waterflea	Semi-Static	48 h	Immobility	n	100	**EC_{50} > 100**	Sewell, I.G., Mulle, D.M., 2001a
Metabolite RPA 406341	*Daphnia magna* Waterflea	Semi-static	48 h	Immobility	n	32	EC_{10} = 34.7 EC_{20} = 40.7 EC_{50} = **51.78**	Sewell, I.G., Mulle, D.M., 2002a
Metabolite RPA 406203	*Daphnia magna* Waterflea	Flow-through	48 h	Immobility	mm	1.8	**EC_{50} = 3.4**	Putt, E., 1998a
Metabolite RPA 406203 (Reg. No. 5079359)	*Daphnia magna* Waterflea	Static	48 h	Immobility	n	10	EC_{50} > 10	Janson, G.-M., 2009a
Algae								
Metabolite RPA 406203 (Reg. No. 5079359)	*P. subcapitata* Green algae	Static	72 h	Growth rate Yield	mm	**1.4** (yield)	E_rC_{10} = 3.51 E_rC_{20} = 9.55 E_rC_{50} = **64.83** E_yC_{10} = 1.84 E_yC_{20} = 3.12 E_yC_{50} = 8.57	Hoffmann, F., 2009a

n…nominal, mm…mean measured

Table 2.8-7: Toxicity of Premis 25 FS to aquatic organisms

Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg ai/L]	EC_{50}/LC_{50} [mg ai/L]	Reference
Fish							
No studies provided							
Aquatic invertebrates							
Daphnia magna Waterflea	Static	48 h	Immobility	n	2.5 (100 prod.)	> 2.5 (> 100 prod.)	Janson, G.M., 2009
Algae							
Pseudokirchneriella subcapitata Green algae	Static	72 h	Growth rate Biomass	n	0.08 (3.13 prod.)	E_rC_{10} = 0.44 (16.98 prod.) E_rC_{20} = 0.74 (28.84 prod.) E_rC_{50} = 2.04 (79.4 prod.) E_yC_{10} = 0.095 (3.8 prod.) E_yC_{20} = 0.169 (6.6 prod.) E_yC_{50} = 0.49	Hoffmann, F. 2009

Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg ai/L]	EC_{50}/LC_{50} [mg ai/L]	Reference
						(19.02 prod.)	
Aquatic macrophytes							
No studies provided							

For the Metabolite RPA 407922 no PEC_{SW} values are available as after re-evaluation in the e-fate section it is considered not to occur at significant amounts in environmental compartments. Two unknown fractions were discovered during the re-evaluation process. For these unknown metabolites Met 6 (MWT 333) and Met 7 (MWT 315) no toxicity studies are available.

An ELS study with *Pimephales promelas* ([redacted] 1998b) is available resulting in an endpoint < 0.024 mg ai/L. As this endpoint is an < value, it comprises some uncertainties. However, a second early life stage test with *Pimephales promelas* was conducted ([redacted] 1998c) resulting in a NOEC of 0.021 mg/L showing that the endpoint for early life stages is in this range.
Furthermore a fish full life cycle test with the same species is available resulting in a NOEC of 0.0114 mg/L. It can therefore be assumed that the early life stage toxicity is covered with this full life cycle study and the endpoint is determined to be 0.0114 mg/L.

2.8.3. Summary of effects on arthropods

The toxicity endpoints for bees and other non-target arthropods are summarised in the following two tables.

Table 2.8-8: Toxicity of triticonazole to honeybees

Test substance	Exposure route	Endpoint	Toxicity	Reference
Triticonazole	Acute oral Acute contact	48 h LD_{50}	> **155.5** µg ai/bee **> 100** µg ai/bee	Schmitzer, S., 1998
	Acute oral Acute contact	48 h LD_{50}	> 96.26 µg ai/bee > 100 µg ai/bee	Hernádi, D., 2006a
BAS 595 01 F	Acute oral Acute contact	48 h LD_{50}	**76.74** µg ai/bee (3287.54 µg formulated product/bee) **> 20** µg ai/bee (856.8 µg product/bee	Hernádi, D., 2007a
	Chronic oral	10 d LC_{50}	**674.2 mg ai/kg** **(12.9 µg ai/bee/d)**	Schmitzer, S., 2014a
		10 d NOEC	**312.5 mg ai/kg** **(8.0 µg ai/bee/d)**	
	Acute larval, single exposure	72 hours LC50	**2.526 mg ai/kg** **(= 85.6 µg ai/larva)**	Kleebaum, K., 2014b
		72 hours NOEC	**0.731 mg ai/kg** **(= 24.8 µg ai/larva)**	

Bold values were used for risk assessment

Table 2.8-9 Toxicity of triticonazole to non-target-arthropods (extended laboratory studies)

Test species	Exposure	Test item	Rate [g ai/ha]	Type of effect	Effect [%]*	Reference

Test species	Exposure	Test item	Rate [g ai/ha]	Type of effect	Effect [%]*	Reference
Poecilus cupreus (larvae)	Exposure to treated wheat seeds in soil	BAS 595 01 F	7.25	Corrected mortality / mean hatching weight/ delay in development time	-5.6 / 6.0 / 0.4	Drexler, A., 2004a
				70 d LR_{50} > 7.25 g ai/ha 70 d ER_{50} > 7.25 g ai/ha		
Poecilus cupreus (larvae)	Exposure to treated wheat seeds in soil	BAS 595 01 F	11.65	Corrected mortality / mean hatching weight/ delay in development time	-5.6 / 4.4 / 1.3	Sattler, F., 2009a
				70 d LR_{50} > 11.65 g ai/ha 70 d ER_{50} > 11.65 g ai/ha		
Aleochara bilineata	Exposure to treated wheat seeds in soil	BAS 595 01 F	9.6	Reproduction (emerged beetles)	- 6.5	Schmitzer, S., 2007a
				80 days ER_{50} > 9.6 g ai/ha		

*negative value means decreased mortality/hatching weight/emerged beetles compared to the control

2.8.4. Summary of effects on non-target soil meso- and macrofauna

Table 2.8-10: Toxicity of triticonazole and its metabolites to soil meso- and macrofauna

Species	Substance	Endpoint	Reference
Eisenia fetida	Triticonazole	56 d NOEC = 125 mg ai/kg soil dw*	Lührs, U., 1999a
	BAS 595 01 F	56 d NOEC = 5.7 mg product/kg soil dw (0.1328 mg ai/kg soil dw)*	Wolf, A., 2009a
	Metabolite RPA 404766 (Reg.No. 5079285)	56 d NOEC = 250 mg ai/kg soil dw	Friedrich, S., 2013a
	Metabolite RPA 407922 (Reg.No. 5079288)	56 d NOEC = 125 mg ai/kg soil dw	Friedrich, S., 2013b
	Metabolite RPA 406341 (Reg.No. 5059144)	56 d NOEC = 5 mg ai/kg soil dw*	Wolf, A., 2006a
Folsomia candida	Triticonazole	28 d NOEC = 62.5 mg/kg soil dw*	Friedrich, S., 2013c
	BAS 595 01 F	28 d NOEC = 500 mg product/kg soil dw (12.2 mg ai/kg soil dw)*	Lührs, U., 2004a
	Metabolite RPA 404766 (Reg.No. 5079285)	28 d NOEC = 500 mg/kg soil dw	Friedrich, S., 2013d
	Metabolite RPA 406341 (Reg.No. 5059144)	28 d NOEC = 25 mg /kg soil dw*	Royer, S., 2006a
	Metabolite RPA 407922 (Reg.No. 5079288)	28 d NOEC = 250 mg /kg soil dw	Friedrich, S., 2013e
Hypoaspis aculeifer	Triticonazole	14 d NOEC = 250 mg ai/kg soil dw*	Schulz, L., 2014a

Species	Substance	Endpoint	Reference
	BAS 595 01 F	14 d NOEC = 500 mg product/kg soil dw (11.7 mg ai/kg soil dw)*	Schulz, L., 2013b
	Metabolite RPA 406341 (Reg.No. 5059144)	14 d NOEC = 5 mg /kg soil dw*	Ganßmann, M., 2014a

* corrected by a factor of 2 due to the log P_{OW} of triticonazole > 2 (log P_{OW} triticonazole: 3.3; log P_{OW} for RPA 406341: 2.2)

No studies on *Hypoaspis aculeifer* with the metabolites RPA 407922 and RPA 404766 were provided. However, studies with the metabolite RPA 406341 showed that the soil mite *Hypoaspis aculeifer* is not the most sensitive species.

2.8.5. Summary of effects on soil nitrogen transformation

Table 2.8-11: Toxicity of triticonazole and its metabolites to non-target micro-organisms (nitrogen transformation)

Test substance	Test concentration	Time	Effects (deviation from control)	Reference
BASF 595 01 F	0.71 mg prod./kg soil dw (0.017 mg ai/kg soil dw)	28 d	-0.8 %	Schulz, L., 2013a
	7.13 mg prod./kg soil dw (0.167 mg ai/kg soil dw)		+10.7 %	
Metabolite RPA 406341 (Reg.No. 5059144)	1 mg/kg soil dw	28 d	-9.59 %	Royer, S., 2006b
	10 mg/kg soil dw		-12.33 %	
Metabolite RPA 404766 (Reg.No. 5079285)	0.1 mg/kg soil dw	42 d	-4.73 %	Stojanowitsch, née Gehrig, M., 2015a
	1 mg/kg soil dw		-24.8 %	
Metabolite RPA 407922 (Reg.No. 5079288)	0.1 mg/kg soil dw	28 d	+7.5%	Schulz, L., 2014b
	1 mg/kg soil dw		+3.5%	

+…increase of nitrogen transformation; -…decrease of nitrogen transformation

2.8.6. Summary of effects on terrestrial non-target higher plants

Testing of non-target terrestrial plants is not part of the data requirements for active substances (Commission Regulation (EU) 283/2013) and/or plant protection products (Commission Regulation (EU) 284/2013) for the intended use as a seed treatment.

2.8.7. Summary of effects on other terrestrial organisms (flora and fauna)

All required and available data have been evaluated in the presented risk assessments. The literature review did not highlight any information on additional species which required further investigation or consideration in the environmental risk assessment process.

2.8.8. Summary of effects on biological methods for sewage treatment

In the study presented (Mead, C., 2000) for first annex I inclusion, no adverse effects for sewage treatment were seen at the highest concentration tested (1000 mg ai/L).

2.8.1. Summary of product exposure and risk assessment

2.8.1.1. Risk assessment for birds

The exposure and risk assessment for birds was conducted according to the EFSA Guidance Document on Risk Assessment for Birds and Mammals (EFSA Journal 2009;7(12):1438)

Table 2.8-12: Acute risk assessment for birds

Crop	Generic focal species	FIR/bw	NAR[1]	TER_A	Assessment level
Cereals BBCH 00/ spring and autumn	Small granivorous bird	0.3	50	252	Tier 1
Cereals seedlings	Small omnivorous bird	0.5	10[b]	755.2	Tier 1
	Large herbivorous bird[a]	0.3	10[b]	1259	Tier 1

[1]NAR = Nominal loading/application rate of active substance in mg/kg seed.
[a]Large herbivorous birds are referred to in the text but not in the table of the EFSA GD. Therefore large herbivorous bird is added here with DDD value used for goose.
[b]NAR/5

Table 2.8-13: Tier 1 long-term risk assessment for birds

Crop	Generic focal species	FIR/bw	NAR[1]	f_{twa}[2]	TER_{LT}	Assessment level
Cereals BBCH 00/ spring and autumn	Small granivorous bird	0.3	50	0.72	**1.80**	Tier 1
				0.64	**2.03**	Tier 1
				0.53	**2.45**	Tier 1
Cereals seedlings	Small omnivorous bird	0.5	10[b]	0.53	7.36	Tier 1
	Large herbivorous bird[a]	0.3	10[b]	0.53	12.26	Tier 1

[1]NAR = Nominal loading/application rate of active substance in mg/kg seed.
[2]The averaging time of 21 days is under debate for seed treatments as the time from sowing to germination usually is shorter, for cereals 10 to 14 days can be assumed. To enable expert discussion, the risk assessment is presented with a worst case germination time of 10 days, with a more realistic value of 14 days and with 21 days as used for spray applications.
[a]Large herbivorous birds are referred to in the text but not in the table of the EFSA GD. Therefore large herbivorous bird is added here with DDD value used for goose.
[b]NAR/5
Bold values do not meet the trigger.

Higher tier long-term risk assessment for birds

A modified exposure study is available proposing a NOEL of 24.7 mg ai/ kg bw. However, after re-evaluation its validity as well as its reliability is considered questionable. Furthermore the usefulness of a study with shortened exposure duration has to be discussed as it is questionable whether all reproductive phases have been assessed and if so whether there were sufficient to detect any effects. Furthermore it should be decided on an expert group level if such studies may be used in general.

Initial residues on cereal seeds on the soil surface were estimated in degradation studies. The worst case residue of 91.88% was used as correction factor.

The decline of residues on cereal seeds on the soil surface was estimated in degradation studies. A interzonal geometric mean DT_{50} of 5.5 days was determined

Based on field studies Skylark, Yellowhammer, chaffinch, Woodpigeon, Rook/Carrion Crow and Pheasant were chosen as focal species. The linnet was also observed in these studies. The applicant provided an argumentation why the linnet should not be considered as relevant focal species. The relevance of the linnet as a focal species in cereal fields should be discussed in general and be decided on an expert group level. Therefore for precautionary reasons the linnet was also presented in the risk assessment.

PT refinement for skylark, yellowhammer and chaffinch was conducted based on field studies.
90th percentile PT consumer only for Skylark – spring cereals: 0.83; winter cereals: 0.76

90th percentile PT consumer only for Yellowhammer– spring cereals: 0.2; winter cereals: 0.35
90th percentile PT consumer only for Chaffinch– spring cereals: 0.63; winter cereals: 0.06

Table 2.8-14: Higher tier long-term risk assessment for granivorous focal species in cereals*

Crop	Focal species	FIR/bw	NAR	Correction factor based on initial residue	PT	ftwa	TER_{LT}
Spring Cereals BBCH 00	Skylark	0.266	50	0.92	0.83	0.568	**3.4**
						0.470	**4.1**
						0.351	5.1
	Yellowhammer	0.296			0.20	0.568	12.6
						0.470	15.2
						0.351	20.4
	Chaffinch	0.320			0.63	0.568	**3.7**
						0.470	**4.5**
						0.351	5.9
	Woodpigeon	0.074			1	0.568	10.1
						0.470	12.2
						0.351	16.4
	Rook	0.121			1	0.568	6.17
						0.470	7.44
						0.351	10.0
	Carrion Crow	0.110			1	0.568	6.80
						0.470	8.19
						0.351	11.0
	Pheasant	0.070			1	0.568	10.7
						0.470	12.9
						0.351	17.3
	Linnet	0.354			1	0.568	**2.11**
						0.470	**2.55**
						0.351	**3.41**
Winter Cereals BBCH 00	Skylark	0.266	50	0.92	0.83	0.568	**3.7**
						0.470	**4.5**
						0.351	6.0
	Yellowhammer	0.296			0.20	0.568	7.2
						0.470	8.7
						0.351	11.7
	Chaffinch	0.320			0.63	0.568	38.8
						0.470	47
						0.351	62.9
	Woodpigeon	0.074			1	0.568	10.1
						0.470	12.2
						0.351	16.4
	Rook	0.121			1	0.568	6.17
						0.470	7.44

Crop	Focal species	FIR/bw	NAR	Correction factor based on initial residue	PT	ftwa	TER_{LT}
						0.351	10.0
	Carrion Crow	0.110			1	0.568	6.80
						0.470	8.19
						0.351	11.0
	Pheasant	0.070			1	0.568	10.7
						0.470	12.9
						0.351	17.3
	Linnet	0.354			1	0.568	**2.11**
						0.470	**2.55**
						0.351	**3.41**

NAR = Nominal loading/application rate of active substance in mg/kg seed.
*The averaging time of 21 days is under debate for seed treatments as the time from sowing to germination usually is shorter, for cereals 10 to 14 days can be assumed. To enable expert discussion, the risk assessment is presented with using the f_{twa} based on DT_{50} of 5.5 days and a worst case germination time of 10 days, with a more realistic value of 14 days and with 21 days as used for spray applications.
Bold values do not meet the trigger.

Drinking water risk assessment:

According to the EFSA Guidance Document on Birds and Mammals (2009) significant contamination of drinking water after the use of a pesticide as seed treatment seems very unlikely to be a critical route or to lead to TER values greater than direct dietary consumption. A drinking water risk assessment therefore is not considered necessary.

Secondary poisoning and biomagnification in terrestrial food chains

The log P_{OW} value of the active substance triticonazole is 3.3 (Chabassol et al, 1991) and for the metabolite RPA 406203 it is 3.5 (Cowlyn, 2014e). Therefore a risk assessment for earthworm to earthworm-eating birds and from fish to fish-eating birds is required. For all other metabolites the log Pow is < 3 (For details please also refer to B.9 - CA).

The risk of RPA 406203 can be considered low as the Z-isomer only is formed under irradiation. Therefore earthworms are not likely to be exposed to RPA 406203.
No toxicological endpoint for RPA 406203 is available therefore as a worst case a 10-fold higher toxicity than the parent is assumed for the risk assessment for fish-eating birds.

Table 2.8-15: Risk for birds from bioaccumulation and food chain behaviour

Parameter	Triticonazole/cereal seeds	RPA 406203
$NOAEL_{long\text{-}term}$ [mg ai/kg bw/d]	19.5	1.95
K_{oc} (Organic carbon adsorption coefficient)	290*	Not necessary
K_{ow} (Octanol water partition coefficient)	1995	
f_{oc} (Organic carbon content of soil)	default value: 0.02	
$PEC_{soil\ 21d\ twa\ accu}$ [mg ai/kg]	0.1863	
BCF_{worm}	4.27	
PEC_{worm} [mg ai/kg]	0.796	
Daily dose [mg ai/kg bw/d]	0.836	
$TER_{earthworm\text{-}eating\ birds}$	23	
Trigger	5	

PECwater (initial, FOCUS step 1) [mg ai/L]	0.0031	0.002
BCFfish	72.55	72.55
PECfish [mg ai/kg]	0.226	0.145
Daily dose [mg ai/kg bw/d]	0.036	0.023
$TER_{fish\text{-}eating\ birds}$	542	84.78
Trigger	5	5

*As the adsorption is pH-dependent no geomean was calculated and the worst case K_{oc} was used.
Bold values do not meet the trigger

Based on the results of the livestock metabolism study in lactating goat (radioactivity associated with edible portions, milk and tissues, accounted for ≤ 1% of the administered dose), the ADME studies with rats and a bioaccumulation study in fish demonstrate that triticonazole has a low potential to bioaccumulate and biomagnify in vertebrates (please also refer to sections B6 and B7).

Overall conclusion for the risk assessment for birds

The acute risk for birds due to exposure of triticonazole in spring and winter cereal fields was assessed as low at tier 1. For long-term exposure no low risk can be concluded at a tier 1 for granivorous birds feeding on freshly drilled treated seeds and a refined risk assessment is required. Seven focal species were identified for pre-emergence cereal fields. These are skylark, yellowhammer, chaffinch, wood pigeon, rook, carrion crow and pheasant. Additionally the linnet is discussed as a potential focal species representing small granivorous birds. For this species no refinement is available but an argumentation by the applicant why it should not be considered as a focal species (Subject to peer review). For the bigger of the focal species, wood pigeon, rook, carrion crow and pheasant, a low long-term risk is indicated. Refined residues on seeds and PT-refinement lead to a low risk for the yellowhammer in spring and winter cereals and for the chaffinch in winter cereals. For the skylark low risk is only possible by using the best case germination time of 21 days.
Further refinement options and supportive additional information was provided by the applicant. Taking into account that the long-term toxicity endpoint for birds may be conservative and using the endpoint estimated in the modified exposure study would lead to a low risk (to be discussed during the peer review or an expert-meeting). Furthermore a refined PD for skylarks is available, which could be used in a weight of evidence approach considering that the TERLT without PD refinement is between 3.2 and 5.1 (depending on the germination time used) in spring cereals and between 3.7 and 6.0 (depending on the germination time used) in winter cereals. For chaffinches a de-husking behaviour can be assumed in a weight of evidence approach considering that the TERLT without de-husking is between 3.7 and 5.9 (depending on the germination time used).
It should be noted, that the studies for PD and PT refinement have all been conducted in Germany. Therefore it is not ascertained that these refinement options account for other than the central zones. The risk for secondary poisoning and biomagnification is low.

2.8.1.2. Risk assessment for mammals

The exposure and risk assessment for mammals was conducted according to the EFSA Guidance Document on Risk Assessment for Birds and Mammals (EFSA Journal 2009;7(12):1438)

Table 2.8-16: Acute risk assessment for mammals

Crop	Generic focal species	FIR/bw	NAR[1]	TER_A	Assessment level
Cereals BBCH 00/ spring and autumn	Small omnivorous mammal	0.24	50	> 167	Tier 1
Cereal seedlings	Small omnivorous mammal	0.24	10[b]	> 834	Tier 1
	Large herbivorous mammal[a]	0.4	10[b]	> 500	Tier 1

[1]NAR = Nominal loading/application rate of active substance in mg/kg seed.
[a]Large herbivorous mammals are referred to in the text but not in the table of the EFSA GD. Therefore large herbivorous bird

is added here with DDD value used for rabbit.
[b]NAR/5
Bold values do not meet the trigger

Table 2.8-17: Tier 1 long-term risk assessment for mammals

Crop	Generic focal species	FIR/bw	NAR[1]	f_{twa}[2]	TER_{LT}	Assessment level
Cereals BBCH 00/ spring and autumn	Small granivorous mammal	0.3	50	0.72	**2.89**	Tier 1
				0.64	**3.26**	Tier 1
				0.53	**3.93**	Tier 1
Cereals seedlings	Small omnivorous mammal	0.24	10[b]	0.53	19.7	Tier 1
	Large herbivorous mammal[a]	0.4	10[b]	0.53	11.7	Tier 1

[1]NAR = Nominal loading/application rate of active substance in mg/kg seed.
[2]The averaging time of 21 days is under debate for seed treatments as the time from sowing to germination usually is shorter, for cereals 10 to 14 days can be assumed. To enable expert discussion, the risk assessment is presented with a worst case germination time of 10 days, with a more realistic value of 14 days and with 21 days as used for spray applications.
[a]Large herbivorous mammals are referred to in the text but not in the table of the EFSA GD. Therefore large herbivorous bird is added here with DDD value used for rabbit.
[b]NAR/5
Bold values do not meet the trigger.

Higher tier long-term risk assessment for mammals

Initial residues on cereal seeds on the soil surface were estimated in degradation studies. The worst case residue of 91.88% was used as correction factor.

The decline of residues on cereal seeds on the soil surface was estimated in degradation studies. A interzonal geometric mean DT_{50} of 5.5 days was determined

As a focal species the wood mous was chosen based on the fact that it is a typical small mammal species, widespread in Europe and common in agricultural land.

For PD refinement of the wood mouse based on the recommendations in the EFSA GD and field studies a worst-case PD of 0.5 was determined.

Table 2.8-18: Higher tier long-term risk assessment with refined PD for the wood mouse in cereals *

Crop	Generic focal species	FIR/bw	NAR[1]	Correction factor based on initial residue	ftwa	PD	NOAEL [mg ai/kg bw]	TER_{LT}
Wood mouse	BBCH 00/ spring and autumn	0.24	50	0.92	0.568	0.5	25	7.97
					0.470			9.64
					0.351			12.90

NAR = Nominal loading/application rate of active substance in mg/kg seed.
*The averaging time of 21 days is under debate for seed treatments as the time from sowing to germination usually is shorter, for cereals 10 to 14 days can be assumed. To enable expert discussion, the risk assessment is presented with using the f_{twa} based on DT_{50} of 5.5 days and a worst case germination time of 10 days, with a more realistic value of 14 days and with 21 days as used for spray applications.
Bold values do not meet the trigger

Drinking water risk assessment:

According to the EFSA Guidance Document on Birds and Mammals (2009) significant contamination of drinking water after the use of a pesticide as seed treatment seems very unlikely to be a critical route or to lead to

TER values greater than direct dietary consumption. A drinking water risk assessment therefore is not considered necessary.

Secondary poisoning and biomagnification in terrestrial food chains

The log P_{OW} value of the active substance triticonazole is 3.3 (Chabassol et al, 1991) and for the metabolite RPA 406203 it is 3.5 (Cowlyn, 2014e). Therefore a risk assessment for earthworm to earthworm-eating mammals and from fish to fish-eating mammals is required. For all other metabolites the log Pow is < 3 (For details please also refer to B.9 - CA).

The risk of RPA 406203 can be considered low as the Z-isomer only is formed under irradiation. Therefore earthworms are not likely to be exposed to RPA 406203.
No toxicological endpoint for RPA 406203 is available therefore as a worst case a 10-fold higher toxicity than the parent is assumed for the risk assessment for fish-eating mammals.

Table 2.8-19: Risk for mammals from bioaccumulation and food chain behaviour

Parameter	Triticonazole/cereal seeds	RPA 406203
$NOAEL_{long\text{-}term}$ [mg ai/kg bw/d]	25	2.5
K_{oc} (Organic carbon adsorption coefficient)	290*	Not necessary
K_{ow} (Octanol water partition coefficient)	1995	
f_{oc} (Organic carbon content of soil)	default value: 0.02	
$PEC_{soil\ 21d\ twa\ accu}$ [mg ai/kg]	0.1863	
BCF_{worm}	4.27	
PEC_{worm} [mg ai/kg]	0.796	
Daily dose [mg ai/kg bw/d]	1.019	
$TER_{earthworm\text{-}eating\ birds}$	24	
Trigger	5	
PECwater (initial, FOCUS step 1) [mg ai/L]	0.0031	0.002
BCFfish	72.55	72.55
PECfish [mg ai/kg]	0.226	0.145
Daily dose [mg ai/kg bw/d]	0.032	0.021
$TER_{fish\text{-}eating\ birds}$	781	119
Trigger	5	5

*As the adsorption is pH-dependent no geomean was calculated and the worst case K_{oc} was used.
Bold values do not meet the trigger

Based on the results of the livestock metabolism study in lactating goat (radioactivity associated with edible portions, milk and tissues, accounted for ≤ 1% of the administered dose), the ADME studies with rats and a bioaccumulation study in fish demonstrate that triticonazole has a low potential to bioaccumulate and biomagnify in vertebrates (please also refer to sections B6 and B7).

Overall conclusion for the risk assessment for mammals

The acute risk for mammals due to exposure of triticonazole in spring and winter cereal fields was assessed as low at tier 1. For long-term exposure no low risk could be concluded at a tier 1 for small omnivorous mammals feeding on freshly drilled treated seeds and a refined risk assessment is required. The wood mouse is considered to be the focal species for pre-emergence cereal fields. Risk assessment with refined residues on the seed and a refined PD for the wood mouse indicate an acceptable long-term risk. Further refinement options and supportive additional information was provided by the applicant. A refined PT for wood mice is available as supporting information.
It has to be noted, that the studies for PD (a worst case value was used for the refinement, which may cover all zones) and PT refinement have all been conducted in Germany. Therefore it is not ascertained that these refinement options account for other than the central zones. The risk for secondary poisoning and biomagnification is low.

2.8.1.3. Risk assessment for aquatic organisms

The risk assessment was conducted according to the Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters, EFSA Journal 2013;11(7):3290.

A summary of all PEC/RAC comparisons based on the most relevant endpoints are given in the following tables. Please note that for FOCUS step 2 only values for the worst case from North or South are listed.

Table 2.8-20: PEC/RAC comparisons for triticonazole, Cereals, 1 x 12.5 g a.s./ha

Compound	Organisms	Time scale	FOCUS Step	PEC_{SW} (µg/L)	Tier 1 $RAC_{sw;ac}$ (µg/L)
triticonazole	Fish	Acute	Step 1	3.07	36
	Fish	Long-term	Step 3, spring and winter cereals worst case scenarios D1 and D2 ditch	0.235 0.915	1.14
	Aquatic invertebrates	Acute	Step 1	3.07	19
	Aquatic invertebrates	Long-term	Step 1	3.07	4.1
	Algae	Long-term	Step 1	3.07	53
RPA 406341	Fish[a]	Acute	Step 1	0.74	3.78
	Aquatic invertebrates	Acute	Step 1	0.74	517.8
	Algae	Long-term	Step 1	0.74	5.57
RPA 404766	Fish[a]	Acute	Step 1	0.55	1.78
	Aquatic invertebrates	Acute	Step 1	0.55	1000
	Algae	Long-term	Step 1	0.55	5.57
RPA 406203	Fish[b]	Acute	Step 1	1.99	3.60
	Aquatic invertebrates	Acute	Step 1	1.99	34
	Algae	Long-term	Step 1	1.99	6483
Met 6 (MWT 333)	Fish[c]	Acute	Step 1	0.41	3.77
	Aquatic invertebrates[c]	Acute	Step 1	0.41	8.23
	Algae	Long-term	Step 1	0.41	5.55
Met 7 (MWT 315)	Fish[d]	Acute	Step 1	0.19	3.75
	Aquatic invertebrates[d]	Acute	Step 1	0.19	7.78
	Algae	Long-term	Step 1	0.19	5.25
Premis 25 FS	Aquatic invertebrates	Acute	Step 1	3.07	25
	Algae	Long-term	Step 1	3.07	204

Values in **bold** are below PECsw, thus indicating an unacceptable risk

[a]toxicity endpoint calculated by considering the molecular weight of the metabolite of 333.8 g/mol and assuming 10-times more toxicity than the parent

[b]toxicity endpoint calculated by considering the molecular weight of the metabolite of 317.8 g/mol and assuming 10-times more toxicity than the parent

[c]toxicity endpoint calculated by considering the molecular weight of the metabolite of 333 g/mol and assuming 10-times more toxicity than the parent

[d]toxicity endpoint calculated by considering the molecular weight of the metabolite of 315 g/mol and assuming 10-times more toxicity than the parent

Bioaccumulation

The accumulation and elimination of triticonazole has been determined in two fish bioaccumulation studies.

The kinetic bioconcentration factor (BCFK) of triticonazole was determined to be 72.55 in whole fish. The bioconcentration factor for edible and non-edible tissues was 9.2 and 114.86, respectively. Depuration was very rapid with a calculated elimination half-life of < 1 day.

According to the EFSA Aquatic Guidance Document (EFSA, 2013) a risk assessment addressing biomagnification is not considered necessary as the BCF is below the trigger of 1000 and the elimination of during the 14-day depuration phase is > 95%.

Overall conclusion for the risk assessment for aquatic organisms

For all aquatic organism groups a low risk could be identified due to exposure to the active substance triticonazole and its metabolites at FOCUS step 1-3 for the intended use as a seed treatment. A study with the sediment dwelling organism *Chironomus riparius* was provided, however its validity and reliability, respectively is questionable. The applicant argues that a study with a sediment dwelling organism is not triggered. However, the RMS disagrees and is of the opinion that based on the data situation testing of a sediment dwelling organism is required.

2.8.1.4. Risk assessment for bees

The risk assessment for honey-bees was conducted according to the draft EFSA Guidance Document (EFSA Journal 2013;11(7):3295).

Table 2.8-21: Risk to honeybees from acute oral exposure to triticonazole – screening step

Crop*	Test substance	Endpoint [µg ai/bee]	CF	$ETR_{acute\ adult\ oral}$	Trigger
Cereals 1 x 12.5 g ai/ha	Triticonazole	48 h LD_{50} > 155.5	2.28	< 0.001	0.2
	BAS 595 01 F	48 h LD_{50} = 76.74		0.001	
Cereals 0.0032 mg ai/seed	Triticonazole	48 h LD_{50} > 155.5	0.7	< 0.001	
	BAS 595 01 F	48 h LD_{50} = 76.74		0.001	
Cereals 0.00105 mg ai/seed	Triticonazole	48 h LD_{50} > 155.5	0.7	< 0.001	
	BAS 595 01 F	48 h LD_{50} = 76.74		0.001	

CF…Calculation factor according to EFSA Journal 2013;11(7):3295
*overall minimum and maximum thousand grain weight values of all intended cereals: 21-64 g
Bold…trigger exceeded

Table 2.8-22: Risk to honeybees from acute contact exposure to triticonazole – screening step

Crop	Test substance	Endpoint [µg ai/bee]	CF	$HQ_{contact}$	Trigger
Cereals 1 x 12.5g ai/ha	Triticonazole	LD_{50} > 100	0.099	< 0.01	14
	BAS 595 01 F	LD_{50} > 20		< 0.06	

CF…Calculation factor according to EFSA Journal 2013;11(7):3295
Bold…trigger exceeded

Table 2.8-23: Chronic oral toxicity to bees – screening step

Crop	Test substance	Endpoint	CF	ETR	Trigger
Cereals 1 x 12.5 g ai/ha	BAS 595 01 F	10d LDD_{50} = 12.9 µg ai/bee/d	2.28	0.002	0.03
Cereals 0.0032 mg ai/seed			0.7	0.0001	
Cereals 0.00105 mg ai/seed				0.0001	

CF…Calculation factor according to EFSA Journal 2013;11(7):3295
*overall minimum and maximum thousand grain weight values of all intended cereals: 21-64 g
Bold…trigger exceeded

Table 2.8-24: larval toxicity to bees – screening step

Crop	Test substance	Endpoint	CF	ETR	Trigger
Cereals 1 x 12.5 g ai/ha	BAS 595 01 F	72 hours NOED = 24.8 µg ai/larva/d	1.32	0.00	0.2
Cereals 0.0032 mg ai/seed			0.4	0.00	
Cereals 0.00105 mg ai/seed				0.00	

CF…Calculation factor according to EFSA Journal 2013;11(7):3295
*overall minimum and maximum thousand grain weight values of all intended cereals: 21-64 g
Bold…trigger exceeded

Furthermore a low risk was identified for the exposure due to drinking water via guttation, surface water and puddle water. The ETR for all scenarios were 0.00 except for the chronic exposure for adult bees (0.004) for larvae (0.03) via guttation water. Both values are well below the triggers of 0.03 and 0.2, respectively.

Overall conclusion for the risk assessment for honey bees

The exposure to triticonazole used as a seed treatment in cereals poses a low risk to bees. Also a low risk due to contaminated drinking water via surface water, puddle water and guttation water respectively could be identified. No specific information is available regarding the toxicity of the metabolites to bees. However, it can be assumed that the metabolites are not more toxic than the active substance. Furthermore contamination of bee relevant matrices is not likely.

2.8.1.5. Risk assessment for non-target arthropods other than bees

Overall conclusion for the risk assessment for non-target arthropods other than bees

In general the risk to non-target arthropods is assessed using the approach recommended in the ESCORT 2 document and the SANCO EC Guidance Document on Terrestrial Ecotoxicology (2002). However for substances applied as seed treatment the recommended risk assessment scheme for spray applications is not suitable.

Non-target arthropods may be exposed to formulated triticonazole by contact with treated seeds in soil. The concentrations tested do not cover the intended application rate of 12.5 g ai/ha. However, the LR_{50} and ER_{50} values estimated by the studies are > values. Observed effects are all less than 10% or even positive.
Further testing was conducted with the macro-soil organisms *Folsomia candida* and *Hyposapis aculeifer*. The risk assessment shows an acceptable risk for these soil dwelling organisms. Considering all available information regarding soil-organisms, the risk can be assumed acceptable.

2.8.1.6. Risk assessment for non-target soil meso- and macrofauna

The risk to non-target soil meso- and macrofauna is assessed using the SANCO EC Guidance Document on Terrestrial Ecotoxicology (2002).

Table 2.8-25: TER long-term for earthworms and other soil macro-organisms

Species	Test substance	max PECsoil [mg/kg soil dw]	TER_{LT}	Trigger
Eisenia fetida	Triticonazole	0.0189	6614	5
	BASF 595 01 F	0.0189	7.03	
	Metabolite RPA 404766 (Reg.No. 5079285)	0.0027	> 10000	5
	Metabolite RPA 406341 (Reg.No. 5059144)	0.0037	1351	
	Metabolite MET 6[a]	0.0022	> 10000	
	Metabolite MET 7[b]	0.0010	> 10000	
Folsomia candida	Triticonazole	0.0189	3307	5
	BASF 595 01 F	0.0189	646	
	Metabolite RPA 404766 (Reg.No. 5079285)	0.0027	> 10000	
	Metabolite RPA 406341 (Reg.No. 5059144)	0.0037	6757	
	Metabolite MET 6[a]	0.0022	> 10000	
	Metabolite MET 7 [b]	0.0010	> 10000	
Hypoaspis aculeifer	Triticonazole	0.0189	> 10000	5
	BASF 595 01 F	0.0189	619	
	Metabolite RPA 404766 (Reg.No. 5079285)[a]	0.0027	9630	
	Metabolite RPA 406341 (Reg.No. 5059144)	0.0037	1351	
	Metabolite MET 6[a]	0.0022	> 10000	
	Metabolite MET 7 [b]	0.0010	> 10000	

* corrected by a factor of 2 due to the log P_{OW} of triticonazole > 2 (log P_{OW} triticonazole: 3.3; log P_{OW} for RPA 406341: 2.2)
**worst case assumption, that the metabolite is ten times more toxic than the parent.
[a]calculated by considering the molecular weight of the metabolite of 333 g/mol and assuming 10-times more toxicity than the parent
[b]calculated by considering the molecular weight of the metabolite of 315 g/mol and assuming 10-times more toxicity than the parent
Bold values do not meet the trigger

Overall conclusion on the risk assessment of non-target soil meso- and macrofauna

Overall, the risk to soil macro- and mesofauna is considered low and no further information is required addressing the risk to soil organisms.

2.8.1.7. Risk assessment for soil nitrogen transformation

The risk to non-target soil nitrogen transformation is assessed using the SANCO EC Guidance Document on Terrestrial Ecotoxicology (2002).

Table 2.8-26: Risk assessment for soil nitrogen transformation

Test substance	Effects < 25% at test concentration	$PEC_{soil, accumulation}$	Risk acceptable Yes/No
BASF 595 01 F	0.167 mg ai/kg soil dw	0.0189 mg ai/kg soil dw	Yes
Metabolite RPA 406341 (Reg.No. 5059144)	10.0 mg/kg soil dw	0.0037 mg/kg soil dw	Yes
Metabolite RPA 404766 (Reg.No. 5079285)	1.0 mg/kg soil dw	0.0027 mg/kg soil dw	Yes
Metabolite MET 6[a]	0.017 mg /kg soil dw	0.0022	Yes
Metabolite MET 7[b]	0.166 mg /kg soil dw	0.0010	Yes

[a]calculated by considering the molecular weight of the metabolite of 333 g/mol and assuming 10-times more toxicity than the parent

[b]calculated by considering the molecular weight of the metabolite of 315 g/mol and assuming 10-times more toxicity than the parent

Overall conclusion on the risk assessment for soil nitrogen transformation

According to the results of the data provided for the active substance triticonazole it can be assumed that the risk for soil micro-organisms is low when applied according to the GAP. A public literature study is available showing a decline of reduction in numbers of microorganisms by applying Premis 025 FS at a dose of 200 ml/100 kg grain and 150 ml/100 kg grain at harvest. These results are considered relevant. However, the study was not conducted according to OECD TG 2016 with the study mainly focussing on structural parameters than on functionality. Therefore results cannot be used in the risk assessment but are considered as supplemental information.

2.8.1.8. Risk assessment for non-target higher plants

Overall conclusion on the risk assessment for non-target higher plants

As the intended use is a seed treatment, the exposure to non-target plants is considered to be negligible and a risk assessment is not required.

2.9. CLASSIFICATION AND LABELLING

Proposed classification according to Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	-	-	-	conclusive but not sufficient for classification
2.2.	Flammable gases	-	-	-	conclusive but not sufficient for classification
2.3.	Flammable aerosols	-	-	-	conclusive but not sufficient for classification
2.4.	Oxidising gases	-	-	-	conclusive but not sufficient for classification
2.5.	Gases under pressure	-	-	-	conclusive but not sufficient for classification
2.6.	Flammable liquids	-	-	-	conclusive but not sufficient for classification
2.7.	Flammable solids	-	-	-	conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	-	-	-	conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	-	-	-	conclusive but not sufficient for classification
2.10.	Pyrophoric solids	-	-	-	conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	-	-	-	conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	-	-	-	conclusive but not sufficient for classification
2.13.	Oxidising liquids	-	-	-	conclusive but not sufficient for classification
2.14.	Oxidising solids	-	-	-	conclusive but not sufficient for classification
2.15.	Organic peroxides	-	-	-	conclusive but not sufficient for

					classification
2.16.	Substance and mixtures corrosive to metals	**-**	**-**	**-**	conclusive but not sufficient for classification
3.1.	Acute toxicity - oral	**-**	**-**	**-**	conclusive but not sufficient for classification
	Acute toxicity - dermal	**-**	**-**	**-**	conclusive but not sufficient for classification
	Acute toxicity - inhalation	**-**	**-**	**-**	conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	**-**	**-**	**-**	conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	**-**	**-**	**-**	conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	**-**	**-**	**-**	conclusive but not sufficient for classification
3.4.	Skin sensitisation	**-**	**-**	**-**	conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	**-**	**-**	**-**	conclusive but not sufficient for classification
3.6.	Carcinogenicity	**-**	**-**	**-**	conclusive but not sufficient for classification
3.7.	Reproductive toxicity	**-**	**-**	**-**	conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	**-**	**-**	**-**	conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	**STOT RE 2**	**-**	**-**	**-**
3.10.	Aspiration hazard	**-**	**-**	**-**	conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	Aquatic acute 1 Aquatic chronic 1	M-factor: 1 M-factor: 1	Aquatic Chronic 2	-
5.1.	Hazardous to the ozone layer	-	-	-	conclusive but not sufficient for classification

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: Warning
Hazard statements: H373, H410
Precautionary statements: P260, P314, P273, P391, P501

Proposed notes assigned to an entry:
Notes in accordance with CLP Regulation, Annex VI, Section 1.1.3

2.10. RELEVANCE OF METABOLITES IN GROUNDWATER

The 80th percentile annual average PEC_{gw} concentrations at 1 m depth were predicted as < 0.1 µg/l for triticonazole, RPA 406341 (Trans-diol), RPA 404766 (Cis-diol) and the metabolite fraction 'Met 7 (MWT 315)' in all cases. Notice, that in case of RPA 404766 (Cis-diol) a refinement step was applied (field *DegT50* of RPA 406341 (Trans-diol) used for RPA 404766 (Cis-diol) as well).

The leaching assessment for the metabolite fraction 'Met 6 (MWT 333)', observed > 5 % AR at two consecutive sampling points in a legacy study (Ayliffe & Austin, 1993), resulted in exceedance of the regulatory threshold of 0.1 µg/L (maximum PEC_{gw} of 0.187 µg/L) in most FOCUS groundwater scenarios.

2.10.1. STEP 1: Exclusion of degradation products of no concern

According to the *Guidance document on the assessment of the relevance of the metabolites in groundwater of substances regulated under Council Directive 91/414/EEC* (Sanco/221/2000 –rev.10- final, 25 February 2003) no degradation products of no concern were detected.

2.10.2. STEP 2: Quantification of potential groundwater contamination

The leaching assessment for the metabolite fraction 'Met 6 (MWT 333)', observed > 5 % AR at two consecutive sampling points in a legacy study (Ayliffe & Austin, 1993), resulted in exceedance of the regulatory threshold of 0.1 µg/L (maximum PEC_{gw} of 0.187 µg/L) in most FOCUS groundwater scenarios.

2.10.3. STEP 3: Hazard assessment – identification of relevant metabolites

2.10.3.1 STEP 3, Stage 1: screening for biological activity

Currently no data is available.

2.10.3.2 STEP 3, Stage 2: screening for genotoxicity

All currently identified mono-hydroxylated metabolites of triticonazole (M595F001, M595F002, M595F004, M595F007, M595F013), hydroxylated on different part of parent molecule and investigated based on their occurrence in residues of plant and animal origin, were devoid of any genotoxic concern, based on the extensive QSAR evaluation (please see Vol 3, B6). Although it is not *a priori* expected that unidentified fraction "MET 6 (MWT 333)", assumed to be a mono-hydroxylated parent, is a fraction of genotoxic concern, this assumption cannot be substantiated by data since no identification has been done yet.

2.10.3.3 STEP 3, Stage 3: screening for toxicity

Triticonazole is included in Annex VI of Regulation (EC) 1272/2008 without any hazard for human health. During the renewal assessment RMS proposed to update triticonazole hazard assessment as STOT RE 2, H373 (based on mortality observed in rabbits). This is however not a hazard class which would classifiy the metabolite as "relevant". Therefore, "MET 6 (MWT 333)" is considered to be not relevant based on the proposed classification for triticonazole. No data on "MET 6 (MWT 333)" exists, since the fraction is not yet identified.

2.10.4. STEP 4: Exposure assessment – threshold of concern approach

According to the current estimates, metabolite fraction "MET 6 (MWT 333)" can exceed regulatory threshold of 0.1 µg/L (maximum PECgw of 0.187 µg/L) but not 0.75 µg/l. Therefore, it is considered that only genotoxicity is to be addressed.

2.10.5. STEP 5: Refined risk assessment

Please see 2.10.4.

2.10.6. Overall conclusion

Open.

2.11. CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

2.11.1. Identity and physical chemical properties

Triticonazole, technical is a racemic mixture of the two enantiomers (1*R*,5*E*)-5-[(4-chlorophenyl)methylene]-2,2-dimethyl-1-(1,2,4-triazol-1-ylmethyl)cyclopentanol and (1*S*,5*E*)-5-[(4-chlorophenyl)methylene]-2,2-dimethyl-1-(1,2,4-triazol-1-ylmethyl)cyclopentanol. Triticonazole possesses a chiral centre in C-1 of the cyclopentane ring and an exocyclic double bond in C-2 of the cyclopentane ring. The minimum purity of the dry material TC (racemate) is 950 g/kg.

The ratio of the enantiomers in the technical material and in formulations (racemic mixture; 1:1 ratio) is deemed to be stable.

The Z-isomer, which could theoretically exist due to the E/Z-isomerism at the double bond, is not included in the definition of the active substance and is not observed in the technical material.

2.11.2. Methods of analysis

Due to the fact that in technical material and in formulations triticonazole is only present as a racemic mixture, no analytical methods for the determination of both enantiomers are required.

2.11.3. Mammalian toxicity

A normal practice for cereal seed treatment as well as storage is the exclusion of light in order to avoid seed germination. Further, treated seeds are also stored in brown paper bags. However, to complete the genotoxicity package of Z-isomer of triticonazole, which can be formed under UV-light via treatment/handling of triticonazole-treated seeds (exposed to sunlight), the notifier submitted a new *in vitro* micronucleus test for the purpose of renewal of triticonazole. Additionally, a non-GLP study has been conducted on conversion from triticonazole to Z-isomer after fresh treatment of seeds with triticonazole and UV light exposure in a period of 10 days. In the study was shown that ratio of triticonazole / Z-isomer is in the range of 99.0 / 1.0% (day 1) to 97.6 / 2.4 % (day 10) and therefore Z-isomer is considered as very minor.

Additionally, QSAR assessment has been submitted for purpose of renewal. Evaluation of the mutagenic potential using CASE Ultra for Ames (statistical and rule based models) and CASE Ultra (statistical) and Toxtree (rule based) for in vivo MNT gives a clear in domain negative prediction.

2.11.4. Operator, Worker, Bystander and Resident exposure

Based on the residue studies and the planned use as seed treatment, realistically no human exposure to the Z-isomer is expected during operating and re-entry work. Thus, no risk assessment on the Z-isomer of triticonazole has been conducted.

2.11.5. Residues and Consumer risk assessment

Triticonazole technical is a racemic mixture of the two enantiomers (1*R*,5*E*)-5-[(4-chlorophenyl)methylene]-2,2-dimethyl-1-(1,2,4-triazol-1-ylmethyl)cyclopentanol and (1*S*,5*E*)-5-[(4-chlorophenyl)methylene]-2,2-dimethyl-1-(1,2,4-triazol-1-ylmethyl)cyclopentanol. Triticonazole possesses a chiral centre in C-1 of the cyclopentane ring

and an exocyclic double bond in C-2 of the cyclopentane ring. The minimum purity of the dry material (racemate) is 950 g/kg.
The ratio of the enantiomers in the technical material and in formulations (racemic mixture; 1:1 ratio) is deemed to be stable.
The Z-isomer, which could theoretically exist due to the E/Z-isomerism at the double bond, is not included in the definition of the active substance and is not observed in the technical material.
All studies were done with the racemic mixture of Triticonazole. There are no detectable residues of Triticonazole at harvest, therefore a separation of enantiomers was not necessary.
Due to the planned use as seed treatment, triticonazole is not expected to be exposed to light and therefore, the formation of the Z isomer (photometabolite RPA 406203) is not considered to be relevant for residue studies. The Z-isomer was also not detected in edible matrices in the plant metabolism study.
Further considerations regarding the influence of isomers on the outcome of the residue behaviour and therefore on the consumer risk assessments are not needed.

2.11.6. Environmental fate

Chiral analysis of representative soil extracts shows that both the *R* and *S* isomers of the racemic parent are comparably degradable. There is no indication for a significant shift in the *R*/*S* ratio during degradation in aerobic soils.

Metabolites RPA 406341 (Trans-diol) and RPA 404766 (Cis-diol) are diastereomers which are hydroxylated at the same position in the cyclopentane ring. Metabolite RPA 406341 (Trans-diol) includes the two enantiomers for which the hydroxyl group has the opposite orientation as the second hydroxyl group in the cyclopentane ring (*RS*, *RS* isomers). Metabolite RPA 404766 (Cis-diol) includes the two enantiomers for which both hydroxyl groups have the same orientation (*RR*, *SS* isomers). Chiral analysis of RPA 406341 (Trans-diol) in representative soil extracts show that an enantioselective degradation of the metabolites is unlikely to occur.

2.11.7. Ecotoxicology

RPA 406203 is the Z-isomer of triticonazole and can be formed under light conditions from triticonazole (the E-isomer).
Studies on terrestrial vertebrates (mammals) and aquatic organisms (Daphnia magna, Pseudokirchneriella subcapitata) are available. The endpoints of the available studies generally indicate that RPA 406203(Z-isomer) is not more toxic than triticonazole (E-isomer). A study was conducted to determine the extent of conversion of the E-isomer of Triticonazole to its Z-isomer on wheat seeds after seed treatment with BAS 595 01 F and subsequent irridation with UV light during a time period of 10 days. After irridation of BAS 595 01 F treated seeds in the laboratory, the overall amount of Z-isomer formed in these trials is very low, and the large majority of residues is made up by the E-isomer.
Furthermore data from a specific field study (BASF docID 2012/1126440) show that the 90th percentile of seeds being exposed on the soil surface is 57 seeds/m2 in the headlands and 24 seeds/m2 in the midfield. Based on a thousand grain weight of 46 g for winter wheat taken from the DAR (September 2003) and a maximum seeding

rate of 250 kg/ha, this leads to the conclusion that under the abovementioned conditions only 5 to 10% of the total amount of sown seeds could be theoretically exposed to sunlight. Together with the low formation rate of the Z-isomer after irradiation of treated seeds it leads to the conclusion that exposure of granivorous birds and mammals to the Z-isomer should be very limited and thus covered by the risk assessment for the E-isomer.

2.12. RESIDUE DEFINITIONS

2.12.1. Definition of residues for exposure/risk assessment

Food of plant origin: Triticonazole

Food of animal origin: Triticonazole

Soil: Triticonazole, RPA 406341 (Trans-diol), RPA 404766 (Cis-diol), RPA 406203 (Z-isomer)[(a)], Met 6 (MWT 333)'[(b)], 'Met 7 (MWT 315)'[(b)]

Groundwater: Triticonazole, RPA 406341 (Trans-diol), RPA 404766 (Cis-diol), RPA 406203 (Z-isomer)[(a)], Met 6 (MWT 333)'[(b)], 'Met 7 (MWT 315)'[(b)]

Surface water: Triticonazole, RPA 406341 (Trans-diol), RPA 404766 (Cis-diol), RPA 406203 (Z-isomer), Met 6 (MWT 333)'[(b)], 'Met 7 (MWT 315)'[(b)]

Sediment: Triticonazole, RPA 406341 (Trans-diol), RPA 404766 (Cis-diol), RPA 406203 (Z-isomer), Met 6 (MWT 333)'[(b)], 'Met 7 (MWT 315)'[(b)]

Air: Triticonazole

(a) RPA 406203 (Z-isomer) has to be included in the exposure assessment in case of spray applications only (exposure to irradiation at the soil surface)
(b) Tentatively identified metabolite fractions observed > 5 % AR at two consecutive sampling points in Ayliffe & Austin (1993)

2.12.2. Definition of residues for monitoring

Food of plant origin: Triticonazole

Food of animal origin: Triticonazole

Soil: Triticonazole

Groundwater: Triticonazole

Surface water: Triticonazole

Sediment: Triticonazole

Air: Triticonazole

Level 3

Triticonazole

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.	X		It is considered that Article 4 of Regulation(EC) No 1107/2009 is complied with Triticonazole for the representative uses (please refer to Section 1.5.1 Level 1 for details of representative uses)
	3.1.1.2. Submission of further information			
		Yes	No	
i)	It is considered that a complete dossier has been submitted	X		With regards to the submission made, a complete dossier is considered to have been submitted, which enables a regulatory decision of Triticonazole to be made. Regarding the data gaps identified in the separate dossiers of the notifiers please refer to point 3.1.4.
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.			Not applicable
	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 minimum purity should be specified as 950 g/kg as TC, identical to reference source DAR 2003 which was the pilot plant. This current specification is supported by the most recent batch analysis from the notifier and considered to be equivalent to the pilot plant. Triticonazole as manufactured is available as TK with a minimum purity of 890 g/kg. This increased as minimum purity for

				the TK was 870 g/kg in the DAR 2003. *(a) the nature and maximum content of certain impurities;* No relevant impurities were specified in the past. However, the current evaluation of the DRAR identified in the TK methanol as relevant impurity maximal contained with 3 g/kg. Methanol was contained in the previous specification of the TK as well with a maximal content of 10 g/kg. *(b) restrictions arising from the evaluation of the information referred to in Article 8 of 1107/2009 taking account of the agricultural, plant health and environmental, including climatic, conditions in question;* *N/A* *(c) type of preparation;* *N/A* *(d) manner and conditions of application;* *N/A* *(e) submission of further confirmatory information to Member States, the Commission and the European Food Safety Authority, (the Authority), where new requirements are established during the evaluation process or as a result of new scientific and technical knowledge;* *N/A* *(f) designation of categories of users, such as professional and non-*

				professional; *N/A* *(g) designation of areas where the use of plant protection products, including soil treatment products, containing the active substance may not be authorised or where the use may be authorised under specific conditions;* *N/A* *(h) the need to impose risk mitigation measures and monitoring after use* *To protect birds and wild mammals the product must be entirely incorporated in the soil; ensure that the product is also fully incorporated at the end of rows.* *To protect birds/wild mammals remove spillages.* The groundwater leaching assessment indicates a risk for metabolite fraction 'Met 6 (MWT 333)' to leach above the threshold of 0.1 µg/L in groundwater. Risk mitigation measures with respect to application frequency may be needed (e.g. application each second year only), as long as identification of fraction MET 6 has not been finalised. *(i) any other particular conditions that result from the evaluation of information made available in the context of Regulation 1107/2009.* *N/A*
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		The data submitted are sufficient to establish an Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL), Acute Reference Dose (ARfD) and Acute Acceptable Operator Exposure Level (AAOEL).
	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 data necessary to establish adequate MRLs and consumer risk assessment were submitted are considered as sufficient for the currend approval process. Based on the assessment of the available data, MRL proposals were derived and a consumer risk assessment was carried out. No risk for consumers could be identified with respect to the representative uses.
	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.			See detailed evaluation in sections 8 and 9.
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.			Sufficient information on efficacy of triticonazole was provided by the notifier. For details please 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		From the toxicological point of view, absence of genotoxicity for non-identified fraction “MET 6 (MWT 333)” should be substantiated by data after the identification of the fraction has been done. The ecotoxicological or environmental relevance of metabolites can be established.

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		Sufficient information has been presented to support the declared technical specification of triticonazole with respect to the identity and content of impurities in the respective technical specification.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.			No FAO specification exists
	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 necessary
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		Adequate analytical methods are available for the determination of triticonazole and all significant impurities in the technical material.
	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		Adequate methods are available and sufficiently sensitive to monitor the respective current residue definition in plant material, soil, drinking water, surface water and air.
	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		Please refer to Level 2 Section 2.2 for further details The information submitted with regards to methods of analysis is sufficient to support approval. Refer also to Level 2, Section 2.5.
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		The ADI of 0.025 mg/kg bw per day is proposed based on the application of a standard safety factor of 100 to the NOAEL of 2.5 mg/kg bw per day, identified in the 1 year dog study. The ARfD of 0.05 mg/kg bw per day is proposed based on the application of

				a standard safety factor of 100 to the NOAEL of 5 mg/kg bw per day, identified in the rabbit developmental study. The AOEL of 0.025 mg/kg bw per day is proposed based on the application of a standard safety factor of 100 to the NOAEL of 2.5 mg/kg bw per day, identified in the 1 year dog study. No correction factor for oral absorption is considered necessary. The AAOEL of 0.05 mg/kg bw per day is proposed based on the application of a standard safety factor of 100 to the NOAEL of 5 mg/kg bw per day, identified in the rabbit developmental study.
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	Triticonazole was tested negative in the standard range of *in vitro* and *in vivo* genotoxicity tests. Classification for mutagenicity is not warranted. Please also refer to Level 2, Section 2.5.4.
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 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.**		X	No treatment related neoplastic findings were observed in any of the studies Triticonazole is not carcinogenic, neither in rats nor in mice. Classification for carcinogenicity is not warranted.
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.			Not applicable

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	The reproductive toxicity of triticonazole has been adequately investigated in rat multigeneration studies and in rat and rabbit developmental toxicity studies. These studies demonstrated that triticonazole does not possess hazardous properties in relation to fertility, reproductive performance or development. Classification for reproductive toxicity is not warranted.
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.			Not applicable
Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties**		X	No evidence of carcinogenicity or reproductive toxicity was seen in the standard carcinogenicity and reproductive toxicity studies.
ii)	It is considered that **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 2 and** in addition the RMS considers the substance **has toxic effects on the endocrine organs and on that basis shall be considered to have endocrine disrupting properties**		X	No evidence of reproductive toxicity, related to endocrine MoA, was seen in the standard reproductive toxicity studies. No evidence of toxic effects on endocrine organs, related to endocrine MoA, was seen throughout the triticonazole dossier.
iii)	Linked to either i) or ii) immediately above. 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			Not applicable

	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: The criterion for persistence (P) is fulfilled (DT_{50} in water > 60 days (aerobic mineralisation, water/sediment total system); DT_{50} in soil < 120 days (field); DT_{50} in sediment > 120 days (water/sediment). There is no indication for long range transport. Bioaccumulation: The bioconcentration factor (BCF_{fish} = 72.55 – please note that the validity of the BCF study is questionable) and the partition co-efficient (log P_{OW} = 3.3) are below the trigger of 5000 and > 5, respectively.
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: The criterion for persistence (P) is fulfilled (DT_{50} in fresh surface water > 40 days (aerobic mineralisation, water/sediment total system); DT_{50} in marine surface water most probably > 60 days (hydrolysis), DT_{50} in soil < 120 days (field), DT_{50} in fresh water sediment > 120 days (water/sediment), no data for marine or estuarine environments). Bioaccumulation: The bioconcentration factor (BCF_{fish} = 72.55 – please note that the validity of the BCF study is questionable) is below the trigger of 2000. Toxicity: The NOEC values for marine and freshwater species are above the trigger of > 0.01 mg ai/L.
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	Persistence: The criterion for very persistent (vP) is fulfilled (DT_{50} in fresh surface water > 60 days (aerobic mineralisation, water/sediment total system); DT_{50} in soil < 180 days (field), DT_{50} in fresh water sediment > 180 days (water/sediment); no data for marine or estuarine environments) Bioaccumulation: The bioconcentration factor is below the trigger of 5000 (BCF_{fish} = 72.55 – please note that the validity of the BCF study is questionable).

Ecotoxicology				
		Yes	No	
	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 intended use is a seed treatment in cereals. Based on the available studies no adverse effects on non-target organisms were identified. However, the long-term risk to granivorous birds from exposure to the EU representative formulation BAS 595 01 F could not be finalised (TER_{LT} < 5 for the three out of seven focal species) For further information please refer to Level 1, Section 2.8.9
	It is considered that, on the basis of the assessment of Community or internationally agreed test guidelines, the substance **HAS** endocrine disrupting properties that may cause adverse effects on non-target organisms.		X	From the toxicological point of view no evidence of carcinogenicity or reproductive toxicity was seen in the reproductive toxicity studies. No evidence of adverse effects on endocrine organs was observed. There is currently no concern regarding endocrine disruption. Based on the available data there is no evidence on endocrine disruption. However at the current state, where no guidance is available it is not possible to draw a final conclusion on the endocrine disrupting potential of triticonazole.
	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.		X	An exposure of non-target organisms based on the proposed GAP uses cannot be excluded.
	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		Based on the available data and the outcome of the risk assessment no risks to honey-bees considering adult and larvae mortality, effects on honey-bee populations and chronic effects were identified. For a detail summary please refer to Level 2, Section 2.8.9.
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		The data were sufficient to propose the following residue definition for enforcement: Plants: Triticonazole Animals: Triticonazole
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.			Triticonazole and its metabolites RPA 406341 (Trans-diol) and RPA 404766 (Cis-diol) as well as the metabolite fraction 'Met 7 (MWT 315)', observed > 5 % AR at two consecutive sampling points in a legacy study (Ayliffe & Austin, 1993), are not predicted to occur in groundwater above the regulatory threshold of 0.1 µg/L with regard to the use applied by the notifier. PEC_{gw} values for the metabolite fraction 'Met 6 (MWT 333)', observed > 5 % in a legacy study (Ayliffe & Austin, 1993), are above the regulatory threshold of 0.1 µg/L in most of the scenarios (max. 0.187 µg/L). The RMS AT notes that these modelling results indicate a high leaching risk for this metabolite fraction. However, it should be kept in mind that metabolite fraction 'Met 6 (MWT 333)' has only been overserved in legacy studies (conducted in 1993 and 1994) applying chromatographic methods which may not have been fully capable to adequately separate all metabolites of triticonazole. In all later studies, applying more sophisticated HPLC separation methods, no metabolites other than RPA 406341 (Trans-diol) and RPA 404766 (Cis-diol) were observed above 5 % AR at two consecutive sampling points.

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	*its ADI, ARfD or AOEL is significantly lower than those of the majority of the approved active substances within groups of substances/use categories- **NO***

				— it meets two of the criteria to be considered as a PBT substance ***- NO*** *— there are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones)* ***- NO*** *— it contains a significant proportion of non-active isomers* ***– NO*** *— it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B, if the substance has not been excluded in accordance with the criteria laid down in point 3.6.3,* *— it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B if the substance has not been excluded in accordance with the criteria laid down in point 3.6.4* ***– NO*** *— if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, reviewed by the Authority, it is considered to have endocrine disrupting properties that may cause adverse effects in humans if the substance has not been excluded in accordance with the criteria laid down in point 3.6.5.]* ***- NO***

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.** In particular it is considered that the substance **should NOT be classified or proposed for classification** in accordance with Regulation (EC) No 1272/2008 as at least one of the following: — carcinogenic, — mutagenic, — toxic to reproduction, — sensitising chemicals, — very toxic or toxic, — explosive, — corrosive. In addition it is considered that **the substance is NOT**: — persistent (half-life in soil more than 60 days), — has a bioconcentration factor higher than 100, — is deemed to be an endocrine disrupter, or — has neurotoxic or immunotoxic effects.			Triticonazole cannot be considered a low risk substance because it should be classified in accordance with Regulation (EC) No 1272/2008 as "Very toxic to aquatic life with long lasting effects" (H400; H410) - classified or to be classified as carcinogenic – **NO** - classified or to be classified as mutagenic – **NO** - classified or to be classified as toxic to reproduction – **NO** - classified or to be classified as sensitising – **NO** - classified or to be classified as very toxic or toxic – **YES (H400; H410)** - classified or to be classified as explosive – **NO** - classified or to be classified as corrosive – **NO** - persistent – **YES** (geometric mean DegT50 in soil (field) > 60 days) - bioconcentration factor higher than 100 – **NO** - endocrine disruptor – **NO** (based on current knowledge) - neurotoxic or immunotoxic effects - **NO**

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				
None				
3.1.4.2. Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
None				
3.1.4.3. Data on uses and efficacy				
None				
3.1.4.4. Data on handling, storage, transport, packaging and labelling				
None				
3.1.4.5. Methods of analysis				
None				

3.1.4.6. Toxicology and metabolism				
Assumption that unidentified fraction "MET 6 (MWT 333)" (< 0.2 µg/l in groundwater) is devoid of genotoxic properties, being most probably mono-hydroxylated parent, should be substantiated by data after the identifiacation has been conducted.	All uses	No confirmation that study available or on-going.		
3.1.4.7. Residue data				
None				
3.1.4.8. Environmental fate and behaviour				
Applicant to submit additional information to support verification of the molecular structures of 'Met 6 (MWT 333)' and 'Met 7 (MWT 315)' observed in Ayliffe & Austin (1993). Additional information should also account for comparative HPLC chromatography with authentic reference substances.	All uses	No confirmation that study available or on-going.		
3.1.4.9. Ecotoxicology				
None				

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)
The long-term risk assessment for granivorous birds feeding on freshly drilled treated seeds could not be finalised	Field application in cereals at 1x12.5 g ai/ha (representative formulation BAS 595 01 F)

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)
None identified in the renewal assessment	Not applicable

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		winter wheat, spring wheat, winter barley,spring barley, rye, triticale, oats
Operator risk	Risk identified	
	Assessment not finalised	
Worker risk	Risk identified	
	Assessment not finalised	
Bystander risk	Risk identified	
	Assessment not finalised	
Consumer risk	Risk identified	
	Assessment not finalised	
Risk to wild non target terrestrial vertebrates	Risk identified	
	Assessment not finalised	X
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified	
	Assessment not finalised	
Risk to aquatic organisms	Risk identified	
	Assessment not finalised	
Groundwater exposure active substance	Legal parametric value breached	
	Assessment not finalised	
Groundwater exposure metabolites	Legal parametric value breached	X
	Parametric value of 10µg/L[(a)] breached	
	Assessment not finalised	X
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

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
Reliability and useability of modified long-term study for	The stuy was conducted with a shortened exposure period. As it is questionable whether all reproductive phases have been assessed and if so whether there were sufficient to detect any effects it is not clear if this kind of

birds	testing is in general acceptable. Furthermore the reliability is questionable as only two concentrations have been tested and the it is not clear which consequences this has on the statistical power
Relevance of the linnet as a focal species	There are some indications that the linnet could be relevant as a focal species in seed crops. However, this issue seems to be handled differently from member state to member state. It would be highly appreciated to have a general decision if the linnet has to be considered in the risk assessment or if it is not considered relevant for this crop.
Groundwater exposure assessment	Need for further identification and exposure assessment for the two tentatively identified metabolite fractions 'Met 6 (MWT 333)' and 'Met 7 (MWT 315)' observed > 5 % AR at two consecutive sampling points in the legacy study Ayliffe & Austin (1993).

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
Risk assessment for non-target arthropods	The UK does not completely agree with the RMS' evaluation of toxicity studies with non-target arthropods. Neither laboratory nor extended toxicity studies were submitted on Aphidius rhopalosiphi and Typhlodromus pyri with the formulation or active substance. This data gap should have been flagged by the RMS. The representative formulation was tested on Poecilus cupreus and Aleochara bilineata in two extended laboratory studies. In these studies, the test application rates, in terms of g triticonazole/ha, were lower than the intended application rate of the representative formulation (Table B. 9-2 of the CP dossier). This should be pointed out in the summary report of these studies.	The RMS is of the opinion that studies with a spray formulation on *T. pyri* and *A. rhopalosiphi* are not applicable for an intended use as seed treatment. Although the intended application rate is not fully covered, the studies do not show relevant effects and all endpoints are > values. Furthermore studies on *Hyposapis aculeifer* and *Folsomia candida* are available, which neither show relevant effects. The risk for non-target arthropods is therefore considerd to be adequately addressed.

3.2. PROPOSED DECISION

[redacted]

3.3. RATIONAL FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH THE APPORVAL OR AUTHORISATION(S), AS APPROPRIATE

3.3.1. Particular conditions proposed to be taken into account to manage the risks identified

[redacted]	[redacted]
[redacted]	[redacted]

3.4. APPENDICES

GUIDANCE DOCUMENTS USED IN THIS ASSESSEMENT

Volume 3 – B1: Identity

None

Volume 3 - B2: Physicochemical properties

None

Volume 3 - B5: Analytical methods

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 (SANCO/3029/99 rev. 4)

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 (SANCO/3030/99 rev. 4)

Guidance document on pesticide residue analytical methods (SANCO/825/00 rev. 8.1)

Volume 3 - B6: Toxicology and metabolism of the active substance

EFSA (2011). Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092

EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665

Guidance on the Application of the CLP Criteria, Version 2.0 (April 2012)

Guidance document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) 283/2013 and Regulation (EU) No 284/2013 (SANCO/10181/2013– rev. 2, May 2013)

Guidance Document 8064/VI/97 rev. 4 on the Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated Under Council Directive 91/414/EEC (SANCO/221/2000 rev. 10 25 February 2003)

Volume 3 - B7: Residues

EC (European Commission), 2011. Appendix D. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs; 7525/VI/95-rev.9

EFSA (2011). Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092

Guidance document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) 283/2013 and Regulation (EU) No 284/2013 (SANCO/10181/2013– rev. 2, May 2013)

OECD (Organisation for Economic Co-operation and Development), 2011; OECD MRL Calculator: User Guide. In: Series on Pesticides No 56. ENV/JM/MONO(2011)2, 01 March 2011.

Volume 3 - B8: Environmental Fate and Behaviour

EFSA (2011). Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092.

EFSA (2014). EFSA 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 subsrances in soil. EFSA Journal 2014; 12(5):3662, 37pp.

EC (2014) Generic guidance for Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration, version: 1.1, 18 December 2014

EC (2014) Assessing Potential for Movement of Active Substances and their Metabolites to Ground Water in the EU. Sanco/13144/2010, version 3, 10 October 2014

EC (2015) Generic guidance for FOCUS surface water Scenarios. Version: 1.4, May 2015

FOCUS (2007). Landscape And Mitigation Factors In Aquatic Risk Assessment. Volume 1. Extended Summary and Recommendations. Report of the FOCUS Working Group on Landscape and Mitigation Factors in Ecological Risk Assessment, EC Document Reference SANCO/10422/2005 v2.0. 169 pp.

FOCUS (2008) Pesticides in air: Considerations for exposure assessment. SANCO/10553/2006, Rev 2, June 2008

Volume 3 - B9: Ecotoxicology

Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters, EFSA Journal 2013;11(7):3290

Risk Assessment for Birds and Mammals, EFSA Journal 2009;7(12):1438

Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/141/EEC, SANCO/10329/2002, 17 October 2002 rev. 2 final

Candolfi et al., 2000, Guidance Document on Regulatory Testing and Risk Assessment Procedures for Plant Protection Products with Non-Target Arthropods, ESCORT 2 SETAC Workshop

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

EFSA (2011). Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092

Guidance document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) 283/2013 and Regulation (EU) No 284/2013 (SANCO/10181/2013– rev. 2, May 2013)

Volume 4 Annex C:

Guidance document on the assessment of the equivalence of technical materials of substances regulated under regulation (EC) No 1107/2009 (SANCO/10597/2003 –rev. 10)

3.5. REFERENCE LIST

EFSA Scientific Report (2005) 33, 1-69, Conclusion on the peer review of triticonazole