European Commission

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

BAS 750F
(Mefentrifluconazole)

Volume 1

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

Version History

When	What
April 2017	Initial DAR

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Level 1

BAS 750 F
(Mefentrifluconazole)

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

This draft assessment report has been prepared to evaluate the dossier for the new active substance BAS 750 F (ISO provisionally approved name: mefentrifluconazole) and its formulated product BAS 750 01 F. The dossier was submitted for the first active approval under Regulation (EC) No 1107/2009 with the United Kingdom carrying out the assessment as the Rapporteur Member State.

The active substance is a fungicide for the control of *Septoria tritici* in cereals. It will be proposed to belong to a new sub-group of triazole fungicides, the isopropanol azoles. This dossier contains data and information to support a limited range of representative uses of the active substance for which it is intended to demonstrate that, for one preparation, the requirements of Regulation (EC) No 1107/2009, Article 4 can be met.

The representative formulation, BAS 750 01 F, is an emulsifiable concentrate containing 100 g active substance/L. The representative uses for BAS 750 01 F are: cereals. These uses are intended to include the proposed major commercial applications and represent exposure scenarios sufficiently rigorous to allow adequate evaluation of risk to humans and the environment.

This application from BASF SE is for the first approval of BAS 750 F in accordance with Regulation (EC) No. 1107/2009. So far, no provisional or final registrations have been granted in any country, so neither EU nor CODEX MRLs exist for BAS 750 F at this point in time. However, alongside this application BASF SE has submitted an application to set specific maximum residue levels (MRLs) as the new active substance does not satisfy the requirements of Annex II/III/IV of Regulation (EC) No 396/2005.

A Harmonised Classification and Labelling report in line with Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2 has also been produced. This has been submitted by the UK CLP Competent Authority to ECHA in December 2016 to follow the aligned evaluation process.

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

The UK acting as the Rapporteur Member State (RMS) evaluated the dossier and produced a DAR (Draft Assessment Report). The DAR was the subject of a joint peer review by France and Austria (co-RMSs).

1.1.3. EU Regulatory history for use in Plant Protection Products

BAS 750 F is a new active substance and products containing it have not previously authorized in the EU.

1.1.4. Evaluations carried out under other regulatory contexts

BAS 750 F is a new active substance with fungicidal action, developed by BASF SE. This dossier is the application of BASF SE for the first approval of BAS 750 F in accordance with Regulation (EC) No. 1107/2009. No registrations or authorizations of BAS 750 F containing plant protection products are existent in EU Member States or elsewhere. An application has been made to Brazil and other global submissions will be rolled out through 2017. Currently there are also no other relevant EU-evaluations of the active substance carried out in the framework of other relevant EU-legislation (e.g. biocides, flavourings, food additives, cosmetics). A nomination form for JMPR evaluation was submitted in 2015 with the intention of an end of 2018 submission for a 2019 evaluation.

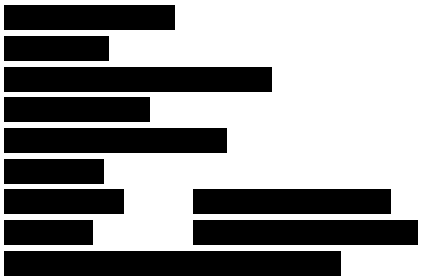
1.2. APPLICANT INFORMATION

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

BASF Agro B.V. Arnhem (NL)
Zürich Branch
Im Tiergarten 7
8055 Zürich
Switzerland

Contact person:

Alternative contact:

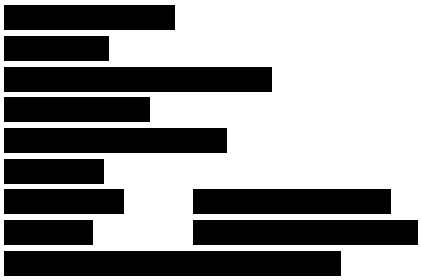


1.2.2. Producer or producers of the active substance

BASF Agro B.V. Arnhem (NL)
Zürich Branch
Im Tiergarten 7
8055 Zürich
Switzerland

Contact person:

Alternative contact:



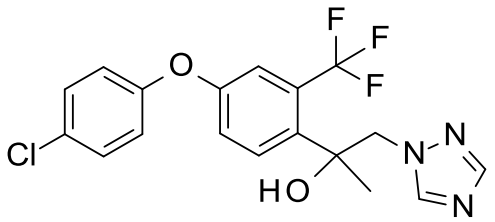
1.2.3. Information relating to the collective provision of dossiers

This application is submitted for the first approval of BAS 750 F in accordance with Article 7f of Regulation (EU) No. 1107/2009.

BASF Agro B.V. Arnhem (NL), Zürich Branch, is the only applicant and owner of a complete data package regarding the new active substance BAS 750 F.

In addition to the data package related to BAS 750 F, as the active substance is in a sub-group of triazole fungicides, a data sharing agreement is in place with Triazole Derivative Metabolite Group (TDMG). BASF is full member of and has access to all data regarding triazole derivative metabolites due to their membership (chairman of the TDMG: [redacted]

1.3. IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1. Common name proposed or ISO-accepted and synonyms	BAS 750 F Mefentrifluconazole (ISO provisionally approved)
1.3.2. Chemical name (IUPAC and CA nomenclature)	
IUPAC	(2RS)-2-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-1-(1H-1,2,4-triazol-1-yl)propan-2-ol
CA	alpha-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-alpha-methyl-1H-1,2,4-triazole-1-ethanol
1.3.3. Producer's development code number	BASF Number: BAS 750 F BASF Registry Number: Reg.No. 5834378
1.3.4. CAS, EEC and CIPAC numbers	
CAS	1417782-03-6
EEC	not assigned
CIPAC	not assigned
1.3.5. Molecular and structural formula, molecular mass	
Molecular formula	$C_{18}H_{15}ClF_3N_3O_2$
Structural formula	
Molecular mass	397.8 g/mol
1.3.6. Method of manufacture (synthesis pathway) of the active substance	Refer to Volume 4 Confidential Information
1.3.7. Specification of purity of the active substance in g/kg	Minimum purity: 970 g/kg
1.3.8. Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1. Additives	Refer to Volume 4 Confidential Information
1.3.8.2. Significant impurities	Refer to Volume 4 Confidential Information
1.3.8.3. Relevant impurities	DMF (max. 0.5 mg/kg)
1.3.9. Analytical profile of batches	Refer to Volume 4 Confidential Information

1.4. INFORMATION ON THE PLANT PROTECTION PRODUCT

1.4.1. Applicant	BASF Agro B.V. Arnhem (NL) Zürich Branch Im Tiergarten 7 8055 Zürich Switzerland Contact person: [redacted]
1.4.2. Producer of the plant protection product	BASF Agro B.V. Arnhem (NL) Zürich Branch Im Tiergarten 7 8055 Zürich Switzerland
1.4.3. Trade name or proposed trade name and producer's development code number of the plant protection product	Code number: BAS 750 01 F Trade name: not available yet
1.4.4. Detailed quantitative and qualitative information on the composition of the plant protection product	
***1.4.4.1.* Composition of the plant protection product**	Refer to Volume 4 Confidential Information
***1.4.4.2.* Information on the active substances**	Pure active substance: 100g/L Technical active substance: 103.6g/L
***1.4.4.3.* Information on safeners, synergists and co-formulants**	Refer to Volume 4 Confidential Information

1.4.5. Type and code of the plant protection product	Emulsifiable Concentrate [Code: EC]
1.4.6. Function	Fungicide
1.4.7. Field of use envisaged	Cereals
1.4.8. Effects on harmful organisms	

1.5. DETAILED USES OF THE PLANT PROTECTION PRODUCT

Refer to table 1.5.1 below

1.5.1. Details of representative uses

PPP (product name/code)	**BAS 750 01 F**	**Formulation type:**	**EC (emulsifiable concentrate)**
active substance	**BAS 750 F**	**Conc. of as:**	**100 g/L**
safener	**n.a.**	**Conc. of safener:**	**n.a.**
synergist	**n.a.**	**Conc. of synergist:**	**n.a.**
Applicant:	**BASF Agro B.V. Arnhem (NL) Zürich Branch**	**professional use**	☒
Zone(s):	**Northern / Central / Southern EU**	**non-professional use**	☐
Verified by MS:	**y/n**		

1	2	3	4	5	6	7	8	10	11	12	13	14
Use-No.	**Member state(s)**	**Crop and/ or situation** **(crop destination / purpose of crop)**	**F G or I***	**Pests or Group of pests controlled** (additionally: developmental stages of the pest or pest group)	**Application**			**Application rate**			**PHI** (days)	**Remarks:** e.g. safener/synergist per ha e.g. recommended or mandatory tank mixtures
					Method / Kind	Timing / Growth stage of crop & season	Max. number of (min. interval between) applications a) per use b) per crop/ season	L product / ha a) max. rate per appl. b) max. total rate per crop/season	g as/ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max		
1	EU28	Cereals	F	*Septoria tritici* – *SEPTTR* further control claims are currently under evaluation	Foliar spray	BBCH 30-69	a) 2 (14) b) 2 (14)	a) 1 5 L/ha b) 3.0 L/ha	150 g as/ha 300 g as/ha	100 - 300	35	

*****Outdoor or field use (F), glasshouse application (G) or indoor application (I)

1.5.2. Further information on representative uses

1.5.2.1 Method of Application

The applicant has stated that BAS 750 F containing products are used as foliar sprays, and can be applied through all conventional sprayers providing they are in good working order and have been calibrated to manufacturer instructions. The proposed application timings are at growth stages from BBCH 30 to BBCH 69.

1.5.2.2 Number and timing of applications and duration of protection

The applicant has indicated that BAS 750 01 F can provide control for up to six weeks after each application when applied before the start of disease attack.

Maximum number of applications and their timings:	max. two applications with a min. interval of 14 days
Growth stages of crops or plants to be protected:	BBCH 30-69
Duration of protection afforded by each application:	up to six weeks
Duration of protection afforded by the maximum number of applications:	up to twelve weeks

1.5.2.3 Necessary waiting periods or other precautions to avoid phytotoxic effects on succeeding crops

The applicant has stated that BAS 750 01 F is a highly selective fungicide with no herbicide activity. There are no waiting periods or limitations for any succeeding crops required.

1.5.2.4 Proposed instructions for use

BAS 750 01 F is a fungicide with protectant and curative properties for disease control in cereal crops.

Time of application
For cereal disease control, apply BAS 750 01 F at the start of disease attack. A maximum of two applications can be made, starting from beginning of stem elongation (BBCH 30) until end of flowering (latest application at BBCH 69). The described application window can be more limited in specific countries or for specific uses. The recommended spray interval is 14-28 days depending on disease pressure and the general spray program strategy.

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.

1.5.4. Overview on authorisations in EU Member States

Not applicable BAS 750 F is a new active substance not previously approved in the EU.

Level 2

BAS 750 F
(Mefentrifluconazole)

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

2.1. IDENTITY

BAS 750 F with the ISO provisionally approved common name Mefentrifluconazole is a new active substance which acts as a fungicide to control *Septoria tritici* in cereals. It is a fungicide belonging to the group of the sterol biosynthesis inhibitors (SBI, mode of action class G). Within the SBIs, it belongs to the sub group of demethylation inhibitor (DMI, G1) and the chemical group of triazoles. Due to its unique isopropanol moiety, it will be proposed to belong to a new sub-group of triazole fungicides, the isopropanol azoles.

2.2. PHYSICAL AND CHEMICAL PROPERTIES

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

The pure active substance BAS 750 F is white, odourless, crystalline powder; as technical grade active substance it is an off-white solid with a moderate thiolic odour. Its melting point is 126 °C and decomposes at approximately 300 °C. It is very slightly – moderately volatile with a vapour pressure of 3.2×10^{-6} Pa at 20 °C and 6.5×10^{-6} at 25 °C and a Henry's Law constant of 1.6×10^{-3}. It is possible that photolytic degradation may occur due to shoulder peaks in its UV/VIS spectrum > 290 nm. Its structure is confirmed by IR, NMR and MS. It is slightly soluble in water, buffer solutions and xylene; moderately soluble in acetone, ethyl acetate, methanol, 1,2-dichloroethane and acetonitrile; and very slightly soluble in n-heptane. The log P_{OW} is 3.4 at pH 7 and has a pKa (calculated) of 3.0. It is not classified as flammable, self-heating, explosive or oxidising in accordance with the CLP regulation.

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

BAS 750 01 F is a clear yellow liquid with a faintly fishy odour. It not classified as explosive, oxidising, highly flammable or as an aspiration hazard in accordance with the CLP Regulation. It has a flashpoint of 128 °C and an auto ignition temperature of 375 °C. It has a pH of around 6.5 in 1% aqueous solution. It is stable after low temperature (7 days at 0 °C), accelerated (2 weeks at 54 °C) and 2 year ambient storage. It has an acceptable level of persistent foam within the concentration range 0.1 – 1.5% which covers lowest-highest in-use concentration. It has an acceptable emulsifiability, emulsion stability and re-emulsifiability in both CIPAC A and D waters determined at concentrations covering the in-use range. It is physically and chemically compatible with 19 other plant protection products in tank mixes.

2.3. DATA ON APPLICATION AND EFFICACY

2.3.1. Summary of effectiveness

This application for this new active has been assessed in line with SANCO/10054/2013 rev 3. At least one representative formulation is proposed and a GAP with the maximum field rate and a summary of effectiveness and crop safety were provided. The applicant states that trials were conducted to the appropriate EPPO standards, and in accordance with GEP, this will be examined at the product authorisation stage. A total of 59 effectiveness trials were conducted in 2014 and 2015 across the 4 EPPO climatic zones. It is considered that the data provided here are sufficient to establish that the active substance is sufficiently effective against a major disease target (Septoria tritici (SEPTTR)) in a major broadacre cereal crop (Wheat TRZAW).

On the basis of the information provided it is concluded that BAS 750 (formulated as 'BAS 750 01F') complies with the efficacy requirements for a new active laid out in SANCO/10054/2013. No further information is required at this stage.

2.3.2. Summary of information on the development of resistance

BAS 750 F is a fungicide belonging to the group of the sterol biosynthesis inhibitors (SBI, mode of action class G). Within the SBIs, it belongs to the sub group of demethylation inhibitor (DMI, G1) and

the chemical group of triazoles. Due to its unique isopropanol moiety, it will be proposed to belong to a new sub-group of triazole fungicides, the isopropanol azoles.

A detailed consideration of the resistance situation was presented. Results of glasshouse sensitivity studies assessing the activity of BAS 750 F and a range of other authorised DMI fungicides against sensitive and shifted strains of *S tritici* was provided. Results of BAS 750F monitoring studies conducted in a range of European countries in 2014 were presented which showed a higher mean sensitivity in *S tritici* compared with epoxiconazole and metconazole. There was no correlation between the sensitivity to BAS 750 F and the SDHI fluxopyroxad in these samples. Further monitoring is stated to be ongoing. Field studies indicate sufficiently effective levels of activity of BAS 750 F against current *S tritici* populations. Overall resistance risk is categorised as 'medium'. Resistance management is required at the product authorisation stage.

2.3.3. Summary of adverse effects on treated crops

No phytotoxicity symptoms were observed in 52 trials, whilst negligible and transient symptoms (1-2 %) were observed in a single trial with the highest dose rates tested (1.0/1.5 l/ha). These symptoms were stated to have quickly disappeared and had no impact on yield. Yield was reported in a total of 45 trials across all 4 EPPO Climatic zones.

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

The applicant states that no following crop or adjacent crop restrictions or warnings are necessary. Data presented in Volume 3 CP Section 9.11 indicate that BAS 750 01F had low levels of activity against a range of non-target plants (pre emergence NOER $\geq$ 1500 ml product/ha and a vegetative vigour E_rC_{50} of $\geq$ 1500 ml product/ha). Taking into account the further reduction in exposure due to crop interception and off target drift the risk to succeeding and adjacent crops would appear to be low. This will need to be considered at the product authorisation stage

2.4. FURTHER INFORMATION

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

Acceptable information has been provided to address these points. Refer to Volume 3 CA and CP, section B.4.

2.4.2. Summary of procedures for destruction or decontamination

Acceptable information has been provided to address these points. Refer to Volume 3 CA and CP, section B.4.

2.4.3. Summary of emergency measures in case of an accident

Acceptable information has been provided to address these points. Refer to Volume 3 CA and CP, section B.4.

2.5. METHODS OF ANALYSIS

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

Analytical methods for the active substance

Technical a.s. (analytical technique)	HPLC-UV (BAS 750 F)
Impurities in technical a.s. (analytical technique)	GC-FID – LOQ 0.01 % w/w (dimethylformamide) For methods for significant impurities see the DAR Volume 4
Plant protection product (analytical technique)	HPLC-UV (BAS 750 F)

Pre-authorisation methods have been submitted in support of studies from each section and these have been considered fully validated, sufficiently validated for the purposes of the regulatory process or fit for purpose to support the studies.

2.5.2. Methods for post control and monitoring purposes

Matrix	Analyte	Method	LOQ	ILV?	Fully validated?
Tomato (fruit)	BAS 750 F	LC-MS/MS	0.01 mg/kg	Yes	Yes
Orange (whole fruit)					
Dry beans (seeds)					
Wheat (grain)					
Dry soybeans (seeds)					
Bovine meat	BAS 750 F	LC-MS/MS	0.01 mg/kg	Yes	Yes
Bovine milk					
Bovine cream					
Bovine fat					
Bovine liver					
Bovine kidney					
Hen eggs					
LUFA 2.2 soil	BAS 750 F	LC-MS/MS	0.002 mg/kg	N/A	Yes
LUFA 2.3 soil	BAS 750 F				
Surface and drinking water	BAS 750 F	LC-MS/MS	30 ng/L	Yes	Yes
Air	BAS 750 F	LC-MS/MS	0.01 ng/L	N/A	Yes
Urine Blood	BAS 750 F	LC-MS/MS	0.01 mg/L	N/A	Yes

2.6. EFFECTS ON HUMAN AND ANIMAL HEALTH

BAS 750 F is a new active substance that acts through the inhibition of ergosterol biosynthesis. It is a racemic mixture of an (R)-enantiomer and an (S)-enantiomer in a 1:1 ratio; all the regulatory toxicology studies used this racemic mixture.

All mammalian toxicology studies were conducted for the purpose of EU and global approval and are reviewed here for the first time for approval of this active substance in the EU. A full dataset of OECD- and GLP-compliant studies is available. The minimum purity of the active substance is specified to be 97 %; all toxicological studies used a technical-grade active substance with comparable purity. No individual significant impurity is present in the specified material or the batches used in the toxicological studies at a concentration greater than 2.3 %. All toxicologically-relevant impurities were present only in trace amounts and did not impact on the classification and labelling of the active substance.

2.6.1. Summary of absorption, distribution and excretion in mammals

The absorption, distribution, excretion and metabolism of BASF 750 F have been investigated in rats by the oral route, with further investigation of plasma kinetics after intra-venous administration. Plasma kinetics have also been investigated in mice. A comparative *in vitro* metabolism study on human, rat and mouse hepatocytes was provided.

For these studies, the active substance was radiolabelled in the chlorophenyl ring (C-label), in the trifluoromethylphenyl ring (TFMP-label) or in the triazole moiety (T-label).

The plasma kinetics of BAS 750 F in rats and mice demonstrated high absorption following oral administration, indicated potential enterohepatic recirculation of the triazole moiety, and showed fast excretion and a more-or-less linear correlation of the internal exposure to the oral dose. The biliary excretion data confirmed that oral absorption in rats was approximately 85 % following single low-dose administration; the same oral absorption value in humans will be assumed. In the absence of specific data, default inhalation absorption of 100 % is assumed. Dermal absorption was low (4 % for the formulation concentrate; see volume 3CP B6).

The biliary excretion experiments confirmed that excretion was fast, more or less complete and occurred to a major extent within three days after oral dosing in rats, predominantly by the faecal route. There was no evidence of accumulation. In addition to the information provided by the plasma kinetics' data, evidence of enterohepatic recirculation of the triazole moiety was provided by the biliary-excretion investigations. The distribution experiments demonstrated that BAS 750 F was rapidly and widely distributed in rats after a single oral administration. The active substance was extensively and rapidly metabolized, resulting in rapid and extensive excretion (biliary and urinary routes). A preferential metabolism and elimination of the S-enantiomer in rats was indicated, which is the enantiomer that is expected to have the higher toxicological activity (see section 2.6.8.).

In a comparative *in vitro* metabolism study, one metabolite was detected following incubation with human hepatocytes, which was also detected in rat hepatocyte samples; hence, the study did not detect a unique human metabolite and the rat metabolism study is concluded to provide results that are representative of human metabolism.

Table 2.6.1. Summary of toxicokinetics' studies

Study / method	Species	Radiolabel	Dose level	Parameters	Reference (Doc ID)
Oral (OECD 417)	Rat, Wistar	C-, TFMP-labels	Single dose: 5 & 180 mg/kg Repeated dose: 14 x 180 mg/kg	Absorption Distribution Excretion Plasma kinetics	[redacted] 2015 a (2015/1208128)
Oral, intra-venous (OECD 417)	Rat, Wistar	T-label	Single oral dose: 5 & 180 mg/kg or 5, 40, 120, 360 mg/kg Repeated dose: 14 x 180 mg/kg Single i.v. dose: 0.4 mg/kg	Absorption Distribution Excretion Plasma kinetics	[redacted] 2016 a (2015/1078847)
Oral (OECD 417)	Rat, Wistar	C-, TFMP-, T-labels	Samples taken from studies above	Excretion Metabolism	[redacted] 2016 a (2015/1107610)
Oral (OECD 417)	Mouse, C57BL	T-label	Single doses of 10, 50, 75 mg/kg bw	Plasma kinetics	[redacted] 2014 a (2014/1018105)
Comparative *in vitro* metabolism	Rat, mouse, human	T-, C-, TFMP-labels	1 µM	Metabolism	Funk *et al*., 2016 a (2015/1020123)

2.6.2. Summary of acute toxicity

The acute toxicity of BAS 750 F has been investigated by the oral, dermal and inhalation routes. *In vitro* and *in vivo* irritation studies are available, whilst skin sensitisation has been investigated in a guinea pig maximisation test. The *in vitro* / *ex vivo* irritation tests were used as pre-tests prior to the conduct of *in vivo* studies and hence were not conducted to GLP (see table 2.6.2).

In an acute oral toxicity study performed to the acute toxic class method, no rats died at the single dose tested of 2000 mg/kg bw (LD_{50} > 2000 mg/kg bw/d). Likewise, BAS 750 F was not acutely toxic by the dermal route (LD_{50} > 5000 mg/kg bw) nor the inhalation route (4-hour LC_{50} > 5.3 mg/l) in rats. It did not meet the criteria for classification for either acute toxicity or STOT-SE (see CLH report for further details).

In an *in vitro* skin irritation test with the EpiDerm human skin model, BAS 750 F did not demonstrate an irritant potential. This was confirmed in a rabbit study.

Prior to the conduct of an eye irritation study in rabbits, two preliminary tests were performed to assess the active substance's potential to induce corrosion / severe eye damage and eye irritation. In an EpiOcular *in vitro* test, BAS 750 F did not show any eye-irritation potential, nor did it demonstrate a potential for corrosivity / severe eye damage in a bovine corneal opacity and permeability (BCOP) test. In an *in vivo* rabbit study, the mean scores calculated for each animal over 24, 48 and 72 hours were 0.0, 0.0 and 0.0 for corneal opacity, iris lesions and conjunctival chemosis and 0.3, 0.3 and 0.7 for redness of the conjunctiva. The ocular reactions were fully reversible within 72 hours after application. BAS 750 F, therefore, did not meet the criteria for classification for eye irritation.

In a guinea pig maximisation test, BAS 750 F induced responses in 60 % of animals. At the intra-dermal induction concentration used (5 %), this level of response indicated that classification in at least sub-category 1B was warranted. Since, from this data, it was not possible to exclude a classification in sub-category 1A, the default position of classification in category 1, i.e. without sub-categorisation, is proposed.

Irradiation of cultures did not increase the toxicity of BAS 750 F in an *in vitro* neutral-red uptake photo-toxicity test.

Table 2.6.2. Summary of acute toxicity studies

Study / method	Species	Result	CLP Classification	Reference (DocID)
Acute oral toxicity (OECD 423)	Wistar rat	LD_{50} > 2000 mg/kg bw	–	[redacted], 2013c (2013/1149656)
Acute dermal toxicity (OECD 402)	Wistar rat	LD_{50} > 5000 mg/kg bw	–	[redacted], 2013b (2013/1149657)
Acute inhalation toxicity (OECD 403) – nose only	Wistar rat	LC_{50} > 5.314 mg/l	–	[redacted], 2014a (2014/1127433)
In vitro skin corrosion / irritation (OECD 431)	EpiDerm human reconstituted skin	Not a skin irritant	-	Remmele, 2012a (2012/1367952)
Skin irritation (OECD 404)	New Zealand White rabbit	Not a skin irritant	–	[redacted], 2013c (2013/1150122)
In vitro eye irritation	EpiOcular (human corneal epithelium model)	Not an eye irritant	-	Remmele, 2012b (2012/1367953)
BCOP (OECD 437)	Bovine corneas	Not corrosive / serious eye damage	-	Remmele 2012c (2012/1367954)
Eye irritation (OECD 405)	New Zealand White rabbit	Not an eye irritant	–	[redacted] 2013a (2013/1150121)
Skin sensitisation (OECD 406) – maximisation test	Guinea pig	Skin sensitiser	Skin Sens. 1 H317	[redacted], 2013a (2013/1150123)
Photo-toxicity (OECD 432)	Balb/c 3T3 cells	Not photo-toxic	–	Cetto & Landsiedel, 2015a (2015/1117503)

2.6.3. Summary of short-term repeated-exposure toxicity

The short-term toxicity of BAS 750 F has been investigated via the oral route in rats, mice and dogs (28-day and 90-day studies; additionally, a one-year study in dogs) and via the dermal route in rats (28 days) (see table 2.6.3). No short-term inhalation toxicity studies were performed because BAS 750 F is not volatile and is not used as a fumigant or aerosol.

The NOAELs presented below are those proposed by the RMS. In addition, the RMS has performed Benchmark-dose (BMD) analysis to provide information on the reliability of the proposed NOAELs. The BMD approach makes extended use of the available dose-response data and so is a scientifically more advanced method compared with the NOAEL for deriving a reference point. It also provides a quantification of the uncertainties in the dose-response data, thus increasing the transparency and robustness of the risk assessment. In 2009, the Scientific Committee[1] recommended that EFSA Scientific Panels and Units apply the BMD approach to chemicals in food (pesticides, additives, contaminants). This position has recently been re-affirmed: 'the Scientific Committee considers that the use of the BMD approach is always better than the NOAEL approach to define a reference point; therefore the application of this guidance document is unconditional for EFSA and is strongly recommended for all parties submitting assessments to EFSA for peer-review' (Hardy *et al.* (2017) [*The EFSA Journal* 2017; 15(1):4658]).

Following oral administration from 28 days to one year, the liver was a clear target organ in all species. The RMS considers the effects to potentially be of relevance to humans and so has taken them into account in the risk assessment (see section 2.6.8.). In doing so, the RMS has tried to make a distinction between liver effects that are potentially adverse and those that are more likely to be adaptive. Hepatocellular hypertrophy is typically related to increased functional capacity: the hepatocyte responds to chemical exposure by increasing its metabolic capacity via the induction of metabolising enzymes in order to maintain the organism's homeostasis. A weight-of-evidence approach is needed to determine at

[1] *The EFSA Journal* (2009), 1150, 1-72.

which exposure level the normal homeostatic response has been exceeded and thus resulted in an adverse effect. These considerations include: the presence of other histology (necrosis, apoptosis, pigment deposition, hyperplasia); supportive clinical-chemistry changes; transient or sustained changes with progression of the effects; the induction of toxicologically-relevant levels of xenobiotic-metabolising enzymes. In line with reviews by the JMPR (2006[2], 2015[3]) and Chemicals Regulation Directorate (2013[4]), the RMS has concluded that findings of hepatocellular hypertrophy without the above-mentioned associated effects are adaptive and thus not relevant for the setting of reference values.

Based on an assessment of normal biological variation in organ weights, the JMPR (2015) has proposed that a rough threshold for adversity of a change in relative liver weight be 15 % for rats and mice. Therefore, in line with this recommendation, the RMS has applied a response level of 15 % to the BMD analysis of relative liver weight increase. Other liver changes, such as histopathology or clinical chemistry findings, have been analysed as separate effects.

Taking into account the above considerations, adverse effects on the liver comprised treatment-related increases in absolute and relative weights, and clinical chemistry alterations and histopathology findings indicative of liver toxicity. Impairment of liver function was observed from 256 mg/kg bw/d in rats and 150 mg/kg bw/d in dogs, whilst clear liver toxicity (including liver foci and hepatocellular necrosis) was reported from 58 mg/kg bw/d in mice. The severity of the liver effects did not markedly increase with an increase in exposure duration from 28 to 90 days, or to one year in dogs. Based upon the dose levels at which liver impairment / toxicity was evident and also the severity of the effects, the mouse was the most sensitive species to liver effects. The lowest NOAEL (11 mg/kg bw/d) was identified in the 90-day mouse study.

Another consistent finding across species was a reduction in body weight and body-weight gain; this wasn't always attributable to a lack of palatability, because it also occurred when BAS 750 F was administered in capsules.

No adverse effects were reported in the dermal study when BAS 750 F was applied at doses up to 1000 mg/kg bw/d. The active substance was therefore not locally or systemically toxic by this route of exposure.

When the findings from the short-term studies, together with those of the chronic / carcinogenicity studies (section 2.6.5.), are compared with the criteria for classification for STOT-RE, the only target organ of toxicity observed at doses below the guidance cut-off value for category 2 was the liver. Based on the nature of the effects and the doses at which these occurred, the mouse was more sensitive than the rat and dog.

Overall, it is concluded that the minimal-to-slight single-cell or multi-focal necrosis and slight increases in the severity of age-related morphological changes in the liver of mice compared with controls were not sufficiently severe or reproducible to warrant classification for repeated-dose toxicity (see CLH dossier for further details).

Table 2.6.3. Summary of short-term toxicity studies

Duration, method	Species, doses (mg/kg bw/d)	NOAEL (mg/kg bw/d)	Adverse effects	Reference (DocID)
ORAL				
28-day (OECD 407)	Rat, Wistar M = 0, 47, 135, 388 F: 0, 47, 138, 334	135	↓ body weights, ↓ feed intake, ↑ relative liver weight,	[redacted] 2015a (2014/1170747) [redacted]

[2] FAO/WHO, 2006: Pesticide residues in food - 2006. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues.

[3] WHO, 2015: Pesticide residues in food: WHO Core Assessment Group on Pesticide Residues. Guidance document for WHO monographers and reviewers WHO/HSE/GOS/2015.1, 1-106 pp.

[4] Chemicals Regulation Directorate, Health & Safety Executive, UK; Investigation of the state of the art on identification of appropriate reference points for the derivation of health-based guidance values (ADI, AOEL and AAOEL) for pesticides and on the derivation of uncertainty factors to be used in human risk assessment. Supporting Publications 2013:EN-413. [169 pp.]. Available online: www.efsa.europa.eu/publications

Table 2.6.3. Summary of short-term toxicity studies

Duration, method	Species, doses (mg/kg bw/d)	NOAEL (mg/kg bw/d)	Adverse effects	Reference (DocID)
ORAL				
		(BMDL$_{15}$ = 147)	impairment of liver function (Relative liver weight)	2015a (2015/1249664)
28-day (OECD 407)	Mouse, C57BL/6 Rj M: 0, 4.8, 15.5, 47.9, 128 F: 0, 5.8, 18.5, 61.0, 145	18.5 (BMDL$_{15}$ = 15)	↓ body weights & body-weight gain, ↑ liver weight, liver toxicity (Relative liver weight)	[redacted] 2014a (2013/1110704)
28-day (OECD 407)	Dog, Beagle M: d1-2: 300 or 1000; d7-35/36: 125 or 250 F: d1: 300 or 500; d3-29/30: 125 or 250	N/A (range-finding study)	Liver toxicity, body-weight effects, clinical signs	[redacted] 2015a (2014/1170748
90-day (OECD 408)	Rat, Wistar M: 0, 27, 76, 256 F: 0, 30, 91, 314	76 (BMDL$_{10}$ -= 91)	↓ body weights & body-weight gain, ↑ liver weight, impairment of liver function (Body-weight gain)	[redacted] 2015b (2015/1198721)
90-day (OECD 408)	Mouse, C57BL/6 Rj M: 0, 2, 11, 58, 74 F: 0, 3, 15, 67, 211	11 (BMDL$_{15}$ = 14)	↓ body-weight gain, liver toxicity (including histopathology changes) (Relative liver weight)	[redacted] 2015a (2014/1046542)
90-day (OECD 409)	Dog, Beagle 0, 15, 90, 180	90 (BMDL$_{15}$ = 18)	↓ food intake, body weight & body-weight gain, impairment of liver function (Relative liver weight)	[redacted] 2015a (2015/1000530)
One-year dog (OECD 452)	Dog, Beagle 0, 10, 30, 150	30 (BMDL$_{15}$ = 11)	15 % increase in relative liver weight (Relative liver weight)	[redacted], 2016 (2016/1000645)
DERMAL				
28-day (OECD 410)	Rat, Wistar 0, 100, 300, 1000	≥ 1000	No adverse effects	[redacted] 2015b (2014/1170751)

2.6.4. Summary of genotoxicity

The genotoxic potential of BAS 750 F has been investigated in a series of *in vitro* studies and one *in vivo* investigation (see table 2.6.4).

A standard dataset of six *in vitro* studies in bacterial and mammalian cells, covering the end-points bacterial-cell mutation, mammalian-cell mutation and clastogenicity / aneuploidy has been submitted. All studies employed limit and / or cytotoxic concentrations. BAS 750 F was negative in all these studies. It was also negative in an *in vivo* micronucleus study in mice following a single-dose, oral administration at doses up to 1500 mg/kg bw. Exposure of the bone marrow was inferred from the measurement of the test material in plasma samples and demonstrated by an inhibition of erythropoiesis (decreased PCE/NCE ratio); hence, this study gave a valid negative result. In conclusion, BAS 750 F was not genotoxic under the conditions of the studies investigated.

Since the available database on the genotoxicity of BAS 750 F did not give rise to any concern from either the *in vitro* or *in vivo* studies, an additional genotoxicity study in germ cells was not required. Photo-mutagenicity tests were not required: the substance's molar absorption coefficient was below that specified in Regulation (EU) 283/2013 as a trigger, and its toxicity was not increased by irradiation when tested in an *in-vitro* 3T3 NRU photo-toxicity assay.

Table 2.6.4. Summary of genotoxicity studies

Study type	Test system	Dose / concentr.	Result	Reference (DocID)
In-vitro reverse mutation assay in bacteria (OECD 471)	TA 1535, TA 1537, TA 98, TA 100, WP2 uvrA; with/without S9-mix	1 - 5000 µg/plate	Negative	Woitkowiak, 2014a (2014/1128030)
		3.3 - 5000 µg/plate	Negative	Woitkowiak, 2015a (2015/1116956)
In vitro forward mutation assay in mammalian cells (OECD 476)	Mouse lymphoma L5178Y cells; with/without S9-mix	3.75 - 60 µg/mL;	Negative	Wollny, 2013a (2015/1112683)
		3.1 - 62.5 µg/mL	Negative	Wollny, 2015b (2015/1101908)
In vitro cytogenicity assay in mammalian cells (micronucleus test) (OECD 487)	V79 cells; with/without S9-mix	0.39 – 50 µg/mL	Negative	Schulz & Landsiedel, 2014a (2013/1375108)
	Human lymphocytes; with/without S9-mix	2.0 - 8.2 µg/mL	Negative	Sokolowski A., 2015a (2015/1101907)
In vivo micronucleus test (OECD 474)	Male NMRI mice; single oral (gavage) application	0, 375, 750, 1500 mg/kg bw	Negative	[redacted] 2014a (2014/1043159)

2.6.5. Summary of long-term toxicity and carcinogenicity

The long-term toxicity and carcinogenicity of BAS 750 F have been investigated in a two-year study in rats and in an 18-month study in mice (see table 2.6.5).

Long-term exposure to BAS 750 F resulted in decreased body weight and body-weight gain in both species. The liver was the only target organ in rats and mice. Treatment-related hepatic effects comprised liver-weight increases, hepatocellular hypertrophy, clinical-chemistry and haematology changes. In mice, histopathology investigations recorded increased incidence and severity of fatty changes and single-cell necrosis. Despite the longer exposure, the effects did not increase in severity in either species compared with the shorter-duration studies. Moreover, the hepatic effects in the short-term studies did not translate to liver carcinogenicity in rats or mice.

In the mouse study, organ-weight changes and some histopathology observations in the kidneys from 50 ppm (9.1 / 12.6 mg/kg bw/d in males / females) and adrenal glands at 200 / 250 ppm (36 / 61.5 mg/kg bw/d) were attributed by the RMS to BAS 750 F exposure but were concluded to be non-adverse, since there were no degenerative changes in either organ. Furthermore, the renal changes probably reflected increased excretion activity, whilst the adrenal changes were those that are commonly associated with mild repetitive stress.

There was no evidence of a treatment-related increase in tumours in either species. It is proposed that BAS 750 F should not be classified for carcinogenicity.

Table 2.6.5. Summary of long-term toxicity studies with BAS 750 F

Duration, method	Species, doses (mg/kg/d)	NOAEL (mg/kg bw/d)	Critical effect	Reference (DocID)
Two-year oral chronic / carcinogenicity (OECD 453)	Rat, Wistar 12-months M: 0, 5, 31, 191 F: 0, 7, 41, 300 24-months M: 0, 4, 25, 163 F: 0, 6, 38, 302	5 (chronic) ($BMDL_{15}$ = 7) > 163 (carcino-genicity)	↑ liver weight, ↓ body weight & body-weight gain, clinical-chemistry changes (Change in urea levels) Not carcinogenic	[redacted] 2016b (2015/1000531) [redacted] 2015a (2015/1261375)
18-month oral carcinogenicity	Mouse, C57BL/6JRj	3.5	↓ body weight & body-weight gain, liver	[redacted] 2015b

Table 2.6.5. Summary of long-term toxicity studies with BAS 750 F

Duration, method	Species, doses (mg/kg/d)	NOAEL (mg/kg bw/d)	Critical effect	Reference (DocID)
(OECD 451)	M: 0, 3.5, 9.1, 36 F: 0, 4.9, 12.6, 61.5	 ($BMDL_{15}$ = 5) > 36 (carcino-genicity)	histopathology (Relative liver weight) Not carcinogenic	(2015/1000532)

2.6.6. Summary of reproductive toxicity

The reproductive toxicity of BAS 750 F has been investigated in a two-generation study in rats and developmental toxicity studies in rats and rabbits (see table 2.6.6).

The two-generation study and the developmental toxicity study in rats were appropriate for hazard identification and risk assessment purposes. The developmental toxicity study in rabbits was acceptable for the identification of a point of departure for risk assessment since a clear NOAEL was identified, although maternal toxicity was not induced at the highest dose administered (25 mg/kg bw/d). The doses chosen were based on range-finding studies in pregnant and non-pregnant rabbits, in which severe toxicity was observed in one of three non-pregnant rabbits at 25 mg/kg bw/d and all three animals at doses of 50 mg/kg bw/d and above. The RMS thus considers the doses administered in the main study to be adequate for the purposes of risk assessment. Overall, there is sufficient information to conclude on developmental toxicity.

In the two-generation study, BAS 750 F administered orally at doses up to 200 mg/kg bw/d did not affect mating or fertility, nor was it embryo- or foeto-toxic. It did not have a specific effect on post-natal pup survival; a small number of early post-natal litter losses appeared to result from inadequate nursing, arising from reduced maternal food intake. Also consequent to maternal toxicity were lower foetal body weights in the high-dose group and some delays in development and markers of sexual development.

In the rat developmental toxicity study, BAS 750 F was administered orally at doses up to 400 mg/kg bw/d, at which maternal toxicity was evident (reduced food consumption, body weight and body-weight gain). There were no effects on embryo / foetal survival or foetal weights, and there were no clearly treatment-related increases in any malformation or variation.

In the rabbit developmental toxicity study, oral administration of BAS 750 F at doses up to 25 mg/kg bw/d did not result in any developmental toxicity or indicate a potential to induce malformations.

It is proposed that BAS 750 F should not be classified for reproductive toxicity or effects on or via lactation.

Table 2.6.6. Summary of reproductive toxicity studies with BAS 750 F

Duration, method	Species, doses (mg/kg bw/d)	NOAEL (mg/kg bw/d)	Adverse effects	Reference (DocID)
Two-generation study, oral (OECD 416)	Rat, Wistar 0, 25, 75, 200	Parental = 25 ($BMDL_{50}$ = 34.1) Fertility = 200 Offspring = 75 ($BMDL_{10}$ = 163.2)	Evidence of liver impairment (Change in alkaline phosphatase) No adverse effects Decreased pup body weight / body-weight gain (Decrease in body-weight gain)	[redacted]., 2015c 2014/1170754

Table 2.6.6. Summary of reproductive toxicity studies with BAS 750 F

Duration, method	Species, doses (mg/kg bw/d)	NOAEL (mg/kg bw/d)	Adverse effects	Reference (DocID)
Developmental toxicity, oral (OECD 414)	Rat, Wistar 0, 50, 150, 400	Maternal = 150 ($BMDL_{10}$ = 40.2) Developmental = 400	Decrease in food consumption & corrected body-weight gain (Corrected body-weight gain) No adverse effects	[redacted] 2015a 2014/1170755
Developmental toxicity, oral (OECD 414)	Rabbit, New Zealand White 0, 5, 15, 25	Maternal & developmental = 25	No adverse effects	[redacted] 2015a 2014/1170755

2.6.7. Summary of neurotoxicity

The acute neurotoxicity of BAS 750 F has been investigated in an oral study in rats (see table 2.6.7). Administration of the test substance at a dose of 2000 mg/kg bw resulted in some neuro-behavioural effects on the day of dosing. These effects comprised unsteady gait in the open-field examinations, reduced motor activity (also in females at 600 mg/kg bw), reduced grip-strength of the fore-limbs (males) and increased distance between the hind-limbs in the landing foot-splay test (males). All these effects were transient and unrelated to structural or functional neuronal damage. The RMS therefore concludes that they were related to general systemic toxicity and impaired well-being subsequent to the application of a high-dose bolus application of test substance.

Information on neurotoxicity following repeated exposure of BAS 750 F was provided by the 90-day oral study in rats, in which there were no adverse findings in the functional observation battery, motor-activity measurements and histopathology of neuronal tissues when the test substance was administered at doses up to 314 mg/kg bw/d.

Table 2.6.7. Summary of acute neurotoxicity study with BAS 750 F

Study, method	Species, Doses (mg/kg bw/d)	NOAEL (mg/kg bw)	Critical effect	Reference (Doc ID)
Acute neurotoxicity (OECD 424)	Rat, Wistar 0, 200, 600, 2000	200 ($BMDL_{20}$ = 342)	Decrease in motor activity	[redacted] 2015 (2014/1170759)

2.6.8. Summary of further toxicological studies on the active substance

The applicant conducted mechanistic studies to explore the mode of action of the liver toxicity in rodents. Studies of liver-enzyme and cell-proliferation induction were performed in Wistar rats and in C57BL/6J mice (wild-type and PXR knockout (KO) / CAR KO strains) after dietary exposure to the same dose levels as those used in the long-term studies. In addition, *in vitro* investigations in primary hepatocyte cultures from human donors and from wild-type / knock-out mice were performed. The applicant concluded that the data indicated that liver effects in C57BL/6J mice, comprising increased serum ALT levels, increased liver weight, hypertrophy and liver cell proliferation, were CAR-mediated and therefore of limited relevance for human risk assessment. The RMS notes that necrosis was observed in some repeated-dose mouse studies with BAS 750 F, albeit of minimal or slight severity. Notwithstanding, it is generally accepted that the CAR mode of action does not result in cytotoxicity. Furthermore, increased liver weight, hypertrophy and changes in clinical chemistry parameters associated with impairment of liver function were observed in the dog studies. Therefore, the RMS concludes that the liver effects observed in the regulatory studies with BAS 750 F in several species cannot be attributed to CAR-mediated processes and should thus be considered to be potentially of relevance to humans.

The standard sub-chronic and chronic toxicity studies on BAS 750 F incorporated measurements of a number of potential immune-related end-points. There were no treatment-related changes in white blood

cell (WBC) count, select differential blood cell counts (lymphocytes, neutrophils, basophils, monocytes) or histology of the spleen, thymus, lymph node or bone marrow in any study. There was also no evidence of a specific immunotoxic effect on any immune-related parameter. Organ-weight changes, for example of the spleen and thymus in some of the high-dose groups, were secondary to decreased body weights and occurred together with general systemic toxicity. The only finding related to immune parameters that occurred without indications of systemic toxicity was a decrease in globulin levels in the high-dose rabbit developmental toxicity study; this observation was not considered to be adverse by the study authors and was most likely to be related to changes in liver function (site of synthesis) in these animals. There was therefore no evidence of a specific effect on immune-related parameters in the available studies and the RMS concludes that specific investigations into the immunotoxicity potential of BAS 750 F are not required.

BAS 750 F does not meet the interim criteria for the identification of a substance with endocrine-disrupting properties under Regulation EC 1107/2009, nor does it meet the World Health Organisation / International Programme on Chemical Safety definition of an endocrine disruptor (WHO / IPCS, 2002)[5]. Nevertheless, the applicant provided information on an *in vitro* aromatase inhibition assay because of the chemical class of the active substance: BAS 750 F belongs to the triazole class of fungicide compounds that act by blockage of sterol biosynthesis; the inhibition of mammalian aromatase (CYP19) is a known side effect of this chemical class. BAS 750 F, the S-enantiomer, the R-enantiomer and the metabolite M750F022 were tested in an *in vitro* system for their effect on human aromatase activity. BAS 750 F and both enantiomers had a measurable effect on aromatase activity. Under the study conditions, the S-enantiomer had the lowest IC_{50} concentration of 0.58 µM, followed by the racemate BAS 750 F with an IC_{50} of 0.92 µM and then the R-enantiomer with an IC_{50} of 2.97 µM. This graduated response of aromatase inhibition for BAS 750 F and its enantiomers was reproduced in all individual test runs. Overall, the IC_{50} values obtained for the racemate and the two enantiomers were all within the same order of magnitude (difference less than a factor of 10), whereas the metabolite M750F022 had a very weak effect on aromatase activity: complete inhibition of aromatase activity could not be achieved even at the solubility limit concentration of 316 µM. The reference compound 4-hydroxy-androstenedione had an IC_{50} of 0.0196 µM. In conclusion, the S-enantiomer of BAS 750 F had the highest activity (lowest IC_{50} concentration), followed by BAS 750 F and then the R-enantiomer. Nevertheless, the activity of BAS 750 F and both enantiomers was at least 30-fold lower than that of the reference chemical. Furthermore, aromatase inhibition in this *in vitro* system did not translate to endocrine-mediated adverse effects in intact organisms.

2.6.9. Summary of toxicological data on impurities and metabolites

BAS 750 F is extensively metabolised in plants and animals. Metabolites that are found in feed and edible food items were grouped according to their chemical similarity and common metabolic pathways. All metabolites but one (M750F022) were formed in the rat at > 10 % of the administered dose and were therefore sufficiently addressed in the toxicological studies performed with BAS 750 F. M750F022 (*syn.* Reg.No. 6011210) was identified as a residue in a hen metabolism study. Since M750F022 was not detected in significant amounts (<< 10 %) in the rat metabolism studies with BAS 750 F, toxicological studies were performed with this metabolite; these comprised an acute oral toxicity study, *in vitro* genotoxicity studies and a 28-day oral study. The aromatase inhibiting-activity of the metabolite was also investigated in an *in vitro* assay (see 2.6.8).

In an acute oral toxicity study in Wistar rats, the LD_{50} was greater than 2000 mg/kg bw.

M750F022 was not mutagenic in bacteria in an Ames test, nor did it induce forward mutations or structural chromosome aberrations *in vitro* in a mouse lymphoma assay. M750F022 was not clastogenic in an *in vitro* micronucleus test when tested up to cytotoxic concentrations on human lymphocytes.

In a 28-day study in mice, M750F022 was administered orally in the diet at concentrations that were equivalent to up to 587 / 718 mg/kg bw/d in males and females, respectively. Administration of 718 mg/kg bw/d M750F022 resulted in reduced food intake and body weight of females and reduced body-weight gain of both sexes. Liver changes were recorded at the mid- and high-dose levels. These comprised statistically significant increases in weight from 180 / 249 mg/kg bw/d, which correlated with hepatocellular

[5] WHO / IPCS, 2002: Global assessment of the state-of-the-science of endocrine disruptors. WHO/IPCS/EDC/02.2.

hypertrophy. Other histopathology findings included a fine granular eosinophilic cytoplasm at 587 / 718 mg/kg bw/d and hepatocellular necrosis in males at 872 and 2500 ppm and one female at 2500 ppm. Clinical chemistry changes in both sexes of the high-dose group, with one finding also in the mid-dose males (decreased triglyceride in males), were indicative of impaired liver function.

The information from the 28-day repeated-dose study in mice and the aromatase assay indicates that M750F022 had a lower potency than BAS 750 F. Furthermore, the nature of the toxicity in the 28-day study with the metabolite was consistent with that of the parent compound, with effects on body weight and liver toxicity. The acute toxicity of both parent and metabolite was low, and there was no indication of a genotoxic potential for either.

In view of the toxicological profiles of these substances, it is proposed to apply the reference values of BAS 750 F to the risk assessment of M750F022, if required.

Table B.6.8.1.1.12. Comparison of the toxicological profile of M750F022 and BAS 750 F

Study, method	M750F022 Reference (Doc ID)	BAS 750 F
Acute oral toxicity in rats (OECED 423)	LD_{50} > 2000 mg/kg bw [redacted] 2015a (2015/1175551)	LD_{50} > 2000 mg/kg bw
Mutagenicity in bacteria (OECED 471)	Negative Woitkowiak, 2015b (2015/1174564) Becker & Kamp, 2015a (2015/1186975)	Negative
Mutagenicity in mammalian cells (OECD 476)	Negative Schulz & Landsiedel, 2015a (2015/1174532)	Negative
Clastogenicity in mammalian cells (OECD 476)	Negative Sokolowski, 2015b (2015/1038964)	Negative
28-day oral (diet) in mice (OECD 407)	$BMDL_{15}$ = 172 mg/kg bw/d (15 % increase in relative liver weight) [redacted] 2015a (2016/1000646)	$BMDL_{15}$ = 15 mg/kg bw/d (15 % increase in relative liver weight)
Aromatase inhibition *in vitro* study (EPA 890.1200)	At 316 µM remaining aromatase activity was 46 % of maximum Mentzel, 2016c (2015/1261377) Mentzel, 2016d (2016/1001905)	IC_{50} = 0.92 µM

There were no groundwater metabolites of concern.

2.6.10. Summary of medical data and information

BAS 750 F has not yet been sold commercially and aside from pilot-scale preparations, it has been handled by only a small number of employees or contract scientists involved in regulatory and field biological testing. Therefore, there is only very limited human data at present. The applicant states that no adverse health effects suspected to be related to BAS 750 F exposure have been reported during medical surveillance programmes of manufacturing-plant personnel. There is no evidence or data available to support any findings in relation to poisoning with BAS 750 F or exposure of the general public, nor are epidemiological studies available.

The applicant's literature search did not return any relevant results.

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

The toxicological profile of BAS 750 F has been investigated in short-term toxicity studies in rats, mice and dogs, in long-term toxicity / carcinogenicity studies in rats and mice, and in reproductive and developmental toxicity studies with rats and rabbits. Its acute neurotoxicity study has been investigated in rats.

An acceptable daily intake (ADI) is usually established from long-term repeated-dose and reproduction studies. The lowest NOAEL from the available long-term studies was 3.5 mg/kg bw/d, determined from the 18-month mouse carcinogenicity study. This value was based on liver histopathology at 9.1 mg/kg bw/d. In comparison, the NOAEL from the rat carcinogenicity study was 5 mg/kg bw/d, based on changes in haematology and clinical chemistry parameters at 31 mg/kg bw/d. The lower NOAEL and LOAEL values from the long-term mouse study were consistent with the overall toxicological picture of BAS 750 F, which demonstrated that the liver effects were the critical effect in mice and dogs (change in body weight, increased liver weight or clinical-chemistry changes generally being the lead effects in rats) and that the mouse was the most sensitive species. The NOAELs of both studies were supported by their respective lowest BMDL values, which were 5 mg/kg bw/d (with a BMDL / BMDU ratio of 2.2) from the 18-month mouse study and 7 mg/kg bw/d from the rat chronic study (but with a large BMDL / BMDU ratio of 19, and so associated with a wider confidence interval).

Therefore, the RMS considers that the value of 3.5 mg/kg bw/d from the 18-month mouse study is the most relevant to use to derive the ADI. Application of the standard factors of 10 for each of intra- and inter-species differences results in an **ADI of 0.04 mg/kg bw/d**.

The applicant proposed a similar ADI of 0.05 mg/kg bw/d, based on a chronic NOAEL (12 months) of 5 mg/kg bw/d from the rat chronic / carcinogenicity study.

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

An ARfD for BAS 750 F was triggered by findings in a range-finding study in rabbits, in which gavage administration of 50 mg/kg bw/d and above caused marked reductions of food intake and associated signs of reduced nutritional condition, reduced faeces and lateral condition within 2-5 days of the treatment commencing, which ultimately led to the sacrifice of the moribund maternal animals. Similar effects were noted in 1 of 3 non-pregnant animals in a second range-finding study at a dose of 25 mg/kg bw/d. However, no adverse effects were observed in a subsequent prenatal developmental toxicity study in pregnant rabbits at doses up to 25 mg/kg bw/d. A BMDL of 40.2 mg/kg bw/d was obtained from the rat developmental toxicity study, based on a decrease in corrected body-weight gain. Another study that would be appropriate for the setting of an ARfD would be the acute neurotoxicity study in rats, but the BMDL for this study (342 mg/kg bw) exceeded the NOAEL from the rabbit developmental toxicity study. BAS 750 F caused other effects that could be attributable to a single acute exposure, most notably liver-enzyme induction and cell proliferation in mice with dietary administration for periods of 3-28 days. However, these were not standard regulatory studies and were not used to identify NOAELs or BMDLs.

Information from the rabbit developmental toxicity study is thus the most relevant for derivation of the ARfD, with a starting point being the NOAEL for maternal toxicity of 25 mg/kg bw/d. The steep dose-response curve is noted, but the RMS considers that an extra factor to account for this is not required: the standard factor of 10 for inter-species differences is sufficiently protective. Application of the standard factor of 10 for intra-species differences results in an **ARfD of 0.25 mg/kg bw/d.**

The applicant proposed the same ARfD of 0.25 mg/kg bw/d based on the NOAEL for maternal toxicity in the rabbit developmental toxicity study.

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

The systemic acceptable operator exposure level (AOEL) is usually derived from short-term toxicity studies (including the two-generation study) in rats, mice and dogs. The lowest NOAEL from the short-term repeated-dose toxicity studies was 11 mg/kg bw/d from the 90-day mouse study, which was based upon liver-weight increases, degenerative liver changes of minimal severity an increased severity of hepatocellular hypertrophy at the LOAEL of 58 mg/kg bw/d. This value was supported by the lowest BMDL of 14 mg/kg bw/d in this study, which was associated with a relatively small confidence interval (BMDU / BMDL = 2.0); this provides confidence in the proposed NOAEL. In comparison, the NOAEL values from the 90-day rat and 90-day dog studies were 76 mg/kg bw/d and 90 mg/kg bw/d, respectively, whilst the NOAEL for parental systemic toxicity in the two-generation rat study was 25 mg/kg bw/d. The NOAEL from the one-year dog study was 30 mg/kg bw/d. The RMS therefore considers it appropriate to use the NOAEL of 11 mg/kg bw/d from the 90-day mouse study to derive the AOEL.

Since an AOEL based on oral studies is an internal (systemic) dose, it is adjusted for the extent of oral absorption. As oral absorption of BAS 750 F is high (85 %), adjustment is not required. Application of the standard factors of 10 for each of intra- and inter-species differences results in a **systemic AOEL of 0.11 mg/kg bw/d**.

The applicant proposed a similar AOEL of 0.11 mg/kg bw/d based on the NOAEL of 11 mg/kg bw/d in the 90-day mouse study.

AAOEL

If an AAOEL is required, this can be derived from the value of the ARfD (0.25 mg/kg bw) with adjustment for oral absorption. As oral absorption for BAS 750F is high (85 %), adjustment is not required and an AAOEL of 0.25 mg/kg bw is established.

2.6.14. Summary of product exposure and risk assessment

Longer term exposure has been modelled using the AOEL of 0.12 mg/kg bw/day. Acute exposure has been modelled using an AAOEL of 0.25 mg/kg bw/day based on the ARfD with no correction for oral absorption.

Exposure to operators

Estimates based on surrogate data contained in the EFSA calculator predict that the proposed use of 'BAS 750 01 F' through field crop sprayers will result in a level of long term systemic exposure equivalent to 16 % of the AOEL for an operator without the need for PPE. For acute exposure to an operator during use of the product 'BAS 750 01 F', the level of systemic exposure is equivalent to 29 % of the AAOEL for an operator not wearing PPE.

On the basis of these estimates and considering the classification of the product as containing an active that may cause an allergic skin reaction (H317), the proposed use of 'BAS 750 01 F' is considered to be acceptable subject to the following operator protection requirement:

- Operators must wear suitable protective gloves and coveralls when handling the concentrate.

Exposure to bystanders

An assessment of acute exposure to bystanders compared to the AAOEL has been conducted using the EFSA calculator. The EFSA calculator predicts that the proposed use of 'BAS 750 01 F' will result in the following levels of systemic exposure to BAS 750 F for unprotected bystanders:

Routes of exposure		**BAS 750 F**
		% of systemic AAOEL
Bystander child Body weight: 10 kg	Drift (95th perc.)	3 %
	Vapour (95th perc.)	<1 %
	Deposits (95th perc.)	1 %
	Re-entry (95th perc.)	1 %
Bystander adult Body weight: 60 kg	Drift (95th perc.)	1%
	Vapour (95th perc.)	<1 %
	Deposits (95th perc.)	<1 %
	Re-entry (95th perc.)	1 %

On the basis of these estimates, the level of acute exposure for unprotected bystanders resulting from the proposed use of 'BAS 750 01 F' is considered to be acceptable.

Exposure to residents

An assessment of long term exposure to residents compared to the AOEL has been conducted using the EFSA calculator. The EFSA calculator predicts that the proposed use of 'BAS 750 01 F' will result in the following levels of systemic exposure to BAS 750 F for unprotected residents:

Routes of exposure		**BAS 750 F**
		% of systemic AOEL
Resident child Body weight: 10 kg	Drift (75th perc.)	3 %
	Vapour (75th perc.)	1 %
	Deposits (75th)perc.)	<1 %
	Re-entry (75th perc.)	3 %
	Sum (mean)	5 %
Resident adult Body weight: 60 kg	Drift (75th perc.)	1 %
	Vapour (75th perc.)	<1 %
	Deposits (75th perc.)	<1 %
	Re-entry (75th perc.)	2 %
	Sum (mean)	2 %

On the basis of these estimates, the level of long term exposure for unprotected residents resulting from the proposed use of 'BAS 750 01 F' is considered to be acceptable.

Exposure to workers

Estimates using EFSA calculator predict that the proposed use of 'BAS750 01 F' will result in a level of systemic exposure to BAS 750 F equivalent to 3 % of the AOEL for an unprotected worker entering treated areas to carry out crop inspection activities.

On the basis of these estimates, the level of exposure for unprotected workers entering and handling crops treated with 'BAS 750 01 F' is considered to be acceptable.

2.7. RESIDUE

2.7.1. Summary of storage stability of residues

BAS 750 F

BAS 750 F has been demonstrated to be stable in all five crop groups; high water (tomato fruit, apple fruit), high oil (soybean seed, rape seed), high protein (dried pea seed, dried bean seed), high starch (wheat grain, potato tuber) and high acid (grape fruit, lemon fruit) for a period of 730 days (~24 months) when stored at ≤-18 °C.

As at least one crop has been considered in all five crop groups, it can be considered that sufficient data is available to support the storage stability of BAS 750 F in all plant commodities for at least 730 days. Additionally, as there is no observed decline in residues across these commodities, specific storage stability data is not required for processed commodities.

BAS 750 F has been demonstrated to be stable in cow tissue (liver, kidney, muscle and fat), milk and cream and hen egg for at least 177 days when stored under deep frozen conditions.

Metabolites

M750F022 is a metabolite formed at relatively high levels in animal commodities (see section B.7.2.2 and B.7.4.1). M750F022 has been demonstrated to be stable in cow tissue (liver, kidney, muscle and fat), milk and cream and hen egg for at least 178 days when stored under deep frozen conditions.

Triazole derivative metabolites (TDMs) are formed during the metabolism of BAS 750 F in plant and animal commodities. The TDMs are 1,2,4-triazole, triazole alanine, triazole acetic acid and triazole lactic acid. Frozen storage stability of these metabolites was considered as part of the TDM review (Triazole Derivative Metabolites Addendum – Confirmatory Data, November 2015) for which BASF was one of the members of the TDM group who submitted the studies. These studies were considered acceptable in the ongoing TDM review. This table includes the studies in which the longest storage period was considered (other studies covering shorter time scales were also presented in the review).

During the TDM review only an interim storage stability study was available for triazole lactic acid (TLA). To support the duration of sample storage in studies considered for BAS 750 F, the full study for TLA has been submitted, and is evaluated in section B.7.1.2. This study demonstrates that TLA is stable in wheat grain, navy bean, orange, canola seed, and lettuce matrices for at least 48 months when stored under deep frozen conditions. As at least one crop has been considered in all five crop groups, it can be considered that sufficient data is available to support the storage stability of TLA in all plant commodities for at least 48 months.

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

Plant

Metabolism was investigated using two radiolabels (BAS 750 F labelled in the C-ring or in the T-ring). Results obtained with both labels show a consistent picture of BAS 750 F metabolism. Investigations were done in three plant species, wheat (cereal crop group), soybean (pulses and oilseed crop group), and grapevine (fruits/fruiting vegetable crop group), foliar applied with BAS 750 F and reflecting the cGAP (critical GAP). Comparable results were obtained for all three crop groups.

In most matrices the unchanged parent is the predominant component of the residue (>60% of the radioactive residue), notably in forage (wheat, soybean), leaf/stalk (grapevine), straw/hull/chaff (wheat, soybean), green pod (soybean) and grape (grapevine). The enantiomer ratio of the two BAS 750 F isomers remains unchanged (racemic mixture).

In wheat grain and soybean seed, the predominant component of the residue is the group of TDM, with triazole alanine as the most abundant compound (formed via cleavage of the T-bridge). In these matrices unchanged parent is present at very low levels if at all.

Other metabolites were formed via two main pathways:

- Initial hydroxylation of the chlorophenyl or propyl-triazole moiety and a subsequent conjugation with glucose, followed by malonylation of the glucose moiety or additional hydroxylation of the chlorophenyl ring (M750F018, 019, 020, 026, 027).
- Conjugation of the hydroxyl group of the propyl-triazole moiety of BAS 750 followed by malonylation or conjugation with another glucose molecule (M750F011, 012, 013, 014, 028).

Absence of detectable cleavage at the ether bridge between C-ring and TFMP-ring (trifluoromethylphenyl-ring, linking C-ring and T-ring) confirms that results obtained with C-labelled samples also provide comprehensive information on the metabolic fate of the TFMP-ring.

Metabolites occurring in plant matrices in major amounts (>10% TRR) and in minor amounts (<10% TRR) are listed in the table below. This table groups the metabolites according to their chemical structure together with their corresponding conjugates. The non-conjugated metabolites that were identified in plant matrices are highlighted (underlined).

Table 2.7.2-1: Residue components identified in plant matrices

Group definition	Residue	
	≥ 10% TRR*	**< 10% TRR**
a) parent and conjugates	**<u>BAS 750 F</u>**	M750F011 M750F012 M750F013 M750F014 M750F028
b) "C-Ring"-hydroxylation of non-cleaved molecule & downstream metabolites / conjugates	M750F018 M750F019 M750F020 M750F026 M750F027	
c) cleavage products & downstream metabolites / conjugates metabolites without the C-Ring		M750F009 M750F010
Triazole-derived metabolites (TDM)	**<u>1,2,4-T, TA, TAA</u>**	**<u>TLA</u>**

**In at least one plant commodity*

Animal

Metabolism was investigated using three radiolabels (BAS 750 F labelled in the C-ring, TFMP-ring or in the T-ring). Results obtained with all labels show a consistent picture of BAS 750 F metabolism. Investigations were done in laying hen and lactating goat, as well as in rat to support toxicology studies (see section CA B.6). For goat and hen the residue was rapidly and extensively eliminated via excreta, and reached a plateau in milk and egg within 7 days. Comparable results were obtained for all three animals, indicating common basic metabolite routes.

In poultry matrices the metabolite M750F022 (and its fatty acid conjugates) is the predominant component of the residue, with unmodified parent BAS 750 F and 1,2,4-triazole also present as significant components. In goat matrices, unmodified parent BAS 750 F and 1,2,4-triazole were the predominant components of the residue, with M750F022 present at much lower levels.

The metabolic pathway is largely based on two main transformation steps in livestock animals:

- hydroxylation at the C-ring (followed by conjugation) (M750F016, 034, 015, 041, 063)
- cleavage at the T-bridge (followed by conjugation) (M750F022-025, 038, 043, 064)

In addition, minor transformation steps were observed in livestock animals:

- cleavage at the ether bridge (followed by conjugation)
- hydroxylation at the T-ring
- hydroxylation of the methyl group (at quaternary C-atom, followed by conjugation)

Differences seen in species and/or matrices are the result of quantitative differences of transformation reactions as well as species-typical conjugation reactions (sulphation, glucuronidation, methylation, glutathione conjugation).

The parent BAS 750 F was applied as a racemic mixture of two enantiomers. Chiral analysis of BAS 750 F revealed a significant change of the ratio in most goat matrices, with proportion of the R-enantiomer of 70-80% in cream, muscle, liver, kidney and fat. In contrast, the racemate was maintained in goat faeces, indicating a preferential metabolism of the S-enantiomer. Such a change was not observed in poultry, but a comparable change was observed in rats (see section CA B.6).

Metabolites occurring in edible livestock matrices in major amounts (>10% TRR) and in minor amounts (<10% TRR) are listed in the table below. This table groups the metabolites according to their chemical structure together with their corresponding conjugates. The non-conjugated metabolites that were identified in food commodities are highlighted (underlined).

Table 2.7.2-2: Residue components identified in edible livestock commodities

Group definition	Residue	
	≥ 10% TRR*	**< 10% TRR**
a) parent and conjugates	**BAS 750 F** M750F068	M750F072
b) "C-ring"-hydroxylation of non-cleaved molecule & downstream metabolites / conjugates	**M750F016** M750F034	**M750F015** **M750F041** M750F063
c) cleavage products & downstream metabolites / conjugates Metabolites without the C-ring		**M750F003**
Metabolites without 1,2,4-T-ring	**M750F022** M750F023 M750F024 M750F025 **M750F038** M750F043 M750F064	-
1,2,4-triazole and triazole-derived metabolites (TDM)	**1,2,4-T**	-

**In at least one commodity*

2.7.3. Definition of the residue

Definition of the residue in plant
For commodities of plant origin, including processed fractions, the following residue definitions are proposed:

Residue definition for MRL enforcement/monitoring (RD-Mo):

- *parent BAS 750 F*

Residue definition for risk assessment (RD-RA):

- *parent BAS 750 F*
- *triazole derivative metabolites (provisional, pending the definition of a common and harmonised approach for all the active substances of the triazole chemical class)*

Based on the evaluation of study results provided in the present dossier, the residue components in plant commodities relevant for consideration in the residue definitions include parent BAS 750 F, as well as the group of triazole derivative metabolites (TDM) and sugar conjugates and cleavage products.

RD-Mo

According to *OECD Guidance on the definition of residue (ENV/JM/MONO(2009)30*), the residue definition for monitoring/MRL enforcement (RD-Mo) should focus on residue components suitable as analyte for multi-residue methods, as well as suitable as general marker compound in food commodities concerned.

Parent BAS 750 F fulfils these criteria since its compatibility with multi-residue methods has been confirmed (see section B.7.2.1.4) and it is a characteristic component of the residue typically accounting for a large proportion of the residue. Although it is either not detected or only present at very low levels in wheat grain and soybean seed, BAS 750 F remains the most appropriate residue component to analyse for in monitoring, as the predominant TDM components in these matrices are not suitable as BAS 750 F specific marker molecules as they are common to a range of pesticides.

In conclusion, the proposed residue for monitoring in plants is BAS 750 F.

RD-RA

According to *OECD Guidance on the definition of residue (ENV/JM/MONO(2009)30)*, the residue definition for risk assessment (RD-RA) should take into account the contribution of residue components to the potential dietary risk considering both the potential for exposure as well as the toxicity relative to the parent compound.

Parent BAS 750 F is the predominant component of the residue in all plant matrices considered, with the exception of wheat grain and soybean seed in which the TDMs (in particular TA) are the most abundant compounds.

TDMs contribute to a large proportion of the residue in all matrices; however these metabolites are common to a range of azole fungicides. Based on different toxicological properties, a separate definition of residue relevant for risk assessment is expected as part of a common approach for azole fungicides. Therefore, TDMs are provisionally included in the RD-RA as part of the present dossier, pending the outcome the EU review of TDMs. At the time of writing, no decision has been made with respect to an EU agreed approach on how to assess TDMs.

Other components present at >10 % TRR are sugar conjugates of BAS 750 F; however as they are present at significantly lower levels than parent, and do not present an increased toxicological risk in comparison to parent, it is not considered necessary to include these metabolites in the residue definition for risk assessment.

Definition of the residue in animal

For commodities of animal origin, the following residue definitions are proposed:

Residue definition for MRL enforcement/monitoring (RD-Mo):

- *parent BAS 750 F*

Residue definition for risk assessment (RD-RA):

- *animal except poultry:*
  - *parent BAS 750 F*
  - *triazole derivative metabolites (provisional, pending the definition of a common and harmonised approach for all the active substances of the triazole chemical class)*
- *poultry:*
  - *sum of parent BAS 750 F, metabolite M750F022 and fatty acid conjugates of M750F022, expressed as parent equivalents*
  - *triazole derivative metabolites (provisional, pending the definition of a common and harmonised approach for all the active substances of the triazole chemical class)*

Based on the evaluation of study results provided in the present dossier, the residue components in animal commodities relevant for consideration in the residue definitions include parent BAS 750 F, metabolite M750F022 and its fatty acid conjugates as well as the group of triazole derivative metabolites (TDM) and several other metabolites including sugar conjugates and cleavage products.

Residue definition for MRL enforcement/monitoring (RD-Mo)

According to *OECD Guidance on the definition of residue (ENV/JM/MONO(2009)30)* the residue definition for monitoring/MRL enforcement (RD-Mo) should focus on those residue components suitable as analyte of multi-residue methods, as well as suitable as general marker compound in food commodities concerned.

Parent BAS 750 F fulfils these criteria since its compatibility with multi-residue methods has been confirmed (see section B.7.2.1.4) and it is a characteristic component of the residue typically accounting for a significant proportion of the residue.

M750F022 is also present in significant amounts in poultry. However, M750F022 not suitable as analyte for multi-residue methods (due to insufficient ionization properties, GC-MS is required, and due to matrix interference a time-intensive methodology is needed to achieve a quantitation limit of 0.01 mg/kg).

TDMs are also present in significant amounts, but are not considered suitable as BAS 750 F specific marker molecules as they are common to a range of pesticides.

In conclusion, the proposed residue for monitoring in animals is BAS 750 F.

Residue definition for risk assessment (RD-RA)

According to *OECD Guidance on the definition of residue (ENV/JM/MONO(2009)30)*, the residue definition for risk assessment (RD-RA) should take into account the contribution of residue components to the potential dietary risk considering both the potential for exposure as well as the toxicity relative to the parent compound.

In commodities of ruminant origin, and by extrapolation of swine origin, parent BAS 750 F is a characteristic component of the residue and typically represents a predominant proportion of the residue. In conclusion, BAS 750 F is suitable to define the relevant residue in these commodities.

In commodities of poultry origin, in addition to parent BAS 750 F residues, significant amounts of metabolite M750F022 are typically present. In some commodities, namely fat, egg and muscle, a significant proportion of M750F022 is present as fatty acid conjugates. Release of M750F022 by hydrolytic cleavage of fatty acid conjugates in the human digestive tract might contribute significantly to the amount of M750F022. Toxicological investigations show that M750F022 (see section CA5.8) has comparable toxicological properties to BAS 750 F. Therefore, the toxicological reference values derived for BAS 750 F can be applied to M750F022. In order to account for a large proportion of the residue it is therefore proposed to define the sum of BAS 750 F, metabolite M750F022 and its fatty acid conjugates as the relevant component of the residue in poultry commodities for risk assessment. The proposed matrix-specific conversion factors (muscle 6.20, fat 16.33, liver 4.94, egg 4.86) take into account both

the matrix-specific contribution of fatty acid conjugates as well as the molecular weight difference between M750F022 and BAS 750 F (details are provided in section B.7.4.5).

In liver of poultry origin only M760F034 was detected at >10% TRR (0.12 mg/kg) for the TFMP label. However as it is only found in one commodity which is a very minor component of the diet, and it is a conjugate of parent BAS 750 F which has low toxicity relative to the expected exposure, it was not considered necessary to include this metabolite in the RD-RA.

TDMs (in particular 1,2,4-triazole) contribute to a large proportion of the residue in all matrices; however these metabolites are common to a range of azole fungicides. Based on different toxicological properties, a separate definition of residue relevant for risk assessment is expected as part of a common approach for azole fungicides. Therefore, TDMs are provisionally included in the RD-RA as part of the present dossier, pending the outcome the EU review of TDMs. At the time of writing, no decision has been made with respect to an EU agreed approach on how to assess TDMs.

Other components present at >10 % TRR in bovine commodities (M750F038, 043, 064, 068) are cleavage products of BAS 750 F and their sugar conjugates, however as they are present at significantly lower levels than parent, are only present in one commodity at >10% TRR, and do not present an increased toxicological risk in comparison to parent, it is not considered necessary to include these metabolites in the residue definition for risk assessment.

In conclusion, the proposed residue for risk assessment in animals except poultry is BAS 750 F, in poultry the proposed residue definition is sum of parent BAS 750 F, metabolite M750F022 and fatty acid conjugates of M750F022, expressed as parent equivalents.

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

The proposed uses of BAS 750 F in the EU are on wheat and barley. The cGAP for both commodities is given in Table 2.7.4-1.

Table 2.7.4-1: Critical GAP for the proposed use in wheat and barley

Crop	Outdoor/ Protected	Growth stage (BBCH)	Maximum number of applications	Minimum application interval (days)	Maximum		Minimum PHI (days)[a)]
					Rate (kg as/ha)	Water (L/ha)	
Cereals	Outdoor	49, 69	2	14	0.15	200	35

[a)] *Timing of the cGAP determined based on growth stage. PHI of 35 days proposed by the applicant, but has not be used for selection of trials*

In support of the representative uses, 17 cGAP-compliant field trials on wheat and 18 cGAP-compliant field trials on barley have been evaluated. It should be noted that in terms of the timing in the trials, the applications are in line with the BBCH growth stages in the proposed GAP, but in most cases the PHI is longer than the 35 days proposed. This is not considered to be of concern as for cereal applications, as the latest time of application is usually defined by the proposed BBCH. The residue trials were performed in various European Member States in both European regions during two growing seasons. A summary of the residues trials data for BAS 750 F residues are given in Table 2.7.4-2.

Table 2.7.4-2: Summary BAS 750 F residue data for the proposed uses

Crop	RAC	Region	n	Residues *[mg/kg]*	STMR *[mg/kg]*		HR *[mg/kg]*	
Wheat	Grain	NEU	8	4 x <0.01, 0.011, 0.014, 0.016, 0.024	0.011	0.01	0.024	0.026
		SEU	9	7 x <0.01, 0.018, 0.026	0.01		0.026	
	Straw	NEU	8	1.9, 2.3, 3.4, 3.6, 3.9, 4.9, 5.5, 10	3.75	3.6	10.0	18.0
		SEU	9	0.5, 0.56, 1.6, 2.9, 3.1, 3.8, 4.6, 9.0, 18.0	3.1		18.0	
Barley	Grain	NEU	9	0.014, 0.06, 0.071, 0.087, 0.1, 0.15, 0.15, 0.19, 0.28	0.1	0.1	0.28	0.41
		SEU	9	0.03, 0.033, 0.07, 0.1, 0.1, 0.14, 0.16, 0.29, 0.41	0.1		0.41	
	Straw	NEU	9	1.0, 1.7, 3.1, 3.9, 4.3, 4.3, 5.6, 6.8, 15.0	4.3	4.25	15.0	18.0
		SEU	9	0.39, 2.1, 2.2, 3.3, 4.2, 4.6, 6.4, 11.0, 18.0	4.2		18.0	

STMR and HR values have been calculated for the NEU and SEU region separately; however the U-test confirms that the NEU and SEU data sets in each case are not statistically different and hence the NEU and SEU results can be combined in each case to provide overall STMR and HR values.

For straw, the Dixon's Q-test indicates that the values of 9, 10 and 18 mg/kg in wheat straw and 11, 15 and 18 mg/kg in barley straw are outliers. No specific deviations to which these elevated values could be attributed to were noted in these trials, hence they have not been discarded, and are used in calculations of the STMR and HR. If these values had been discarded, the residue levels in straw would have remained high enough to trigger consideration of livestock feeding studies, and hence would not have impacted upon other areas of the risk assessment.

The final application to cereals in the proposed cGAP is after formation of the edible part of the crop, therefore, in accordance with SANCO 7525/VI/95 rev. 10.2 (Appendix D: Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs), trials on barley can be extrapolated to support application to oats, and trials on wheat can be extrapolated to support application to rye. Triticale is in the same MRL class as wheat and hence wheat trials can also be used in support of application to triticale. Therefore, sufficient data are available to support the proposed cGAP on the cereals crop group. The STMR, HR and MRLs for cereal grain and straw are given in Table 2.7.4-3.

Table 2.7.4-3: STMR, HR and MRL for the proposed cereal uses

Crop	RAC	STMR *[mg/kg]*	HR *[mg/kg]*	MRL[1)] *[mg/kg]*
Wheat	Grain	0.01	0.026	0.04
	Straw	3.6	18.0	*30*
Rye	Grain	0.01	0.026	0.04
	Straw	3.6	18.0	*30*
Triticale	Grain	0.01	0.026	0.04
	Straw	3.6	18.0	*30*
Barley	Grain	0.1	0.41	0.6
	Straw	4.25	18.0	*30*
Oats	Grain	0.1	0.41	0.6
	Straw	4.25	18.0	*30*

[1)] MRLs for straw calculated using the EU-OECD MRL calculator for information only, as MRLs for livestock feed are not currently required

Triazole derivative metabolites were also considered in the residue trials. For 1,2,4-triazole, no residues exceeding the LOQ were detected in any sample, both for treated samples and untreated samples. For TA, TAA, and TLA, residue levels above LOQ were determined, both for treated samples and untreated samples. It is considered that these residues are to a certain extent treatment unrelated as residue levels in treated and untreated samples are similar. A summary of STMR and HR for TDM residues are given in Table 2.7.4-4. TDMs are common to a range of triazole containing pesticides, and therefore it is likely that they were present in the soil prior to the current study and application of BAS 750 F.

Table 2.7.4-4: Summary TDM residue data for the proposed uses

Crop	Commodity	TA				TAA				TLA			
		Untreated *[mg/kg]*		Treated *[mg/kg]*		Untreated *[mg/kg]*		Treated *[mg/kg]*		Untreated *[mg/kg]*		Treated *[mg/kg]*	
		STMR	HR	STMR	HR	STMR	HR	STMR	HR	STMR	HR	STMR	HR
Wheat	Grain	0.14	1.0	0.25	1.5	0.03	0.29	0.068	0.36	0.01	0.32	0.01	0.092
	Straw	0.088	0.83	0.035	0.47	0.013	0.76	0.029	0.16	0.029	1.1	0.077	1.5
Barley	Grain	0.101	1.9	0.25	2.6	0.069	0.59	0.081	0.55	0.047	1.1	0.011	1.2
	Straw	0.03	0.83	0.087	0.71	0.022	0.76	0.035	0.33	0.12	10	0.44	11

A summary of the residues of TDMs in treated cereal grain as presented in the TDM review (Triazole Derivative Metabolites Addendum – Confirmatory Data, November 2015) is given in Table 2.7.4-5.

Table 2.7.4-5: Summary TDM residue data on cereals from the TDM Review

Crop	Commodity	1,2,4-T		TA		TAA		TLA	
		STMR *[mg/kg]*	HR *[mg/kg]*	STMR *[mg/kg]*	HR *[mg/kg]*	STMR *[mg/kg]*	HR *[mg/kg]*	STMR *[mg/kg]*	HR *[mg/kg]*
Cereal	Grain	0.05	0.08	0.62	2.20	0.79	1.73	0.022	0.16
	Straw	0.05	0.05	0.12	0.65	0.24	0.78	0.37	1.1

Residue data obtained in the present field study with BAS 750 F on cereals are comparable to the TDM residue data previously submitted by the Triazole Derivative Metabolite Group (TDMG). As the results are comparable, it is not considered necessary to undertake a new risk assessment for TDMs arising from application of BAS 750 F on cereals, as this is covered by the risk assessment performed in the TDM review.

STMRs for each TDM metabolite are lower in the trials conducted with BAS 750 F; therefore no increase on the chronic risk assessment would be observed (NB: the highest EU MS NEDIs in the TDM

review are 14.5% (1,2,4-T), 1.5% (TA), 1.1% (TAA) and 0.2% (TLA) of the respective ADIs (1,2,4-T: 0.05 mg/kg, TA, TAA, TLA: 1 mg/kg). Slightly higher HRs are determined for TA and TLA in barley grain in comparison to those reported in the TDM review; however these are not considered to significantly impact the acute risk assessment. The highest EU MS NESTI for wheat is 2.5%, of the ARfD (1 mg/kg) for TAA (cereals contribute <1% of the ARfD for TA and TLA); hence a minor increase in the HR would not significantly affect the acute risk assessment.

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

The maximum animal burden is greater than >0.004 mg/kg bw/day for all animals (except breeding pig), therefore feeding studies were undertaken on poultry and ruminants.

Laying hens were dosed with BAS 750 F at nominal doses of 0.15, 1.5, 4.5 and 15.0 mg/kg feed (predicted dietary burden in laying hens 2.2 mg/kg dry matter (DM)) over a period of 34 days. Eggs and tissue samples were analysed for BAS 750 F, M750F022 and TDMs. The study demonstrated that BAS 750 F residues present in feed items were transferred to poultry commodities showing a linear dose-residue-dependency. Residues in eggs reached a plateau level within 10 days indicating absence of accumulation for parent BAS 750 F, its metabolite M750F022 and 1,2,4-triazole. Residues in eggs and tissues declined rapidly within a few days after withdrawal of the dose.

Lactating cows were dosed with BAS 750 F at nominal doses of 1.5, 7.5, 50 and 150 mg/kg feed (predicted dietary burden in cattle 6.2 mg/kg DM) over a period of 28 days. Milk and tissue samples were analysed for BAS 750 F, M750F022 and TDMs. The study demonstrated that BAS 750 F residues present in feed items were transferred to ruminant commodities showing a linear dose-residue-dependency. Residues in milk reached a plateau level indicating absence of accumulation for parent BAS 750 F, its metabolite M750F022 and 1,2,4-triazole. Residues in milk and tissues declined rapidly after dose withdrawal.

The residue levels determined in the feeding studies have been used to determine the STMR, HR and MRL for animal commodities using the Excel calculator proposed by EFSA.

Calculations for poultry must account for both the different residue definitions for risk assessment and monitoring, as well as the matrix specific conversion factors for fatty acid conjugates of M750F022.

Residues of BAS 750 F and M750F022 at the four feeding levels were taken from the feeding study. The values for BAS 750 F are used directly for the calculations based on the residue definition for monitoring (parent BAS 750 F only). For calculation of the values for the residue definition for risk assessment (sum of parent BAS 750 F, metabolite M750F022 and fatty acid conjugates of M750F022, expressed in parent equivalents) the following process was used:

- Conversion of M750F022 residue data to BAS 750 F equivalents based on molecular weight (x1.15).
- Multiplication of M750F022 residue data (as mg/kg BAS 750 F equivalents) with a matrix-specific correction factor to account for the amounts of fatty acid-conjugates of M750F022 (4X (fat), 1.5X (muscle, egg), and 1X (liver))
- Summation of calculated M750F022 residue data with BAS 750 F residue data
- Derivation of conversion factor (CF) using Excel calculator based on RD-MO and RD-RA

The STMR and HR estimations and MRL proposals are given in Table 2.7.5-1. The conversion factors calculated are 6.2 for muscle, 16.3 for fat, and 4.9 for liver and egg.

Table 2.7.5-1: Poultry commodities: MRL proposal and conversion factor

Poultry									
Closest level		Residues at closest level (mg/kg)		Estimated value at 1N level		MRL proposal (mg/kg)	CF	**STMR (mg/kg)**	**HR (mg/kg)**
0.096 mg/kg bw [1)]									
0.6 N	Layer			$STMR_{Mo}$ (mg/kg)	HR_{Mo} (mg/kg)				
12.9 N	Broiler	Mean	Highest						
	Meat [2)]	-	-	-	-	-	-	**0.07**	**0.10**
	Muscle	0.01	0.01	0.01	0.011	0.015	6.2	**0.06**	**0.07**
	Fat	0.01	0.01	0.01	0.022	0.03	16.3	**0.16**	**0.36**
	Liver [3)]	0.01	0.017	0.011	0.026	0.03	4.9	**0.05**	**0.13**
	Egg	0.01	0.01	0.01	0.011	0.015	4.9	**0.05**	**0.05**

[1)] 1.5 mg/kg DM (dose group C) [2)] *STMR and HR for meat calculated based on composition of10% fat and 90 % muscle as BAS 750 F and M750F022 are fat soluble,* [3)] *Also used for poultry kidney*

Calculations for ruminants (and swine) are more straightforward than for poultry as the proposed residue definition for both monitoring and risk assessment is parent BAS 750 F only. The STMR and HR estimations and MRL proposals are given in Table 2.7.5-2. Data for all three fat types were entered separately as significantly different residue data were observed for the three fat types; the 'fat' STMR, HR and MRL in the table below is taken from the fat type which gave the highest levels.

Table 2.7.5-2: Ruminant and swine commodities: MRL proposals

Closest level	Residues at the closest feeding level (mg/kg)		Estimated value at 1N level		MRL proposal (mg/kg)
	Mean	Highest	STMR (mg/kg)	HR (mg/kg)	
Bovine					
0.192 mg/kg bw [2)]					
0.8 N Dairy C.					
1.3 N Beef C.					
Meat[1)]	-	-	0.024	0.062	-
Muscle	0.010	0.010	0.014	0.032	**0.04**
Fat (perineal)	0.049	0.059	0.062	0.197	**0.2**
Liver	0.150	0.182	0.088	0.337	**0.4**
Kidney	0.048	0.074	0.021	0.105	**0.1**
Milk	0.010	0.010	0.010	0.017	**0.02**
Fat per	0.049	0.059	0.062	0.197	0.2
Fat Sub.	0.023	0.041	0.026	0.080	0.08
Fat Mes.	0.053	0.077	0.063	0.184	0.2
Sheep					
0.192 mg/kg bw [2)]					
0.4 N Lamb					
0.5 N Ewe					
Meat[1)]	-	-	0.032	0.118	-
Muscle	0.010	0.010	0.017	0.052	**0.06**
Fat (perineal)	0.049	0.059	0.092	0.384	**0.4**
Liver	0.150	0.182	0.141	0.652	**0.7**
Kidney	0.048	0.074	0.033	0.248	**0.3**
Milk	0.010	0.010	0.010	0.026	**0.03**
Fat per	0.049	0.059	0.092	0.384	0.4
Fat Sub.	0.023	0.041	0.019	0.328	0.4
Fat Mes.	0.053	0.077	0.083	0.350	0.4
Swine					
0.034 mg/kg bw [3)]					
7.9 N Finishing					
10.3N Breeding					
Meat[1)]	-	-	0.019	0.026	-
Muscle	0.010	0.010	0.010	0.000	**0.01***
Fat (perineal)	0.015	0.017	0.002	0.002	**0.01***
Liver	0.031	0.034	0.004	0.004	**0.01***
Kidney	0.012	0.014	0.002	0.002	**0.01***
Milk	0.017	0.018	0.002	0.002	**0.01***
Fat per	0.015	0.017	0.002	0.002	0.01*
Fat Sub.	0.018	0.018	0.002	0.002	0.01*
Fat Mes.	0.010	0.010	0.010	0.000	0.01*

[1)] *STMR and HR for meat calculated based on composition of 20% fat and 80 % muscle as BAS 750 F and M750F022 are fat soluble,* [2)]7.5 mg/kg DM (dose group C), [3)]1.5 mg/kg DM (dose group B)

2.7.6. Summary of effects of processing

In the nature of the residues processing study, under conditions representative of pasteurisation (pH 4, 90 °C, 20 min), baking, boiling, brewing (pH 5, 100 °C, 60 min) and sterilisation (pH 6, 120 °C, 20 min) BAS 750 F was stable. No degradation product exceeding 2% of total radioactivity was detected and no change in the isomer ratio was observed. BAS 750 F can be regarded as stable to hydrolysis and the nature of the residue is not affected by processing operations. Stability of TDMs under high temperature hydrolysis has not been considered in this dossier; however it was in the TDM review (Triazole Derivative Metabolites Addendum – Confirmatory Data, November 2015), whereupon they were found to be stable. The following summary is taken from this review:

"The test compounds triazole alanine, triazole acetic acid, triazole lactic acid and 1,2,4-triazole were stable under three sets of hydrolytic conditions representative of the main food processing procedures (pasteurization, baking, brewing, boiling and sterilization). No significant amounts of hydrolysis products of these triazole derived metabolites could be detected after the high temperature hydrolysis

mimicking industrial and domestic food processing. The mass balance was complete in each test; no radioactivity has been lost. Consequently, it can be concluded that food processing does not change the nature of the triazole derived metabolites (triazole alanine, triazole acetic acid, triazole lactic acid or 1,2,4-triazole)."

The representative uses of BAS 750F are for application on wheat and barley, therefore a magnitude of the residues study on each of these crops was presented. A summary of the processing factors determined for BAS 750 F is given in Table 2.7.6-1.

For wheat, BAS 750 F was concentrated on processing (PF>1) to germ, middlings, shorts, bran and aspirated grain fractions. For barley, BAS 750 F was concentrated on processing (PF>1) to flour, bran, malt sprouts and brewers grain. For other processed wheat and barley commodities the processing factor was less than 1.

In both studies, control samples of RAC (raw agricultural commodity) and processed commodities contained the TDMs TA, TLA and TAA. TDMs are common metabolites from a range of pesticides, and hence are often present in soil. These results are not considered to have an adverse impact on the study, as the processing factors for these metabolites are not impacted by their source. TDMs were not formed on processing (see section 7.5.1); however as they are present in the RAC (either through treatment with BAS 750 F or due to their presence in the soil) a consideration of the effect of processing on their levels has been made. A summary of the processing factors determined for TDMs is given in Table 2.7.6-1.

For 1,2,4-triazole in wheat and barley and TLA in wheat grain, processing factors could not be calculated due to residue level <LOQ. For barley, TLA was concentrated on processing (PF>1) to flour and beer, but for other processed commodities the processing factor was less than 1.

For both TA and TAA in processed wheat commodities, these metabolites were concentrated on processing to middlings, bran and shorts. TA was also concentrated on processing to germ, and TAA on processing to gluten and whole grain bread. In barley both metabolites were concentrated on processing to flour, bran and malt sprouts. For other processed wheat and barley commodities the processing factor was less than 1.

Levels of TDMs in processed wheat and barley were also considered in the TDM review, and the results obtained were broadly in agreement with the results obtained in this evaluation. The following summary is taken from this review:

"For wheat, the data clearly show that the triazole derived metabolite TA does not concentrate in flour (straight, type 550 or wholemeal) or aspirated grain fractions, but concentrates in bran (fine and coarse) and germ. The results for TA in shorts and meal were more variable and overall residues levels were similar to the raw agricultural commodity. The results for TAA in all commodities were variable but showed a concentration in bran though overall residues levels in all other processed commodities were similar to the raw agricultural commodity. Limited data in flour or bran indicated that T does not concentrate whereas TLA does concentrate in these commodities. In most studies, residues of T were below the LOQ of 0.01 mg/kg in the raw agricultural commodity and all the processed commodities.

In barley, the data show that the triazole derived metabolites TA and TAA do not concentrate in brewer's malt, brewer's grain brewer's yeast or beer. For most commodities TLA was not found but the results showed that this metabolite concentrates in brewer's malt. Residues of 1,2,4-T were below the LOQ of 0.01 mg/kg in the raw agricultural commodity and all the processed commodities."

Table 2.7.6-1: Median processing factors for wheat and barley commodities

Crop	Matrix	Median Processing Factor			
		BAS 750 F	**TA**	**TAA**	**TLA**
Wheat	bran	**2.94**	*2.86*	*1.35*	-
	flour	**<0.29**	*0.51*	*0.81*	-
	germ	**1.12**	*0.97*	*0.70*	-
	middlings	**2.26**	*2.74*	*1.42*	-
	shorts	**3.53**	*3.54*	*2.00*	-
	gluten	**0.55**	*0.51*	*1.15*	-
	gluten feed meal	**<0.29**	*0.19*	*0.95*	-
	starch	**<0.29**	*<0.03*	*<0.05*	-
	whole meal flour	**0.79**	*1*	*0.90*	-
	whole grain bread	**0.56**	*0.86*	*1.19*	-
	milled by-products	**0.62**	*0.58*	*0.65*	-
	aspirated grain fraction	**38.46**	*0.69*	*0.63*	-
Barley	pearled barley (pot b.)	**0.12**	*0.84*	*0.71*	*0.52*
	flour	**3.67**	*1.20*	*2.11*	*3.86*
	bran	**5.00**	*2.08*	*1.33*	*0.64*
	brewing malt	**0.5**	*0.51*	*0.89*	*0.23*
	malt sprouts	**1.09**	*1.72*	*2.71*	*< 0.07*
	beer	**<0.04**	*< 0.04*	*0.15*	*1.71*
	brewers grain (dried)	**2.38**	*< 0.04*	*0.08*	*< 0.07*
	brewers yeast	**0.19**	*0.60*	*0.22*	*0.30*

2.7.7. Summary of residues in rotational crops

To investigate residues in rotational crops, a nature of the residue study and a magnitude of the residue study have been conducted in different crops representing three different crop categories, namely leafy vegetables, root and tuber vegetables and cereals. BAS 750 F was applied at 300 g ai/ha to bare soil, corresponding to a BAS 750 F concentration in soil of 0.1 mg/kg (soil depth 20 cm, soil density 1.5 g/cm^3). The rotational crops were cultivated after soil aging intervals of 30, 120 and 365 days, samples were taken at both mature and immature growth stages. The trials were conducted at a dose level which is worst case with respect to the expected plateau level of BAS 750 F in soil.

Based on results obtained in the nature of the residue study conducted with two labels (C-label, T-label), the residue in rotational crops is identified as unchanged parent BAS 750 F as well as the triazole derivative metabolites (TDM). The ratio of R- and S-enantiomers of BAS 750 F residue in plant remained unchanged compared with the test substance, indicating absence of preferential metabolism or uptake. Overall, the metabolism in rotational crops is similar to metabolism in primary crops (see section 7.2.1) with no rotational crop specific metabolites. The magnitude of both BAS 750 F and TDM was investigated under field conditions. Based on the results obtained in the magnitude of the residue study, no residues of BAS 750 F are expected in rotational crops for the use of BAS 750 F on cereals. The residue data obtained for the TDMs are comparable to the data on rotational crops considered in the TDM review. As for primary crop trials (see B.7.3.3), slight variations in the levels of TDMs in rotational crops are not considered to have any significant impact on the risk assessment, and hence no further consideration is required.

In conclusion, for the use of BAS 750 F supported in the present dossier, no replant restrictions are required. As no significant residues of BAS 750 F are expected, the default MRL of 0.01 mg/kg is appropriate for rotational crops.

2.7.8. Summary of other studies

At present there are no agreed EU guidance documents or test methods to address these data requirements (residue level in bee and pollen products). At the SCoPAFF (PPP legislation) meeting in October 2014 the COM emphasised, as laid down in document SANCO/10181/2013 Rev 2.1, that these data requirements can be waived until test methods or guidance documents are made available. SANCO/10181/2013 Rev 2.1 states:

In some cases, agreed test methods or guidance documents are not yet available for particular data requirements. In these cases, waiving of these particular data requirement points is considered acceptable as long as no test methods or guidance documents are published in form of an update of the Commission Communications 2013/C 95/01 and 2013/C 95/02. Applicants should follow on a routine basis the current developments, e.g. activities of the European Food Safety Authority for guidance documents and in particular publications in the Official Journal.

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

2.7.9.1 Chronic exposure

TMDI Calculation

BAS 750 F
The TMDI calculation was performed with the current EFSA model (version 2) using an ADI of 0.04 mg/kg bw/day and (proposed) MRLs as listed in Table 2.7.10-1 (the conversional factors for poultry outlined in Table 2.7.5-1 were applied to the poultry MRLs).

The summary of the chronic assessment is presented in Table 2.7.9.1-1. The ADI utilization ranges from 0.2 to 3.8 % ADI. The highest TDMI was 3.8% ADI for the "IE adult", the highest contributors are barley (1.9% ADI) and sheep liver (0.4% ADI).

The TMDI is well below the ADI for all European sub-population groups, therefore no health effects due to chronic exposure are expected.

TDMs
As data obtained on the levels of TDM residues from use of BAS 750 F are comparable to the TDM data previously considered in the TDM review (Triazole Derivative Metabolites Addendum – Confirmatory Data, November 2015) it is not considered necessary to undertake a new chronic risk assessment for TDMs arising from the application of BAS 750 F, as this is covered by the risk assessment performed in the TDM review.

In the TDM review, the highest EU MS NEDIs in the TDM review are 14.5% (1,2,4-T), 1.5% (TA), 1.1% (TAA) and 0.2% (TLA) of the respective ADIs (1,2,4-T: 0.05 mg/kg, TA, TAA, TLA: 1 mg/kg). Hence any minor alterations in the STMRs would not significantly impact the chronic risk assessment in the review, therefore no further consideration is required in this evaluation.

Table 2.7.9.1-1: EFSA PRIMo (rev. 2) TMDI calculation for chronic risk assessment for BAS 750 F

BAS 750 F			
Status of the active substance:		Code no.	
LOQ (mg/kg bw):	0 01	proposed LOQ:	
Toxicological end points			
ADI (mg/kg bw/day):	**0.04**	ARfD (mg/kg bw):	**0.26**
Source of ADI:	**DAR**	Source of ARfD:	**DAR**
Year of evaluation:	**2017**	Year of evaluation:	**2017**

Prepare workbook for refined calculations

Undo refined calculations

The risk assessment has been performed on the basis of the MRLs collected from Member States in April 2006. For each pesticide/commodity the highest national MRL was identified (proposed temporary MRL = pTMRL).
The pTMRLs have been submitted to EFSA in September 2006.

Chronic risk assessment

	TMDI (range) in % of ADI minimum - maximum
	0 – 4
No of diets exceeding ADI	---

Highest calculated TMDI values in % of ADI	MS Diet	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	pTMRLs at LOQ (in % of ADI)
3 8	E adult	1.9	Barley	0.4	Sheep: Liver	0 3	Oats	0.6
3.4	NL child	1.5	Milk and milk products: Cattle	0.5	Wheat	0.4	FRUIT (FRESH OR FROZEN)	0.7
2 9	WHO cluster diet E	1.2	Barley	0.4	Wheat	0 3	Poultry: Meat	0.5
2 9	WHO Cluster diet B	0.9	Wheat	0.4	Barley	0.4	VEGETABLES	0.8
2.7	DE child	0.7	Milk and milk products: Cattle	0.6	FRUIT (FRESH OR FROZEN)	0.4	Wheat	0.8
2 6	FR infant	1.3	Milk and milk products: Cattle	0.5	VEGETABLES	0.4	FRUIT (FRESH OR FROZEN)	0.9
2 5	WHO Cluster diet F	0.9	Barley	0.4	Wheat	0 2	Oats	0.4
2 2	DK child	0.6	Oats	0.6	Wheat	0.4	Rye	0.4
2.1	WHO regional European diet	0.5	Barley	0.3	Wheat	0 2	Milk and milk products: Cattle	0.4
2.1	ES child	0.6	Milk and milk products: Cattle	0.4	Wheat	0 3	Poultry: Meat	0.4
2.1	WHO cluster diet D	0.7	Wheat	0.3	Barley	0 2	Milk and milk products: Cattle	0.4
1 8	ES adult	0.7	Barley	0.2	Milk and milk products: Cattle	0 2	Wheat	0.2
1.7	NL general	0.6	Barley	0.3	Milk and milk products: Cattle	0 2	Wheat	0.3
1 6	FR toddler	0.4	VEGETABLES	0.3	FRUIT (FRESH OR FROZEN)	0 3	Wheat	0.8
1 5	SE general population 90th percentile	0.6	Milk and milk products: Cattle	0.3	Wheat	0 3	VEGETABLES	0.4
1.4	UK Infant	0.4	Oats	0.3	Wheat	0 2	Birds' eggs	0.4
1.1	UK Toddler	0.4	Wheat	0.2	FRUIT (FRESH OR FROZEN)	0 2	Birds' eggs	0.4
1 0	LT adult	0.2	Milk and milk products: Cattle	0.1	Oats	0.1	VEGETABLES	0.2
1 0	FR all population	0.3	Wheat	0.2	FRUIT (FRESH OR FROZEN)	0 2	Poultry: Meat	0.3
0 9	IT kids/toddler	0.7	Wheat	0.1	VEGETABLES	0.1	FRUIT (FRESH OR FROZEN)	0.2
0 9	PT General population	0.4	Wheat	0.2	FRUIT (FRESH OR FROZEN)	0.1	VEGETABLES	0.4
0 8	DK adult	0.2	Wheat	0.2	Oats	0.1	VEGETABLES	0.2
0 6	IT adult	0.4	Wheat	0.1	VEGETABLES	0.1	FRUIT (FRESH OR FROZEN)	0.2
0 6	UK vegetarian	0.2	Wheat	0.1	VEGETABLES	0.1	FRUIT (FRESH OR FROZEN)	0.2
0 5	FI adult	0.1	Oats	0.1	Wheat	0.1	Rye	0.2
0 5	UK Adult	0.2	Wheat	0.1	VEGETABLES	0.1	FRUIT (FRESH OR FROZEN)	0.2
0 2	PL general population	0.2	VEGETABLES	0.1	FRUIT (FRESH OR FROZEN)	0 0	PULSES, DRY	0.2

Conclusion:

The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI.
A long-term intake of residues of BAS 750 F is unlikely to present a public health concern.

2.7.9.2 Acute exposure

IESTI Calculation

BAS 750 F

A refined IESTI calculation was performed with the current EFSA model (version 2) using an ARfD of 0.25 mg/kg bw/day and HRs as listed in Table 2.7.9.2-1.

Commodity	HR *mg/kg*
Barley: grain	**0.41**
Oat: grain	**0.41**
Rye: grain	**0.026**
Wheat: grain	**0.026**
Bovine/Horse: Muscle	**0.065**
Bovine/Horse: Fat	**0.197**
Bovine/Horse: Liver	**0.337**
Bovine/Horse: Kidney	**0.105**
Bovine/Horse: Edible offal	**0.105**
Sheep/Goat: Muscle	**0.118**
Sheep/Goat: Fat	**0.384**
Sheep/Goat: Liver	**0.652**
Sheep/Goat: Kidney	**0.248**
Sheep/Goat: Edible offal	**0.248**
Poultry: Muscle	**0.1**
Poultry: Fat	**0.36**
Poultry: Liver	**0.13**
Poultry: Kidney	**0.13**
Poultry: Edible offal	**0.13**
Milk and milk products: Cattle/Horse	**0.017**
Milk and milk products: Sheep/Goat	**0.026**
Birds' eggs	**0.05**

The summary of the acute assessment is presented in Table 2.7.9.2-1. For children, the highest ARfD utilization was 1.0% for consumption of bovine liver and second highest for cattle milk/milk products (0.8%). For adults, the highest ARfD utilization was 1.1% for consumption of barley.

In both cases the IESTI is well below the ARfD for all commodities and European sub-population groups, therefore no health effects due to acute exposure are expected.

TDMs
As data obtained on the levels of TDM residues from use of BAS 750 F are comparable to the TDM data previously considered in the TDM review (Triazole Derivative Metabolites Addendum – Confirmatory Data, November 2015) it is not considered necessary to undertake a new acute risk assessment for TDMs arising from the application of BAS 750 F, as this is covered by the risk assessment performed in the TDM review.

In the TDM review, the highest EU MS NESTI for wheat is 2.5%, of the ARfD (1 mg/kg) for TAA (cereals contribute <1% of the ARfD for TA and TLA), hence a minor increase in the HR would not significantly impact the acute risk assessment, and therefore no further consideration is required in this evaluation.

Table 2.7.9.2-1: EFSA PRIMo (rev. 2) IESTI calculation for acute risk assessment for BAS 750 F (HRs)

	Acute risk assessment /children - refined calculations						Acute risk assessment / adults / general population - refined calculations					
The acute risk assessment is based on the ARfD.												
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), for lettuce a variability factor of 5 was used. In the **IESTI 2** calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce the calculation was performed with a variabilty factor of 3.												
Threshold MRL is the calculated residue level which would leads to an exposure equivalent to 100 % of the ARfD.												
Unprocessed commodities	**No of commodities for which ARfD/ADI is exceeded (IESTI 1):**		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 2):**		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 1):**		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 2):**		---
	IESTI 1	***)**	****)**	**IESTI 2**	***)**	****)**	**IESTI 1**	***)**	****)**	**IESTI 2**	***)**	**)
	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)
	1.0	Bovine: Liver	0.337 / -	1.0	Bovine: Liver	0.337 / -	1.1	Barley	0.41 / -	1.1	Barley	0.41 / -
	0.8	Milk and milk	0.017 / -	0.8	Milk and milk	0.017 / -	0.5	Poultry: Meat	0.1 / -	0.5	Poultry: Meat	0.1 / -
	0.6	Oats	0.41 / -	0.6	Oats	0.41 / -	0.3	Bovine: Liver	0.337 / -	0.3	Bovine: Liver	0.337 / -
	0.5	Sheep: Meat	0.118 / -	0.5	Sheep: Meat	0.118 / -	0.2	Oats	0.41 / -	0.2	Oats	0.41 / -
	0.4	Poultry: Meat	0.1 / -	0.4	Poultry: Meat	0.1 / -	0.2	Poultry: Liver	0.13 / -	0.2	Poultry: Liver	0.13 / -
	No of critical MRLs (IESTI 1)			---			**No of critical MRLs (IESTI 2)**			---		
Processed commodities	**No of commodities for which ARfD/ADI is exceeded:**		---				**No of commodities for which ARfD/ADI is exceeded:**		---			
			*****)**						*****)**			
	Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)				Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)			
	0.2	Apple juice	0.01 / -				0.1	Bread/pizza	0.04 / -			
	0.2	Orange juice	0.01 / -				0.0	Orange juice	0.01 / -			
	0.2	Wheat flour	0.04 / -				0.0	Apple juice	0.01 / -			
	0.2	Carrot, juice	0.01 / -				0.0	Wine	0.01 / -			
	0.1	Grape juice	0.01 / -				0.0	Pineapples preserved	0.01 / -			
*) The results of the IESTI calculations 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. **) pTMRL: provisional temporary MRL ***) pTMRL: provisional temporary MRL for unprocessed commodity												
Conclusion												
For BAS 750 F IESTI 1 and IESTI 2 were calculated for food commodities for which pTMRLs were submitted and for which consumption data are available.												
No exceedance of the ARfD/ADI was identified for any unprocessed commodity.												
For processed commodities, no exceedance of the ARfD/ADI was identified.												

2.7.10. Proposed MRLs and compliance with existing MRLs

Based on the residues trials data and livestock feeding studies, the MRLs as outlined in Table 2.7.10-1 are proposed for commodities of animal and plant original for the proposed use on cereals.

Table 2.7.10-1: Proposed MRLs for BAS 750 F for use on cereals

Code number	Commodity	Proposed MRL *mg/kg*
500010	Barley: grain	**0.6**
500050	Oat: grain	**0.6**
500070	Rye: grain	**0.04**
500090	Wheat: grain	**0.04**
1011010	Swine: Muscle	**0.01***
1011020	Swine: Fat free of lean meat	**0.01***
1011030	Swine: Liver	**0.01***
1011040	Swine: Kidney	**0.01***
1011050	Swine: Edible offal	**0.01***
1012010	Bovine: Muscle	**0.04**
1012020	Bovine: Fat	**0.2**
1012030	Bovine: Liver	**0.4**
1012040	Bovine: Kidney	**0.1**
1012050	Bovine: Edible offal	**0.1**
1013010	Sheep: Muscle	**0.06**
1013020	Sheep: Fat	**0.4**
1013030	Sheep: Liver	**0.7**
1013040	Sheep: Kidney	**0.3**
1013050	Sheep: Edible offal	**0.3**
1014010	Goat: Muscle	**0.06**
1014020	Goat: Fat	**0.4**
1014030	Goat: Liver	**0.7**
1014040	Goat: Kidney	**0.3**
1014050	Goat: Edible offal	**0.3**
1015010	Horse: Muscle	**0.04**
1015020	Horse: Fat	**0.2**
1015030	Horse: Liver	**0.4**
1015040	Horse: Kidney	**0.1**
1015050	Horse: Edible offal	**0.1**
1016010	Poultry: Muscle	**0.015**
1016020	Poultry: Fat	**0.03**
1016030	Poultry: Liver	**0.03**
1016040	Poultry: Kidney	**0.03**
1016050	Poultry: Edible offal	**0.03**
1020010	Milk and milk products: Cattle	**0.02**
1020020	Milk and milk products: Sheep	**0.03**
1020030	Milk and milk products: Goat	**0.03**
1020040	Milk and milk products: Horse	**0.02**
1030000	Birds' eggs	**0.015**

** denotes MRL at the LOQ*

2.7.11. Proposed import tolerances and compliance with existing import tolerances

No import tolerances are proposed and there are no existing import tolerances.

2.8. FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1. Summary of fate and behaviour in soil

The Applicant submitted three laboratory aerobic degradation studies assessing the breakdown behaviour of BAS 750 F in four soils. BAS 750 F was found to degrade to non-extractable residues at quantities ranging from 12.6% to 26.7% Applied Radioactivity (AR) by the end of the study period. A maximum quantity of 9.7% AR was observed to mineralise to CO_2 by the end of the studies. No 'major' metabolites (metabolites occurring at concentrations >10%, >5% at two consecutive timepoints or >5% and increasing at study termination) were detected in the studies. Although it is not a legislative requirement, the Applicant proposes to consider the metabolite 1,2,4-triazole (M750F001) (which occurred at a maximum concentration of 5.1% AR) within the risk assessment due to its widespread occurrence in the environment; it is to be included in the soil and groundwater exposure calculations.

Kinetic analysis was undertaken on the degradation results from the four soils. The minimum resulting DegT50 value calculated by best-fit kinetics (non-normalised) was 434 days, indicating field dissipation studies are necessary.

Although the best-fit degradation of BAS 750 F was found to follow biphasic kinetics, the SFO kinetic fits for each of the soils were deemed acceptable to derive modelling endpoints. The modelling $DegT_{50}$ values (normalised to 20°C and pF2) ranged between 104 and 477 days with a geometric mean value of 268 days. No evidence of pH dependence was observed for degradation in the four soils.

The Applicant submitted a study from which the formation fraction of 1,2,4-triazole from BAS 750 F was estimated in a conservative manner. The RMS accepts the study and the outcomes are further considered in the groundwater risk assessment. However, a discussion on this topic is expected during the EU review; the co-RMS (France) had some reservations on the acceptability of the approach due to laboratory degradation parameters being used in this study and field data being used for the groundwater modelling.

An anaerobic degradation study assessing the degradation behaviour of BAS 750 F in anaerobic conditions in four soils was submitted by the Applicant. BAS 750 F was observed to degrade slowly under anaerobic conditions and no new or novel major metabolites were detected. Kinetic analysis resulted in DT_{50} values in excess of 349 days for the soils (at 20°C and 50% MWHC).

Two field dissipation studies have been submitted by the Applicant. One study was based in the EU and the other in the USA. The studies monitored the dissipation behaviour of BAS 750 F and the potential formation of 1,2,4-triazole and M750F003 (detected at a maximum concentration of 1.8% in the aerobic laboratory degradation studies). Negligible amounts of 1,2,4-triazole were detected in the six EU trials and no residues of M750F003 were detected. In the US study, 1,2,4-triazole and M750F003 were detected in all six trial sites. However, given the interim nature of the US field study, the US results are not further considered at this time.

Kinetic analysis was conducted on the results from the six EU trials. The longest non-normalised $DegT_{50}$ of BAS 750 F occurred at the Italian site and was 846.6 days (SFO); this value is appropriate for use in the soil exposure calculations.

However, for all six trial sites, the SFO kinetic fits were deemed acceptable to derive the modelling endpoints. The normalised $DegT_{50}$ values ranged between 96.5 days and 610.8 days with a geometric mean value of 200.0 days. In line with the EFSA $DegT_{50}$ guidance, because the mean laboratory degradation rate of BAS 750 F was >240 days, the geometric mean value of 200 days from the field dissipation trials is appropriate for use in the surface water and groundwater exposure calculations. As a result, BAS 750 F was shown to fulfil the Persistent and very Persistent criteria of the PBT and vPvB assessment.

The Applicant submitted two soil accumulation studies, one with a test site in the UK, the other with a test site in Germany. Both studies are still ongoing and no residue data were presented. Therefore, these accumulation studies are not further considered at this stage.

A soil photolysis study was submitted by the Applicant which determined the extent of degradation of BAS 750 F when exposed to a xenon lamp simulating 15 days of continuous natural light. Less than 10% degradation of BAS 750 F was observed in the study period and no new metabolites requiring further investigation were detected. Kinetic analysis on the photodegradation of BAS 750 F indicated DT_{50} values of 93 and 170 days for the chlorophenyl and triazole labels respectively resulting in a mean value of 131.5 days. When converted to days of natural summer sunlight (at approximately 49° N), this equates to an average DT_{50} value of 351 days. When compared to the DT_{50} values of the laboratory degradation and field dissipation studies, light is expected to have a limited influence on the degradation behaviour of BAS 750 F in soil.

The adsorption and desorption behaviour of BAS 750 F was determined using 8 soils. The K_{FOC} values ranged between 2010.28 and 4930.94 mL/g for the 8 soils. The geometric mean value was calculated as being 3455.6 mL/g and the arithmetic mean of the 1/n values was 0.975; these are appropriate for use in the exposure calculations.

The Applicant calculated K_{OC} values for the major metabolites detected in the aquatic photolysis and water/sediment study using KocWIN. The RMS accepted the Applicant's approach and the K_{OC} values calculated are appropriate for use in the surface water exposure calculations.

The Applicant also submitted a study with the aim of revising the default foliar DT_{50} value. However, the RMS identified several issues with the design of this study that could not be fully resolved. Therefore, this study was not considered further. As a result, the default foliar DT_{50} value of 10 days is appropriate for use in the exposure calculations.

2.8.2. Summary of fate and behaviour in water and sediment

The Applicant submitted a hydrolytic degradation study of BAS 750 F over 30 days, 25°C and at pH 4, 5, 7 and 9. BAS 750 F was shown to be stable over these ranges with only negligible degradation occurring.

An aqueous photolysis study was conducted in pure water at pH 7 and at 25°C. The study lasted 15 days with the samples continuously exposed to a xenon lamp to mimic natural light. BAS 750 F was observed to degrade rapidly over the study period with four 'major' metabolites being formed: M750F005, M750F006, M750F007 and M750F008.

Kinetic analysis was undertaken on the degradation of BAS 750 F; the a.s. was observed to follow SFO kinetics and a DT_{50} value of 2.3 days was calculated. The Applicant proposed using default DT_{50} values of 1000 days in the surface water exposure calculations for all four metabolites. Given this will result in a more conservative risk assessment, the RMS accepts the Applicant's proposal.

The Applicant submitted a study determining the ready biodegradability of BAS 750. The study lasted 28 days and was undertaken at 22 ± 2°C using activated sludge. Only very minor biodegradation was observed in the test period, therefore, BAS 750 F is not readily biodegradable.

The aerobic mineralisation of BAS 750 F was tested to OECD 309 guidelines. Stream water was used containing suspended sediment. Very little degradation (<5%) and mineralisation occurred throughout the 63 day study period for both test concentration (10 µg/L and 100 µg/L), therefore, kinetic analysis could not be undertaken.

The behaviour of BAS 750 F in two water/sediment systems was investigated by the Applicant. The study was conducted over 100 days and at 20 ± 1 °C in the dark. BAS 750 F was observed to dissipate rapidly from the water phase, mostly partitioning to sediment. By the end of the study period, <5% BAS 750 F was detected in the water phase with 45.6 to 67.3% in the sediment phase. Two major metabolites were detected in the study: 1,2,4-triazole (M750F001) and M750F003. 1,2,4-triazole was detected at a maximum concentration of 10.2% in the water phase and 4.9% in the sediment phase at day 100. M750F003 was detected at a maximum concentration of 3.3% in the water phase and 5.9% in the sediment phase at day 100; the mean day 100 values in water and sediment were 3.1% and 5.4% respectively. A maximum amount of 9.6% AR was observed to mineralise to CO_2 and a maximum 26.6% was observed to degrade to non-extractable residue.

DT_{50} values indicate that BAS 750 F can be classed as Persistent in sediment. It is unclear if BAS 750 F fulfils the very Persistent criterion, however, as it has already been classified as vP in soil, even if further data was produced, it would not alter the overall categorisation of BAS 750 F. Furthermore, because the extent of photolysis in the natural surface water environment is unclear and BAS 750 F has been shown to quickly partition to sediment, the true persistence of BAS 750 F in water is unclear. Without further data on the influence of photolysis on natural water bodies, BAS 750 F is classified as potentially persistent.

The total system $DegT_{50}$ modelling endpoints for both test systems were 125.5 and 212.8 days (geometric mean value of 163.4 days). Because BAS 750 F was observed to quickly partition to the sediment phase, the Applicant proposed assigning the total system geomean DT_{50} value (163.4 days) to the sediment compartment in the surface water exposure calculations and assigning the default DT_{50} of 1000 days to the water compartment. The RMS accepts the Applicant's approach.

No kinetic analysis of the major metabolites arising from the water/sediment study was undertaken because 1,2,4-triazole has already agreed EU endpoints and M750F003 was assigned default DT_{50} values of 1000 days.

The Applicant has submitted a case justifying why the formation of nitrosamines is not expected to occur from the degradation of BAS 750 F at WwTWs. The RMS accepts the Applicant's justification.

2.8.3. Summary of fate and behaviour in air

The atmospheric half-life of BAS 750 F was calculated as being 1.67 days (12 hour day). Because of this, and its low vapour pressure, BAS 750 F is unlikely to be transported long and short distances.

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

None available.

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

Soil: BAS 750 F, 1,2,4-triazole (not formally triggered but done to demonstrate safe use)

Surface water: BAS 750 F, 1,2,4-triazole, M750F003, M750F005, M750F006, M750F007, M750F008

Sediment: BAS 750 F, 1,2,4-triazole, M750F003, M750F005, M750F006, M750F007, M750F008

Groundwater: BAS 750 F, 1,2,4-triazole (not formally triggered but done to demonstrate safe use)

2.8.6. Summary of exposure calculations and product assessment

BAS 750 01 F is the representative formulation supporting the application for the approval of the active substance BAS 750 F in Europe. Environmental exposure assessments were conducted for BAS 750 F based on the intended use pattern: crop – cereals, BBCH 30-69, max no. applications – 2, minimum interval between applications – 14 days and an application rate of 150 g/ha.

<u>Soil</u>

Tier 1 PEC_{soil} calculations were undertaken for BAS 750 F and 1,2,4-triazole. The application scheme considered within the calculations is 2 x 150g a.s. /ha with a 14 day interval. Within the calculations a crop interception of 80% was considered; as considered appropriate for winter and spring cereals at the earliest proposed growth stage application (BBCH 30). The $DegT_{50}$ value was set to 846.6 days (longest non-normalised field dissipation value). A soil bulk density of 1.5g/cm^3 and a soil depth of 5cm were considered.

As the field dissipation $DegT_{90}$ of BAS 750 F is greater than 1 year (365 days) PECsoil accumulation values were also determined using the same parameters as outlined above.

For 1,2,4-triazole, a maximum total dose approach was undertaken, based on the peak occurrence and molecular weight correction of the metabolite.

Further details are provided in section B.8.2 of Volume 3CP of the DAR.

Groundwater

Four tiers of groundwater modelling were proposed by the Applicant based on refining the formation fraction of 1,2,4-triazole, and taking into account biphasic degradation of the metabolite.

At tier 1, the formation fraction (*ff*) of 1,2,4-triazole was set to 1 and the longest, slow phase, DT_{50} was used. At tier 2, a *ff* of 1 was selected and degradation rates of the fast and slow phases were calculated based on the *ff* and the 'g' value. At tier 3, a worst case observed *ff* of 0.65 was selected and degradation rates of the fast and slow phases were calculated based on the *ff* and the 'g' value. At tier 4, the arithmetic mean *ff* (0.4) was selected and degradation rates of the fast and slow phases were calculated based on the *ff* and the 'g' value.

A full summary of calculations are presented in section B.8.3 of Volume 3CP of the DAR. The tier 1 PEC_{GW} values resulted in concentrations <0.1 µg/L for BAS 750 F and 1,2,4-triazole. As a result, no further consideration of parent or metabolite is required as there is no risk of leaching of BAS 750 F or 1,2,4-triazole into groundwater at the modelled GAP.

Tier 1- 80th percentile annual leachate concentrations of BAS 750F following application to spring and winter cereals (2 x 150g a.s/ha; 14 day interval from BBCH 30)			
Spring Cereals			
Scenario	PEC_{gw} (µg/L)		
	PEARL	PELMO	MACRO
Châteaudun	<0.000001	<0.001	<0.001
Hamburg	0.000001	<0.001	
Jokioinen	<0.000001	<0.001	
Kremsmünster	<0.000001	<0.001	
Okehampton	<0.000001	<0.001	
Porto	<0.000001	<0.001	
Winter Cereals			
Scenario	PEC_{gw} (µg/L)		
	PEARL	PELMO	MACRO
Châteaudun	<0.000001	<0.001	<0.001
Hamburg	<0.000001	<0.001	
Jokioinen	<0.000001	<0.001	
Kremsmünster	<0.000001	<0.001	
Okehampton	<0.000001	<0.001	
Piacenza	0.000001	<0.001	
Porto	<0.000001	<0.001	
Sevilla	<0.000001	<0.001	
Thiva	<0.000001	<0.001	

Tier 1- 80th percentile annual leachate concentration of 1,2,4- triazole following application to spring and winter cereals (2 x 150g a.s/ha; 14 day interval with 80% crop interception).			
Spring Cereals			
Scenario	PEC_{gw} (µg/L)		
	PEARL	PELMO	MACRO
Châteaudun	0.011702	0.006	0.0215
Hamburg	0.089997	0.075	
Jokioinen	0.025241	0.023	
Kremsmünster	0.054583	0.049	
Okehampton	0.075468	0.068	
Porto	0.043854	0.059	
Winter Cereals			
Scenario	PEC_{gw} (µg/L)		
	PEARL	PELMO	MACRO
Châteaudun	0.014478	0.009	0.0239
Hamburg	0.078986	0.085	
Jokioinen	0.025779	0.033	
Kremsmünster	0.052159	0.056	
Okehampton	0.079980	0.081	
Piacenza	0.043659	0.052	
Porto	0.040808	0.068	
Sevilla	<0.000001	<0.001	
Thiva	0.008704	0.003	

Surface water and sediment

Surface water and sediment exposure calculations were undertaken by the applicant for BAS 750 F, 1,2,4-triazole, M750F003, M750F005, M750F006, M750F007 and M750F008.

BAS 750 F required up to Step 4 calculations in water, however, the metabolites only required calculations up to Step 2.

The Applicant proposes tier 2 and 3 PEC_{SW} calculations for BAS 750 F. Tier 2 calculations are based on revising the crop interception values in the MACRO model to be in line with the groundwater crop interception values. Whilst the RMS accepts the principle of this refinement, the Applicant had not correctly carried out this modelling for all scenarios and so the tier 2 calculations are not considered further at this stage. The tier 3 calculations are based on refining the foliar DT_{50} value. However, the RMS did not consider the related study, submitted by the Applicant, to be of sufficient quality to accurately refine the DT_{50} value. As a result, the tier 3 calculations are also not considered further at this stage. Despite the higher tier refinements not being accepted at this stage, this does not affect approval because safe use can still be identified.

For further information, see section B.8.5 of Volume 3CP of the DAR.

Air

No exposure estimates provided because the atmospheric half-life of BAS 750 F was calculated as being 1.67 days (12 hour day). Because of this, and its low vapour pressure, BAS 750 F is unlikely to be transported for long and short distances.

Other routes of exposure

No further routes of exposure are expected

2.9. EFFECTS ON NON-TARGET SPECIES

2.9.1. Summary of effects on birds and other terrestrial vertebrates

Toxicity to birds: Toxicity data have been provided addressing acute, short-term and long-term toxicity to birds for the active substance BAS 750 F. For further details of the underlying studies see Section III CA B.9.1. A full list of the available endpoints is provided in the list of endpoints and in the relevant risk assessments for the formulation. The following endpoints have been used to address the risk assessment:

- **Acute toxicity –** Three acute oral toxicity studies have been submitted performed on *Colinus virginianus*, *Anas platyrhynchos* and *Serinus canaria*. The critical **LD_{50}** of **816 mg a.s./kg b.w.** is based on data for *Colinus virginianus*.
- **Short-term toxicity data –** Studies performed with BAS 750 F on dietary toxicity for *Colinus virginianus* and *Anas platyrhynchos* were submitted. However, under Regulation (EC) 1107/2009 these data are not required and are not used in the risk assessment.
- **Long-term toxicity –** Two reproductive studies on *Colinus virginianus* and *Anas platyrhynchos* were submitted and evaluated as valid. The critical endpoint is a **NOAEL 25.3 mg a.s./kg b.w./day** for *Colinus virginianus*.
- No relevant metabolites have been identified for consideration in the risk assessment for birds.

Toxicity to mammals: No toxicity data have been submitted for the ecotoxicology section, although data has been considered within the toxicology assessment (see III CA B.6 for details of the underlying studies). Endpoints for use in the mammalian risk assessment have been established for acute and long-term toxicity. The following endpoints have been used within the risk assessment:

- **Acute toxicity -** The toxicity estimate used to address the toxicity of the active substance in the risk assessment is **LD_{50} = >2000 mg a.s./kg b.w** from an acute oral toxicity test to rats**.**
- **Long-term toxicity -** The critical endpoint is **$NOAEL_{parents}$ = 25 mg a.s./kg b.w./day** from a reproductive two generation study on rats. At the LOAEL, 75mg/kg bw/d, increased cholesterol in males, liver weight in males and females, and increased alkaline phosphatase concentrations in males and females was reported. This endpoint is considered to be relevant for ecotoxicological risk assessments and has been used.
- No relevant metabolites have been identified for consideration in the risk assessment for mammals.

2.9.2. Summary of effects on aquatic organisms

Toxicity data have been provided to address BAS 750 F, relevant metabolites and the formulated product BAS 750 01 F. The first tier toxicity data used in the risk assessments are summarised here (Active substance, Table 2.9.2-1; metabolites, Table 2.9.2-2). For full details of all the available toxicity data, see the list of endpoints and Section III CA B.9.

Toxicity to fish: Four acute fish studies were submitted and concluded as acceptable. The most sensitive species was *Oncorhynchus mykiss* with a 96 h LC_{50} of 0.532 mg BAS 750 F/L. Two chronic studies, both early life stage studies, were evaluated and considered acceptable. The critical endpoint was a 36 d NOEC of 0.027 mg a.s./L for *Danio rerio.*

Toxicity to aquatic invertebrates: Three aquatic invertebrate studies were submitted and evaluated as acceptable. The most sensitive species was *Daphnia magna* with a 48 h EC_{50} of 0.944 mg BAS 750 F/L. One study was performed on *Crassostrea virginica* (oyster) and the 96 h EC_{50} was based upon shell growth (0.947 mg BAS 750 F/L). Four chronic toxicity studies were submitted covering three species of *Daphnia* and *Americamysis bahia*. *Daphnia magna* was the most sensitive species with a bounded endpoint,a 21 day EC_{10} of 0.0161 mg BAS 750 F/L.

Toxicity to algae: Four acceptable algal species were tested in growth inhibition tests for growth rate, and the most sensitive species is *Skeletonema costatum* with a 72 h E_rC_{50} of 0.679 mg BAS 750 F/L and a 72 h E_rC_{10} of 0.373 mg BAS 750 F/L.

Toxicity to aquatic plants: *Lemna gibba* was the only species of aquatic plant tested; the study was considered acceptable. The 7 day E_rC_{50} for this species was > 2.017 mg BAS 750 F/L and the 7 day NOE_rC was ≥ 2.017 mg BAS 750 F/L.

Toxicity to sediment dwellers: One chronic toxicity study was submitted, performed on *Chironomus riparius* (spiked sediment). This study had a 28 day NOEC of ≥1.158mg BAS 750 F/ kg dry sediment. Additionally, three acute or sub-chronic toxicity studies were submitted. The most sensitive species, *Chironomus dilutus*, had a 10 day NOEC of 7.08 mg BAS 750 F/ kg dry sediment.

Metabolite data: Data for fish, *Daphnia* and algae on the relevant metabolites have been submitted with the exception of M750F001 (1,2,4-triazole), for which endpoints have been previously agreed (PRAPeR Expert Meeting 13 (2006)). Additional QSAR data were submitted for metabolites to establish endpoints for fish in order to minimise vertebrate testing. The endpoints for sediment dwellers for metabolites have been based upon those of the active substance as the aquatic invertebrate data for all metabolites and the sediment dweller data for metabolites indicate no increase in toxicity compared to the active substance.

Formulation data: Acute formulation data have been submitted for fish, *Daphnia* and algae, with a blank formulation study performed on *Daphnia*. It was concluded that based on the toxicity of the active substance and the formulation BAS 750 01 F expressed in terms of the active substance, the toxicity of the formulated product is greater than that of the active substance. Therefore the endpoints from the formulated product have been considered within the active substance risk assessment for aquatic organisms. Additionally, the blank formulation for the *Daphnia* indicates the co-formulants may be contributing to the toxicity of the formulation

2.9.3. Summary of effects on arthropods

Toxicity to Bees: Toxicity data have been provided addressing acute and long term toxicity to honeybees, honeybee larvae and bumblebees for the active substance (BAS 750 F) and the formulation (BAS 750 01 F). The submitted data are considered sufficient to address the data requirements according to Commission Regulation (EU) 283/2013. For further details of the underlying studies see Section III CA B.9.3 (for the formulation study see Section III CP B.9.5). A full list of the available endpoints is provided in the list of endpoints and in the relevant risk assessments for the formulation. The following endpoints have been used to address the risk assessment:

- **Acute toxicity to honeybees:** Two studies (consisting of oral and contact routes of exposure, with the active substance BAS 750 F and the formulation BAS 750 01 F) have been submitted, performed on the honeybee *Apis mellifera* and concluded as acceptable for use in the risk assessment. The critical endpoints are 48 hour oral/contact LD_{50} of >100 µg a.s./bee.
- **Acute toxicity to bumblebees:** A single study (consisting of oral and contact routes of exposure) with the active substance BAS 750 F has been submitted, performed on the bumblebee *Bombus terrestris* and concluded as reliable. This study provides additional information as the risk assessment scheme for bumblebees has not been formally adopted yet. The endpoints are 96 hour oral/contact LD_{50}s of >195.4/>200 µg a.s./bee.
- **Chronic toxicity to honeybees:** A single study with the active substance BAS 750 F has been submitted, performed on the honeybee *Apis mellifera.* It was concluded to be reliable. This study provides additional information as the chronic risk assessment scheme for honeybees has not been formally adopted yet. The endpoints are a 10 day chronic LD_{50} of >110.5 µg a.s./bee/day and a 10 day chronic NOED of ≥110.5 µg a.s./bee/day.
- **Toxicity to honeybee larvae:** Two studies with the active substance BAS 750 F have been submitted, examining 8-day and 21-day periods of exposure with *Apis mellifera* larvae, however only the 8 day study was considered to be reliable. The endpoints are an 8 day LD_{50} of 43.9 µg a.s./larva and an 8 day NOED of 29.7 µg a.s./larva.

Toxicity to other non-target arthropods (NTA): Toxicity data have been provided addressing the toxicity of the formulation BAS 750 01 F to NTA other than bees. These consist of two tier 1 tests using the two indicator species (*Typhlodromus pyri* and *Aphidius rhopalosiphi*) and three extended laboratory studies on the two indicator species already listed and on the acceptable additional species *Chrysoperla carnea.* For further details of the underlying studies see Section III CP B.9.5.2. A full list of the available endpoints is provided in the list of endpoints and in the relevant risk assessments for the formulation. The following endpoints have been used to address the risk assessment:

- **Tier 1 studies:** Two studies with the indicator species *T. pyri* and *A. rhopalosiphi* were submitted and considered acceptable. The following LR50 values were used for the risk assessment: *T. pyri* – 769.1 ml/ha; *A. rhopalosiphi* – 95.4 ml/ha.
- **Extended laboratory studies:** Three extended laboratory studies on the two indicator species already listed and on the acceptable additional species *Chrysoperla carnea* were submitted and considered acceptable. The L/ER50 for all three species was >3000 ml/ha.

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

Toxicity to non-target soil meso- and macrofauna: Toxicity data has been provided addressing the chronic toxicity of the active substance, formulation and metabolite 1,2,4-triazole to non-target soil meso- and macro-fauna. The submitted data were considered sufficient to address the data requirements according to Commission Regulation (EU) 283/2013. For further details of the underlying studies see Section III CA B.9.4 (for the formulation studies see Section III CP B.9.7). A full list of the available endpoints is provided in the list of endpoints and in the relevant risk assessments for the formulation. The following endpoints have been used to address the risk assessment:

- **Chronic toxicity to earthworms:** Two studies with the active substance BAS 750 F and the formulation BAS 750 01 F have been provided, performed on the earthworm *Eisenia fetida* and considered acceptable for use in the risk assessment. Reference was also made to a previously evaluated study examining the chronic toxicity of the metabolite 1,2,4-triazole on the earthworm *Eisenia fetida.* The critical endpoints (adjusted for the high log Pow of the active substance) were an EC_{10} of 2.65 mg/kg dry soil (BAS 750 F); and NOECs of 1.0 mg /kg dry soil (1,2,4-triazole; not adjusted) and ≥3.98 mg a.s./kg dry soil (BAS 750 in BAS 750 01 F).

- **Field studies with earthworms:** Two field studies with the formulations BAS 750 01 F (100g BAS750F/L) and BAS 752 AM F (consists of 50 g/L Fluxapyroxad and 100 g/L BAS 750 F) were submitted, although were not required. The studies do not indicate that the use of either product has a negative impact on earthworm populations at 6L BAS 750 01 F/ha and 8L BAS 752 AM F/ha. For further details, please refer to the risk assessment in Section III CP B.9.8.1.

- **Chronic toxicity to other soil macro-organisms:** Five studies with the active substance BAS 750 F, formulation BAS 750 01 F and the metabolite 1,2,4-triazole were submitted, performed on the indicator species *Folsomia candida* and *Hypoaspis aculeifer*. Reference was also made to a previously evaluated study examining the chronic toxicity of the metabolite 1,2,4-triazole on the collembolan, *Folsomia candida.* The critical endpoints were as follows:

  - ***H. aculeifer*:** $NOEC_{corr}$- ≥500 mg/kg dry soil (BAS 750 F); $NOEC_{corr}$- 8.96 mg/kg dry soil (BAS 750 F in BAS 750 01 F); NOEC – 171 mg/kg dry soil (1,2,4-triazole)

  - ***F. candida*:** $NOEC_{corr}$- ≥200 mg/kg dry soil (BAS 750 F); $NOEC_{corr}$- ≥12.035 mg/kg dry soil (BAS 750 F in BAS 750 01 F); NOEC – 1.8 mg/kg dry soil (1,2,4-triazole).

2.9.5. Summary of effects on soil nitrogen transformation

Toxicity to soil micro-organisms: Toxicity data have been provided addressing the chronic toxicity of the active substance, formulation and metabolite 1,2,4-triazole to soil micro-organisms. The submitted data are considered sufficient to address the data requirements according to Commission Regulation (EU) 283/2013. For further details of the underlying studies see Section III CA B.9.5 (for the formulation studies see Section III CP B.9.9). A full list of the available endpoints is provided in the list of endpoints and in the relevant risk assessments for the formulation. The following endpoints have been used to address the risk assessment:

- **Effects on soil nitrogen transformation:** Two studies with the active substance BAS 750 F and the formulation BAS 750 01 F have been provided, performed on soil micro-organisms and considered acceptable for use in the risk assessment. Reference was also made to a previously evaluated study examining the effects of the metabolite 1,2,4-triazole on soil nitrogen transformation. The critical endpoints are <25 % effects on soil nitrogen transformation at rates of

2.53 mg/kg dry soil (BAS 750 F); 0.333 mg /kg dry soil (1,2,4-triazole) and ≥2.4 mg a.s./kg dry soil (BAS 750 in BAS 750 01 F).

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

Toxicity to terrestrial non-target higher plants (NTP): Toxicity data have been provided addressing the toxicity of the formulation BAS 750 01 F to NTPs. The submitted data are considered sufficient to address the data requirements according to Commission Regulation (EU) 283/2013. For further details of the underlying studies see Section III CP B.9.11. A full list of the available endpoints is provided in the list of endpoints and in the relevant risk assessments for the formulation. The following endpoints have been used to address the risk assessment:

- **Toxicity to NTPs:** Two studies examining the effects of the formulation BAS 750 01 F on seedling emergence and vegetative vigour were submitted and found to be acceptable. The following species were tested: Oilseed rape *(Brassica napus)*, lettuce (*Lactuca sativa)*, tomato (*Solanum lycopersicum*), green cabbage (*Brassica oleracea)*, soy bean (*Glycine max*), carrot (*Daucus carota*), onion (*Allium cepa*), ryegrass (*Lolium multiflorum*), wheat (*Triticum aestivum*) and corn (*Zea mays*). The critical endpoint for both seedling emergence and vegetative vigour was the ER50 >1.5 L/ha.

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

Toxicity to other terrestrial organisms (flora and fauna): Toxicity data (four studies) have been provided addressing the acute toxicity of the active substance BAS 750 F and formulation BAS 750 01 F to earthworms and the effects of the same compounds on soil carbon transformation. The submitted data are not required and provide additional information only. For further details of the underlying studies see Section III CP B.9.113 and Section III CA B.9.7. A full list of the available endpoints is provided in the list of endpoints and in the relevant risk assessments for the formulation.

2.9.8. Summary of effects on biological methods for sewage treatment

Toxicity to activated sewage sludge: A single study was provided addressing the effects of the active substance BAS 750 F on oxygen consumption of activated sewage sludge. For further details please refer to Section III CA B.9.8. The endpoint used in the risk assessment was a 3 hour EC_{50} ≥1000 mg a.s./L.

2.9.9. Summary of product exposure and risk assessment

2.9.9.1 Risk assessment for birds

Acute risk: Using the critical LD_{50} of 816 mg a.s./kg bw, the screening step for the proposed uses of BAS 750 01 F resulted in a TER_A value of 28.55, greater than the trigger value of 10, indicating the acute risk to birds as low.

Long-term risk: With the critical NOAEL of 25.3 mg a.s./kg b.w./day, the screening step resulted in an unacceptable risk to birds with a TER_{LT} of 3.5 compared to the trigger value of 5. Therefore further consideration was required. At the first tier risk assessment, there was an acceptable risk for all scenarios. For cereals at BBCH 30-39, the TER was 42.1 for the small omnivorous bird "lark", and for cereals at BBCH ≥40, the TER was 68.9 for the small omnivorous bird "lark", both greater than the trigger value of 5.

Bioconcentration: The Log K_{OW} of BAS 750 F is 3.4 (III CA B.2.7) and therefore is considered to have the potential to bioaccumulate. Therefore the risk to vermivorous and pescivorous birds from consuming BAS 750 F contaminated prey must be considered. As the TER_{LT} values for earthworm-eating and fish-eating birds are 716.8 and 20.07 respectively (i.e. greater than trigger value of 5), the risk is considered acceptable.

Risks from drinking water: The ratio of the ratio of effective application rate (in g/ha) to relevant endpoint (in mg/kg b.w./d) for BAS 750 F is 0.142 and 11.56 for the acute and long-term endpoints respectively. As these ratios do not exceed 3000 (BAS 750 F is considered a sorptive substance due to a K_{OC} of 3455.6), further assessment of the risk to birds from drinking water via puddles is not required. As the proposed use is on cereals, no consideration of the risk to birds from drinking water via leaves is required.

Risks from metabolites: Four metabolites approached or exceeded 10% TRR on potential food items for birds and mammals: M750F001 (1,2,4-triazole), M750F029, M750F030, and M750F031. As for all four metabolites the toxicity was considered to be less than that of the active substance, the residues were found to be far below the maximum RUDs and the log K_{OW} values are all <3, no secondary poisoning assessment is considered necessary and the risk is considered to be covered by the active substance.

Conclusion: It can be concluded that acceptable acute and long-term risks have been demonstrated for birds following applications of BAS 750 F to cereals.

2.9.9.2 Risk assessment for mammals

Acute risk: Using the critical LD_{50} of >2000 mg a.s./kg bw, the screening step for the proposed uses of BAS 750 01 F resulted in a TER_A value of >93.8, greater than the trigger value of 10, indicating the acute risk to mammals as low.

Long-term risk: With the critical NOAEL of 25 mg a.s./kg b.w./day, the screening step resulted in an unacceptable risk to mammals with a TER_{LT} of 4.65 compared to the trigger value of 5. Therefore further consideration was required. At the first tier risk assessment, there was an acceptable risk for all scenarios. For cereals at BBCH ≥20, the TER was 118.2 for the small insectivorous mammal "shrew", and for cereals at BBCH 30-39, the TER was 57.6 for the small omnivorous mammal “mouse”. For cereals at BBCH ≥40 the TER was 10.4 for the small herbivorous mammal "vole” and for cereals at BBCH ≥40 the TER was 97.7 for the small omnivorous mammal “mouse”. As all of these ratios are greater than the trigger value of 5, the risk is considered acceptable.

Bioconcentration: The Log K_{OW} of BAS 750 F is 3.4 (III CA B.2.7) and therefore is considered to have the potential to bioaccumulate. Therefore the risk to vermivorous and pescivorous mammals from consuming BAS 750 F contaminated prey must be considered. As the TER_{LT} values for earthworm-eating and fish-eating mammals are 581 and 22.21 respectively (i.e. greater than trigger value of 5), the risk is considered acceptable.

Risks from drinking water: The ratio of the ratio of effective application rate (in g/ha) to relevant endpoint (in mg/kg b.w./d) for BAS 750 F is 0.146 and 11.70 for the acute and long-term endpoints respectively. As these ratios do not exceed 3000 (BAS 750 F is considered a sorptive substance due to a K_{OC} of 3455.6), further assessment of the risk to mammals from drinking water via puddles is not required. As the proposed use is on cereals, no consideration of the risk to mammals from drinking water via leaves is required.

Risks from metabolites: Four metabolites approached or exceeded 10% TRR on potential food items for birds and mammals M750F001 (1,2,4-triazole), M750F029, M750F030, and M750F031. As for all four metabolites the toxicity was considered to be less than that of the active substance, the residues were found to be far below the maximum RUDs and the log K_{OW} values are all <3, no secondary poisoning assessment is considered necessary and the risk is considered to be covered by the active substance.

Conclusion: It can be concluded that acceptable acute and long-term risks have been demonstrated for mammals following applications of BAS 750 F to cereals.

2.9.9.2 Risk assessment for aquatic life

Based on the results from the FOCUS STEP 1 exposure assessment in surface water, the following can be concluded for the use of BAS 750 01 F on cereals.

STEP 1:

- Active substance – The risk to algae and aquatic plants is acceptable. For all other groups on both acute and chronic scales the RAC (Regulatory Acceptable Concentration) is less than the STEP 1 PEC_{SW} so further consideration is required.
- Formulated product – the risk has been accounted for by the formulated product endpoints expressed in terms of active substance, so the risk from the formulated product will be considered with the assessment of the active substance

STEP 2:

- Active substance – The acute risk to aquatic products from BAS 750 F is acceptable, but not for BAS 750 01 F expressed in proportion of BAS 750 F. All other groups require further consideration as the RAC is less than at least one of South or North Europe, single or multiple application scenarios' PEC_{SW}.

STEP 3: An acceptable acute risk was demonstrated for fish (BAS 750 F) and aquatic invertebrates (BAS 750 F and BAS 750 01 F expressed as BAS 750 F), and an acceptable chronic risk was concluded. There was an unresolved acute risk for fish (BAS 750 01 F expressed as BAS 750 F) and an unresolved chronic risk for aquatic invertebrates for some scenarios. Therefore further consideration at STEP 4 was required.

Safe scenarios for spring cereals: D4 pond, D5 pond
Safe scenarios for winter cereals: D4 pond, D5 pond, R1 pond

STEP 4: An acceptable acute risk was demonstrated for fish ((BAS 750 01 F expressed as BAS 750 F) for all scenarios. The chronic risk to aquatic invertebrates was resolved for all scenarios at STEP 4 with the exception of D1 ditch and D2 ditch both for multiple (two) applications on winter cereals. Following this, additional chronic data on three other aquatic invertebrate species was used to calculate a geometric mean chronic endpoint. When using this RAC of 2.87µg a.s./L, the risk is resolved for all scenarios. In conclusion, the following safe scenarios have been identified.

Spring cereals single applications: All scenarios
Spring cereals two applications: All scenarios
Winter cereals single applications: All scenarios
Winter cereals two applications: All scenarios

An overall summary of the outcome of the aquatic risk assessment is presented in Table 2.9.9.2.

Table 2.9.9.2: Summary of risk posed to aquatic organisms from the active substance

Test substance	Test group	Test species	RAC (µg/L or µg/kg)	Maximum STEP assessed	Unacceptable scenarios at STEP 4
BAS 750 F	Acute fish	*O. mykiss*	5.32	STEP 3	-
	Chronic fish	*D. rerio*	2.7	STEP 3	-
	Acute aquatic invertebrates	*D. magna*	9.44	STEP 2	-
	Chronic aquatic invertebrates	Geometric mean of 4 species	28.7	STEP 4	None
	Algae	*S. costatum*	67.9	STEP 1	-
	Aquatic plants	*L. gibba*	>201.7	STEP 1	-
	Sediment dwelling organisms	*C. riparius*	≥ 115.8	STEP 3	-
BAS 750 01 F (expressed as a.s. in f.p.)[1]	Acute fish	*O. mykiss*	0.524	STEP 4	None
	Acute aquatic invertebrates	*D. magna*	1.813	STEP 3	-
	Algae	*P. subcapitata*	8.51	STEP 2	-

[1]Calculated based upon a density of 0.993g/cm^3

Risk to sediment dwelling organisms: An assessment has been made of the potential risk to sediment dwelling organisms. The risk was unresolved at STEP 1, and resolved at STEP 2 except for multiple applications to southern Europe. All scenarios were acceptable at STEP 3.

Risk from metabolites: For all the relevant metabolites of BAS 750 F, the PEC_{sw} were below the most sensitive surface water RAC for each metabolite at STEP 1. Therefore the risk to surface water aquatic organisms was acceptable. The risk posed to sediment dwelling organisms was acceptable for all relevant metabolites at STEP 1, except for M750F005, M750F006 and M750F007 where there was an acceptable risk for all scenarios and applications at STEP 2.

Bioaccumulation: A bioconcentration study was previous submitted and indicated that the BCF was low (385) for BAS 750 F and that depuration was rapid with a $t1/2_g$ of 0.60 days (based on total radioactivity).

Endocrine disruption: A fish sexual development test on *Danio rerio* was submitted. There are currently no defined criteria for identifying endocrine disruptors or interpreting the significance of any affects in ecotoxicology studies under the Commission Regulation (EU) No. 2009/1107. As a result of this, endpoints have not been defined and a risk assessment has not been conducted. Discussion of endocrine effects has been undertaken within the toxicology section (III CA B.6.8.3), although from an ecotoxicological perspective it cannot be concluded if endocrine disruptive effects are or are not taking place.

2.9.9.3 Risk assessment for Arthropods

Risk to Bees

The risk assessment has been performed according to SANCO/10329/2002 rev 2 final, since the new EFSA GD "Guidance on the risk assessment of plant protection products on bees (*Apis mellifera, Bombus* spp. and solitary bees)" (EFSA Journal 2013; 1187):3295) has not yet been noted by the Standing Committee on Plants, Animals, Food and Feed.

Hazard quotients for honeybees were calculated for oral exposure and contact exposure to BAS 750 F and BAS 750 01 F. An HQ < 50 indicates low risk to honeybees in the field.

Under Commission Regulation No 283/2013 and 284/2013, chronic toxicity to adult honeybees and toxicity to honeybee brood need to be addressed. However there is currently no agreed risk assessment

scheme available to assess the risk for bees based on chronic adult and/or larvae data.
Therefore these data have not been used to assess the risk to this organism group. The risk to bees is concluded to be acceptable based on the data available for acute toxicity to honeybees, as per current noted guidance.

Risk to other non-target arthropods (NTA)
The risk to NTA was considered according to the guidance document on Regulatory Testing and Risk Assessment Procedures for Plant Protection Products with Non-Target Arthropods from the ESCORT 2 workshop (Candolphi *et al.*, 2000). The predicted environmental rate (PER) off-field was calculated to be 606.9 ml product/ha. An acceptable off-field risk was concluded using Tier 1 data, taking into account a vegetation distribution factor (VDF) of 10. However, tier 1 data were not sufficient to demonstrate an acceptable risk in the in-field environment, where the PER was calculated to be 2550 mL/ha. An acceptable in-field risk was demonstrated taking into account extended laboratory data, which indicated L/ER_{50} >3000 mL/ha for all species tested.

2.9.9.4 Risk assessment for soil non-target meso- and macro-fauna

Risk to earthworms
Chronic toxicity data for earthworms was used to demonstrate an acceptable risk at first tier, using the TER approach. The $NOEC/EC_{10}$ (whichever was worst case) was compared to the maximum PECsoil for each compound. All TER values were greater than the trigger of 5, indicating an acceptable risk.

Risk to non-target soil macro-organisms
Chronic toxicity data for soil macro-organisms were used to demonstrate an acceptable risk at first tier, using the TER approach. The $NOEC/EC_{10}$ (whichever was worst case) was compared to the maximum PECsoil for each compound. All TER values were greater than the trigger of 5, indicating an acceptable risk.

2.9.9.5 Risk assessment for soil nitrogen transformation

The maximum rate tested at which < 25 % effects occurred after 28 days was compared to the maximum PECsoil. All the tested rates exceeded the maximum PECsoil for each compound, indicating an acceptable risk to soil nitrogen transformation.

2.9.9.6 Risk assessment for effects on non-target terrestrial plants (NTP):

BAS 750 01 F is a fungicide and is therefore not expected to have any significant herbicidal activity.

According to the Terrestrial Guidance Document [*Anonymous (2002b). Guidance Document on terrestrial ecotoxicology under council directive 91/414/EEC. SANCO/10329/2002. 17 October 2002*] the risk to non-target plants should be considered acceptable if less than 50% effect on all species tested is seen at the maximum single application rate. In the seedling emergence and vegetative vigour tests with BAS 750 01 F (please see B.9.6.2 for detailed summaries), the ER_{50} exceeded the maximum intended application rate of BAS 750 01 F. It can therefore be concluded that the proposed use of BAS 750 01 F poses no unacceptable risk to non-target plants.

2.9.9.7 Risk Assessment for biological methods for sewage treatment

The risk to biological methods for sewage treatment is considered acceptable. The EC_{50} produced in the activated sewage sludge test (Hammer S., 2014a) was greater than 1000 mg a.s./L. This suggests limited risk to sewage treatment facilities. Additionally the EC_{50} is > 3000 times greater than the FOCUS step 1 initial PEC_{SW} (50.25 µg/L). Dilution prior to reaching sewage treatment works may also be expected to reduce the risk further.

2.10. 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	-	-	-	Data conclusive but not sufficient for classification
2.2.	Flammable gases	-	-	-	Hazard class not applicable (solid)
2.3.	Flammable aerosols	-	-	-	Hazard class not applicable (solid)
2.4.	Oxidising gases	-	-	-	Hazard class not applicable (solid)
2.5.	Gases under pressure	-	-	-	Hazard class not applicable (solid)
2.6.	Flammable liquids	-	-	-	Hazard class not applicable (solid)
2.7.	Flammable solids	-	-	-	Data conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	-	-	-	Data conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	-	-	-	Hazard class not applicable (solid)
2.10.	Pyrophoric solids	-	-	-	Data conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	-	-	-	Data conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	-	-	-	Data conclusive but not sufficient for classification
2.13.	Oxidising liquids	-	-	-	Hazard class not applicable (solid)
2.14.	Oxidising solids	-	-	-	Data conclusive but not sufficient for classification
2.15.	Organic peroxides	-	-	-	Data conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	-	-	-	Hazard class not applicable
3.1.	Acute toxicity - oral	-	-	-	Data conclusive but not sufficient for classification

	Acute toxicity - dermal	-	-	-	Data conclusive but not sufficient for classification
	Acute toxicity - inhalation	-	-	-	Data conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	-	-	-	Data conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	-	-	-	Data conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	-	-	-	Data lacking
3.4.	Skin sensitisation	Skin sens 1	-	-	
3.5.	Germ cell mutagenicity	-	-	-	Data conclusive but not sufficient for classification
3.6.	Carcinogenicity	-	-	-	Data conclusive but not sufficient for classification
3.7.	Reproductive toxicity	-	-	-	Data conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	-	-	-	Data conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	-	-	-	Data conclusive but not sufficient for classification
3.10.	Aspiration hazard	N/A (solid)	-	-	
4.1.	Hazardous to the aquatic environment	Classify: Acute Category 1 H400, Chronic Category 1 H410	The M factor for both acute and chronic category 1 is 1.	-	
5.1.	Hazardous to the ozone layer	-	-	-	Data 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:	Pictogram:	GHS07 GHS09
	Signal word:	'Warning'
	Hazard statements::	H317 'May cause an allergic skin reaction' H400 'Very toxic to aquatic life'* H410 'Very toxic to aquatic life with long lasting effects' * Not required on product labels to avoid duplication
	Precautionary statements:	Applicant to propose based on above Hazard Statements

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

2.11. RELEVANCE OF METABOLITES IN GROUNDWATER

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

Only two metabolites (M750F001 (1,2,4-triazole) and M750F003) were observed in laboratory studies conducted to investigate the metabolism of BAS 750 F in soil. Field studies showed no substantial formation of either of the metabolites. Thus, based on lab and field data it is not expected that 1,2,4-triazole nor M750F003 will be substantially produced from BAS 750 F field conditions. Considering the obtained information no groundwater assessment is required.

Although not a legislative requirement, the metabolite 1,2,4-triazole (M750F001) (which occurred at a maximum concentration of 5.1% AR) has been considered within the risk assessment due to its potential occurrence as a common metabolite of azole fungicides. Therefore, it has been included in the soil and groundwater exposure calculations.

Apart from M750F001 (1,2,4-triazole) and M750F003, only minor degradation products were detected in aerobic soil metabolism studies with BAS 750 F; these are not relevant for the environmental risk assessment due to their low occurrences.

Carbon dioxide is produced but is also not relevant as it is defined as a degradation product of no concern (SANCO/221/2000 – rev.10 – final).

2.11.2. STEP 2: Quantification of potential groundwater contamination

A full summary of all groundwater modelling calculations are presented in section B.8.3 of Volume 3CP, Section 8 of the DAR. All the tier 1 PEC_{GW} values resulted in concentrations <0.1 µg/L for BAS 750 F and 1,2,4-triazole. No further consideration of parent or metabolite is required and non-relevance of metabolites is addressed at Step 2.

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

2.11.3.1 STEP 3, Stage 1: screening for biological activity

Not required. See step 2 above.

2.11.3.2 STEP 3, Stage 2: screening for genotoxicity

Not required. See step 2 above.

2.11.3.3 STEP 3, Stage 3: screening for toxicity

Not required. See step 2 above.

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

Not required. See step 2 above.

2.11.5. STEP 5: Refined risk assessment

Not required as all metabolites <0.1 µg/L.

2.11.6. Overall conclusion

As noted at section 2.8.6 above, all metabolites are predicted to be <0.1 µg/L. No further consideration of relevance required.

2.12. CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

2.12.1. Identity and physical chemical properties

The approximate 1:1 ratio of the enantiomers has been experimentally demonstrated for two batches of BAS 750 F.

2.12.2. Methods of analysis

An HPLC-UV DAD method for the determination of the enantiomeric ratio of BAS 750 F in TGAI and formulations has been sufficiently validated to demonstrate that it is fit for purpose.

2.12.3. Mammalian toxicity

BAS 750 F (LS 5834378) is a racemic mixture of an (R)-enantiomer (LS 5934591) and an (S)-enantiomer (LS 5934588) in a 1:1 ratio. All mammalian toxicology studies used the racemate in a 1:1 ratio. Thus, the proposed human health risk assessment of BAS 750 F, which is based on toxicological studies with the racemic mixture, covers the worst-case human exposure scenario and adequately considers the isomeric composition of BAS 750 F. An investigation into the mammalian toxicity of the enantiomers demonstrated that the S-enantiomer was more toxicologically active (greater aromatase-inhibiting activity in an *in vitro* system) than the R-enantiomer. However, in a rat metabolism study, the ratio between S- and R-enantiomer shifted towards a higher relative amount of the R-enantiomer (approximately 20-30 % S to 70-80 % R); this indicated that there is preferential metabolism and elimination of the potentially more toxic S-enantiomer in rats.

2.12.4. Operator, Worker, Bystander and Resident exposure

The operator, worker, bystander and resident exposure assessment of BAS 750F covers the worst-case human exposure scenario and adequately considers the isomeric composition of BAS 750 F.

2.12.5. Residues and Consumer risk assessment

A slight shift in the isomeric ratio of BAS 750 F was detected in some Residues studies. The largest shift occurred in the goat metabolism study, whereby, the R-isomer was recorded at 70-80% and the S-isomer 20-30%. As the R-isomer is less toxicologically active the shift is not considered to be of concern

2.12.6. Environmental fate

A slight shift in the isomeric ratio of BAS 750 F was detected in the Fate and Behaviour studies. The largest shift occurred in the aqueous photolysis study, whereby, the R-isomer was recorded at 43.3% and the S-isomer at 56.7% at study termination; the shift is not significant enough to warrant further consideration.

2.12.7. Ecotoxciology

For soil organisms no toxicological data on each enantiomer is available. To evaluate a theoretical potential impact of such a shift, under a worst case assumption that the shift in the enantiomeric ratio would reach 0:100 of the more toxic compound and under the worst case assumption that the more toxic enantiomer is responsible for all the toxicity, all the endpoints would be halved.. There is an acceptable risk presented to all groups with the exception of earthworms based upon the worst case assumption, noting it is also acceptable for the formulation. Therefore some further consideration of the risk is required. Two earthworm field studies are available. Schulz L.,2015b (B.9.7.1/3) is considered sufficiently reliable to be used as a refinement (B.9.8.1), and indicates no toxic effects at an application rate of 6L BAS 750 01 F/ha. Hamberger A., 2015a B.9.7.1/2 is also considered sufficiently reliable to be used in risk assessments, and indicates no toxic effects at the maximum application rate of 8.0 L BAS 752 AM F/ha (800g BAS 750 F/ha and 500g BAS 700 F/ha).

2.13. RESIDUE DEFINITIONS

2.13.1. Definition of residues for exposure/risk assessment

Food of plant origin:

- parent BAS 750 F
- triazole derivative metabolites (provisional, pending the definition of a common and harmonised approach for all the active substances of the triazole chemical class)

Food of animal origin:

- animal except poultry:
  - parent BAS 750 F
  - triazole derivative metabolites (provisional, pending the definition of a common and harmonised approach for all the active substances of the triazole chemical class)
- poultry:
  - sum of parent BAS 750 F, metabolite M750F022 and fatty acid conjugates of M750F022, expressed as parent equivalents
  - triazole derivative metabolites (provisional, pending the definition of a common and harmonised approach for all the active substances of the triazole chemical class)

Soil: BAS 750 F, 1,2,4-triazole

Groundwater: BAS 750 F, 1,2,4-triazole

Surface water: BAS 750 F, 1,2,4-triazole, M750F003, M750F005, M750F006, M750F007 and M750F008

Sediment: BAS 750 F, 1,2,4-triazole, M750F003, M750F005, M750F006, M750F007 and M750F008

Air: BAS 750 F

2.13.2. Definition of residues for monitoring

Food of plant origin: BAS 750 F

Food of animal origin: BAS 750 F

Soil: BAS 750 F

Groundwater: BAS 750 F

Surface water: BAS 750 F

Sediment: BAS 750 F

Air: BAS 750 F

Level 3

BAS 750 F
(Mefentrifluconazole)

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.	✓		It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with for BAS 750F for use as a fungicide on cereals (refer to Level 1, Table 1.5.1 for details of the representative use considered).
3.1.1.2. Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted	✓		It is considered that a sufficiently complete dossier has been submitted to establish that risks are acceptable and no critical areas of concern are identified. Potential mitigation measures (see 3.3.1 below) may reasonably be expected to be managed or addressed by Member States when considering product authorisations.
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.	n/a	n/a	
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.	✓		(a) the minimum degree of purity of the active substance; 970 g/kg (b) the nature and maximum content of certain impurities; The level of the toxicologically relevant impurity DMF (N,N-dimethylformamide) in the specification is set at a maximum of 0.5 g/kg.

				(c) 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 (d) type of preparation; n/a (e) manner and conditions of application; n/a (f) 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 (g) designation of categories of users, such as professional and non-professional; n/a (h) 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 (i) the need to impose risk mitigation measures and monitoring after use; <u>Mitigation required:</u> Member States should consider the risk to aquatic organisms and in particular the need for risk mitigation in the form of no spray buffer zones and/or vegetated filter strips (j) any other particular conditions that result from the evaluation of information made available in the context of Regulation 1107/2009. Explain if some of the information to be submitted relates only to specified products/uses/use scenarios] 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).	✓		The dossier contains sufficient information to establish reference doses.
	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.	✓		The dossier contains the information necessary to carry out a risk assessment and for enforcement purposes. Residue definitions in plant and animal commodities have been determined. Residue levels in primary and succeeding crops have been determined. Consideration of processing on the magnitude of the residue has been made. Maximum residue levels have been determined for the relevant commodities. No acute or chronic risk to consumers has been identified.
	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.	✓		This is considered to apply to the representative use examined.
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.	✓		Field studies indicate sufficiently effective levels of activity of BAS 750 F against current *S tritici* populations. Overall resistance risk is categorised as 'medium'. The risk to succeeding and adjacent crops would appear to be low. The active was crop safe and there were no issues with regard to following and adjacent crops. Further information will be examined at the product stage to ensure that the product itself fully complies with the data requirements for efficacy.

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.	✓		Sufficient information provided for the representative uses.
Composition				
		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.	✓		The specification of the active substance has been set as detailed in the Volume 4 of the DAR. The minimum purity of the active substance is 970 g/kg. The identity and content of isomers/diastereoisomers, impurities and additives, where relevant, has been sufficiently addressed by the data submitted by the applicant. The content of impurities of toxicological, ecotoxicological or environmental concern have been set within acceptable limits.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	n/a	n/a	There is no relevant FAO specification.
	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	n/a	n/a	There is no relevant FAO specification.
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.	✓		The methods of analysis of the active substance and impurities of toxicological, ecotoxicological or environmental concern present at > 1g/kg in the active substance have been satisfactorily validated in accordance with SANCO/3030/99 rev.4 as detailed in the Volume 4 of the DAR..
	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.	✓		All methods of analysis for residues of the active substance and metabolites in plant, animal and environmental matrices and drinking water have been either satisfactorily validated in accordance with SANCO/3029/99 rev.4 (for pre-registration methods) and/or SANCO/825/00 rev.8.1 (for post-registration methods) or have been found to be fit for purpose.
	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.	✓		

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.	✓		Reference doses (ADI, ARfD, AOEL) can be established from the available toxicological studies (see section 2.6). These are derived from NOAELs (supported by BMDL values) as the reference points identified from standard regulatory studies, with the application of a standard safety margin of 100.
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.**		✓	A full dataset of *in vitro* toxicity studies has been conducted, in which the active substance was applied at limit or cytotoxic concentrations. All tests were negative. A valid negative result was obtained in an *in vivo* micronucleus test. It is therefore concluded that the active substance does not demonstrate any genotoxic potential. BAS 750 F does not meet the criteria for classification for germ cell mutagenicity.
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.**		✓	The long-term toxicity and carcinogenicity potential of the active substance has been investigated in rats and mice (see section 2.6.5.). There was no evidence of a treatment-related increase in tumours in either species. It is proposed that BAS 750 F should not be classified for carcinogenicity
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.	n/a	n/a	Not applicable as BAS 750 F is not considered to be a carcinogen
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 reproductive toxicity of the active substance has been investigated in a two-generation study in rats and in developmental toxicity studies in rats and

	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.**			rabbits (see section 2.6.6.). The substance did not result in specific effects on reproduction or development. It is proposed that BAS 750 F should not be classified for reproductive toxicity.
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.	n/a	n/a	Not applicable as BAS 750 F is not considered to be a a reproductive toxicant.
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**		✓	Not applicable – the active substance is proposed not to be classified for either carcinogenicity or reproductive toxicity.
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**		✓	Not applicable – the active substance is proposed not to be classified for reproductive toxicity and did not exhibit toxic effects on the endocrine organs.
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 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.	n/a	n/a	Not applicable

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.		✓	A substance is deemed to meet the P criterion in a POP assessment if the $DegT_{50}$ is > 2 months in water, > 6months in sediment or > 6months in soil. In the aerobic laboratory soil degradation studies (see Level 2 for further information), best-fit $DegT_{50}$ values ranged between 434 and >1000 days. Therefore, the RMS is of the opinion that BAS 750 F fulfils the P criterion. However, BAS 750 F does not meet the potential for long range transport criteria because it has a calculated DT_{50} in air of 1.67 days, which is below the threshold of 2 days. The log K_{OW} value of 3.4 for BAS 750 F is greater than the log K_{OW} trigger value of 3. An experimental bioconcentration study in fish is available to consider bioaccumulation further. In the experimental study, whole fish BCF values for BAS 750 F of 385 were less than 500 indicating a low potential for bioaccumulation.
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.		✓	A substance is deemed to meet the P criterion in a PBT assessment if the half-life in soil is >120 days. As indicated above, BAS 750 F fulfils this criterion. It also breaches the P criterion in the sediment system as the DT_{50} values calculated in the water/sediment study are greater than the 120 day threshold (see Level 2 for further information). Because the extent of photolysis in natural surface water is unclear, the persistence of BAS 750 F in water is not known. Therefore, it is classified as potentially persistent in water. As above, BAS 750 F is not considered bioaccumulative as the experimental lipid-normalised whole-fish BCF was 385, less than the criteria value of 500. The criteria for toxic classification is a long-term endpoint for a marine or freshwater organism of <0.01 mg/L. The both the unbounded NOEC for *Americanamysis bahia* of ≥0.0132 and the most sensitive bounded aquatic endpoint, and EC_{10} of 0.0161 for *Daphnia magna* are greater than this value, BAS 750 F is not considered toxic.

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.		✓	A substance is deemed to meet the P criterion in a vPvT assessment if the half-life in soil is >180 days. As indicated above, BAS 750 F fulfils this criterion. It is unclear if it breaches the vP criteria in water or sediment, therefore, it is classified as potentially vP in water and sediment. Whole fish BCF values for BAS 750 F of 385 were less than 5000 and therefore BAS 750 F is not classed as very bioaccumulative.
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.	✓		There is an acceptable ecotoxicological risk posed to all organisms from the proposed use of BAS 750 01 F.
	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.	n/a	n/a	Member States should note that there are currently no defined criteria for identifying endocrine disruptors or interpreting the significance of any affects in ecotoxicology studies under the Commission Regulation (EU) No. 2009/1107. Because of this, endpoints have not been defined and a risk assessment has not been conducted. It cannot be concluded if endocrine disruptive effects are or are not taking place.
	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.	n/a	n/a	There has been no further consideration of the endocrine disrupting properties.
	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	✓		An acceptable risk to bees is concluded at the first tier risk assessment with all HQs <50 for all proposed uses and applications of BAS 750 01 F considered by the assessment.

	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.			Under Commission Regulation No 283/2013 and 284/2013, chronic toxicity to adult honeybees and toxicity to honeybee brood need to be addressed. However there is currently no agreed risk assessment scheme available to assess the risk for bees based on chronic adult and/or larvae data. Therefore these data have not been used to assess the risk to this organism group, although the data have been assessed where available. The risk to bees is concluded to be acceptable based on the data available for acute toxicity to honeybees, as per current noted guidance.
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.	✓		The following environmental residues have been established: <u>For exposure/risk assessment:</u> *Food of plant origin*: parent BAS 750 F triazole derivative metabolites (provisional, pending the definition of a common and harmonised approach for all the active substances of the triazole chemical class) *Food of animal origin*: animal except poultry: - parent BAS 750 F - triazole derivative metabolites (provisional, pending the definition of a common and harmonised approach for all the active substances of the triazole chemical class) poultry: - sum of parent BAS 750 F, metabolite M750F022 and fatty acid conjugates of M750F022, expressed as parent equivalents - triazole derivative metabolites (provisional, pending the definition of a common and harmonised approach for all the active substances of the triazole chemical class)

				Soil: BAS 750 F, 1,2,4-triazole *Groundwater:* BAS 750 F, 1,2,4-triazole *Surface water:* BAS 750 F, 1,2,4-triazole, M750F003, M750F005, M750F006, M750F007 and M750F008 *Sediment:* BAS 750 F, 1,2,4-triazole, M750F003, M750F005, M750F006, M750F007 and M750F008 *Air:* BAS 750 F <u>For monitoring:</u> *All:* BAS 750 F
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.	✓		As noted at section 2.8.6 above, all metabolites are predicted to be <0.1 µg/L. No further consideration of groundwater metabolite relevance required.

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		✓	It is considered as a result of this evaluation that BAS 750F **does not meet the criteria** necessary to identify it as a candidate for substitution, i.e. it does not meet the criteria necessary to be identified as a candidate as follows: The ADI, ARfD or AOEL is not significantly lower than those of the

				majority of the approved active substances within groups of substances/use categories, It does not meet the criteria to be considered as a PBT substance. There are no 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), It does not contain a significant proportion of non-active isomers, as both enantiomers showed biological activity on all tested pathogens It is not classified or proposed for classification, 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 not classified or proposed for classification, 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, It is not considered to have endocrine disrupting properties that may cause adverse effects in humans.

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.		✓	BAS 750F **may not** be regarded as low risk because of the proposed toxicological and environmental classification: Skin Sensitisation Category 1: H317 - 'May cause an allergic skin reaction' Aquatic Acute Category 1: - 'H400 very toxic to aquatic life' Aquatic Chronic Category 1: - 'H410 very toxic to aquatic life with long lasting effects'

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				
None				
3.1.4.7. Residue data				
None.				
3.1.4.8. Environmental fate and behaviour				
None.				
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)
None identified.	All representative uses

3.1.6. Critical areas of concern

An issue is listed as a critical area of concern:
(a) where the substance does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II of Regulation (EC) No 1107/2009 and the applicant has not provided detailed evidence that the active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, taking into account risk mitigation measures to ensure that exposure of humans and the environment is minimised, or
(b) where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) 546/2011, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

Critical area of concern identified	Relevance in relation to representative use(s)
None identified	All representative uses

3.1.7. Overview table of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in 3.3.1, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)
All columns are grey as the material tested in the toxicological studies has not been demonstrated to be representative of the technical specification.

Representative use		All Uses (cereals)(X[1])
Operator risk	Risk identified	X
	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	
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified	
	Assessment not finalised	
Risk to aquatic organisms	Risk identified	X
	Assessment not finalised	
Groundwater exposure active substance	Legal parametric value breached	
	Assessment not finalised	
Groundwater exposure metabolites	Legal parametric value breached	
	Parametric value of 10µg/L[(a)] breached	
	Assessment not finalised	
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
None	*[specify the reasons why expert consultation is considered necessary]*

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
Relevant impurities	Co-RMS AT is of the opinion that [redacted] and [redacted] should be additionally considered as relevant impurities since they show additional (or more severe) toxic properties compared to BAS 750F. According to GD on technical equivalence this applies even if they are measured below 1 g/kg. For relevant impurities safe use should be demonstrated and method for analysis in PPP provided.	*As a non-genotoxic impurity of toxicological concern, an impurity concentration of [redacted] can be regarded as an acceptable upper limit concentration [see Appendix V of SANCO-10597-2003_Rev.10.1]. However, the amount of [redacted] present is actually far below this level, since it is present only in trace amounts and does not contribute towards the classification of BAS 750 F. Moreover, the presence of this impurity has been adequately addressed in the toxicology studies (the batch with the highest level was tested in the 90-day rat study and rabbit developmental toxicity study). The US-EPA has defined a conservative chronic oral reference dose (ADI) for [redacted] which is above the proposed ADI for BAS 750 F (0.04 mg/kg bw/d). On this basis, the RMS concludes that the toxicological properties of BAS 750 F will not be influenced by the presence of the impurity [redacted] in any relevant way.* *In BAS 750 F batches used for toxicological tests, [redacted] was present at low concentrations (up to [redacted], but well below 1*

		g/kg). [redacted] shows a relatively high formation from BAS 750 F via metabolism (3.1 - 20% of administered radiolabeled BAS 750 F is recovered in rat urine as [redacted] Therefore, owing to high-level formation of [redacted] via metabolism of BAS 750 F, the low [redacted] impurity levels in the TGAI would constitute only an insignificant proportion of the overall [redacted] burden (< 0.1 g/kg as impurity limit versus 31-200 g/kg ([redacted] formation via metabolism of TGAI)). Moreover, there is no indication for any significant [redacted] formation from 3-year storage data available for TGAI batches. The available data clearly indicates that at the low-level impurity levels of [redacted] in TGAI (less than 1 g/kg), the toxicological properties of the TGAI will not be influenced in any relevant way. Therefore, by comparison with the active substance BAS 750 F and consideration of its metabolism, [redacted] is not considered to fulfil the definition of a "relevant impurity" of BAS 750 F TGAI.
ARfD/ AAOEL	*Both Co-RMSs have proposed a lower ARfD and AAOEL based on a reduced NOAEL (15 mg/kg bw/d) in the rabbit developmental toxicity study, on the basis of maternal toxicity (reduced body-weight gain on gestation days 0-7 compared with controls) at 25 mg/kg bw/d. FR has also taken into account its proposed developmental toxicity NOAEL of 15 mg/kg bw/d in setting the ARfD.*	*The RMS proposes that the ARfD and AAOEL are 0.25 mg/kg bw/d, based upon a maternal NOAEL in this study of 25 mg/kg bw/d (the highest dose tested). The reduction in body-weight gain early in the study occurred before treatment commenced (on gestation day 6). The mean carcass weights and corrected body weight were comparable between all the groups. The RMS concluded that there was no evidence of a specific effect on development in this study. The RMS considers that the maternal and developmental NOAEL is 25 mg/kg bw/d.*
AOEL/ADI	*Co-RMS AT proposed the ADI/AOEL to be derived upon an overall mouse NOAEL from 90 days and chronic mouse study and this to be at 3.5 mg/kg bw/d (based on dose spacing). Both ADI and AOEL would than result in 0.035 mg/kg*	*The RMS proposes that the AOEL be based on the 90-day mouse study with a NOAEL of 11 mg/kg bw/d and a BMDL of 14 mg/kg bw/d, which had a relatively small confidence interval. This study was well conducted and suitable for the*

	bw/d.	*setting of NOAEL and LOAEL values and thus an AOEL. Therefore the systemic AOEL is 0.11 mg/kg bw/d. Additional findings at the LOAEL of the 18-month study reflect an exacerbation of age-related effects that are seen also in controls (fatty change) of the 18-month study but are not observed in the 90-day study up to the highest dose tested.* *A BMDL value of 5 mg/kg bw/d (with a small confidence interval) was obtained from the 18-month mouse study. Dose-spacing is taken into account in the BMD approach; therefore this approach supports a higher value for the AOEL than for the ADI.* *The ADI and AOEL are thus consistent with each other, since one would normally expect a shorter duration of exposure to result in a higher reference value, in agreement with Haber's rule that toxicity is a function of time and dose.*
Honey bee risk assessment	*The risk assessment for honey bees was conducted according to the Terrestrial Guidance Document (SANCO/10329/2002) and the EPPO Scheme (1992). Co-RMS AT agrees with the RMS UK and the Co-RMS France that the EFSA Guidance Document (EFSA Journal 2013;11(7):3295) has not yet been noted by the Standing Committee on Plants, Animals, Food and Feed. However, AT is of the opinion that the EFSA Guidance Document should nevertheless be used for the bee risk assessment to cover the chronic risk to bees (adults and larvae) and other routes of exposure (e.g. drinking water and guttation water,...) which are not yet considered in the honey bee assessment.*	The EFSA guidance referred to has not been noted at the EU level. Therefore RMS policy is to use the SANCO terrestrial guidance document, being the current noted guidance. The RMS agrees that there is not currently an agreed approach whereby these data can be used in the regulatory risk assessment. There have studies been performed to address the Annex points 8.3.1.1, 8.3.1.2 and 8.3.1.3 of Regulation 283/2013 and submitted with the application, but this is before the implementation of the relevant EFSA guidance document (EFSA Journal 2013;11(7):3295). The RMS has assessed these studies; however, a formal risk assessment using these data will not be performed.

3.2. PROPOSED DECISION

[redacted]

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

[redacted]

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

3.4. APPENDICES

GUIDANCE DOCUMENTS USED IN THIS ASSESSEMENT

General:

- Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under council directive 91/414/EEC **Sanco/221/2000 rev.10**

- Guidance on the application of the CLP criteria; guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures **Version 4.0 June 2015**

Volume 3 B5: Analytical Methods:

- SANCO/3030/99 rev.4: Technical Material and preparations: guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414

- SANCO/3029/99 rev .4: Residues: guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, section 4) and Annex III (part A, Section 5) of directive 91/414

- SANCO/825/00 rev.8.1: Guidance document on pesticide residues analytical methods

Volume 3 B6: Mammalian toxicology:

- *Guidance on Dermal Absorption; EFSA Panel on Plant Protection Products and their Residues (PPR)*. **EFSA Journal 2012; 10(4): 2665**

- FAO/WHO, 2006: Pesticide residues in food - 2006. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues.

- WHO, 2015: Pesticide residues in food: WHO Core Assessment Group on Pesticide Residues. Guidance document for WHO monographers and reviewersWHO/HSE/GOS/2015.1, 1-106 pp.

- WHO / IPCS, 2002: Global assessment of the state-of-the-science of endocrine disruptors. WHO/IPCS/EDC/02.2.

Volume 3 B7: Residues:

- EC (European Commission), 2010. Classes to be used for the setting of EU pesticide Maximum Residue Levels (MRLs). SANCO 10634/2010 Rev. 0, finalized in the Standing Committee on the Food Chain and Animal Health at its meeting of 23-24 March 2010.

- EC (European Commission), 2016. Appendix D. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. 7525/VI/95-rev.10.2.

- FAO (Food and Agriculture Organization of the United Nations), 2009. Submission and evaluation of pesticide residues data for the estimation of Maximum Residue Levels in food and feed. Pesticide Residues. 2nd Ed. FAO Plant Production and Protection Paper 197, 264 pp.

- OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in crops. No. 501, OECD, Paris 2007.

- OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in rotational crops. No 502, Paris 2007.

- OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in livestock, No. 503, OECD, Paris 2007.

- OECD, 2007, OECD Guidelines for the testing of chemicals – Residues in rotational crops (limited field studies). No 504, Paris 2007.

- OECD, 2007. OECD Guidelines for the testing of chemicals – Stability of pesticide residues in stored commodities. No 506, OECD, Paris 2007.

- OECD, 2007. OECD Guidelines for the testing of chemicals – Nature of the pesticide residues in processed commodities, high temperature hydrolysis. No 507, Paris 2007.

- OECD, 2008. OECD Guidelines for the testing of chemicals – Magnitude of pesticide residues in processed commodities. No 508, Paris 2008.

- OECD, 2009. OECD Guidelines for the testing of chemicals – Crop field trial. No 509, Paris 2009.

- OECD, 2009, Guidance document on the definition of residue, (ENV/JM/MONO(2009)30), Series on testing and assessment No. 63 and Series on pesticides No. 31

- Residues trials and MRL calculations, Proposals for a harmonised approach for the selection of the trials and data used for the estimation of MRL, STMR and HR, EFSA, September 2015

- Estimation of animal intakes and HR, STMR and MRL calculations for products of animal origin, EFSA, September 2015

Volume 3 B8: Environmental Fate and Behaviour:

- Generic guidance for Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration; FOCUS, version 1.1, 18 December 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; European Food Safety Authority, 23 July 2014, EFSA Journal 2014; 12(5):3662.

- Evidence Needed to Identify POP, PBT and vPvB Properties for Pesticides; DG SANCO Working Document, Brussels, 25.09.2012 – rev. 3.

- Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT/vPvB Assessment; European Chemicals Agency, Version 2.0 – November 2014, ECHA-14-G-07-EN.

- Generic Guidance for Tier 1 FOCUS Ground Water Assessments; FOCUS, Version 2.2, May 2014.

- Generic guidance for FOCUS surface water Scenarios; FOCUS, Version 1.4, May 2015.

- European Commission, 2003. Guidance Document on Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated under Council Directive 91/414/EEC. SANCO/221/2000-rev. 10 - final, 25 February 2003.

Volume 3 B9: Ecotoxicology:

- European Food Safety Authority; Guidance Document on Risk Assessment for Birds & Mammals, EFSA Journal 2009; 7(12):1438.

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

- GUIDANCE DOCUMENT ON THE ASSESSMENT OF THE EQUIVALENCE OF TECHNICAL MATERIALS OF SUBSTANCES REGULATED UNDER Regulation (EC) No 1107/2009, SANCO/10597/2003 –rev. 10.1, 13 July 2012

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