



# Draft Assessment Report

## Evaluation of Active Substances

Plant Protection Products

Prepared according to **Regulation (EC) 1107/2009**  
as it applies in Great Britain (GB PPP)

### Cinmethylin (BAS 684 H)

### Volume 1

Great Britain

November 2020

**Version History**

<b>When</b>	<b>What</b>
November 2020	Initial DAR

## Table of contents

<b>1. STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THIS REPORT HAS BEEN PREPARED AND BACKGROUND INFORMATION ON THE APPLICATION .....</b>	<b>7</b>
<b>1.1. CONTEXT IN WHICH THIS DRAFT ASSESSMENT REPORT WAS PREPARED.....</b>	<b>7</b>
1.1.1. Purpose for which the draft assessment report was prepared .....	7
1.1.2. Regulatory history for use in Plant Protection Products .....	7
1.1.3. Evaluations carried out under other regulatory contexts .....	7
<b>1.2. APPLICANT INFORMATION .....</b>	<b>8</b>
1.2.1. Name and address of applicant(s) for approval of the active substance .....	8
1.2.2. Producer or producers of the active substance .....	8
1.2.3. Information relating to the collective provision of dossiers.....	8
<b>1.3. IDENTITY OF THE ACTIVE SUBSTANCE .....</b>	<b>8</b>
1.3.1. Common name proposed or ISO-accepted and synonyms .....	8
1.3.2. Chemical name (IUPAC and CA nomenclature) .....	8
1.3.3. Producer's development code number .....	9
1.3.4. CAS, EEC and CIPAC numbers .....	9
1.3.5. Molecular and structural formula, molecular mass .....	9
1.3.6. Method of manufacture (synthesis pathway) of the active substance .....	9
1.3.7. Specification of purity of the active substance in g/kg.....	9
1.3.8. Identity and content of additives (such as stabilisers) and impurities .....	9
1.3.9. Analytical profile of batches .....	9
<b>1.4. INFORMATION ON THE PLANT PROTECTION PRODUCT.....</b>	<b>10</b>
<b>1.5. DETAILED USES OF THE PLANT PROTECTION PRODUCT .....</b>	<b>11</b>
1.5.1. Details of representative uses .....	11
1.5.2. Further information on representative uses .....	16
1.5.3. Details of other uses applied for to support the setting of MRLs for uses beyond the representative uses .....	17
1.5.4. Overview on authorisations in EU Member States .....	17
<b>2. SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT.....</b>	<b>19</b>
<b>2.1. IDENTITY .....</b>	<b>19</b>
<b>2.2. PHYSICAL AND CHEMICAL PROPERTIES .....</b>	<b>19</b>
2.2.1. Summary of physical and chemical properties of the active substance .....	19
2.2.2. Summary of physical and chemical properties of the plant protection product .....	19
<b>2.3. DATA ON APPLICATION AND EFFICACY.....</b>	<b>20</b>
2.3.1. Summary of effectiveness .....	20
2.3.2. Summary of information on the development of resistance .....	20
2.3.3. Summary of adverse effects on treated crops.....	20
2.3.4. Summary of observations on other undesirable or unintended side-effects .....	21
<b>2.4. FURTHER INFORMATION .....</b>	<b>21</b>
2.4.1. Summary of methods and precautions concerning handling, storage, transport or fire .....	21
2.4.2. Summary of procedures for destruction or decontamination .....	21
2.4.3. Summary of emergency measures in case of an accident .....	21
<b>2.5. METHODS OF ANALYSIS.....</b>	<b>22</b>
2.5.1. Methods used for the generation of pre-authorisation data .....	22
2.5.2. Methods for post control and monitoring purposes.....	22

<b>2.6. EFFECTS ON HUMAN AND ANIMAL HEALTH .....</b>	<b>24</b>
2.6.1. Summary of absorption, distribution and excretion in mammals .....	24
2.6.2. Summary of acute toxicity .....	27
2.6.3. Summary of short-term toxicity .....	31
2.6.4. Summary of genotoxicity .....	38
2.6.5. Summary of long-term toxicity and carcinogenicity .....	40
2.6.6. Summary of reproductive toxicity .....	43
2.6.7. Summary of neurotoxicity .....	48
2.6.8. Summary of further toxicological studies on the active substance .....	49
2.6.9. Summary of toxicological data on impurities and metabolites .....	51
2.6.10. Summary of medical data and information .....	52
2.6.11. Overview of all available studies relevant to reference value setting .....	52
2.6.12. Toxicological end point for assessment of risk following long-term dietary exposure – ADI .....	60
2.6.13. Toxicological end point for assessment of risk following acute dietary exposure – ARfD (acute reference dose) .....	60
2.6.14. Toxicological end point for assessment of occupational, bystander and residents risks – AOEL .....	61
2.6.15. Toxicological end point for assessment of occupational, bystander and residents risks – AAOEL .....	61
2.6.16. Summary of product exposure and risk assessment .....	61
<b>2.7. RESIDUE .....</b>	<b>63</b>
2.7.1. Summary of storage stability of residues .....	63
2.7.2. Summary of metabolism, distribution and expression of residues in plants, poultry, lactating ruminants, pigs and fish .....	64
2.7.3. Definition of the residue .....	89
2.7.4. Summary of residue trials in plants and identification of critical GAP .....	97
2.7.5. Summary of feeding studies in poultry, ruminants, pigs and fish .....	99
2.7.6. Summary of effects of processing .....	101
2.7.7. Summary of residues in rotational crops .....	102
2.7.8. Summary of other studies .....	102
2.7.9. Estimation of the potential and actual exposure through diet and other sources .....	103
2.7.10. Proposed MRLs and compliance with existing MRLs .....	113
2.7.11. Proposed import tolerances and compliance with existing import tolerances .....	113
<b>2.8. FATE AND BEHAVIOUR IN THE ENVIRONMENT .....</b>	<b>113</b>
2.8.1. Summary of fate and behaviour in soil .....	113
2.8.2. Summary of fate and behaviour in water and sediment .....	121
2.8.3. Summary of fate and behaviour in air .....	124
2.8.4. Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products .....	125
2.8.5. Definition of the residues in the environment requiring further assessment .....	125
2.8.6. Summary of exposure calculations and product assessment .....	125
<b>2.9. EFFECTS ON NON-TARGET SPECIES .....</b>	<b>132</b>
2.9.1. Summary of effects on birds and other terrestrial vertebrates .....	132
2.9.2. Summary of effects on aquatic organisms .....	134
2.9.3. Summary of effects on arthropods .....	137
2.9.4. Summary of effects on non-target soil meso- and macrofauna .....	140
2.9.5. Summary of effects on soil nitrogen transformation .....	141
2.9.6. Summary of effects on terrestrial non-target higher plants .....	141
2.9.7. Summary of effects on other terrestrial organisms (flora and fauna) .....	142
2.9.8. Summary of effects on biological methods for sewage treatment .....	142
2.9.9. Summary of product exposure and risk assessment .....	142
<b>2.10. CLASSIFICATION AND LABELLING .....</b>	<b>154</b>
<b>2.11. RELEVANCE OF METABOLITES IN GROUNDWATER .....</b>	<b>154</b>
<b>2.12. CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT .....</b>	<b>154</b>
2.12.1. Identity and physical chemical properties .....	154

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2.12.2. Methods of analysis.....	155
2.12.3. Mammalian toxicity .....	155
2.12.4. Operator, Worker, Bystander and Resident exposure .....	160
2.12.5. Residues and Consumer risk assessment.....	160
2.12.6. Environmental fate .....	161
2.12.7. Ecotoxicology .....	163
<b>2.13. RESIDUE DEFINITIONS .....</b>	<b>190</b>
2.13.1. Definition of residues for exposure/risk assessment.....	190
2.13.2. Definition of residues for monitoring .....	190
<b>3. PROPOSED DECISION WITH RESPECT TO THE APPLICATION.....</b>	<b>192</b>
<b>3.1. BACKGROUND TO THE PROPOSED DECISION .....</b>	<b>192</b>
3.1.1. Proposal on acceptability against the decision making criteria – Article 4 and annex II of Regulation No 1107/2009.....	192
3.1.2. Proposal – Candidate for substitution .....	203
3.1.3. Proposal – Low risk active substance.....	205
3.1.4. List of studies to be generated, still ongoing or available but not peer reviewed .....	206
3.1.5. Issues that could not be finalised.....	209
3.1.6. Critical areas of concern.....	209
3.1.7. Overview table of the concerns identified for each representative use considered .....	210
3.1.8. Area(s) where expert consultation is considered necessary .....	211
<b>3.2. PROPOSED DECISION .....</b>	<b>216</b>
<b>3.3. RATIONALE FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH THE APPROVAL OR AUTHORISATION(S), AS APPROPRIATE .....</b>	<b>216</b>
3.3.1. Particular conditions proposed to be taken into account to manage the risks identified .....	216
<b>3.4. APPENDICES .....</b>	<b>217</b>
<b>3.5. REFERENCE LIST .....</b>	<b>220</b>

# Level 1

**CINMETHYLIN**

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

### **1.1. CONTEXT IN WHICH THIS DRAFT ASSESSMENT REPORT WAS PREPARED**

#### **1.1.1. Purpose for which the draft assessment report was prepared**

This draft assessment report has been prepared to evaluate the dossier for the new, pesticidal active substance BAS 684 H (ISO provisionally approved name: cinmethylin) and its formulated product BAS 684 03 H. This dossier was submitted by BASF Agro B.V. (“BASF”) for the first approval of this substance in Great Britain (GB) under Regulation No 1107 with the evaluation performed by the Chemicals Regulation Division of the Health and Safety Executive. BASF also have an ongoing application for the approval of cinmethylin as a new active substance in the EU, with the evaluation being performed by the Netherlands as Rapporteur Member State (RMS).

Cinmethylin is a herbicide with residual activity applied to winter cereals and oilseed rape to control the growth of annual grasses and several broadleaf weed species. The original GB dossier was the same as the dossier submitted to Europe and contains data and information to support several representative uses of the active substance to demonstrate that, for the representative product BAS 684 03H, the requirements of Regulation 1107, Article 4 can be met.

BAS 684 03 H, is an emulsifiable concentrate (EC) formulation containing 750 g active substance/L. The current GB product application is for approval of BAS 684 03H for use on winter cereals (winter wheat and winter barley). However, the representative uses of BAS 684 03 H presented in the dossier, and evaluated in this report, are for the use of BAS 684 03H on winter cereals (winter wheat and winter barley) and oilseed rape. These uses are the proposed major applications of cinmethylin and have been evaluated as they are representative of exposure scenarios that allow an appropriate evaluation of the risk to humans and the environment from the use of cinmethylin.

This dossier is the application for the first approval of BAS 684 H in accordance with Regulation 1107. Currently, BAS 684 H does not have an entry under Annex VI of Regulation (EC) No 1272/2008. However, a mandatory classification and labelling report has been prepared under GB CLP by HSE, with HSE acting as the Agency. This will be submitted to the Secretary of State, with consent from the devolved administrations to follow the aligned evaluation process.

#### **1.1.2. Regulatory history for use in Plant Protection Products**

BAS 684 H (cinmethylin) is a new active substance and products containing it have not previously been authorised in Great Britain.

#### **1.1.3. Evaluations carried out under other regulatory contexts**

Cinmethylin is a new, herbicidal active substance developed by the applicant (BASF). BASF provided a dossier in support of their application for the first approval of this pesticide in Great Britain in accordance with Regulation No. 1107. No registrations or authorisations of cinmethylin-containing plant protection products currently exist in the UK or EU Member States, however, there is an authorisation for a product in Australia.

There is also an ongoing application for the approval of cinmethylin as a new active substance in the EU, with the evaluation being performed by the Netherlands as Rapporteur Member State (RMS) and France as co-Rapporteur Member State (co-RMS). The applicant has not provided details of any other evaluations by non-EU countries or international organisations, nor of any information exchange within the OECD. Furthermore, no other relevant EU-evaluations of the active substance have been carried out under other EU-legislation.

**1.2. APPLICANT INFORMATION****1.2.1. Name and address of applicant(s) for approval of the active substance**

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

Contact person:

[REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]

**1.2.2. Producer or producers of the active substance**Producer of Cinmethylin (legal entity)

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

Contact person:

[REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]

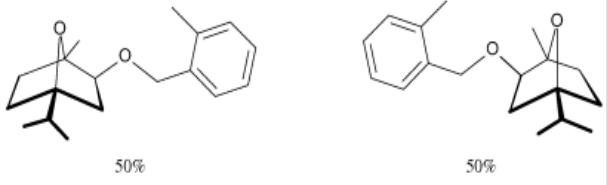
**1.2.3. Information relating to the collective provision of dossiers**

BASF Agro B.V. Arnhem (NL), Freienbach Branch, is the only applicant and owner of a complete data package regarding the new active substance BAS 684 H.

**1.3. IDENTITY OF THE ACTIVE SUBSTANCE**

<b>1.3.1. Common name proposed or ISO-accepted and synonyms</b>	Cinmethylin (ISO 1750 published)
<b>1.3.2. Chemical name (IUPAC and CA nomenclature)</b>	
IUPAC	<i>rac</i> -(1 <i>R</i> ,2 <i>S</i> ,4 <i>S</i> )-1-methyl-4-(1-methylethyl)-2-[(2-methylphenyl)methoxy]-7-oxabicyclo[2.2.1]heptane
CA	<i>rel</i> -(1 <i>R</i> ,2 <i>S</i> ,4 <i>S</i> )-1-methyl-4-(1-methylethyl)-2-[(2-methylphenyl)methoxy]-7-oxabicyclo[2.2.1]heptane



<b>1.3.3. Producer's development code number</b>	BAS 684 H Reg.No. 900202 SES2558 CL 180828 (SD95481) (WL95481) (IN-YA168) (IN-42326) (N.B. 5103-156)
<b>1.3.4. CAS, EEC and CIPAC numbers</b>	
CAS	87818-31-3
EEC	Not yet assigned
CIPAC	Not yet listed
<b>1.3.5. Molecular and structural formula, molecular mass</b>	
Molecular formula	C <sub>18</sub> H <sub>26</sub> O <sub>2</sub>
Structural formula	
Molecular mass	274.40 g/mol
<b>1.3.6. Method of manufacture (synthesis pathway) of the active substance</b>	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR.
<b>1.3.7. Specification of purity of the active substance in g/kg</b>	Minimum purity: 940 g/kg
<b>1.3.8. Identity and content of additives (such as stabilisers) and impurities</b>	
<i>1.3.8.1. Additives</i>	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR
<i>1.3.8.2. Significant impurities</i>	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR
<i>1.3.8.3. Relevant impurities</i>	<b>Reg No. 4359586</b> (1SR,2RS,4RS)-1-methyl-4-(propan-2-yl)-7-oxabicyclo[2.2.1]heptan-2-ol : <b>4 g/kg</b> ;  <b>Toluene: 0.5 g/kg</b>
<b>1.3.9. Analytical profile of batches</b>	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR

**1.4. INFORMATION ON THE PLANT PROTECTION PRODUCT**

<b>1.4.1.</b> Applicant	BASF Agro B.V., Arnhem (NL) – Freienbach Branch Huobstrasse, 3 8808 Pfäffikon SZ Switzerland
<b>1.4.2.</b> Producer of the plant protection product	BASF Agro B.V., Arnhem (NL) – Freienbach Branch Huobstrasse, 3 8808 Pfäffikon SZ Switzerland
<b>1.4.3.</b> Trade name or proposed trade name and producer's development code number of the plant protection product	Cinmethylin Proposed registered trademarks (synonyms): Luximo, Teqimo, Consuris Code number: BAS 684 03 H, BAS 684 AL H
<b>1.4.4.</b> Detailed quantitative and qualitative information on the composition of the plant protection product	
<b>1.4.4.1. Composition of the plant protection product</b>	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR
<b>1.4.4.2. Information on the active substances</b>	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR
<b>1.4.4.3. Information on safeners, synergists and co-formulants</b>	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR
<b>1.4.5.</b> Type and code of the plant protection product	Emulsifiable Concentrate [code : EC]
<b>1.4.6.</b> Function	Herbicide
<b>1.4.7.</b> Field of use envisaged	Use in agriculture as a soil residual herbicide applied pre – to post-emergence of cereals and oilseed rape.
<b>1.4.8.</b> Effects on harmful organisms	<p>Cinmethylin provides soil residual and foliar activity, with application either before or after weed emergence, leading to root and shoot growth inhibition of sensitive plants. After uptake, cinmethylin is translocated acropetally within the xylem.</p> <p>After green leaf area starts to show symptoms of discoloration and yellowing, affected plants wither and die back due to starvation of the plant as absorbed sunlight can no longer be transformed into energy to sustain plant viability.</p>

## 1.5. DETAILED USES OF THE PLANT PROTECTION PRODUCT

### 1.5.1. Details of representative uses

#### 1.5.1.1 Initial Intended Uses in Great Britain

Crop and/or situation (a)	Region	Product Name	F G I (b)	Pests or group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					Type (d-f)	Rate L/ha	Method kind (f-h)	Growth stage and season (j)	Number min max (k)	Interval between applications (min)	Kg a.i./ha min max (g/hl)	Water l/ha min max	Lk a.i./ha min max (*) (g/ha)		
winter wheat (TRZAW), winter barley (HORVW)	GB	BAS 684 03 H	F	blackgrass (ALOMY), ryegrass (LOLSS),	-	0.666	SP	pre-emergence (BBCH 00-08)	a) 1 b) 1	N/A	a) 0.500 b) 0.500	100 -400	-	-	Representative use
winter wheat (TRZAW), winter barley (HORVW)	GB	BAS 684 03 H	F	blackgrass (ALOMY), ryegrass (LOLSS),	-	0.666	SP	post-emergence (BBCH 09-29)	a) 1 b) 1	N/A	a) 0.500 b) 0.500	100 – 400	-	-	Representative use
winter wheat (TRZAW), winter barley (HORVW)	GB	BAS 684 03 H	F	annual meadowgrass (POAAN) and annual dicots	-	0.666	SP	pre-emergence (BBCH 00-08)	a) 1 b) 1	N/A	a) 0.250 b) 0.250	100 – 400	-	-	Representative use
winter wheat (TRZAW), winter barley (HORVW)	GB	BAS 684 03 H	F	annual meadowgrass (POAAN) and annual dicots	-	0.666	SP	post-emergence (BBCH 09-29)	a) 1 b) 1	N/A	a) 0.250 b) 0.250	100 - 400	-	-	Representative use

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

- (a) For crops, the EU and Codex classification (both) should be taken into account ; where relevant, the use situation should be described (e.g. fumigation of a structure)
- (b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)
- (c) e.g. biting and suckling insects, soil born insects, foliar fungi, weeds
- (d) e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
- (e) GCPF Codes – GIFAP Technical Monograph N° 2, 1989
- (f) All abbreviations used must be explained
- (g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
- (h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant – type of equipment used must be indicated

(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **In certain cases, where only one variant synthesised, it is more appropriate to give the rate for the variant (e.g. benthialvalicarb-isopropyl).**

(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application

(k) Indicate the minimum and maximum number of application possible under practical conditions of use

(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha)

(m) PHI - minimum pre-harvest interval

**1.5.1.2 Representative Uses covered in the dossier**

BAS 684 03 H

PPP (BAS 684 03 H)

active substance

cinmethylin

safener

n.a.

synergist

n.a.

Applicant:

BASF

Zone(s):

central/southern

Field of use

Herbicide

Formulation type

EC

Conc. of as:

750 g/L

Conc. of safener:

n.a.

Conc. of synergist:

n.a.

professional use

X

non professional use

Use- No.	Region/EU 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:
					Method / kind	Timing / Growth stage of crop & season	Max. number (min. interval between applicatio ns)  a) per use  b) per crop / season	kg/L product / ha a) max. rate per appl.  b) max. total rate per crop/season	Kg as/ha a) Max rate per appl. b) max. total rate per crop/seas on	Water L/ha  Min - max		
	Central Zone											

1	BE, DE, NL, UK	winter wheat (TRZAW)	F	blackgrass (ALOMY), ryegrass (LOLSS), windgrass (APESV), annual bluegrass (POAAN) and annual dicots	SP	pre-emergence (BBCH 00-08)	a) 1 b) 1	a) 0,666 b) 0,666	0,500 0,500	100 - 400		representative use
2	BE, DE, NL, UK	winter wheat (TRZAW)	F	blackgrass (ALOMY), ryegrass (LOLSS), windgrass (APESV), annual bluegrass (POAAN) and annual dicots	SP	post- emergence (BBCH 09-29)	a) 1 b) 1	a) 0,666 b) 0,666	0,500 0,500	100 - 400		representative use
3	BE, DE,NL,UK	winter wheat (TRZAW)	F	windgrass (APESV), annual bluegrass (POAAN) and annual dicots	SP	pre-emergence (BBCH 00-08)	a) 1 b) 1	a) 0,333 b) 0,333	0,250 0,250	100 - 400		representative use
4	BE, DE,NL,UK	winter wheat (TRZAW)	F	windgrass (APESV), annual bluegrass (POAAN) and annual dicots	SP	post- emergence (BBCH 09-29)	a) 1 b) 1	a) 0,333 b) 0,333	0,250 0,250	100 - 400		representative use

5	BE, DE,NL,UK	winter oilseed rape (BRSNW)	F	windgrass (APESV), annual bluegrass (POAAN) and annual dicots	SP	pre-emergence (BBCH 00-08)	a) 1 b) 1	a) 0,333 b) 0,333	0,250 0,250	100 - 400		representative use
6	BE, DE,NL,UK	winter oilseed rape (BRSNW)	F	windgrass (APESV), annual bluegrass (POAAN) and annual dicots	SP	post- emergence (BBCH 09-18)	a) 1 b) 1	a) 0,333 b) 0,333	0,250 0,250	100 - 400		representative use
	Southern Zone											
1	FR	winter wheat (TRZAW)	F	blackgrass (ALOMY), ryegrass (LOLSS), annual bluegrass (POAAN) and annual dicots	SP	BBCH 00-08	a) 1 b) 1	a) 0,666 b) 0,666	0,500 0,500	100 - 400		representative use
2	FR	winter wheat (TRZAW)	F	blackgrass (ALOMY), ryegrass (LOLSS), annual bluegrass (POAAN) and annual dicots	SP	BBCH 09-29	a) 1 b) 1	a) 0,666 b) 0,666	0,500 0,500	100 - 400		representative use

3	FR	winter wheat (TRZAW)	F	windgrass (APESV), annual bluegrass (POAAN) and annual dicots	SP	pre-emergence (BBCH 00-08)	a) 1 b) 1	a) 0,333 b) 0,333	0,250 0,250	100 - 400		representative use
4	FR	winter wheat (TRZAW)	F	windgrass (APESV), annual bluegrass (POAAN) and annual dicots	SP	post-emergence (BBCH 09-29)	a) 1 b) 1	a) 0,333 b) 0,333	0,250 0,250	100 - 400		representative use
5	FR	winter oilseed rape (BRSNW)	F	windgrass (APESV), annual bluegrass (POAAN) and annual dicots	SP	pre-emergence (BBCH 00-08)	a) 1 b) 1	a) 0,333 b) 0,333	0,250 0,250	100 - 400		representative use
6	FR	winter oilseed rape (BRSNW)	F	windgrass (APESV), annual bluegrass (POAAN) and annual dicots	SP	post-emergence (BBCH 09-18)	a) 1 b) 1	a) 0,333 b) 0,333	0,250 0,250	100 - 400		representative use

- \* For uses where the column „Remarks“ in marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s).
- (a) For crops, the EU and Codex classification (both) should be taken into account ; where relevant, the use situation should be described (e.g. fumigation of a structure)
- (b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)
- (c) e.g. biting and suckling insects, soil born insects, foliar fungi, weeds
- (d) e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
- (e) GCPF Codes – GIFAP Technical Monograph N° 2, 1989
- (f) All abbreviations used must be explained
- (g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
- (h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant – type of equipment used must be indicated
- (i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **In certain cases, where only one variant synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**
- (j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
- (k) Indicate the minimum and maximum number of application possible under practical conditions of use
- (l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha)
- (m) PHI - minimum pre-harvest interval

### 1.5.2. Further information on representative uses

#### Method of Application

Cinmethylin containing products are used as soil residual herbicides applied in a pre- to post-emergence situation during early development of the crop. Spray solution is prepared by diluting BAS 684 03 H at a max. dose rate of 500 g ai/ha in 100-400 l/ha water as the spray carrier. Application can be made through all conventional sprayers by using finely distributing nozzles. Calibration of the spray equipment needs to be ensured according to manufactures instruction.

#### Number and timing of applications and duration of protection

BAS 684 03 H can provide soil residual control during the most critical early development period of winter cereals and oilseed rape. Weeds are efficiently controlled when the application is made prior to their emergence up to the development of the first leaves (BBCH 11/12).

Maximum number of applications and their timings:	1
Growth stages of crops or plants to be protected: <ul style="list-style-type: none"> <li>• Winter wheat and winter barley</li> <li>• Winter oilseed rape*</li> </ul>	BBCH 00-29 BBCH 00-18
Development stages of the harmful organism concerned:	BBCH 00-13
Duration of protection afforded by each application:	during the most critical early development period of cereals and oilseed rape
Duration of protection afforded by the maximum number of applications:	---

NB. \* = Currently not a proposed use in GB

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

**Report:** CP 3.7/1  
Sievernich B., 2018 a  
Succeeding crop report BAS 684 H  
2018/1050815

**Guidelines:** EPPO PP1/207 (2)

**GLP:** no

After normal harvest of a crop treated with BAS 684 03 H, all crops can be sown following on from a normal crop harvest. Further trial work is running to investigate on waiting periods required to replace the treated crop in case of a crop failure (e.g. winter kill). Results will be summarized and discussed with the biological assessment dossier for the corresponding product approval.

#### Proposed instructions for use

Cinmethylin containing products are proposed for use in agriculture as a soil residual herbicide applied pre- to post-emergence of winter cereals and oilseed rape.



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

MRLs have been proposed based on the GB uses (Table 1.5.1.1) of wheat and barley – see Volume 1, Section 2.7.10.

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

**1.5.4. Overview on authorisations in EU Member States**

Whilst cinmethylin is not yet approved in the EU, an application is currently undergoing consideration for the approval of cinmethylin as a new active substance (NAS) within the EU (the Netherlands are RMS). Therefore, there are currently no authorisations for the use of plant protection products containing cinmethylin within EU Member States. The representative uses being considered in the EU cinmethylin application are detailed under Volume 1, Section 1.5., Table 1.5.1.2 above.

## **Level 2**

**CINMETHYLIN**

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

### **2.1. IDENTITY**

Acceptable data have been submitted to support the manufacturing site of cinmethylin and the proposed specification based on full scale manufacturing is considered supported by the available data. The following impurities identified in technical cinmethylin are considered to be of toxicological or ecotoxicological relevance:

<b>Reg No 4539586:</b> (1SR,2RS,4RS)-1-methyl-4-(propan-2-yl)-7-oxabicyclo[2.2.1]heptan-2-ol:	<b>Max. 4 g/kg</b>
<b>Toluene:</b>	<b>Max. 0.5 g/kg</b>

### **2.2. PHYSICAL AND CHEMICAL PROPERTIES**

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

Cinmethylin is a clear colorless liquid with faint fruity smell, with a boiling point of 330 °C (pure). Cinmethylin is not classified as flammable, explosive, or oxidising. The autoignition temperature of Cinmethylin technical material 375 °C with a flashpoint of 156.5 °C. The pure active substance is almost insoluble in pure water (0.058 g/L at pH 7.0), with no dissociation observed with the pH range 3.2 - 10.9 and a n-octanol/water partition coefficient log P<sub>OW</sub> of 4.5 at 20 °C. UV/VIS, IR, NMR, and MS spectra are available for the active substance.

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

The representative formulation BAS 684 03 H is an emulsifiable concentrate (EC) containing 750 g/L of the active substance Cinmethylin with proposed in-use concentrations of 0.0825 - 0.666 %v/v.

The appearance of the product is that of clear light yellow liquid with an faint ether-like odour. It is considered not to have explosive and oxidising properties. It is considered not (highly) flammable, as the flash point was measured at 145 °C. It has an auto-ignition temperature of 353 °C, which indicates that the formulation is not self-heating. When diluted with 1 % deionised water or CIPAC water D the pH value is 6.5. The kinematic viscosity at 40 °C is 21.3 mm<sup>2</sup>/s, therefore the formulation is not classified as an aspiration hazard. The surface tension of the neat formulation is 26.3 mN/m and at a dilution of 0.7 % and 0.03 % of 33.7 mN/m and 42.6 mN/m respectively, indicating that the formulation is surface active. The relative density is 1.002 and the absolute density is 1.002 g/mL at 20 °C and 0.986 g/mL at 40 °C.

Following both 7 days at 0 °C and 2 weeks at 54 °C, neither the active substance content nor the physical, chemical and technical properties were changed, indicating that stability at low and high temperatures. The accelerated storage stability data indicate a shelf life of 2 years at ambient temperature when stored in HDPE containers with an inner barrier, e.g. HDPE/PA or f-HDPE. Data to address the content of the relevant impurity Reg No 4539586 in the product before and after storage are required, however this will be addressed as part of the 2 year storage stability study for the product (therefore is not required for active approval).

The technical characteristics are acceptable for a EC formulation. BAS 684 03 H is applied at 0.33 - 0.67 L/ha (250 - 500 g as/ha) using water volumes of 100 - 400 L/ha, resulting in in-use concentrations of 0.0825 - 0.666 %v/v.

Studies regarding the combination of BAS 684 03 H with eleven other commercial plant protection products were submitted and these data are considered acceptable to demonstrate physical and chemical compatibility of these tank mixtures.

## 2.3. DATA ON APPLICATION AND EFFICACY

### 2.3.1. Summary of effectiveness

To evaluate the efficacy of BAS 684 H in the Maritime EPPO climatic zone, 154 field trials on winter wheat (TRZAW), 17 field trials on winter barley (HORVW), 6 field trials on winter triticale (TTLWI), 3 trials on winter rye (SECCW) and 17 trials in winter oilseed rape (BRSNW) were conducted in the period of 2015-2017. These trials were undertaken by BASF country organisations and contract research organisations located in northern France (FR), Germany (DE), Austria (AT), Denmark (DK) and the United Kingdom (UK).

All trials have been conducted according to EPPO standards by GEP accredited organisations, either by field development staff of BASF country subsidiaries or by contract research organisations.

Trials were designed, conducted and reported in accordance with general EPPO standards PP1/225(2), PP1/135(4), PP1/152(4), PP1/278(1), and PP1/181(4) regarding design, analyses and reporting.

The results show that generally Blackgrass (ALOMY), Perennial Ryegrass (LOLPE), Italian Ryegrass (LOLMU), annual meadowgrass (POAAN), loose silky bent (APESV) and poppy (PAPRH) are controlled, with some variations in the level of control for each weed. For product authorisation, additional results may be required for certain crops in line with EPPO PP1/226 'Number of efficacy trials' depending on whether species are considered major or minor.

Overall, there is evidence that the proposed dose would be “sufficiently effective” and that the supported GAP is representative.

Refer to Section B.3.9 in Volume 3CP.

### 2.3.2. Summary of information on the development of resistance

Cinmethylin inhibits a unique and novel target enzyme in fatty acid (FA) biosynthesis for which no HRAC-classification have been assigned yet. FAs and FA-derived complex lipids are essential in living organisms. They are important components of cellular membranes and signalling molecules, and they serve as a major energy reserve in storage tissues. Therefore, depleting plants of FAs has dramatic physiological impact. Cell membranes are irreversibly disrupted, which has a detrimental effect on emerging plant tissue. In pre-emergence treatments, seedlings quickly become non-viable when FA storage is exhausted. In addition, transport and receptor functions, indispensable for photosynthetic activity can no longer be fulfilled. This results in a starvation of the plant, since absorbed sunlight can no longer be transformed into energy to sustain plant viability.

Cinmethylin is a new herbicide in the GB and the EU and represents a novel mode of action. However, the active substance has been authorised for some years in Australia and Asia. As of yet no resistance issues have been recorded ([www.weedscience.org](http://www.weedscience.org)). The data presented in the baseline sensitivity trials above do not demonstrate any significant indication of a loss of activity in the biotypes tested. Therefore, HSE considers that the resistance risk of the active substance itself is low.

The targets proposed include the major grassweed Blackgrass. Blackgrass is major agricultural weed of cereals with an extensive history of resistance issues. As such the inherent risk of this target is considered to be high. Overall, the inherent risk of resistance developing to cinmethylin as a result of the authorisation of 'BAS 684 03 H' is considered to be moderate rather than low as proposed by the applicant. However, the applicant has proposed a resistance management strategy which involves the use of robust doses, correct application timing and the use of cultural control and crop rotation to help prevent development of resistant biotypes. In addition, the strategy is advocating not relying on a single herbicide mode of action. These modifiers are expected to reduce the risk of resistance to 'low' and guidance to this effect must appear on product labels or as part of product stewardship.

### 2.3.3. Summary of adverse effects on treated crops

The proposed crops are stated as winter wheat and winter barley. Oilseed rape has been included as a representative use. However, no use in oilseed rape is being sought in Great Britain. Therefore, only trials on winter cereals were submitted and assessed for crop safety.

To demonstrate the crop safety when treated pre-emergence a total of 76 efficacy trials and 34 selectivity trials were assessed for phytotoxicity. A further 38 selectivity trials were conducted to support post-emergence uses. These trials were conducted in winter wheat (TRZAW) and winter barley (HORVW) crops. Trials were conducted between 2015 and 2018 in countries across the Maritime EPPO climatic region (UK, DE, AT, FR and DK). The trials were designed and conducted according to approved EPPO standards and undertaken by Officially Recognised Trials Organisations. BAS 684 03 H was applied at its recommended dose rate (500 g cinmethylin/ha) in each of the efficacy trials. In the selectivity trials, in addition to the recommended rate a 2N dose rate was also used. Phytotoxicity was observed in a number of the trials after application with the proposed and 2N doses. In some of these trials a corresponding decrease in yield was observed. Therefore, extensive label warnings are required to mitigate the risk. These adverse effects and the warnings required will be further discussed and implemented at product authorisation.

No data has been submitted to support the representative use on Oilseed Rape. However, in terms of the GAP the uses fall within the risk envelope for cereals in terms of dose rate and method of application. Under Regulation No 1107/2009 Annex II point 3.2 it is stated that “an active substance alone or associated with a safener or synergist shall only be approved where 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”. As BASF have demonstrated efficacy and crop safety of the representative use on winter wheat no further information is required at active substance level. However, crop selectivity trials on oilseed rape will be required at product authorisation.

The submitted data support crop safety in Winter Wheat and Barley. Further information in terms of crop safety and selectivity will be required to support the use of cinmethylin in oilseed rape. This will be considered at product authorisation.

Refer to Section B.3.11 in Volume 3CP.

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

Rotational crop trials were conducted with the recommended dose rate of BAS 684 03 H (500 g cinmethylin/ha) to consider the risk of damage to a range of potential succeeding crops. These included various crop groups (brassicas, cereals, legumes, vegetables and cover crops). Data indicate that, after a normal crop rotation, there are likely to be no negative effects on the following crops tested. Data have also been submitted to support resowing after crop failure. A more detailed assessment of these aspects of succeeding crops will be conducted at product evaluation.

Trials were conducted to determine the potential impact on a range of adjacent crops. BASF have demonstrated that there is no substantive risk against any of the crops tested, even the most sensitive ones based on submitted non-target plant testing. A more detailed assessment of the effects on adjacent crops will be included in the appropriate product evaluations.

Refer to Section B.3.12 in Volume 3 CP.

### **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 methods and precautions (see Volumes 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 methods and precautions (see Volumes 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 methods and precautions (see Volumes 3 CA and CP, section B.4).

## 2.5. METHODS OF ANALYSIS

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

Acceptable methods have been submitted for the determination of the active substance and all significant and relevant impurities in the technical material as manufactured.

Acceptable methods have been submitted for the determination of the active substance and the relevant impurity toluene in the plant protection product. A method for the determination of the relevant impurity Reg No 4539586, (1SR,2RS,4RS)-1-methyl-4-(propan-2-yl)-7-oxabicyclo[2.2.1]heptan-2-ol, in the plant protection product is required. This requirement could be set as a confirmatory data requirement if evidence or a justification is provided to demonstrate that that levels of the impurity in the product are unlikely to increase during storage.

Acceptable methods have been submitted for the determination of cinmethylin and selected metabolites in various matrices used in support of all areas of the risk assessment.

### 2.5.2. Methods for post control and monitoring purposes

Acceptable methods have been submitted for the determination of cinmethylin and selected metabolites in various matrices for use in post-approval monitoring and control.

A summary of the monitoring methods is presented below:

Matrix/Crop group	Analytes(s)	Method	LOQ	ILV?	Fully validated
High water High acid High oil High protein High starch No group (cereal straw and whole plant)	Cinmethylin	LC-MS/MS	0.01 mg/kg	Yes	Yes
Egg Fat Kidney Liver Milk Meat (bovine)	Cinmethylin	LC-MS/MS	0.010 mg/kg	Yes	Yes
Honey	Cinmethylin	LC-MS/MS	0.010 mg/kg	Yes	Yes
Soil (LUFA 2.36) Sediment	Cinmethylin (enantiomers)	LC-MS/MS	0.005 mg/kg	n/a	Yes LOQ < EC <sub>10</sub> for most sensitive soil organism (41.80 mg a.s./kg dw soil; earthworms)
Surface water Ground water	Cinmethylin (enantiomers) M684H001 M684H004	LC-MS/MS	0.03 µg/L 0.03 µg/L 0.03 µg/L	Yes	Yes LOQ < most sensitive NOEC
Air	Cinmethylin	LC-MS/MS	0.05 µg/m <sup>3</sup>	n/a	Yes LOQ < “c” (18 µg/m <sup>3</sup> based

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					on AOEL <sub>systemic</sub> )
Whole blood Urine	Cinmethylin M684H011	LC-MS/MS	0.01 mg/L	n/a	Yes
Body tissues	Cinmethylin	Refer to the method for liver			Yes

## 2.6. EFFECTS ON HUMAN AND ANIMAL HEALTH

### 2.6.1. Summary of absorption, distribution and excretion in mammals

The toxicokinetics of cinmethylin have been largely investigated in rats via oral dosing only. There are two data sets available, a new/modern data set (3 studies, Table 2.6.1-1) using both  $^{14}\text{C}$ -phenyl labelled cinmethylin and  $^{14}\text{C}$ -cyclohexyl labelled cinmethylin in rats only, and an older set of studies conducted with  $^{14}\text{C}$ -phenyl labelled cinmethylin only. The earlier set of studies are available as brief summaries and the original test reports were not considered by HSE. These summaries are included for completeness and supportive information only. There is also an *in vitro* comparative metabolism study, employing primary hepatocytes from humans, rats, dogs and rabbits exposed to  $^{14}\text{C}$ -phenyl labelled cinmethylin and  $^{14}\text{C}$ -cyclohexyl labelled cinmethylin. Furthermore, there is some toxicokinetic information available on cinmethylin and some of its metabolites from the rat and mouse chronic dosing toxicodynamic studies.

**Table 2.6.1-1. Summary of new/modern toxicokinetic studies**

Study reference	Study type	Dose level [mg/kg bw/d]	Remarks
██████, 2018	Determination of kinetic parameters in plasma, absorption, tissue distribution, excretion balance (urine, feces, bile)	Single oral low 15. Single oral high 350. Multiple oral high 350. Single i.v. 1.	An oral absorption value of 100 % is proposed. For post-hepatic systemic bioavailability, a value of 70 % is proposed and a default inhalation absorption value of 100 % is assumed.
██████ 2018a	Sample generation for investigation of metabolism in tissues and plasma at $T_{\max}$	Single oral low 15. Single oral high 350.	This study was performed to investigate further the distribution of cinmethylin and collect tissue samples for analysis of metabolites.
██████, 2018	Investigation of metabolism in urine, feces, bile, tissues, plasma	Single oral low 15. Single oral high 350. Multiple oral high 350.	Cinmethylin was rapidly and extensively metabolised with no significant, post-hepatic exposure to unchanged cinmethylin. No unchanged cinmethylin was detected in the bile.  Two urinary metabolites, M684H010 (2-hydroxymethyl benzoate) and M684H011 (2-hydroxypropyl cinmethylin benzoate) were present above 10 % of the administered dose.  There is some preferential metabolism for the (+)enantiomer.
Funk-Weyer & Ufer, 2017	Comparative <i>in vitro</i> metabolism study. Primary hepatocytes from humans, Wistar rats, Beagle dogs and New Zealand White rabbits	10 $\mu\text{M}$ cinmethylin	No unique metabolites were identified from human hepatocytes.



### Absorption

Cinmethylin is well absorbed from the gastrointestinal tract (75.4 % to 98.5 % of the administered dose) in the dose range 15 - 350 mg/kg bw. The maximum plasma concentrations for oral administration, were achieved 1 hour after low dose (15 mg/kg bw) administration (both radiolabels) and 4 - 8 hours after high dose (350 mg/kg bw) administration (for the  $^{14}\text{C}$ -phenyl and  $^{14}\text{C}$ -cyclohexane radiolabels, respectively). For male rats administered 350 mg/kg bw cinmethylin ( $^{14}\text{C}$ -cyclohexane label), an earlier  $C_{\text{Max}}$ -value was also observed at 1 hour post dose. It is possible this indicates some biphasic absorption at the high dose. Absorption appears to be independent of dose, sex and position of the radiolabel.

Although uptake from the GIT (gastrointestinal tract) is extensive, it appears that post-hepatic systemic exposure to unchanged cinmethylin and/or its metabolites accounts for around 50 % of the administered dose, with a significant amount excreted in bile within 6 hours of gavage dosing (33.77 % to 56.72 % of the administered dose noted at the low dose and 12.56 % to 35.36 % of the administered dose at the high dose). It is possible that cinmethylin and/or its metabolites excreted into the bile within 6 hours of gavage dosing might not be systemically available.

Therefore, HSE has proposed an **oral absorption value of 100 %**. From this toxicokinetic experiment, dose corrected post hepatic systemic bioavailability values of 66 % and 73 % for males and females respectively were obtained and an overall average value of 70% can be calculated. This value is considered to be more robust and less uncertain than that derived from the bile-duct cannulation experiment. Overall, HSE proposes a **post-hepatic systemic bioavailability value of 70 %**. There are no data to determine the absorption of cinmethylin across the respiratory tract. However, based on the extensive oral absorption, **a default inhalation absorption value of 100 % can be assumed**. Dermal absorption of cinmethylin from its representative product is addressed in the CP-B6 document.

### Distribution

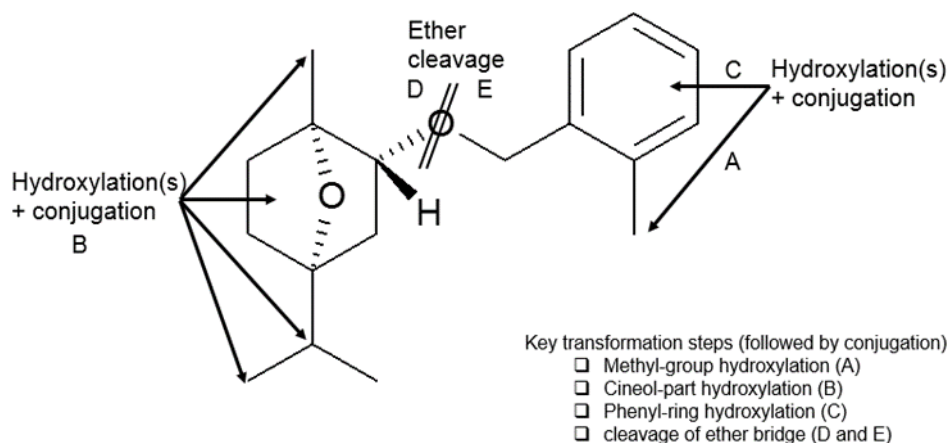
Distribution of radiolabelled cinmethylin and/or its metabolites was predominately to the organs of metabolism and excretion, the liver and kidneys and also the adrenals and adipose tissues. There was no evidence of retention in any organs/tissues at any dose level. Limited information on plasma concentrations of cinmethylin and four metabolites (M684H001, M684H010, M684H011 and M684H026) from lifetime toxicodynamic studies conducted in rats and mice confirmed that there is little or no detectable unchanged cinmethylin in blood plasma following repeated exposure. The levels of the metabolites in plasma were significantly higher than those of the parent in these studies.

### Metabolism

*In vivo* toxicokinetic investigations of metabolism found that cinmethylin was rapidly and extensively metabolised such that there was no significant, post-hepatic exposure to unchanged cinmethylin. The main biotransformation reactions identified are:

- Hydroxylation at the cyclohexane and/or benzyl ring
- Hydroxylation of the alkyl groups at the benzyl and/or cyclohexane ring
- Oxidation of the hydroxylated methyl group at the benzyl ring to a carboxy group
- Cleavage of the ether bridge
- Conjugation with glucuronic acid•
- Conjugation with glycine

Cinnmethylin showing sites of key metabolic transformation reactions



Two urinary metabolites, M684H010 (2-hydroxymethyl benzoate) and M684H011 (2-hydroxypropyl cinnmethylin benzoate) were present above 10 % of the administered dose. With the exception of M684H011 which was present in the urine at a higher concentration in low dose animals than in the high dose animals, there were no other sex, dose or positional differences in urinary, plasma or biliary metabolites. No unchanged cinnmethylin was detected in plasma, urine or bile. The most abundant (13 – 21 % of the administered dose) metabolite in bile was M684H012 (M684H012a + M684H012b) abbreviated to cinnmethylin benzyl alcohol glucuronide. No individual metabolites were present in the faeces above 6 % of the administered dose. M684H011 was the most prominent metabolite in faeces, present at 1.7 % to 5.8 % of the administered dose. Only a small number of plasma metabolites were identified (4 - 6) and none were present above 1 % of the administered dose. However, analysis of plasma levels of cinnmethylin and four metabolites (M684H001 or cinnmethylin benzoate, M684H010, M684H011 and M684H026 or 2-hydroxypropyl 2-hydroxycineol) from the rat and mouse chronic studies showed that the levels of these metabolites were significantly higher than those of the parent compound.

The ratio of the (-)/(+) enantiomers of unchanged cinnmethylin in representative methanol extracts of liver and faeces shifted from 50:50 (-)/(+) in the starting material towards higher relative amounts of the (-) enantiomer and ranged from approximately 70:30 to 76:24 (-)/(+) in faeces extracts and from approximately 63:37 to 69:31 (-)/(+) in liver extracts. These data indicate some preferential metabolism for the (+) enantiomer.

Limited information from an *in vitro* comparative metabolism study employing primary hepatocytes from humans, rats, dogs and rabbits exposed to  $^{14}\text{C}$ -phenyl labelled cinnmethylin and  $^{14}\text{C}$ -cyclohexyl labelled cinnmethylin found no unique metabolites were formed by human primary hepatocytes.

### Excretion

Excretion via both the urine and faeces is rapid, and essentially complete within 48 hours of oral dosing. There is no evidence for a preferential route, although excretion via the urine was slightly higher (52 – 60 % of the administered dose) than faecal excretion. Faecal excretion was mainly due to biliary elimination. The expired air is not a significant route of excretion for cinnmethylin. There is no evidence for dose or sex-dependent differences in urinary or faecal excretion. Comparing urinary excretion in non-bile duct cannulated animals with bile duct cannulated animals suggests that there is some enterohepatic recirculation but it is of relatively minor importance. There do not appear to be any clear differences between single high dose and repeated high dose animals for both  $^{14}\text{C}$  cyclohexyl and  $^{14}\text{C}$ -phenyl labelled cinnmethylin, in males or females.

There is no toxicokinetic information from other relevant routes of exposure. However, given the significant first-pass effect, quantitative differences in the degree of systemic exposure to unchanged cinnmethylin and metabolites would be anticipated following inhalation or dermal exposure.

The earlier toxicokinetic studies, conducted with  $^{14}\text{C}$ -phenyl labelled cinnmethylin only do not contradict the conclusions on the toxicokinetics of cinnmethylin from the more modern data set.

Residue definition for body fluids and tissues in humans

The applicant has proposed a residue definition for monitoring in body fluids and tissues of cinmethylin and M684H011.

Following a detailed consideration (see Vol. 3 CA B6) HSE concludes that the following metabolite(s) may be suitable for the residue definition for body fluids and tissues in humans:

Substance (i.e. metabolite)	Compartment (in body fluid and/or tissue)	Justification (evidence from study data)
M684H010	Body fluid - urine	Another significant metabolite, M684H010 was identified in the urine of rats administered <sup>14</sup> C-phenyl radiolabelled cinmethylin only (3.47 - 18.86 %) (██████████ 2018)

No other metabolites were detected at sufficient amounts in compartments analysed to recommend as a suitable substances for the residue definition for body fluids and tissues in humans.

**2.6.2. Summary of acute toxicity**

The acute toxicity of cinmethylin was investigated in multiple studies conducted via the oral, dermal and inhalation routes. Studies of skin irritancy, eye irritancy and skin sensitisation were also conducted. No phototoxicity studies have been provided as testing is not triggered according to data requirements in Reg 283/2013. The available studies, some conducted in the 1980s and others more recently (2016 and 2017) have not previously been evaluated.

The following key conclusions have been made with regards to the acute toxicity of cinmethylin:

- The results of the acute toxicity studies show that classification for skin sensitisation 1; H317 (May cause an allergic skin reaction) is required. Further details are available in aligned Mandatory Classification and Labelling (MCL) dossier.
- No further classification for acute toxicity is proposed.
- The data requirements of Regulation 283/2013 have been met.

**Table 2.6.2-1. Summary of acute toxicity studies with cinmethylin**

Study and Acceptability	Species/ Strain/	Sex	Acceptable	Result	Classification according to Reg. No. 1272/2008
Acute oral toxicity study  ██████████ 2016a (2016/1273410)  Batch: COD-002038 Purity (%): 93.5 (-) / (+) ratio = 48:52  <i>Acceptable Relied upon</i>	Rat (Wistar)	F* only	Y	LD <sub>50</sub> > 2000 mg/kg bw.	No classification.
Acute oral toxicity study  ██████████ 1982 (CI-411-001)  Batch: 1-3-0-0 Purity (%): 93.3 (-) / (+) ratio = not specified.	Rat (Fischer 344)	M & F *	Y	LD <sub>50</sub> 4550 mg/kg bw.	No classification.

Study and Acceptability	Species/ Strain/	Sex	Acceptable	Result	Classification according to Reg. No. 1272/2008
<i>Acceptable Supplementary</i>					
<p>Acute oral toxicity study</p> <p>██████████ 1982 (CI-411-002)</p> <p>Batch: 513B Purity (%): not specified. (-) / (+) ratio = not specified.</p> <p><i>Acceptable</i></p>	Mice (B6C3F1)	M & F *	Y	LD <sub>50</sub> > 5000 mg/kg bw.	No classification.
<p>Acute dermal toxicity</p> <p>██████████ 2016a (2016/1225928)</p> <p>Batch: COD-002038 Purity (%): 93.5 (-) / (+) ratio = 48:52</p> <p><i>Acceptable Relied upon</i></p>	Rat (Wistar)	M & F	Y	LD <sub>50</sub> > 5000 mg/kg bw.	No classification.
<p>Acute dermal toxicity</p> <p>██████████ 1981a (CI-412-001)</p> <p>Batch: 513A (1-3-0-0) Purity (%): 93.3 (-) / (+) ratio = not specified.</p> <p><i>Acceptable Supplementary</i></p>	Rabbit (NZW)	M & F	Y	LD <sub>50</sub> > 2029 mg/kg bw.	No classification.
<p>Acute inhalation toxicity study</p> <p>██████████, 2017 (2017/1068662)</p> <p>Batch: COD-002038 Purity (%): 93.5 (-) / (+) ratio = 48:52</p> <p><i>Acceptable Relied upon</i></p>	Rat (Wistar)	M & F	Y	LC <sub>50</sub> > 5.3 mg/L	No classification.
Acute inhalation toxicity study	Rat (Fischer 344)	M & F	Y	LC <sub>50</sub> > 3.5 mg/L	No classification.

Study and Acceptability	Species/ Strain/	Sex	Acceptable	Result	Classification according to Reg. No. 1272/2008
<p>██████ <i>et al.</i>, 1986 (CI-413-001)</p> <p>Batch: 513P Purity (%): 91.8 (-) / (+) ratio = not specified.</p> <p><i>Acceptable</i></p>					
<p><i>In vitro</i> skin irritation and corrosion study</p> <p>Remmele, 2017a (2016/1302127)</p> <p>Batch: COD-002038 Purity (%): 93.5 (-) / (+) ratio = 48:52</p> <p><i>Acceptable</i> <i>Relied upon</i></p>	Human epidermis model	-	Y	Non-corrosive, inconclusive for irritation	Inconclusive.
<p><i>In vivo</i> dermal irritation study</p> <p>██████ 2016b (2016/1225929)</p> <p>Batch: COD-002038 Purity (%): 93.5 (-) / (+) ratio = 48:52</p> <p><i>Acceptable</i> <i>Relied upon</i></p>	Rabbit (NZW)	F only	Y	Slightly irritating	No classification.
<p><i>In vivo</i> dermal irritation study</p> <p>██████ 1981b (CI-412-001)</p> <p>Batch: 513A (1-3-0-0) Purity (%): 93.3 (-) / (+) ratio = not specified.</p> <p><i>Acceptable</i> <i>Supplementary</i></p>	Rabbit (NZW)	M & F	Y	Slightly irritating	No classification.
<p><i>In vitro</i> eye irritation study</p> <p>Remmele, 2017b (2016/1302128)</p>	Bovine & human cornea models	-	Y	Not irritating	No classification.

Study and Acceptability	Species/ Strain/	Sex	Acceptable	Result	Classification according to Reg. No. 1272/2008
Batch: COD-002038 Purity (%): 93.5 (-) / (+) ratio = 48:52  <i>Acceptable Relied upon</i>					
<i>In vivo</i> eye irritation study  ██████ 2016b (2016/1326828)  Batch: COD-002038 Purity (%): 93.5 (-) / (+) ratio = 48:52  <i>Acceptable Not relied upon, reported for transparency.</i>	Rabbit (NZW)	F only	Y <sup>a</sup>	Not irritating	No classification
<i>In vivo</i> eye irritation study  ██████ 1981c (CI-412-001)  Batch: 513A (1-3-0-0) Purity (%): 93.3 (-) / (+) ratio = not specified.  <i>Acceptable Used in a WoE approach</i>	Rabbit (NZW)	M & F	Y	Mildly irritating	No classification.
<i>In vivo</i> skin sensitisation study (Buehler test)  ██████ 2016c (2016/1330875)  Batch: COD-002038 Purity (%): 93.5 (-) / (+) ratio = 48:52  <i>Acceptable Relied upon</i>	Guinea pigs (Dunkin Hartley)	F only	Y	Skin sensitiser	<b>Skin Sens 1; H317</b>
<i>In vivo</i> skin sensitisation study (Buehler test)  ██████████████████ 1982 (CI-416-001)	Guinea pigs (Dunkin Hartley)	M & F	N - concentration used was not appropriate	Inconclusive	Inconclusive

Study and Acceptability	Species/ Strain/	Sex	Acceptable	Result	Classification according to Reg. No. 1272/2008
Batch: 513D Purity (%): not specified. (-) / (+) ratio = not specified.  <i>Not acceptable</i>					
<i>In vivo</i> skin sensitisation study (GPMT)  ██████ 1988 (CI-416-002)  Batch: 513F Purity (%): 92.0 (-) / (+) ratio = not specified.  <i>Not acceptable</i>	Guinea pigs (Dunkin Hartley)	M & F	N – lack of reliability data	Inconclusive	Inconclusive

M – male

F – female

\* - fasted animals

a - the study is considered to be in contravention of Article 62 of Regulation (EC) 1272/2008. This study was not relied on.

Based upon the results of these studies, cinmethylin is of low acute toxicity via the oral ( $LD_{50} > 2000$  mg/kg bw), dermal ( $LD_{50} > 5000$  mg/kg bw) and inhalation (4hr  $LC_{50} > 5.3$  mg/L) routes. It is not corrosive to the skin and eye and although it is slightly irritating to the skin and eye, it does not meet the CLP criteria (Regulation (EC) No 1272/2008) and so no classification is required for skin or eye irritation. However, skin sensitisation was observed in a Buehler test. Therefore, no classification is required for acute oral, dermal and inhalation toxicity; nor is classification required for skin and eye irritation. However, classification is required for skin sensitisation.

Acute toxicity endpoints for cinmethylin		Classification (1272/2008)
Rat $LD_{50}$ oral	$> 2000$ mg/kg bw	-
Rat $LD_{50}$ dermal	$> 5000$ mg/kg bw	-
Rat 4hr- $LC_{50}$ inhalation	$> 5.3$ mg/L air/4 h, nose only	-
Skin irritation	Non-irritant	-
Eye irritation	Non-irritant	-
Skin sensitisation	Sensitising (Buehler test)	<b>Skin Sens 1 ; H317</b>
Phototoxicity	Study not required	-

Phototoxicity testing is not required as the criteria in Commission Regulation (EU) No 283/2013 setting out the data requirements for active substances are not met.

### 2.6.3. Summary of short-term toxicity

The short-term toxicity of cinmethylin has been investigated in rats, mice and dogs via the oral (dietary) route of exposure in 28- and 90-day studies; two 1-year studies and one 18-month study in dogs are also available. Modern studies conducted according to GLP and OECD test guidelines are available in both rats and mice, at 28- and 90-days. In addition older studies, not all of which were conducted according to GLP and OECD test guidelines are available in rats and mice (90-day), as well as dogs (5-week, 90-day, 1-year and 18-months); nevertheless, the HSE considers that these studies were well-conducted and are sufficiently reliable to contribute

to the overall picture of the repeated-dose toxicity of cinmethylin. The short-term toxicity via the dermal route of exposure has been investigated in a 28-day study in rats. The main findings are summarised (Table 2.6.3-1) below. Further information on the repeated dose toxicity of cinmethylin is also available from the rat 2-generation study (see section B.6.6.1.) and in the chronic studies in rats and mice (see section B.6.5.).

The following key conclusions were obtained from the evaluation of the short-term toxicity information:

- In studies in rats, mice and dogs, the target organs were the liver, thyroid and nasal cavities.
- Classification for repeated dose toxicity is not required. Further details are available in the aligned MCL dossier.
- The data requirements of Regulation 283/2013 have been met.

**Table 2.6.3-1. Summary of short-term toxicity studies with cinmethylin**

Study and acceptability	Species/ Strain/ Groups	Doses	NOAEL (mg/kg bw/d) [ppm]	Effects at the LOAEL
28-day oral (dietary)  GLP compliant Guideline compliant  Cinmethylin Batch: COD- 001794 Purity (%): 97.5 (-) / (+) ratio = 70:30  ██████, 2015 (2015/1076329)  <i>Acceptable</i>	Rat (Wistar)  5/sex/dose	0, 1500, 5000 and 15000 ppm  Equivalent to: M: 0, 137, 477 and 1522 mg/kg bw/d  F: 0, 141, 477 and 1331 mg/kg bw/d	M: 137 F: 141 [1,500]	<u>5,000 ppm (477 mg/kg bw/d)</u> ↑water consumption (21 % in ♂). Changes in clinical chemistry parameters (GGT, protein, globulin, albumin, cholesterol, triglycerides, glucose, calcium) (♂+♀). ↑liver weight, absolute (23 % in ♂, 11 % in ♀) and relative (22 % in ♂, 18 % in ♀). ↑kidney weight, relative (15 % in ♂). Histopathology of the liver – enlarged with hepatocellular hypertrophy (♂+♀). Histopathology of the thyroid - follicular hypertrophy/hyperplasia (♂+♀). Histopathology of the kidney - eosinophilic droplets (♂) (not relevant to humans).
28-day oral (dietary)  GLP compliant Guideline compliant  Cinmethylin Batch: COD- 001919 Purity (%): 96.2 (-) / (+) ratio = 51:49	Mice (C57BL/6J Rj)  5/sex/dose	0, 400, 1200 and 4000 ppm  Equivalent to : M: 0, 95.1, 295.9 and 791.4 mg/kg bw/d  F: 0, 92.4, 254, 1015.6 mg/kg bw/d	M: 296 F: 254 [1,200]	<u>4,000 ppm (791/1016 mg/kg bw/d):</u> ↓body weight gain (♂). Changes in clinical chemistry parameters (BIL, PROT, ALB, GLOB, CHOL, TRIG) (♂). ↑liver weight, absolute (16 % in ♂, 26 % in ♀) and relative (19 % in ♂, 22 % in ♀).



Study and acceptability	Species/ Strain/ Groups	Doses	NOAEL (mg/kg bw/d) [ppm]	Effects at the LOAEL
<p>██████████, 2016 (2014/1162710)</p> <p><i>Acceptable</i></p>				
<p>5-week oral (dietary)</p> <p>Non-GLP Non-guideline</p> <p>Cinmethylin Batch: 513J Purity (%): 92.4 (-) / (+) ratio = not specified.</p> <p>██████████, 1984 (CI-420-004)</p> <p><i>Acceptable in a WoE approach</i></p>	<p>Beagle dogs</p> <p>2/sex/dose</p>	<p>0, 300, 3000, 10000 and 30000 ppm</p> <p>Equivalent to: M: 0, 8.8, 131.1, 338.7 and 330.0 mg/kg bw/d</p> <p>F: 0, 10.5, 103.6, 334.2 and 433.6 mg/kg bw/d</p>	<p>M: 131 F: 104 [3,000]</p>	<p><u>≥ 10,000 ppm (330/334 mg/kg bw/d):</u>            ↑liver weight, absolute (38 % in ♂, 20 % in ♀)            and relative (35 % in ♂,            27 % in ♀).            Histopathology of the            liver – hepatopathology.</p>
<p>90-day oral (dietary)</p> <p>GLP compliant Guideline compliant</p> <p>Cinmethylin Batch: COD- 001919 Purity (%): 96.2 (-) / (+) ratio = 51:49</p> <p>██████████, 2018a (2014/1228370)</p> <p><i>Acceptable</i></p>	<p>Rat (Wistar)</p> <p>10/sex/dose</p>	<p>0, 1000, 3000 and 10000 ppm</p> <p>Equivalent to: M: 0, 67, 211 and 792 mg/kg bw/d</p> <p>F: 0, 79, 240 and 814 mg/kg bw/d</p>	<p>M: 67 F: 79 [1,000]</p>	<p><u>3,000 ppm (211/240 mg/kg bw/d):</u>            Changes in            haematology            parameters            (↓prothrombin time)            (♀).            Changes in clinical            chemistry parameters            (♂+♀).            ↑liver weight, absolute            (12 % in ♂, 12 % in ♀)            and relative (18 % in ♂,            11 % in ♀).            Histopathology of the            liver – hypertrophy            (♂+♀).            Histopathology of the            thyroid - follicular            hypertrophy/hyperplasia            (♂+♀).            Histopathology of the            nasal cavity –            proteinaceous exudation            and degeneration of the            olfactory epithelium            (♂+♀).</p>
<p>90-day oral (dietary)</p> <p>Non-GLP Non-guideline</p> <p>Cinmethylin Batch: 513D Purity (%): not</p>	<p>Rat (Fischer 344)</p> <p>30/sex/dose (total) 10/sex/dose (sacrificed at week 7) 20/sex/dose (sacrificed at week</p>	<p>0, 30, 100, 300 and 1000 ppm</p> <p>Equivalent to: M: 0, 2.18, 7.51, 22.51 and 75.78 mg/kg bw/d</p> <p>F: 0, 2.61, 8.73,</p>	<p>M: 76 F: 89 [1,000]</p>	<p>Not applicable, no adverse effects were seen at the top dose.</p>

Study and acceptability	Species/ Strain/ Groups	Doses	NOAEL (mg/kg bw/d) [ppm]	Effects at the LOAEL
specified. (-) / (+) ratio = not specified.  ██████████, 1983 (CI-425-001)  <i>Supplementary</i>	13)	26.08 and 88.56 mg/kg bw/d		
90-day oral (dietary)  GLP compliant Guideline compliant  Cinmethylin Batch: COD- 001919 Purity (%): 96.2 (-) / (+) ratio = 51:49  ██████████, 2018b (2015/1005983)  <i>Acceptable</i>	Mice (C57BL/6J Rj)  10/sex/dose	0, 200, 1000 and 5000 ppm  Equivalent to : M: 0, 43, 201 and 1200 mg/kg bw/d  F: 0, 58, 285 and 1304 mg/kg bw/d	M: 43 F: 58 [200]	<u>1,000 ppm (201/285 mg/kg bw/d):</u> ↓body weight gain (17 % in ♀). Changes in clinical chemistry parameters (TRIG, TPROT, ALB, CHOL) (♂). ↑liver weight, absolute (9 % in ♂) and relative (10 % in ♂).
90-day oral (dietary)  Non-GLP Non-guideline  Cinmethylin Batch: 513D Purity (%): not specified. (-) / (+) ratio = not specified.  ██████████ 1983 (CI-425-002)  <i>Supplementary</i>	Mice (B6C3F1)  30/sex/dose (total) 10/sex/dose (sacrificed at week 7) 20/sex/dose (sacrificed at week 13)	0, 30, 100, 300 and 1000 ppm  Equivalent to : M: 0, 3.81, 11.50, 39.57 and 123.11 mg/kg bw/d  F: 0, 4.36, 13.85, 42.57 and 129.66 mg/kg bw/d	M: 123 F: 130 [1,000]	Not applicable, no adverse effects were seen at the top dose.
90-day oral (dietary)  GLP compliant Non-guideline (OECD)  Cinmethylin Batch: #925 Purity (%): not specified. (-) / (+) ratio = not specified.	Beagle dogs  6/sex/dose	0, 2, 100, 200, 3000 and 6000 ppm  Equivalent to : M: 0, 0.06, 2.9, 5.6, 96.5 and 180.5 mg/kg bw/d  F: 0, 0.06, 3.0, 5.8, 91.9 and 192.3 mg/kg bw/d	M: 5.6 F: 5.8 [200]	<u>3,000 ppm (96.5/91.9 mg/kg bw/d):</u> ↑liver weight, absolute (21 % in ♂, 16 % in ♀) and relative (16 % in ♂, 22 % in ♀). Histopathology of the prostate - delay in glandular development.

Study and acceptability	Species/ Strain/ Groups	Doses	NOAEL (mg/kg bw/d) [ppm]	Effects at the LOAEL
<p>██████ 1987 (CI-425-003)</p> <p><i>Acceptable in a WoE approach</i></p>				
<p>1-year oral (dietary)</p> <p>GLP compliant Non-guideline (OECD)</p> <p>Cinmethylin Batch: 513L Purity (%): 91 (-) / (+) ratio = not specified. and Batch: 513N Purity (%): 93 (-) / (+) ratio = not specified.</p> <p>██████ 1985 (CI-427-002)</p> <p><i>Acceptable in a WoE approach</i></p>	<p>Beagle dogs</p> <p>6/sex/dose</p>	<p>0, 300, 3000 and 10000 ppm</p> <p>Equivalent to : M: 0, 7.9, 83.4, and 253.9 mg/kg bw/d</p> <p>F: 0, 7.9, 81.4 and 284.8 mg/kg bw/d</p>	<p>M: 7.9 F: 7.9 [300]</p>	<p><u>3,000 ppm (83.4/81.4 mg/kg bw/d):</u> ↓body weight (4 % in ♂, 12 % in ♀). ↓body weight gain (16 % in ♂, 33 % in ♀). Changes in white blood cell parameters (♀). Alterations in clinical chemistry parameters (ALP+ALB) (♂+♀). ↑liver weight, absolute (24 % in ♂, 11 % in ♀) and relative (27 % in ♂, 26 % in ♀). Histopathology of the prostate - delay in glandular development.</p>
<p>1-year oral (dietary)</p> <p>GLP compliant Non-guideline (OECD)</p> <p>Cinmethylin Batch: 925 (6-4-0- 0) Purity (%): 92.4 (-) / (+) ratio = not specified.</p> <p>██████ 1988a (CI-427-003)</p> <p><i>Acceptable in a WoE approach</i></p>	<p>Beagle dogs</p> <p>6/sex/dose</p>	<p>0, 2, 30, 100, 200 and 3000 ppm</p> <p>Equivalent to : M: 0, 0.044, 0.68, 2.3, 4.7 and 80.8 mg/kg bw/d</p> <p>F: 0, 0.048, 0.74, 2.4, 4.3 and 70.7 mg/kg bw/d</p>	<p>M: 4.7 F: 4.3 [200]</p>	<p><u>3,000 ppm (80.8/70.7 mg/kg bw/d):</u> White blood cell parameters (♂+♀). ↑ALP (♀). ↑liver weight, absolute (23 % in ♂) and relative (26 % in ♂). ↑incidence small prostates.</p>
<p>1-year oral with 6 months recovery (dietary)</p> <p>GLP compliant Non-guideline (OECD)</p>	<p>Beagle dogs</p> <p>6/sex/dose</p>	<p>0, 2, 30, 100, 200 and 3000 ppm</p> <p>Equivalent to : M: 0, 0.04, 0.63, 2.3, 4.1 and 64.3 mg/kg bw/d</p>	<p>M: 4.1 [200]</p> <p>F: 71.2 [3000]</p>	<p><u>3,000 ppm (64.3 mg/kg bw/d):</u> ↑ White blood cell parameters at week 52, recovering after 6 months (♂).</p>

Study and acceptability	Species/ Strain/ Groups	Doses	NOAEL (mg/kg bw/d) [ppm]	Effects at the LOAEL
Cinmethylin Batch: #925 Purity (%): not specified. (-) / (+) ratio = not specified.  [REDACTED] 1988b (CI-427-004)  <i>Acceptable in a WoE approach</i>		F: 0, 0.04, 0.62, 2.1, 4.1 and 71.2 mg/kg bw/d		
28-day dermal  GLP compliant Guideline compliant  Cinmethylin Batch: COD-002038 Purity (%): 93.5 (-) / (+) ratio = 48:52  [REDACTED], 2018c (2017/1094162 and 2018/1091459)  <i>Acceptable</i>	Rat Wistar, Crl :WI(Han)  10/sex/dose	M & F: 0, 100, 300 and 1000 mg/kg bw/d	Local dermal toxicity: 100 (M & F).  Systemic toxicity: 1000 (M & F).	Local dermal toxicity: 300 mg/kg bw/d: Slight erythema at treated skin site.  Systemic toxicity: Not applicable, no adverse effects were seen at the top dose.

OralRat

In rats the main target organs of toxicity were the liver, thyroid, kidney and nasal cavity.

Adverse increases ( $\geq 15\%$ ) in liver weight were seen from 477 mg/kg bw/d in the 28-day study and from 211 mg/kg bw/d in the new/modern 90-day study. In addition, similar effects on the liver were seen from 115 mg/kg bw/d in the 2-generational study and at 144 mg/kg bw/d in the chronic toxicity study. These effects were associated with histopathological findings (hepatocellular hypertrophy) and alterations in some clinical chemistry parameters indicative of liver toxicity (e.g. GGT, protein, globulin, albumin, cholesterol, triglycerides and glucose) from 477 mg/kg bw/d in the 28-day study and from 211 mg/kg bw/d in the new/modern 90-day study.

Thyroid weight was increased at 792 mg/kg bw/d in the new/modern 90-day study. In addition, adverse thyroid histopathology (follicular hypertrophy/hyperplasia) was seen from 477 mg/kg bw/d in the 28-day study and from 211 mg/kg bw/d in the new/modern 90-day study. Similar effects on the thyroid were seen at 394 mg/kg bw/d in the 2-generational study and at 265 mg/kg bw/d in the chronic toxicity study.

Adverse nasal cavity histopathology (proteinaceous exudation and olfactory epithelium degeneration) was seen from 211 mg/kg bw/d in the new/modern 90-day study. Similar findings were not noted in the 28-day study but were recorded at 394 mg/kg bw/d in the 2-generational study and from 45 mg/kg bw/d in the chronic toxicity study.

Adverse effects on the kidney (increased weight with associated histopathology (eosinophilic droplets)) were seen in males only, from 477 mg/kg bw/d the 28-day study and from 211 mg/kg bw/d the 90-day study. These

droplets were shown (in the 90-day study) to be due to accumulation of  $\alpha_2$ -globulin, a male rat specific phenomenon of no relevance to humans.

In addition to toxic effects in these organs, decreases in body weight and/or body weight gain were observed at 1522 mg/kg bw/d in the 28-day study and from 792 mg/kg bw/d in the new/modern 90-day study. Changes in haematology parameters (e.g. prothrombin time and monocyte counts) were observed at 1331 mg/kg bw/d in the 28-day study and from 240 mg/kg bw/d in the new/modern 90-day study. Increases in water consumption were observed from 477 mg/kg bw/d in the 28-day study.

Overall, taking into account the full range of observation, **the lowest relevant subchronic NOAEL in the rat was 67 mg/kg bw/d**. The LOAEL was 211 mg/kg bw/d based on changes in clinical chemistry parameters, increases in liver weight, adverse liver, thyroid and nasal cavity histopathology in the new/modern 90-day study.

#### *Mouse*

In mice the main target organ of toxicity was the liver; however, on chronic exposure, effects on the nasal cavity were also seen.

Adverse increases ( $\geq 15\%$ ) in liver weight were seen at 791 mg/kg bw/d in the 28-day study and from 201 mg/kg bw/d in the new/modern 90-day study. These effects were associated with alterations in some clinical chemistry parameters indicative of liver toxicity (e.g. protein, globulin, albumin, cholesterol and triglycerides) at 791 mg/kg bw/d in the 28-day study and from 201 mg/kg bw/d in the new/modern 90-day study.

Adverse histopathological findings were seen in the nasal cavity after 18-month exposure (in the long-term toxicity study) from the mid dose in males (162 mg/kg bw/d) and at the top dose in females (939 mg/kg bw/d). Nasal cavity findings included an increase in metaplasia and degeneration/regeneration of olfactory epithelium in males and females.

In addition to toxic effects in the liver and the nasal cavity, decreases in body weight were observed at 1200 mg/kg bw/d in the new/modern 90-day study. Decreases in body weight gain were observed at 791 mg/kg bw/d in the 28-day study and from 285 mg/kg bw/d in the new/modern 90-day study. Decreases in food consumption were observed at 1304 mg/kg bw/d in the new/modern 90-day study. Changes in some white blood cell parameters were also observed at 1200 mg/kg bw/d in the new/modern 90-day study.

Overall, taking into account the full range of observation, **the lowest relevant subchronic NOAEL in the mouse was 48 mg/kg bw/d**. The LOAEL was 201 mg/kg bw/d based on decreases in body weight gain, changes in clinical chemistry parameters and increases in liver weight in the new/modern 90-day study.

#### *Dog*

In dogs the main target organs of toxicity were the liver, haematological system, kidney, prostate and testes.

Adverse increases ( $\geq 15\%$ ) in liver weight were seen from 334 mg/kg bw/d in the 5-week study, from 92 mg/kg bw/d in the 90-day study, from 81 mg/kg bw/d in the first 1-year study (■■■■■, 1985) and at the top dose of 81 mg/kg bw/d in the second 1-year study (■■■■■ 1988a). These effects were associated with histopathological findings (hepatocellular hypertrophy) from 334 mg/kg bw/d in the 5-week study and alterations in some clinical chemistry parameters indicative of liver toxicity (e.g. ALP and ALB) at 180 mg/kg bw/d in the 90-day study, from 81 mg/kg bw/d in the first 1-year study and at the top dose of 71 mg/kg bw/d in the second 1-year study.

Haematological effects were seen from 81 mg/kg bw/d in the first 1-year study, from 71 mg/kg bw/d in the second 1-year study and from 64.3 mg/kg bw/d in the third 1-year study (however, these changes were reversed following a 6-month recovery period).

Adverse kidney histopathology (tubular nephropathy) was seen from 330 mg/kg bw/d in the 5-week study.

Prostate histopathology revealed a delay in glandular development from 96.5 mg/kg bw/d in the 90-day study and from 83.4 mg/kg bw/d in the first 1-year study. In addition, an increase in the incidence of small prostates was seen at 81 mg/kg bw/d in the second 1-year study. Adverse testes histopathology (atrophy) was seen at 254 mg/kg bw/d in the first 1-year study. The effects on prostate and testes were considered the secondary consequence of the delayed body weight development caused by the treatment.

In addition, decreases in body weight were observed at 330 mg/kg bw/d in the 5-week study and from 81 mg/kg bw/d in the first 1-year study. Decreases in body weight gain were observed from 81 mg/kg bw/d in the first 1-year study; these were observed were associated with a delayed glandular development of the prostate and testes. Decreased in food consumption were observed at 330 mg/kg bw/d in the 5-week study and at 254 mg/kg bw/d in the first 1-year study. Clinical signs of toxicity were observed at 330 mg/kg bw/d in the 5-week study (emaciation and dehydration), at 180 mg/kg bw/d in the 90-day study (stool abnormalities) and at 254 mg/kg bw/d in the first 1-year study.

Overall, taking into account the full range of observations, the lowest subchronic NOAEL in the dog was 4.3 mg/kg bw/d from the second 1-year study in the dog; the LOAEL in this study was 71 mg/kg bw/d. However, in the first 1-year study in the dog, the highest NOAEL was 7.9 mg/kg bw/d, with a LOAEL of 81 mg/kg bw/d. Since the first study provides the highest NOAEL which lies below the lowest LOAEL in this relevant species and study type, **the most reliable subchronic NOAEL in the dog was 7.9 mg/kg bw/d.**

#### Dermal

In a 28-day dermal study in rats no systemic effects were recorded at the top dose of 1000 mg/kg bw/d. However, localised dermal effects - slight erythema were observed from 300 mg/kg bw/d. **The NOAEL was 1000 mg/kg bw/d for systemic toxicity and 100 mg/kg bw/d for local dermal toxicity.**

#### Conclusion

Several effects were observed consistently between species; the main target organ of toxicity was the liver, with increases in liver weights, effects on some clinical chemistry parameters (indicative of liver damage) and/or changes to liver histopathology consistently seen in all three species. Adverse effects on the thyroid, including weight increases and changes to its histopathology (e.g. follicular hypertrophy/hyperplasia), were also seen in rat studies but not in mice and dogs. Histopathology of the nasal cavity was noted in rats and mice and tubular nephropathy was observed in the dog after exposure for 5 weeks. Adverse effects on the prostate, including increases in the incidence of small prostates and changes to its histopathology, and testes including changes to its histopathology (e.g. atrophy), were also seen in dog studies but not in rats and mice. However, these were considered the secondary consequence of the delayed body weight development caused by the treatment.. Adverse effects on body weight development and on some haematological parameters were observed in the rat, mouse and dog. Adverse effects on the kidney were observed in the dog. Localised dermal effects (slight erythema) were observed in the rat.

The dog was the most sensitive species, with adverse effects being observed at lower dose levels than in other species (e.g. observed LOAELs of 71 mg/kg bw/d in the dog compared to 211 mg/kg bw/d and 201 mg/kg bw/d in the rat and mouse, respectively).

**The lowest relevant NOAEL from all the available short-term toxicity studies therefore was 7.9 mg/kg bw/d** from the first 1-year study in the dog (██████ 1985). The LOAEL in this study was 81 mg/kg bw/d, based on decreases in body weight and body weight gain, changes in some haematology and clinical chemistry parameters, increases in liver weight and histopathology of the prostate.

#### **2.6.4. Summary of genotoxicity**

The genotoxic potential of cinmethylin has been investigated in a series of modern *in vitro* and *in vivo* studies. An old rat cytogenetics study is also available. A summary of the available genotoxicity studies is presented (Table 2.6.4-1) below.

The following key conclusions were obtained from the evaluation of the genotoxic information:

- Cinmethylin is not genotoxic.
- Classification for genotoxicity is not required. Further details are available in the aligned MCL dossier.
- The data requirements of Regulation 283/2013 have been met.

**Table 2.6.4-1. Summary of genotoxicity studies with cinmethylin**

Test system and Acceptability	Concentration/ dose levels	Purity (%)	Results	Reference
<b><i>In vitro studies</i></b>				
Ames Test (Reverse mutation assay) <i>S. typhimurium</i> strains (TA 98, TA 100, TA 1535, TA 1537) <i>E. coli</i> strain (WP2/uvrA) +/- S9	33 - 5600 µg/plate  Batch COD-002345 - artificial batch with increased impurity levels. 89.6 % (-) / (+) ratio = not specified.	89.6	Negative	Woitkowiak, 2018a (2018/1029052)
<i>Acceptable modern study</i>	33 - 5200 µg/plate  Batch COD-002314 - batch with new impurity. (-) / (+) ratio = 50:50	97.5	Negative	Woitkowiak, 2018b (2018/1029052)
<i>In vitro</i> forward mutation assay in mammalian cells (Mouse lymphoma assay). Mouse lymphoma L5178Y cells. +/- S9	3.8 – 80.0 µg/plate  Batch COD-002038. 93.5 % (-) / (+) ratio = 48:52	93.5	Negative	Sokolowski, 2018 (2018/1066678)
<i>Acceptable modern study</i>				
<i>In vitro</i> micronucleus test in human lymphocytes +/- S9	21.8 - 111 µg/plate  Batch COD-002038-[impurity] (-) / (+) ratio = 48:52	93.2	Negative	Naumann, 2018 (2018/1027282)
<i>Acceptable modern study</i>				
<b><i>In vivo studies</i></b>				
<i>In vivo</i> micronucleus test in mouse bone marrow (male and female NMRI mice) Oral, gavage	0, 500, 1000 and 2000 mg/kg bw  Batch COD-001950. 96.3 % (-) / (+) ratio = not specified.	96.3	Negative	██████████ 2018 (2018/1048783)
<i>Acceptable modern study</i>				
<i>In vivo</i> chromosome aberration assay in rat bone marrow (male and female Fischer 344 mice) Oral, gavage	0, 304, 1014 and 3043 mg/kg bw  Batch 513F. Purity (%): not specified. (-) / (+) ratio = not specified.	92	Negative	██████████ 1983 (CI-435-004)
<i>Old supplemental study</i>				

Cinmethylin was negative in these studies.

Cinmethylin was negative, when tested up to limit test concentrations, in two modern, GLP and guideline compliant Ames tests, using two different batches with different impurity profiles. Cinmethylin was non-mutagenic in a modern, GLP and guideline compliant mouse lymphoma thymidine kinase locus assay, in the presence and absence of metabolic activation up to cytotoxic concentrations. Cinmethylin was clearly not clastogenic or aneugenic to human lymphocytes in a modern, guideline compliant *in vitro* micronucleus assay conducted up to cytotoxic concentrations. Overall, there was no evidence of genotoxicity across these *in vitro* studies.

A modern, GLP and guideline compliant *in vivo* micronucleus test in mouse bone marrow, via oral administration, was available. No increase in the incidence of micronuclei was induced. Bone marrow exposure was demonstrated in this assay directly by the presence of cinmethylin and/or its metabolites in blood and indirectly by the systemic toxicity observed in the study from the mid dose. In an older, GLP but not strictly guideline compliant *in vivo* chromosome aberration assay in rat bone marrow, cinmethylin did not exhibit clastogenic activity. Overall, there was no evidence of genotoxicity across these *in vivo* studies.

According to Regulation (EU) 283/2013, photo-mutagenicity testing is not required for substances with a UV/VIS molar extinction/absorption coefficient less than  $1000 \text{ L} \times \text{mol}^{-1} \times \text{cm}^{-1}$ . There is no relevant absorption in the range 290 - 700 nm and the ultraviolet/visible molar extinction/absorption coefficient of the active substance is less than  $10 \text{ L} \times \text{mol}^{-1} \times \text{cm}^{-1}$  (see chemistry evaluation section B.2.4). Photo-mutagenicity testing is therefore not required for cinmethylin.

Overall, the HSE concludes that cinmethylin was not genotoxic *in vitro* or *in vivo* in a series of investigations that, together, meet the data requirements of Regulation 283/2013. Classification of cinmethylin for mutagenicity is not warranted.

### 2.6.5. Summary of long-term toxicity and carcinogenicity

The long-term toxicity and carcinogenic potential of cinmethylin have been investigated in rats (Wisatr and F-344) and mice (C57BL and B6C3F1), via the oral (dietary) route of exposure, in 18-month and 24-month studies. For each species two studies are available - one new/modern standard guideline study and one older study not conducted according to GLP and OECD test guidelines. The main findings are summarised (Table 2.6.5-1) below.

The following key conclusions were obtained from the evaluation of the long-term toxicity and carcinogenicity information:

- There is equivocal evidence of carcinogenicity in the female rat (liver carcinomas in female Wistar rats at 317 mg/kg bw/d) but not in the male rat or mice.
- HSE notes that the carcinogenicity response observed is very weak, sex- and species-specific, and occurs in the presence of significant generalised toxicity (effects on body weight, body weight gain and histopathology of thyroid and nasal cavities). In addition, although the liver is a target organ of toxicity in the rat, there was no clear evidence of pre-neoplastic lesions and/or adenomas. It is also noted that the incidence of liver carcinoma was within the extended laboratory HCD range and the Rita database HCD. Overall, there is insufficient evidence to classify cinmethylin for carcinogenicity. Further details on classification are available in the aligned MCL report.
- The data requirements of Regulation 283/2013 have been met.

**Table 2.6.5-1. Summary of long-term and carcinogenicity studies with cinmethylin**

Study and acceptability	Species/ Strain/ Groups	Doses	NOAEL (mg/kg bw/d) [ppm]	Effects at the LOAEL
24-month oral (dietary)	Rat (Wistar)	0, 200, 1000 and 5000 ppm	Carcinogenicity: F: 59 [1,000]	Carcinogenicity: <u>5,000 ppm (317 mg/kg bw/d):</u> ↑liver carcinomas (♀) – equivocal evidence of carcinogenicity.
GLP compliant. Guideline compliant.	Chronic phase: 10/sex/dose (12-months)	Equivalent to: Chronic phase: M: 0, 10, 51 and 265 mg/kg bw/d		
Cinmethylin Batch: COD-	Carcinogenicity phase:	F: 0, 13, 69 and		



Study and acceptability	Species/ Strain/ Groups	Doses	NOAEL (mg/kg bw/d) [ppm]	Effects at the LOAEL
002038 Purity (%): 93.5 (-) / (+) ratio = 48:52  2018 (2017/1093414)  <i>Acceptable</i>	50/sex/dose (24-months)	351 mg/kg bw/d  Carcinogenicity phase: M: 0, 9, 45 and 242 mg/kg bw/d  F: 0, 11, 59 and 317 mg/kg bw/d	Systemic chronic toxicity: M: 9 [200]  F: 59 [1,000]	Systemic chronic toxicity: <u>1,000 ppm (45 mg/kg bw/d):</u> Histopathology of the nasal cavities - degeneration/regeneration of the olfactory epithelium and proteinaceous exudate (♂).
24-month oral (dietary)  Non-GLP. Non-guideline.  Cinmethylin Batch: 513F (5-4- 0-0) Purity (%): 92 (-) / (+) ratio = not specified.  1985 (CI-427-001)  <i>Supplementary</i>	Rat (Fischer 344)  Chronic phase: 10/sex/dose (6- and 12-months) 15/sex/dose (18-months)  Carcinogenicity phase: 50/sex/dose (24-months)	0, 30, 100 and 3000 ppm  Equivalent to: Chronic and carcinogenicity phases: M: 0, 1.4, 4.7 and 144.2 mg/kg bw/d  F: 0, 1.7, 5.8 and 177.4 mg/kg bw/d	Carcinogenicity: M: 144 F: 177 [3,000]  (highest tested dose).  Systemic chronic toxicity: M: 4.7 F: 5.8 [100]	Carcinogenicity: N/A – cinmethylin demonstrated no carcinogenic potential.  Systemic chronic toxicity: <u>3,000 ppm</u> <u>(144/177 mg/kg bw/d):</u> ↑mortality (♂). ↑clinical signs of toxicity (hunched appearance and pale eyes) (♂). ↓food consumption (♂+♀). ↓body weight (♂+♀). ↓body weight gain (♂+♀). Changes in haematology parameters (indicative of mild anaemia and thrombocytosis) (♂+♀). ↑liver weight, relative (23 % in ♂, 14 % in ♀). ↑kidney weight (16 % in ♂) and kidney histopathology (severe chronic nephropathy) (not relevant to humans). ↑GGT (♂+♀). Histopathology of the liver (♂+♀).
18-month oral (dietary)  GLP compliant. Guideline compliant.  Cinmethylin Batch: COD- 002038	Mice (C57BL/6J Rj)  Chronic phase: 6/sex/dose (63- days)  Carcinogenicity phase: 50/sex/dose	0, 150, 1000 and 5000 ppm  Equivalent to: Chronic phase: M: 0, 32.1, 223.1 and 1175 mg/kg bw/d  F: 0, 34.8, 301.1	Carcinogenicity: M: 904 F: 939 [5,000]  (highest tested dose).	Carcinogenicity: N/A – cinmethylin demonstrated no carcinogenic potential.

Study and acceptability	Species/ Strain/ Groups	Doses	NOAEL (mg/kg bw/d) [ppm]	Effects at the LOAEL
Purity (%): 93.5 (-) / (+) ratio = 48:52  ██████, 2018d (2017/1094161)  <i>Acceptable</i>	(18-months)	and 1225 mg/kg bw/d  Carcinogenicity phase: M: 0, 25, 162.3 and 904 mg/kg bw/d  F: 0, 27, 183.8 and 939 mg/kg bw/d	Systemic chronic toxicity: M: N/A F: N/A  BMDL <sub>10</sub> (for body weight effects): 37.5	Systemic chronic toxicity: <u>150 ppm (25/27 mg/kg bw/d) (lowest tested dose):</u> ↓terminal body weight (♂+♀). ↓body weight gain (♂+♀). ↓food consumption (♀).
24-month oral (dietary)  Non-GLP. Non-guideline.  Cinmethylin Batch: 513F (5-4- 0-0) Purity (%): 92 (-) / (+) ratio = not specified.  ██████ 1986 (CI-428-001)  <i>Limited</i>	Mouse (B6C3F1)  Chronic phase: 10/sex/dose (12-months)  Carcinogenicity phase: 50/sex/dose (24-months)  120/sex controls; 20/sex for 12-months and 100/sex for 24-months.	0, 30, 100 and 1000 ppm  Equivalent to: Chronic and carcinogenicity phases: M: 0, 7.2, 22.1 and 231 mg/kg bw/d  F: 0, 8.3, 26.8 and 272 mg/kg bw/d	Carcinogenicity: N/A - no firm conclusion could be drawn.  Systemic chronic toxicity: M: 22.1 F: 26.8 [100]	Carcinogenicity: N/A - no firm conclusion could be drawn.  Systemic chronic toxicity: <u>1,000 ppm</u> <u>(231/272 mg/kg bw/d):</u> ↑liver weight, absolute (22 % in ♂, 19 % in ♀) and relative (27 % in ♂, 13 % in ♀).

In the new/modern study in rats, an increase in the incidence of liver carcinomas was observed in females at the top dose of 317 mg/kg bw/d at which systemic toxicity occurred. Systemic toxicity included: decreases in body weight and body weight gain, increases in GGT and liver weight, histopathology of the liver (cytoplasmic alterations and hypertrophy), thyroid (hypertrophy/hyperplasia and altered colloid) and nasal cavities (degeneration/regeneration of the olfactory epithelium and proteinaceous exudate). At a lower dose still - 45 mg/kg bw/d, adverse histopathology of the nasal cavities was observed.

In the older study in rats, there were no treatment-related increases in the incidence, severity or onset of tumours in any tissue up to the top dose of 177 mg/kg bw/d. At this dose systemic toxicity occurred; there was an increase in mortality, clinical signs of toxicity, liver weight (with concomitant histopathology) and GGT. Decreases in food consumption, body weight and body weight gain, and changes in some haematology parameters were also observed.

Therefore, there is equivocal evidence of carcinogenicity in the female rat at 317 mg/kg bw/d. Overall, **the lowest relevant NOAEL for carcinogenicity in the rat was 59 mg/kg bw/d.** The lowest NOAEL for systemic chronic toxicity in the rat was 4.7 mg/kg bw/d from the older chronic study in the rat; the LOAEL in this study was 144 mg/kg bw/d. However, in the new/modern chronic study in the rat the highest NOAEL was 9 mg/kg bw/d, with a LOAEL of 45 mg/kg bw/d. Since the new/modern study provides the highest NOAEL which lies below the lowest LOAEL in this relevant species and study type, **the most reliable NOAEL for systemic chronic toxicity in the rat was 9 mg/kg bw/d.**

In the new/modern study in mice, there were no treatment-related increases in the incidence, severity or onset of tumours in any tissue up to the top dose 939 mg/kg bw/d. At this dose systemic toxicity occurred; there was a decrease in terminal body weight, body weight gain and food consumption (from the low dose of 25/27 mg/kg bw/d), adverse histopathology of the nasal cavities (degeneration/regeneration of the olfactory epithelium and proteinaceous exudate) from the mid dose of 162 mg/kg bw/d, and an increase in liver weight with concomitant histopathology at the top dose of 904 mg/kg bw/d.

The older study in mice was considered inconclusive with regards to carcinogenicity due to limitations in the study. No clear evidence of systemic toxicity was apparent up to the top dose of 272 mg/kg bw/d, at which there was only an adverse increase (> 15 %) in liver weight.

Overall, cinmethylin was not carcinogenic in mice up to the highest dose tested of 939 mg/kg bw/d. **A LOAEL for systemic chronic toxicity in the mouse of 25/27 mg/kg bw/d (M/F) was identified. Alternatively, the lowest BMDL<sub>10</sub> for effects on body weight in females – 37.5 mg/kg bw/d, can be considered as a suitable reference point.**

Overall, therefore, there is equivocal evidence of carcinogenicity in the female rat, but the evidence is insufficient for classification. Further details are available in the aligned MCL report.

### 2.6.6. Summary of reproductive toxicity

The reproductive toxicity of cinmethylin has been investigated in a new/modern guideline dietary 2-generation study in rats and a new/modern guideline gavage pre-natal developmental toxicity study in rabbits. A relatively old pre-natal developmental toxicity study in rats is considered to be of sufficient quality to meet the data requirements. An older 2-generation study in rats and the two older pre-natal developmental toxicity studies in rabbits have been discounted due to significant limitations, which compromise their reliability. The main findings are summarised (Table 2.6.6-1) below.

The following key conclusions were obtained from the evaluation of the reproductive toxicity information:

- There were no effects on fertility and reproductive performance up to dose levels causing generalised toxicity.
- There were no specific developmental effects in rats or rabbits up to doses causing maternal toxicity.
- Classification for reproductive toxicity is not required. Further details are available in the aligned MCL dossier.
- The data requirements of Regulation 283/2013 have been met.

**Table 2.6.6-1. Summary of reproductive toxicity studies with cinmethylin**

Study and acceptability	Species/ Strain/ Groups	Doses	NOAEL (mg/kg bw/d) [ppm]	Effects at the LOAEL
2-generation study (dietary).  GLP-compliant. OECD test guideline (No. 416) compliant.  Cinmethylin Batch: COD- 002038 Purity (%): 93.5 (-) / (+) ratio = 48:52  [REDACTED] 2018a 2017/1094504 and [REDACTED] 2018/1099151  <i>Acceptable.</i>	Rat (Wistar).  Male and female.  25/sex/dose.	0, 125/250, 500/1000 and 2500/5000 ppm.  Equivalent to: 0, 19.7-21.8, 79.4- 87.7 and 412-450 mg/kg bw/d in males.  0, 21.4-22.8, 82.2- 90.1 and 417-460 in females (pre- mating)  0, 20.6-20.7, 81.3- 81.6 and 394- 395 mg/kg bw/d in females (during gestation).  0, 23.5-23.8, 93.8- 96.9 and 473- 481 mg/kg bw/d in females (during lactation).	Reproductive toxicity: <b>394</b> [2500/5000]  (the highest dose tested)	Reproductive toxicity: N/A – no adverse treatment-related findings were observed up to the top dose.
			Parental toxicity: <b>80</b> [500/1000]	Parental toxicity: <u>2,500/5,000 ppm</u> <u>(394 - 481 mg/kg</u> <u>bw/d):</u> ↓food consumption (♀) ↓body weight (♀) ↓body weight gain (♀) ↑liver weight, absolute (19-24 % in ♂, 19-20 % in ♀) and relative (22- 26 % in ♂, 21-25 % in ♀). ↑thyroid weight, absolute (15-21 % in ♂, 15-22 % in ♀) and relative (17- 23 % in ♂, 19-24 % in ♀). Histopathology of the thyroid – hypertrophy/hyperp lasia of follicular epithelial cells. Histopathology of the nasal cavity – degeneration/regen eration of the olfactory epithelium.
			Developmental/Off spring toxicity: <b>394</b> [2500/5000]  (the highest dose tested)	Developmental/Off spring toxicity: N/A – no adverse treatment-related findings were observed up to the top dose.
2-generation study (dietary).  GLP-compliant. Non-OECD test guideline	Rat (Sprague Dawley).  Male and female.  20-30/sex/dose.	0, 200, 2000 and 20000 ppm  Equivalent to: 0, 11.3-16.1, 115- 163 and 1289-2125	Reproductive toxicity: Not set due to study limitations.	Reproductive toxicity: N/A - due to study limitations.
			Parental and offspring toxicity:	Parental and offspring toxicity:

Study and acceptability	Species/ Strain/ Groups	Doses	NOAEL (mg/kg bw/d) [ppm]	Effects at the LOAEL
compliant.  Cinmethylin Batch: 513K Purity (%): 92.4 (-) / (+) ratio = not specified. and Batch: 513N Purity (%): 93 (-) / (+) ratio = not specified.  ■■■■■, 1986 CL430-001  <i>Not acceptable</i>		mg/kg bw/d in males.  0, 13.9-17.3, 139-170 and 1450-2213 mg/kg bw/d in females (during pre-mating).  0, 12.8-14.7, 130-148 and 1434-1609 mg/kg bw/d in females (during gestation).  0, 30.4-34.0, 280-353 and 2256-2893 mg/kg bw/d in females (during lactation).	Not set due to study limitations.	N/A - due to study limitations.
Pre-natal developmental toxicity study (oral gavage)  GLP compliant. Non-OECD test guideline compliant.  Cinmethylin Batch: 513H Purity (%): 92.4 (-) / (+) ratio = not specified.  ■■■■■, 1984 CI-432-001  <i>Acceptable</i>	Rat (Sprague Dawley).  Male and female.  25 pregnant females/dose.	0, 30, 300, 1000 and 2000 mg/kg bw/d.	Maternal toxicity: <b>30</b>	Maternal toxicity: <u>300 mg/kg bw/d</u> : Clinical observations (excess salivation and urine-stained abdominal fur). ↓body weight gain (seen in the first few days of the study and over the administration period).
			Developmental toxicity: <b>300</b>	Developmental toxicity: <u>1000 mg/kg bw/d</u> : ↑incidence of anomalies (predominantly variations) – indicative of delayed development.
Pre-natal developmental toxicity study (oral gavage)  GLP compliant. OECD test guideline No. 414 (2001) compliant.  Cinmethylin Batch: COD-	Rabbit (New Zealand White).  Female.  25 inseminated females/dose.	0, 25, 80, 250 and 320 mg/kg bw/d.	Maternal toxicity: <b>80</b>	Maternal toxicity: <u>250 mg/kg bw/d</u> : ↓body weight gain (22 %) (over the duration of the study, including the first few days of administration (GD 6 – 9)). ↑liver weight, absolute (18 %) and relative (21 %).

Study and acceptability	Species/ Strain/ Groups	Doses	NOAEL (mg/kg bw/d) [ppm]	Effects at the LOAEL
001950 Purity (%): 96.3 (-) / (+) ratio = not specified.  2018 b 2015/1158053  <i>Acceptable</i>			Developmental toxicity: <b>80</b>	Clinical chemistry (↑GGT, 51 %). Developmental toxicity: <u>250 mg/kg bw/d</u> : ↓foetal weight (14 %).
Pre-natal developmental toxicity study (oral gavage)  GLP compliant. Non-OECD test guideline compliant.  Cinmethylin Batch: 513N Purity (%): 93 (-) / (+) ratio = not specified.  <i>Not acceptable.</i>  1985 CI-432-002	Rabbit (New Zealand White).  Female.  19-20 inseminated females/dose.	0, 3, 30 and 100 mg/kg bw/d.	Not set due to study limitations.	N/A - due to study limitations.
Pre-natal developmental toxicity study (oral gavage)  GLP compliant. Non-OECD test guideline compliant.  Cinmethylin Batch: not specified. Purity (%): 92.4 (-) / (+) ratio = not specified.  <i>Not acceptable.</i>  1987 CL-432-003	Rabbit (New Zealand White).  Female.  20 inseminated females/dose.	0, 30, 200, 500 and 750 mg/kg bw/d.	Not set due to study limitations.	N/A - due to study limitations.

### Effects on Sexual Function and Fertility

The potential of cinmethylin to adversely affect sexual function and fertility has been well investigated in a standard 2-generational dietary study conducted in rats.

Cinmethylin did not adversely affect fertility and reproduction; oestrus cyclicity, mating performance and fertility, differential ovarian follicle count, pup survival and sex ratio were not affected by treatment up to the top dose of 394 - 481 mg/kg bw/d. At this dose parental but not offspring toxicity occurred. In addition, examination of the reproductive organs and specific investigations of sperm parameters did not reveal any treatment-related changes. Therefore, **a NOAEL for reproductive toxicity of 394 mg/kg bw/d** (highest dose tested) can be identified from this study.

In relation to general toxicity in parental animals, reductions in food consumption, body weights and body weight gains were recorded at the top dose of 394 – 481 mg/kg bw/d. Increases in liver and thyroid weights (with concomitant thyroid histopathology) were also seen at the top dose of 394 – 481 mg/kg bw/d. In addition, adverse histopathological changes were seen in the nasal cavities at the top dose of 394 – 481 mg/kg bw/d. There were no treatment-related effects in parental animals at the low and mid doses. Therefore, **a NOAEL of 80 mg/kg bw/d can be identified for parental toxicity** from this study. **As no offspring toxicity was observed up to the top dose, a NOAEL of 394 mg/kg bw/d** (highest dose tested) can be identified from this study.

### Developmental Toxicity

The developmental toxicity of cinmethylin has been investigated in gavage pre-natal developmental toxicity studies, conducted in rats (an older study) and rabbits (a guideline new/modern study). Additional information on the developmental toxicity potential of cinmethylin is also available from the new/modern 2-generation study.

In the rat developmental study, there were no effects of treatment on malformations (external, visceral and skeletal) up to the top dose of 2,000 mg/kg bw/d. Foetal weight was reduced at 2000 mg/kg bw/d in males and females; in addition, there was a marginal increase in post-implantation loss (due to two whole litter resorptions) at the top dose of 2,000 mg/kg bw/d. Incidences of skeletal and visceral variations were increased in the top two doses, from 1,000 mg/kg bw/d. At the top dose of 2000 mg/kg bw/d, the incidences of visceral (slight to moderate dilated ventricles in the brain) and skeletal variations such as wavy ribs and incompletely ossified structures were also significantly increased. Most developmental effects (skeletal variations, incomplete ossification, decreased foetal weight and post-implantation loss) were considered the unspecific, secondary consequence of the maternal toxicity recorded from 300 mg/kg bw/d (limited number of clinical signs of toxicity and decreases in body weight gain). No maternal toxicity was observed at the low dose (30 mg/kg bw/d). The increased incidence of slight to moderate dilated ventricles in the brain at 2,000 mg/kg bw/d (a dose much higher than the limit dose) was associated with severe maternal toxicity (deaths, significant reductions in body weights, numerous clinical signs of toxicity and liver effects). Slight to moderate dilation of brain ventricles is considered to be a variation and to represent a developmental delay with no detrimental or irreversible consequences for the foetus. Therefore, it is most likely that this abnormality was the secondary consequence of the excessive maternal toxicity occurring at the high dose of 2000 mg/kg bw/d. Overall, there was no evidence of specific developmental toxicity in the rat. Based on these findings, **the NOAELs proposed by the HSE for maternal and developmental toxicity in the rat are 30 and 300 mg/kg bw/d, respectively**, based on the lack of relevant effects at these dose levels.

In the rabbit developmental study, there were no effects of treatment on external, skeletal and soft tissue alterations (malformations and variations) up to the top dose of 320 mg/kg bw/d. Foetal weight was reduced from 250 mg/kg bw/d, at which maternal toxicity (reduced body weight gain, increased liver weight with associated changes in clinical chemistry (GGT)) occurred. Based on these findings, **the NOAELs proposed by the HSE for developmental and maternal toxicity in the rabbit are 80 mg/kg bw/d**, based on the lack of relevant effects at these dose levels.

In addition, in the rat 2-generation study, there were no effects of treatment on pup survival, sex ratio, pup bodyweight, nipple development, anogenital parameters and sexual maturation of pups (vaginal opening and preputial separation) up to the top dose of 394 – 481 mg/kg bw/d. At this dose parental (reduced food consumption, body weight, body weight gain, increased liver and thyroid weight, histopathology of the thyroid and nasal cavity) but not offspring toxicity occurred.

Classification for reproductive toxicity (either fertility or development) is therefore not required. Further details are available in the aligned MCL dossier.

### 2.6.7. Summary of neurotoxicity

The neurotoxic potential of cinmethylin has been investigated in Wistar rats in an oral (gavage) acute neurotoxicity study. Neurobehavioural parameters and histopathological examinations of neuronal tissues (i.e. sciatic nerve) were also part of the examinations of the 28-day and 90-day dietary toxicity studies in Wistar rats.

The following key conclusions were obtained from the evaluation of the neurotoxicity information:

- Cinmethylin is acutely neurotoxic from a dose of 1,000 mg/kg bw. An acute neurotoxicity NOAEL of 300 mg/kg bw was established.
- However, no neurotoxicity or neuropathology was observed on repeated exposure.

**Table 2.6.7-1. Summary of neurotoxicity studies with cinmethylin**

Study and Acceptability	Species/ Strain/ Groups	Doses	NOAEL (mg/kg bw) [ppm]	Effects at the LOAEL
Acute oral (gavage) neurotoxicity  GLP compliant Guideline compliant  Cinmethylin Batch: COD- 002038 Purity (%): 93.5 (-) / (+) ratio = 48:52  ██████████, 2018e (2016/1345328)  <i>Acceptable</i>	Rat (Wistar)  10/sex/dose	0, 300, 1000 and 2000 mg/kg bw	Acute neurotoxicity: M: 1000 F: 300  Systemic toxicity: M: 1000 F: 300	Acute neurotoxicity: <u>1,000 mg/kg bw</u> Alterations in FOB and MA parameters (e.g. retarded righting response, reduced number of rearings and decreased motor activity) (♀), on the day of administration only.  Systemic toxicity: <u>1,000 mg/kg bw</u> Salivation and clinical signs of toxicity, on the day of administration only.

In the acute oral (gavage) neurotoxicity study in the rat, cinmethylin was acutely neurotoxic (changes in FOB and MA parameters) from the mid dose of 1,000 mg/kg bw in females and at the top dose of 2,000 mg/kg bw in males. In addition, minimal axonal degeneration of the sciatic nerve was seen at the top dose in both sexes (more pronounced in females). These acute neurotoxic effects were observed in the presence of some generalised toxicity (clinical signs of toxicity), which occurred from the mid dose (1,000 mg/kg bw) in females and at the top dose in males. Based on these findings, **a NOAEL of 300 mg/kg bw was identified for both acute neurotoxicity and generalised toxicity in the rat.**

In rats, clinical findings potentially relating to neurotoxicity (e.g. ataxia, hypoactivity, loss of righting reflex, hypersensitive to touch and depression of myotactic placing reflex) were observed in the old acute oral toxicity study (██████████, 1982) at doses of 1014 – 5680 mg/kg bw. Similarly, clinical findings potentially relating to neurotoxicity (e.g. decreased activity and tip-toe gait) were observed in the old acute inhalation toxicity study (██████████ *et al.*, 1986) at 3.5 mg/L. However, such effects were not seen up to 2,000 mg/kg bw or 5 mg/L in the more reliable modern oral and inhalation acute toxicity studies in the rat. No clinical signs of toxicity were seen by the dermal route up to 5,000 mg/kg bw.

In mice, clinical findings potentially related to neurotoxicity (e.g. hypoactivity and unsteady stance) were observed only in a relatively old acute oral toxicity study (██████████, 1982) at 5072 mg/kg bw. These effects were observed sporadically and animals recovered within 4 days.

Overall, there was no clear evidence of neurotoxicity in the acute toxicity (LD50) studies; however, it should be noted that no specific neurobehavioural or neuropathology investigations are generally performed in these studies.



There were no neurotoxic effects of cinmethylin observed across all functional observations (FOB) and motor activity (MA) investigations and no neuropathology findings following repeated exposure in the new/modern 28- and 90-day oral studies in rats and mice, as well as the 28-day dermal study in rats up to doses ranging from 700 to 1,000 mg/kg bw/d.

It is most likely that the minimal axonal degeneration of the sciatic nerve and associated FOB and MA findings noted at 2,000 mg/kg bw/d in a specific rat neurotoxicity study are the acute consequences of high gavage doses of cinmethylin, possibly related to a C<sub>max</sub>, bolus effect.

Overall, cinmethylin is acutely neurotoxic from a dose of 1,000 mg/kg bw (NOAEL = 300 mg/kg bw); however, no neurotoxicity or neuropathology was observed on repeated exposure. Based on these effects, classification with STOT-SE 2 (H371) is proposed (see aligned MCL report).

## 2.6.8. Summary of further toxicological studies on the active substance

### Mechanistic studies investigating liver effects

Two relatively old mechanistic studies on liver enzyme activity induction, one each in rats and mice, after single gavage and repeated dietary cinmethylin administration for 7 weeks, were submitted. In addition, ToxCast data considering non-endocrine related endpoints were presented.

The study in rats showed limited evidence of induction of hepatic CYP (cytochrome P) activities, preferentially in females from a dose of 29.2 mg/kg bw/d. Similarly, the study in mice showed limited evidence of induction of hepatic CYP activities, in both sexes from a dose of 38.9/40.7 mg/kg bw/d in males and females respectively.

ToxCast data were evaluated and summarised. Cinmethylin was tested in 689 assay endpoints and generated 43 hit calls in these assay endpoints (12 are discussed under the evaluation of endocrine disrupting properties). The cytotoxicity region, relevant to identify assays potentially confounded by cytotoxicity, is centered around the median cytotoxicity AC<sub>50</sub> (activity concentration at 50 % of maximal activity) of 23.54 µM, with the lower limit of the cytotoxicity region being 3.63 µM. Up to 23.54 µM, only a few assays were active. The most sensitive endpoint has been shown to be the induction of the gene response element PXRE (pregnane X receptor (PXR) response elements). PXRE induction reached half-maximal response (AC<sub>50</sub>) at 2.631 µM and maximal response of near 4-fold induction at 30 µM. Furthermore, ToxCast identified induction of gene expression of three human CYP450 enzyme transcripts, activity towards butyryl cholinesterase and towards the solute carrier protein SLC6 as endpoints reactive up to the median cytotoxicity level. All other endpoints were not sensitive up to the median cytotoxicity region. Overall, cinmethylin can be considered as a rather inactive substance. All ToxCast data are of limited value to the risk assessment and are considered to be supplemental information.

Overall, the information presented (the two liver mechanistic studies conducted in the 1980s and the ToxCast data) is not sufficient to either propose or establish a MoA for the liver effects seen in all three species investigated (rat, mouse and dog). The only conclusion that can be drawn is that some liver CYP activities are marginally increased in rats and mice, possibly as a consequence of PXR activation.

### Endocrine Disruption (ED)

An assessment for potential endocrine disrupting properties of cinmethylin in line with the new EFSA/ECHA guidance (<https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311>) and the recently published scientific criteria (Regulation 605/2018) has been provided by the applicant. The following summary conclusions are reached by HSE.

### Estrogenity (E), androgency (A) and steroidogenesis (S) modalities

In all species investigated (rat, mouse and dog) there were no specific adverse effects on reproductive organs and related endocrine glands (e.g. adrenal, pituitary, mammary). In addition, there were no specific adverse effects on reproduction in the rat and on development in rats and rabbits. The effects on the prostate in the dog and on post-implantation loss in rats were the unspecific secondary consequence of generalised/maternal toxicity. The ToxCast/EDSP21 'in vitro mechanistic' dataset indicates that cinmethylin does not specifically perturb the pathways related to endocrine activity for the E, A and S-modalities. EAS-mediated parameters have been

sufficiently investigated, based on a modern two-generation reproductive toxicity study by [REDACTED] (2018a) (OECD TG No. 416; test protocol according to latest version of January 2001). Based on scenario 1a of the ECHA/EFSA guidance for the identification of endocrine disruptors in the context of Regulations (EU) 528/2012 and (EC) No 1107/2009, there is no indication of adversity for the EAS modalities. In addition, EAS adversity has been sufficiently investigated. There is also robust evidence from the ToxCast ER bioactivity model of a lack of endocrine activity for the E modality. The first condition of the ED criteria is not met; therefore, it is possible to conclude that cinmethylin does not meet the ED criteria for the EAS modalities and that these modalities have been sufficiently investigated.

#### Thyroid (T) modalities

Effects on thyroid weight (increases) were recorded in studies in rats (in the 90-day and 2-generation study) but no treatment related changes were seen in studies in mice and dogs. Effects on thyroid histopathology (hypertrophy/hyperplasia and altered colloid) were consistently recorded in study in rats (in the 28-day, 90-day, chronic toxicity/carcinogenicity and 2-generation study) but no treatment related changes were seen in studies in mice and dogs. The ToxCast/EDSP21 ‘*in vitro* mechanistic’ dataset indicates that cinmethylin does not specifically perturb the pathways related to direct thyroid activity. The applicant suggested that thyroid effects are a consequence of liver enzyme induction (postulated indirect MoA), however, this is not sufficiently substantiated. A detailed comparative MoA analysis is necessary to assess whether thyroid adversity is secondary to liver toxicity. The weight of evidence analysis should include a time- and dose-concordance analysis of liver and thyroid effects. T-mediated adversity has been sufficiently investigated, based on the following studies in which thyroid effects were identified:

- 28-day oral toxicity studies in the rat (OECD TG No. 407)
- 90-day oral toxicity studies in the rat (OECD TG No. 408)
- Chronic toxicity / carcinogenicity studies in the rat (OECD TG No. 453)
- 2-generation reproductive toxicity study in the rat (OECD TG No. 416).

However, T-mediated activity (in particular UGT and thyroid hormones) has not been sufficiently addressed. Based on scenario 1b of the ECHA/EFSA guidance for the identification of endocrine disruptors in the context of Regulations (EU) 528/2012 and (EC) No 1107/2009, there is an overall indication of adversity. Some information from ToxCast on thyroid activity (direct thyroid MoAs) has been presented and direct thyroid MoAs have been excluded; however, more detailed information is required to substantiate the postulated indirect MoA. HSE notes that the assessment of the proposed thyroid MoA is very concise; in addition, there is a lack of thyroid hormone (e.g. T3, T4, TSH) measurements, CAR/PXR activation and UGT data (MIE - molecular initiating event). It is not possible to conclude (in the limited study by [REDACTED], 2011) that in the absence of morphological changes in the thyroid any changes in hormone levels can be excluded. Mechanistic data to support the postulated indirect MoA is required. In addition, a detailed comparative MoA analysis is necessary to assess whether thyroid adversity is secondary to liver effects. The weight of evidence analysis should include a more in-depth time- and dose-concordance analysis of liver and thyroid effects, including additional information on some key events.

#### Overall

HSE concludes that for the EAS modalities cinmethylin is not an ED and its ED potential has been sufficiently investigated. However, in relation to the T modality a conclusion cannot be reached as further information is required. The following further data and information is being generated by the applicant:

- *In vivo* thyroid hormone and enzyme induction study in rats
- *In vitro* comparative enzyme activity study in rat and human hepatocytes
- Description of the postulated MoA
- Empirical support of the postulated MoA
- Conclusion on MoA analysis
- A case to address the potential for effects on post-natal neurological development in offspring
- A case to address the potential relevance to humans (or lack thereof) of the proposed MoA

### **Immunotoxicity**

No specific immunotoxicity study with cinmethylin is available. However, an assessment of the immunotoxicity potential of cinmethylin can be performed by considering the available repeat dose toxicity, carcinogenicity and reproductive toxicity studies. The standard regulatory studies conducted with cinmethylin have assessed its potential impact on a number of immune-related endpoints including haematological parameters such as white blood cell count, spleen and thymus weights, histopathology of the spleen, thymus, lymph nodes and bone marrow. There were no consistent 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 no evidence of a specific immunotoxic effect on any immune-related parameter. Sporadic effects on single parameters were observed in some studies but none supported a specific and consistent immunotoxic effect.

Overall, HSE concludes that cinmethylin does not affect the immune system, and a specific *in vivo* immunotoxicity study is not required.

## **2.6.9. Summary of toxicological data on impurities and metabolites**

### **Relevant impurities**

The toxicity of impurity Reg. No. **4539586** (cineol alcohol) was investigated in a range of the studies. Genotoxicity data are available for cineol alcohol. Based on two Ames tests (Barfknecht *et al.*, 1986; Brooks & Wiggins, 1987) and two chromosome aberration tests (Meyer & Wiggins, 1988a and 1988b) cineol alcohol is considered not to be genotoxic. Studies in rodents provide evidence for moderate acute oral (██████████ 1986a), and low acute dermal (██████████ 1988a) and inhalation toxicity (██████████, 1985a). No potential for skin irritation in rabbits (██████████, 1987a) and no dermal sensitisation in guinea pigs (██████████, 1986b) was reported. Cineol alcohol was found to be a severe eye irritant in rabbits (██████████ 1985a). Cineol alcohol has harmonised classification as Eye Dam. Cat. 1 (H318). A 28-day oral toxicity study in rats was submitted. In this study, effects on body weight and haematology were identified at 100 mg/kg bw/day in females.

On the basis of the harmonised classification for Eye Dam. 1, for which the generic concentration limit (GCL) is 1 % (for classification of a mixture with Eye Irrit. 2), and taking into account that cinmethylin is not classified for eye irritation, at a maximum level of 0.4 % (which is higher than 1/10 of the GCL for classification<sup>1</sup> of a mixture with Eye Irrit. 2), the toxicological relevance of impurity Reg. No. 4539586 (cineol alcohol) cannot be excluded. Overall, impurity 4539586 is a toxicologically relevant impurity of cinmethylin. However, at the specified level it is of no toxicological concern as it does not trigger classification of cinmethylin.

### **Metabolites**

The following metabolites were selected for potential inclusion in the plant and/or livestock residue definitions for risk assessment based on their significant occurrence in the plant and livestock metabolism studies:

- M684H001 (cinmethylin benzoate)
- M684H002 (chemical name available in Volume 3 CA B6)
- M684H005 (chemical name available in Volume 3 CA B6)
- M684H006 (chemical name available in Volume 3 CA B6)
- M684H009 (N-(2-methylbenzoyl)glycine)
- M684H010 (2-hydroxymethyl benzoate)
- M684H012 (sum of isomers) (cinmethylin benzyl alcohol glucuronide)
- M684H021 (sum of isomers) (chemical name not available)
- M684H022 (sum of isomers) (chemical name not available)
- M684H026 (2-hydroxypropyl 2-hydroxycineol)
- M684H039 (chemical name not available)
- M684H058 (1-O-(2-methylbenzoyl) hexopyranuronic acid)
- M684H059 (2-benzofuran-1(3H)-one)

<sup>1</sup> ECHA (2019) Interpreting the definition of relevant impurities.

To assess the toxicological properties of these metabolites, all the available data (including data relating to cinmethylin) were considered. These included presence of these metabolites in rat ADME and toxicity studies performed with the parent, structural similarity to the parent, *in silico* genotoxicity assessment, read across prediction of genotoxicity and data gathering from online sources (i.e. ECHA REACH and C&L databases).

For **M684H001, M684H002, M684H005, M684H006, M684H010, M684H012 and M684H026**, the toxicity of these metabolites is covered by the toxicity data of the parent and if a risk assessment were to be required, the **dietary reference values of cinmethylin** could be used. Therefore, these metabolites are considered to be of equivalent toxicity to the parent, toxicologically relevant and potential candidates for inclusion in the residue definitions for risk assessment.

Metabolite **M684H009** (the glycine conjugate of 2-methylbenzoic acid) is a minor metabolite of fatty acids and is listed in the human metabolome database as a naturally occurring compound. This metabolite is considered to be of no toxicological concern and of significantly lower toxicity than cinmethylin. On this basis, it should not be considered further (from a toxicological point view) for the purposes of the residue definitions. However, if a dietary risk assessment were to be required, the **BAT (Biological Tolerance) value of 57 mg/kg bw/day** could be used as a reference value.

Metabolite **M684H058** (the glucuronide conjugate of 2-methylbenzoic acid) is of no toxicological concern (and of significantly lower toxicity than cinmethylin), as highlighted by the use of the TTC Cramer Class I value in the Scientific Opinion of Flavouring Group Evaluation 20. On this basis, M684H058 should not be considered further (from a toxicological point view) for the purposes of the residue definitions. However, if a risk assessment were to be required, the chronic **TTC Cramer Class I value of 30 µg/kg bw/day** could be used as reference value.

For **M684H021, M684H022, M684H039 and M684H059**, there are negative genotoxicity (Q)SAR predictions but no information on relative levels in rat and/or mouse plasma compared to the parent or on levels in rat excreta > 10 % of the administered dose. Therefore, the toxicity of these metabolites is not covered by the toxicity data of the parent and if a dietary risk assessment were to be required, the **Cramer class III TTC chronic value of 1.5 µg/kg bw/day and acute value of 5 µg/kg bw<sup>2</sup>** could be used in a first-tier assessment. In addition, due to the structural similarity of metabolites M684H021, M684H022 and M684H039, these metabolites should be combined in the assessment; M684H059 is not structurally similar to metabolites M684H021, M684H022 and M684H039 and does not need to be combined in the assessment. Overall, these metabolites are of potential higher toxicity than cinmethylin, toxicologically relevant and potential candidates for inclusion in the residue definitions for risk assessment.

#### 2.6.10. Summary of medical data and information

Cinmethylin is a new herbicide active ingredient, which has not yet been sold commercially and aside from pilot scale preparations, has been handled by only a limited number of employees or contract scientists involved in regulatory and field biological testing. Therefore, human data is limited at this time. Adverse health effects suspected to be related to cinmethylin exposure have not been observed. There is no evidence or data available to support any findings in relation to poisoning with cinmethylin.

#### 2.6.11. Overview of all available studies relevant to reference value setting

The following table gives an overview of all the available studies relevant to reference values setting.

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<sup>2</sup> EFSA (2012) Scientific Opinion on Evaluation of the Toxicological Relevance of Pesticide Metabolites for Dietary Risk Assessment, EFSA Journal 2012;10(07):2799

**Table 2.6.11-1. Summary of all studies relevant to setting of reference values**

Study, guideline, reference, acceptability	Species, doses tested	NOAEL mg/kg bw/d [ppm]	LOAEL mg/kg bw/d [ppm]	Adverse effects at LOAEL
28-day oral (dietary)  GLP compliant Guideline compliant ██████ <i>et al.</i> , 2015 (2015/107632 9)  <i>Acceptable</i>	Rat (Wistar)  0, 1500, 5000 and 15000 ppm  Equivalent to: M: 0, 137, 477 and 1522 mg/kg bw/d  F: 0, 141, 477 and 1331 mg/kg bw/d	M: 137 F: 141 [1,500]	M: 477 F: 477 [5000]	<u>5,000 ppm (477 mg/kg bw/d)</u> ↑water consumption (21 % in ♂). Changes in clinical chemistry parameters (GGT, protein, globulin, albumin, cholesterol, triglycerides, glucose, calcium) (♂+♀). ↑liver weight, absolute (23 % in ♂, 11 % in ♀) and relative (22 % in ♂, 18 % in ♀). ↑kidney weight, relative (15 % in ♂). Histopathology of the liver – enlarged with hepatocellular hypertrophy (♂+♀). Histopathology of the thyroid - follicular hypertrophy/hyperplasia (♂+♀). Histopathology of the kidney - eosinophilic droplets (♂) (not relevant to humans).
28-day oral (dietary)  GLP compliant Guideline compliant ██████ 2016 (2014/116271 0)  <i>Acceptable</i>	Mice (C57BL/6J Rj)  0, 400, 1200 and 4000 ppm  Equivalent to : M: 0, 95.1, 295.9 and 791.4 mg/kg bw/d.  F: 0, 92.4, 254, 1015.6 mg/kg bw/d	M: 296 F: 254 [1,200]	M: 791 F: 1016 [4,000]	<u>4,000 ppm (791/1016 mg/kg bw/d)</u> : ↓body weight gain (♂). Changes in clinical chemistry parameters (BIL, PROT, ALB, GLOB, CHOL, TRIG) (♂). ↑liver weight, absolute (16 % in ♂, 26 % in ♀) and relative (19 % in ♂, 22 % in ♀).
5-week oral (dietary)  Non-GLP Non-guideline ██████, 1984 (CI-420-004)	Beagle dogs  0, 300, 3000, 10000 and 30000 ppm  Equivalent to: M: 0, 8.8, 131.1, 338.7	M: 131 F: 104 [3,000]	M: 330 F: 334 [3,000]	<u>≥ 10,000 ppm (330/334 mg/kg bw/d)</u> : ↑liver weight, absolute (38 % in ♂, 20 % in ♀) and relative (35 % in ♂, 27 % in ♀). Histopathology of the liver – hepatopathology.

Study, guideline, reference, acceptability	Species, doses tested	NOAEL mg/kg bw/d [ppm]	LOAEL mg/kg bw/d [ppm]	Adverse effects at LOAEL
<i>Acceptable in a WoE approach</i>	and 330.0 mg/kg bw/d F: 0, 10.5, 103.6, 334.2 and 433.6 mg/kg bw/d			
90-day oral (dietary)  GLP compliant Guideline compliant  ██████████, 2018a (2014/122837 0)  <i>Acceptable</i>	Rat (Wistar)  0, 1000, 3000 and 10000 ppm  Equivalent to: M: 0, 67, 211 and 792 mg/kg bw/d  F: 0, 79, 240 and 814 mg/kg bw/d	M: 67 F: 79 [1,000]	M: 211 F: 240 [3,000]	<u>3,000 ppm (211/240 mg/kg bw/d):</u> Changes in haematology parameters (↓prothrombin time) (♀). Changes in clinical chemistry parameters (♂+♀). ↑liver weight, absolute (12 % in ♂, 12 % in ♀) and relative (18 % in ♂, 11 % in ♀). Histopathology of the liver – hypertrophy (♂+♀). Histopathology of the thyroid - follicular hypertrophy/hyperplasia (♂+♀). Histopathology of the nasal cavity – proteinaceous exudation and degeneration of the olfactory epithelium (♂+♀).
90-day oral (dietary)  Non-GLP Non-guideline  ██████████ 1983 (CI-425-001)  <i>Supplementary</i>	Rat (Fischer 344)  0, 30, 100, 300 and 1000 ppm  Equivalent to: M: 0, 2.18, 7.51, 22.51 and 75.78  F: 0, 2.61, 8.73, 26.08 and 88.56	M: 76 F: 89 [1,000]	N/A.	Not applicable, no adverse effects were seen at the top dose.
90-day oral (dietary)  GLP compliant Guideline	Mice (C57BL/6J Rj)  0, 200, 1000 and 5000 ppm	M: 43 F: 58 [200]	M: 201 F: 285 [1,000]	<u>1,000 ppm (201/285 mg/kg bw/d):</u> ↓body weight gain (17 % in ♀). Changes in clinical chemistry parameters

Study, guideline, reference, acceptability	Species, doses tested	NOAEL mg/kg bw/d [ppm]	LOAEL mg/kg bw/d [ppm]	Adverse effects at LOAEL
compliant ██████████ 2018b (2015/1005983) <i>Acceptable</i>	Equivalent to : M: 0, 43, 201 and 1200 mg/kg bw/d  F: 0, 58, 285 and 1304 mg/kg bw/d			(TRIG, TPROT, ALB, CHOL) (♂). ↑liver weight, absolute (9 % in ♂) and relative (10 % in ♂).
90-day oral (dietary)  Non-GLP Non-guideline ██████████ 1983 (CI-425-002) <i>Supplementary</i>	Mice (B6C3F1)  0, 30, 100, 300 and 1000 ppm  Equivalent to : M: 0, 3.81, 11.50, 39.57 and 123.11 mg/kg bw/d  F: 0, 4.36, 13.85, 42.57 and 129.66 mg/kg bw/d	M: 123 F: 130 [1,000]	N/A.	Not applicable, no adverse effects were seen at the top dose.
90-day oral (dietary)  GLP compliant Non-guideline (OECD) ██████████ 1987 (CI-425-003) <i>Acceptable in a WoE approach</i>	Beagle dogs  0, 2, 100, 200, 3000 and 6000 ppm  Equivalent to : M: 0, 0.06, 2.9, 5.6, 96.5 and 180.5 mg/kg bw/d  F: 0, 0.06, 3.0, 5.8, 91.9 and 192.3 mg/kg bw/d	M: 5.6 F: 5.8 [200]	M: 97 F: 92 [3,000]	<u>3,000 ppm (96.5/91.9 mg/kg bw/d):</u> ↑liver weight, absolute (21 % in ♂, 16 % in ♀) and relative (16 % in ♂, 22 % in ♀). Histopathology of the prostate - delay in glandular development.
1-year oral (dietary)  GLP compliant Non-guideline (OECD) ██████████ 1985 (CI-427-002) <i>Acceptable in a WoE approach</i>	Beagle dogs  0, 300, 3000 and 10000 ppm  Equivalent to :  M: 0, 7.9, 83.4, and 253.9 mg/kg bw/d  F: 0, 7.9, 81.4	<b>M: 7.9</b> <b>F: 7.9</b> [300]	M: 83 F: 81 [3,000]	<u>3,000 ppm (83.4/81.4 mg/kg bw/d):</u> ↓body weight (4 % in ♂, 12 % in ♀). ↓body weight gain (16 % in ♂, 33 % in ♀). Changes in white blood cell parameters (♀). Alterations in clinical chemistry parameters (ALP+ALB) (♂+♀). ↑liver weight, absolute (24 % in ♂, 11 % in ♀) and relative (27 % in ♂,

Study, guideline, reference, acceptability	Species, doses tested	NOAEL mg/kg bw/d [ppm]	LOAEL mg/kg bw/d [ppm]	Adverse effects at LOAEL
	and 284.8 mg/kg bw/d			26 % in ♀). Histopathology of the prostate - delay in glandular development.
1-year oral (dietary)  GLP compliant Non-guideline (OECD)  █ 1988 (CI-427-003)  <i>Acceptable in a WoE approach</i>	Beagle dogs  0, 2, 30, 100, 200 and 3000 ppm  Equivalent to : M: 0, 0.044, 0.68, 2.3, 4.7 and 80.8 mg/kg bw/d  F: 0, 0.048, 0.74, 2.4, 4.3 and 70.7 mg/kg bw/d	<b>M: 4.7</b> <b>F: 4.3</b> [200]	M: 81 F: 71 [3,000]	<u>3,000 ppm (80.8/70.7 mg/kg bw/d):</u> White blood cell parameters (♂+♀). ↑ALP (♀). ↑liver weight, absolute (23 % in ♂) and relative (26 % in ♂). ↑incidence small prostates.
24 month oral (dietary)  GLP compliant. Guideline compliant  █ 2018 (2017/1093414)  <i>Acceptable</i>	Rat (Wistar)  0, 200, 1000 and 5000 ppm  Equivalent to: Chronic phase: M: 0, 10, 51 and 265 mg/kg bw/d F: 0, 13, 69 and 351 mg/kg bw/d  Carcinogenicity phase: M: 0, 9, 45 and 242 mg/kg bw/d F: 0, 11, 59 and 317 mg/kg bw/d	Carcinogenicity: F: 59 [1,000]  Systemic chronic toxicity: M: 9 [200]  F: 59 [1,000]	Carcinogenicity: M: 242 F: 317 [5,000]  (highest tested dose).  Systemic chronic toxicity: M: 45 [1,000]  F: 317 [5,000]	Carcinogenicity: <u>5,000 ppm (317 mg/kg bw/d):</u> ↑liver carcinomas (♀)  Systemic chronic toxicity: <u>1,000 ppm (45 mg/kg bw/d):</u> Histopathology of the nasal cavities - degeneration/regeneration of the olfactory epithelium and proteinaceous exudate (♂).
24 month oral (dietary)  Non-GLP. Non-guideline.  █ 1985	Rat (Fischer 344)  0, 30, 100 and 3000 ppm  Equivalent to:	Carcinogenicity: M: 144 F: 177 [3,000]  (highest tested dose).	Carcinogenicity: N/A.	Carcinogenicity: N/A – cinmethylin demonstrated no carcinogenic potential.



Study, guideline, reference, acceptability	Species, doses tested	NOAEL mg/kg bw/d [ppm]	LOAEL mg/kg bw/d [ppm]	Adverse effects at LOAEL
(CI-427-001) <i>Supplementary</i>	Chronic and carcinogenicity phases: M: 0, 1.4, 4.7 and 144.2 mg/kg bw/d  F: 0, 1.7, 5.8 and 177.4 mg/kg bw/d	Systemic chronic toxicity: M: 4.7 F: 5.8 [100]	Systemic chronic toxicity: M: 144 F: 177 [3,000]	Systemic chronic toxicity: <u>3,000 ppm</u> <u>(144/177 mg/kg bw/d)</u> : ↑mortality (♂). ↑clinical signs of toxicity (hunched appearance and pale eyes) (♂). ↓food consumption (♂+♀). ↓body weight (♂+♀). ↓body weight gain (♂+♀). Changes in haematology parameters (indicative of mild anaemia and thrombocytosis) (♂+♀). ↑liver weight, relative (23 % in ♂, 14 % in ♀). ↑kidney weight (16 % in ♂) and kidney histopathology (severe chronic nephropathy) (not relevant to humans). ↑GGT (♂+♀). Histopathology of the liver (♂+♀).
18-month oral (dietary)  GLP compliant. Guideline compliant  ██████████ 2018d (2017/1094161)  <i>Acceptable</i>	Mice (C57BL/6J Rj)  0, 150, 1000 and 5000 ppm  Equivalent to: Chronic phase: M: 0, 32.1, 223.1 and 1175 mg/kg bw/d  F: 0, 34.8, 301.1 and 1225 mg/kg bw/d  Carcinogenicity phase: M: 0, 25, 162.3 and 904 mg/kg bw/d	Carcinogenicity: M: 904 F: 939 [5,000]  (highest tested dose).  Systemic chronic toxicity: M: N/A F: N/A  BMDL <sub>10</sub> (for body weight effects): 37.5	Carcinogenicity: N/A.  Systemic chronic toxicity: M: 25 [150] F: 27 [150]	Carcinogenicity: N/A – cinmethylin demonstrated no carcinogenic potential.  Systemic chronic toxicity: <u>150 ppm (25/27 mg/kg bw/d) (lowest tested dose)</u> : ↓terminal body weight (♂+♀). ↓body weight gain (♂+♀). ↓food consumption (♀).

Study, guideline, reference, acceptability	Species, doses tested	NOAEL mg/kg bw/d [ppm]	LOAEL mg/kg bw/d [ppm]	Adverse effects at LOAEL
	F: 0, 27, 183.8 and 939 mg/kg bw/d			
24 month oral (dietary)  Non-GLP. Non-guideline.  ██████ 1986 (CI-428-001)  <i>Limited</i>	Mouse (B6C3F1)  0, 30, 100 and 1000 ppm  Equivalent to: Chronic and carcinogenicity phases: M: 0, 7.2, 22.1 and 231 mg/kg bw/d  F: 0, 8.3, 26.8 and 272 mg/kg bw/d	Carcinogenicity: N/A - no firm conclusion could be drawn.  Systemic chronic toxicity: M: 22.1 F: 26.8 [100]	Carcinogenicity: N/A.  Systemic chronic toxicity: M: 231 F: 272 [1,000]	Carcinogenicity: N/A - no firm conclusion could be drawn.  Systemic chronic toxicity: <u>1,000 ppm (231/272 mg/kg bw/d):</u> ↑liver weight, absolute (22 % in ♂, 19 % in ♀) and relative (27 % in ♂, 13 % in ♀).
Acute oral neurotoxicity study  GLP compliant Guideline compliant  ██████, 2018e 2016/1345328  <i>Acceptable</i>	Rat (Wistar)  0, 300, 1000 and 2000 mg/kg bw/d.	Acute neurotoxicity: M: 1,000 F: 300  Systemic toxicity: M: 1,000 F: 300	Acute neurotoxicity: M: 2,000 F: 1,000  Systemic toxicity: M: 2,000 F: 1,000	Acute neurotoxicity: <u>1,000 mg/kg bw</u> Alterations in FOB and MA parameters (e.g. retarded righting response, reduced number of rearings and decreased motor activity) (♀), on the day of administration only.  Systemic toxicity: <u>1,000 mg/kg bw/d :</u> Salivation and clinical signs of toxicity (♀), on the day of administration only. <u>2,000 mg/kg bw/d :</u> As above (♂)
2-generation study (dietary).  GLP-compliant.  t.	Rat (Wistar)  0, 125/250, 500/1000 and 2500/5000	Reproductive toxicity: 394 [2500/5000]  (the highest dose tested)	Reproductive toxicity: N/A	Reproductive toxicity: N/A – no adverse treatment-related findings were observed up to the top dose.

59

Study, guideline, reference, acceptability	Species, doses tested	NOAEL mg/kg bw/d [ppm]	LOAEL mg/kg bw/d [ppm]	Adverse effects at LOAEL
Pre-natal developmental toxicity study (oral gavage)  GLP compliant. Guideline compliant  ██████████ ██████████ 2018b 2015/1158053  <i>Acceptable</i>	Rabbit (New Zealand White).  0, 25, 80, 250 and 320 mg/kg bw/d.	Maternal toxicity: 80	Maternal toxicity: 250	Maternal toxicity: <u>250 mg/kg bw/d</u> : ↓body weight gain (22 %) (over the duration of the study, including the first few days of administration (GD 6 – 9)). ↑liver weight, absolute (18 %) and relative (21 %). Clinical chemistry (↑GGT, 51 %).
		Developmental toxicity: 80	Developmental toxicity: 250	Developmental toxicity: <u>250 mg/kg bw/d</u> : ↓foetal weight (14 %).

### 2.6.12. Toxicological end point for assessment of risk following long-term dietary exposure – ADI

The most suitable studies for the derivation of the ADI (Acceptable Daily Intake) are chronic studies. For cinmethylin, over this timeframe and the overall dataset, the highest NOAEL below the lowest LOAEL in the most sensitive relevant species is 7.9 mg/kg bw/d identified from the two 1 year dog studies, with the lowest LOAEL of 71 mg/kg bw/d for effects on the liver with associated increase in ALP, effects on haematology and prostates. HSE considered that the **NOAEL of 7.9 mg/kg bw/d** from the 1-year dog study (██████████ 1985) is the most appropriate starting point for the derivation of the ADI. The effects on the liver, haematology and prostate seen in the dog are considered to be relevant to humans. This is supported by the NOAEL of 9 mg/kg bw/d from the modern 24-month rat study (Buessen *et al.*, 2018).

By applying a standard assessment factor of 100 (there is no evidence to suggest that it is necessary to deviate from this default), an **ADI of 0.08 mg/kg bw/d** is derived.

The ADI of cinmethylin also applies to the following plant/livestock metabolites: M684H001, M684H002, M684H005, M684H006, M684H010, M684H012 and M684H026.

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

Cinmethylin is not acutely toxic by the oral route. However, cinmethylin was found to be acutely neurotoxic from 1,000 mg/kg bw/d (with a NOAEL of 300 mg/kg bw/d). In addition, in the rat gavage developmental study, a decrease in maternal body weight gain was seen at the beginning of the dosing period from the mid dose of 300 mg/kg bw/d. This effect seen in the maternal animals is considered to be a potentially acute effect relevant to the derivation of the ARfD. A **NOAEL of 30 mg/kg bw/d** (for maternal toxicity) was identified from this study (██████████, 1984) for this effect at the LOAEL of 300 mg/kg bw/d. The effects driving this NOAEL could be partly due to the method of administration (gavage) of cinmethylin in the study. Such effects may not be relevant to the derivation of the ARfD and its use in the risk assessment (oral exposures). However, the effects cannot be excluded as being solely related to treatment by the gavage route and is therefore considered appropriate for the derivation of the ARfD.

By applying a standard assessment factor of 100 (there is no evidence to suggest that it is necessary to deviate from this default), an **ARfD value of 0.3 mg/kg bw** is derived.

The ARfD of cinmethylin also applies to the following plant/livestock metabolites: M684H001, M684H002, M684H005, M684H006, M684H010, M684H012 and M684H026.

#### **2.6.14. Toxicological end point for assessment of occupational, bystander and residents risks – AOEL**

The most suitable studies for the derivation of the systemic AOEL (Acceptable Operator Exposure Level) are medium-term studies. For cinmethylin, over this timeframe, the highest NOAEL in the most sensitive relevant species is 7.9 mg/kg bw/d identified from the two 1-year dog studies, with the lowest LOAEL of 71 mg/kg bw/d for effects on the liver with associated increase in ALP, effects on haematology and prostates. Overall, HSE considered that the **NOAEL of 7.9 mg/kg bw/d** from the 1-year dog study (■■■■■, 1985) is the most appropriate starting point for the derivation of the AOEL. The effects on the liver, haematology and prostate seen in the dog are considered to be relevant to humans.

An oral absorption value of 100 % and a value for post-hepatic systemic availability of 70 % (see section 2.6.1 above) have been established. By adjusting the NOAEL with the post-hepatic systemic availability value of 70 % and by applying a standard assessment factor of 100 (there is no evidence to suggest that it is necessary to deviate from this default), an **AOEL of 0.06 mg/kg bw/d** is derived.

#### **2.6.15. Toxicological end point for assessment of occupational, bystander and residents risks – AAOEL**

The ARfD was based on a NOAEL of 30 mg/kg bw/d, identified from the rat gavage developmental toxicity study (■■■■■, 1984). The effects driving this NOAEL (decrease in maternal body weight seen at the beginning of the dosing period from the mid dose of 300 mg/kg bw/d) could be partly due to the method of administration (gavage) of cinmethylin in the study. Such effects may not be relevant to the derivation of the AAOEL and its use in the risk assessment of inhalation and dermal exposures. However, the effects cannot be excluded as being solely related to treatment by the gavage route and is therefore considered appropriate for the derivation of the AAOEL. Therefore HSE considered that the **NOAEL of 30 mg/kg bw/d** from the rat gavage developmental study, although conservative, is a suitable starting point for the derivation of the AAOEL.

An oral absorption value of 100 % and a value for post-hepatic systemic availability of 70 % (see section 2.6.1 above) have been established. By adjusting the NOAEL with the post-hepatic systemic availability value of 70 % and by applying a standard assessment factor of 100 (there is no evidence to suggest that it is necessary to deviate from this default), an **AAOEL of 0.21 mg/kg bw/d** is derived.

#### **2.6.16. Summary of product exposure and risk assessment**

##### **Operator exposure**

Estimates of operator exposure to BAS 684 H (cinmethylin) for the proposed uses of the representative product 'BAS 684 03 H' have been calculated using the EFSA Calculator. An acceptable long-term systemic operator exposure equal to 31% of the AOEL of BAS 684 H (cinmethylin) and an acceptable acute systemic operator exposure equal to 51% of the AAOEL of BAS 684 H (cinmethylin) is predicted for an operator that applies the product 'BAS 684 03H' without using PPE.

The product 'BAS 684 03 H' is classified for human health effects:

- H315 – Causes skin irritation
- H317 – May cause an allergic skin reaction
- H318 – Causes serious eye damage
- H371 – May cause damage to nervous system (STOT-SE 2)

The use of suitable protective gloves, suitable protective coveralls and face protection (faceshield) when handling the concentrate are therefore required.

### Bystander and resident exposure

Exposure to bystanders and residents has been calculated using the EFSA Calculator. The exposure assessment for inhalation of vapour has been conducted using the EFSA Guidance default value for average concentration in air in the 24 hours after application of  $15 \mu\text{g}/\text{m}^3$  for moderately volatile substances with a vapour pressure between  $5 \times 10^{-3}$  Pa and  $10^{-2}$  Pa. BAS 684 H (cinmethylin) has a vapour pressure of  $8.1 \times 10^{-3}$  Pa at  $20^\circ\text{C}$  and  $1.5 \times 10^{-2}$  Pa at  $25^\circ\text{C}$  according to DAR04 Volume 3(AS) Section B2. The vapour pressure of BAS 684 H (cinmethylin) is therefore within the specified range for moderately volatile substances at  $20^\circ\text{C}$  but marginally higher than the top limit of  $10^{-2}$  Pa at  $25^\circ\text{C}$ .

It is considered that for the proposed application of 'BAS 684 03 H' in the GB the use of the default value of  $15 \mu\text{g}/\text{m}^3$  for moderately volatile active substances is acceptable to estimate bystander and resident exposure to BAS 684 H (cinmethylin) vapour given that the top cut off point for moderately volatile active substances is a somewhat arbitrary value, and the vapour pressure of BAS 684 H (cinmethylin) is only marginally above this top cut off point. In addition, the temperature during application of 'BAS 684 03 H' to winter wheat and barley in the UK at growth stages of BBCH 00-29 is likely to be significantly lower than the maximum temperature of  $42^\circ\text{C}$  measured in the surrogate Californian Environmental Protection Agency study that was used to support the default value for moderately volatile substances of  $15 \mu\text{g}/\text{m}^3$ .

A summary of the estimated bystander and resident exposure, as modelled using default values in the EFSA Calculator is provided in the table below. The proposed in-use spray dilutions are not classified for skin sensitisation therefore no local effects are expected for resident and bystanders.

Table 2.6.16-1 Estimated resident (longer term) exposure to BAS 684 H (cinmethylin)

BAS 684 H (cinmethylin)		
Model data		% of systemic AOEL (0.06 mg/kg bw/day)
Tractor mounted boom spray application outdoors to low crops Buffer zone: 2-3 m Drift reduction technology: none DT <sub>50</sub> : 30 days DFR: $3 \mu\text{g}/\text{cm}^2/\text{kg a.s.}/\text{ha}$ Interval between treatments: 365 days Vapour pressure: moderately volatile substances with a vapour pressure between $5 \times 10^{-3}$ Pa and $10^{-2}$ Pa		
Number of applications and application rate:		1 x 0.5 kg a.s./ha
Resident child Body weight: 10 kg	Drift (75 <sup>th</sup> perc.)	49
	Vapour (75 <sup>th</sup> perc.)	27
	Deposits (75 <sup>th</sup> perc.)	3
	Re-entry (75 <sup>th</sup> perc.)	31
	Sum (mean)	81
Resident adult Body weight: 60 kg	Drift (75 <sup>th</sup> perc.)	12
	Vapour (75 <sup>th</sup> perc.)	6
	Deposits (75 <sup>th</sup> perc.)	1
	Re-entry (75 <sup>th</sup> perc.)	17
	Sum (mean)	26

Table 2.6.16-2 Estimated bystander (acute) exposure to BAS 684 H (cinmethylin)

BAS 684 H (cinmethylin)		
Model data		% of systemic AAOEL (0.21 mg/kg bw/day)
Tractor mounted boom spray application outdoors to low crops Buffer zone: 2-3 m Drift reduction technology: none DT <sub>50</sub> : 30 days DFR: 3 µg/cm <sup>2</sup> /kg a.s./ha Interval between treatments: 365 days Vapour pressure: moderately volatile substances with a vapour pressure between 5 x 10 <sup>-3</sup> Pa and 10 <sup>-2</sup> Pa		
Number of applications and application rate:		1 x 0.5 kg a.s./ha
Bystander child Body weight: 10 kg	Drift (95 <sup>th</sup> perc.)	32
	Vapour (95 <sup>th</sup> perc.)	8
	Deposits (95 <sup>th</sup> perc.)	3
	Re-entry (95 <sup>th</sup> perc.)	9
Bystander adult Body weight: 60 kg	Drift (95 <sup>th</sup> perc.)	9
	Vapour (95 <sup>th</sup> perc.)	2
	Deposits (95 <sup>th</sup> perc.)	1
	Re-entry (95 <sup>th</sup> perc.)	5

For proposed uses of 'BAS 684 03 H' the predicted exposure of a child and adult resident and bystander to BAS 684 H (cinmethylin) from spray drift, vapour, surface deposits and re-entry into treated crops pathways are within acceptable limits.

### Worker exposure

For the proposed uses of the product 'BAS 684 03 H' an acceptable worker exposure equal to 26% of the AOEL of BAS 684 H (cinmethylin) is predicted for a worker that performs crop inspection / irrigation activities wearing normal workwear (arms, legs and body covered).

## 2.7. RESIDUE

### 2.7.1. Summary of storage stability of residues

Residues of BAS 684 H are considered stable in all tested plant matrices (barley whole plant without roots, bean pods with seeds, oilseed rape seed, bean dried seed, wheat grain, grapes and wheat straw) for 24 months under frozen conditions ( $\leq -18$  °C). This accommodates the time period that the samples are stored for in the supporting residue trials (Volume 3, Section 7.3, maximum of 502 days). As residues of BAS 684 H have been shown to be stable in all five commodity categories (high water, high oil, high protein, high starch and high acid) it can be assumed that BAS 684 H residues are stable in all other commodities for the same duration of time under the same storage conditions (24 months at  $\leq -18$  °C).

Residues of M684H005 are considered stable in wheat whole plant without roots, wheat grain, rape seed, grapes and bean dried seed for 32 months under frozen conditions. For the matrices wheat straw and kale whole plant without roots a decline in the residues of M684H005 is observed over the 32 month period. In wheat straw this decline is from 79.4 – 68.5 % and in kale whole plant without roots is from 85.0 – 55.8 %.

It can be concluded that residues of M684H005 are considered sufficiently stable in wheat straw for 32 months as the decline observed is only slightly over 10 %. The low value at day 0 of 79.4 % could be attributed to the

analytical method as the procedural recoveries are also low; within a range of 76.5 – 88.7 % over the whole study period.

It can be concluded that residues of M684H005 are considered just sufficiently stable in kale whole plant without roots for 24 months, within this period the observed decline was from 85.0 – 64.6 % (absolute decline was 20.4 %). The slightly low value at day 0 of 85.0 % could be attributed to the analytical method as the procedural recoveries are within a similar range of 93.7 – 80.0 % over the period of the study. As the procedural recoveries are within a similar range it is considered appropriate to compare the decrease to the time zero (i.e. 85.0 %) rather than 100 %. A significant decline from 64.6 – 55.8 % is observed between 24 and 32 months therefore M684H005 is not considered stable in kale whole plant without roots for 32 months. To further support the stability for 24 months in kale it is noted that for wheat whole plant without roots, which is also considered a high-water commodity, residue levels are stable of 32 months frozen storage. It is recommended that for a future use on high-water commodities (especially leafy commodities similar to kale) it is preferable that samples are analysed before 24 months due to some observed degradation being recorded.

As residues of M684H005 have been shown to be stable in all five commodity categories (high water, high oil, high protein, high starch and high acid) it can be assumed that M684H005 residues are stable in all other commodities for the same duration of time under the same storage conditions (24 months at  $\leq -18^{\circ}\text{C}$ ).

It is considered appropriate that storage stability data have only been provided for the metabolite M684H005. In an ideal situation storage stability data would have been provided for metabolite M684H006 however, conclusions can be made based on the whole data package. The metabolite M684H005 is the precursor to M684H006. This is supported by the plant metabolism studies (see proposed pathway diagrams) and the *in-vitro* livestock studies where both metabolites M684H005 and M684H006 are rapidly cleaved to form M684H002 under physiological conditions. Also, as the content of M684H006 is determined as M684H005 no additional data are required at this time to support the storage stability of both metabolites.

This 24 month period accommodates the time period that the majority of samples are stored for in the supporting residue trials (see Volume 3, Section 7.3 for further details, range of 274 – 872 days), the exception being the trials in CA 6.3.2/1, Ale 2017a where the samples were stored for a maximum of 872 days before analysis of M684H005 and M684H006. However, as these residue trials are in wheat, and acceptable storage stability has been shown in wheat whole plant, wheat grain and wheat straw for 32 month (970 days) it is considered acceptable to rely on these data. This is further discussed in Volume 3, Section 7.3.

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

### **Plants**

#### **Primary crops**

The primary crop metabolism of BAS 684 H has been investigated in wheat (cereals), oilseed rape (pulses and oilseeds) and carrot (root crops). Metabolism was investigated in each study using two radiolabels:  $^{14}\text{C}$ -uniformly labelled for the phenyl ring and in the  $^{14}\text{C}$ -labelled in the 4-position of the cyclohexane ring. The results of each metabolism study are summarized in Table 2.7.2-1 and Table 2.7.2-2; in these tables the metabolites in the ERR (extractable radioactive residues) and RRR (residual radioactive residues) are broken down separately. The metabolites identified in the primary crop metabolisms studies, summed across the ERR and RRR, are summarized in Table 2.7.2-3.

#### *Wheat*

Metabolism of BAS 684 H in wheat was investigated after foliar spray application at  $1 \times 0.50 \text{ kg as/ha}$  to wheat at BBCH 29 (1N compared to the representative uses on wheat and barley). Wheat forage was sampled 11-13 days after application; wheat grain and straw were sampled at harvest 56 days after application. The highest TRRs were in wheat straw: 5.954 mg eq/kg and 9.732 mg eq/kg in phenyl and cyclohexane label respectively; followed by wheat forage: 2.632 mg eq/kg and 2.678 mg eq/kg in phenyl and cyclohexane label respectively. TRRs were the lowest in wheat grain: 0.009 mg eq/kg and 0.012 mg eq/kg for phenyl and cyclohexane label respectively, and therefore the extracts (0.005 – 0.007 mg eq/kg, 53.9 – 60.7 % TRR) were not further analysed.



Within the same matrix, the TRRs were comparable for both labels.

Wheat matrices were extracted with methanol and water. The overall extractability was high for wheat forage and straw ranging from 85.7% TRR to 96.2% TRR (2.531 – 8.353 mg eq/kg) and was low for wheat grain ( $\leq 60.7\%$  TRR ( $\leq 0.007$  mg eq/kg)). For wheat forage and straw, radioactive residues were mainly extracted with methanol. For wheat grain, radioactive residues were extracted in similar small amounts with methanol and water.

The residues after solvent extraction were further solubilised by ammonia and enzyme incubations. For all matrices, ammonia solubilisation released the highest portions of radioactive residues. Further procedures solubilised small portions of radioactive residues ranging from 0.1% TRR to 15.6% TRR (0.001 – 0.772 mg eq/kg). For wheat forage and straw, the final residues were each below or equal to 1.9% TRR or 0.122 mg eq/kg and are not considered to be bioavailable. For wheat grain, the final residues were each below or equal to 0.003 mg eq/kg (30.5 % TRR).

BAS 684 H was extensively metabolized with low concentrations of parent BAS 684 H found in wheat forage up to 0.081 mg eq/kg (3.1% TRR) and 0.054 mg eq/kg (2.0% TRR) for the phenyl and cyclohexane label, respectively. Parent BAS 684 H was not detected in wheat straw for the cyclohexane label. In all matrices and for both  $^{14}\text{C}$ -labels, the most abundant metabolite was M684H006; detected up to 0.796 mg eq/kg (29.7% TRR) in wheat forage (cyclohexane label) and up to 1.798 mg eq/kg (18.5% TRR) in wheat straw (cyclohexane label). The second most abundant metabolite in both matrices was M684H005 (for both labels); detected up to 0.396 mg eq/kg (14.8% TRR) in wheat forage (cyclohexane label) and up to 1.440 mg eq/kg (14.8% TRR) in wheat straw (cyclohexane label). Other minor metabolites identified ( $<10\%$  TRR) were: M684H007, M684H015, M684H016, M684H017, M684H047, M684H048 and M684H055.

Up to 37 peaks  $\geq 0.01$  mg/kg in the extracts of wheat forage and straw were not identified, including up to 7 unidentified peaks  $\geq 0.05$  mg/kg at a maximum of 0.289 mg eq/kg or 4.8% TRR. Attempts were made to identify these peaks including comparison of retention times and MS data with a range of reference items for postulated metabolites. For some extracts, poor peak resolution and co-elution of peaks hindered identification. Whilst further identification would have been preferable, there are no representative uses on cereal forage; for cereal straw, the dietary burden is significantly below 0.004 mg/kg bw/day and the animal metabolism studies are significantly overdosed ( $> 300$  N) compared to the dietary burden (Vol 1 Section 2.7.5). Therefore the extent of identification does not affect the overall consumer risk assessment for the representative uses. Additionally, the levels of metabolites M684H005 and M684H006 in wheat straw in the residues trials (Vol 3 CA B.7.3.1) are lower than in the metabolism study by a factor of approximately 100, hence the levels of the unidentified components may be lower in practice. The major components of the residue have been identified and a clear metabolic pathway has been elucidated with all likely metabolites excluded by comparison to reference standards. Therefore the extent of identification is not considered a major deficiency for the representative uses. If there are future uses on cereals, including forage uses, which significantly increase the dietary burden, consideration should be made of whether these conclusions remain valid.

In wheat, no cleavage of the molecule was observed.

#### *Oilseed rape*

Metabolism of BAS 684 H in oilseed rape was investigated after foliar spray application at  $1 \times 0.24 - 0.25$  kg as/ha to crops at BBCH 18 (1N compared to the future proposed use on oilseed rape). Oilseed rape seeds, hulls and straw were sampled at harvest 90 days after application. The highest TRRs were in rape straw: 3.730 mg eq/kg and 3.417 mg eq/kg in phenyl and cyclohexane label respectively; followed by hulls: 0.552 mg eq/kg and 0.577 mg eq/kg for the phenyl and cyclohexane label respectively. TRRs were the lowest in seeds: 0.100 mg eq/kg and 0.083 mg eq/kg for the phenyl and cyclohexane label respectively. Within the same matrix, the TRRs were comparable for both labels.

The extractability of the oilseed rape matrices with cyclohexane, methanol and water ranged from 61.4% TRR to 89.5% TRR (0.051 – 2.323 mg eq/kg). For oilseed rape straw, the major portions of radioactive residues were extracted with methanol at 72.7% TRR (2.713 mg eq/kg) and 73.5% TRR (2.512 mg eq/kg) for the phenyl and the cyclohexane-label, respectively. For oilseed rape hulls, similar portions were extracted with methanol and water. For oilseed rape hulls, similar portions were extracted with methanol (35.7% TRR (0.197 mg eq/kg) and 35.3% TRR (0.204 mg eq/kg) for the phenyl and cyclohexane label, respectively) and water (35.9% TRR (0.198

mg eq/kg) and 45.9% TRR (0.265 mg eq/kg) for the phenyl and cyclohexane label, respectively). For oilseed rape seeds, the extractabilities of both labels were highly comparable.

The residues after solvent extraction were further solubilised by ammonia and subsequent enzyme incubations. For oilseed rape straw and hulls (both labels), the highest portions of radioactive residues were solubilised by ammonia treatment (ranging between 0.054 – 0.202 mg eq/kg or 5.4 – 9.7% TRR). For oilseed rape seeds (both labels), the highest portions of radioactive residues were solubilised by macerozyme treatment (ranging between 0.008 – 0.010 mg eq/kg (9.6 – 10.1% TRR). For oilseed rape seeds of the phenyl label, high portions were additionally released by ammonia and amylase/  $\beta$ -amylglycosidase incubation (0.009 mg eq/kg (8.8% TRR) and 0.003 mg eq/kg (2.8% TRR) respectively). The final residues were each below or equal to 11.5% TRR (0.010 mg eq/kg) or 0.061 mg eq/kg (1.6% TRR) and are not considered to be bioavailable.

In oilseed rape seeds parent BAS 684 H was the only identified compound at 0.014 mg eq/kg (13.7% TRR) and 0.004 mg eq/kg (4.3% TRR) in phenyl and cyclohexane label, respectively. The remaining radioactivity was sufficiently characterised by extraction with solvents of various polarities and solubilisation with various enzymes.

In oilseed rape straw, a number of metabolites were identified; the two major metabolites identified were M684H005 and M684H006. M684H005 was detected at 0.487 mg eq/kg (13.0% TRR) and 0.755 mg eq/kg (22.1% TRR) in phenyl and cyclohexane label, respectively. M684H006 was detected in rape seed straw at 0.439 mg eq/kg (11.8% TRR) and 0.046 mg eq/kg (1.4% TRR) in phenyl and cyclohexane label, respectively. Other minor metabolites identified (<10% TRR) in straw were: M684H007, M684H008, M684H015, M684H016, M684H046, M684H047, M684H048, M684H051 and M684H055. In straw, parent BAS 684 H was detected for the phenyl label only at 0.043 mg eq/kg (1.2% TRR).

In rape hulls no major compounds were identified (>10% TRR). In rape hulls phenyl label the most abundant metabolite was M684H006 at 0.046 mg eq/kg (8.3% TRR) and for the cyclohexane label the most abundant metabolite was M684H016 at 0.031 mg eq/kg (5.4% TRR). Parent BAS 684 H in hulls was detected in trace amounts in phenyl label only at 0.003 mg eq/kg (0.5% TRR).

Additionally, metabolite M684H051, which was not identified in the wheat study, was identified in rape seed straw at 0.097 mg eq/kg (2.6 % TRR) and 0.103 mg eq/kg (3.0% TRR) in phenyl and cyclohexane label, respectively and in rape seed hulls (cyclohexane label) at 0.010 mg eq/kg (1.7% TRR).

Up to 17 peaks  $\geq 0.01$  mg/kg in the extracts of oilseed rape straw and hulls were not identified, including up to 5 unidentified peaks  $\geq 0.05$  mg/kg at a maximum of 0.096 mg/kg or 2.6% TRR. Attempts were made to identify these peaks including comparison of retention times and MS data with a range of reference items for postulated metabolites. For some extracts, poor peak resolution and co-elution of peaks hindered identification. Given oilseed rape straw and hulls are neither food nor feed commodities there is no effect on the dietary burden and overall consumer risk assessment hence the degree of characterisation and identification performed is considered acceptable.

In oilseed rape no cleavage of the molecule was observed.

### *Carrot*

Metabolism of BAS 684 H in carrot was investigated after foliar spray application at  $1 \times 0.50 - 0.51$  kg as/ha to crops at BBCH 12 – 13 (there are no representative uses on root crops). Roots and leaves were sampled at harvest 67 days after application. The highest TRRs were in carrot leaves at 0.442 mg eq/kg and 0.571 mg eq/kg for the phenyl and cyclohexane label respectively. The lowest TRRs were in carrot roots at 0.093 mg eq/kg and 0.152 mg eq/kg for the phenyl and cyclohexane label respectively.

Carrot roots and leaves were extracted with methanol and water, where major portions of radioactive residues were extracted with methanol (up to 73.0% TRR (0.417 mg eq/kg)). Smaller amounts were subsequently extracted with water (below or equal to 5.0% TRR (or 0.026 mg eq/kg)).

The residues after solvent extraction were further solubilised by ammonia and enzyme incubations. For carrot roots, the highest portions of radioactive residues were solubilised by macerozyme/ cellulase treatment (up to 19.5% TRR (0.030 mg eq/kg)). For carrot leaves (both labels), ammonia treatment released main portions of

radioactive residues (up to 11.4% TRR or 0.054 mg eq/kg). The residues of carrot leaves (both labels) were further sequentially incubated with pepsin and pancreatin to investigate the bioavailability of bound residues, which released additional 1.2% TRR (0.005 mg eq/kg) (phenyl-label) and 0.8% TRR (0.005 mg eq/kg) (cyclohexane label). The final residues were each below or equal to 7.0% TRR (0.040 mg eq/kg) and are not considered to be bioavailable.

In carrot leaves, parent BAS 684 H was the most significant residue at levels of 0.107 mg eq/kg (24.1% TRR) and 0.159 mg eq/kg (27.9% TRR) for the phenyl and cyclohexane label respectively. Other identified metabolites were detected at concentrations below 10% TRR: M684H005, M684H006, M684H047, M684H048 (and isomers), M684H050 (and isomers) and M684H051. Up to 8 unidentified peaks  $\geq 0.01$  mg/kg were additionally characterised, however these were at a maximum of 0.030 mg eq/kg or 5.3 % TRR and sufficient characterisation and identification was performed.

In carrot roots, parent BAS 684 H was found at low levels, 0.003 mg eq/kg (3.5% TRR) and 0.012 mg eq/kg (7.9% TRR) for the phenyl and cyclohexane label respectively. No additional metabolites were identified in carrot roots. In carrot, no cleavage of the molecule was observed.

A major proportion of the residues in carrot roots was identified as carbohydrates at 0.073 mg eq/kg (78.4% TRR) and 0.113 mg eq/kg (74.1% TRR) for the phenyl and cyclohexane label respectively, by identification of glucose and fructose in the root extracts using a sugar-specific HPLC method. Additionally, fermentation of the extract resulted in the formation of ethanol. Given application was made at BBCH 12-13, a significant proportion of the active substance will have reached the soil (crop interception value of 25%, EFSA Journal 2014;12(5):3662). Harvest of root samples was made 67 days after application allowing sufficient time for some degradation of BAS 684 H in soil to occur given the  $DT_{50}$  for BAS 684 H is 53.9 days (Volume 3 CA B.8.1). The aerobic soil metabolism study shows no major metabolites are formed, rather numerous unidentified small degradation products are formed (each  $<5\%$  of the applied radioactivity). This is also consistent with the results of the rotational crop metabolism study in which no major metabolites are observed in following crops (Section CA B.7.6.1). It is concluded that the soil degradation products are taken up by the carrot root and metabolised further. The identification of glucose and fructose in the root extracts and ethanol after fermentation provide evidence for the radioactive soil degradation products entering sugar biosynthesis. Given almost 60% of the RRR in roots was solubilised by macerozyme/cellulase, and that glucose and its derivatives are used in the synthesis of cell walls, this provides further evidence for the formation of carbohydrates.

Table 2.7.2-1 Summary of primary crop metabolism studies (expressed as %TRRs)

	Cereal/grass crops						Pulses and oilseeds						Root crops			
Study reference	2017/1004405						2017/1110861						2017/1186063			
Crop	Wheat						Oilseed rape						Carrots			
Outdoor/Indoor	Indoor						Indoor						Indoor			
Type of application	Spray						Spray						Foliar spray			
Method of application	automated spray track						automated spray track						automated spray track			
Formulation type	EC						EC						EC			
Number treatments	1						1						1			
Timing of treatments (dd/mm/yyyy)	Phenyl: 29.05.2015; Cyclohexane: 27.05.2015						Phenyl: 20.10.2015; cyclohexane: 23.10.2015						P: 04.11.2016; C: 03.11.2016			
g a.s./ha/treatment	500						250						500			
Growth stage at application (BBCH)	29						18						12-13			
Total application rate (g a.s./ha)	500						250						No intended use			
PHI (days)	56						90						67			
N rate	1N						1N						No intended use			
Phytotoxicity observed (Y/N)	Not reported						Not reported						Not reported			
<sup>14</sup> C labelling	<sup>14</sup> C-phenyl			<sup>14</sup> C-cyclohexane			<sup>14</sup> C-phenyl			<sup>14</sup> C-cyclohexane			<sup>14</sup> C-phenyl		<sup>14</sup> C-cyclohexane	
Treatments group	500 g a.s./ha						250 g a.s./ha						500 g a.s./ha			
Plant part	Forage	Straw	Grain	Forage	Straw	Grain	Straw	Hulls	Seeds	Straw	Hulls	Seeds	Roots	Leaves	Roots	Leaves
DALA	11	56	56	13	56	56	90	90	90	90	90	90	67	67	67	67
TRR (mg/kg) calculated	2.632	5.954	0.009	2.678	9.732/8.271	0.012	3.73	0.552	0.1	3.417	0.577	0.083	0.093	0.442	0.152	0.571
%TRR																
Total extractable residues	96.2	85.7	53.9	95.2	85.8	60.7	89.1	71.6	63.0	89.5	81.3	61.4	65.7	76.5	66.0	77.5
BAS 684 H	3.1	0.4		2.0			1.2	0.5	13.7			4.3	3.5	24.1	7.9	27.9
M684H005	10.7	14.3		14.8	11.5		10.5	1.6		20.8	0.7			1.8		0.4
M684H006	29.2	12.1		29.7	18.5		11.8	8.3		1.4	3.1			2.6		2.4
M684H007	8.1	2.7		6.6	4.3		3.3				2.0					
M684H008							5.4	1.0		6.9						
M684H015	2.4	1.3		4.3	3.3		1.4				0.7					
M684H016	5.1	3.6		8.2	3.9		4.5	5.6			5.4					
M684H046							3.0			2.5						
M684H047	3.3	2.1		2.5	4.4		4.4			2.1	2.2			1.2		2.0
M684H048					0.2		4.8			6.9	2.5					
M684H048 (and isomers / M684H050 (and isomers)														7.1		2.1
M684H050														7.3		2.7
M684H051							2.6			2.8	1.7			0.4		
M684H055	2.4	1.8		2.2	1.3		1.6				1.0					
Carbohydrates													59.0		55.1	
Total identified	64.3	38.4		70.3	47.5		54.6	17.0	13.7	43.4	19.3	4.3	62.6	44.4	62.9	37.4
Organosoluble fractions (cyclohexane)			22.7			27.6			32.2			28.7				
Aqueous soluble fractions			31.2			33.1							3.1		3.1	
Polar components														6.1		6.3
OH-metabolites							1.8			0.6	1.3					
Number of additionally characterised peaks (in methanol+water extracts)	23+24	38+25		33+19	60+16		17+2	17+12	3+2	11+6	24+16	16+1		21+7		27+8
Maximum of additionally characterised peaks	4.7	4.8		2.7	2.7		2.6	4.4	8.4	6.8	5.6	3.9		4.1		5.3
Sum of additionally characterised peaks	27.4	45.2		29.2	43.0		20.2	44.8	21.0	36.7	59.0	25.5		26.1		33.9
Total Characterised	27.4	45.2	53.9	29.2	43.0	60.7	34.0	55.5	47.5	39.3	61.9	52.3	3.1	32.1	3.1	40.1
Unextractable radioactive residues	3.8	14.3	46.1	4.8	14.2	39.3	10.9	28.4	37.0	10.5	18.7	38.6	34.3	23.5	34.0	22.5
Ammonia solubilisate	1.3	7.9	15.6	1.9	7.9	12.1	5.4	9.7	8.8	6.0	5.8	4.0	3.7	11.4	3.4	9.4
Ammonia wash	0.2	0.9														
Macerozyme solubilisate	0.7	1.8		1.1	3.2		1.4	4.3	10.1	1.0	2.7	9.6	19.4	1.7	19.5	1.3
Tyrosinase solubilisate	0.2	0.7		0.4	0.7		0.5	0.6	0.3	0.4	0.5	1.1				
Amylase solubilisate	0.1	0.3		0.2	0.3		0.3	1.8	2.8	0.1	0.7	2.2				
Pepsin solubilisate		0.1			0.1		0.1	0.3	0.5	0.1	0.2	2.4		0.4		0.4
Pancreatin solubilisate		0.2			0.2		0.2	0.5	0.4	0.1	0.6	0.9		0.8		0.4
Amylase / amyloglycosidase solubilisate																
Glycosidase solubilisate													3.3	0.5	3.3	0.4
Sum of solubilised radioactive residue	2.5	11.9	15.6	3.5	12.3	12.1	7.8	17.1	22.8	7.8	10.5	20.2	26.4	14.9	26.1	11.9
M684H005	0.6	2.9			3.3		2.5	0.4		1.3						
M684H006											0.1					
M684H008							1.1	0.7		0.9						
M684H046										0.9						
M684H047											0.1					
M684H048										0.3						
M684H051										0.2						
Carbohydrates													19.4		19.0	
Total identified from RRR	0.6*	2.9*			3.3*		3.6*	1*		3.6*	0.2*		19.4**		19.0**	
Total Characterised by HPLC	0.6	6.4			5.2		3.4	7.5		2.0	5.7		3.7	11.4	3.8	9.4
Total Characterised	1.8	7.7	15.6	3.5	6.4	12.1	3.7	14.8	22.8	3.6	9.4	20.2				
Sum of identified and characterised residues in the RRR	2.4	10.7	15.6	3.5	9.7	12.1	7.3	15.8	22.8	7.1	9.5	20.2	26.4	14.9	26.1	11.9
Bound/PES	0.8	1.9	30.5	1.3	1.3	27.2	1.6	5.4	9.0	1.1	4.3	11.5	4.7	6.6	4.5	7.0
Accountability	95.0	96.2	100.0	104.3	101.4	100.0	97.5	93.6	93.1	90.9	95.1	88.3	96.8	98.0	96.7	96.4

\* : Identified from ammonia solubilise

\*\* : Identified as carbohydrate

Table 2.7.2-2 Summary of primary crop metabolism studies (expressed in mg eq/kg)

Treatments group Plant part	Cereal/grass crops						Pulses and oilseeds						Roots crops			
	14C-phenyl			14C-cyclohexane			14C-phenyl			14C-cyclohexane			14C-phenyl		14C-cyclohexane	
	500 g a.s./ha						250 g a.s./ha						500 g a.s./ha			
	Forage	Straw	Grain	Forage	Straw	Grain	Straw	Hulls	Seeds	Straw	Hulls	Seeds	Roots	Leaves	Roots	Leaves
DALA	11	56	56	13	56	56	90	90	90	90	90	90	67	67	67	67
mg eq/kg																
Total extractable residues	2.531	5.101	0.005	2.548	8.353	0.007	3.323	0.395	0.063	3.058	0.469	0.051	0.061	0.338	0.1	0.442
BAS 684 H	0.081	0.026		0.054			0.043	0.003	0.014			0.004	0.003	0.107	0.012	0.159
M684H005	0.296	1.028		0.396	1.120		0.393	0.009		0.755	0.004			0.008		0.002
M684H006	0.770	0.720		0.796	1.798		0.439	0.046		0.046	0.018			0.011		0.014
M684H007	0.212	0.162		0.177	0.423		0.122				0.012					
M684H008							0.202	0.005		0.268						
M684H015	0.063	0.080		0.116	0.317		0.054				0.004					
M684H016	0.135	0.214		0.219	0.379		0.170	0.031			0.031					
M684H046							0.111			0.116						
M684H047	0.088	0.126		0.066	0.432		0.164			0.072	0.013			0.005		0.011
M684H048					0.022		0.180			0.243	0.014					
M684H048 (and isomers) / M684H050 (and isomers)														0.031		0.012
M684H050														0.032		0.015
M684H051							0.097			0.103	0.010			0.002		
M684H055	0.063	0.108		0.058	0.127		0.060				0.006					
Carbohydrates													0.073		0.113	
Total identified	1.708	2.464		1.881	4.619		20.350	0.094	0.014	1.604	0.112	0.004	0.058	0.196	0.096	0.213
Organosoluble fractions (cyclohexane)			0.002			0.003			0.032			0.024				
Aqueous soluble fractions			0.003			0.004							0.003		0.005	
Polar components														0.027		0.036
OH-metabolites							0.065			0.022	0.008					
Number of additionally characterised peaks (in methanol+water extracts)	23+24	38+25		33+19	60+16		17+2	17+12	3+2	11+6	24+16	16+1		21+7		27+8
Maximum of additionally characterised peaks	0.124	0.289		0.073	0.263		0.096	0.024	0.008	0.234	0.032	0.003		0.018		0.030
Sum of additionally characterised peaks	0.722	2.691		0.782	4.184		0.755	0.247	0.021	1.254	0.340	0.021		0.115		0.193
Total Characterised	0.722	2.691	0.005	0.782	4.184	0.007	1.268	0.306	0.047	1.343	0.357	0.044	0.003	0.142	0.005	0.229
Unextractable radioactive residues	0.100	0.853	0.004	0.13	1.379	0.005	0.407	0.157	0.037	0.359	0.108	0.032	0.032	0.104	0.052	0.128
Ammonia solubilisate	0.034	0.468	0.001	0.05	0.772	0.001	0.202	0.054	0.009	0.207	0.033	0.003	0.003	0.051	0.005	0.054
Ammonia wash	0.006	0.051														
Macerozyme solubilisate	0.019	0.107		0.028	0.308		0.052	0.024	0.010	0.033	0.015	0.008	0.018	0.007	0.030	0.007
Tyrosinase solubilisate	0.006	0.043		0.012	0.065		0.017	0.003	<0.001	0.015	0.003	0.001				
Amylase solubilisate	0.002	0.018		0.005	0.026		0.009	0.010	0.003	0.004	0.004	0.002				
Pepsin solubilisate		0.006			0.008		0.003	0.001	<0.001	0.003	0.001	0.002		0.002		0.002
Pancreatin solubilisate		0.014			0.016		0.007	0.003	<0.001	0.005	0.003	0.001		0.003		0.002
Amylase / amyloglycosidase solubilisate																
Glycosidase solubilisate													0.003	0.002	0.005	0.002
Sum of solubilised radioactive residue	0.066	0.707	0.001	0.094	1.195	0.001	0.290	0.094	0.023	0.266	0.060	0.017	0.025	0.066	0.040	0.068
M684H005	0.015	0.175			0.320		0.094	0.002		0.043						
M684H006											0.001					
M684H008							0.039	0.004		0.032						
M684H046										0.030						
M684H047											<0.001					
M684H048										0.009						
M684H051										0.007						
Total identified from RRR	0.015*	0.175*			0.320*		0.134*	0.006*		0.122*	0.001*		0.018**		0.029**	
Total Characterised by HPLC	0.722	0.379			0.509		0.128	0.041		0.070	0.033		0.003	0.051	0.006	0.054
Total Characterised	0.048	0.461	0.001	0.05	0.625	0.001	0.138	0.082	0.023	0.122	0.054	0.017				
Sum of identified and characterised residues in the RRR	0.063	0.636	0.001	0.829	0.945	0.001	0.272	0.087	0.023	0.038	0.055	0.017	0.007	0.066	0.011	0.068
Acid/base hydrolysis																
Bound/PES	0.021	0.113	0.003	0.035	0.122	0.003	0.061	0.03	0.009	0.038	0.025	0.01	0.004	0.029	0.007	0.040
Accountability	2.499	5.728	0.009	2.793	9.869	0.012	3.636	0.517	0.093	3.107	0.549	0.074	0.090	0.433	0.147	0.550

\* : Identified from ammonia solubilise

\*\* : Identified as carbohydrate

Table 2.7.2-3 Summary of identified metabolites in primary crop metabolism studies

	Cereal/grass crops						Pulses and oilseeds						Root crops			
Crop	Wheat						Oilseed rape						Carrots			
<sup>14</sup> C labelling	<sup>14</sup> C-phenyl			<sup>14</sup> C-cyclohexane			<sup>14</sup> C-phenyl			<sup>14</sup> C-cyclohexane			<sup>14</sup> C-phenyl		<sup>14</sup> C-cyclohexane	
Plant part	Forage	Straw	Grain	Forage	Straw	Grain	Straw	Hulls	Seeds	Straw	Hulls	Seeds	Roots	Leaves	Roots	Leaves
<b>TRR (mg/kg) calculated</b>	<b>2.632</b>	<b>5.954</b>	<b>0.009</b>	<b>2.678</b>	<b>9.732/8.271</b>	<b>0.012</b>	<b>3.73</b>	<b>0.552</b>	<b>0.1</b>	<b>3.417</b>	<b>0.577</b>	<b>0.083</b>	<b>0.093</b>	<b>0.442</b>	<b>0.152</b>	<b>0.571</b>
	<b>% TRR</b>															
BAS 684 H	3.1	0.4		2.0			1.2	0.5	13.7			4.3	3.5	24.1	7.9	27.9
M684H005	11.3	17.2		14.8	14.8		13.0	2.0		22.1	0.7			1.8		0.4
M684H006	29.2	12.1		29.7	18.5		11.8	8.3		1.4	3.2			2.6		2.4
M684H007	8.1	2.7		6.6	4.3		3.3				2.0					
M684H008							6.5	1.7		7.8						
M684H015	2.4	1.3		4.3	3.3		1.4				0.7					
M684H016	5.1	3.6		8.2	3.9		4.5	5.6			5.4					
M684H046							3.0			3.4						
M684H047	3.3	2.1		2.5	4.4		4.4			2.1	2.3			1.2		2.0
M684H048					0.2		4.8			7.2	2.5					
M684H048 (and isomers / M684H050 (and isomers))														7.1		2.1
M684H050														7.3		2.7
M684H051							2.6			3.0	1.7			0.4		
M684H055	2.4	1.8		2.2	1.3		1.6				1.0					
Carbohydrates													78.4		74.1	
	<b>mg eq/kg</b>															
BAS 684 H	0.081	0.026		0.054			0.043	0.003	0.014			0.004	0.003	0.107	0.012	0.159
M684H005	0.311	1.203		0.396	1.440		0.487	0.011		0.798				0.008		0.002
M684H006	0.770	0.720		0.796	1.798		0.439	0.046		0.046	0.019			0.011		0.014
M684H007	0.212	0.162		0.177	0.423		0.122				0.012					
M684H008							0.241	0.009		0.300						
M684H015	0.063	0.080		0.116	0.317		0.054				0.004					
M684H016	0.135	0.214		0.219	0.379		0.170	0.031			0.031					
M684H046							0.111			0.146						
M684H047	0.088	0.126		0.066	0.432		0.164			0.072	0.014			0.005		0.011
M684H048					0.022		0.180			0.252	0.014					
M684H048 (and isomers) /M684H050 (and isomers)														0.031		0.012
M684H050														0.032		0.015
M684H051							0.097			0.110	0.010			0.002		
M684H055	0.063	0.108		0.058	0.127		0.060				0.006					
Carbohydrates													0.073		0.113	

*Soybean, peanut and rice studies*

The applicant provided plant metabolism studies from the 1980s performed in soybean, peanuts and rice, labelled only in a single ring (phenyl- $U-^{14}C$ ). The studies have been evaluated in Vol 3 CA B.7.2. The studies were not performed to OECD Guideline 501, and there are deficiencies in the conduct and reporting of the studies, such as insufficient information on storage stability, which do not allow them to be relied on quantitatively. The soybean and peanut studies were not conducted to GLP and the rice study was conducted under paddy conditions. Nonetheless, the studies are considered to provide supporting information, particularly qualitatively, for example regarding the types of metabolites identified and for comparison to the new plant metabolism studies. The metabolites identified in these studies are broadly consistent with those identified in the new plant metabolism studies, i.e. conjugated hydroxylated metabolites, mono- and di-hydroxylated metabolites identified after deconjugation, and no cleavage of parent BAS 684 H. The studies support the metabolic pathway elucidated by the new studies, i.e. hydroxylation and subsequent conjugation with sugars.

*Stereoisomer-specific analysis*

Stereoisomer-specific analysis was performed in the plant metabolism studies on wheat, oilseed rape and carrot as detailed in Section 2.12.5 below. A shift in the enantiomeric ratio of BAS 684 H towards the (-)-enantiomer in carrot leaves was observed. A shift towards one of the diastereomers of M684H005 is observed in wheat straw, wheat forage and oilseed rape straw. However the toxicological evaluation has concluded that the enantiomers of BAS 684 H, M684H005 and M684H006 are of equivalent toxicity (Vol 1 Section 2.12.3) hence the shift in stereoisomeric ratios is not concluded to affect the consumer risk assessment.

*Metabolic pathway*

A consistent picture of BAS 684 H metabolism is observed for both phenyl and cyclohexane labels and across 3 crop groups (pulses and oilseeds, cereals and root crops).

In plants, the metabolic pathway is largely based on:

- hydroxylation of parent BAS 684 H at various positions; and
- subsequent conjugation of these hydroxyl groups to form glycosides and malonyl glycosides

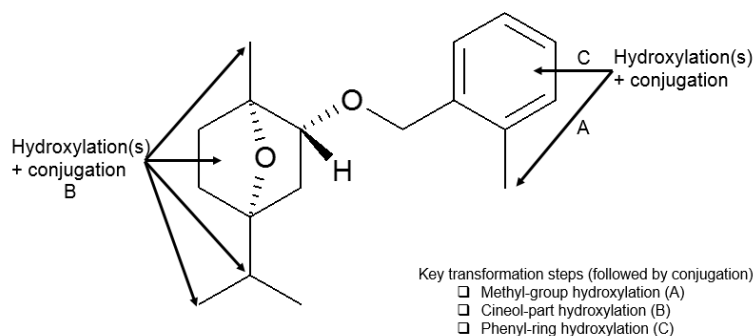
Metabolites occurring in plant matrices in major amounts (>10% TRR) and in minor amounts (<10% TRR) are listed in Table 2.7.2-4. This table groups the metabolites according to their chemical structure. The transformation reactions are summarised in Figure 2.7.2-1. The metabolic routes in plant are shown in Figure 2.7.2-2.

Table 2.7.2-4 Metabolites in plant matrices

<b>A-branch</b> (hydroxylation at the methyl group and further phase I and phase II metabolites)	<b>B-branch</b> (hydroxylation at the cineol-part and further phase I and phase II metabolites)	<b>C-branch</b> (hydroxylation at the phenyl-ring and further phase I and phase II metabolites)
<b>M684H005</b>	M684H046	M684H007
<b>M684H006</b>	M684H047	M684H008
	M684H048	
	M684H050	
	M684H051	
	M684H055	

Metabolites with a content of >10% TRR are indicted in **bold** font

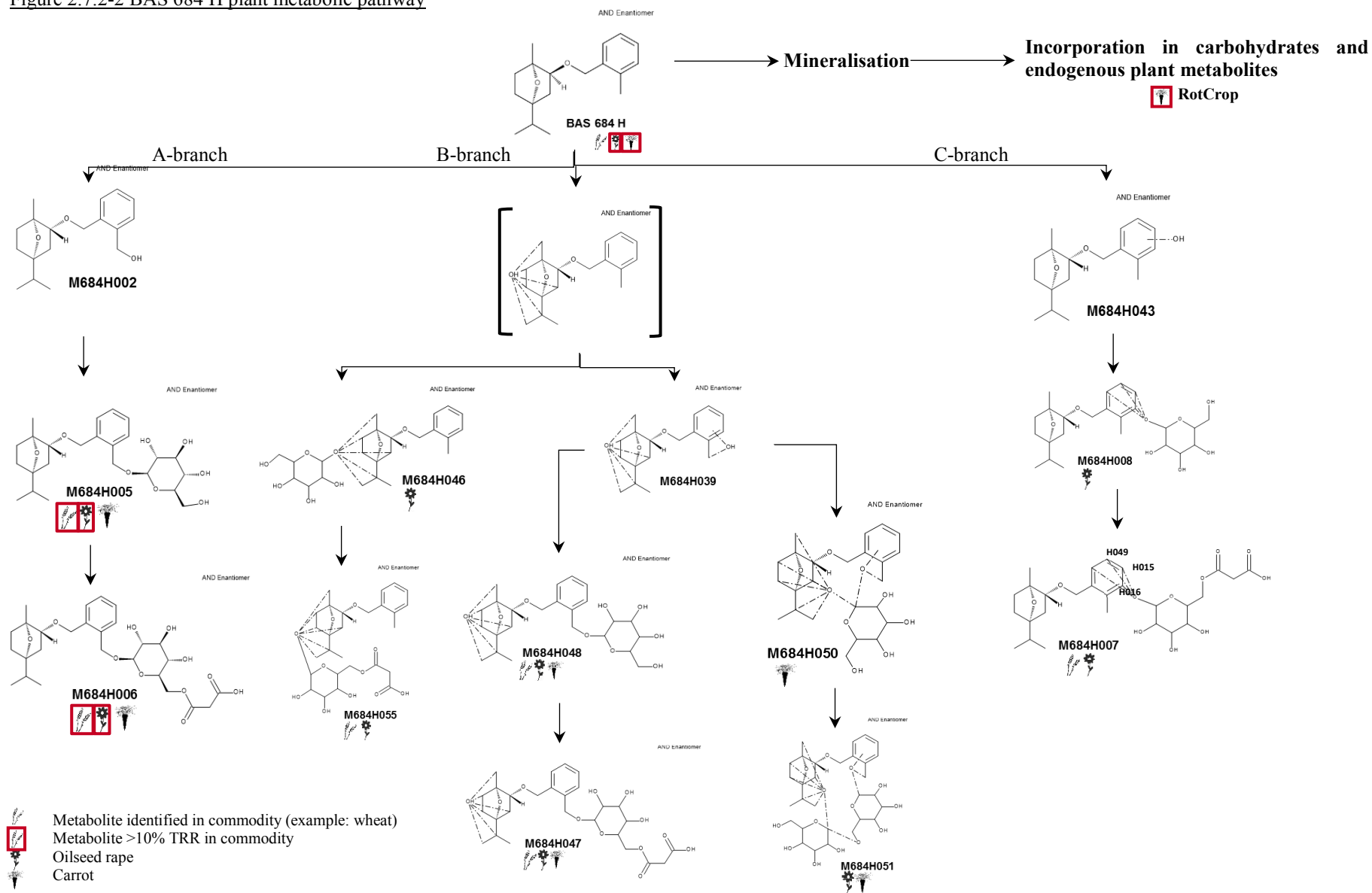
Figure 2.7.2-1 BAS 684 H transformation reactions in plant



M684H002 is proposed as a key metabolite in the pathway however it has not been identified in the plant metabolism studies. It has been identified as the main deconjugated form of metabolites M684H005 and M684H006 in cleavage experiments performed as part of the plant metabolism studies. The process of conjugation to form M684H005 and M684H006 is concluded to take place quicker than the initial hydroxylation such that at sampling no significant amounts of the unconjugated M684H002 are detected.



Figure 2.7.2-2 BAS 684 H plant metabolic pathway



## Rotational crops

Representative uses on cereals (wheat and barley) and the future proposed use on oilseed rape can be grown in rotation and field soil degradation studies indicate the DT<sub>90</sub> value for cinmethylin is a maximum of 207.6 days (Volume 3 CA B.8.1) therefore a consideration of residues in rotational crops is required, but there is no potential for accumulation of parent cinmethylin over multiple years of use. There are no major soil metabolites for BAS 684 H and therefore no potential for accumulation of soil metabolites over multiple years of use.

A confined rotational crop study was conducted with two labels (phenyl label, cyclohexane label) on spinach (leafy vegetable group), radish (root and tuber group) and wheat (small grain group). BAS 684 H was applied at 0.50 kg a.s./ha to bare soil. The application rate for each label (g a.s./ha) corresponds to 1 N compared to the representative critical GAPs on barley and wheat (1 x 500 g a.s./ha) and 2 N compared to the future proposed critical GAP on oilseed rape (1 x 250 g a.s./ha). Plant back intervals of 30, 120 and 365 days were investigated.

The study is summarised in

Table 2.7.2-5 (phenyl label) and Table 2.7.2-6 (cyclohexane label). Low to moderate translocation of radioactive residues from soil into the plants was observed. The TRRs in rotational crop matrices showed similar levels for the two labels and was generally low for all samples, being  $\leq 0.132$  mg eq/kg for both labels, however this value was for wheat hay (120 DAT, phenyl label). TRRs in food commodities were  $\leq 0.016$  mg eq/kg (wheat grain 30 DAT, cyclohexane label).

For both labels, the extractability of radioactive residues with methanol and water ranged from 29.1 – 76.6% TRR (0.005 – 0.045 mg eq/kg) for immature and mature spinach, radish leaves and roots, wheat forage, hay and straw. For wheat grain, the extractability with methanol/water was lower with 10.9 – 14.4% TRR (0.001 – 0.002 mg eq/kg) at 30 DAT. At 120 DAT, the extractability of wheat grains increased to 33.8% TRR (0.005 mg eq/kg).

The residues after solvent extraction of all matrices were further characterised using a sequential solubilisation procedure applying ammonia treatment and enzymatic cleavage steps. Selected samples were also characterised by consecutive treatment with simulated gastric fluid (pepsin) and simulated intestinal fluid (pancreatin). In general, the amounts of released radioactive residues were similar in both labels and the main portions of radioactive residues were released in the macerozyme solubilisation steps. For wheat grain, the main portions were released with ammonia ( $\leq 19.4\%$  TRR, 0.003 mg eq/kg), macerozyme ( $\leq 17.5\%$  TRR, 0.003 mg eq/kg) and amylase ( $\leq 29.2\%$  TRR, 0.005 mg eq/kg). The final unextractable residues ( $\leq 0.044$  mg eq/kg (maximum: wheat hay 30 d PBI) or  $\leq 44.8\%$  TRR (maximum: wheat straw 30 d PBI)) are not considered bioavailable, since they are not released upon incubation with artificial gastric juice and artificial intestinal fluid.

The only identified component was parent BAS 684 H, which was detected in immature spinach (30 DAT, phenyl label), radish leaves (30 DAT, phenyl label), wheat hay (30 DAT, phenyl label), wheat straw (30 DAT, both labels) and wheat straw (120 DAT, both labels). The unchanged parent compound was present at or below 0.002 mg eq/kg or 6.0% TRR.

Other than a peak at 76 min (discussed below), the other peaks individually accounted for up to 0.014 mg eq/kg (10.4 % TRR, wheat hay 30 d PBI cyclohexane label) or 29.2 % TRR (0.003 mg eq/kg radish leaves 30 d PBI cyclohexane label). The maximum peak at 0.014 mg eq/kg (10.4 % TRR) in wheat hay at 30 d PBI (cyclohexane label) was found in the water phase following partitioning of the methanol extract at a low retention time using a polar gradient elution and so is concluded to be a polar metabolite. Given this was only observed in wheat hay; it is considered acceptable that further attempts to identify this peak have not been made.

A component denoted peak at 76 min (based on retention time in HPLC chromatograms used for quantification) was observed at a maximum of 38.3 % TRR (0.022 mg eq/kg) in wheat straw at a PBI of 120 d (phenyl label). Significant attempts were made to identify the peak. Therefore, 1.7 kg of homogenized wheat straw (phenyl label, 120 DAT) was sequentially extracted to isolate and analyse the peak at 76 min. However, repeated structure elucidation attempts were of limited success. No significant ions could be detected by HPLC-MS. The isotopic pattern of the initially applied test item of BAS 684 H was not recoverable in the analysed sample hence the peak does not contain the parent molecular structure or fragments thereof. After treatment with acetylating agents (using acetic anhydride and pyridine), no conversion of the peak was observed. Enzymatic incubation with  $\beta$ -glucosidase produced a decrease in the peak at 76 min and a new peak at 39 min. Therefore the peak at 76 min may consist of glucosyl-related structures. Treatment of another aliquot with  $\alpha$ -amylase did not show

significant conversions; similar conversions were observed with only buffer solution present hence the conversions are concluded not to be due to the action of  $\alpha$ -amylase.

Given the peak at 76 min does not share any MS fragments with the applied BAS 684 H test item, the aerobic soil metabolism study shows BAS 684 H is extensively degraded to numerous small polar fragments with a  $DT_{50}$  for BAS 684 H of 53.9 days (Volume 3 CA B.8.1), and the peak is not observed in the primary crop metabolism studies, it is concluded that the peak at 76 min is likely to be formed in crops after uptake of small polar fragments from the soil and further metabolised in the crop e.g. conjugation with glucose. Therefore the peak at 76 min can be characterised as a natural endogenous compound (including glucosyl conjugates).

In conclusion, BAS 684 H is extensively metabolized in the rotational crop study after application to bare soil. The proposed metabolic pathway of BAS 684 H in rotational crops is shown in Figure 2.7.2-3.

Figure 2.7.2-3 Proposed metabolic pathway of BAS 684 H in rotational crops

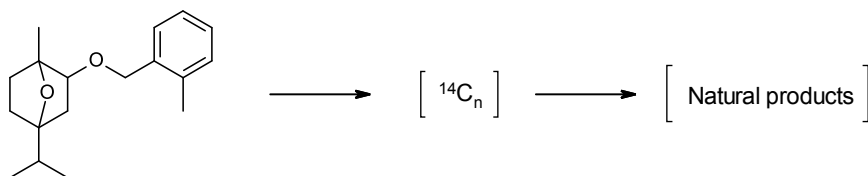


Table 2.7.2-5 Summary of confined rotational crop study – phenyl label

## Cinmethylin

## Volume 1 – Level 2

Study reference	2016/1321090																							
Outdoor/Indoor	Indoor																							
Formulation type	EC																							
Bare soil application: Y/N	Y																							
Time interval from last application and planting	30/120/365																							
Dose of application (g a.s./ha)	500																							
N rate	1N																							
Ploughing at 20 cm depth: Y/N	Y																							
Phytotoxicity observed (Y/N)	N																							
Storage: sampling to extraction/analysis (days/months)	13 to 197 days to extraction/ 32 to 714 days to analysis																							
<b><sup>14</sup>C labelling</b>	<b><sup>14</sup>C-phenyl-BAS 684 H</b>																							
Crop type	Leafy vegetables						Root and tuber vegetables						Cereal											
Crop	Spinach	Spinach	Spinach	Spinach	Spinach	Spinach	Radish	Radish	Radish	Radish	Radish	Radish	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat
Plant back intervals (days)	30	30	120	120	365	365	30	30	120	120	365	365	30	30	30	30	120	120	120	120	365	365	365	365
PHI (days after sowing)	26	39	33	48	28	41	56	56	69	69	62	62	48	48	104	104	55	55	169	169	54	54	112	112
Plant part	Immature	Mature	Immature	Mature	Immature	Mature	Leaves	Root	Leaves	Root	Leaves	Root	Forage	Hay	Straw	Grain	Forage	Hay	Straw	Grain	Forage	Hay	Straw	Grain
TRR (mg/kg)	0.012	0.011	0.007	0.006	0.005	0.005	0.013	0.006	0.005	0.001	0.01	0.002	0.028	0.132	0.088	0.014	0.006	0.057	0.058	0.009	0.011	0.06	0.024	0.004
<b>%TRR</b>																								
Total extractable residues	50.1	57.1	n/e	n/e	n/e	n/e	55.6	n/e	n/e	n/e	76.6	n/e	37.1	34	34.2	10.9	n/e	70.8	76.1	n/e	67	61.7	50.8	n/e
BAS 684 H	6						1.5							1.4	1.2				1.2			n.d		
Total identified	6						1.5							1.4	1.2				1.2					
Peak at 76 min														1.2	1.2				38.3			18.6	5.4	
Total characterised from ERR	35.5	38.9					44.1				62.2		32.7	27.1	25.6	10.9		58.5	70.0		53.8	55.8	44.4	
Total characterised from RRR	37.6	28.1					28.5				10.1		14.5	16.4	13.4	63.1		11.9	6.8		9.7	10.8	13.2	
Total identified and characterised	79.1	66.9					74.0				72.3		47.2	44.9	40.2	74.0		70.4	78.1		63.6	66.6	57.6	
Unextractable radioactive residues	49.9	42.9	n/e	n/e	n/e	n/e	44.4	n/e	n/e	n/e	23.4	n/e	62.9	66	65.8	89.1	n/e	29.2	23.9	n/e	33	38.3	49.2	n/e
Ammonia solubilisate	2.2	7.5					2.1				2.4		4.3	4.7	5.2	19.4		2.9	3.5	n/e	2.2	5.8	9.4	
Macerozyme / cellulase solubilisate	31.0	18.4					22.3				4.6		6	7.3	4.3	17.4		7.4	2.2	n/e	5.3	2.9	2.2	
Tyrosinase solubilisate	2.0	0.7					2.1				1.6		2.3	2.3	1.7	1.3		0.9	0.7	n/e	1.1	0.9	0.9	
Amylase / amyloglucosidase											0.6		0.9	1.1	1.1	22.8		0.3	0.3	n/e	0.8	0.7	0.6	
Sum of released residue	35.2	26.6					26.5				9.2		13.5	15.4	12.5	60.9		11.5	6.7	n/e	9.4	10.3	13.1	
Pepsin solubilisate	2.0	1.3					1.3				0.3		0.5	0.6	0.7	0.5		0.2	0.1	n/e	0.2	0.2	0.1	
Pancreatin solubilisate	0.5	0.2					0.7				0.5		0.4	0.5	0.3	1.7		0.3	0.1	n/e	0.2	0.1	0.2	
Sum of solubilised residue	37.6	28.1					28.5				10.1		14.5	16.4	13.4	63.1		11.9	6.8	n/e	9.7	10.8	13.2	
Bound/PES	7.8	3.8					5.7				4.3		32.7	33.8	44.8	8.1		8.3	9.4	n/e	15	18.8	26.6	
Sum of solubilised residue and final residue	45.4	31.9					34.2				14.4		47.2	50.2	58.2	71.2		20.3	16.2	n/e	24.7	29.6	39.8	
Grand total of identified, characterised and final residue	86.9	70.8					79.7	79.9			76.6		79.9	78.7	85	82.2		78.7	87.5	n/e	78.5	85.4	84.2	
<b>mg eq/kg</b>																								
Total extractable residues	0.006	0.007	n/e	n/e	n/e	n/e	0.007	n/e	n/e	n/e	0.008	n/e	0.010	0.045	0.030	0.001	n/e	0.041	0.044	n/e	0.008	0.037	0.012	n/e
BAS 684 H	0.001						<0.001							0.002	0.001				0.001					
Total identified	0.001						<0.001							0.002	0.001				0.001					
Peak at 76 min														0.002	0.001				0.022			0.011	0.001	
Total characterised from ERR	0.004	0.004					0.006				0.006		0.009	0.036	0.023	0.001		0.033	0.041		0.006	0.034	0.011	
Total characterised from RRR	0.004	0.003					0.004				0.001		0.004	0.022	0.012	0.009		0.007	0.004		0.001	0.006	0.003	
Total identified and characterised	0.009	0.008					0.009				0.007		0.013	0.059	0.035	0.010		0.040	0.046		0.007	0.040	0.014	
Unextractable radioactive residues	0.006	0.005	n/e	n/e	n/e	n/e	0.006	n/e	n/e	n/e	0.002	n/e	0.018	0.087	0.058	0.012	n/e	0.017	0.014	n/e	0.004	0.023	0.012	n/e
Ammonia solubilisate	<0.001	0.001					<0.001				<0.001		0.001	0.006	0.005	0.003		0.002	0.002		<0.001	0.004	0.002	
Macerozyme / cellulase solubilisate	0.004	0.002					0.003				<0.001		0.002	0.010	0.004	0.002		0.004	0.001		0.001	0.002	0.001	
Tyrosinase solubilisate	<0.001	<0.001					<0.001				<0.001		0.001	0.003	0.002	<0.001		<0.001	<0.001		<0.001	0.001	<0.001	
Amylase / amyloglucosidase							<0.001				<0.001		<0.001	0.001	0.001	0.003		<0.001	<0.001		<0.001	<0.001	<0.001	
Sum of released residue	0.004	0.003					0.003				0.001		0.004	0.020	0.012	0.008		0.006	0.003		0.001	0.006	0.003	
Pepsin solubilisate	<0.001	<0.001					<0.001				<0.001		<0.001	0.001	0.001	<0.001		<0.001	<0.001		<0.001	<0.001	<0.001	
Pancreatin solubilisate	<0.001	<0.001					<0.001				<0.001		<0.001	0.001	<0.001	<0.001		<0.001	<0.001		<0.001	<0.001	<0.001	
Sum of solubilised residue	0.004	0.003					0.004				0.001		0.004	0.022	0.012	0.009		0.007	0.004		0.001	0.006	0.003	
Bound/PES	0.001	<0.01					0.001				<0.001		0.009	0.044	0.039	0.001		0.005	0.005		0.002	0.011	0.006	
Sum of solubilised residue and final residue	0.005	0.004					0.004				0.001		0.013	0.066	0.051	0.010		0.012	0.009		0.003	0.018	0.010	
Grand total of identified, characterised and final residue	0.010	0.008					0.010				0.008		0.022	0.104	0.075	0.011		0.045	0.051		0.009	0.051	0.020	

n/e = not extracted

Table 2.7.2-6 Summary of confined rotational crop study – cyclohexane label

<sup>14</sup> C labelling	<sup>14</sup> C-cyclohexane-BAS 684 H																							
Crop type	Leafy vegetables						Root and tuber						Cereal											
Crop	Spinach	Spinach	Spinach	Spinach	Spinach	Spinach	Radish	Radish	Radish	Radish	Radish	Radish	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat	Wheat
Plant back intervals (days)	30	30	120	120	365	365	30	30	120	120	365	365	30	30	30	120	120	120	365	365	365	365	365	365
PHI (days after sowing)	26	39	33	48	28	41	56	56	69	69	62	62	48	48	104	104	55	55	169	169	54	54	112	112
Plant part	Immature	Mature	Immature	Mature	Immature	Mature	Leaves	Root	Leaves	Root	Leaves	Root	Forage	Hay	Straw	Grain	Forage	Hay	Straw	Grain	Forage	Hay	Straw	Grain
TRR (mg/kg)	0.013	0.008	0.001	0.002	0.001	0.002	0.009	0.004	0.002	0.001	0.003	0.001	0.025	0.132	0.061	0.016	0.001	0.018	0.02	0.013	0.003	0.009	0.006	0.002
%TRR																								
Total extractable residues	45.1	n/e	n/e	n/e	n/e	n/e	56.1	n/e	n/e	n/e	n/e	n/e	33.2	32.2	32	14.4	n/e	29.1	48.3	33.8	n/e	n/e	n/e	n/e
BAS 684 H															1.0				1.3					
Total identified															1.0				1.3					
Peak at 76 min															1.5				7.6					
Total characterised from ERR	31.2						55.4						25.4	22.9	24.7	14.4		29.1	28.3	33.8				
Total characterised from RRR	41.2						26.6						18.9	13.8	13.7	68.9		22.6	13.6	49.2				
Total identified and characterised	72.4						82.1						44.3	36.7	39.4	83.2		51.7	43.2	83.0				
Unextractable radioactive residues	54.9	n/e	n/e	n/e	n/e	n/e	43.9	n/e	n/e	n/e	n/e	n/e	66.8	67.8	68.0	85.6	n/e	70.9	51.7	66.2	n/e	n/e	n/e	n/e
Ammonia solubilise	3.4	n/e					5.6						1.7	1.5	5.2	19.3		5.1	4.0	7.3				
Macerozyme / cellulase solubilise	31.7	n/e					13.2						11.8	6.8	3.9	17.5		11.8	6.4	11.5				
Tyrosinase solubilise	2.4	n/e					2.7						2.8	2.4	2.2	1.9		0.8	1.9	2.3				
Amylase / amyloglucosidase		n/e											1.1	1.6	1.2	29.2		1.2	0.6	24.5				
Sum of released residue	37.5	n/e					21.5						17.4	12.3	12.5	67.9		18.9	12.9	45.6				
Pepsin solubilise	3.2	n/e					4.2						0.8	0.8	0.8	0.5		2.7	0.6	1.3				
Pancreatin solubilise	0.5	n/e					0.9						0.6	0.7	0.4	0.5		1.0	0.2	2.4				
Sum of solubilised residue	41.2	n/e					26.6						18.9	13.8	13.7	68.9		22.6	13.6	49.2				
Bound/PES	8.8	n/e					16.0						33.2	31.6	43.1	7.6		19.2	26.7	7.1				
Sum of solubilised residue and final residue	50.0	n/e					42.7						52.1	45.3	56.7	76.4		41.8	40.3	56.4				
Grand total of identified, characterised and final resid	81.2	n/e					98.1						77.5	68.2	82.5	90.8		70.9	69.9	90.2				
mg eq/kg																								
Total extractable residues	0.006	n/e	n/e	n/e	n/e	n/e	0.005	n/e	n/e	n/e	n/e	n/e	0.008	0.043	0.019	0.002	n/e	0.005	0.010	0.005	n/e	n/e	n/e	n/e
BAS 684 H							<0.001								0.001				<0.001					
Total identified							<0.001								0.001				<0.01					
Peak at 76 min															0.001				0.002					
Total characterised from ERR	0.004						0.005						0.006	0.030	0.015	0.002		0.005	0.006	0.005				
Total characterised from RRR	0.005						0.002						0.005	0.018	0.008	0.011		0.004	0.003	0.007				
Total identified and characterised	0.009						0.008						0.011	0.048	0.024	0.013		0.009	0.009	0.011				
Unextractable radioactive residues	0.007	n/e	n/e	n/e	n/e	n/e	0.004	n/e	n/e	n/e	n/e	n/e	0.017	0.090	0.041	0.014	n/e	0.013	0.010	0.009	n/e	n/e	n/e	n/e
Ammonia solubilise	<0.001						0.001						<0.001	0.002	0.003	0.003		0.001	0.001	0.001				
Macerozyme / cellulase solubilise	0.004						0.001						0.003	0.009	0.002	0.003		0.002	0.001	0.002				
Tyrosinase solubilise	<0.001						<0.001						0.001	0.003	0.001	<0.001		<0.001	<0.001	<0.001				
Amylase / amyloglucosidase													<0.001	0.002	0.001	0.005		<0.001	<0.001	0.003				
Sum of released residue	0.004						0.002						0.004	0.016	0.007	0.011		0.003	0.002	0.006				
Pepsin solubilise	<0.001						<0.001						<0.001	0.001	<0.001	<0.001		<0.001	<0.001	<0.001				
Pancreatin solubilise	<0.004						<0.001						<0.001	0.001	<0.001	<0.001		<0.001	<0.001	<0.001				
Sum of solubilised residue	0.005						0.002						0.005	0.018	0.008	0.011		0.004	0.003	0.007				
Bound/PES	0.001						0.001						0.008	0.042	0.026	0.001		0.003	0.005	0.001				
Sum of solubilised residue and final residue	0.006						0.004						0.013	0.060	0.034	0.012		0.008	0.008	0.008				
Grand total of identified, characterised and final resid	0.010						0.009						0.019	0.090	0.050	0.014		0.013	0.014	0.012				

n/e = not extracted

### Animal

Metabolism in livestock was investigated using two radiolabels (BAS 684 H labelled in the phenyl ring and the cyclohexane ring). Investigations were done in laying hen and lactating goat, as well as in rat to support toxicology studies (see Volume 3, section 6) and in fish (see Volume 3, section 7) although the metabolism in fish has not been fully evaluated. In addition to these studies, old goat metabolism studies of BAS 684 H performed in the 1980s (CA 6.2.3/3 – 6.2.3/5) have been evaluated along with *in-vitro* studies for hen and goat to support the metabolism of the major plant metabolites M684H005 and M684H006.

In summary the major compounds found in products of animal origin were parent BAS 684 H, M684H001 and M684H012 (A-branch), M684H021, M684H022 and M684H039 (B-branch) and cleavage products M684H026 (D-branch), M684H009, M684H010 and M684H059 (E-branch). Metabolite M684H029 was exclusively found in goat urine and faeces, but not in any edible livestock matrix and is therefore is not considered relevant for consumer exposure. Full details of the metabolites found and % TRR values are provided in the text below and shown in Table 2.7.2-7 to Table 2.7.2-10.

### *Poultry*

BAS 684 H was administered orally to twenty hens in two radiolabelled forms (phenyl and cyclohexane labels) for eleven consecutive days (nominal dose of 12 mg/kg feed/day corresponding to 0.90 – 0.94 mg/kg bw/day, 900 - 940 N for poultry).

Approximately 98.3 % and 96.9 % of the administered dose were recovered in total for the phenyl and cyclohexane label, respectively. The main fraction was excreted via excreta accounting for approximately 91.3 % (phenyl label) and 87.3 % (cyclohexane label). Radioactive residues recovered in the cage wash and rinse accounted for up to 3.8 % (phenyl label) and 4.6 % (cyclohexane label). Radioactive residues associated with edible portions (egg and tissues) accounted for up to 0.1 % (phenyl label) and 0.2 % of the administered dose (cyclohexane label).

Residues in eggs of the phenyl label increased to a plateau at 7 and 9 days with a concentration of 0.076 mg eq/kg (egg white) and 0.053 mg eq/kg (egg yolk), respectively. For the cyclohexane label, a plateau of 0.122 mg eq/kg (egg white) and 0.070 mg eq/kg (egg yolk) was reached after 7 days. There was then a very gradual increase in concentration in the egg yolk up to a maximum of 0.075 mg eq/kg at day 10.

The main portions of radioactive residues were recovered in excreta (6.397 – 7.010 mg eq/kg). In the edible matrices, the highest TRR concentrations were calculated for liver (0.221 – 0.223 mg eq/kg). For all other matrices, the TRR was in a range from 0.051 mg eq/kg to 0.083 mg eq/kg (phenyl label) and from 0.078 mg eq/kg to 0.115 mg eq/kg (cyclohexane label).

Egg yolk, egg white, muscle and liver samples were extracted with methanol and water. Fat samples were extracted with a mixture of acetonitrile and iso-hexane, and subsequently with water. In general, the extractability was high ranging from 93.0 % TRR to 99.3 % TRR, except for egg yolk (phenyl label; 77.0 % TRR) and liver (71.4% TRR and 82.5% TRR for the phenyl and cyclohexane labels, respectively). Radioactive residues in the RRR obtained after extraction of egg yolk (phenyl label) and liver amounted to 17.5 – 28.6 % TRR, which were further investigated. The RRR of all other relevant matrices were below or equal to 7.0 % TRR (0.004 mg eq/kg, phenyl label) and 8.9 % TRR (0.007 mg eq/kg, cyclohexane label).

Identification of metabolites was based on HPLC-MS analysis of fractions obtained from extracts of egg white and liver (phenyl label) and co-chromatography experiments with reference samples, diluted application solution (phenyl label) and isolated MS identified metabolites from egg white. In some cases, peaks were assigned by comparison of the retention times and metabolite patterns.

For both labels, the unchanged parent compound BAS 684 H (0.001 – 0.014 mg eq/kg or 1.0-18.0% TRR), one of four isomers of M684H021 and the metabolites M684H001 (0.001 – 0.016 mg eq/kg or 1.3-22.4% TRR), M684H039 (0.001 – 0.012 mg eq/kg or 2.0-18.8% TRR), M684H027 (0.009 – 0.012 mg eq/kg or 3.9 – 5.3% TRR) with a latter co-eluting MS-characterized compound (M306, only present at trace levels) and M684H011 (0.001 – 0.007 mg eq/kg or 1.2 – 3.3% TRR) were identified. For the phenyl label, additionally the

label specific metabolites M684H010 (0.002 – 0.021 mg eq/kg or 2.7 – 40.8% TRR) and M684H059 (0.007 – 0.043 mg eq/kg or 12.5 – 20.8% TRR), and all four isomers of M684H021 (sum of M684H021: 0.002 – 0.025 mg eq/kg or 2.7 – 39.1% TRR) were detected. One of the isomers of M684H021 co-eluted with metabolite M684H058. For the cyclohexane label, the label specific metabolite M684H026 (0.022 – 0.094 mg eq/kg or 27.3 – 56.5% TRR) was additionally recorded. Further, another label specific peak was detected in all matrices of this label eluting at approximately 7.5 min, which was further characterized by HPLC and enzyme treatment.

### *Ruminant*

BAS 684 H was administered orally to two lactating goats in two radiolabelled forms (phenyl and cyclohexane label) for seven consecutive days (nominal dose of 12 mg eq/kg feed/day corresponding to 0.21 – 0.49 mg/kg bw/day, ~ 300 – 390 N for dairy cattle).

Radioactive residues in plasma increased to a maximum of 0.079 mg eq/kg (goat 1) and 0.063 mg eq/kg (goat 2) after 1-3 h post first dose for the phenyl label and to 0.091 mg eq/kg (goat 3 and 4) after 1-4 h post first dose for the cyclohexane label.

Residues in milk from goats of the phenyl label reached a maximum of 0.015 mg eq/kg after 4 days for goat 1 and a maximum of 0.008 mg eq/kg after 5 days for goat 2. For the cyclohexane label, the level of radioactive residues increased to an initial maximum of 0.011 mg eq/kg after 2 days for goat 3 and remained consistent from day 3-5 (0.009 - 0.010 mg eq/kg) before a slight increase at day 6 to a maximum of 0.013 mg eq/kg. Residues in the milk increased to a plateau maximum of 0.020 mg eq/kg after 2 days for goat 4. It is noted that a plateau was reached in goats 1 and 4 which had the slightly higher doses of labelled BAS 684 H compared to goats 2 and 3 where no definitive plateau was recorded, based on the 24 hour milk samples (calculated from PM and AM milk collections **Error! Reference source not found.**). However, additional PM milk samples are available on the last dosing day 7. The results from these samples (goat 2 0.011 and goat 3 0.014 mg eq/kg) when compared to the values from the previous PM milk samples indicate a plateau has been reached. Overall these data are considered acceptable as a plateau is reached at the higher dose rates after 5 days, no additional data are required at this time.

Approximately 94.8 % and 92.0 % of the administered dose were recovered in total for the phenyl and cyclohexane label, respectively. Thereby, the major portion of radioactive residues was determined for faeces, urine, cage wash and rinse, GI tract and contents. Radioactive residues associated with edible portions (milk and tissues) accounted for a maximum of 0.6 % (phenyl label, liver) and 0.5 % of the administered dose (cyclohexane label, liver).

The main portions of radioactive residues were recovered in urine, faeces and bile (2.129 – 16.314 mg eq/kg). In the relevant matrices, the highest TRR concentrations were calculated for liver and kidney (0.361 – 0.681 mg eq/kg). For all other edible matrices, the TRR was in a range from 0.002 mg eq/kg to 0.022 mg eq/kg.

Radioactive residues were extracted with methanol and water (milk, muscle, liver, kidney and faeces), or only methanol (workup 2 of liver), or acetonitrile, iso-hexane and water (fat). In general, the extractability was high ranging from 90.2 % TRR to 99.3 % TRR, except for liver and faeces (both labels) being between 62.1 % TRR and 77.6 % TRR. From liver, aliquots of the RRR of both labels were incubated subsequently with protease, pepsin and pancreatin which released additional 30.9 % TRR and 36.3 % TRR for the phenyl and cyclohexane label, respectively.

Structure elucidation of metabolites was based on HPLC-MS and NMR analysis and co-chromatography experiments with isolated, MS-and NMR-identified metabolites and reference samples. In some cases, peaks were assigned by comparison of the retention times and metabolite patterns. The unchanged parent compound BAS 684 H was detected in milk of the cyclohexane label and in liver and fat of both labels, ranging from 0.001 - 0.097 mg eq/kg (7.3 – 22.3 % TRR). Regarding only the relevant matrices (milk, tissues and organs), further metabolites identified for both labels were M684H001 (< 0.001 – 0.032 mg eq/kg or 1.0 – 4.8 % TRR), M684H011 (< 0.001 – 0.019 mg eq/kg or 1.2 – 2.9 % TRR), two isomers of M684H012 (sum of M684H012: < 0.001 - 0.067 mg eq/kg or 2.8 – 17.9 % TRR) and two isomers of M684H022 (sum of M684H022: < 0.001 – 0.068 mg eq/kg or 4.6 – 14.4 % TRR). In addition, metabolites M684H034, M684H052, M684H056 and M684H057 ranging from < 0.001 mg eq/kg to 0.030 mg eq/kg or from 0.4 % TRR to 6.7 % TRR were detected. The label specific metabolites M684H026 (cyclohexane label) and M684H009 (phenyl label) were identified in milk, tissues and organs ranging from < 0.001 mg eq/kg to 0.092 mg eq/kg or from 2.9 % TRR to 71.6 % TRR.



Table 2.7.2-7 Summary of %TRR for poultry

Study reference	2017/1068568									
Animal	Poultry (hen)									
Number of animals	20 (10 per label)									
number of applications	once per day									
mg/kg bw/day	0.90 mg/kg bw/day of 14C-phenyl-BAS 684 H, 0.94 mg/kg bw/day of 14C-cyclohexane-BAS 684 H									
mg/kg DM basis	12.03 mg/kg bw/day of 14C-phenyl-BAS 684 H, 11.99 mg/kg bw/day of 14C-cyclohexane-BAS 684 H									
Number dosing days	11									
Time of sacrifice after the final dose (hours)	3 -6									
14C labelling	14C-phenyl-BAS 684 H, 14C-cyclohexane-BAS 684 H									
Plateau reached in eggs and milk (days)	7									
Storage: sampling to extraction/analysis (days/mo)	133 days to extraction/ 268-464 days to analysis	133 days to extraction/ 266 days to analysis	90 days to extraction/ 263 days to analysis	90 days to extraction/ 263 days to analysis	259 days to extraction/ 467 days to analysis	133 days to extraction/ 464 days to analysis	133 days to extraction/ 266 days to analysis	90 days to extraction/ 263 days to analysis	90 days to extraction/ 263 days to analysis	129 days to extraction/ 467 days to analysis
labelling	14C-phenyl-BAS 684 H					14C-cyclohexane-BAS 684 H				
Matrix	Egg yolk	white (work u	Muscle	Liver	Fat	Egg yolk	Egg white	Muscle	Liver	Fat
TRR [mg/kg]	0.058	0.065	0.051	0.223	0.083	0.078	0.115	0.096	0.221	0.079
Sampling time	Day 7-10	Day 7-10	Terminal	Terminal	Terminal	Day 7-10	Day 7-10	Terminal	Terminal	Terminal
Total extractable residues (% TRR)	77.0	98.9	93.0	71.4	96.7	91.1	99.3	98.0	82.5	98.5
BAS 684 H	1.6				13.4	1.8	1.0			18.0
M684H001	2.1	22.4	6.0	6.9	8.3	1.4	13.7	1.3	4.5	7.8
M684H002										
M684H009										
M684H010	2.7		40.8	6.2	24.7					
M684H011				3.3	2.0				1.3	1.2
M684H012a										
M684H012b										
M684H012, sum of isomers										
M684H021_22.1_LC02/ M684H058		19.8								
M684H021_24.6_LC02	8.3	6.9	13.9	6.7	2.7	6.2	3.9	5.8	5.4	3.4
M684H021_32.5_LC02		4.9								
M684H021_33.5_LC02		7.6								
M684H021, sum of isomers	8.3	39.1	13.9	6.7	2.7					
M684H022_32.0_LC07										
M684H022_34.0_LC07										
M684H022, sum of isomers										
M684H026						34.7	33.4	56.5	42.5	27.3
M684H027				5.3					3.9	
M684H029										
M684H034										
M684H039	10.9	18.8	2.9			4.1	9.4			
M684H052										
M684H056										
M684H057										
M684H059	12.5		14.7	19.3	20.8					
Total identified (% TRR)	38.2	80.3	78.2	47.7	72.1	48.2	61.4	63.6	57.6	57.9
Organosoluble fractions										
Aqueous soluble fractions										
Neutral fraction										
Acidic fraction										
Polar fraction										
Total Characterized (% TRR)	39.2	11.3	11.4	19.9	27.4	42.2	34.3	35.7	31.4	34.5
Unknowns										
Not analysed fractions										
Unresolved										
Unextractable radioactive residues(% TRR)	23.0	1.1	7.0	28.6	3.3	8.9	0.7	2.0	17.5	1.5
Acid/base hydrolysis										
Enzymatic hydrolysis (protease)	16.2			19.8					9.5	
Enzymatic hydrolysis (pepsin)										
Enzymatic hydrolysis (pancreatin)										
Sum of enzym solubilizates										
Total identified and characterized (% TRR)	93.5	91.6	89.6	87.4	99.5	90.5	95.7	99.3	98.5	92.3
Bound/PES(% TRR)	8.9	1.1	7.0	8.1	3.3	8.9	0.7	2.0	3.1	1.5
Sum of solubilized radioactive residue + final residue	25.1			27.9					12.6	
Accountability (% TRR)	102.4	92.7	96.6	95.5	102.8	99.3	96.4	101.4	101.6	93.8

Table 2.7.2-8 Summary of metabolites in mg eq/kg for poultry

14C labelling	14C-phenyl-BAS 684 H					14C-cyclohexane-BAS 684 H				
Matrix	Egg yolk	white (work u	Muscle	Liver	Fat	Egg yolk	Egg white	Muscle	Liver	Fat
Sampling time	Day 7-10	Day 7-10	Terminal	Terminal	Terminal	Day 7-10	Day 7-10	Terminal	Terminal	Terminal
Total extractable residues	<b>0.045</b>	<b>0.064</b>	<b>0.047</b>	<b>0.16</b>	<b>0.081</b>	<b>0.071</b>	<b>0.114</b>	<b>0.094</b>	<b>0.182</b>	<b>0.078</b>
BAS 684 H	0.001				<b>0.011</b>	0.001	0.001			<b>0.014</b>
M684H001	0.001	<b>0.014</b>	0.003	<b>0.015</b>	0.007	0.001	<b>0.016</b>	0.001	0.010	0.006
M684H002										
M684H009										
M684H010	0.002		<b>0.021</b>	<b>0.014</b>	<b>0.021</b>					
M684H011				0.007	0.002				0.003	0.001
M684H012a										
M684H012b										
M684H012, sum of isomers										
M684H021_22.1_LC02 / M684H058		<b>0.013</b>								
M684H021_24.6_LC02	0.005	0.004	0.007	<b>0.015</b>	0.002	0.005	0.004	0.006	<b>0.012</b>	0.003
M684H021_32.5_LC02		0.003								
M684H021_33.5_LC02		0.005								
M684H021, sum of isomers	0.005	<b>0.025</b>	0.007	<b>0.015</b>	0.002					
M684H022_32.0_LC07										
M684H022_34.0_LC07										
M684H022, sum of isomers										
M684H026						<b>0.027</b>	<b>0.038</b>	<b>0.054</b>	<b>0.094</b>	<b>0.022</b>
M684H027				<b>0.012</b>					0.009	
M684H029										
M684H034										
M684H039	0.006	<b>0.012</b>	0.001			0.003	<b>0.011</b>		nor detected	
M684H052										
M684H056										
M684H057										
M684H059	0.007		0.007	<b>0.043</b>	<b>0.017</b>					
<b>Total identified (mg/kg TRR)</b>	<b>0.022</b>	<b>0.052</b>	<b>0.040</b>	<b>0.107</b>	<b>0.060</b>	<b>0.038</b>	<b>0.070</b>	<b>0.061</b>	<b>0.127</b>	<b>0.046</b>
Organosoluble fractions										
Aqueous soluble fractions										
Neutral fraction										
Acidic fraction										
Polar fraction										
<b>Total Characterized (mg/kg TRR)</b>	<b>0.023</b>	<b>0.007</b>	<b>0.006</b>	<b>0.044</b>	<b>0.023</b>	<b>0.033</b>	<b>0.039</b>	<b>0.034</b>	<b>0.069</b>	<b>0.027</b>
Unknowns										
Not analysed fractions										
Unresolved										
<b>Unextractable radioactive residues(% TRR)</b>	<b>0.013</b>	<b>0.001</b>	<b>0.004</b>	<b>0.064</b>	<b>0.003</b>	<b>0.007</b>	<b>0.001</b>	<b>0.002</b>	<b>0.039</b>	<b>0.001</b>
Acid/base hydrolysis										
Enzymatic hydrolysis (protease)	0.009			0.044					0.021	
Enzymatic hydrolysis (pepsin)										
Enzymatic hydrolysis (pancreatin)										
<b>Sum of enzym solubilizates</b>										
<b>Total identified and characterized</b>	<b>0.054</b>	<b>0.059</b>	<b>0.046</b>	<b>0.195</b>	<b>0.083</b>	<b>0.070</b>	<b>0.110</b>	<b>0.095</b>	<b>0.218</b>	<b>0.073</b>
<b>Bound/PES(% TRR)</b>	<b>0.005</b>	<b>0.001</b>	<b>0.004</b>	<b>0.018</b>	<b>0.003</b>	<b>0.007</b>	<b>0.001</b>	<b>0.002</b>	<b>0.007</b>	<b>0.001</b>
<b>Sum of solubilized radioactive residue + final res</b>	<b>0.015</b>			<b>0.062</b>					<b>0.028</b>	
<b>Accountability (% TRR)</b>	<b>0.059</b>	<b>0.060</b>	<b>0.049</b>	<b>0.213</b>	<b>0.086</b>	<b>0.077</b>	<b>0.110</b>	<b>0.097</b>	<b>0.225</b>	<b>0.075</b>

Table 2.7.2-9 Summary of %TRR for ruminants

Study reference	2017/1037602																											
Animal	Ruminant (goat)																											
Number of animals	4 (2 per label)																											
number of applications	Once per day																											
mg/kg bw/day	0.38/0.21 (14C-phenyl) 0.28/0.49 (14C-cyclohexane)																											
mg/kg DM basis	12 (nominal)																											
Number dosing days	7																											
Time of sacrifice after the final dose (hours)	4 - 5																											
14C labelling	14C-phenyl-BAS 684 H, 14C-cyclohexane-BAS 684 H																											
Plateau reached in eggs and milk (days)	4																											
Storage: sampling to extraction/analysis (days/months)	162 days to extraction/ 275 days to analysis	161 days to extraction/ 293 days to analysis	132 days to extraction/ 181 days to analysis	103 days to extraction/ 272 days to analysis	146 days to extraction/ 176 days to analysis										118 days to extraction/ 274 days to analysis	120 days to extraction/ 299 days to analysis	132 days to extraction/ 294 days to analysis	103 days to extraction/ 272 days to analysis	146 days to extraction/ 272 days to analysis									
labelling	14C-phenyl-BAS 684 H														14C-cyclohexane-BAS 684 H													
Matrix	Milk	Muscle	Fat		Liver (work up 1)	Liver (work up 2)	Kidney	Urine	Bile	Feces	Milk	Muscle	Fat		Liver (work up 1)	Liver (work up 2)	Kidney	Urine	Bile	Feces								
TRR [mg/kg]	0.01	0.011	0.01		0.681	0.361	9.792	11.44	2.429		0.013	0.022	0.019		0.656	0.472	13.682	16.314	2.129									
Sampling time	Day 4-6	Terminal	Terminal		Terminal	Terminal	Day 4-6	Terminal	Day 4-6	Day 4-6	Day 4-6	Terminal	Terminal	Terminal	Terminal	Terminal	Terminal	Day 4-6	Terminal	Day 4-6								
Total extractable residues (% TRR)	99.0	90.2	96.5	65.0	64.0	94.6			71.7		99.3	94.6	96.5	62.1	63.7	97.7			77.6									
BAS 684 H			14.9		14.3						8.5		22.3		7.3													
M684H001		2.2			4.7		0.6		6					4.8	1		0.9			3.3								
M684H002							0.1										1											
M684H009	71.6	3.3				11.9	12.9		1									1										
M684H010																			2.3									
M684H011		n			2.2	1.2	1.6		2.2			1.6		2.9	1.7	2.3				2.3								
M684H012a					1	4.6	2.9		0.4			0.6		1	2.8	3.6				0.7								
M684H012b		3.1			4.9	13.4	11.9		1.6		2.2		4.2	9.3	9.7					2.6								
M684H012, sum of isomers		3.1			5.8	17.9	14.9		2		2.8		5.2	12.1	13.3					3.3								
M684H021, 22.1 LC02 / M684H058																												
M684H021, 24.6 LC02																												
M684H021, 32.5 LC02																												
M684H021, 33.5 LC02																												
M684H021, sum of isomers																												
M684H022, 32.0 LC07		1.5			1.6	3.5	5.2		2.2					2.5	5.7	5.8				3.1								
M684H022, 34.0 LC07		3.1			3	8	8.3		1.6					2.8	8.7	8				2.4								
M684H022, sum of isomers		4.6			4.6	11.5	13.5		3.8					5.3	14.4	13.8				5.5								
M684H026										27.4	23.6	5.7		14.1	2.9	2				2								
M684H027																												
M684H029																		2.2		1.1								
M684H034		1.9				6.5	7.6										4.7	3.3		1.6								
M684H039																												
M684H052		1.4			3.3	3.9	1.6					3.3		4.5	4.2	6.3				1.1								
M684H056		5.2			1.6	2	2.9		2.1			0.4		1.6	3.4	3.7				2.5								
M684H057					4.3	6.7	7.1		2.1					2.3	6.1	5.5				2.5								
M684H059																												
Total identified (% TRR)	71.6	21.7	14.9		40.7	61.7	62.8		19.1	35.9	31.7	28		35.8	50.5	54.4				25.3								
Organosoluble fractions																												
Aqueous soluble fractions																												
Neutral fraction																												
Acidic fraction																												
Polar fraction																												
Total Characterized (% TRR)	12.7	57.8	72.2		21.4	23.9	30.4		52.7	57.8	52	67.1			38.1	39.3				48.8								
Unknowns																												
Not analysed fractions																												
Unresolved																												
Unextractable radioactive residues(% TRR)	1.0	9.8	3.5	35	35.5	2.4			28.3	0.7	5.4	3.2	37.9	37.3	1.9					22.4								
Acid/base hydrolysis																												
Enzymatic hydrolysis (protease)				21.5											30.7													
Enzymatic hydrolysis (pepsin)				8.4											4.8													
Enzymatic hydrolysis (pancreatin)				1											0.7													
Sum of enzym solubilizes				30.9											36.3													
Total identified and characterized (% TRR)	95.5	79.5	87.1		93	85.6	93.1		71.8	93.8	83.7	95.1	97.2		88.6	93.6				74.1								
Bond PFS(% TRR)	1	9.8	3.5	23	2.4	0.4			28.3	0.7	5.4	3.2		1.3	1.9	1.3				22.4								
Sum of solubilized radioactive residue + final residue					33.2										37.5													
Accountability (% TRR)	96.4	89.2	90.6		95.3	87.9	93.6		100.1	94.4	89.1	98.3		98.5	90.5	94.9				96.7								

Table 2.7.2-10 Summary of metabolites in mg eq/kg for ruminants

14C labelling										14C-cyclohexane-BAS 684 H								
Matrix	Milk	Muscle	Fat	ver (work up	ver (work up	Kidney	Urin	Bile	Feces	Milk	Muscle	Fat	Liver (work u	Liver (work u	Kidney	Urin	Bile	Feces
Sampling time	Day 4-6	Terminal	Terminal	Terminal	Terminal	Terminal	Day 4-6	Terminal	Day 4-6	Day 4-6	Terminal	Terminal	Terminal	Terminal	Terminal	Day 4-6	Terminal	Day 4-6
Total extractable residues	0.01	0.01	0.01	0.443	0.436	0.352			1.741	0.013	0.021	0.018	0.407	0.418	0.463			1.652
BAS 684 H			0.002		0.097					0.001		0.004	0.048					
M684H001		<0.001			0.032		0.057		0.146				0.032		0.005	0.125		0.071
M684H002							0.012									0.140		
M684H009	0.007	<0.001				0.044	1.263		0.025									
M684H010									0.052									
M684H011					0.015	0.004	0.154				<0.001		0.019		0.008	0.314		0.049
M684H012a		<0.001			0.007	0.017	0.286		0.010		<0.001		0.006		0.013	0.493		0.014
M684H012b					0.033	0.050	1.169		0.038		<0.001		0.028		0.044	1.333		0.056
M684H012, sum of isomers		<0.001			0.040	0.067	1.454		0.048		0.001		0.034		0.057	1.826		0.071
M684H021, 22.1 LC02 / M684H058																		
M684H021, 24.6 LC02																		
M684H021, 32.5 LC02																		
M684H021, 33.5 LC02																		
M684H021, sum of isomers																		
M684H022, 32.0 LC07		<0.001			0.011	0.013	0.513		0.052				0.016		0.027	0.797		0.066
M684H022, 34.0 LC07		<0.001			0.020	0.030	0.808		0.039				0.018		0.041	1.096		0.051
M684H022, sum of isomers		0.001			0.031	0.043	1.316		0.091				0.034		0.068	1.893		0.117
M684H026										0.004	0.005	0.001	0.092		0.014	0.279		0.042
M684H027																		
M684H029																0.297		0.024
M684H034		<0.001				0.024	0.746								0.022	0.445		0.034
M684H039																		
M684H052		0.001			0.022	0.014	0.155				0.001		0.030		0.020	0.863		0.024
M684H056		<0.001			0.011	0.008	0.286		0.051		<0.001		0.010		0.016	0.503		0.053
M684H057					0.029	0.025	0.697		0.050				0.015		0.029	0.753		0.053
M684H059																		
<b>Total identified (mg/kg TRR)</b>	<b>0.007</b>	<b>0.002</b>	<b>0.002</b>		<b>0.277</b>	<b>0.229</b>	<b>6.145</b>		<b>0.465</b>	<b>0.005</b>	<b>0.007</b>	<b>0.005</b>	<b>0.235</b>		<b>0.240</b>	<b>7.438</b>		<b>0.538</b>
Organosoluble fractions																		
Aqueous soluble fractions																		
Neutral fraction																		
Acidic fraction																		
Polar fraction																		
<b>Total Characterized (mg/kg TRR)</b>	<b>0.001</b>	<b>0.006</b>	<b>0.007</b>		<b>0.146</b>	<b>0.089</b>	<b>2.974</b>		<b>1.279</b>	<b>0.008</b>	<b>0.012</b>	<b>0.013</b>	<b>0.165</b>		<b>0.181</b>	<b>5.374</b>		<b>1.039</b>
Unknowns																		
Not analysed fractions																		
Unresolved																		
<b>Unextractable radioactive residues(% TRR)</b>	<b>&lt;0.001</b>	<b>0.001</b>	<b>&lt;0.001</b>		<b>0.016</b>	<b>0.009</b>			<b>0.689</b>	<b>&lt;0.001</b>	<b>0.001</b>	<b>&lt;0.001</b>	<b>0.248</b>	<b>0.245</b>	<b>0.009</b>			<b>0.477</b>
Acid/base hydrolysis																		
Enzymatic hydrolysis (protease)					0.146									0.202				
Enzymatic hydrolysis (pepsin)					0.058									0.032				
Enzymatic hydrolysis (pancreatin)					0.007									0.004				
<b>Sum of enzym solubilizes</b>					<b>0.21</b>									<b>0.238</b>				
<b>Total identified and characterized</b>	<b>0.01</b>	<b>0.008</b>	<b>0.009</b>		<b>0.634</b>	<b>0.318</b>	<b>9.12</b>		<b>1.744</b>	<b>0.012</b>	<b>0.019</b>	<b>0.018</b>	<b>0.638</b>	<b>0.42</b>	<b>12.812</b>			<b>1.578</b>
<b>BoundPES(% TRR)</b>	<b>&lt;0.001</b>	<b>0.001</b>	<b>&lt;0.001</b>		<b>0.016</b>	<b>0.009</b>	<b>0.043</b>		<b>0.689</b>	<b>&lt;0.001</b>	<b>0.001</b>	<b>&lt;0.001</b>	<b>0.008</b>	<b>0.009</b>	<b>0.174</b>			<b>0.477</b>
<b>Sum of solubilized radioactive residue + final residue</b>					<b>0.226</b>								<b>0.246</b>					
<b>Accountability (% TRR)</b>	<b>0.01</b>	<b>0.01</b>	<b>0.009</b>		<b>0.649</b>	<b>0.327</b>	<b>9.163</b>		<b>2.433</b>	<b>0.012</b>	<b>0.02</b>	<b>0.019</b>	<b>0.646</b>	<b>0.429</b>	<b>12.985</b>			<b>2.055</b>

The metabolic routes in livestock are shown in Figure 2.7.2-5 and Figure 2.7.2-6 and the transformation reactions summarised in

Figure 2.7.2-4.

In livestock, the metabolic pathway is largely based on:

- hydroxylation of the parent compound at various positions
- subsequent conjugation of these hydroxyl groups with glucuronide
- cleavage at the ether bridge

#### *Old ruminant studies*

The new livestock metabolism data package is in agreement with the general metabolic pathway shown by the old goat metabolism studies of BAS 684 H performed in the 1980s (CA 6.2.3/3 – 6.2.3/5). In these studies, the highest TRRs were observed in faeces and urine (50.0 and 79.0 mg eq/kg respectively) followed by liver and kidney (4.14 and 3.84 mg eq/kg respectively). Whilst the study states a plateau in milk was reached after 2 days at 0.09 mg eq/kg, only 3 days of samples were collected which is insufficient to derive a robust conclusion from. Only skimmed milk, liver and excreta were extracted in which BAS 684 H was metabolised into numerous metabolites, however these metabolites were not identified in skimmed milk and liver. Identification was only performed on excreta samples, in which the main metabolites identified were hydroxylated derivatives of BAS 684 H, however they were only identified after deconjugation. Additionally, the studies were not performed to GLP or in accordance with OECD Guideline 503, they provide no details on storage stability and the animal was dosed for only 4 days. Whilst the 1980s studies are deficient and cannot be fully relied upon, they are considered to provide supporting information, particularly that there is a good correlation between the metabolite structures in the old and new studies.

#### *Stereoisomer-specific analysis*

The parent BAS 684 H was administered as a racemic mixture of two enantiomers (a ratio of the (-) and (+) enantiomers of approximately 43:57 in the poultry application solution (phenyl label) and 49:51 in the ruminant application (cyclohexane label)). Chiral analysis in the matrices containing the highest proportions of BAS 684 H revealed a ratio of the (-) and (+) enantiomers was approximately 62:38 in poultry (fat, cyclohexane label) and a ratio of the (-) and (+) enantiomers was approximately 53:47 in goat (liver, cyclohexane label). These changes in ratio are not considered significant, further discussion is provided in Section 2.12.

#### *In-vitro studies for M684H005 and M684H006*

The related plant metabolism studies showed only low amounts of the unchanged parent compound, but main portions of metabolites M684H005 and M684H006 after application of BAS 684 H to plants. Hence, livestock animals, being fed with plant material obtained after application of BAS 684 H, are more likely exposed to metabolites M684H005 and M684H006. To avoid additional *in-vivo* studies for investigation of the metabolism of metabolites M684H005 and M684H006 in animals, alternative *in-vitro* approaches were applied to demonstrate suitability of the animal metabolism studies, dosed with BAS 684 H. Following information from peer reviewed literature, hen intestine pieces were used to investigate the potential metabolism of both metabolites (M684H005 and M684H006) in a part of the GI tract of hens. For lactating ruminants, a RUSITEC methods was utilised where rumen fluid was used to investigate the potential metabolism of both metabolites in a part of the GI tract of ruminants. Overall the *in-vitro* data for the metabolites M684H005 and M684H006 are considered appropriate to support the metabolism in poultry and lactating ruminants. Metabolites M684H002, M684H005 and M684H006 are hydroxylated or conjugated forms of parent BAS 684 H. The results of the *in-vitro* study are as expected, the metabolites M684H005 and M684H006 are cleaved to form M684H002. From a toxicological perspective, metabolite M684H002 is equivalent to parent BAS 684 H. Metabolite M684H002 is not found in the hen metabolism study but is found in the goat metabolism study of BAS 684 H in urine and the metabolic pathway shows it is a key intermediate for several other metabolites. Exposure to M684H002 would likely be comparable to exposure from BAS 684 H. Therefore, no additional data are required to support the lactating ruminant metabolism of the major plant metabolites M684H005 and M684H006.

Figure 2.7.2-4 BAS 684 H transformation reactions in animals

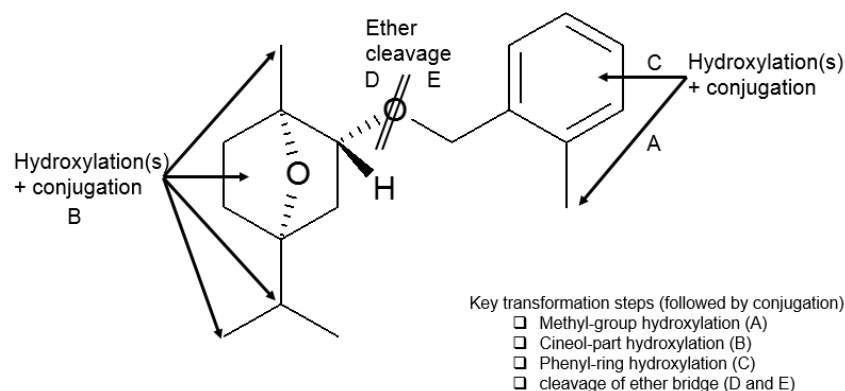


Figure 2.7.2-5 and Figure 2.7.2-6 show the key metabolism pathways determined for the animal commodities.

Metabolites occurring in edible livestock matrices in major amounts (> 10 % TRR) are listed in bold text in Table 2.7.2-11. This table groups the metabolites according to their chemical structure, together with their corresponding conjugates.

Table 2.7.2-11 Metabolites in edible livestock matrices

<b>A-branch</b> (hydroxylation at the methyl group and further phase I and phase II metabolites)	<b>B-branch</b> (hydroxylation at the cineol-part and further phase I and phase II metabolites)	<b>C-branch</b> (hydroxylation at the phenyl-ring and further phase I and phase II metabolites)	<b>D-branch</b> (cleavage products cineol-part and further phase I and phase II metabolites)	<b>E-branch</b> (cleavage products phenyl part and further phase I and phase II metabolites)
<b>M684H001</b>	<b>M684H021</b>	M684H034	<b>M684H026</b>	<b>M684H009</b>
M684H011	<b>M684H022</b>			<b>M684H010</b>
<b>M684H012</b>	M684H027			M684H058
M684H056	<b>M684H039</b>			<b>M684H059</b>
	M684H052			
	M684H057			

Metabolites with a content of >10% TRR are indicated in **bold** font

Figure 2.7.2-5 BAS 684 H: metabolic routes in livestock – A-, B- and C-branch (hydroxylated and conjugated metabolites)

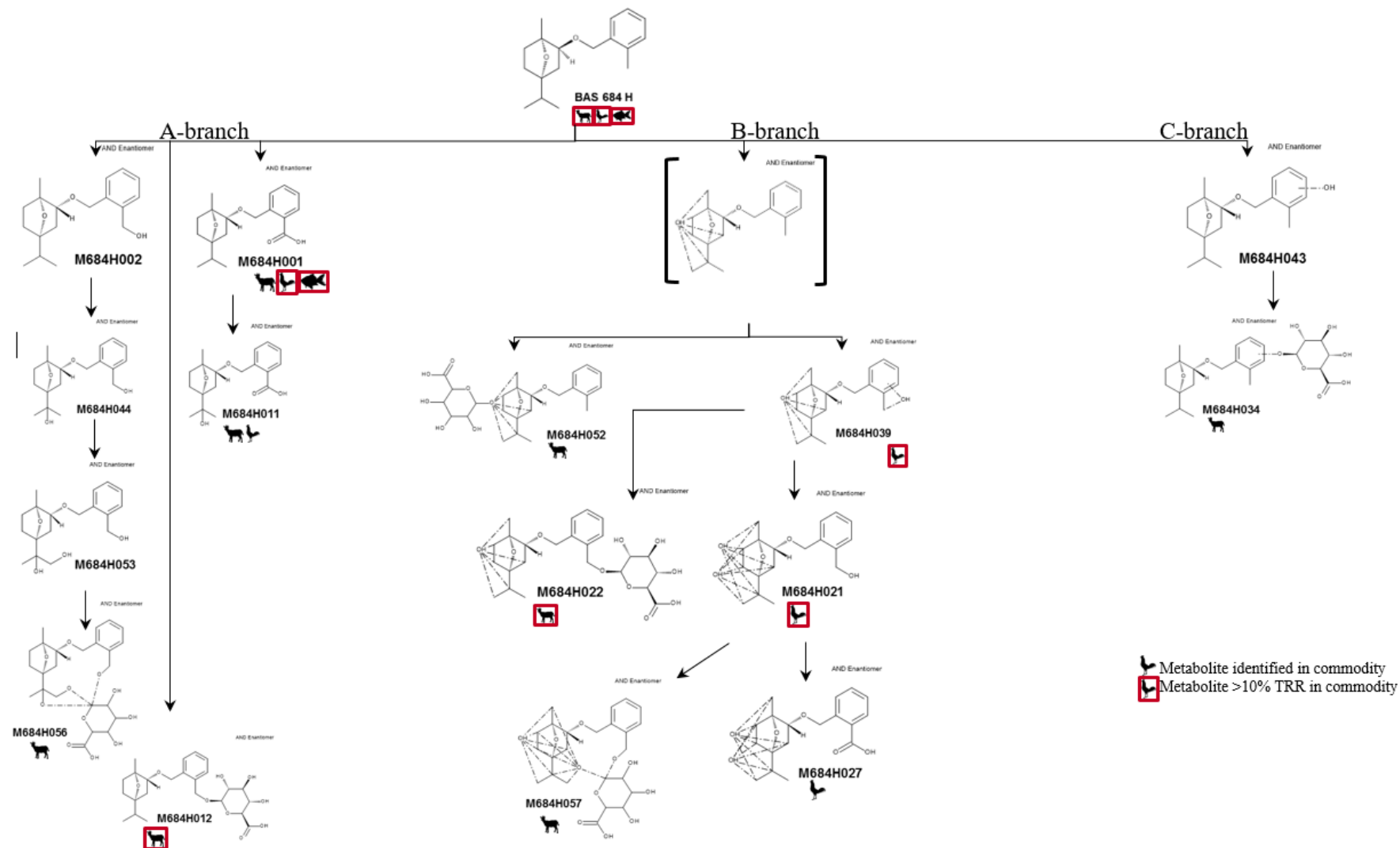
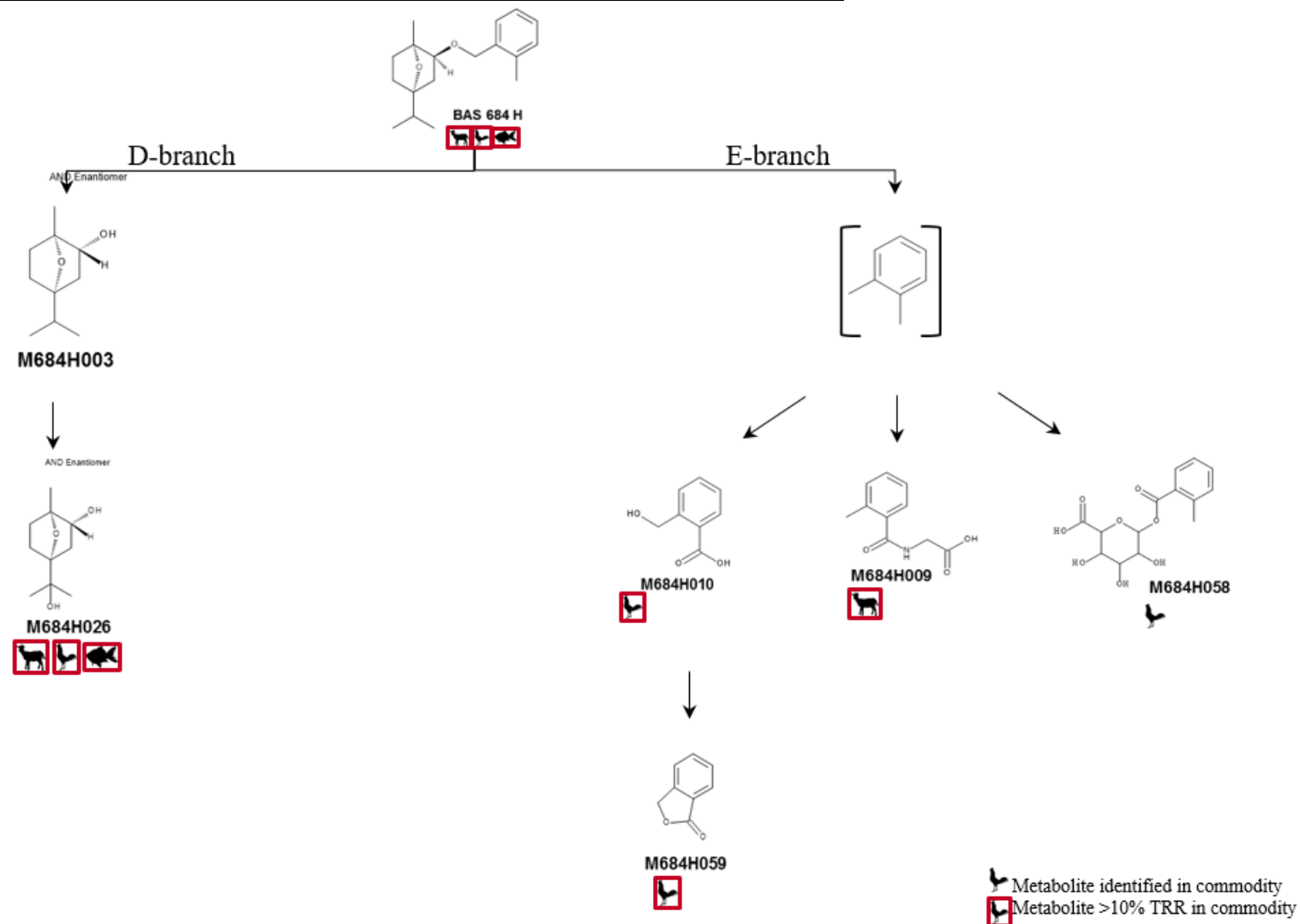




Figure 2.7.2-6 BAS 684 H: metabolic routes in livestock – D- and E-branch (cleavage products)



### 2.7.3. Definition of the residue

#### Plant

##### *Primary crops*

An overview of the major compounds found at >10% TRR in plant matrices is given in Table 2.7.3-1. The only major compounds >10% TRR found in food commodities were parent BAS 684 H (up to 13.7% TRR (0.014 mg eq/kg) in oilseed rape seed) and carbohydrates (up to 78.4% TRR or 0.113 mg eq/kg in carrot roots); no major metabolites >10% were identified in food commodities for the commodities studied in the plant metabolism studies. Given the carbohydrates are natural products, it is not appropriate to consider these further for inclusion in the residue definitions. In wheat forage, wheat straw and oilseed rape straw, major metabolites >10% TRR were the sugar conjugates M684H005 (up to 22.1% TRR (0.755 mg eq/kg) in oilseed rape straw) and M684H006 (up to 29.7% TRR (0.796 mg eq/kg) in wheat forage). In oilseed rape hulls and wheat grain, no major compounds were identified. Wheat forage and oilseed rape straw are neither feed nor food commodities (there are no representative forage uses). The only relevant feed commodity is wheat straw, in which two major metabolites were found, namely M684H005 (up to 17.3% TRR or 1.440 mg eq/kg) and M684H006 (up to 18.5% TRR or 1.798 mg eq/kg).

Table 2.7.3-1: Major compounds >10% TRR in plant matrices

Compound (radiolabel)	Wheat forage		Wheat straw		Carrot leaves		Carrot roots		Oilseed rape seeds		Oilseed rape straw	
	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR
BAS 684 H (phenyl)	0.081	3.1	0.026	0.4	0.107	24.1	0.003	3.5	<b>0.014</b>	<b>13.7</b>	0.043	1.2
BAS 684 H (cyclohexane)	0.054	2.0	Not detected		<b>0.159</b>	<b>27.9</b>	0.012	7.9	0.004	4.3	Not detected	
M684H005 (phenyl)	0.296	11.2	1.028	<b>17.3</b>	0.008	1.8	Not detected		Not detected		0.487	13.0
M684H005 (cyclohexane)	<b>0.396</b>	<b>14.8</b>	<b>1.440</b>	14.8	0.002	0.4	Not detected		Not detected		<b>0.755</b>	<b>22.1</b>
M684H006 (phenyl)	0.770	29.2	0.720	12.1	0.011	2.6	Not detected		Not detected		<b>0.439</b>	<b>11.8</b>
M684H006 (cyclohexane)	<b>0.796</b>	<b>29.7</b>	<b>1.798</b>	<b>18.5</b>	0.014	2.4	Not detected		Not detected		0.046	1.4

For major compounds (>10% TRR): Higher residue of the two labels highlighted in **bold**

Parent BAS 684 H is included in the plant residue definition given its occurrence in the plant metabolism studies. BAS 684 H was identified above 10% TRR in oilseed rape seeds at 13.7 % TRR (0.014 mg eq/kg, phenyl label), and in carrot leaves at 24.1% TRR (0.107 mg eq/kg, phenyl label) and 27.9% TRR (0.159 mg eq/kg, cyclohexane label). BAS 684 H is also detected at lower levels <10% TRR in: oilseed rape straw, hulls and seeds (cyclohexane label); wheat forage and straw (both labels); and carrot roots (both labels).

M684H005 is included in the plant residue definition given its occurrence in the plant metabolism studies and toxicological relevance. M684H005 was identified above 10% TRR in wheat forage at 11.2 %TRR (0.296 mg eq/kg, phenyl label) and 14.8 % TRR (0.396 mg eq/kg, cyclohexane label); wheat straw at 17.3% TRR (1.028 mg eq/kg, phenyl label) and 14.8% TRR (1.440 mg eq/kg, cyclohexane label); and oilseed rape straw at 13.0% TRR (0.487 mg eq/kg, phenyl label) and 22.1% TRR (0.755 mg eq/kg, cyclohexane label). M684H005 was identified at lower levels <10% TRR in oilseed rape hulls (both labels) and carrot leaves (both labels). The toxicological evaluation (Vol 3 CA B.6.8.1) concluded that metabolite M684H005 is toxicologically relevant and of equivalent toxicity to parent BAS 684 H and therefore a potential candidate for inclusion in the residue definition from a toxicological perspective. The toxicological reference values for BAS 684 H can be used for M684H005.

M684H006 is included in the plant residue definition given its occurrence in the plant metabolism studies and toxicological relevance. M684H006 was identified above 10% TRR in wheat forage at 29.2% TRR (0.770 mg

eq/kg, phenyl label) and 29.7% TRR (0.796 mg eq/kg, cyclohexane label), wheat straw at 12.1% TRR (0.720 mg eq/kg, phenyl label) and 18.5% TRR (1.798 mg eq/kg, cyclohexane label) and oilseed rape straw at 11.8% TRR (0.439 mg eq/kg, phenyl label). M684H006 was identified at lower levels <10% TRR in carrot leaves (both labels), oilseed rape straw (cyclohexane label) and oilseed rape hulls (both labels). The toxicological evaluation (Vol 3 CA B.6.8.1) concluded that metabolite M684H006 is toxicologically relevant and of equivalent toxicity to parent BAS 684 H and therefore a potential candidate for inclusion in the residue definition from a toxicological perspective. The toxicological reference values for BAS 684 H can be used for M684H006.

#### *Rotational crops*

The only identified residue observed in rotational crops was BAS 684 H: at a 30 d PBI in immature spinach, radish leaves, wheat hay and straw; and at a 120 d PBI in wheat straw; at a maximum of 0.002 mg eq/kg or 6.0% TRR.

A component characterised as a natural endogenous compound (including glucosyl conjugates) was observed at a maximum of 38.3% TRR (0.022 mg eq/kg) in wheat straw at a 120 PBI. The applicant proposed that this compound is likely formed from the degradation of BAS 684 H in soil to small polar fragments and uptake of these by the plant followed by metabolism into natural products within the plant. This is considered acceptable and consistent with the environmental fate evaluation (Volume 3CA B.8.1), in which the aerobic soil metabolism study demonstrates BAS 684 H is degraded into numerous minor fragments with a DT<sub>50</sub> of 53.9 days. Hence it is not considered appropriate to include this component in the residue definition.

The metabolism in rotational crops is similar to the metabolism observed in primary crops, particularly the metabolism observed in carrot as a primary crop where BAS 684 H was the only identified component and a significant proportion of the residue was made up by natural products, likely due to breakdown of BAS 684 H in the soil and uptake by the plant.

#### *Processed commodities*

BAS 684 H was observed to be stable under standard hydrolysis conditions in the study provided. Therefore, the processing of BAS 684 H is not expected to modify the nature of the residues. The effect of processing upon the nature of metabolites M684H005 and M684H006 has not been investigated under standard hydrolysis conditions. However, given residues of M684H005 and M684H006 are <0.01 mg/kg in wheat grain and rape seeds in the residues trials, standard hydrolysis studies for these metabolites are not required for the representative uses on wheat and barley or the future proposed use on oilseed rape as concluded in Section 2.7.6.

The residue definition for the raw agricultural commodity (RAC) is also applicable to processed commodities for the representative uses on wheat and barley and future proposed use on oilseed rape. Further data on the nature of residues of M684H005 and M684H006 under standard hydrolysis conditions may be requested in future depending on the residue levels of these metabolites.

#### *Residue definition for risk assessment*

M684H005 and M684H006 are included in the residue definition for risk assessment given their occurrence in various crop matrices from the primary crop metabolism studies and given they are toxicologically relevant as discussed above. As M684H005 and M684H006 are covered by the toxicity data of parent BAS 684 H and the toxicological reference values for BAS 684 H (ARfD and ADI) can be used for M684H005 and M684H006 (Vol 3 CA B.6.8.1), the metabolites are included as a sum with BAS 684 H.

The metabolism of cinmethylin is similar across 3 crop groups (pulses and oilseeds, cereals, root crops) based on the data currently available hence a general residue definition can be set. However, it should be noted that the wheat and oilseed rape metabolism studies were not overdosed; they were only performed at the proposed application rate. In the wheat metabolism study, no identification was performed on wheat grain due to low residues and in the oilseed rape metabolism study, residues in rape seeds were also low and only parent BAS 684 H was identified. The 1980s soybean metabolism studies indicate a qualitative difference in the chromatographic patterns of the extracts of soybean foliage and seeds, with the seeds containing more polar residues. Therefore particular attention should be paid to any future uses, particularly those with higher application rates or in different crop groups, to ensure that the uses are sufficiently supported by metabolism data.

The metabolism in rotational crops is similar to the metabolism observed in primary crops. The residue definition is also applicable to processed commodities for the representative uses on wheat and barley and future proposed use on oilseed rape.

Residue definition for risk assessment: sum of BAS 684 H, M684H005 and M684H006, expressed as BAS 684 H

*Residue definition for monitoring*

Parent BAS 684 H is considered a sufficient marker in primary crops, rotational crops and processed commodities. BAS 684 H is the only component identified in food commodities of primary crops (oilseed rape seeds and carrot roots) and rotational crops (immature spinach) and BAS 684 H is stable under standard hydrolysis conditions.

Residue definition for monitoring: BAS 684 H

An analytical method for the enforcement of the proposed residue definition with an LOQ of 0.01 mg/kg in high water, high acid, high oil, high protein and high starch commodities is available (Method L0337/01, Vol 3 CA B5.2.1).

No conversion factor (monitoring to risk assessment) has been set as residue values in edible plant commodities are all < LOQ.

**Animal**

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

Residue definition for MRL enforcement/monitoring (RD-Mo): Parent BAS 684 H

Residue definition for risk assessment (RD-RA): Not applicable.

The following section discusses the relevance of the residue components identified in animal food items (for details on their toxicological assessment refer to Volume 3, section 6).

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.

Generally, for deciding on the residue definition, components >10% TRR are taken into consideration. An overview of major metabolites found in livestock matrices and their level of occurrence is given in Table 2.7.3-2 and Table 2.7.3-3.

Based on the dietary burden as shown in Section 2.7.5, the available metabolism studies can be considered to be dosed at 300 – 390 N and 900 – 940 N (based on mg/kg bw/day) for ruminants and poultry, respectively. However, the detected metabolites, (even those > 10 % TRR), are present at < 0.1 mg eq/kg, considering the N rate residues of the metabolism studies residues in products of animal origin are not expected to exceed 0.01 mg eq/kg.

Table 2.7.3-2 Major compounds in poultry matrices, results taken from metabolism study in Section B7

Designation	Egg yolk		Egg white <sup>1</sup>		Muscle		Liver		Fat	
	[mg/kg]	[% TRR]	[mg/kg]	[% TRR]	[mg/kg]	[% TRR]	[mg/kg]	[% TRR]	[mg/kg]	[% TRR]
Phenyl label; actual dose 0.90 mg/kg bw/day, 900 N										
BAS 684 H	0.001	1.6	Not detected		Not detected		Not detected		0.011	13.4
M684H001	0.001	2.1	0.014	22.4	0.003	6.0	0.015	6.9	0.007	8.3
M684H010	0.002	2.7	Not detected		0.021	40.8	0.014	6.2	0.021	24.7
M684H021 22.1 LC02 / M684H058 <sup>3</sup>	Not detected		0.013	19.8	Not detected		Not detected		Not detected	
M684H021, sum of isomers <sup>1</sup>	0.005	8.3	0.025	39.1	0.007	13.9	0.015	6.7	0.002	2.7
M684H039	0.006	10.9	0.012	18.8	0.001	2.9	Not detected		Not detected	
M684H059	0.007	12.5	Not detected		0.007	14.7	0.043	19.3	0.017	20.8
Cyclohexane label; actual dose 0.94 mg/kg bw/day, 940 N										
BAS 684 H	0.001	1.8	0.001	1.0	Not detected		Not detected		0.014	18.2
M684H001	0.001	1.4	0.016	13.7	0.001	1.3	0.010	4.5	0.006	7.8
M684H021, sum of isomers <sup>2</sup>	0.005	6.2	0.004	3.9	0.006	5.8	0.012	5.4	0.003	3.4
M684H026	0.027	34.7	0.038	33.4	0.054	56.5	0.094	42.5	0.022	27.3
M684H039	0.003	4.1	0.011	9.4	Not detected		Not detected		Not detected	

<sup>1</sup> 4 isomers<sup>2</sup> 1 isomer<sup>3</sup> Peak shared between M684H021\_22.1\_LC02 and M684H058

Table 2.7.3-3 Major compounds in ruminant matrices, results taken from metabolism study in Section B7

Designation	Milk		Muscle		Fat		Liver		Kidney	
	[mg/kg]	[% TRR]	[mg/kg]	[% TRR]	[mg/kg]	[% TRR]	[mg/kg]	[% TRR]	[mg/kg]	[% TRR]
Phenyl label; actual dose 0.21 – 0.38 mg/kg bw/day, 300 N										
BAS 684 H	Not detected		Not detected		0.002	14.9	0.097	14.3	Not detected	
M684H009	0.007	71.6	<0.001	3.3	Not detected		Not detected		0.044	11.9
M684H012, sum of isomers <sup>1</sup>	Not detected		<0.001	3.1	Not detected		0.040	5.8	0.067	17.9
M684H022, sum of isomers <sup>1</sup>	Not detected		0.001	4.6	Not detected		0.031	4.6	0.043	11.5
Cyclohexane label; actual dose 0.28 – 0.49 mg/kg bw/day, 390 N										
BAS 684 H	0.001	8.5	Not detected		0.004	22.3	0.048	7.3	Not detected	
M684H012, sum of isomers <sup>1</sup>	Not detected		0.001	2.8	Not detected		0.034	5.2	0.057	12.1
M684H022, sum of isomers <sup>1</sup>	Not detected		Not detected		Not detected		0.034	5.3	0.068	14.4
M684H026	0.004	27.4	0.005	23.6	0.001	5.7	0.092	14.1	0.014	2.9

<sup>1</sup> 2 isomers

For these major metabolites toxicology has made the following conclusions:

Metabolite	Covered by parent	Tox. compared to parent	Ref. value	Tox. relevant
M684H001	Y	Equivalent	Parent	Y
M684H009	N	Significantly lower	(BAT) 57 mg/kg bw/d	No tox. concern
M684H010	Y	Equivalent	Parent	Y
M684H012, sum of isomers	Y	Equivalent	Parent	Y
M684H058	N	Significantly lower	(Cramer class I TTC value) 30 µg/kg bw/d	No tox. concern
M684H021, sum of isomers	N	Potentially higher	(Cramer class III TTC value) 1.5 µg/kg bw/d	Y
M684H022, sum of isomers	N	Potentially higher	(Cramer class III TTC value) 1.5 µg/kg bw/d	Y
M684H026	Y	Equivalent	Parent	Y
M684H039	N	Potentially higher	(Cramer class III TTC value) 1.5 µg/kg bw/d	Y
M684H059	N	Potentially higher	(Cramer class III TTC value) 1.5 µg/kg bw/d	Y

Four of these metabolites; M684H021 (sum of all isomers), M684H022 (sum of all isomers), M684H039 and M684H059 have a potentially higher toxicity compared to parent and have been assigned the Cramer class III TTC reference value. An indicative exposure screening of these metabolites has been completed using the inputs provided in Table 2.7.3-4 and Table 2.7.3-5. The metabolites M684H021, M684H022 and M684H039 have been combined in the risk assessment as there are similarities in the structures. The inputs used in the chronic and acute exposure calculations are shown in Table 2.7.3-6 and Table 2.7.3-7, and summaries of the calculated exposures using both the UK models and EFSA PRIMo revision 3.1 are provided below. Where the metabolites were detected in multiple matrices or in both the cyclohexane and phenyl labelled studies the highest value was used in the calculated exposure. As the egg samples (both egg white and egg yolk) are pooled (see Volume 3, Section 7) it is not possible to accurately calculate a whole egg equivalent value for each metabolite, therefore the highest residue from either egg yolk or egg white is used in the exposure screening. The following reference values were used<sup>3</sup>:

TTC Cramer class III chronic value = 1.5 µg/kg bw/d  
TTC Cramer class III acute value = 5 µg/kg bw

<sup>3</sup> EFSA (2012) Scientific Opinion on Evaluation of the Toxicological Relevance of Pesticide Metabolites for Dietary Risk Assessment, EFSA Journal 2012;10(07):2799

Table 2.7.3-4 Summary of metabolites for indicative exposure screening - poultry

Matrix	Phenyl label (mg eq/kg)					Cyclohexane label (mg eq/kg)				
	egg white	egg yolk	muscle	fat	liver	egg white	egg yolk	muscle	fat	liver
M684H021, sum of isomers	0.025	0.005	0.007	0.002	0.015	0.004	0.005	0.006	0.003	0.012
M684H022, sum of isomers	-	-	-	-	-	-	-	-	-	-
M684H039	0.012	0.006	0.001	-	-	0.011	0.003	-	-	-
SUM (021, 022, 039)	0.037	0.011	0.008	0.002	0.015	0.015	0.008	0.006	0.003	0.012
M684H059	-	0.007	0.007	0.017	0.043	-	-	-	-	-

‘-’: Not found at all in the study (see Volume 3, Section 7.2.3), however are shown for completeness as the metabolites M684H021, M684H022 and M684H039 are being summed together for the TTC screening.

Table 2.7.3-5 Summary of metabolites for indicative exposure screening - ruminants

Matrix	Phenyl label (mg eq/kg)					Cyclohexane label (mg eq/kg)				
	Milk	Liver	Kidney	Muscle	Fat	Milk	Liver	Kidney	Muscle	Fat
M684H021, sum of isomers	-	-	-	-	-	-	-	-	-	-
M684H022, sum of isomers	-	0.031	0.043	0.001	-	-	0.034	0.068	-	-
M684H039	-	-	-	-	-	-	-	-	-	-
SUM (021, 022, 039)	-	0.031	0.043	0.001	-	-	0.034	0.068	-	-
M684H059	-	-	-	-	-	-	-	-	-	-

‘-’: Not found or detected in the ruminant study (see Volume 3, Section 7.2.3), however are shown for completeness as the metabolites M684H021, M684H022 and M684H039 are being summed together for the TTC screening.

Table 2.7.3-6 Inputs for UK exposure calculation

Commodity	Input metabolites M684H021, M684H022 and M684H039 mg eq/kg	Notes	Input metabolite M684H059 mg eq/kg	Notes
Poultry	0.008	Poultry muscle, phenyl labelled metabolism study	0.007	Poultry muscle, phenyl labelled metabolism study
Meat fat	0.003	Poultry fat, cyclohexane labelled metabolism study	0.017	Poultry fat, phenyl labelled metabolism study
Meat excl. poultry & offal	0.001	Ruminant muscle, phenyl labelled metabolism study	0	-
All types of kidney	0.068	Ruminant kidney, cyclohexane labelled metabolism study	0	-

All types of Liver	0.034	Ruminant liver, cyclohexane labelled metabolism study	0.043	Poultry liver, phenyl labelled metabolism study
Other types of offal	0	-	0	-
Eggs	0.037	Egg white, phenyl labelled metabolism study	0.007	Egg yolk, phenyl labelled metabolism study
Milk	0	-	0	-

Table 2.7.3-7 Inputs for exposure calculation using EFSA PRIMo revision 3.1

Commodity	Input metabolites M684H021, M684H022 and M684H039 <i>mg eq/kg</i>	Notes	Input metabolite M684H059 <i>mg eq/kg</i>	Notes
Swine/Bovine/Horse/ Sheep/Goat/Other: Muscle	0.001	Ruminant muscle, phenyl labelled metabolism study	0	-
Swine/Bovine/Horse/ Sheep/Goat/Other: Fat	0	-	0	-
Swine/Bovine/Horse/ Sheep/Goat/Other: Liver	0.034	Ruminant liver, cyclohexane labelled metabolism study	0	-
Swine/Bovine/Horse/ Sheep/Goat/Other: Kidney	0.068	Ruminant kidney, cyclohexane labelled metabolism study	0	-
Swine/Bovine/Horse/ Sheep/Goat/Other: Edible offal	0	-	0	-
Poultry: Muscle	0.008	Poultry muscle, phenyl labelled metabolism study	0.007	Poultry muscle, phenyl labelled metabolism study
Poultry: Fat	0.003	Poultry fat, cyclohexane labelled metabolism study	0.017	Poultry fat, phenyl labelled metabolism study
Poultry: Liver	0.015	Poultry liver, phenyl labelled metabolism study	0.043	Poultry liver, phenyl labelled metabolism study
Poultry: Kidney	0	-	0	-
Poultry: Edible offal	0	-	0	-
Milk and milk products: Cattle/Horse/ Sheep/Goat/Other	0	-	0	-
Birds' eggs	0.037	Egg white, phenyl labelled metabolism study	0.007	Egg yolk, phenyl labelled metabolism study

N.B. Ruminant data is being used to support all animal matrices.

The following conclusions can be made from each of the models:



Chronic assessment (TTC Cramer class III acute value = 1.5 µg/kg bw/day)

	Consumption (µg/kg bw/day)	Consumer group
<b>M684H021, M684H022 and M684H039</b>		
UK	0.258	Infant
EFSA PRIMo	0.06	UK infant
<b>M684H059</b>		
UK	0.133	Infant
EFSA PRIMo	0.01	FR child 3-15 yr

Acute assessment (TTC Cramer class III acute value = 5 µg/kg bw)

	Consumption (µg/kg bw)	Consumer group
<b>M684H021, M684H022 and M684H039</b>		
UK	0.46	Infants consuming eggs
EFSA PRIMo	0.46	Children consuming chicken eggs
<b>M684H059</b>		
UK	0.35	Infants consuming liver
EFSA PRIMo	0.20	Adults consuming poultry liver

As both the chronic and acute exposure is significantly below the threshold values using both the UK and EU models no further consideration is required for these metabolites in the context of the animal residue definition.

Exposure screening assessments for the other significant metabolites (M684H001, M684H009, M684H010, M684H012, M684H058 and M684H026) have not been completed. These metabolites have been assigned as either equivalent toxicity to parent BAS 684 H, or lower toxicity e.g. Cramer class I or BAT reference values. As these metabolites are all expected (accounting for the N rate) at < 0.01 mg/kg no further consideration of these metabolites is necessary. Therefore, all significant metabolites identified in the animal metabolism studies do not need to be included in either the risk assessment or monitoring definitions at this time. However, it is noted that a reconsideration of the residue definition and an updated TTC exposure assessment will be required if future additional uses which results in a more critical dietary burden are requested.

Overall conclusions:

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

The residue definition for MRL enforcement (RD-Mo) should focus on those residue components suitable as analytes in multi-residue methods, suitable to indicate possible pesticide misuse, as well as suitable as general marker compound in food commodities concerned.

Parent BAS 684 H fulfils these criteria since its compatibility with multi-residue methods has been confirmed. Significant residues in products of animal origin are not expected from the proposed uses and therefore BAS 684 H can be considered as a default marker to detect misuse of BAS 684 H, noting it is present at >10 % TRR in poultry fat and ruminant liver and fat.

- *parent BAS 684 H*

An analytical method for the enforcement of the proposed residue definition with an LOQ of 0.01 mg/kg in milk, egg, meat, liver, kidney and fat matrices is available (Method L0385/01, Vol 3 CA B5.2.2).

Residue definition for risk assessment (RD-RA):

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.

No relevant consumer exposure by food items of animal origin is present from either parent BAS 684 H or its metabolites. Based on the N rates, the TRR in the animal metabolism studies are not expected to exceed 0.01 mg/kg when recalculated to 1N. In addition, if an animal metabolism study had not been provided it would not

have been triggered based on the dietary burden. Therefore, a residue definition for risk assessment is not currently required.

- *not needed*

This conclusion is based on the requested uses as detailed in Section 1.5, if additional uses are required in the future then the need for a RD-RA in animal matrices (and the sufficiency of the toxicological data available) should be re-considered based on an updated animal dietary burden and also considering an updated TTC exposure assessment.

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

The proposed use of BAS 648 H in the GB is on winter cereals (wheat and barley). A proposed use in winter oilseed rape is included in the dossier, to facilitate a future application for extension of use into oilseed rape and evaluation of the oilseed rape residues data has also been completed. The representative formulation BAS 684 03 H is an emulsifiable concentrate (EC) containing 750 g/L of the active substance. The cGAP for these commodities are shown in Table 2.7.4-1.

Table 2.7.4-1 Critical GAP for the proposed use in cereals and oilseeds

Crop	Outdoor/ Protected	Growth stage (BBCH)	Maximum number of applications	Minimum application interval (days)	Maximum		Minimum PHI (days)
					Rate (kg a.s./ha)	Water (L/ha)	
Cereals (wheat and barley)	Outdoor	29	1	N/A	0.5	200	N/A
Oilseeds (oilseed rape)	Outdoor	18	1	N/A	0.25	200	N/A

##### Cereal summary

The residue trials were performed in various European Member States in both European regions (N-EU, 12 trials; S-EU 12 trials) during three growing seasons (2015, 8 trials; 2016, 8 trials; 2017, 8 trials) and thereby fulfil the requirements of seasonal and geographical distribution.

The field trial data for the seasons 2015 and 2016 (8 trials N-EU trials, 8 trials S-EU) was performed with the formulated product BAS 684 02 H. For the season 2017, field trial data has been generated with the representative formulation BAS 684 03 H (4 trials N-EU, 4 trials S-EU). As detailed in Volume 3 Section 7, the differences of the formulations (both EC type) are considered negligible and therefore no comparative residues trials were considered necessary.

Table 2.7.4-2 Summary of BAS 684 H residue data for the proposed use in cereals

Region	Residue levels (mg/kg) observed in the supervised residue trials relevant to the supported GAPs (Monitoring RD†)	Residue levels (mg/kg) observed in the supervised residue trials relevant to the supported GAPs (Risk assessment RD†)	HR (mg/kg)	STMR (mg/kg)	MRL (mg/kg)
<b>Grain</b>					
N-EU	12× <0.01*	12 x < 0.016*	0.016*	0.016*	0.01*
S-EU	12× <0.01*	12 x < 0.016*	-	-	-
<b>Straw</b>					
N-EU	12× <0.01*	10 x < 0.016*, 0.018, 0.024	0.024	0.016*	-
S-EU	11× <0.01*, 0.026	4 x < 0.016*, 0.018, 0.022, 0.024, 0.029, 0.036, 0.052, 0.062, 0.25	-	-	-

\* Detected at or below the limit of quantification (LOQ)

† Residue definition (RD) for monitoring is BAS 684 H

Residue definition (RD) for risk assessment is sum of BAS 684 H, M684H005 and M684H006, expressed as BAS 684 H  
Note data from the SEU are not being used in the risk assessment therefore HR, STMR and MRL values have not been determined.

No conversion factor (monitoring to risk assessment) has been set as residue values in edible plant commodities are all < LOQ.

#### Oilseeds summary

The residue trials were performed in various European Member States in both European regions (N-EU 8 trials; S-EU 8 trials) during two growing seasons (2016, 8 trials; 2017, 8 trials) and thereby fulfil the requirements of seasonal and geographical distribution.

The field trial data available for the season 2016 (4 trials N-EU trials, 4 trials S-EU) was generated with the formulated product BAS 684 02 H. For the season 2017, field trial data was generated with the representative formulation BAS 684 03 H (4 trials N-EU trials, 4 trials S-EU). As detailed in section Volume 3, section 7, the differences of the formulations (both EC type) are considered negligible and therefore no comparative residues trials were considered necessary.

Table 2.7.4-3 Summary of BAS 684 H residue data for the proposed use in oilseeds

Region	Residue levels (mg/kg) observed in the supervised residue trials relevant to the supported GAPs (Monitoring RD†)	Residue levels (mg/kg) observed in the supervised residue trials relevant to the supported GAPs (Risk assessment RD†)	HR (mg/kg)	STMR (mg/kg)	MRL (mg/kg)
N-EU	8× <0.01*	8 x < 0.016*	0.016*	0.016*	0.01*
S-EU	8× <0.01*	8 x < 0.016*	-	-	-

\* Detected at or below the limit of quantification (LOQ)

† Residue definition (RD) for monitoring is BAS 684 H

Residue definition (RD) for risk assessment is sum of BAS 684 H, M684H005 and M684H006, expressed as BAS 684 H  
Note data from the SEU are not being used in the risk assessment therefore HR and STMR values have not been determined.

No conversion factor (monitoring to risk assessment) has been set as residue values in edible plant commodities are all < LOQ.

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

### *Dietary burden*

The dietary burden has been performed according to the approach presented in the OECD Guidance document on residues in livestock, series on pesticides No 73 for a total of 9 animal species. All feed items which might be treated with the active substance under evaluation have been considered (wheat, barley and oilseed rape). In this calculation only the representative (wheat and barley) and future (oilseed rape) uses of BAS 684 H have been considered. Calculations are performed using the Excel calculator proposed by EFSA (pesticides\_mrl\_guidelines\_animal\_model\_2017). The following assumptions have been made:

- 1) The highest likely inclusion rate of all crops which may have been treated has been used with the proviso that the aggregate does not exceed 100% diet;
- 2) All produce eaten which may have been treated, has been treated and contains residues as summarized below;
- 3) There is no loss of residue during transport, storage, preparation of feed or processing prior to consumption.

The dietary burden considers components of the plant RD-RA (sum of BAS 684 H, M684H005 and M684H006 expressed as BAS 684 H). The residues are calculated using residues data from NEU only. The inputs for the dietary burden are presented in Table 2.7.5-1.

Table 2.7.5-1 Inputs for the dietary burden

Feed commodity	Median dietary burden		Maximum dietary burden	
	(mg/kg)	Comment	(mg/kg)	Comment
RD-RA Plant commodities: Sum of BAS 684 H, M684H005 and M684H006 expressed as BAS 684 H				
Wheat grain	0.016	STMR	0.016	STMR
Wheat straw	0.024	STMR	0.024	HR
Barley grain	0.016	STMR	0.016	STMR
Barley straw	0.024	STMR	0.024	HR
Rape meal	0.016	STMR x PF <sup>†</sup>	-	-
Brewers grain (dried)	0.016	STMR (barley grain) x PF <sup>†</sup>	-	-
Canola (rape seed meal)	0.016	STMR (rape meal) x PF <sup>†</sup>	-	-
Distiller's grain (dried)	0.016	STMR (wheat grain) x PF <sup>†</sup>	-	-
Wheat gluten (meal)	0.016	STMR (wheat grain) x PF <sup>†</sup>	-	-
Wheat (milled by-products)	0.016	STMR (wheat grain) x PF <sup>†</sup>	-	-

<sup>†</sup> PF = 1; waiving the use of default processing factors (PF) as residues in the RAC are < LOQ

The maximum and median calculated animal intakes are reported in Table 2.7.5-2.

Table 2.7.5-2 Median and Maximum dietary burden of BAS 684 H by domestic animals

**New data requirements**

(Regulation (EU) No 283/2013)

Relevant groups	Dietary burden expressed in				Most critical diet (a)	Most critical commodity (b)		Trigger exceeded (Yes/No)
	mg/kg bw per day		mg/kg DM					0.004
	Median	Maximum	Median	Maximum				mg/kg bw
Cattle (all diets)	0.001	0.001	0.02	0.02	Dairy cattle	Wheat gluten	meal	No
Cattle (dairy only)	0.001	0.001	0.02	0.02	Dairy cattle	Wheat gluten	meal	No
Sheep (all diets)	0.001	0.001	0.02	0.03	Lamb	Wheat gluten	meal	No
Sheep (ewe only)	0.001	0.001	0.02	0.03	Ram/Ewe	Wheat gluten	meal	No
Swine (all diets)	0.001	0.001	0.02	0.02	Swine (finishing)	Barley	grain	No
Poultry (all diets)	0.001	0.001	0.02	0.02	Poultry layer	Wheat gluten	meal	No
Poultry (layer only)	0.001	0.001	0.02	0.02	Poultry layer	Wheat gluten	meal	No

(a): When several diets are relevant (e.g. cattle, sheep and poultry "all diets"), the most critical diet is identified from the maximum dietary burdens expressed as "mg/kg bw per day"

(b): The most critical commodity is the major contributor identified from the maximum dietary burden expressed as "mg/kg bw per day".

### ***Feeding studies***

No feeding study is required for ruminants, poultry, pigs and or fish.

The requirements for feeding studies are set out according to Commission Regulation (EU) No 283/2013 with data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market as well as and in OECD guidelines.

Feeding studies are required:

- (1) If metabolism studies indicate that significant residues (above 0.01 mg/kg for each analyte) may occur in any edible animal tissue, considering the residue levels in potential feeding stuff obtained at the 1x dose rate.
- (2) However, feeding studies shall not be required where intake is below 0.004 mg/kg bw/d, except in cases where the residue, namely the active substance, its metabolites or breakdown products, as defined in the residue definition for risk assessment, tends to accumulate.

In the context of this document, feed burden calculations were performed using the EU Animal Model 2017 considering only the representative (wheat and barley) and future (oilseed rape) uses and the residues according to the risk assessment residue definition (sum of BAS 684 H, metabolites M684H005 and M684H006, expressed as BAS 684 H).

The resulting maximum dietary burden for all the various livestock species are 0.001 mg/kg bw/d (0.02 mg/kg feed DM).

Thus, for poultry, pigs and cattle, the intakes are not exceeding the trigger value of 0.004 mg/kg bw/d.

Comparing the feed burdens with the metabolism studies on hens and goats overdosing factors of 900 – 940 N for poultry and 300 – 390 N for ruminants have been derived. When the over-dosing factors are applied to the TRR measured in animal feedstuffs in the metabolism studies it shows the residues in all edible animal tissues are expected to be < 0.01 mg/kg at the maximum reasonable worst-case feed burden.

## **2.7.6. Summary of effects of processing**

### **Nature of the residue**

The nature of residues of BAS 684 H upon processing was investigated in a standard hydrolysis study conducted with two labels of BAS 684 H (phenyl label and cyclohexane label) simulating pasteurisation, baking/boiling/brewing and sterilisation conditions. BAS 684 H was observed to be stable upon processing under all 3 representative conditions.

The residue definition for risk assessment also includes metabolites M684H005 and M684H006. The effect of processing upon the nature of metabolites M684H005 and M684H006 has not been investigated under standard hydrolysis conditions. However, given residues of M684H005 and M684H006 are <0.01 mg/kg in wheat grain and rape seeds in the residues trials, standard hydrolysis studies for these metabolites are not required for the representative uses on wheat and barley or the future proposed use on oilseed rape.

The applicant has submitted the argument that cleavage experiments performed within the primary crop metabolism studies on wheat, oilseed rape and carrot under basic and acidic conditions demonstrate that the malonylglucoside M684H006 is converted into the glucoside M684H005 and that M684H005 is stable under such conditions. Upon standard hydrolysis conditions, these reactions are likely to occur however the extent of such degradation is not known. It may be possible that further deconjugation of M684H005 and M684H006 into M684H002 may occur. Given the structural similarity of M684H002 to parent BAS 684 H, and the stability of BAS 684 H under standard hydrolysis conditions, it is plausible that M684H002 would not degrade further under standard hydrolysis conditions however no data is available to confirm this.

The residue definition for processed commodities is concluded to be the same as for the raw agricultural commodity (RAC) for the representative uses on wheat and barley and future proposed use on oilseed rape. Further data on the nature of residues of M684H005 and M684H006 under standard hydrolysis conditions may be requested in future depending on the residue levels of these metabolites.

### **Magnitude of the residue**

Studies on the magnitude of residues in processed commodities are not required as residues were < 0.1 mg/kg in all the RACs analysed in the NEU trials on wheat or oilseed rape, parent BAS 684 H is stable upon processing and no degradation products of toxicological concern are formed upon processing.

### **2.7.7. Summary of residues in rotational crops**

Representative uses on cereals (wheat and barley) and the future proposed use on oilseed rape can be grown in rotation and field soil degradation studies indicate the DT<sub>90</sub> value for cinmethylin is a maximum of 207.6 days (Volume 3 CA B.8.1) therefore a consideration of residues in rotational crops is required, but there is no potential for accumulation over multiple years of use. There are no major soil metabolites for BAS 684 H and therefore no potential for accumulation of soil metabolites over multiple years of use.

### **Nature of the residue**

The nature of the residue has been addressed in Section 2.7.1 above.

### **Magnitude of the residue**

Studies investigating the magnitude of residues in rotational crops are not required as no components of the residue were identified at  $\geq 0.01$  mg/kg in the confined rotational crop study.

In conclusion, for the use of BAS 684 H supported in the present dossier, no significant residues in rotational crops are expected (for both the representative uses on wheat and barley and the future proposed use on oilseed rape) hence no replant restrictions are required.

### **2.7.8. Summary of other studies**

#### **Effect on the residue level in pollen and bee products**

At the date of submission (22/6/2018) there were no agreed EU guidance documents or test methods to address these data requirements. Since submission the Technical guidelines for determining the magnitude of pesticide residues in honey and setting Maximum Residue Levels in honey (SANTE/11956/2016 rev. 9) have been noted with an agreed implementation date of 1<sup>st</sup> January 2020.

The applicant has submitted the information in Volume 3, section 7.7.1 based on a draft version of the guidelines.

The HSE evaluator agrees with the applicant's statement that the future proposed use on oilseed rape with application at post-emergence before BBCH 18 is considered to be the worst case GAP for honey residues. The information/data provided confirms that residues of sum of BAS 684 H, M684H005 and M684H006, expressed as BAS 684 H in aerial parts of the crop are likely to be < 0.20 mg/kg at flowering based upon the proposed use on oilseed rape. Assuming a 1:1 transfer between aerial parts of the crop the worst case residues expected in honey are 0.20 mg/kg. Residues of BAS 684 H in the aerial parts of the crop are likely to be < 0.01 mg/kg at flowering based upon the future proposed use on oilseed rape.

The acute and chronic intakes based on these worst case residues are expected to be < 0.3 mg/kg bw (ARfD) and < 0.08 mg/kg bw/day (ADI) PRIMo). It is noted that the applicant has based the assessment on both NEU and SEU trials data, however risk assessment in other areas have only considered the NEU data to support the use in the UK. The HR value of 0.2 mg/kg at the attractive period of the crop (i.e. flowering BBCH 65) is found in the NEU data, therefore only relying on the NEU data would not affect the overall conclusions.

As at the date of submission (22/6/2018) there were no agreed EU guidance documents or test methods to address these data requirements, the submission has not been critically evaluated, although it is noted that no significant risk to consumers based on the future proposed use on oilseed rape exists.

The trials on oilseed rape are considered worst-case compared to the representative uses on wheat and barley therefore residues of BAS 684 H in honey based on the representative uses are expected to be < 0.01 mg/kg. Given a monitoring method for BAS 684 H in honey is available with an LOQ of 0.01 mg/kg (method L0337/03, Vol 3 CA B5.2.2), the MRL for BAS 684 H in honey is proposed at approval at 0.01\* mg/kg. This MRL would also accommodate the future proposed use on oilseed rape given residues of BAS 684 H in aerial parts of the crop are likely to be < 0.01 mg/kg at flowering.

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

Two sets of consumer risk assessment have been conducted to predict the chronic exposure scenarios for consumers, based on the predicted level of BAS 684 H (sum of BAS 684 H, M684H005 and M684H006, expressed as BAS 684 H) within food items.

The first of these approaches uses the EFSA PRIMo version 3.1 calculator to predict the dietary intakes for consumer groups across the EU. An EU assessment has been performed for the primary crop uses.

The second form of the assessment utilises the UK national calculator and considers a diverse range of consumer groups relevant to the UK.

The following toxicological reference values have been used in the consumer risk assessments:

ADI (mg/kg bw/day)	0.08
ARfD (mg/kg bw)	0.3

#### *Acute and chronic EU dietary intake estimates*

The EU MS national TMDIs, IEDIs and IESTIs for the active and commodities listed below have been calculated using PRIMo - Pesticide Residues Intake Model (revision 3.1).

The following assumptions have been made:

- 1) All produce eaten which may have been treated, has been treated and contains residues at the proposed MRL (TMDI) or STMR (IEDI) or HR (IESTI), as given below.

Commodity	TMDI	IEDI	IESTI
	MRL (mg/kg)	STMR (mg/kg)	HR (STMR for grain, oilseeds and milk) (mg/kg)
Wheat	0.01*	0.016*	0.016*
Barley	0.01*	0.016*	0.016*
Oilseed rape	0.01*†	0.016*	0.016*
All animal meat, preparations of meat, offal	0.01*	0.01*‡	0.01*‡
Milk	0.01*	0.01*‡	0.01*‡
Bird's eggs	0.01*	0.01*‡	0.01*‡
Honey	0.01*	0.01*	0.01*

\* LOQ

† Not a representative use and therefore no MRL set, however been input into risk assessment as a future potential use.

‡ No RD-RA set for animal commodities and no residues expected, however MRL values have been used for completeness.



- 2) There is no loss of residue during transport or storage, or processing of foods prior to consumption.

A full description of PRIMo and the underlying assumptions is in the document: ‘Use of EFSA pesticide residues intake model (EFSA PRIMo revision 3.1)’ available at the following link:  
<http://www.efsa.europa.eu/en/applications/pesticides/tools>

Information is also included in the PRIMo model in the tab ‘Background information’.

The relevant intake estimates for the TMDI are presented in Table 2.7.9-1, the IEDI in Table 2.7.9-2 and the IESTI in Table 2.7.9-3.

For the TMDI, chronic intakes for all consumer groups are below the ADI of 0.08 mg/kg bw/day, the critical consumer group are NL toddlers with intakes estimated as up to 0.8 % of the ADI. For the IEDI, chronic intakes for all consumer groups are below the ADI of 0.08 mg/kg bw/day, the critical consumer group is NL toddler with intakes estimated as up to 0.9 % of the ADI. Therefore, no chronic health effects are expected. Acute intakes for all consumer groups are below the ARfD of 0.3 mg/kg bw. The most critical group are children consuming milk: cattle with an estimated consumption of 0.4 % ARfD. Therefore, no acute health effects are expected.

Table 2.7.9-1 EFSA model (PRIMo) TMDI for chronic risk assessment – rev. 3.1 for BAS 684 H


<div><p>European Food Safety Authority</p><p>EFSA PRIMo revision 3.1; 2019/03/19</p></div>			Cinmethylin					Input values															
			LOQs (mg/kg) range from: to:					Details - chronic risk assessment		Supplementary results - chronic risk assessment													
			Toxicological reference values																				
			ADI (mg/kg bw/day):		0.08		ARfD (mg/kg bw):		0.3		Details - acute risk assessment/children		Details - acute risk assessment/adults										
			Source of ADI:		dDAR		Source of ARfD:		dDAR														
Year of evaluation:		2020		Year of evaluation:		2020																	
Comments:																							
Normal mode																							
Chronic risk assessment: JMPR methodology (IEDI/TMDI)																							
No of diets exceeding the ADI : ---																							
		Calculated exposure (% of ADI)		MS Diet		Exposure (µg/kg bw per day)		Highest contributor to MS diet (in % of ADI)		Commodity / group of commodities		2nd contributor to MS diet (in % of ADI)		Commodity / group of commodities		3rd contributor to MS diet (in % of ADI)		Commodity / group of commodities		MRLs set at the LOQ (in % of ADI)		commodities not under assessment (in % of ADI)	
TMDI(NED)/IEDI calculation (based on average food consumption)		0.8%		NL toddler		0.68		0.7%		Milk: Cattle		0.0%		Wheat		0.0%		Bovine: Muscle/meat					
		0.6%		UK infant		0.45		0.5%		Milk: Cattle		0.0%		Wheat		0.0%		Eggs: Chicken					
		0.5%		FR toddler 2 3 yr		0.37		0.4%		Milk: Cattle		0.0%		Wheat		0.0%		Bovine: Muscle/meat					
		0.4%		FR child 3 15 yr		0.33		0.3%		Milk: Cattle		0.1%		Wheat		0.0%		Bovine: Muscle/meat					
		0.4%		NL child		0.33		0.3%		Milk: Cattle		0.1%		Wheat		0.0%		Swine: Muscle/meat					
		0.3%		UK toddler		0.27		0.3%		Milk: Cattle		0.0%		Wheat		0.0%		Bovine: Muscle/meat					
		0.3%		DE child		0.27		0.2%		Milk: Cattle		0.1%		Wheat		0.0%		Eggs: Chicken					
		0.3%		DK child		0.22		0.2%		Milk: Cattle		0.1%		Wheat		0.0%		Swine: Muscle/meat					
		0.3%		ES child		0.22		0.2%		Milk: Cattle		0.1%		Wheat		0.0%		Bovine: Muscle/meat					
		0.3%		SE general		0.21		0.2%		Milk: Cattle		0.1%		Bovine: Muscle/meat		0.0%		Wheat					
		0.2%		RO general		0.20		0.1%		Milk: Cattle		0.1%		Wheat		0.0%		Swine: Muscle/meat					
		0.2%		FR infant		0.19		0.2%		Milk: Cattle		0.0%		Wheat		0.0%		Swine: Muscle/meat					
		0.2%		DE general		0.17		0.2%		Milk: Cattle		0.0%		Wheat		0.0%		Swine: Muscle/meat					
		0.2%		DE women 14-50 yr		0.17		0.2%		Milk: Cattle		0.0%		Wheat		0.0%		Swine: Muscle/meat					
		0.2%		GEMS/Food G15		0.16		0.1%		Milk: Cattle		0.1%		Wheat		0.0%		Swine: Muscle/meat					
		0.2%		GEMS/Food G07		0.16		0.1%		Milk: Cattle		0.1%		Wheat		0.0%		Poultry: Muscle/meat					
		0.2%		GEMS/Food G11		0.15		0.1%		Milk: Cattle		0.0%		Wheat		0.0%		Swine: Muscle/meat					
		0.2%		GEMS/Food G08		0.15		0.1%		Milk: Cattle		0.1%		Wheat		0.0%		Swine: Muscle/meat					
		0.2%		GEMS/Food G10		0.14		0.1%		Milk: Cattle		0.0%		Wheat		0.0%		Poultry: Muscle/meat					
		0.2%		NL general		0.13		0.1%		Milk: Cattle		0.0%		Wheat		0.0%		Swine: Muscle/meat					
		0.1%		GEMS/Food G06		0.11		0.1%		Wheat		0.0%		Milk: Cattle		0.0%		Poultry: Muscle/meat					
		0.1%		ES adult		0.11		0.1%		Milk: Cattle		0.0%		Wheat		0.0%		Bovine: Muscle/meat					
		0.1%		FR adult		0.09		0.1%		Milk: Cattle		0.0%		Wheat		0.0%		Swine: Muscle/meat					
		0.1%		IE adult		0.09		0.1%		Milk: Cattle		0.0%		Wheat		0.0%		Bovine: Muscle/meat					
		0.1%		DK adult		0.09		0.1%		Milk: Cattle		0.0%		Wheat		0.0%		Swine: Muscle/meat					
		0.1%		LT adult		0.07		0.0%		Milk: Cattle		0.0%		Wheat		0.0%		Swine: Muscle/meat					
		0.1%		IT toddler		0.07		0.1%		Wheat		0.0%		Barley									
		0.1%		UK adult		0.06		0.0%		Milk: Cattle		0.0%		Wheat		0.0%		Bovine: Muscle/meat					
		0.1%		UK vegetarian		0.06		0.0%		Milk: Cattle		0.0%		Wheat		0.0%		Eggs: Chicken					
		0.1%		IE child		0.05		0.0%		Milk: Cattle		0.0%		Wheat		0.0%		Swine: Muscle/meat					
		0.1%		IT adult		0.04		0.1%		Wheat		0.0%		Barley									
		0.0%		PT general		0.04		0.0%		Wheat		0.0%		Barley									
		0.0%		FI 3 yr		0.01		0.0%		Wheat		0.0%		Rapeseeds/canola seeds		0.0%		Barley					
		0.0%		FI 6 yr		0.01		0.0%		Wheat		0.0%		Barley		0.0%		Rapeseeds/canola seeds					
		0.0%		FI adult		0.00		0.0%		Wheat		0.0%		Barley		0.0%		Rapeseeds/canola seeds					
				Column7						Grapefruits				Grapefruits									
Conclusion: The estimated long-term dietary intake (TMDI/NED/IEDI) was below the ADI. The long-term intake of residues of Cinmethylin is unlikely to present a public health concern.																							

Table 2.7.9-2 EFSA model (PRIMo) IEDI for chronic risk assessment – rev. 3.1 for BAS 684 H


 European Food Safety Authority EFSA PRIMo revision 3.1; 2019/03/19			<b>Cinmethylin</b>				Input values							
			LOQs (mg/kg) range from: to:				<div>Details - chronic risk assessment</div> <div>Supplementary results - chronic risk assessment</div> <div>Details - acute risk assessment/children</div> <div>Details - acute risk assessment/adults</div>							
			<b>Toxicological reference values</b>											
			ADI (mg/kg bw/day):		0.08		ARID (mg/kg bw):		0.3					
Source of ADI:		dDAR		Source of ARID:		dDAR								
Year of evaluation:		2020		Year of evaluation:		2020								
Comments:														
Normal mode														
Chronic risk assessment: JMPR methodology (IEDI/TMDI)														
			No of diets exceeding the ADI : ---									Exposure resulting from		
	Calculated exposure (% of ADI)	MS Diet	Exposure (µg/kg bw per day)	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	MRLs set at the LOQ (in % of ADI)	commodities not under assessment (in % of ADI)			
TMDI/NED/IEDI calculation (based on average food consumption)	0.9%	NL toddler	0.71	0.7%	Milk: Cattle	0.1%	Wheat	0.0%	Rapeseeds/canola seeds					
	0.6%	UK infant	0.46	0.5%	Milk: Cattle	0.1%	Wheat	0.0%	Eggs: Chicken					
	0.5%	FR toddler 2 3 yr	0.38	0.4%	Milk: Cattle	0.1%	Wheat	0.0%	Bovine: Muscle/meat					
	0.4%	FR child 3 15 yr	0.36	0.3%	Milk: Cattle	0.1%	Wheat	0.0%	Bovine: Muscle/meat					
	0.4%	NL child	0.35	0.3%	Milk: Cattle	0.1%	Wheat	0.0%	Swine: Muscle/meat					
	0.4%	UK toddler	0.30	0.3%	Milk: Cattle	0.1%	Wheat	0.0%	Bovine: Muscle/meat					
	0.4%	DE child	0.29	0.2%	Milk: Cattle	0.1%	Wheat	0.0%	Eggs: Chicken					
	0.3%	DK child	0.25	0.2%	Milk: Cattle	0.1%	Wheat	0.0%	Swine: Muscle/meat					
	0.3%	ES child	0.25	0.2%	Milk: Cattle	0.1%	Wheat	0.0%	Bovine: Muscle/meat					
	0.3%	SE general	0.23	0.2%	Milk: Cattle	0.1%	Wheat	0.1%	Bovine: Muscle/meat					
	0.3%	RO general	0.23	0.1%	Milk: Cattle	0.1%	Wheat	0.0%	Swine: Muscle/meat					
	0.2%	GEMS/Food G15	0.20	0.1%	Wheat	0.1%	Milk: Cattle	0.0%	Swine: Muscle/meat					
	0.2%	FR infant	0.19	0.2%	Milk: Cattle	0.0%	Wheat	0.0%	Swine: Muscle/meat					
	0.2%	GEMS/Food G07	0.19	0.1%	Wheat	0.1%	Milk: Cattle	0.0%	Poultry: Muscle/meat					
	0.2%	DE general	0.19	0.2%	Milk: Cattle	0.0%	Wheat	0.0%	Swine: Muscle/meat					
	0.2%	DE women 14-50 yr	0.18	0.2%	Milk: Cattle	0.0%	Wheat	0.0%	Swine: Muscle/meat					
	0.2%	GEMS/Food G11	0.18	0.1%	Milk: Cattle	0.1%	Wheat	0.0%	Barley					
	0.2%	GEMS/Food G08	0.18	0.1%	Wheat	0.1%	Milk: Cattle	0.0%	Swine: Muscle/meat					
	0.2%	GEMS/Food G10	0.17	0.1%	Wheat	0.1%	Milk: Cattle	0.0%	Poultry: Muscle/meat					
	0.2%	GEMS/Food G06	0.16	0.1%	Wheat	0.0%	Milk: Cattle	0.0%	Poultry: Muscle/meat					
	0.2%	NL general	0.15	0.1%	Milk: Cattle	0.0%	Wheat	0.0%	Swine: Muscle/meat					
	0.2%	ES adult	0.12	0.1%	Milk: Cattle	0.0%	Wheat	0.0%	Barley					
	0.1%	IT toddler	0.11	0.1%	Wheat	0.0%	Barley							
	0.1%	FR adult	0.11	0.1%	Milk: Cattle	0.0%	Wheat	0.0%	Swine: Muscle/meat					
	0.1%	IE adult	0.10	0.1%	Milk: Cattle	0.0%	Wheat	0.0%	Bovine: Muscle/meat					
	0.1%	DK adult	0.09	0.1%	Milk: Cattle	0.0%	Wheat	0.0%	Swine: Muscle/meat					
	0.1%	LT adult	0.08	0.0%	Milk: Cattle	0.0%	Wheat	0.0%	Swine: Muscle/meat					
	0.1%	UK adult	0.07	0.0%	Milk: Cattle	0.0%	Wheat	0.0%	Bovine: Muscle/meat					
	0.1%	UK vegetarian	0.07	0.0%	Wheat	0.0%	Milk: Cattle	0.0%	Eggs: Chicken					
	0.1%	IT adult	0.07	0.1%	Wheat	0.0%	Barley							
	0.1%	PT general	0.06	0.1%	Wheat	0.0%	Barley							
	0.1%	IE child	0.06	0.0%	Milk: Cattle	0.0%	Wheat	0.0%	Swine: Muscle/meat					
	0.0%	FI 3 yr	0.02	0.0%	Wheat	0.0%	Rapeseeds/canola seeds	0.0%	Barley					
	0.0%	FI 6 yr	0.02	0.0%	Wheat	0.0%	Barley	0.0%	Rapeseeds/canola seeds					
	0.0%	FI adult	0.01	0.0%	Wheat	0.0%	Barley	0.0%	Rapeseeds/canola seeds					
		Column7				Grapefruits		Grapefruits						
<b>Conclusion:</b> The estimated long-term dietary intake (TMDI/NED/IEDI) was below the ADI. The long-term intake of residues of Cinmethylin is unlikely to present a public health concern.														

Table 2.7.9-3 EFSA model (PRIMo) IESTI for acute risk assessment – rev. 3.1 for BAS 684 H

Acute risk assessment /children					Acute risk assessment / adults / general population				
Details - acute risk assessment /children					Details - acute risk assessment/adults				
The acute risk assessment is based on the ARfD.									
The calculation is based on the large portion of the most critical consumer group.									
Show results for all crops									
Unprocessed commodities	Results for children				Results for adults				
	No. of commodities for which ARfD/ADI is exceeded (IESTI):				No. of commodities for which ARfD/ADI is exceeded (IESTI):				
	---				---				
	IESTI				IESTI				
	Highest % of ARfD/ADI		MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI		MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	
	0.4%	Milk: Cattle	0 / 0.01	1.2	0.1%	Milk: Cattle	0 / 0.01	0.39	
	0.08%	Milk: Goat	0 / 0.01	0.24	0.06%	Milk: Goat	0 / 0.01	0.18	
0.08%	Wheat	0 / 0.02	0.23	0.05%	Milk: Sheep	0 / 0.01	0.15		
0.06%	Poultry: Muscle/meat	0 / 0.01	0.17	0.04%	Wheat	0 / 0.02	0.13		
Expand/collapse list									
Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)									
Processed commodities	Results for children				Results for adults				
	No of processed commodities for which ARfD/ADI is exceeded (IESTI):				No of processed commodities for which ARfD/ADI is exceeded (IESTI):				
	---				---				
	IESTI				IESTI				
	Highest % of ARfD/ADI		MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI		MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	
	0.1%	Wheat / milling (flour)	0 / 0.02	0.19	0.0%	Barley / beer	0 / 0	0.12	
	0.0%	Wheat / milling (wholemea	0 / 0.02	0.09	0.02%	Wheat / bread/pizza	0 / 0.02	0.07	
	0.0%	Barley / cooked	0 / 0.02	0.06	0.02%	Wheat / pasta	0 / 0.02	0.06	
	0.0%	Barley / milling (flour)	0 / 0.02	0.03	0.02%	Wheat / bread	0 / 0.02	0.06	
	0.0%	Rapeseeds / oils	0 / 0.03	0.01	#NUM!	#NUM!	#NUM!	#NUM!	
Conclusion:									
No exceedance of the toxicological reference value was identified for any unprocessed commodity.									
A short term intake of residues of Cinmethylin is unlikely to present a public health risk.									
For processed commodities, no exceedance of the ARfD/ADI was identified.									

***Chronic (long term) UK dietary intake estimates – UK NTMDI and NEDIs***

The UK NEDIs for the active and commodities listed below have been calculated for ten consumer groups as detailed in the Regulatory Update 21/2005. The following assumptions have been made:

- 1) Upper range of normal (97.5th percentile) consumption of each individual crop which may have been treated.
- 2) All produce eaten which may have been treated has been treated and contains residues at the MRL (NTMDI) or median residue (STMR) (NEDI) found in the trials to support the GAP, as given below

Commodity	NTMDI	NEDI
	MRL (mg/kg)	STMR (mg/kg)
Wheat	0.01*	0.016*
Barley	0.01*	0.016*
Oilseed rape	0.01*†	0.016*
All animal meat, preparations of meat, offal	0.01*	0.01*‡
Milk	0.01*	0.01*‡
Bird's eggs	0.01*	0.01*‡
Honey§	-	-

\* LOQ

† Not a representative use and therefore no MRL set, however been input into risk assessment as a future potential use.

‡ No RD-RA set for animal commodities and no residues expected, however MRL values have been used for completeness.

§ Honey is not a commodity that can be input into the UK consumer risk assessment models.

- 3) There is no loss of residue during transport or storage, or processing of foods prior to consumption.

The relevant intakes are presented in Table 2.7.9-4 and Table 2.7.9-5.

For the NTMDI, chronic intakes for all consumer groups are below the ADI of 0.08 mg/kg bw/day, UK intakes estimated as up to 1 % of the ADI (critical consumer group infant). For the NEDI, chronic intakes for all consumer groups are below the ADI of 0.08 mg/kg, all consumer groups have intakes of up to 1 % ADI (critical consumer group infant). Therefore, no chronic health effects are expected.

Table 2.7.9-4 UK NTMDI for 10 consumer groups (calculated using chronic consumer version 1.1) for BAS 684 H

Active substance: Cinmethylin			ADI: 0.08 mg/kg bw/day			Source: dDAR						
			TOTAL INTAKE based on 97.5th percentile									
			ADULT	INFANT	TODDLER	4-6 YEARS	7-10 YEARS	11-14 YEARS	15-18 YEARS	VEGETARIAN	ELDERLY (OWN HOME)	ELDERLY (RESIDENTIAL)
mg/kg bw/day			0.00015	0.00110	0.00070	0.00044	0.00030	0.00020	0.00016	0.00017	0.00013	0.00019
% of ADI			<1%	1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%
STMR		P	COMMODITY INTAKES									
Commodity	(mg/kg)		(mg/kg bw/day)									
Oilseeds	0.01		0.00003	0.00006	0.00007	0.00007	0.00006	0.00004	0.00004	0.00005	0.00003	0.00004
Barley	0.01		0.00000	L/C	0.00000	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000
Wheat	0.01		0.00004	0.00003	0.00008	0.00009	0.00007	0.00005	0.00004	0.00004	0.00003	0.00003
Poultry	0.01		0.00002	0.00002	0.00003	0.00003	0.00002	0.00002	0.00002	0.00002	0.00002	0.00001
Meat fat	0.01		0.00000	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Meat excl. poultry & offal	0.01		0.00002	0.00004	0.00004	0.00003	0.00003	0.00002	0.00002	0.00000	0.00002	0.00002
All types of kidney	0.01		0.00000	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	L/C	0.00000	0.00000
All types of Liver	0.01		0.00000	0.00002	0.00002	0.00000	0.00000	0.00001	0.00000	L/C	0.00001	0.00000
Other types of offal	0.01		0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00000	0.00000	0.00001	0.00001
Eggs	0.01		0.00001	0.00005	0.00003	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001
Milk	0.01		0.00008	0.00098	0.00056	0.00029	0.00018	0.00012	0.00009	0.00010	0.00009	0.00012
* 0.00000 corresponds to <0.000005 mg/kg bw/day (any value ≥0.000005 is rounded to 0.00001)												
L/C Low consumption (<0.1 g/day) or low number of consumers (<4)												

Body weights of the 10 consumer groups are as detailed in the regulatory update 21/2005.  
Residues below the LOQ have been assumed to be at the LOQ for the purpose of this calculation

Table 2.7.9-5 UK NEDI for 10 consumer groups (calculated using chronic consumer version 1.1) for BAS 684 H

Active substance: Cinmethylin		ADI: 0.08 mg/kg bw /day		Source: dDAR								
		TOTAL INTAKE based on 97.5th percentile										
		ADULT	INFANT	TODDLER	4-6 YEARS	7-10 YEARS	11-14 YEARS	15-18 YEARS	VEGETARIAN	ELDERLY (OWN HOME)	ELDERLY (RESIDENTIAL)	
	mg/kg bw/day	0.00017	0.00115	0.00077	0.00051	0.00035	0.00024	0.00020	0.00021	0.00015	0.00022	
	% of ADI	<1%	1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	
	STMR	P	COMMODITY INTAKES									
Commodity	(mg/kg)		(mg/kg bw/day)									
Oilseeds	0.016		0.00005	0.00010	0.00012	0.00011	0.00009	0.00006	0.00006	0.00007	0.00005	0.00006
Barley	0.016		0.00000	L/C	0.00001	0.00001	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000
Wheat	0.016		0.00006	0.00004	0.00014	0.00014	0.00011	0.00008	0.00006	0.00007	0.00005	0.00006
Poultry	0.01		0.00002	0.00002	0.00003	0.00003	0.00002	0.00002	0.00002	0.00002	0.00002	0.00001
Meat fat	0.01		0.00000	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Meat excl. poultry & offal	0.01		0.00002	0.00004	0.00004	0.00003	0.00003	0.00002	0.00002	0.00000	0.00002	0.00002
All types of kidney	0.01		0.00000	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	L/C	0.00000	0.00000
All types of Liver	0.01		0.00000	0.00002	0.00002	0.00000	0.00000	0.00001	0.00000	L/C	0.00001	0.00000
Other types of offal	0.01		0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00000	0.00000	0.00001	0.00001
Eggs	0.01		0.00001	0.00005	0.00003	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001
Milk	0.01		0.00008	0.00098	0.00056	0.00029	0.00018	0.00012	0.00009	0.00010	0.00009	0.00012
* 0.00000 corresponds to <0.000005 mg/kg bw /day (any value ≥0.000005 is rounded to 0.00001)												
L/C Low consumption (<0.1 g/day) or low number of consumers (<4)												

Body weights of the 10 consumer groups are as detailed in the regulatory update 21/2005.  
Residues below the LOQ have been assumed to be at the LOQ for the purpose of this calculation

***Acute (short term) UK dietary intake estimates – UK NESTIs***

The UK NESTIs for the active and commodities listed below have been calculated for ten consumer groups as detailed in the Regulatory Update 21/2005. The following assumptions have been made:

- 1) Upper range of normal (97.5th percentile) consumption of each individual crop which may have been treated.
- 2) All produce eaten which may have been treated has been treated and contains residues at the highest residue found in the trials considered to support GAP, as given below.

Commodity	<i>NESTI</i>
	HR (STMR for grain, and oilseeds) (mg/kg)
Wheat	0.016*
Barley	0.016*
Oilseed rape	0.016*
All animal meat, preparations of meat, offal	0.01*‡
Milk	0.01*‡
Bird's eggs	0.01*‡
Honey§	-

‡ No RD-RA set for animal commodities and no residues expected, however MRL values have been used for completeness.

§ Honey is not a commodity that can be input into the UK consumer risk assessment models.

- 3) There is no loss of residue during transport or storage, or processing of foods prior to consumption.

The relevant intake assessment is presented in



Table 2.7.9-6.

Acute intakes for all consumer groups are below the ARfD of 0.3 mg/kg bw. The most critical group are infants consuming milk with an estimated consumption of 0.4 % ARfD, therefore no acute health effects are expected.

Table 2.7.9-6 UK NESTIs for 10 consumer groups (calculated using acute consumer version 1.2) for BAS 684 H

[Goto Inputs](#)

## Acute Intakes (97.5th percentiles)

commodity	HR	P	adult		infant		toddler		4-6 year old child		7-10 year old child	
			NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD
<b>Oilseeds</b>	0.02		0.00010	<0.1	0.00019	0.1	0.00022	0.1	0.00023	0.1	0.00017	0.1
Barley	0.02		0.00001	<0.1	0.00000	<0.1	0.00001	<0.1	0.00003	<0.1	0.00009	<0.1
Wheat	0.02		0.00010	<0.1	0.00021	0.1	0.00021	0.1	0.00023	0.1	0.00017	0.1
Poultry	0.01		0.00006	<0.1	0.00007	<0.1	0.00009	<0.1	0.00009	<0.1	0.00007	<0.1
Meat fat	0.01		0.00001	<0.1	0.00002	<0.1	0.00002	<0.1	0.00002	<0.1	0.00001	<0.1
Meat excl.poultry & offal	0.01		0.00005	<0.1	0.00012	<0.1	0.00010	<0.1	0.00009	<0.1	0.00008	<0.1
All types of kidney	0.01		0.00002	<0.1	0.00002	<0.1	0.00004	<0.1	0.00002	<0.1	0.00002	<0.1
All types of liver	0.01		0.00003	<0.1	0.00008	<0.1	0.00007	<0.1	0.00002	<0.1	0.00003	<0.1
Other types of offal	0.01		0.00003	<0.1	0.00007	<0.1	0.00007	<0.1	0.00006	<0.1	0.00005	<0.1
Eggs	0.01		0.00003	<0.1	0.00012	<0.1	0.00008	<0.1	0.00007	<0.1	0.00005	<0.1
Milk	0.01		0.00013	<0.1	0.00124	0.4	0.00073	0.2	0.00047	0.2	0.00030	0.1

commodity	HR	P	11-14 year old child		15-18 year old child		vegetarian		Elderly - own home		Elderly - residential	
			NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD
<b>Oilseeds</b>	0.02		0.00013	<0.1	0.00011	<0.1	0.00015	0.1	0.00008	<0.1	0.00009	<0.1
Barley	0.02		0.00001	<0.1	0.00001	<0.1	0.00001	<0.1	0.00001	<0.1	0.00001	<0.1
Wheat	0.02		0.00014	<0.1	0.00013	<0.1	0.00013	<0.1	0.00007	<0.1	0.00007	<0.1
Poultry	0.01		0.00006	<0.1	0.00005	<0.1	0.00012	<0.1	0.00005	<0.1	0.00003	<0.1
Meat fat	0.01		0.00001	<0.1	0.00001	<0.1	0.00000	<0.1	0.00000	<0.1	0.00000	<0.1
Meat excl.poultry & offal	0.01		0.00006	<0.1	0.00006	<0.1	0.00003	<0.1	0.00004	<0.1	0.00003	<0.1
All types of kidney	0.01		0.00001	<0.1	0.00002	<0.1	0.00000	<0.1	0.00002	<0.1	0.00001	<0.1
All types of liver	0.01		0.00004	<0.1	0.00002	<0.1	0.00000	<0.1	0.00002	<0.1	0.00002	<0.1
Other types of offal	0.01		0.00005	<0.1	0.00002	<0.1	0.00001	<0.1	0.00002	<0.1	0.00002	<0.1
Eggs	0.01		0.00004	<0.1	0.00003	<0.1	0.00004	<0.1	0.00002	<0.1	0.00002	<0.1
Milk	0.01		0.00021	0.1	0.00018	0.1	0.00015	<0.1	0.00011	<0.1	0.00014	<0.1

Pesticide Cinmethylin

ARfD 0.300 mg/Kg bw/day

Source dDAR

\* 0.00000 corresponds to &lt;0.000005 mg/kg bw/day (any value ≥0.000005 is rounded to 0.00001)

Body weights of the 10 consumer groups are as detailed in the regulatory update 21/2005.

Residues below the LOQ have been assumed to be at the LOQ for the purpose of this calculation

### 2.7.10. Proposed MRLs and compliance with existing MRLs

To support the GB representative uses of BAS 684 H on wheat and barley, the MRLs in Table 2.7.10-1 are proposed for commodities of plant and animal origin.

There are no GB representative uses on oilseeds hence no MRLs are proposed on oilseeds in the framework of the approval.

The trials on oilseed rape are considered worst-case compared to the representative uses on wheat and barley therefore residues of BAS 684 H in honey based on the representative uses are expected to be <0.01 mg/kg. Given a monitoring method for BAS 684 H in honey is available with an LOQ of 0.01 mg/kg (method L0337/03 Vol 3 CA B5.2.2), the MRL for BAS 684 H in honey is proposed at approval at 0.01\* mg/kg. This MRL would also accommodate the future proposed use on oilseed rape given residues of BAS 684 H in aerial parts of the crop are likely to be <0.01 mg/kg at flowering.

Table 2.7.10-1 Proposed MRLs

Code number	Commodity	Proposed MRL (mg/kg)
0500010	Barley	0.01*
0500090	Wheat	0.01*
1010000	Commodities from	-
1011000	(a) swine	0.01*
1012000	(b) bovine	0.01*
1013000	(c) sheep	0.01*
1014000	(d) goat	0.01*
1015000	(e) equine	0.01*
1016000	(f) poultry	0.01*
1017000	(g) other farmed terrestrial animals	0.01*
1020000	Milk	0.01*
1030000	Bird's eggs	0.01*
1040000	Honey	0.01*

\* 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

#### Route of degradation in soil (laboratory studies)

Three laboratory studies were provided for investigating the degradation of cinmethylin in soil, covering aerobic degradation, anaerobic degradation, and soil photolysis. No major metabolites were observed in the soil in these three studies, with no breakdown products observed above 5% of the applied radioactivity (AR) in each study. Four kinetic evaluations were also submitted to calculate the degradation rate for cinmethylin in soils.

The aerobic degradation of cinmethylin was investigated under laboratory conditions in four soils: two from Europe and two from North America [see report KCA 7.1.1.1/1]. By the study end (120 DAT), cinmethylin accounted for between 0.6 – 47.3% total applied radioactivity (TAR) across the four soils. Non-extractable residues (NER) peaked at 12 – 36.5% AR at 90 or 120 DAT, with some soils observing slight falls in NER levels by the study end at 120 DAT. CO<sub>2</sub> peaked at 23.3 – 47.7% total applied radioactivity (TAR) at 90 or 120 DAT; again, levels reduced slightly in some soils by 120 DAT. Aerobic degradation was therefore a major route of degradation for cinmethylin.

The anaerobic metabolism of cinmethylin was also studied in four soils, two European and two North American, under laboratory conditions [see report KCA 7.1.1.2/1]. All four soils undertook an aerobic incubation phase for

between 10-30 days (corresponding to approximately one half-life in the respective soil) prior to flooding to induce anaerobic conditions for the remaining 103 – 105 days, giving a total duration of 118 – 120 days, depending on the soil. By the study end, cinmethylin accounted for 35.1 – 65.1% AR, with most of the degradation having occurred during the aerobic phase. NER were a major sink, accounting for 15 – 41.2% AR by 118/120 DAT, and CO<sub>2</sub> accounted for 8.1 – 17.0% AR. The HSE evaluator concluded that anaerobic metabolism is not a major route of degradation for cinmethylin.

The soil photolysis of cinmethylin was studied in one soil over 15 days under artificial, continuous lighting [see report KCA 7.1.1.3/1]. After 15 days of irradiation, cinmethylin accounted for 56.3 – 63.1% AR, NER accounted for 5.1 – 9.4% AR and volatiles accounted for 2.6 – 4.5% AR. In dark control samples, cinmethylin accounted for 61.7 – 71.8% AR, NER accounted for 7.3 – 11.1% AR and volatiles accounted for 6.9 – 7.2% AR after 15 days. The HSE evaluator concluded that photolysis is a minor route of degradation for cinmethylin.

#### **Rate of degradation in soil (laboratory studies)**

For each laboratory study, the rate of degradation was calculated through the derivation of endpoints for cinmethylin. Regarding aerobic degradation, the maximum non-normalised DegT<sub>50</sub> was observed in the Lufa 2.2 soil at 93.6 days. Therefore, terrestrial field dissipation studies were required.

The rate of degradation was determined for the individual enantiomers and showed that the (-)-enantiomer (Reg. No. 5925581) degraded at a faster rate under aerobic degradation than the (+)-enantiomer (Reg. No. 5925632). In the soil demonstrating the slowest degradation (Lufa 2.2), the DT<sub>50</sub> for the (-)-enantiomer was 67.4 days compared to 113.5 days for the (+)-enantiomer.

Anaerobic degradation occurred slowly for cinmethylin, with a maximum DT<sub>50</sub> of 1710 days. For soil photolysis, DT<sub>50</sub>s were 24.1 days for photolysis samples and 25.9 days for dark control samples, demonstrating a small influence of photolysis on the degradation of cinmethylin.

Table 2.8.1-1

Summary of laboratory aerobic degradation modelling endpoints for cinmethylin and its two enantiomers.

Cinmethylin (BAS 684 H)	Dark aerobic conditions (modelling endpoints)							
Soil type	pH (H <sub>2</sub> O)	pH (CaCl <sub>2</sub> )	Temp °C	% MWHC	DT <sub>50</sub> (d)	DT <sub>90</sub> (d)	St. (χ <sup>2</sup> )	Method of calculation
Lufa 2.2	6.3	5.6	20	pF2	192.8 <sup>a</sup>	541.4	0.9	DFOP
Lufa 5M	8.0	7.4	20	pF2	19.1	63.5	6.18	SFO
LAD-SCL-PF	8.2	8.0	20	pF2	43.5	144.4	3.02	SFO
MSL-PF	6.7	6.3	20	pF2	74.6 <sup>a</sup>	178.1	3.11	DFOP
Geometric mean					58.8			
(-)-enantiomer (Reg No. 5925581)	Dark aerobic conditions (modelling endpoints)							
Soil type	pH (H <sub>2</sub> O)	pH (CaCl <sub>2</sub> )	Temp °C	% MWHC	DT <sub>50</sub> (d)	DT <sub>90</sub> (d)	St. (χ <sup>2</sup> )	Method of calculation
Lufa 2.2	6.3	5.6	20	pF2	165.0 <sup>a</sup>	450.8	1.3	DFOP
Lufa 5M	8.0	7.4	20	pF2	15.4	51.1	4.5	SFO
LAD-SCL-PF	8.2	8.0	20	pF2	34.7	115.4	4.1	SFO
MSL-PF	6.7	6.3	20	pF2	54.6 <sup>a</sup>	122.0	1.1	DFOP
Geometric mean					46.8			
(+)-enantiomer (Reg No. 5925632)	Dark aerobic conditions (modelling endpoints)							
Soil type	pH (H <sub>2</sub> O)	pH (CaCl <sub>2</sub> )	Temp °C	% MWHC	DT <sub>50</sub> (d)	DT <sub>90</sub> (d)	St. (χ <sup>2</sup> )	Method of calculation
Lufa 2.2	6.3	5.6	20	pF2	145.0 <sup>a</sup>	450.2	2.2	DFOP
Lufa 5M	8.0	7.4	20	pF2	21.5	71.5	6.2	SFO
LAD-SCL-PF	8.2	8.0	20	pF2	56.4	187.3	7.3	SFO
MSL-PF	6.7	6.3	20	pF2	73.4 <sup>a</sup>	206.5	0.5	DFOP
Geometric mean					59.9			

<sup>a</sup> Pseudo-SFO DT<sub>50</sub> derived from the DFOP slow phase (k<sub>2</sub>) DT<sub>50</sub>.

Table 2.8.1-2

Summary of trigger/persistence endpoints for cinmethylin in anaerobic conditions.

<b>Cinmethylin (BAS 684 H)</b>	<b>Dark anaerobic conditions (non-normalised trigger and persistence endpoints)</b>						
<b>Soil type</b>	<b>pH (CaCl<sub>2</sub>)</b>	<b>Temp °C</b>	<b>% MWHC</b>	<b>DT<sub>50</sub> (d)</b>	<b>DT<sub>90</sub> (d)</b>	<b>St. (<math>\chi^2</math>)</b>	<b>Method of calculation</b>
Lufa 2.2	5.4	20	Flooded Soil	1710	5660	1.1	SFO
Lufa 5M	7.2	20	Flooded Soil	651	2160	0.6	SFO
North Dakota	6.3	20	Flooded Soil	241	800	1.5	SFO
Wyoming	8.1	20	Flooded Soil	1680	5570	4.6	SFO
<b>Maximum (non-normalised)</b>				<b>1710</b>	<b>5660</b>		

Table 2.8.1-3

Summary of trigger/persistence endpoints for the photolytic degradation of cinmethylin.

Cinmethylin (BAS 684 H)	Photolysis study (non-normalised trigger and persistence endpoints)						
Experiment (LUFA 5M soil)	pH (CaCl <sub>2</sub> )	Temp °C	% MWHC	DT <sub>50</sub> (d)	DT <sub>90</sub> (d)	St. (χ <sup>2</sup> )	Method of calculation
Light	6.9 – 7.2	22	60	24.1	92.2	2.0	DFOP
Dark control			60	25.9	86.0	2.8	SFO
Photolysis only degradation rate				Not derived due to use of biphasic kinetics			

#### Enantiomeric ratio changes (laboratory studies)

In the aerobic degradation study, a more rapid degradation of the (-)-enantiomer was observed in some soils that led to shifts in the enantiomeric ratio. For example, in the LAD-SCL-PF soil (cinmethylin DT<sub>50</sub> = 43.5 days), the ratio shifted to 23:77 after 120 days, with 9.4% of cinmethylin remaining. Conversely, in the soil displaying the longest DT<sub>50</sub> (Lufa 2.2; 192.8 days), the ratio measured 46:54 after 120 days, with 40% of cinmethylin remaining. Overall, there is a 13.1 day difference in the geomean modelling DT<sub>50</sub>s for the aerobic degradation of enantiomers, with the (-)-enantiomer degrading faster.

A similar trend was observed in the aerobic phase of the anaerobic degradation study [see report KCA 7.1.1.2/1], with variable enantiomeric ratios observed by 10 DAT. The Lufa 2.2 soil displayed a slight shift to a ratio of 46:54 with 60.5% cinmethylin remaining after 10 days, whereas the North Dakota soil exhibited a ratio of 29:71 with 48% cinmethylin remaining after 10 days. However, all four soils showed little change in the enantiomeric ratio once anaerobic conditions had been established.

In the soil photolysis study [see report KCA 7.1.1.3/1], the enantiomeric ratio also did not display a notable change, shifting to 46:54 after 15 days with 56% of applied cinmethylin remaining.

HSE concludes that changes in enantiomeric ratio are driven by the faster degradation of the (-)-enantiomer in aerobic soils. Anaerobic degradation and photolysis do not appear to influence the enantiomeric ratio, consistent with the route of degradation being primarily aerobic degradation.

**Rate of degradation (field studies)**

Two terrestrial field dissipation studies were submitted by the Applicant that investigated the behaviour of cinmethylin under field conditions: one in Europe (six soils) and one in the United States (six soils). Several studies to support the field studies were also submitted. Of these, one US soil was rejected by the HSE evaluator for deriving endpoints on the basis that an ecoregion similarity study supplied by the Applicant showed that only five soils were sufficiently relevant to European conditions [see report KCA 7.1.2.2.1/09].

In the European field study, the test item was incorporated immediately after application to exclude surface processes and to enable a straightforward generation of modelling endpoints to be used for calculation of predicted environmental concentrations as recommended by EFSA [EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT<sub>50</sub> values of active substances of plant protection products and transformation products of these active substances in soil. EFSA Journal 2014:12(5):3662]. In the US field study, the test item was not incorporated, though it was still possible to derive normalised degradation endpoints for modelling inputs by following guidance for “legacy studies” in the EFSA guidance. Plot locations corresponded closely to the growing regions for the intended GAP in Europe, and studies were conducted on bare soil.

For the consideration of persistence and the calculation of PEC<sub>soil</sub>, non-normalised degradation rates were also determined. From the 11 field sites, the longest DT<sub>50</sub> was 53.9 days (Texas soil) and the longest DT<sub>90</sub> was 207.6 days (Denmark soil). Therefore, field accumulation studies were not necessary for cinmethylin.

In accordance with the EFSA DegT<sub>50</sub> guidance (2014), the hypothesis that laboratory and field degradation are equal was tested. The *EFSA DegT<sub>50</sub> Endpoint Selector* was used by the UK evaluator to check the null hypothesis. The tool confirmed that cinmethylin degrades at a significantly faster rate in the field than in the laboratory (Student's t Test;  $t = 3.7$ ;  $\alpha = 0.25$ ). Therefore, the geomean of the field DegT<sub>50 matrix</sub> was used for exposure assessment purposes. The final DT<sub>50</sub> was 11.1 days for cinmethylin; this value was normalised to pF2 and 20 °C.

Table 2.8.1-4

Summary of modelling endpoints for cinmethylin (time step normalisation performed).

Parent	Aerobic conditions								
Field dissipation study	Soil type (indicate if bare or cropped soil was used)	Location (country or USA state)	pH CaCl <sub>2</sub> <sup>a</sup>	pH H <sub>2</sub> O <sup>b</sup>	Depth (cm) <sup>c</sup>	St. (χ <sup>2</sup> )	DT <sub>50</sub> (d) Norm. <sup>d</sup>	DT <sub>90</sub> (d) Norm.	Method of calculation
Gut, T., 2017a (KCA 7.1.2.2.1/01) Gut, T., 2017b (KCA 7.1.2.2.1/02)	Loamy fine sand, bare soil	Höltinghausen, Germany	4.80	-	0-15	9.7	29.9 <sup>e</sup>	99.4	FOMC
	Very fine sandy loam, bare soil	Dugliolo di Budrio, Italy	7.66	-	0-20	5.6	47.0 <sup>e</sup>	156.0	FOMC
	Sand, bare soil	Røllum, Denmark	4.62	-	0-30	9.4	15.3	50.7	SFO
	Loam, bare soil	Banbury, UK	6.70	-	0-25	8.1	5.4	18.0	SFO
	Silt, bare soil	Saint-Amand, Belgium	6.12	-	0-30	5.0	8.0 <sup>e</sup>	26.6	FOMC
	Coarse sandy loam, bare soil	Almayate, Spain	7.70	-	0-25	10.3	13.9	46.2	SFO
Mitchell et al., 2018a (KCA 7.1.2.2.1/5) <sup>f</sup>	Silt loam, bare soil	New York, US	5.14	5.7	0-45	9.7	19.2	63.8	SFO
	Sandy loam, bare soil	North Carolina, US	5.55	6.1	0-15	10.5	6.7	22.4	SFO
	Clay loam, bare soil	Texas, US	6.77	7.3	0-30	18.4	9.9	33.1	SFO
	Sand, bare soil	Washington, US	7.59	8.1	0-15	16.0	3.7	12.2	SFO
	Sandy loam, bare soil	California, US	7.69	8.2	0-30	9.9	5.2	17.3	SFO
Geometric mean (if not pH dependent)							11.1		
pH dependence							No		

<sup>a</sup> pH values are mean values for the soil across the depths at which residues were detected. US field study pH values were converted to be expressed as a CaCl<sub>2</sub> pH value using the method reported in EFSA (2017).

<sup>b</sup> Measured in a saturated soil paste made from distilled water. pH values are mean values for the soil across the depths at which residues were detected.

<sup>c</sup> Residue depth refers to the depths at which residues were detected, plus the following depth where the Applicant added values corresponding to 0.5 × LOD.

<sup>d</sup> Normalised using a Q<sub>10</sub> of 2.58 and Walker equation coefficient of 0.7, values are DegT50matrix.

<sup>e</sup> Calculated as DT<sub>50</sub> = DT<sub>90</sub> / 3.32 (less than 10% of initial concentration at last sampling).

<sup>f</sup> One soil, North Dakota, was excluded from consideration of modelling endpoints as it was deemed not ecologically or climatically relevant to Europe following an ENASGIPS crosswalk exercise and consideration of the actual climatic conditions measured during the conduct of the field study.



Table 2.8.1-5

Summary of trigger/persistence endpoints for cinmethylin.

Parent	Aerobic conditions								
Field dissipation study	Soil type (indicate if bare or cropped soil was used)	Location (country or USA state)	pH-CaCl <sub>2</sub> <sup>a</sup>	pH-H <sub>2</sub> O <sup>b</sup>	Depth (cm) <sup>c</sup>	DT <sub>50</sub> (d) actual	DT <sub>90</sub> (d) actual	St. (χ <sup>2</sup> )	Method of calculation
Gut, T., 2017a (KCA 7.1.2.2.1/01) Gut, T., 2017b (KCA 7.1.2.2.1/02)	Loamy fine sand, bare soil	Höltinghausen, Germany	4.80	-	0-15	38.7	191.4	10.6	FOMC
	Very fine sandy loam, bare soil	Dugliolo di Budrio, Italy	7.66	-	0-20	27.3	178.5	3.7	FOMC
	Sand, bare soil	Røllum, Denmark	4.62	-	0-30	38.9	207.6	11.2	FOMC
	Loam, bare soil	Banbury, UK	6.70	-	0-25	15.2	55.6	8.0	DFOP
	Silt, bare soil	Saint-Amand, Belgium	6.12	-	0-30	14.8	74.9	4.7	DFOP
	Coarse sandy loam, bare soil	Almayate, Spain	7.70	-	0-25	22.6	87.4	8.8	DFOP
Mitchell J. <i>et al.</i> , 2018a (KCA 7.1.2.2.1/05) <sup>d</sup>	Silt loam, bare soil	New York, US	5.14	5.7	0-45	14.9	170.9	9.4	DFOP
	Sandy loam, bare soil	North Carolina, US	5.55	6.1	0-15	4.2	18.2	3.3	FOMC
	Clay loam, bare soil	Texas, US	6.77	7.3	0-30	53.9	179.2	15.7	SFO
	Sand, bare soil	Washington Site, US	7.59	8.1	0-15	2.5	20.5	8.4	FOMC
	Sandy loam, bare soil	California Site, US	7.69	8.2	0-30	12.9	42.7	18.1	SFO
Maximum							207.6		

<sup>a</sup> pH values are mean values for the soil across the depths at which residues were detected. US field study pH values were converted to be expressed as a CaCl<sub>2</sub> pH value using the method reported in EFSA (2017).

<sup>b</sup> Measured in a saturated soil paste made from distilled water. pH values are mean values for the soil across the depths at which residues were detected.

<sup>c</sup> Residue depth refers to the depths at which residues were detected, plus the following depth where the Applicant added values corresponding to 0.5 × LOD.

<sup>d</sup> One soil, North Dakota, was excluded from consideration of trigger endpoints as it was deemed not ecologically or climatically relevant to Europe following an ENASGIPS crosswalk exercise and consideration of the actual climatic conditions measured during the conduct of the field study.

### pH dependence

There is no evidence of pH dependence on the degradation of cinmethylin or as its individual enantiomers.

### Sorption behaviour of cinmethylin

The Applicant submitted one laboratory study to investigate the sorption behaviour of cinmethylin, plus one study conducting QSAR estimation of adsorption coefficients for three metabolites that arise in aqueous environments.

Adsorption of cinmethylin was investigated in eight soils (five European, two North American, one Japanese), using the batch equilibrium test [see report KCA 7.1.3.1.1/1]. The Applicant could not study the desorption behaviour of cinmethylin due to the substance's tendency to volatilise. Of the eight soils, five were considered acceptable by the HSE evaluator for evaluating sorption behaviour. Within these soils, organic carbon content ranged 0.66 – 4.34%, and the pH (CaCl<sub>2</sub>) ranged 4.4 – 7.1. The adsorption K<sub>FOC</sub> ranged 266.45 – 510.13 mL/g, geomean 317.8 mL/g. The calculated arithmetic mean Freundlich exponent (1/n) was 0.97. No pH dependence was observed in the sorption of cinmethylin, though there was a strong dependence of K<sub>FOC</sub> on organic carbon content.

Adsorption of two cinmethylin metabolites that arise in aquatic environments was determined via QSAR estimation. For M684H001, the K<sub>FOC</sub> was determined to be 430.2 mL/g (MCI method) or 85.6 mL/g (Log K<sub>ow</sub> method). For M684H003, the K<sub>FOC</sub> was determined to be 18.6 mL/g (MCI method) or 20.1 mL/g (Log K<sub>ow</sub> method). For M684H004, the K<sub>FOC</sub> was determined to be 422.4 mL/g (MCI method) or 104.6 mL/g (Log K<sub>ow</sub> method).

Column leaching, lysimeter and field leaching studies were not triggered for cinmethylin.

**Table 2.8.1-6** Overview of adsorption isotherms for cinmethylin on five soils.

Soil	Soil type (USDA)	C <sub>org</sub> (%)	pH (CaCl <sub>2</sub> )	K <sub>F</sub> (mL/g)	K <sub>FOC</sub> (mL/g)	1/n	R <sup>2</sup>
Li 10	Loamy sand	0.89	6.1	4.54	510.13	1.00	0.998
Lufa 2.3	Sandy loam	0.66	5.3	1.88	284.29	0.96	0.999
New Jersey	Loam	1.30	6.5	3.46	266.45	0.94	0.991
La Gironde	Silty clay loam	1.92	7.1	5.19	270.15	0.98	0.984
Gunma	Loam	4.34	4.4	13.49	310.77	0.96	0.993
Geomean					317.80		
Arithmetic mean						0.97	

### Persistence

The Applicant considered whether cinmethylin fulfils the persistence (P) or very persistent (vP) criteria within the PBT and vPvB assessments, which are defined according to Section 3.7.2.1. and 3.7.3.1, respectively, of Annex II of Regulation 1107/2009 as follows:

*An active substance, safener or synergist fulfils the persistence criterion where:*

- The half-life in soil is higher than 120 days.

*An active substance, safener or synergist fulfils the 'very persistent' criterion where:*

- the half-life in soil is higher than 180 days.

The relevant endpoints for the persistence assessment were identified based on the DG SANCO working document on "Evidence Needed to Identify POP, PBT and vPvB Properties for Pesticides" [SANCO 2012. DG SANCO Working Document on "Evidence Needed to Identify POP, PBT and vPvB Properties for Pesticides". Brussels: European Commission Health and Consumers Directorate-General. Report 25.09.2012 - rev. 3.]. According to this document, when available, field degradation half-lives are relevant for the P and vP assessment.

Considering the geomean DegT<sub>50</sub> of 11.1 days derived from the field dissipation studies, cinmethylin was found to be neither persistent (P) nor very persistent (vP) in the soil, in line with the DG SANCO definitions. See Section CA Section B.8.1.5 for further discussion.

## 2.8.2. Summary of fate and behaviour in water and sediment

### Aqueous hydrolysis

The aqueous hydrolysis of cinmethylin was investigated at four pH levels (4, 5, 7 and 9) over 31 days. The Applicant also investigated the enantiomer ratio for any changes through the duration of the study. Cinmethylin was hydrolytically stable in aqueous solution at all four pH levels, with all samples measuring above 96.2% AR after 31 days. It was not possible to calculate degradation rates, and as a result the HSE evaluator concluded that hydrolysis is not a route of degradation for cinmethylin.

### Aqueous photolysis

The aqueous photolysis of cinmethylin was explored in two studies. In the direct photolysis study, photolysis was studied over 15 days of continuous artificial irradiation (equivalent to 17.4 days of natural sunlight at 40°N) in a sterile aqueous buffer solution. Cinmethylin levels decreased from an average of 100% AR to 77% AR in the photolysis samples, and 96% in the dark control samples. The DT<sub>50</sub> was 41.8 days in artificial light, or 48.5 days in natural sunlight. It was not possible to calculate the quantum yield as the UV spectrum of cinmethylin showed no absorption above 290 nm and hence no overlap with the spectrum of sunlight.

The Applicant also submitted an indirect photolysis study, investigating the degradation of cinmethylin in a sterile natural water collected from a pond in Germany. After 15 days of artificial irradiation, cinmethylin levels decreased from an average of 100% AR to 68% AR. In dark controls, cinmethylin levels decreased to 95% on average. The DT<sub>50</sub> for indirect photolysis was 30.0 days in artificial light, or 34.8 days in natural sunlight. A photolysis-only degradation rate could not be determined due to no reliable endpoints for the dark control samples, though as before, this degradation can likely be attributed to photolytic processes.

In the case of both photolysis studies, a photolysis-only degradation rate could not be determined due to a lack of reliable endpoints for the dark control samples. With the hydrolysis study showing no notable hydrolytic degradation, the HSE evaluator concluded that the degradation observed can be attributed to photolytic processes.

One major metabolite, M684H003, was identified in the indirect photolysis study. Metabolite levels increased steadily through the duration of the study, peaking at 11.0% AR after 15 days and showing no decline pattern by the study end. As a result, it was not possible to derive a degradation rate for this metabolite.

**Table 2.8.2-1** Summary of trigger endpoints for the direct photolysis of cinmethylin following 15 days of continuous irradiation.

Study	DT <sub>50</sub> (d)	DT <sub>90</sub> (d)	χ <sup>2</sup> error (%)	Method of calculation	DT <sub>50</sub> natural sunlight (d)
Photolysis	41.8	139.0	2.4	SFO	48.5
Dark	> 1000	> 1000	1.4	SFO	> 1000

**Table 2.8.2-2** Summary of trigger endpoints for the indirect photolysis of cinmethylin following 15 days of continuous irradiation in sterile natural water.

Study	Parent/metabolite	DT <sub>50</sub> (d)	DT <sub>90</sub> (d)	χ <sup>2</sup> error (%)	Method of calculation	DT <sub>50</sub> natural sunlight (d)
Photolysis	Cinmethylin	30.0 <sup>a</sup>	99.6 <sup>a</sup>	-	SFO	34.8
	M684H003 <sup>b</sup>	> 1000	> 1000	14.6	SFO	> 1000
Dark	Cinmethylin	> 1000	> 1000	1.4	SFO	> 1000

<sup>a</sup> Degradation rates are geomeans derived from two radiolabel experiments.

<sup>b</sup> Metabolite was present only in the cyclohexane-labelled experiment.

### Ready biodegradability

An active substance can be classed as readily biodegradable if at least 60% biodegradation occurs within a 10 day window. Cinmethylin did not meet this criteria and is therefore not classed as readily biodegradable.

### Aerobic mineralisation in surface water

The aerobic mineralisation of cinmethylin was investigated in a pure water environment in a pelagic test at two concentrations: 10 µg/L and 50 µg/L. The study used two radiolabelling positions which sufficiently covered the potential degradation of the parent compound. After 63 days of incubation, between 62 – 85% AR remained in

water at the low concentration, and 81 – 91% AR remained at the high concentration. Volatiles peaked at 2.9 – 5% AR at 63 days.

One metabolite, M684H001, exceeded 10% AR, peaking at 13.1% AR after 63 days. It was not possible to derive a degradation rate for the metabolite due to it only being present in three sampling points and showing no decline phase during the study; as a result, the HSE evaluator has included a default DT<sub>50</sub> of 1000 days.

The HSE evaluator concluded that these results indicate that very minor degradation of cinmethylin occurs in open water (pelagic) systems.

**Table 2.8.2-3** Trigger endpoints derived from the aqueous aerobic mineralisation study.

Parent	63 day study				
Concentration	pH	DT <sub>50</sub> (d)	DT <sub>90</sub> (d)	St. ( $\chi^2$ )	Method of calculation
10 µg/L	7.3	138	457	1.4	SFO
50 µg/L		334	1110	1.8	SFO
<b>M684H001</b>	<b>Max. 13.1% AR at 63 DAT</b>				
	7.3	1000 <sup>a</sup>	-	-	-

<sup>a</sup> Endpoints could not be derived as the metabolite concentration was still rising at 63 DAT, hence default DT<sub>50</sub> of 1000 days.

#### Water/sediment studies

The Applicant studied the degradation of cinmethylin in two aerobic water/sediment systems, with one system taken from a pond-like side-arm of a river, and one taken from a small stream. For both systems, total radioactive residues in the water decreased from initial levels of 80 – 92% AR to 2.6 – 9.6% AR after 100 days. Cinmethylin peaked in sediment at 55.9% AR after 56 days, with levels declining to 16 – 30% AR by 100 days.

One major metabolite, M684H001, was identified by the Applicant, with levels in water peaking at 6.5 – 11.4% AR after 28 days in water, and at 1.8 – 3.8% AR in sediment after 28 – 56 days. The degradation rate and formation fraction were not derived for the metabolite as they are not required for UK-only applications.

The degradation rate for cinmethylin in the total system was 39.2 days. For the purpose of UK-specific surface water risk assessments, the water dissipation rate was 8.8 days.

The HSE evaluator concluded that aerobic metabolism is a major route of degradation for cinmethylin in aquatic systems.

**Table 2.8.2-4** Modelling endpoints for cinmethylin derived from the water-sediment study.

Parent	Distribution (Max. in sediment 55.9 % after 56 d)					
Whole system degradation rates						
Water / sediment system	pH water	pH sed (CaCl <sub>2</sub> )	Temp. °C	DegT <sub>50</sub> /DegT <sub>90</sub> whole system	St. (χ <sup>2</sup> %)	Method of calculation
Berghäuser Altrhein, Germany	7.58	6.90	20 ± 2	38.7 / 128.4	11.8	SFO
Ranschgraben, Germany	7.30	5.90	20 ± 2	39.7 / 131.8	6.3	SFO
Geometric mean DegT <sub>50</sub> whole system				39.2		
Water compartment dissipation rates (for UK surface water assessment)						
Water / sediment system	pH water	pH sed (CaCl <sub>2</sub> )	Temp. °C	DisT <sub>50</sub> /DisT <sub>90</sub> water	St. (χ <sup>2</sup> %)	Method of calculation
Berghäuser Altrhein, Germany	7.58	6.90	20 ± 2	5.1 / 17.0	11.5	SFO
Ranschgraben, Germany	7.30	5.90	20 ± 2	8.8 / 25.2	4.4	DFOP
Maximum DisT <sub>50</sub>				8.8		

Table 2.8.2-5

Trigger endpoints for cinmethylin and its enantiomers derived from the water-sediment study.

Parent (Max. in sediment 55.9% after 56 d) – Trigger endpoints							
System	Phase	pH <sup>a</sup>	Temp. °C	DT <sub>50</sub> (d) <sup>a</sup>	DT <sub>90</sub> (d) <sup>a</sup>	St. (χ <sup>2</sup> )	Method of calculation
Berghäuser Altrhein	Total		20 ± 2	38.7	128.4	11.8	SFO
	Water	7.58		5.2 <sup>b</sup>	21.5	3.6	DFOP
	Sediment	6.9		81.3	270.1	22.9	SFO
Ranschgraben	Total			39.7	131.8	6.3	SFO
	Water	7.30		4.8 <sup>b</sup>	25.2	4.4	DFOP
	Sediment	5.9		56.1	>1000	0.5	FOMC
Maximum	Total		39.7	131.8			
	Water		5.2	25.2			
	Sediment		81.3	>1000			
(-)-enantiomer (Reg. No. 5925581) – Trigger endpoints							
Berghäuser Altrhein	Total		20 ± 2	57.9	192.4	19.9	SFO
Ranschgraben	Total			49.2	163.5	8.8	SFO
Maximum	Total			57.9	192.4		
(+)–enantiomer (Reg. No. 5925632) – Trigger endpoints							
Berghäuser Altrhein	Total		20 ± 2	29.2	96.9	21.9	SFO
Ranschgraben	Total			30.0	99.6	11.6	SFO
Maximum	Total			30.0	99.6		

<sup>a</sup> For total system, degradation rates (DegT<sub>50/90</sub>) are shown. For water and sediment systems, dissipation rates (DisT<sub>50/90</sub>) are shown.

<sup>b</sup> Overall DT<sub>50</sub> shown

Table 2.8.2-6

Peak formation (as % AR) of cinmethylin and relevant metabolites in water and sediment. Note peak formations listed here are the greatest of all aquatic studies and are therefore suitable for use in modelling.

Compartment	Peak Formation (%AR)	
	Cinmethylin	M684H001
Water	-	11.4 % (Berghäuser Altrhein, 28d)
Sediment	55.9 % (Berghäuser Altrhein, 56d)	3.8 % (Ranschgraben, 28d)

### Enantiomeric ratio changes

The Applicant investigated the enantiomeric ratio throughout the course of most of the aquatic degradation studies. In the hydrolysis study there was no change from the 50:50 enantiomer ratio at any pH after 31 days. There was also no significant change in the ratio after 15 days in the direct photolysis study or in the indirect photolysis study. The HSE evaluator concludes that chemical degradation of cinmethylin does not alter the enantiomer ratio.

Regarding biological degradation, the Applicant did not explore the enantiomer ratio in relation to ready biodegradability; however, no biodegradation was observed. The enantiomer ratio did not change significantly due to aerobic mineralisation. However, large changes in the enantiomer ratio were observed in the water-sediment study, with the ratio shifting towards the (-)-enantiomer. In one system (Berghäuser Altrhein), changes were observed in both the water and sediment portions, with water shifting to 60:40 after 14 days, and the ratio in the sediment shifting from 57:43 at 14 DAT to 71:29 at 100 DAT with 30% and 24% of the initially applied cinmethylin remaining in the sediment respectively. Enantiomeric shifts were less pronounced in the

Ranschgraben system, with ratios observed in the water at approximately 55:45 at 14 DAT. In the sediment, initial ratios of 55:45 at 14 DAT shifted to 67:33 by 100 DAT in both radiolabels.

The HSE evaluator concludes that changes in the enantiomeric ratio in aquatic systems are driven by the aerobic degradation, with more rapid degradation of the (+)-enantiomer. In the water-sediment study, the (-)-enantiomer DT<sub>50</sub> (57.9 days) is almost twice as long as the (+)-enantiomer DT<sub>50</sub> (30.0 days). This contrasts with the degradation of the enantiomers in the soil, where the (-)-enantiomer degrades more rapidly than the (+)-enantiomer.

#### pH dependence

As the hydrolytic degradation study showed no hydrolysis or influence of pH on hydrolysis, the HSE evaluator concluded that there is no pH dependence of cinmethylin degradation in aquatic systems.

#### Persistence

Cinmethylin was found to be neither persistent (P) nor very persistent (vP) in the water or sediment compartments, in line with the DG SANCO definitions. See Section B.8.2.4 for further discussion.

### 2.8.3. Summary of fate and behaviour in air

Cinmethylin is estimated to degrade in air with a DT<sub>50</sub> of 0.178 days (12 hr day) based on calculations using the AOPWIN software.

A volatilisation study was submitted that shows high rates of volatilisation. After 24 hours, volatilisation from soil reached 73% and volatilisation from plant surfaces reached 89%.

Due to the high rates of volatilisation, the Applicant also provided a semi-field study to investigate the transport of cinmethylin via air in a semi-outdoor large wind tunnel study. Maximum deposition was observed 48 hours after application, with 0.82% of the applied amount measured at 1 m. 0.14 – 0.17% was measured at 20 m.

The HSE evaluator concludes that volatilisation is a major route of dissipation for cinmethylin, and that it is short lived in the air. Additionally, there are no concerns relating to local and global effects, such as tropospheric accumulation.

**Table 2.8.3-1** Summary of endpoints for the route and rate of cinmethylin degradation in the air.

Study	Endpoint	
Photochemical oxidative degradation	Hydroxyl radical degradation rate	0.178 d (12 h day)
	Ozone attack degradation rate	Could not be derived
Volatilisation	Volatilisation rate: soil	73% (24 h)
	Volatilisation rate: plant	89% (24 h)

**Table 2.8.3-2** Relative and absolute deposition of cinmethylin (formulated as BAS 684 03 H) over 96 hours and 20 m distance (mean, n = 2).

Distance (m)	Deposition relative to the amount applied to the target area (%)				
	12 hours	24 hours	48 hours	72 hours	96 hours
1	0.59	0.71	0.82	0.71	0.67
3	0.42	0.47	0.56	0.50	0.41
5	0.34	0.38	0.43	0.38	0.35
10	0.22	0.26	0.29	0.26	0.22
15	0.16	0.20	0.22	0.21	0.17
20	0.14	0.14	0.17	0.14	0.14
Background	<LOD	<LOD	<LOD	<LOD	<LOQ

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

As this is a new active substance, there are no monitoring data currently available.

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

According to the results presented, the following compounds are to be considered for the environmental risk assessment.

Soil:

Cinmethylin (parent only)

Groundwater:

Cinmethylin (parent only)

Surface Water:

Cinmethylin

M684H001

M684H003

Sediment

Cinmethylin (parent only)

Air:

Cinmethylin (parent only)

#### **2.8.6. Summary of exposure calculations and product assessment**

PEC<sub>soil</sub>

The predicted environmental concentrations in soil (PEC<sub>soil</sub>) of cinmethylin were calculated using standard methodology (i.e. 5 cm depth and 1.5 g cm<sup>-3</sup> bulk density). Actual and time-weighted average values are presented for the active substance and maximum values are presented for the formulation.

**Table 2.8.6-1**

PEC<sub>soil</sub> of cinmethylin following single application to winter cereals and winter oilseed rape, calculated for 5 cm soil depth and a bulk density of 1.5 g/cm<sup>3</sup>. Crop interception was assumed to be 0%.

	Crop	Winter cereals		Winter oilseed rape	
	Application rate	1 x 500 g a.s. ha <sup>-1</sup>		1 x 250 g a.s. ha <sup>-1</sup>	
	Time [d]	PEC <sub>soil,act</sub> [mg kg <sup>-1</sup> ]	PEC <sub>soil,twa</sub> [mg kg <sup>-1</sup> ]	PEC <sub>soil,act</sub> [mg kg <sup>-1</sup> ]	PEC <sub>soil,twa</sub> [mg kg <sup>-1</sup> ]
Global max.	0	0.667	-	0.333	-
Short-term	1	0.658	0.662	0.329	0.331
	2	0.650	0.658	0.325	0.329
	4	0.633	0.650	0.317	0.325
Long-term	7	0.609	0.638	0.305	0.319
	14	0.557	0.610	0.278	0.305
	21	0.509	0.584	0.254	0.292
	28	0.465	0.560	0.233	0.280
	48	0.360	0.497	0.180	0.249
	100	0.184	0.375	0.092	0.188

Derived from SFO DT<sub>50</sub> = 53.9 d

**Table 2.8.6-2**

PEC<sub>soil</sub> for the formulation BAS 684 03 H following a single application to winter cereals and winter oilseed rape, as supplied by the Applicant.

Crop	Application rate of formulation [L ha <sup>-1</sup> ]	Formulation density [g L <sup>-1</sup> ]	Crop interception [%]	Effective soil load [g ha <sup>-1</sup> ]	PEC <sub>soil,max</sub> [mg kg <sup>-1</sup> ]
Winter cereals	0.666	1000	0	666	0.888
	0.333			333	0.444

#### PEC<sub>soil, accumulation</sub>

As the DT<sub>90</sub> for cinmethylin did not exceed 365 days, PEC<sub>soil,accumulation</sub> values were not required for risk assessment.

#### PEC<sub>gw</sub>

The PEC<sub>gw</sub> of cinmethylin has been assessed with standard FOCUS scenarios following the approach laid out in the Generic Guidance for Tier 1 FOCUS Ground Water Assessments, 2014) to obtain outputs from FOCUS PELMO 5.5.3, FOCUS PEARL 4.4.4, and FOCUS MACRO 5.5.4.

A summary of the overall maximum PEC<sub>gw</sub> are presented in the table below.



**Table 2.8.6-3** 80<sup>th</sup> percentile annual leachate concentrations of cinmethylin following pre-emergence or spring application to winter cereals and winter oilseed rape.

Crop	Scenario	PEC <sub>gw</sub> (µg/L)			
		PEARL 4.4.4	PELMO 5.5.3 <sup>a</sup>		MACRO 5.5.4
			Pre-em.	Spring	
Winter cereals	Châteaudun	<0.001	<0.001	<0.001	<0.001
	Hamburg	<0.001	<0.001	<0.001	- <sup>b</sup>
	Kremsmünster	<0.001	<0.001	<0.001	
	Okehampton	<0.001	<0.001	<0.001	
Winter oilseed rape	Châteaudun	<0.001	<0.001	<0.001	<0.001
	Hamburg	<0.001	<0.001	<0.001	- <sup>b</sup>
	Kremsmünster	<0.001	<0.001	<0.001	
	Okehampton	<0.001	<0.001	<0.001	

<sup>a</sup> The Applicant considered pre-emergence application scenarios in all three models. The HSE evaluator decided to run an additional set of scenarios considering a spring application covering the later growth stages in the GAP table (BBCH 09-29 for winter wheat, 09-18 for winter oilseed rape)

<sup>b</sup> Scenarios not defined for the model

#### PEC<sub>sw</sub>

Predicted environmental concentrations in surface water (PEC<sub>sw</sub>) and sediment (PEC<sub>sed</sub>) for the active substance cinmethylin and its metabolites M684H001 and M684H003 were determined in a UK specific assessment considering spray drift and drainflow.

#### Spray drift

Due to the volatilisation from plant and soil surfaces, the Applicant adapted the spray drift assessment to include active substance deposited following volatilisation. In all cases, the substances were below their RACs with a 1 m buffer zone. Therefore, no further assessment was required for spray drift.

**Table 2.8.6-4** Maximum PEC<sub>sw</sub> and PEC<sub>sed</sub> for cinmethylin, M684H001 and M684H003 following a single application to field crops – pre-emergence, post-emergence and spring application.

Entry pathway	Buffer zone (m)	Cinmethylin		M684H001		M684H003	
		PEC <sub>sw,max</sub> (µg/L)	PEC <sub>sed,max</sub> (µg/kg)	PEC <sub>sw,max</sub> (µg/L)	PEC <sub>sed,max</sub> (µg/kg)	PEC <sub>sw,max</sub> (µg/L)	PEC <sub>sed,max</sub> (µg/kg)
Spray drift	1	4.617	0.101	0.584	0.898	0.318	n/a <sup>a</sup>
Spray drift incl. deposition after volatilisation	3	2.517	6.0	- <sup>b</sup>	- <sup>b</sup>	- <sup>b</sup>	- <sup>b</sup>
	5	1.667	4.0	- <sup>b</sup>	- <sup>b</sup>	- <sup>b</sup>	- <sup>b</sup>

<sup>a</sup> Not measured in sediment.

<sup>b</sup> Not calculated because the metabolites passed the risk assessment with a 1 m buffer zone.

**Table 2.8.6-5** Maximum PEC<sub>sw</sub> for formulation BAS 684 03 H for the pre-emergence use of 0.666 L product/ha in winter cereals.

Buffer distance (m)	Application rate of formulation (L/ha)	Formulation density (g/mL)	Application rate of formulation (g/ha)	Drift rate (%)	Formulation PEC <sub>sw,max</sub> (µg/L)
1	0.666	1.0 <sup>a</sup>	666	2.77	6.149
5				0.57	1.265

<sup>a</sup> Density value from CA Volume 3, Section B.8.2.14.

### Drainage

The drainage assessment was conducted for cinmethylin and its water metabolites M684H001 and M684H003 as the HSE evaluator reasoned that the metabolites could form once the parent had drained to surface waters, thereby providing a conservative risk assessment for surface water exposure via drainage.

Two tiers of drainage assessment were required due to cinmethylin PEC<sub>sw</sub> values exceeding the aquatic plant RAC at Tier 1. These results are presented below with the results of the higher tier drainage assessment conducted using WEBFRAM and MACRO. Higher tier results from WEBFRAM were compared to two RACs: an aquatic plant RAC (*Lemna spp*) and an aquatic invertebrate RAC (*Chironomus lugibris*). When considering the predicted concentrations against the aquatic plant RAC, median exceedance probabilities for cinmethylin did not exceed 1.2% in winter wheat, or 18% in winter barley. Overall exceedance rates did not exceed 1.5%. The trigger value for median exceedance probability is 60% while the overall exceedance trigger value is 10%. Therefore, cinmethylin and its metabolites M684H001 and M684H003 are unlikely to pose a risk to surface waters.

**Table 2.8.6-6** Maximum PEC<sub>sw</sub> via drainflow for cinmethylin following a single application to field crops.

Entry pathway	Substance	Pre-emergence Post-emergence		Spring application	
		PEC <sub>sw,max</sub> (µg/L)	PEC <sub>sed,max</sub> (µg/kg)	PEC <sub>sw,max</sub> (µg/L)	PEC <sub>sed,max</sub> (µg/kg)
Drainage – Tier 1	Cinmethylin	26.923	69.462	21.538	55.569
	M684H001	3.404	5.236	2.723	4.189
	M684H003	1.856	n/a	1.485	n/a

n/a – not applicable due to metabolite not being detected in sediment.

**Table 2.8.6-7**      Median exceedance probabilities (%) for each scenario following application of cinmethylin to winter wheat.

Climate scenario	Soil class			
	Denchworth	Hanslope	Brockhurst	Clifton
<b><i>Lemna</i> RAC (8.88 µg/L)</b>				
<b>Pre-emergence (15 October)</b>				
Dry	0.0	0.147	0.0	0.0
Medium	0.164	0.469	0.0	0.0
Wet	0.366	0.898	0.0	0.0
<b>Post-emergence (1 November)</b>				
Dry	0.122	0.404	0.0	0.0
Medium	0.352	0.868	0.0	0.0
Wet	0.567	1.20	0.0	0.0
<b>Spring application (30 March)</b>				
Dry	0.365	0.709	0.0	0.0
Medium	0.469	1.01	0.0	0.0
Wet	0.593	1.16	0.0	0.0
<b><i>Chironomus</i> RAC (20.6 µg/L)</b>				
<b>Pre-emergence (15 October)</b>				
Dry	0.0	0.0	0.0	0.0
Medium	0.0	0.0	0.0	0.0
Wet	0.0	0.0	0.0	0.0
<b>Post-emergence (1 November)</b>				
Dry	0.0	0.0	0.0	0.0
Medium	0.0	0.0	0.0	0.0
Wet	0.0	0.0	0.0	0.0
<b>Spring application (30 March)</b>				
Dry	0.0	0.0	0.0	0.0
Medium	0.0	0.0	0.0	0.0
Wet	0.0	0.0	0.0	0.0

**Table 2.8.6-8** Median exceedance probabilities (%) for each scenario following application of cinmethylin to winter barley.

Climate scenario	Soil class			
	Denchworth	Hanslope	Brockhurst	Clifton
<b>Lemna RAC (8.88 µg/L)</b>				
<b>Pre-emergence (15 October)</b>				
Dry	1.88	1.97	0.0	0.0
Medium	7.19	4.39	0.0	0.0
Wet	13.30	6.89	0.0	0.0
<b>Post-emergence (1 November)</b>				
Dry	10.50	4.59	0.0	0.0
Medium	15.30	6.51	0.0	0.0
Wet	17.80	7.72	0.0	0.0
<b>Spring application (30 March)</b>				
Dry	10.70	4.56	0.0	0.0
Medium	15.10	6.61	0.0	0.0
Wet	18.0	7.82	0.0	0.0
<b>Chironomus RAC (20.6 µg/L)</b>				
<b>Pre-emergence (15 October)</b>				
Dry	0.0	0.17	0.0	0.0
Medium	0.12	0.65	0.0	0.0
Wet	0.27	1.34	0.0	0.0
<b>Post-emergence (1 November)</b>				
Dry	0.33	1.06	0.0	0.0
Medium	0.42	1.51	0.0	0.0
Wet	0.51	1.84	0.0	0.0
<b>Spring application (30 March)</b>				
Dry	0.34	1.07	0.0	0.0
Medium	0.45	1.54	0.0	0.0
Wet	0.52	1.80	0.0	0.0

**Table 2.8.6-9** Summary of threshold exceedance for cinmethylin considering all years, scenarios, and cropping area for winter wheat.

Application scenario	Proportion of cropped area where exceedances occur [%]	Proportion of cropped area with zero exceedance [%]	Proportion of undrained area [%]	Overall exceedance [%]
<b>Lemna RAC (8.88 µg/L)</b>				
Pre-emergence	24.1	39.0	36.8	<b>0.057</b>
Post-emergence	28.6	34.5	36.8	<b>0.128</b>
Spring application	28.6	34.5	36.8	<b>0.196</b>
<b>Chironomus RAC (20.6 µg/L)</b>				
Pre-emergence	0.0	63.1	36.8	<b>0.0</b>
Post-emergence	0.0	63.1	36.8	<b>0.0</b>
Spring application	0.0	63.1	36.8	<b>0.0</b>

**Table 2.8.6-10** Summary of threshold exceedance for cinmethylin considering all years, scenarios, and cropping area for winter barley.

Application scenario	Proportion of cropped area where exceedances occur [%]	Proportion of cropped area with zero exceedance [%]	Proportion of undrained area [%]	Overall exceedance [%]
<b><i>Lemna</i> RAC (8.88 µg/L)</b>				
Pre-emergence	19.2	35.0	45.6	<b>0.71</b>
Post-emergence	19.2	35.0	45.6	<b>1.41</b>
Spring application	19.2	35.0	45.6	<b>1.41</b>
<b><i>Chironomus</i> RAC (20.6 µg/L)</b>				
Pre-emergence	17.2	37.0	45.6	<b>0.06</b>
Post-emergence	19.2	35.0	45.6	<b>0.20</b>
Spring application	19.2	35.0	45.6	<b>0.20</b>

***Higher tier drainflow assessment: July 2020 update***

In the original assessment presented above, the risk assessment passed based on the aquatic plant RAC. However, due to stricter risk assessment criteria for aquatic invertebrates, there was uncertainty over the risk assessment for *Chironomus spp.* using WEBFRAM, in particular the degree to which the PEC exceeded the RAC. Additional modelling using MACRO was submitted and evaluated by the HSE evaluator. This gave an explicit presentation of PECs for further comparison against the RAC.

The modelling was compared against both RACs; no exceedances of the *Chironomus* RAC were observed in the 30 modelled years. One year out of 30 exceeded the RAC for *Lemna*, occurring in the pre- and post-emergence scenarios. This equates to a 3% exceedance rate in one climate and soil scenario (Denchworth Medium). Maximum stream concentrations were 10.709 µg/L and 9.825 µg/L for pre- and post-emergence applications respectively.

Table 2.8.6-11

The number of years in which the concentration of cinmethylin in surface water exceeds the RAC in a 30 year MACRO simulation following application of BAS 684 03 H to winter cereals.

Climate scenario	Soil class			
	Denchworth	Hanslope	Brockhurst	Clifton
<b>Chironomus RAC (20.6 µg/L)</b>				
<b>Pre-emergence (15 October) <sup>a</sup></b>				
Dry	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
Medium	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
Wet	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
<b>Post-emergence (1 November) <sup>b</sup></b>				
Dry	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
Medium	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
Wet	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
<b>Spring application (30 March) <sup>a</sup></b>				
Dry	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
Medium	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
Wet	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
<b>Lemna RAC (8.88 µg/L)</b>				
<b>Pre-emergence (15 October) <sup>b</sup></b>				
Dry	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
Medium	1/30 (3%)	0/30 (-)	0/30 (-)	0/30 (-)
Wet	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
<b>Post-emergence (1 November) <sup>b</sup></b>				
Dry	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
Medium	1/30 (3%)	0/30 (-)	0/30 (-)	0/30 (-)
Wet	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
<b>Spring application (30 March) <sup>b</sup></b>				
Dry	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
Medium	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)
Wet	0/30 (-)	0/30 (-)	0/30 (-)	0/30 (-)

<sup>a</sup> Modelling undertaken by the Applicant and validated by the HSE evaluator

<sup>b</sup> Modelling undertaken by the HSE evaluator

#### PEC<sub>air</sub>

The atmospheric half life of cinmethylin was determined to be below the trigger of 2 days (0.178 days based on a 12 hour day). As a result, exposure and long-range transport are not anticipated for cinmethylin in air. Therefore, no calculation of PEC from airborne transport was conducted.

## 2.9. EFFECTS ON NON-TARGET SPECIES

### 2.9.1. Summary of effects on birds and other terrestrial vertebrates

#### Birds

Toxicity data addressing acute and long-term toxicity to birds for the active substance cinmethylin has been provided. For further details of the underlying studies see Section B.9 (AS). A full list of the available endpoints is provided in the list of endpoints and in the relevant risk assessments for the representative formulation. The following endpoints have been used to perform the risk assessment:

Discussion about how these endpoints were chosen from the submitted studies is found in Section B.9.1.1. (PPP: 'BAS 684 03 H').

## Cinmethylin

### Acute toxicity

The acute toxicity estimate used to address the toxicity of the active substance in the risk assessment is **LD<sub>50</sub> >2000 mg a.s./kg bw and the extrapolated LD<sub>50</sub> > 3776 mg a.s./kg bw.**

### Long-term toxicity

The chronic toxicity estimate used to address the long-term toxicity of the active substance in the risk assessment is **NOEL = 99.1 mg a.s./kg bw/d.**

## Mammals

Toxicity data have been provided and considered within the human health assessment (see Section B.6 (CA) 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 to perform the risk assessment:

## Cinmethylin

### Acute toxicity

The acute toxicity estimate used to address the toxicity of the active substance in the risk assessment is **LD<sub>50</sub> >2000 mg/kg bw/d.**

### Long-term toxicity to the active substance

The chronic toxicity estimate used to address the long-term toxicity of the active substance in the risk assessment is **NOAEL<sub>reproduction</sub> = 58 mg/kg bw/d.**

## Endocrine disruption assessment for birds and mammals:

For birds when considering reproductive toxicity the NOAEL values were the highest test concentration of 1200 mg a.s./kg diet for both avian studies, equivalent to 99.1 mg a.s./kg b.w./day. No treatment related effects were observed based on the parameters measured that are considered sensitive but not diagnostic of EATS. In accordance with EFSA/ECHA guidance the gross pathology findings should be reported. This was the case for both avian studies and no treatment related effects were observed.

HSE concludes that endocrine disruption in birds from cinmethylin resulting in population level effects is unlikely on the basis of the current dataset and guidance document scope.

For wild mammals the toxicology data and conclusions for endocrine disruption were considered (see section 2.6.8). It was possible to conclude for Estrogen, Androgen and Steroidogenesis (EAS) modalities that the endocrine disruption criteria are not met for wild mammals. However, Thyroid (T) activity was observed; increased thyroid weights/follicular cell hypertrophy/hyperplasia and/or altered colloid but a robust toxicology conclusion against criteria was not possible. Further information is being provided by applicant for the toxicology assessment meaning it is currently not possible to reach a robust conclusion for wild mammals regarding T modality.

## Overall conclusion:

Overall, for birds cinmethylin is not considered to be an endocrine disruptor. Regarding wild mammals, cinmethylin is not an endocrine disruptor when considering EAS modalities based on EFSA/ECHA guidance 2018 and agreed regulatory criteria. However, for Thyroid (T) modality further toxicology information is being provided and currently it is not possible to reach a conclusion for wild mammals.

For full discussion of the ecotoxicology endocrine disruption assessment for birds and mammals see volume 3 CA dossier, section B.9.1.5. It should be noted the wild mammals conclusion will be updated once further information has been provided by applicant and evaluated.

## 2.9.2. Summary of effects on aquatic organisms

Toxicity data to address cinmethylin, and relevant metabolites have been provided. The first tier toxicity data used in the risk assessments are summarised here (active substance, table 2.10.2-1; and metabolites, table 2.10.2-2). For full details of all the available toxicity data see the list of endpoints and Section B.9 (CA and CP). Formulation toxicity data has also been submitted (table 2.10.2-3).

Table 2.9.2-1: First tier toxicity data relevant to the active substance, cinmethylin, for use in the risk assessment

Test substance	Test organism	Test system	Endpoint (mg a.s./L)		Reference
Acute toxicity to fish					
Cinmethylin (COD-002038)	<i>Cyprinus carpio</i>	96-hours, static	LC <sub>50</sub>	<b>5.75</b> (g.m)	█ (2017a) & (2018b) <sup>#</sup>
Long-term toxicity to fish					
Cinmethylin (COD-002038)	<i>Pimephales promelas</i>	35-days, flow through, early-life-stage study	NOEC*	<b>0.59</b> (m.m)	█ (2017a)
			EC <sub>10</sub> (bdl)*	0.92 (m.m)	
Bioconcentration in fish					
Cinmethylin (COD-002038)	<i>Lepomis macrochirus</i>	17 days uptake and 7 days depuration	BCF <sup>##</sup>	707 L kg <sup>-1</sup> (whole fish at 0.5 µg eq/L) 688 L kg <sup>-1</sup> (whole fish at 5 µg eq/L) Geometric mean of 697 L kg <sup>-1</sup>	█ (2017b)
Cinmethylin (COD-002038)	<i>Lepomis macrochirus</i>	Metabolism study supporting Salinas <i>et al</i> (2017b)	BCF (parent)	Geometric mean (whole fish 0.5 and 5 µg a.s./L) recalculated based on cinmethylin content to <b>100.4</b> ** using data from Salinas <i>et al</i> 2017b	█ (2017b) & █ (2018a)
Acute toxicity to invertebrates					
Cinmethylin (COD-002038)	<i>Daphnia magna</i>	48-hours, static	EC <sub>50</sub>	<b>7.26</b> (nom.)	Haerthe (2016a)
Long-term toxicity to invertebrates					
Cinmethylin (COD-002038)	<i>Daphnia magna</i>	21-days, static renewal	NOEC	<b>0.29</b> (g.m) <sup>###</sup>	Rzodeczko (2017b)
			EC <sub>10</sub>	> 0.29 (g.m) <sup>###</sup>	
Toxicity to algae					
Cinmethylin (COD-002038)	<i>Pseudokirchneriella subcapitata</i>	72-hours, static	ErC <sub>50</sub>	<b>23.04</b> (g.m)	Kauf (2017a)
			ErC <sub>10</sub>	> 1.765 (g.m) <sup>a</sup>	
Toxicity to aquatic macrophytes					
Cinmethylin (COD-002038)	<i>Lemna gibba</i>	7-days, static, water only	ErC <sub>50</sub>	<b>0.0888</b> g.m (f.n.) > 0.2580 g.m (d.w.)	Vlechev (2017a)



Test substance	Test organism	Test system	Endpoint (mg a.s./L)		Reference
			ErC <sub>10</sub>	0.0285 g.m (f.n.) 0.0300 g.m (d.w.)	
Other aquatic organisms					
Cinmethylin (WL95481)	<i>Chironomus lugubris</i>	96-hour, static	LC <sub>50</sub>	> 2.06 (g.m) <u>Supporting information only</u>	Pearson & Stephenson (1987a) <sup>b</sup>

nom. = nominal; m.m = arithmetic mean measured; g.m. = geometric mean measured; f.n. = frond number, d.w. = dry weight, bdl = body length

**Bold** values are recommended for use in risk assessment at tier-1.

\* It should be noted the EC<sub>10</sub> and EC<sub>20</sub> values calculated only considered body length and body weight. The NOEC is based on survival.

\*\* BCF value recalculated based on metabolism study (██████████ 2018a). In this study at end of exposure period cinmethylin (BAS 684 H) accounted for 24.1 % TRR/0.085 mg a.s./kg (Total Radioactive Residue) at 0.5 µg a.s./L and 8.6 % TRR/0.045 mg a.s./kg at 5 µg a.s./L. The metabolite M684H012 accounted for 24.1 % TRR, 14.7 % TRR, M684H022 (isomer 1) for 7.7 % TRR, 4.2 % TRR, M684H022 (isomer 2) for 8.0 % TRR, 10.6 % TRR, M684H026 for 8.2 % TRR, 5.2 % TRR at 0.5 and 5 µg a.s./L. In order to account for the metabolites present using this study the HSE evaluator has re-calculated the BCF endpoints based on cinmethylin to 170 and 59 for 0.5 and 5 µg a.s./L, corresponding to a geometric mean of 100.4.

# Amendment to final report also considered.

### BCF normalised to 5 % lipid content in accordance with OECD 305

#### Based on time weighted average concentration. Due to lack of analytical measurements during study for three test concentrations only the lowest and highest concentrations could be calculated. Therefore, this endpoint is considered conservative.

<sup>a</sup> Uncertainty regarding statistically derived value hence conservative approach has been taken and a greater than value reported.

<sup>b</sup> Study considered suitable as supporting information only by the HSE evaluator due to uncertainties; not possible to confirm validity criteria were met and lack of control without solvent (see study summary for further details). Used in illustrative risk assessment.

#### Bioaccumulation consideration (cinmethylin):

The BCF values from ██████████ 2017b were 707 and 688 L kg<sup>-1</sup> at 0.5 and 5 µg eq/L respectively when corrected for lipid content. A supporting metabolism study (██████████ 2018a) was also submitted hence it is possible to ascertain the BCF for the parent (cinmethylin) and identify metabolites present. In order to account for the metabolites present using this study the HSE evaluator has re-calculated the BCF endpoints based on cinmethylin to 170 and 59 for 0.5 and 5 µg a.s./L, corresponding to a geometric mean of 100.4. As stated in EFSA aquatic guidance 2013 biomagnification must be considered for compounds where the BCF is > 1000 and the elimination of radioactivity during the 14-day depuration phase in the bioconcentration study is < 95 % and the substance is stable in water or sediment (DegT<sub>90</sub> > 100 days). The environmental fate section details the worst case DT<sub>90</sub> in water to be 25.2 days and > 100 days in sediment meeting the 'stability' criteria for sediment. The BCF value (geomean) was 100 and based on the metabolism study (██████████ 2018a) the worst case DT<sub>50</sub> value considering total radioactivity was 1.12 days hence both are within the triggers detailed and further consideration is not required.

#### Toxicity to aquatic invertebrates (cinmethylin):

When considering the acute toxicity to aquatic invertebrates only one valid GLP study is available testing *Daphnia magna* producing an EC<sub>50</sub> value of 7.26 µg a.s./L. However, several other species were also assessed in the study Pearson & Stephenson (1987a) suggesting lower endpoints and that the *Daphnia* study may not be protective. The lowest LC<sub>50</sub> value was unbound at > 2.06 µg a.s./L. Whilst these studies were only considered suitable as supporting information a risk assessment has been performed using the lowest unbound value to derive a separate illustrative RAC for use in the risk assessment.

**Toxicity to aquatic plants (cinmethylin):**

Several additional studies testing additional plant species (*Myriophyllum spicatum*, *Elodea canadensis* and *Egeria densa*) were submitted that were not considered suitable for use in the risk assessment. The endpoints and phytotoxicity data from all available studies were considered in detail (see CP, section 9 dossier) and the *Lemna gibba* endpoint listed in table 2.10.2-1 (shown in bold) was determined to be the most sensitive for use in the risk assessment.

**Toxicity to aquatic sediment dwellers (cinmethylin):**

The study Pearson & Stephenson (1987a) determined an LC<sub>50</sub> for *Chironomus lugubris* based on water only exposure. However, this study was only considered suitable as supporting information by the HSE evaluator and the LC<sub>50</sub> value was above the highest test concentration i.e. > 2.06 mg a.s./L (g.m.).

In accordance with EFSA aquatic guidance document 2013 consideration of toxicity to *Chironomus* sp is required if the substance accumulates in sediment (water/sediment study demonstrates > 10 % of applied radioactivity at or after day 14 present in the sediment) and the chronic *Daphnia* test shows an EC<sub>10</sub>/NOEC of < 0.1 mg a.s./L. Whilst the cinmethylin levels were above 10 % after day 14, peaking at 55.9 % at 56 days the chronic *Daphnia* endpoints were above the trigger of 0.1 mg a.s./L. Therefore, further consideration is not required.

Table 2.9.2-2: First tier toxicity data for the metabolites of cinmethylin for use in risk assessment

Test substance	Test organism	Test system	Endpoint (mg a.s./L)		Reference
Acute toxicity to fish					
Cineole alcohol (M684H003)	<i>Oncorhynchus mykiss</i> (also known as <i>Salmo gairdneri</i> )	96-hours, static	LC <sub>50</sub>	> <b>1000</b> (nom.) <u>Supporting information only</u> <sup>#</sup>	██████ (1988a)
Acute toxicity to invertebrates					
M684H001	<i>Daphnia magna</i>	48-hours, static	EC <sub>50</sub>	> 100 (nom.)	Turek (2018a)
Cineole alcohol (M684H003)		48-hours, static	EC <sub>50</sub>	<b>840</b> (nom.) <u>Supporting information only</u> <sup>#</sup>	Girling (1988a)
Toxicity to aquatic macrophytes					
M684H001	<i>Lemna gibba</i>	7-days, static, water only	ErC <sub>50</sub>	> 78.3 g.m (f.n.) > 78.3 g.m (d.w.)	Rzodeczko (2017e)
			ErC <sub>10</sub>	16.2 g.m (f.n.) 22.4 g.m (d.w.)	
Cineole alcohol (M684H003)	<i>Lemna gibba</i>	7-days, static, water only	ErC <sub>50</sub>	> 100 nom. (f.n. and d.w.)	Turek (2018c)
			EC <sub>10/20</sub>	Limit study, not possible to calculate	
M684H004	<i>Lemna gibba</i>	7-days, static, water only	ErC <sub>50</sub>	3.28 g.m (f.n.) > 23.47 g.m (d.w.)	Rzodeczko (2017f)
			ErC <sub>10</sub>	0.881 g.m (f.n.) 1.08 g.m (d.w.)	

nom. = nominal; g.m. = geometric mean measured f.n. = frond number, d.w. = dry weight

**Bold** values are recommended for use in risk assessment at tier-1.

<sup>#</sup> Not considered suitable for quantitative use as insufficient information provided to confirm analytical method was validated.

<sup>a</sup> Uncertainty regarding statistically derived endpoint hence based on experimental data, noting these endpoints have not been used in the risk assessment.

Table 2.9.2-3: First tier toxicity data for the formulation 'BAS 684 03H' for use in risk assessment

Test substance	Test organism	Test system	Endpoint mg product/L (mg a.s./L)		Reference
Acute toxicity to fish					
‘BAS 684 03 H’	<i>Cyprinus carpio</i>	96-hours, static	LC <sub>50</sub>	5.86 ( <b>4.32</b> ) g.m	<div></div> (2017a) <sup>#</sup>
Acute toxicity to invertebrates					
‘BAS 684 03 H’	<i>Daphnia magna</i>	48-hours, static	EC <sub>50</sub>	14.5 ( <b>10.68</b> ) nom.	Turek (2017a)
Toxicity to algae					
‘BAS 684 03 H’	<i>Pseudokirchneriella subcapitata</i>	72-hours, static	ErC <sub>50</sub>	26.3 ( <b>19.37</b> ) nom.	Turek (2017b)
			ErC <sub>10</sub>	15.4 (11.34) nom. <sup>a</sup>	
Toxicity to aquatic macrophytes					
‘BAS 684 03 H’	<i>Lemna gibba</i>	7-days, static, water only	ErC <sub>50</sub>	<b>0.167 (0.123)</b> g.m. f.n. > 8.97 (> 6.607) g.m. d.w.	Rzodeczko (2017b)
			ErC <sub>10</sub>	0.053 (0.039) g.m. f.n. 0.063 (0.046) g.m. d.w.	

nom. = nominal; g.m. = geometric mean measured; ini. = initial measured

f.n. = frond number, d.w. = dry weight, t.l. = Total shoot length, w.w. = wet weight, f.w. = fresh weight, b.n. = blade number

**Bold values are recommended for use in risk assessment at tier-1.**

<sup>#</sup> Amendment to final report also considered.

<sup>a</sup> Uncertainty as ErC<sub>10</sub> and ErC<sub>20</sub> values are similar and confidence limits overlap, noting these endpoints are not used in the risk assessment.

#### Endocrine disruption assessment for aquatic organisms:

For the cinmethylin endocrine disruption assessment two studies testing aquatic organisms and measuring endocrine parameters were conducted: Fish Short Term Reproduction Assay (FSTRA) testing zebra fish (██████████ 2020) and an Amphibian Metamorphosis Assay (AMA) testing African clawed frog (██████████ 2020a). The early life stage study testing fathead minnow detailed in table 2.9.2-1 (██████████, 2017a) was also considered as it included parameters that are sensitive to but not diagnostic of Estrogen, Androgen, Thyroid and Steroidogenesis modalities (EATS).

Currently a robust conclusion for EAS modalities in aquatic organisms has not been reached for cinmethylin as further consideration of the FSTRA is being provided by the applicant i.e. justification for the chosen maximum tolerated concentration tested in FSTRA.

In the AMA study, there were indications of endocrine effects (T modality) following exposure to cinmethylin at the highest concentration tested. Further consideration of these effects are being provided by the applicant. This includes mode of action analysis in-line with EFSA/ECHA 2018, further histological data (of samples taken during AMA) and historical control analysis. Currently no further vertebrate testing is planned.

#### Overall conclusion:

Currently a robust conclusion on endocrine disruption for aquatic organisms **cannot be reached**.

For full details of the endocrine disruption assessment of aquatic organisms see volume 3 CA dossier, section B.9.1.5. This section will be updated once further information is provided by applicant.

### 2.9.3. Summary of effects on arthropods

#### Bees

### Studies conducted with the active substance

Acute oral and acute contact studies were submitted for the active substance both for the honeybee (*Apis mellifera*) and the bumblebee (*Bombus terrestris*). In addition a chronic honeybee larvae repeated exposure study (22d) was submitted for the active substance. All of the submitted studies were considered valid after evaluation. It should be noted that the bumblebee studies and honeybee larval study were not used in the risk assessment due to a lack of noted guidance.

### Studies conducted with formulations BAS 684 02 H and BAS 684 03 H

Several bee studies have been conducted using BAS 684 02 H which has been used in place of the representative formulation BAS 684 03 H. A formulation comparison between the two has been undertaken in the confidential Volume 4. It was concluded that conducting a risk assessment using data from BAS 684 02 H studies would be suitably protective of the risk from the representative formulation BAS 684 03 H.

Acute oral and acute contact studies were submitted using formulation BAS 684 02 H both for honeybee (*Apis mellifera*) and the bumblebee (*Bombus terrestris*). All studies were considered valid after evaluation.

For the acute contact study conducted with *Apis mellifera* the evaluator noted that one bee was 'moribund' for the duration of the study at the top dose tested. However the risk assessment that follows demonstrates a large margin of safety for the acute contact risk assessment and hence this result in the study is not of concern.

It should be noted that the valid bumblebee studies and chronic adult honeybee formulation study will not be used in the risk assessment due to a lack of noted guidance regarding this area of risk assessment.

A chronic larvae repeated exposure (22d) study was submitted using the representative formulation BAS 684 03 H. This study was considered valid after evaluation however it will not be used in the risk assessment due to a lack of noted guidance.

The toxicity endpoints for bees are summarised in the table below.

Table 2.9.3-1: Effects on bees

Species	Test substance	Time scale/type of endpoint	End point	Toxicity
<i>Apis mellifera</i>	a.s., BAS 684 H	Acute	Oral toxicity (LD <sub>50</sub> )	>200.0 µg a.s./bee
<i>Bombus terrestris</i>	a.s., BAS 684 H	Acute	Oral toxicity (LD <sub>50</sub> )	> 195.4 µg a.s./bee
<i>Apis mellifera</i>	Preparation 'BAS 684 02 H'	Acute	Oral toxicity (LD <sub>50</sub> )	> 294.7 µg BAS 684 02 H/bee
<i>Bombus terrestris</i>	Preparation 'BAS 684 02 H'	Acute	Oral toxicity (LD <sub>50</sub> )	> 258.5 µg BAS 684 02 H/bee
<i>Apis mellifera</i>	a.s., BAS 684 H	Acute	Contact toxicity (LD <sub>50</sub> )	>200.0 µg a.s./bee
<i>Bombus terrestris</i>	a.s., BAS 684 H	Acute	Contact toxicity (LD <sub>50</sub> )	>200.0 µg a.s./bee
<i>Apis mellifera</i>	Preparation 'BAS 684 02 H'	Acute	Contact toxicity (LD <sub>50</sub> )	> 272.0 µg BAS 684 02 H/bee
<i>Bombus terrestris</i>	Preparation 'BAS 684 02 H'	Acute	Contact toxicity (LD <sub>50</sub> )	> 272.0 µg BAS 684 02 H/bee

<i>Apis mellifera</i>	Preparation 'BAS 684 02 H'	Chronic adult (10d repeated exposure)	EC <sub>10</sub> EC <sub>20</sub> LDD <sub>50</sub> LC <sub>50</sub> NOEDD NOEC	86.5 µg a.s./bee/day 110.1 µg a.s./bee/day 143.2 µg a.s./bee/day 3.982 g a.s./kg food 48.6 µg a.s./bee/day 1.284 g a.s./kg food
<i>Apis mellifera</i>	a.s., BAS 684 H	Bee brood development	EC <sub>10</sub> EC <sub>20</sub> ED <sub>50</sub> EC <sub>50</sub> NOED NOEC	45.1 µg a.s./larva 100.7 µg a.s./larva > 100.1 µg a.s./larva > 650 mg a.s./kg food ≥ 100.1 µg a.s./larva ≥ 650 mg a.s./kg food
<i>Apis mellifera</i>	Preparation 'BAS 684 03 H'	Bee brood development	EC <sub>10</sub> EC <sub>20</sub> ED <sub>50</sub> EC <sub>50</sub> NOED NOEC	116.3 µg BAS 684 03 H/larva 124.7 µg BAS 684 03 H /larva > 133.4 µg BAS 684 03 H /larva > 844 mg BAS 684 03 H /kg food 66.7 µg BAS 684 03 H /larva 422 mg BAS 684 03 H/kg food

<sup>1</sup> Studies presented in CA document.

<sup>2</sup> Due to the lack of currently noted guidance, these endpoints are presented as additionally supporting information only.

<sup>3</sup> BAS 684 02 H formulation has been compared to the representative formulation BAS 684 03 H in the confidential section Volume 4 and the two are considered comparable.

**Bold** endpoints will be used in the risk assessment.

### Non-target arthropods other than bees

The toxicity endpoints for non-target arthropods other than bees are summarised in the tables below.

Table 2.9.3-2: Effects on non-target arthropods other than bees

Test substance	Species	Exposed life stage	Study type	Application rate [L/ha]	Corrected mortality <sup>1)</sup> [%]	Sublethal effects <sup>2)</sup> [%]
BAS 684 03 H	<i>Aphidius rhopalosiphi</i>	adults	Laboratory test using artificial substrate, 2D exposure scenario (glass plate)	0.04375 0.0875 0.175 0.350 0.700 <b>LR<sub>50</sub> = 0.136 L/ha</b>	0.0 41.0 56.4 89.7 100.0	n.d.
BAS 684 03 H	<i>Aphidius rhopalosiphi</i>	adults	Extended laboratory test using natural substrate, 3D exposure scenario (barley plants)	0.04375 0.0875 0.175 0.350 0.700 <b>LR<sub>50</sub> &gt; 0.7 L/Ha</b> <b>ER<sub>50</sub> &gt; 0.7 L/Ha</b>	-3.6 0 -3.6 0 7.1	-16.0 -3.9 -2.6 -6.1 -5.2
BAS 684 03 H	<i>Typhlodromus pyri</i>	protonymphs	Laboratory test using artificial substrate, 2D	0.0625 0.125 0.250	0 1.0 1.0	n.d.

Test substance	Species	Exposed life stage	Study type	Application rate [L/ha]	Corrected mortality <sup>1)</sup> [%]	Sublethal effects <sup>2)</sup> [%]
			exposure scenario (glass plate)	0.500 1.000 <b>LR<sub>50</sub> = 0.764 L/ha</b>	9.1 77.8	
BAS 684 03 H	<i>Aleochara bilineata</i>	adults	Extended laboratory test using natural substrate, 2D exposure scenario (sandy soil)	0.7 1.4 <b>LR<sub>50</sub> &gt; 1.4 L/ha</b> <b>ER<sub>50</sub> &gt; 1.4 L/ha</b>	n.d. n.d.	6.4 7.2

<sup>1)</sup> Positive values indicate an increase in mortality; negative values indicate a decrease in mortality, relative to the control.

<sup>2)</sup> Positive values indicate a decrease in reproduction; negative values indicate an increase in reproduction, relative to the control.  
n.d. = not determined.

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

### Earthworms and other soil macro-organisms

Toxicity data to address cinmethylin, and relevant metabolites have been provided. The first tier toxicity data used in the risk assessments are summarised here for both active and formulation. Table 2.10.4-1 summarises the earthworm data and table 2.10.4-2 the other soil macro-organisms. For full details of all the available toxicity data see the list of endpoints and Section B.9 (CA and CP).

Table 2.9.4-1: First tier earthworm toxicity data relevant to the active substance, cinmethylin and formulation for use in the risk assessment

Test substance	Test species	Endpoint	Value [mg a.s./kg dry soil]	Reference
Chronic toxicity				
Cinmethylin	<i>Eisenia andrei</i>	NOEC	87.8*	Friedrich (2016a)
		EC <sub>10</sub>	83.5* <sup>#</sup>	
		NOEC <sub>CORR</sub> <sup>1)</sup>	43.90*	
		EC <sub>10</sub> <sub>CORR</sub> <sup>1)</sup>	<b>41.8*</b>	
BAS 684 03 H		NOEC	87.25* <sup>##</sup>	Friedrich (2018a)
		EC <sub>10</sub>	87.69* <sup>##</sup>	
		NOEC <sub>CORR</sub> <sup>1)</sup>	<b>43.63*<sup>##</sup></b>	
		EC <sub>10</sub> <sub>CORR</sub> <sup>1)</sup>	43.85* <sup>##</sup>	

<sup>1)</sup> Corrected by factor of 2 due to lipophilic substance (i.e. log<sub>Pow</sub> > 2)

\* There is uncertainty when using these study endpoints. As cinmethylin is volatile and analytical measurements were not taken during the laboratory studies. This has been discussed further below.

<sup>#</sup> As detailed in volume 3, section CA dossier B9 there was some uncertainty regarding this endpoint compared to the experimental data. However, the statistically derived EC<sub>10</sub> value is considered suitably protective (more conservative than the experimental data) and valid by the HSE evaluator.

<sup>##</sup> Endpoint expressed as active cinmethylin, considering the measured content of cinmethylin in study and a density of BAS 684 03 H of 1.001 g/cm<sup>3</sup>.

Bold values have been used in the risk assessment, the HSE evaluator has used the lowest value either NOEC or EC<sub>10</sub> in the risk assessment as a worst-case approach.

Table 2.9.4-2: First tier other soil macro-organisms excluding earthworms toxicity data relevant to the active substance, cinmethylin and formulation for use in the risk assessment

Test substance	Test species	Endpoint	Value [mg a.s./kg dry soil]	Reference
<b>Chronic toxicity</b>				
BAS 684 03 H	<i>Folsomia candida</i>	##NOEC	137*#	Friedrich (2017a)
BAS 684 03 H	<i>Folsomia candida</i>	##EC <sub>10</sub>	134*#	
BAS 684 03 H	<i>Folsomia candida</i>	##NOEC CORR <sup>1)</sup>	68.5*#	
BAS 684 03 H	<i>Folsomia candida</i>	##EC <sub>10</sub> CORR <sup>1)</sup>	<b>67*#</b>	
BAS 684 03 H	<i>Hypoaspis aculeifer</i>	##NOEC	232*#	Schulz (2017a)
BAS 684 03 H	<i>Hypoaspis aculeifer</i>	##EC <sub>10</sub>	204*#	
BAS 684 03 H	<i>Hypoaspis aculeifer</i>	##NOEC CORR <sup>1)</sup>	116*#	
BAS 684 03 H	<i>Hypoaspis aculeifer</i>	##EC <sub>10</sub> CORR <sup>1)</sup>	<b>102*#</b>	

<sup>1)</sup> Corrected by factor of 2 due to lipophilic substance (i.e. log<sub>Pow</sub> > 2)

\* There is uncertainty when using these study endpoints. As cinmethylin is volatile and analytical measurements were not taken during the laboratory studies. This has been discussed further below.

# Endpoint expressed as active cinmethylin, considering the nominal content of cinmethylin and a density of BAS 684 03 H of 1.001 g/cm<sup>3</sup>.

## With all these endpoints there is some uncertainty as cinmethylin is volatile and analytical measurements were not taken during studies to confirm exposure.

Bold values have been used in the risk assessment, the HSE evaluator has used the lowest value either NOEC or EC<sub>10</sub> in the risk assessment as a worst-case approach.

## 2.9.5. Summary of effects on soil nitrogen transformation

Studies on nitrogen transformation in soil are available for the active substance cinmethylin and the representative formulation BAS 684 03 H. A summary of the available data and endpoints used in the risk assessment is provided in Table 2.10.5-1.

Table 2.9.5-1: First tier soil nitrogen transformation rate studies relevant to active substance, cinmethylin and formulation for use in the risk assessment

Test substance	Test species	Endpoint		Reference
Cinmethylin	Nitrogen transformation 14-28 d	<25% effect	<b>7.17 mg a.s./kg dws</b>	Schulz (2016a)
BAS 684 03 H	Nitrogen transformation 14-28 d	<25% effect	<b>4.92 mg a.s./kg dws<sup>#</sup></b>	Schulz (2017b)

dws = dry weight soil; a.s. = active substance;

# Endpoint expressed as active cinmethylin, considering the nominal content of cinmethylin and a density of BAS 684 03 H of 1.001 g/cm<sup>3</sup>.

**Bold values:** endpoints used for risk assessment

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

A summary of the potential effects of BAS 684 03 H on seedling emergence and vegetative vigor is provided in Table 2.9.6-1.

Table 2.9.6-1: Summary of effects on terrestrial non-target plants following exposure to ‘BAS 684 03 H’

Test substance	Test system	Test species	Endpoints g a.s./ha	Reference
BAS 684 03 H	21 d <sup>1)</sup> Seedling emergence	Ryegrass (monocotyledon)	ER <sub>50</sub> emergence = 109 ER <sub>50</sub> plant length = 81.3 ER <sub>50</sub> plant weight = <b>31.3</b>	Friedemann & Stroemel 2018a
BAS 684 03 H	21 d Vegetative vigor	Ryegrass (monocotyledon)	ER <sub>50</sub> plant length > 1032 ER <sub>50</sub> plant weight = <b>523.3</b>	Friedemann & Stroemel 2017a

<sup>1)</sup> 28 days for onion, bold values represent most sensitive species based on seedling emergence and vegetative vigour

#### Phytotoxicity:

Given cinmethylin is volatile and an herbicide the phytotoxicity observed in the laboratory studies was also considered.

An NOER of 21.9 ml product/ha equivalent to 16.1 g a.s./ha based on phytotoxicity was determined in the seedling emergence study. It was not possible to determine a NOER in the vegetative vigour study where phytotoxicity was observed at the lowest test concentration (87.5 ml product/ha equivalent to 64.5 g a.s./ha). In this study phytotoxicity was observed for two species with the following maximums based on replicates; chlorosis of 1 %, deformation and stunting both 10 %. After detailed consideration of both studies (for full discussion refer to CP, section 9 dossier) the HSE evaluator considered the phytotoxicity NOER of 21.9 ml product/ha equivalent to 16.1 g a.s./ha to be protective of seedling emergence and vegetative vigour effects.

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

No further data was submitted. HSE considers there are no data gaps for the ecotoxicology assessment of cinmethylin, noting the endocrine disruption assessment is ongoing and not complete.

### 2.9.8. Summary of effects on biological methods for sewage treatment

The toxicity study conducted testing the active is summarised in table 2.9.8-1 below.

Table 2.9.8-1: Endpoints for activated sludge exposed to cinmethylin

Test item	Test system	Endpoint (mg a.s./L)	Reference
Cinmethylin	Activated sludge respiration inhibition	EC <sub>50</sub> (3h) > 1000	Hammer (2016a)

### 2.9.9. Summary of product exposure and risk assessment

#### 2.10.9.1. Risk assessment for birds and mammals

##### Birds

The results of the risk assessments of the active substance for its representative formulation are summarised here. Risk assessments were conducted according to EFSA Bird and Mammal Guidance Document (2009).

##### Risk assessment for ‘BAS 684 03 H’

The risk to birds from the active substance was assessed based on the proposed use on winter cereals at single application rates of 0.25 and 0.50 kg a.s./ha for both BBCH ranges of bare soil (00-09) and early growth (10-29).



Risk assessment was also conducted for winter oil seed rape for bare soil at BBCH 00-09 and 10-18 at the single application rate of 0.25 kg a.s./ha.

The acute risk to birds from cinmethylin was shown to be acceptable at the screening step. For bare soil at 1 x 250 g a.s./ha the DDD=6.325 mg/kg bw/d and TER >597. For bare soil at 1 x 500 g a.s./ha the DDD=12.65 mg/kg bw/d and TER>298.5. For cereals at 1 x 250 g a.s./ha the DDD=39.7 mg/kg bw/d and TER>95.1. For cereals at 1 x 500 g a.s./ha the DDD=79.40 mg/kg bw/d and TER>47.6. Finally for oil seed rape at 1 x 250 g a.s./ha the DDD=39.7 mg/kg bw/d and TER>95.1. The acute trigger was 10.

The chronic risk to birds from cinmethylin was shown to be acceptable at the screening step. For bare soil at 1 x 250 g a.s./ha the DDD=1.51 mg/kg bw/d and TER=65.61. For bare soil at 1 x 500 g a.s./ha the DDD=3.02 mg/kg bw/d and TER=32.8. For cereals at 1 x 250 g a.s./ha the DDD=8.59 mg/kg bw/d and TER=11.54. For cereals at 1 x 500 g a.s./ha the DDD=17.17 mg/kg bw/d and TER=5.8. Finally for oil seed rape at 1 x 250 g a.s./ha the DDD=8.59 mg/kg bw/d and TER=11.54. The long-term trigger was 5.

### **Secondary poisoning**

The risk to birds from consuming fish contaminated with cinmethylin was acceptable (DDD = 3.03 mg/kg bw/d and TER=32.74).

The risk to birds from consuming earthworms contaminated with cinmethylin was initially unacceptable when the worst case calculated Bioconcentration factor of 67.34 was used in the risk assessment. The long-term trigger was 5. For cereals at 1 x 500 g a.s./ha the DDD=46.81 mg/kg bw/d and TER=2.12. For bare soil, cereals and oilseed rape at 1 x 250 g a.s./ha the DDD=23.40 mg/kg bw/d and TER=4.24. The Applicant proposed higher tier refinements including a new earthworm bioconcentration study which was considered acceptable and the refined BCF endpoint of 1.12 was used to refine the failing TER values. For cereals at 1 x 500 g a.s./ha the DDD=0.778 mg/kg bw/d and TER=127.38. For bare soil, cereals and oilseed rape at 1 x 250 g a.s./ha the DDD=0.390 mg/kg bw/d and TER=254.10.

### **Drinking water**

Acceptable acute and chronic risks for exposure of birds to cinmethylin via drinking water were established for the puddle scenario.

### **Metabolite risk assessment**

Cinmethylin metabolites formed in plant metabolism studies at >10% in wheat and oil seed rape were M684H005 and M684H006 and since these were not found in hen metabolism studies, further consideration of the risk to birds was required.

It was confirmed by an HSE Toxicologist that the conjugation with glycosides reaction is not one of the main biotransformation steps proposed in the studies conducted on rats which was why metabolites M684H005 and M684H006 do not occur. The HSE Residues specialist confirmed the same with regards to hens and goats.

The Applicant proposed that when M684H005 and M684H006 are consumed they would be hydrolysed to M684H002 which is considered to be chemically similar to the two plant metabolites in question which HSE agreed with. The Applicant proposes that metabolite M684H002 is considered to be covered by the active substance data. The HSE Residues Specialist agreed that metabolites considered to be M684H002-related are present in hen metabolic pathways. These are namely M684H001, M684H010, M684H059, M684H011, M684H021 and M684H027; all found in hen egg yolk, egg white, hen muscle, fat and liver.

Therefore, although M684H002 has not been specifically detected in the hen metabolism studies there is evidence to support its presence in hens dosed with the active substance and also that it is metabolised to other downstream metabolites that have been detected. Therefore, the toxicity of M684H002 is potentially covered by active substance toxicity data in birds. Therefore the active substance toxicity endpoint was used when assessing the risk from these metabolites.

Data from HSE evaluated residues trials conducted on oilseed rape and wheat were used in the risk assessment. The trials measured concentrations of M684H005 and M684H006 summed and the maximum measured values were used in the assessment as a worst-case approach; 4.40 mg/kg for wheat and 1.5 mg/kg for oilseed rape.

Both of these identified metabolites have a calculated log Pow of < 3, as such a low risk to birds from these metabolites via secondary poisoning would be expected and no further assessment of the risk is required.

The residue trial data being incorporated in the risk assessment involved the maximum application rate proposed for cereals (500g a.s./ha) and oilseed rape (250g a.s./ha). Since there was no available residue data for bare soils, the value for the trials on cereals (wheat) was used as the maximum application rate for bare soils is in line with that used in these trials (i.e. 500g a.s./ha).

For bare soil, cereals and oil seed rape the acute risk assessment was acceptable at the screening step. For bare soil, the DDD=1.232 mg/kg bw/d and TER>3064. For the cereals the DDD=9.944 mg/kg bw/d and TER>379.7. For the oilseed rape the DDD=3.39 mg/kg bw/d and TER>1113.9. The acute trigger was 10.

For bare soil, cereals and oil seed rape the chronic risk assessment was acceptable at the screening step. For bare soil, the DDD=1.232 mg/kg bw/d and TER= 80.4. For the cereals the DDD=9.944 mg/kg bw/d and TER= 10. For the oilseed rape the DDD=3.39 mg/kg bw/d and TER= 29.2. The chronic trigger was 5.

#### **Isomeric ratio of cinmethylin and metabolite M684H005 (all non-target organism groups)**

Residues studies with cinmethylin and metabolite M684H005 have indicated that that ratios of the isomers (active and metabolite) formed change over time. Further consideration demonstrated an acceptable risk for the proposed uses for all non-target organism groups (see vol 1, section 2.12.7 for full details).

#### **Overall conclusion for the risk to birds from ‘BAS 684 03 H’**

The risk to birds from ‘BAS 684 03 H’ is considered to be acceptable for the proposed uses.

#### **Mammals**

The results of the risk assessments of the active substance for its representative formulation are summarised here. Risk assessments were conducted according to EFSA Bird and Mammal Guidance Document (2009).

#### **Risk assessment for ‘BAS 684 03 H’**

The risk to mammals from the active substance was assessed based on the proposed use on winter cereals at single application rates of 0.25 and 0.50 kg a.s./ha for both BBCH ranges of bare soil (00-09) and early growth (10-29). Risk assessment was also conducted for winter oil seed rape for bare soil at BBCH 00-09 and 10-18 at the single application rate of 0.25 kg a.s./ha.

The acute risk to mammals from cinmethylin was shown to be acceptable at the screening step. For bare soil at 1 x 250 g a.s./ha the DDD=3.6 mg/kg bw/d and TER >555.6. For bare soil at 1 x 500 g a.s./ha the DDD=7.2 mg/kg bw/d and TER>277.8. For cereals at 1 x 250 g a.s./ha the DDD=29.6 mg/kg bw/d and TER>67.6. For cereals at 1 x 500 g a.s./ha the DDD=59.20 mg/kg bw/d and TER>33.8. Finally for oil seed rape at 1 x 250 g a.s./ha the DDD=29.60 mg/kg bw/d and TER>67.6. The acute trigger was 10.

The chronic risk to mammals from cinmethylin was shown to be acceptable at the screening step for all uses at the lower application rate of 1 x 250 g a.s./ha. For bare soil at 1 x 250 g a.s./ha the DDD=0.87 mg/kg bw/d and TER=66.32. For bare soil at 1 x 500 g a.s./ha the DDD=1.75 mg/kg bw/d and TER=33.14. For cereals at 1 x 250 g a.s./ha the DDD=6.40 mg/kg bw/d and TER=9.1. For oil seed rape at 1 x 250 g a.s./ha the DDD=6.40 mg/kg bw/d and TER=9.06. For the higher application rate of 500 g a.s./ha on cereals, the screening step risk assessment failed with a DDD=12.8 mg/kg bw/d and TER=4.5 and therefore below the long-term trigger of 5. This was resolved at Tier 1 however with DDDs ranging from 0.5-5.9 mg/kg bw/d and TERs ranging from 9.8-115.

**Secondary poisoning**

The risk to mammals from consuming fish contaminated with cinmethylin was acceptable (DDD=2.70 mg/kg bw/d and TER=21.46).

The risk to mammals from consuming earthworms contaminated with cinmethylin was initially unacceptable when the worst case calculated Bioconcentration factor of 67.34 was used in the risk assessment. The long-term trigger was 5. For cereals at 1 x 500 g a.s./ha the DDD=57.06 mg/kg bw/d and TER=1.02. For bare soil, cereals and oilseed rape at 1 x 250 g a.s./ha the DDD=28.53 mg/kg bw/d and TER=2.03. The Applicant proposed higher tier refinements including a new earthworm bioconcentration study which was considered acceptable and the refined BCF endpoint of 1.12 was used to refine the failing TER values. For cereals at 1 x 500 g a.s./ha the DDD=0.948 mg/kg bw/d and TER=61.18. For bare soil, cereals and oilseed rape at 1 x 250 g a.s./ha the DDD=0.475 mg/kg bw/d and TER=122.11.

**Drinking water**

Acceptable acute and chronic risks for exposure of birds to cinmethylin via drinking water were established for the puddle scenario.

**Metabolite risk assessment**

Cinmethylin metabolites formed in plant metabolism studies at >10% in wheat and oil seed rape were M684H005 and M684H006 and since these were not found in rat metabolism studies, further consideration of the risk to mammals was required.

It was confirmed by an HSE Toxicologist that the conjugation with glycosides reaction is not one of the main biotransformation steps proposed in the studies conducted on rats which was why metabolites M684H005 and M684H006 do not occur. The HSE Residues specialist confirmed the same with regards to hens and goats.

The Applicant proposed that when M684H005 and M684H006 are consumed they would be hydrolysed to M684H002 which is considered to be chemically similar to the two plant metabolites in question which HSE agreed with. The Applicant proposes that metabolite M684H002 is considered to be covered by the active substance data.

HSE Toxicologists agreed with this proposal due to the structural similarity between M684H002 and metabolite M684H012 which is a major rat metabolite in bile. Therefore M684H002 is considered to be supported by information on M684H012 which is covered by the active substance data. Consequently this suggests that the active substance mammalian endpoints and risk assessment will cover the dietary risk to mammals from M684H005 and M684H006. Therefore the active substance toxicity endpoint was used when assessing the risk from these metabolites.

Data from HSE evaluated residues trials conducted on oilseed rape and wheat were used in the risk assessment. The trials measured concentrations of M684H005 and M684H006 summed and the maximum measured values were used in the assessment as a worst-case approach; 4.40 mg/kg for wheat and 1.5 mg/kg for oilseed rape.

Both of these identified metabolites have a calculated log Pow of < 3, as such a low risk to mammals from these metabolites via secondary poisoning would be expected and no further assessment of the risk is required.

The residue trial data being incorporated in the risk assessment involved the maximum application rate proposed for cereals (500g a.s./ha) and oilseed rape (250g a.s./ha). Since there was no available residue data for bare soils, the value for the trials on cereals (wheat) was used as the maximum application rate for bare soils is in line with that used in these trials (i.e. 500g a.s./ha).

For bare soil, cereals and oil seed rape the acute risk assessment was acceptable at the screening step. For bare soil, the DDD=0.748 mg/kg bw/d and TER>2673. For the cereals the DDD=5.852 mg/kg bw/d and TER>341. For the oilseed rape the DDD=1.995 mg/kg bw/d and TER>1003. The acute trigger was 10.

For bare soil, cereals and oil seed rape the chronic risk assessment was acceptable at the screening step. For bare soil, the DDD=0.748 mg/kg bw/d and TER= 77.5. For the cereals the DDD=5.852 mg/kg bw/d and TER= 9.91. For the oilseed rape the DDD=1.995 mg/kg bw/d and TER= 29.1. The chronic trigger was 5.

### **Overall conclusion for the risk to mammals from ‘BAS 684 03 H’**

The risk to mammals from ‘BAS 684 03 H’ is considered to be acceptable for the proposed uses.

### **2.9.9.2. Risk assessment for aquatic organisms**

#### **Cinmethylin assessment:**

The results of the risk assessments for the active cinmethylin are summarised below for spray drift and drainflow exposure respectively. Risk assessments were conducted according to the guidance document EFSA (2013). For additional information regarding the details of a specific risk assessment see the relevant CP dossier, Section B.9.4.

Table 2.9.9.2-1: Aquatic organisms: acceptability of risk (PEC/RAC < 1) for cinmethylin for each organism group based on standard worst-case calculations for proposed use

Group		Fish acute	Fish chronic	Invertebrate acute		Invertebrate chronic	Algae	Higher-Plant
Test species		<i>C. carpio</i>	<i>P. promelas</i>	<i>D. magna</i>	<i>C. lugubris</i>	<i>D. magna</i>	<i>P. subcapitata</i>	<i>L. gibba</i>
Endpoint (µg a.s./L)		LC <sub>50</sub> 5750	NOEC 590	EC <sub>50</sub> 7260	LC <sub>50</sub> >2060	NOEC 290	E <sub>r</sub> C <sub>50</sub> 23040	E <sub>r</sub> C <sub>50</sub> 88.8
AF		100	10	100	100	10	10	10
RAC (µg a.s./L)		57.5	59	72.6	20.6	29	2304	8.88
Entry pathway / Buffer zone [m] / season	PEC <sup>gl-sw</sup> <sub>max</sub> (µg a.s./L)	PEC/RAC (= ETR)						
Spray drift Standard distance (1 m)	4.617	0.080	0.078	0.0636	0.2241	0.159	0.002	0.520
Drain flow	26.923	0.468	0.456	0.371	1.307	0.928	0.012	3.032

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration; PEC/RAC ratios above the relevant trigger of 1 are shown in **bold**; Shaded RAC indicates study was considered as supporting information due to issues confirming validity criteria. This risk assessment has been included as illustrative due to the species potentially being more sensitive than the valid standard study testing *Daphnia magna*.

Based on the above assessment an acceptable risk from spray drift exposure was demonstrated for the proposed use without mitigation measures. However, higher tier consideration of drainflow is required for aquatic invertebrates and plants.

#### **Higher tier drain flow consideration:**

The applicant submitted higher tier drain flow modelling using WEBFRAM and MACRO (evaluated in the fate CP dossier, section 8.4).

Following ecotoxicology consideration an acceptable risk was demonstrated for all uses and organisms (see CP dossier section 9 for details).

Metabolites of cinmethylin:

The risk assessment for the ecotoxicologically relevant metabolites of cinmethylin (M684H001 and M684H003) has been summarised below (see table 2.10.9.2-2). It should be noted two of the studies were only considered suitable as supporting information (these have been highlighted below see shaded columns).

Table 2.9.9.2-2: Aquatic organisms: acceptability of risk (PEC/RAC < 1) for cinmethylin metabolites for each organism group based on standard worst-case calculations for proposed use

Group	Exposure	Fish (Acute)	Inverteb. acute		Aquatic plants	
Test species		<i>O. mykiss</i>	<i>D. magna</i>		<i>L. gibba</i>	
Metabolite:		M684H003	M684H001	M684H003	M684H001	M684H003
Endpoint (µg metabolite/L)		LC <sub>50</sub> >1000000	EC <sub>50</sub> >100000	EC <sub>50</sub> 840000	ErC <sub>50</sub> >78300	ErC <sub>50</sub> >100000
AF		100	100	100	10	10
RAC (µg metabolite/L)		10000	1000	8400	7830	10000
Spray drift entry / Buffer zone [m]	PEC <sub>sw-ini</sub> (µg metabolite/L)	PEC/RAC (= ETR)				
M684H001 standard distance (1 m)	0.584	--	0.000584	--	0.0000746	--
M684H003 standard distance (1 m)	0.318	0.0000318	--	0.0000378	--	0.0000318
M684H001 Drainage	3.404	--	0.003404	--	0.0004347	--
M684H003 Drainage	1.856	0.0001856	--	0.000221	--	0.0001856

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentrations, -- = not applicable as different metabolite PEC

Shaded RAC indicates study was considered as supporting information due to issues confirming analytical method was sufficiently validated.

It was noted that no algal studies testing the relevant metabolites were submitted. However, the PEC / RAC ratios based on the PEC<sub>sw, ini</sub> and the RAC<sub>ppp</sub> values indicate an acceptable risk to aquatic organisms with a wide margin of safety (minimum factor of x 294). In addition, it was noted that the exposure concentrations for both metabolites based on spray drift are within those for the parent cinmethylin where an acceptable risk was demonstrated. When considering drainage exposure values these are within the parent by a significant amount (minimum factor of x8) at first tier, which when considering the parent toxicity (cinmethylin) would result in an acceptable risk. Given the available data for aquatic organisms demonstrates the metabolites are less toxic than cinmethylin this further supports an acceptable risk for the metabolites. No further consideration of metabolites is required.

Cinmethylin formulation assessment:

The risk assessment for the representative formulation is shown below.

Table 2.9.9.2-3: Formulation risk assessment: ( $PEC_{sw, ini} / RAC_{ppp} < 1$ ) for each organism group based on  $PEC_{sw, ini}$  values resulting from spray drift entry of the formulation after application of cinmethylin for the proposed use

Group	Exposure	Fish (Acute)	Inverteb. acute	Algae	Aquatic plants
Test species		<i>O. mykiss</i>	<i>D. magna</i>	<i>P. subcapitata</i>	<i>L. gibba</i>
Endpoint ( $\mu\text{g product/L}$ )		LC <sub>50</sub> 5860	EC <sub>50</sub> 14500	E <sub>r</sub> C <sub>50</sub> 26300	E <sub>r</sub> C <sub>50</sub> 167
AF		100	100	10	10
RAC ( $\mu\text{g product/L}$ )		58.6	145	2630	16.7
Spray drift entry / Buffer zone [m]	$PEC_{sw-ini}$ ( $\mu\text{g product/L}$ )	PEC/RAC (= ETR)			
standard distance (1 m)	6.149	0.105	0.042	0.002	0.368

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentrations

The PEC / RAC ratios based on the  $PEC_{sw, ini}$  and the  $RAC_{ppp}$  values indicate an acceptable risk to aquatic organisms at a standard distance of 1 m for the proposed uses of the representative formulation 'BAS 684 03 H'.

#### **Overall conclusion for risk to aquatic organisms:**

An acceptable risk to aquatic organisms for the proposed uses can be concluded.

#### ***2.9.9.3. Risk assessment for bees***

##### **Risk assessment for 'BAS 684 03 H'**

The acute risk to adult honeybees was assessed in accordance with the SANCO Terrestrial guidance document (SANCO/10329/2002). The critical acute contact and oral LD<sub>50</sub> values were compared with the maximum individual application rate for the representative uses to derive a Hazard Quotient (HQ) for each exposure route. HQ values of  $\leq 50$  indicate a low acute risk to honeybees. For the proposed use of the representative formulation 'BAS 684 03 H', HQs for the formulation and active substance fell well below the trigger of 50, indicating an acceptable acute risk to bees. The acute contact and oral risk assessments are summarised below:

Table 2.9.9.3-1: HQ calculations for honeybees for the proposed use of 'BAS 684 03 H'

Test substance	Application rate [g/ha]	Endpoint	LD <sub>50</sub> [ $\mu\text{g/bee}$ ]	Hazard quotient HQ	Trigger
<b>Risk assessment on adult honeybees</b>					
BAS 684 H	500	48 h oral	> 200.0	< 2.5	50
		48 h contact	> 200.0	< 2.5	
BAS 684 02 H	679.32 <sup>1</sup>	48 h oral	> 294.7	< 2.3	
		48 h contact	> 272.0	< 2.5	

<sup>1</sup> Taking into account the density of BAS 684 02 H of 1.020 g/cm<sup>3</sup>.

<sup>2</sup> Risk assessment conducted with differing formulation is more worst case than the risk from the representative formulation.

Bumblebee and chronic honeybee endpoints were available in addition to those above. These have not been used in the risk assessment due to a current lack of agreed guidance. However, they did not indicate a likelihood of the active substance being toxic to bees.

#### 2.9.9.4. Risk assessment for other non-target arthropods

##### Risk assessment for 'BAS 684 03 H'

The risk assessment for non-target arthropods other than bees was conducted in accordance with ESCORT 2. The proposed uses of 'BAS 684 03 H' are as a spray treatment on bare soil, cereal crops and oil seed rape with a worst-case application rate of 1 application of 0.666 L product/ha. The tier 1 endpoints available for *A. rhopalosiphi* and *T. pyri* were used in the first tier in- and off-field risk assessment. All endpoints passed the off-field assessment, but one endpoint from the *A. rhopalosiphi* study failed the in-field assessment and required further data on that and one additional species. The risk assessment is summarised below:

Table 2.9.9.4-1: Tier 1 off-field risk assessment for non-target arthropods exposed to 'BAS 684 03 H'

Species	LR <sub>50</sub> [L/ha]	PER <sub>off-field</sub> [L/ha]	Correction factor	HQ <sub>off-field</sub>	Trigger value
<i>Aphidius rhopalosiphi</i> , Tier I, 2D exposure scenario	0.136	0.00184	10	0.135	2
<i>Typhlodromus pyri</i> , Tier I, 2D exposure scenario	0.764			0.024	2

Table 2.9.9.4-2: Tier 1 in-field risk assessment for non-target arthropods exposed to 'BAS 684 03 H'

Species	LR <sub>50</sub> [L/ha]	PER <sub>in-field</sub> [L/ha]	HQ <sub>in-field</sub>	Trigger value
<i>Aphidius rhopalosiphi</i> , Tier I, 2D exposure scenario	0.136	0.666	<b>4.897</b>	2
<i>Typhlodromus pyri</i> , Tier I, 2D exposure scenario	0.764		0.872	2

PER = predicted environmental rate.

HQ values shown in **bold** is above the relevant trigger.

The in-field HQ for *A. rhopalosiphi* exceeds the trigger of 2, therefore further consideration was required (see table below) which involved tier II studies with *A. rhopalosiphi* and additional species; *Aleochara bilineata*.

Table 2.9.9.4-3: Lethal and sublethal effect levels for non-target arthropods exposed to BAS 684 03 H in winter wheat (worst case use)

Species	LR <sub>50</sub> [L/ha]	ER <sub>50</sub> [L/ha]	PER <sub>in-field</sub> [L/ha]
<i>Aphidius rhopalosiphi</i> , Tier II, 3D exposure scenario	> 0.7	> 0.7	0.666
<i>Aleochara bilineata</i> , Tier II, 2D exposure scenario	n.d.	> 1.4	

PER = predicted environmental rate.

n.d. = not determined.

Based on the reported values, the 50% effect levels for both non-target arthropod species are greater than the in-field PER. Therefore, it is concluded that there is a low in-field risk to non-target arthropods following application of 'BAS 684 03 H' to winter wheat and oilseed rape.

#### 2.9.9.5. Risk assessment for non-target soil meso and macrofauna

The risk assessment is performed according to the Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC (SANCO/10329/2002 rev 2 final). The standard risk assessment is based on TER values. If the long-term TER is below 5 further consideration of the risk is required. The toxicity endpoints have been corrected by a factor of 2 where the Log P<sub>ow</sub> of the relevant substance is below 2 (this applies to the active substance). This is shown in table 2.10.9.5-1. It should be noted no relevant soil metabolites were identified.

Table 2.9.9.5-1 Chronic risk to earthworms and other soil macro-organisms from ‘worst case’ GAP (single application at 500 g a.s./ha to winter cereals).

Test organism	Test substance	Toxicity endpoint# (mg a.s./kg dws)	PECsoil (mg a.s./kg dws)	TER	Trigger
<i>Eisenia fetida</i>	Cinmethylin	41.8	0.667	63	5
<i>Eisenia fetida</i>	BAS 684 03 H	43.6	0.667	65	5
<i>Folsomia candida</i>	BAS 684 03 H	67.0	0.667	100	5
<i>Hypoaspis aculeifer</i>	BAS 684 03 H	102.0	0.667	153	5

# Most conservative value of either NOEC or EC<sub>10</sub>, noting endpoints have been corrected by factor of 2 as log<sub>pow</sub> > 2)

\* There is uncertainty when using these study endpoints. As cinmethylin is volatile and analytical measurements were not taken during the laboratory studies.

The resulting TER values for all organisms are above the trigger value of 5 for the formulated product and the active substance (earthworm only). In the absence of studies the risk from cinmethylin to *Folsomia candida* and *Hypoaspis aculeifer* could not be assessed. However, given the representative formulation contains a single active it is likely the formulation assessment is protective of the risk from the active. Furthermore, there was a wide margin of safety at first tier based on the formulation assessment and the active would have to be at least 13 times more toxic to demonstrate a potential risk. Therefore, the HSE evaluator considers the formulation studies can be used to address the risk from the active.

Whilst the above assessment demonstrates acceptable risk there is uncertainty regarding the extent of exposure in these studies and hence the endpoints have the potential to underestimate the toxicity. This has been considered further below (for full details refer to volume 3 CP section 9 dossier).

#### Consideration of potential volatilisation:

The soil toxicity studies provided (Friedrich (2016a; 2017a; 2018a) and Schulz (2017a)) were conducted to the following OECD guidelines; 222, 226 and 232 which state: ‘For volatile, unstable or readily degrading substances (e.g. data generated from a TG 307 study may be considered), or where there is otherwise uncertainty in maintaining the nominal soil concentration, analytical measurements of the exposure concentrations at the beginning, during and at the end of the test should be considered.’ As detailed in the chemistry dossier (volume 3, CA section 2) the vapour pressure of cinmethylin is 8.1 x 10<sup>-3</sup> Pa at 20 °C suggesting there is potential for volatilisation. Two environmental fate studies that investigated volatilisation were considered. Based on the study Stewart & Abernathy, 2016a there is evidence to support that when cinmethylin is mixed into soil the loss from volatilisation appears to be relatively minor (maximum 15.6 % loss) compared to that observed in Hassink 2017b study where spray application was used (73 % loss). It should be noted there were uncertainties with both studies that have been discussed in detail in section B.9.8, volume 3, CP section 9 dossier.

When considering the quantitative ecotoxicology risk assessment (table 2.9.9.5-1) there was a margin of safety for all soil macro-organisms (minimum of 12.6). The worst case endpoint based on the available data was the active study testing earthworms with a corrected endpoint of 41.8 mg a.s./kg dry soil. Using this endpoint if there was a 91.8 % loss of cinmethylin during the toxicity study an acceptable risk would still be demonstrated i.e. an endpoint of 3.4 mg a.s./kg dry soil with a PEC of 0.667 mg a.s./kg dry soil results in a TER of 5.1. A loss from volatilisation of 91.8 % is likely to be unrealistic when considering the study Stewart & Abernathy, 2016a, where volatiles were measured and the maximum loss was 15.6 %. In addition, the fate exposure PEC value is a worst case maximum and does not allow for volatilisation. Therefore, it could be argued that comparing an initial PEC<sub>soil</sub> with an initial ecotoxicity endpoint is justified. This is because initial equivalent values would be compared, noting this relies on similar rates of loss following peak exposure. Finally, whilst there are uncertainties when comparing to ecotoxicity studies, the supporting information from the aerobic fate soil



degradation study (Stewart & Abernathy, 2016a) suggests that when cinmethylin is mixed into soil loss from volatilisation is low.

Overall, based on the available information the HSE ecotoxicology evaluator considers an acceptable risk to earthworms and other soil macro-organisms can be concluded for the proposed uses.

#### 2.9.9.6. Risk assessment for soil micro-organisms

The risk assessment is performed according to the Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC (SANCO/10329/2002 rev 2 final). The magnitude of effect is compared to the untreated control. PEC<sub>soil</sub> values have been compared to concentrations at which < 25 % effects on nitrogen transformation were observed in Table 2.10.9.6-1

Table 2.9.9.6-1: Risk to soil micro-organisms from ‘worst case’ GAP (single application at 500 g a.s./ha to winter cereals).

Test substance	Test design	<25 % effects concentration (mg a.s./kg dws)	PEC <sub>soil</sub> (mg a.s./kg dws)	Acceptable risk?
Cinmethylin	Nitrogen transformation 28 d	7.17	0.667	Yes
BAS 684 03 H		4.92	0.667	Yes

The comparison of the initial maximum PEC<sub>soil</sub> for the worst-case use with the nitrogen transformation study results indicates less than 25 % effects would be expected to occur for all representative uses from the active substance and formulated product. An acceptable risk to soil micro-organisms is therefore concluded.

Whilst the above assessment demonstrates acceptable risk there is uncertainty regarding the extent of exposure in these studies and hence the endpoints have the potential to underestimate the toxicity. This has been considered further below.

#### Consideration of potential volatilisation:

The nitrogen transformation rate studies provided Schulz (2016a and 2017b)) were conducted according to OECD 216 which states the following steps should be taken when assessing volatile substances:

- When testing volatile chemicals, losses during treatment should be avoided as far as possible and an attempt should be made to ensure homogeneous distribution in the soil (e.g. the test substance should be injected into the soil at several places).
- When volatile substances are tested, sealable and gas-tight containers should be used. These should be of a size such that approximately one quarter of their volume is filled with the soil sample.
- Incubation of soil samples can be performed in two ways: as bulk samples of each treated and untreated soil or as a series of individual and equally sized subsamples of each treated and untreated soil. However, when volatile substances are tested, the test should only be performed with a series of individual subsamples.

As detailed in the chemistry dossier (volume 3, CA section 2) the vapour pressure of cinmethylin is  $8.1 \times 10^{-3}$  Pa at 20 °C suggesting there is potential for volatilisation. Two environmental fate studies that investigated volatilisation were considered. Based on the study Stewart & Abernathy, 2016a there is evidence to support that when cinmethylin is mixed into soil the loss from volatilisation appears to be relatively minor (maximum 15.6 % loss) compared to that observed in Hassink 2017b study where spray application was used (73 % loss). It should be noted there were uncertainties with both studies that have been discussed in detail in section B.9.10, volume 3, CP section 9 dossier.

Nonetheless, when considering the quantitative ecotoxicology risk assessment (table 2.9.9.6-1) there was a margin of safety for all soil micro-organisms (minimum of 7.4). The worst case endpoint based on the available data was the active study testing soil micro-organisms with an endpoint of 4.92 mg a.s./kg dry soil. Using this endpoint if there was a 86.4 % loss of cinmethylin during the ecotoxicity study an acceptable risk would still be demonstrated i.e. an endpoint of 0.667 mg a.s./kg dry soil compared with a PEC of 0.667 mg a.s./kg dry soil. A loss from volatilisation of 86.4 % is likely to be unrealistic when considering the study Stewart & Abernathy, 2016a, where volatiles were measured and the maximum loss was 15.6 %. In addition, the fate exposure PEC value is a worst case maximum and does not allow for volatilisation. Therefore, it could be argued that

comparing an initial  $PEC_{soil}$  with an initial ecotoxicity endpoint is justified. This is because initial equivalent values would be compared, noting this relies on similar rates of loss following peak exposure. Finally, whilst there are uncertainties when comparing to ecotoxicity studies, the supporting information from the aerobic fate soil degradation study (Stewart & Abernathy, 2016a) suggests that when cinmethylin is mixed into soil loss from volatilisation is low.

Overall, based on the available information the HSE ecotoxicology evaluator considers an acceptable risk to soil micro-organisms can be concluded for the proposed uses.

#### 2.9.9.7. Risk assessment for terrestrial non-target higher plants

##### Spray drift:

The risks to non-target plants were determined based on the Working Document for terrestrial ecotoxicology, SANCO 10329/2002 rev 2 final and are shown in tables 2.9.9.7-1 (seedling emergence) and 2.9.9.7-2 (vegetative vigour) below for the risk from spray drift. Only the most sensitive species has been shown, for full details refer to CP, section 9 dossier.

Table 2.9.9.7-1: Post emergence TER values (seedling emergence)

Crop use	Species	ER <sub>50</sub> (g a.s./ha)	Off-field exposure			Trigger value
			Distance m	PER g a.s./ha	TER	
Winter wheat	ryegrass	31.3	1	13.85	<b>2.26</b>	5
Winter oilseed rape	ryegrass	31.3	1	6.93	<b>4.52</b>	5

PER = predicted environmental rate at highest application rate, bold value indicates below trigger value

Table 2.9.9.7-2: Post emergence TER values (vegetative vigour)

Crop use	Species	ER <sub>50</sub> (g a.s./ha)	Off-field exposure			Trigger value
			Distance m	PER g a.s./ha	TER	
Winter wheat	ryegrass	523.3	1	13.85	38	5
Winter oilseed rape	ryegrass	523.3	1	6.93	76	5

PER = predicted environmental rate at highest application rate

All TER values for vegetative vigour are above the trigger value indicating an acceptable risk for the proposed use. For the seedling emergence assessment TER values are above the trigger of 5 for all tested plant species (see CP dossier section 9 for full details) except for ryegrass. Thus, further consideration is required.

As refinement option, a probabilistic risk assessment approach based on SSD data was proposed using a median  $HC_5$  value. However, the use of a median  $HC_5$  was rejected due to wide confidence limits, inclusion of unbound values and differences in sensitivities between groups (monocotyledons were more sensitive than dicotyledons based on the available data). To allow for these uncertainties the lower 90 % confidence limit  $HC_5$  (for monocotyledons) was used in the refined risk assessment. It should be noted this results in an endpoint lower than that considered in the first tier risk assessment and therefore does not address the risk as demonstrated below.

Table 2.9.9.7-3: Post emergence TER values (seedling emergence) using SSD endpoint (lower HC<sub>5</sub> 90 % confidence interval)

Crop use	Species tested	#HC <sub>5</sub> (g a.s./ha)	Off-field exposure			Trigger value
			Distance m	PER g a.s./ha	TER	
Winter wheat	SSD	1.25	1	13.85	<b>0.09</b>	1
			5	2.85	<b>0.44</b>	1
Winter oilseed rape	SSD	1.25	1	6.93	<b>0.18</b>	1
			5	1.43	<b>0.87</b>	1

PER = predicted environmental rate at highest application rate, bold value indicates below trigger value

# = Lower 90 % confidence interval, bold value indicates TER is below trigger value.

As the risk from spraydrift for the proposed use was not resolved the following label mitigation is required:

**‘Extreme care must be taken to avoid spray drift onto non-crop plants outside of the target area.’**

Given cinmethylin exceeds the trigger for volatilisation (environmental fate data requirement 7.3.2, 283-2013), the risk from volatilisation has been considered below. This includes consideration of phytotoxicity given the active is a herbicide.

#### Risk assessment (Volatilisation):

As detailed in the environmental fate dossier (volume 3, CA) volatilisation of cinmethylin requires further consideration based on vapour pressure exceeding triggers of  $V_p = 10^{-5}$  Pa (plant) or  $10^{-4}$  Pa (soil) at 20°C as outlined in 283/2013 data requirements. Therefore, the applicant submitted a wind tunnel study further investigating volatilisation that has been evaluated in the fate dossier (Wallace (2017a), section B.8.3.2, volume 3, CA dossier). It is noted that biological assessments were not made during the study, ideally ryegrass (most sensitive species based on available laboratory data) should have been exposed and any phytotoxicity recorded. Therefore the laboratory studies were considered and an NOER of 21.9 ml product/ha equivalent to 16.1 g a.s./ha based on phytotoxicity derived.

There is no agreed risk assessment scheme for the evaluation of the risk to non-target plants from volatilisation. Given the lack of an agreed scheme and difficulties incorporating the exposure based on air concentration, the HSE evaluator has focused on the aqueous deposition values determined in the wind tunnel study (Wallace (2017a)) to consider the risk from volatilisation, noting as shown in table B.9.12-7 there will be some exposure via air.

Based on the deposition values the maximum was 0.82 % at a 1-meter distance and 0.43 % at 5 meters. This has been considered in a quantitative assessment below for the proposed use. The quantitative assessment has been based on the first-tier assessment for spray drift using the derived NOER based on phytotoxicity. The risk assessment is shown in the table below.

Table 2.9.9.7-4: Volatilisation TER values, using phytotoxicity endpoint and wind tunnel study to derive exposure.

Crop use	NOER based on phytotoxicity (g a.s./ha)	Off-field exposure			Trigger value
		Distance m	PER g a.s./ha	TER	
Winter wheat (500 g a.s./ha)	16.1	1	4.10	<b>3.93</b>	5
		5	2.15	7.49	5
Winter oilseed rape (250 g a.s./ha)	16.1	1	2.05	7.85	5

PER = predicted environmental rate at highest application rate, bold value indicates below trigger value

# = Lower 90 % confidence interval, bold value indicates TER is below trigger value.

It should be noted there is no agreed scheme for the assessment of volatilisation to non-target plants, therefore the above assessment has been based on agreed spray drift scheme.

Based on the above assessment the HSE evaluator proposes a **5-metre buffer zone** for the proposed use on **winter wheat** to address the risk from volatilisation to non-target plants. For the proposed use on winter oilseed rape a buffer zone is not required when considering volatilisation. This assessment is not based on an agreed risk assessment scheme but is in-line with UK mitigation for other herbicide products when considering the risk to non-target plants from volatilisation.

#### Overall conclusion for non-target plants:

For both uses the following label mitigation is required to address the risk to non-target plants from spray drift:

**‘Extreme care must be taken to avoid spray drift onto non-crop plants outside of the target area.’**

For the risk from volatilisation an agreed risk assessment scheme is not currently available. However, based on the above assessment a **buffer zone of 5 metres** is recommended by HSE for the proposed use on **winter wheat at 500 g a.s./ha**. A buffer zone is not required for the proposed use on winter oilseed rape (250 g a.s./ha).

#### 2.9.9.8. Risk assessment for effects on biological methods for sewage treatment

Studies are not required for the formulation as only tests conducted with the active substance are considered necessary to assess the potential risk to biological sewage treatment systems. A summary of the toxicity study is shown in the table below.

Table 2.9.9.8-1: Endpoints for activated sludge exposed to cinmethylin

Test item	Test system	Endpoint (mg a.s./L)	Reference
Cinmethylin	Activated sludge respiration inhibition	EC <sub>50</sub> (3h) > 1000	Hammer (2016a)

Treatment rates up to 1000 mg a.s./L diflufenican had no effect on the respiration rate of activated sewage sludge and indicate that microbial activity in these systems is at low risk. The worst-case PEC<sub>sw</sub> was 0.004617 mg a.s./L which is significantly lower than the EC<sub>50</sub> value of > 1000 mg a.s./L.

## 2.10. CLASSIFICATION AND LABELLING

Classification and labelling is currently under evaluation. A mandatory classification and labelling report is being prepared under GB CLP by HSE. Therefore, this section will be completed at a later stage following the aligned evaluation process and when the report is complete.

## 2.11. RELEVANCE OF METABOLITES IN GROUNDWATER

A full summary of all groundwater modelling calculations is presented in section B.8.3 of Volume 3CP, Section 8 of the DAR. All the tier 1 PEC<sub>GW</sub> values resulted in concentrations < 0.1 µg/L for cinmethylin; there were no metabolites of concern. No further consideration of parent is required and there are no groundwater metabolites above the trigger value. Therefore, no relevance assessment required.

## 2.12. CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

### 2.12.1. Identity and physical chemical properties

The active substance cinmethylin consists of two enantiomers in approx. 50:50 ratio, i.e. a racemic mixture. The applicant has stated that both enantiomers are biologically active, with the R(-) enantiomer more biologically active than the S(+) (although S(+) does contribute to biological activity).

Data were provided where the enantiomeric ratio in five batches of cinmethylin technical material were determined using a chiral HPLC method with DAD/UV detection. The results demonstrate the presence of the enantiomers in approx. 50:50 ratio.

### 2.12.2. Methods of analysis

Cinmethylin is manufactured as a 50:50 racemic enantiomer mixture therefore generally enantiomer specific methods of analysis are not required. Methods of analysis used for some data generation studies were enantiomer specific, where it was considered relevant. The methods provided for post authorisation monitoring in soil, sediment and water were also enantiomer specific, however are they not required to be as the associated residue definitions do not require the determination of the separate enantiomers.

### 2.12.3. Mammalian toxicity

Cinmethylin is manufactured and placed on the market as a 50:50 racemic enantiomer mixture consisting of (-)-cinmethylin (Reg.No. 5925581) and (+)-cinmethylin (Reg.No. 5925632). Enantiomer-specific analysis was performed to investigate enantiomer metabolism in plants (carrots, wheat and oilseed rape) and livestock (hen and goat). This demonstrated that changes in the stereoisomeric excess (SE) were > 10 %. All batches used for the new/modern toxicological studies had a racemic composition of approx. 50:50, except for batch COD-001794 (used in the 28-day study in the rat – [REDACTED], 2015), which had an (-)/(+) enantiomer ratio of 70:30. No information on the isomeric ratio was provided for the old studies, but these are either unreliable, supplementary or used in a weight-of-evidence approach with the new/modern studies. There are no studies conducted with the individual enantiomers. In addition, there is no equivalent 28-day rat study performed with racemic cinmethylin for direct comparison with the [REDACTED] (2015) study. Therefore, the results of the [REDACTED] (2015) study have been compared (Table 2.12.3-1) with the findings of the rat 90-day and carcinogenicity studies (c.50:50).

There were no treatment-related effects on mortality, clinical signs of toxicity, food consumption and/or FOB and MA in studies using batches with (-)/(+) enantiomer ratio of 70:30 and c.50:50. An effect on water consumption was revealed in the 28-day study (70:30 used), which was not identified in longer-term studies (90-day and 2-year, 50:50 used). Changes in other toxicological parameters investigated, particularly effects on target organs (liver and thyroid), revealed comparable results across studies and batches. Only effects on the nasal cavities were not identified in the 28-day study (70:30 used) compared to the 90-day and carcinogenicity studies (c.50:50 used). However, this difference is likely to be due to the longer duration of treatment in the studies with racemic cinmethylin. Although a direct quantitative comparison between the studies is not possible as treatment duration and doses employed were different, from the limited information available, it can be concluded that there were no major changes in the toxicological profile of the two different batches with (-)/(+) enantiomer ratio of 70:30 and c.50:50. This suggests that the two enantiomers have similar toxicity and that one is not significantly more toxic than the other.

Additionally, as a (Q)SAR tool, DEREK Nexus was used to predict the toxicity of the two different enantiomers (DocID 2018/1086609, prediction run on 23 April 2018 using Derek Nexus 6.0.1). No alerts were identified for either enantiomers, although the reliability of such predictions for complex toxicity endpoints remains low.

A metabolism study was conducted to determine whether there is any preferential metabolism of the two enantiomers in rats after oral administration ([REDACTED], 2018; described in the Volume 3 CA\_B6 document). These data indicate some preferential metabolism for the (-) enantiomer; the ratio of the (-)/(+) enantiomers shifted from 50:50 towards higher relative amounts of the (+) enantiomer (approximately 30:70). HSE notes that the toxicity data (which support the human risk assessment) generated with racemic cinmethylin would have tested the isomeric ratio of 30:70 (-)/(+) produced *in vivo* in mammals.

Overall, there seems to be a mismatch between the hazard data (what was tested, ie c.50:50) and what consumers are exposed to (between 26:74 and 62:38) with regard to the isomeric composition of cinmethylin. However, the available toxicological data indicate that the two enantiomers have comparable toxicity. Therefore, it is considered that exposure to isomeric ratios different from the tested c.50:50 would have no significant impact on the risk assessment.

Metabolites M684H002, M684H005 and M684H006 also occur in plants as two stereoisomers which result from the same stereogenic element of the parent substance. Noting that i) cinmethylin isomers have comparable toxicity and ii) the toxicity of metabolites M684H002, M684H005 and M684H006 are considered equivalent to and covered by the toxicity data of the parent, consequently, the two isomers of these metabolites are also considered toxicologically equivalent.

**Table 2.12.3-1. Comparison of toxicological data in rats in studies using different batches with different isomeric compositions**

Study		28-day rat ██████, 2015 2015/1076329				90-day rat ██████, 2018a 2014/1228370				2-year rat ██████, 2018 2017/1093414			
Batch (-)/(+) ratio		COD-001794 70:30				COD-001919 51:49				COD-002038 48:52			
Dose	[ppm]	0	1500	5000	15000	0	1000	3000	10000	0	200	1000	5000
	[mg/kg bw/d]	0	137/ 141	477	1522/ 1331	0	67/ 79	211/ 240	792/ 814	0	9/ 11	45/ 59	242/ 317
Mortality		No treatment-related deaths.				No treatment-related deaths.				No treatment-related deaths.			
Clinical signs of toxicity		No treatment-related clinical signs of toxicity.				No treatment-related clinical signs of toxicity.				No treatment-related clinical signs of toxicity.			
FC ♂ day 28	[g]	23.2	23.2	26.0	23.3	23.8	21.5	21.4	24.9	21.1	21.1	21.1	21.7
	[Δ%]	-	0	12.1	0.4	-	-9.7	-10.1	4.4	-	0.2	0.2	7.8
FC ♀ day 28	[g]	15.9	15.9	15.6	15.0	17.4	16.8	21.4	22.6	15.3	14.7	15.3	14.6
	[Δ%]	-	0	-1.9	-5.7	-	-3.7	23.0	29.6	-	-3.6	0.4	-4.7
Food consumption		No treatment-related, adverse effects.				No treatment-related, adverse effects.				No treatment-related, adverse effects.			
Water consumption		There were adverse effects on water consumption from the mid-dose in males and at the top dose in females.				No treatment-related changes were observed.				No treatment-related changes were observed.			
BW ♂ day 28	[g]	293.8	290.9	297.8	262.8	292.9	286.1	282.1	<b>254.7**</b>	288.4	287.2	284.7	<b>274.9**</b>
	[Δ%]	-	-1.0	1.4	-10.6	-	-2.3	-3.7	-13.1	-	-0.4	-1.3	-4.7
BW ♀ day 28	[g]	197.7	192.4	185.5	189.4	185.0	185.1	186.6	<b>170.9*</b>	187.8	185.0	187.7	184.6
	[Δ%]	-	-2.7	-6.2	-4.2	-	0	0.9	-7.6	-	-1.5	-0.1	-1.7
Body weight		Changes in body weight of high dose male rats (1522 mg/kg bw/d) are considered treatment-related and adverse.				Changes in body weight were treatment-related and adverse in the top dose (both sexes).				There were treatment-related and adverse effects on body weight in males and females at the top dose.			
BWC ♂ day 0-28	[g]	141.4	140.8	147.9	<b>111.8*</b>	139.4	130.2	128.1	<b>99.7**</b>	131.4	131.4	129.0	<b>121.3**</b>
	[Δ%]	-	-0.4	4.6	-20.9	-	-6.6	-8.1	-28.5	-	0	-1.8	-7.7
BWC ♀ day 0-28	[g]	62.5	56.4	50.5	55.4	60.4	57.6	59.5	<b>45.5**</b>	66.1	64.7	66.9	63.0
	[Δ%]	-	-9.8	-19.2	-11.4	-	-4.7	-1.5	-24.7	-	-2.1	1.2	-4.7
Body weight gain		Changes in body weight gain of high dose				Changes in body weight gain were treatment-				There were treatment-related and adverse			

Study		28-day rat ██████, 2015 2015/1076329				90-day rat ██████ 2018a 2014/1228370				2-year rat ██████ 2018 2017/1093414			
Batch (-)/(+) ratio		COD-001794 70:30				COD-001919 51:49				COD-002038 48:52			
Dose	[ppm]	0	1500	5000	15000	0	1000	3000	10000	0	200	1000	5000
	[mg/kg bw/d]	0	137/ 141	477	1522/ 1331	0	67/ 79	211/ 240	792/ 814	0	9/ 11	45/ 59	242/ 317
		male rats (1522 mg/kg bw/d) are considered treatment-related and adverse.				related and adverse in the top dose (both sexes).				effects on body weight gain in males and females at the top dose.			
FOB and MA		No treatment-related effects.				No treatment-related effects.				-			
Haematology		There were treatment-related and adverse effects on haematology parameters (reduced prothrombin time and increased monocyte counts) at the top dose.				Treatment-related and adverse effects on prothrombin time were seen from the mid dose.				There were no treatment-related haematology findings.			
Clinical chemistry		Treatment-related and adverse effects on certain clinical chemistry parameters (GGT, protein, globulin, albumin, cholesterol, triglycerides, glucose, calcium), mainly indicative of liver toxicity and alterations in liver metabolism, were seen from the mid dose (477 mg/kg bw/d).				Treatment-related and adverse effects in some clinical chemistry parameters (GGT, CHOL, PROT, ALB, GLOB, ions from the mid dose and GLU, CREAT and TRI at the top dose), indicative of liver toxicity were seen in both sexes from the mid dose.				There was an increase in GGT at the top dose in both sexes.			
Urinalysis		No treatment-related effects.				Changes in males from the mid dose, which were species specific and not relevant to humans.				Changes in males at the top dose, which were species specific and not relevant to humans.			
Organ weight		Treatment-related and adverse effects on organ weight were seen in the liver (both sexes) and kidney (in males) from the mid dose group (477 mg/kg bw/d).				Treatment-related, adverse and human relevant changes in organ weights were seen in the liver from the mid dose in both sexes and in the thyroid at the top dose in both sexes.				Changes in liver weights were considered treatment-related and adverse at the top dose in males and females.			
Gross pathology		Livers of all males and females in the top dose group were enlarged and showed a dark brown discoloration.				At top dose, the livers of 9/10 males and all females showed a dark brown discoloration.				There were no treatment-related gross pathology findings.			
Histopathology		Treatment-related and adverse histopathology was observed in the liver (both sexes), thyroid (both sexes) and kidney (in males) from the mid dose group (477				Treatment-related and adverse histopathological changes were observed in the liver, thyroid and nasal cavity in both sexes from the mid dose.				Treatment-related and adverse non-neoplastic findings were observed in the liver, nasal cavity and thyroid in rats, at both 12 and 24 months, in females at the top dose and in			



Study		28-day rat ██████████, 2015 2015/1076329				90-day rat ██████████, 2018a 2014/1228370				2-year rat ██████████, 2018 2017/1093414			
Batch (-)/(+) ratio		COD-001794 70:30				COD-001919 51:49				COD-002038 48:52			
Dose	[ppm]	0	1500	5000	15000	0	1000	3000	10000	0	200	1000	5000
	[mg/kg bw/d]	0	137/ 141	477	1522/ 1331	0	67/ 79	211/ 240	792/ 814	0	9/ 11	45/ 59	242/ 317
		mg/kg bw/d). The kidney findings are not relevant to humans.								males from the mid dose.			
NOAEL (M/F mg/kg bw/d)		137 / 141				67 / 79				For systemic chronic toxicity 9 (males) 59 (females)			
LOAEL (M/F mg/kg bw/d)		477				211 / 240				45 / 59			

#### 2.12.4. Operator, Worker, Bystander and Resident exposure

As noted under 2.12.3 above, cinmethylin is manufactured and placed on the market as a 50:50 racemic enantiomer of (-)-cinmethylin (Reg.No. 5925581) and (+)-cinmethylin (Reg.No. 5925632). Toxicological studies used (-)/(+) enantiomer ratios of 70:30 and c.50:50 or no information on the isomeric ratio was provided for the old studies. The toxicological data indicates that i) the two enantiomer ratios of 70:30 and c.50:50 have similar toxicological activity and ii) the two enantiomers have comparable toxicity. It is therefore considered that cinmethylin does not have any isomeric concerns and exposure to isomeric ratios different from the tested c.50:50 would have no significant impact on the risk assessment for operator, worker and bystander/resident.

#### 2.12.5. Residues and Consumer risk assessment

##### Plants

###### *Primary crops: wheat and oilseed rape*

In the wheat and oilseed rape metabolism studies, BAS 684 H was not detected in sufficient amounts to determine the enantiomeric ratio. Instead, the ratio was investigated for the two diastereomers of the main metabolite M684H005. Chromatographic separation of stereoisomers was performed by HPLC using a column with a chiral stationary phase.

In wheat forage and straw, compared to the applied parent BAS 684 H, the ratio of the (-):(+)-enantiomer of parent BAS 684 H changed from 51:49 to a diastereomeric ratio for M684H005 (diastereomer 1: diastereomer 2) of 36:64 for wheat forage, and 24:66 for wheat straw.

In oilseed rape straw, compared to the applied parent BAS 684 H, the ratio of the (-):(+)-enantiomer of parent BAS 684 H changed from 48:52 to a diastereomeric ratio for of M684H005 (diastereomer 1: diastereomer 2) of 26:74.

A shift in the diastereomeric ratio of M684H005 towards the later eluting diastereomer (diastereomer 2) was observed in wheat forage, wheat straw and oilseed rape straw. As the parent BAS 684 H consists of two enantiomers and metabolite M684H005 of two corresponding diastereomers, no direct correlation can be made. However, as the same HPLC method was used and the stereogenic centre of parent BAS 684 H is still present, the elution sequence may indicate the later eluting diastereomer could originate from the later eluting enantiomer of parent BAS 684 H, the (+)-enantiomer, however no reference standard was available to confirm this.

###### *Primary crops: carrots*

In carrots, the enantiomeric ratio of BAS 684 H was determined in the methanol extract of carrot leaves (phenyl label and cyclohexane label) containing sufficient amounts of the parent compound. The ratio of the (-):(+)-enantiomer of BAS 684 H showed a shift from 51:49 in the applied test item to ratios of 41:59 (phenyl label) and 43:57 (cyclohexane label) in the carrot leaves. In carrot roots, insufficient amounts of BAS 684 H were present to allow a reliable stereoisomeric analysis and no other metabolites were identified.

###### *Rotational crops*

In the confined rotational crop study, residues of parent BAS 684 H were too low ( $\leq 0.002$  mg/kg) to allow determination of the enantiomeric ratio and no other metabolites were identified.

##### Animals

The parent BAS 684 H was applied as a racemic mixture of two enantiomers (a ratio of the (-) and (+) enantiomers of approximately 43:57 in the application solution). Chiral analysis of BAS 684 H revealed a ratio of the (-) and (+) enantiomers was approximately 62:38 in poultry (fat, cyclohexane label) and a ratio of the (-) and (+) enantiomers was approximately 53:47 in goat (liver, cyclohexane label).

### Effect on consumer risk assessment

Given the toxicological evaluation has concluded that the enantiomers of parent BAS 684 H, and the diastereomers of M684H005 and M684H006 are all of equivalent toxicity (Vol 1 Section 2.12.3), the shifts in stereoisomeric ratios observed in the plant metabolism studies are not considered to affect the consumer risk assessment. The consumer risk assessment performed is considered to cover any ratio of enantiomers of parent BAS 684 H and any ratio of diastereomers of M684H005 and M684H006.

### 2.12.6. Environmental fate

The enantiomeric ratio of cinmethylin was monitored by the applicant throughout all relevant studies in which enantiospecific degradation and/or enrichment could be envisioned (see sections CA 7.1 and CA 7.2).

No conversion, i.e. no formation of one enantiomer from the other, was observed. However, the moderate change of the enantiomeric ratio observed in several instances indicate that the two enantiomers of BAS 684 H may degrade at different rates. The HSE evaluator agrees with this statement.

For this reason, DT<sub>50</sub> and DT<sub>90</sub> values were calculated in all fate studies for cinmethylin as well as for the two enantiomers (Reg. No. 5925581 and Reg. No. 5925632).

#### Soil:

The aerobic degradation of cinmethylin in soil has been investigated in a laboratory study with four different soils, and under field conditions in a total of eleven field trials: six in Europe and five in the United States.

As the modelling DegT<sub>50</sub> values normalised to reference conditions obtained in the terrestrial field dissipation study are significantly lower than the laboratory modelling DegT<sub>50</sub> values based on the evaluation using the EFSA DegT<sub>50</sub> Endpoint Selector, the applicant concluded that only the normalised DegT<sub>50</sub> from field studies are considered for exposure assessment. [EFSA (2014): *EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil. EFSA Journal 2014;12(5):3662 [37 pp.]. doi:10.2903/j.efsa.2014.3662*]. The HSE evaluator agrees with this statement.

The modelling endpoints obtained for cinmethylin and its two enantiomers in the terrestrial field dissipation study performed in the EU and US are summarised in Table 2.13.6-1.

**Table 2.13.6-1: Summary of modelling endpoints obtained under field conditions for cinmethylin and its two enantiomers (Reg. No. 5925581 and Reg. No. 5925632)**

	Cinmethylin		(-)-enantiomer Reg. No. 5925581		(+) -enantiomer Reg. No. 5925632	
	Kinetic	DegT <sub>50</sub> [d]	Kinetic	DegT <sub>50</sub> [d]	Kinetic	DegT <sub>50</sub> [d]
<b>Terrestrial field dissipation</b>						
Germany	FOMC	29.9 <sup>a</sup>	FOMC	25.4 <sup>a</sup>	FOMC	33.9 <sup>a</sup>
Italy	FOMC	47.0 <sup>a</sup>	FOMC	40.6 <sup>a</sup>	FOMC	52.5 <sup>a</sup>
Denmark	SFO	15.3	SFO	14.2	SFO	16.2
UK	SFO	5.4	SFO	4.4	SFO	6.4
Belgium	FOMC	8.0 <sup>a</sup>	FOMC	6.4 <sup>a</sup>	FOMC	9.4 <sup>a</sup>
Spain	SFO	13.9	SFO	10.7	SFO	17.2
New York	SFO	18.3	SFO	17.3	SFO	20.1
North Carolina	SFO	6.8	SFO	6.5	SFO	7.0
Texas	SFO	9.9	SFO	8.7	SFO	11.5
Washington	SFO	3.7	SFO	3.5	SFO	3.8
California	SFO	5.2	SFO	5.0	SFO	5.4
Geomean	-	<b>11.1</b>	-	<b>9.7</b>	-	<b>12.3</b>
Arithmetic mean	-	<b>14.9</b>	-	<b>13.0</b>	-	<b>16.7</b>
Standard deviation	-	<b>13.1</b>	-	<b>11.3</b>	-	<b>14.7</b>
Coefficient of variation	-	<b>113%</b>	-	<b>115%</b>	-	<b>113%</b>

<sup>a</sup> DT<sub>90</sub>/3.32

The difference between the average DegT<sub>50</sub> of the racemate and the average DegT<sub>50</sub> of the respective enantiomers is small in comparison to the overall variability of the DegT<sub>50</sub> between the different trials. For this reason, the applicant considered the racemate to be a good descriptor for the behaviour of both enantiomers and further evaluation of the environmental exposure is conducted with the racemate only. The HSE evaluator agreed with this conclusion.

#### Water/sediment

The trigger endpoints obtained for cinmethylin and for the two enantiomers in the water/sediment study are summarized in Table 2.13.6-2.

**Table 2.13.6-2: Summary of trigger endpoints obtained in the water/sediment study for cinmethylin and the two enantiomers (Reg. No. 5925581 and Reg. No. 5925632)**

	Compartment	Test system	Kinetic model	DegT <sub>50</sub> [d]
Cinmethylin	Total system	Berghäuser Altrhein	SFO	38.7
		Ranschgraben	SFO	39.7
Reg. No. 5925581	Total system	Berghäuser Altrhein	SFO	57.9
		Ranschgraben	SFO	49.2
Reg. No. 5925632	Total system	Berghäuser Altrhein	SFO	29.2
		Ranschgraben	SFO	30.0

As for the soil compartment, the applicant considered the racemate to be a good descriptor for the behaviour of both enantiomers and further evaluation of the environmental exposure is conducted with the racemate only. The HSE evaluator agreed with this conclusion.

### 2.12.7. Ecotoxicology

Mayer (2018) considered the isomeric composition of endpoints used in the risk assessment (BASF DocIC 2018/1090772). This report considered all non-target organism groups except for bees and other non-target arthropods. The report has been considered further by the HSE below. The text in italics was provided by the applicant.

#### 1.1.1.-1 Birds and other vertebrates:

*‘Generally, in avian and mammalian toxicity studies with BAS 684 H a racemic mixture consisting of 50:50 [(-)-BAS 684 H / (+)-BAS 684 H+] was tested. Studies in mammals were conducted with an exposure towards a higher ratio to the more biological active enantiomer (70:30 (-)-BAS 684 H / (+)-BAS 684 H). The comparison of a 28-d study in rats tested at a ratio of 70:30 with a 90-d and a carcinogenicity study in rats tested at a ratio of around 50:50 revealed comparable toxicological effects with respect to food consumption, body weight and body weight gain). Additionally, the effects on target organs were comparable in these studies.*

*For mammals the toxicological properties of the two enantiomeric forms of BAS 684 H are therefore considered to be not significantly different and no further testing was initiated. For birds, no different toxicological properties of the enantiomeric forms are expected either. In general BAS 684 H has a low toxicity in both the quail and the mallard with no mortality or any impact on parental or reproductive endpoints up to the highest tested dose in all studies. Thus, no further tests on isomers in birds or mammals are considered necessary.*

*For the exposure of birds and mammals to a potential shift in the ratio of the two enantiomers in food items information is available from plant metabolism studies (see chapter 1.5 above). In wheat and oilseed rape metabolism studies, the parent BAS 684 H was not detected in sufficient amounts to determine the enantiomeric ratio. However, in carrot leaves the ratio of the (-) and (+)-enantiomer of BAS 684 H showed no significant shift, changing from 51:49 in the applied test item to ratios of 41:59 (phenyl label) and 43:57 (cyclohexane label). Thus, no relevant shift towards any enantiomer is expected for plant food items relevant for birds and mammals.*

*Considering the comparable toxicological profile of different ratios of both enantiomers of BAS 684 H and the observation of a no significant shift in plant metabolism studies no specific risk assessment for the enantiomers are deemed necessary for birds and mammals.’*

#### **HSE comments:**

##### *Cinmethylin*

The residue studies referenced above have been evaluated by the HSE residues evaluator in section B.7.2.1.6, volume 3, B7 residue dossier (see this section for full details of methodology). Cinmethylin was not detected at sufficient levels (< 0.01 mg a.s./kg) in all oilseed rape and wheat (forage, straw and grain) matrices for both <sup>14</sup>C-labels. In the carrot study cinmethylin was detected and the results are shown in the table below for carrot leaves.

Table 2.12.7-1: Determination of the diastereomer ratio of cinmethylin, 67 days after application (target rate of 500 g a.s./ha)

Matrix	Cinmethylin (-) stereoisomer A1 [%AR]	Cinmethylin (+) stereoisomer A2 [%AR]	SE [%]	SE Change
Test item	51.0	49.0	2	0
<b>Phenyl-label</b>				
Leaves	40.6	59.4	18	-16
<b>Cyclohexane-label</b>				
Leaves	43.0	57.0	14	-14

SE = stereoisomers excess,  $SE = [(A1\% \text{ AR} - A2\% \text{ AR}) / (A1\% \text{ AR} + A2\% \text{ AR})]$

The analyses with enantiomer-specific HPLC method of the isolated fractions demonstrate that changes in the stereoisomeric excess (SE) are >10 %. Therefore, they are considered significant by the residue specialist (HSE evaluator).

On the basis of the residue data on carrots it is feasible that there are significant shifts in enantiomeric ratios hence this may also occur in other vegetation that birds and mammals may consume meaning the toxicity of the enantiomers requires further consideration.

Bird and mammal consideration of Mayer (2018):

It was noted that only the toxicology studies submitted tested different enantiomeric ratios on vertebrates beyond approx. 50:50. The HSE toxicology evaluator considered these in section 2.12.3 (above) and concluded that the two enantiomers have comparable toxicity. Therefore, from an ecotoxicology perspective, when considering wild mammals, the potential shift in ratios is acceptable. However, for bird's further consideration is required. Following a request for information from HSE CRD the applicant provided a position paper (Wich, 2020). The points from this paper have been considered below.

Toxicity studies:

The available toxicity data for birds (for full details refer to volume 3, CA, section 9 dossiers) are presented in the table below.

Table 2.12.7-2: Toxicity endpoints for the risk assessment for birds for BAS 684 H

Species	Substance	Exposure System	Results	Reference (BASF DocID)
<b>Acute toxicity</b>				
<i>Colinus virginianus</i>	BAS 684 H	Oral, 1 d Acute	LD <sub>50</sub> > 2000 mg a.s./kg b.w. <b>LD<sub>50</sub> extrapolated &gt; 3776 mg a.s./kg b.w.<sup>1</sup></b>	██████ (2016a) (2016/7005980)
<b>Chronic toxicity</b>				
<i>Colinus virginianus</i>	BAS 684 H	Dietary Reproductive toxicity (20 weeks)	<b>NOEL = 99.1 mg a.s./kg b.w./d</b> NOEC = 1200 mg a.s./kg diet	██████████ (2016a) (2016/7009945)
<i>Anas platyrhynchos</i>	BAS 684 H	Dietary Reproductive toxicity (21 weeks)	NOEL = 174 mg a.s./kg b.w./d NOEC = 1200 mg a.s./kg diet	██████████ (2018c) (2017/7016288)

**Bold** indicates endpoints used in risk assessment.

<sup>1</sup> Extrapolation according to EFSA (2009) Chapter 2.1.2. has been applied to the acute endpoint LD<sub>50</sub> >2000 mg a.s./kg bw (■■■■■ 2016a) since 10 animals were tested and there were no mortalities at the limit dose (extrapolation factor = 1.888).

It is noted that the duration of the acute study is a single day, therefore in accordance with EFSA guidance for risk assessment of active substances that have stereoisomers (EFSA journal 2019;17(8):5804) confirmation of the stereoisomeric excess changes is unlikely to be necessary (i.e. when single feed prepared and duration ≤ 24 hours). Therefore the lack of measurements in the acute toxicity study is considered appropriate. However, the two reproductive studies are over a longer time frame (minimum of 20 weeks) hence measurements of ratios ideally would have been taken, noting feed preparations were prepared weekly. The following is stated in the EFSA guidance document for stereoisomers: '*In case of long-term feeding studies, the need for demonstrating the stereoisomeric proportion in the food is likely to be necessary.*'

It should be noted that there were no observed effects at the highest dose tested in the reproductive study suggesting this endpoint is conservative despite any enantiomeric ratio changes during the study not being known.

#### Exposure:

In the position paper (Wich, 2020) both the hen and rat metabolism studies were referenced with argumentations shown in italics below. These points have been discussed in consultation with the HSE toxicology and residue evaluators.

#### ***Animal metabolism***

*Information from preferential metabolism of the (-/+) enantiomers of BAS 684 H in terrestrial vertebrates was investigated in hens, goats and rats.*

*In these three species a shift towards the (-) enantiomer was observed. Details of the shift in laying hens and rats are given in Table 2.*

*In the hen metabolism study BAS 684 H were administered for 11 days to laying hens at a dose of around 12 mg/kg feed. While eggs were collected from day 1 to 11 days, tissues like muscle, liver and fat were collected 3-6 hours after the last dosing. Overall BAS 684 H was not detected in muscle and liver, but in eggs and fat. Enantiomers were investigated in fat, indicating a shift from 43:57 (-/+) of the applied test item (representatively determined for the phenyl label) to a ratio of the (-) and (+)-enantiomers of approximately 62:38 with the cyclohexane label.*

*In the rat metabolism study specific investigations of the enantiomers were made in liver and feces. Animals were dosed at low and high rates (15 and 350 mg/kg bw/d) and at a 15-d repeated high rate of 350 mg/kg bw/d. The ratio of the (-/+) enantiomers was approximately 48:52 and 49:51 in the application formulations of the phenyl- and cyclohexane label, respectively. The ratio of the (-/+) enantiomers of BAS 684 H ranged from approximately 70:30 to 76:24 in feces extracts and from approximately 63:37 to 69:31 in liver extracts.*

**Table 2:** *Isomeric ratio of BAS 684 H in animal metabolism studies.*

Study type	Matrix	Ratio test item BAS 684 H (-/+)	Analysed BAS 684 H (-/+)	Isomeric excess (%)	Reference
Metabolism of [14C]- BAS 684 H in hen	Fat	Cyclohexane label			2017/1068568 CA 6.2.2/1
		43:57	62:38	38 %	
Metabolism of [14C]- BAS 684 H in goat	Liver	Cyclohexane label			2017/1037602 CA 6.3.3/1
		49:51	53:47	8 %	
Metabolism of [14C]- BAS 684 H in rat	Liver	Cyclohexane label			2017/1158148 2018/1072281 2017/1145830 2017/1078601 / CA 5.1.1/1-4
		49:51	69:31	42 %	
		Phenyl label			
		48:52	63:37	30 %	
	Feces	Cyclohexane label			
		49:51	76:24	56 %	
		Phenyl label			
		48:52	70:30	44 %	

*In both hens and rats a shift towards the (-) enantiomer was observed in different matrixes, indicating a faster metabolism of the (+) enantiomer.*

*Indeed the metabolism in animals reveals a different shift than the metabolism in plants. In plants a slightly faster metabolization of the phytotoxic more active (-) enantiomer leads to a small shift towards the (+) enantiomer. Taken together, even if birds will consume plants containing residues with a slight shift towards the (+) enantiomer, this enantiomer will be faster metabolized than the (-) enantiomer as demonstrated by the hen and rat metabolism studies.*

*This indicates that birds can well metabolize both isomers and a slight shift towards the (+) isomer is unlikely to lead to a change in the toxicity profile.*

#### HSE comments:

Whilst it appears that one enantiomer metabolises faster than the other, the conclusion stated above cannot be confirmed based on the available information. This could be due to other factors e.g. conversion or preferential uptake.

The hen metabolism study (█ 2018) has been considered in detail in the residue dossier (for full details see CA dossier B7, volume 3, section B.7.2.1.7). The following key conclusions were reached following administration of cinmethylin for 11 days at 12 mg a.s./kg feed;

- The main fraction of the initial dose was excreted via excreta, accounting for approximately 91.3 % (phenyl label) and 87.3 % (cyclohexane label).
- Residues of cinmethylin in eggs of the phenyl label increased to a plateau at 7 and 9 days with a concentration of 0.076 mg/kg (egg white) and 0.053 mg/kg (egg yolk), respectively. For the cyclohexane label, a plateau of 0.122 mg/kg (egg white) and 0.070 mg/kg (egg yolk) was reached after 7 days.
- The main portions of cinmethylin radioactive residues were recovered in excreta (6.397 – 7.010 mg a.s./kg). In the edible matrices, the highest TRR (Total Radioactive Residues) concentrations were calculated for liver (0.221 – 0.223 mg a.s./kg). For all other matrices, the TRR was in a range from 0.051 to 0.083 mg a.s./kg (cyclohexane label).
- Residual Radioactive Residues (RRR) obtained after extraction of egg yolk (phenyl label) and liver amounted to 19.3 – 35.0 % TRR. The RRR of all other relevant matrices were below or equal to 11.1 % TRR (0.004 mg/kg phenyl label) and 9.9 % TRR (0.007 mg/kg cyclohexane label).

The conclusions from the hen metabolism study (█ 2018) provide supporting information that the majority of cinmethylin would be excreted (6.397 – 7.010 mg a.s./kg) and relatively low levels (maximum of 0.223 mg a.s./kg) would remain based on the matrices measured (egg yolk, egg white, muscle, liver and fat) following ingestion of cinmethylin by birds. Hence, although the enantiomeric ratios appear to have changed during the study (initial ratio of 50:50) the overall levels of cinmethylin that remain within the hen was relatively low compared to initial dose. Therefore, the metabolism study and bird toxicity data suggest that cinmethylin is likely to pass through birds if consumed and be of relatively low toxicity.



Whilst several mammalian metabolism studies were referenced there is uncertainty in the read across and relevance for birds. Nonetheless it was noted that based on the rat study (██████████, 2018) no changes to enantiomeric ratios of cinmethylin (i.e. 50:50 ratio as per test item) were detected in plasma, urine or bile, changes were only observed in faeces and liver (see table 2 for ratio changes). In terms of % of initial dose the following ranges were observed; < 1 % in bile, 1.97 – 4.5 % in faeces and < 0.1 % in plasma. Therefore, in the majority of matrices measured there was no change to enantiomeric ratio and the two where there were changes showed relatively low amounts of cinmethylin compared to the initial dose.

Several plant residue trials were also referenced by the applicant in the position paper (Wich, 2020). The summaries of data are presented in tables 2.12.7-18 to 2.12.7-22 taken from the CA, section B7, volume 3 dossier. Whilst it is unclear whether formulation would impact enantiomeric ratios it was noted that a total of two formulations were tested, one was the representative ('BAS 684 03H') and the other (BAS 684 02 H) is considered comparable from an ecotoxicology perspective (as detailed in volume 4 dossier, section C.1.4.1.). Several of these studies cover the proposed GAP and were conducted in central zone/UK. Based on the available trials, cinmethylin residue levels following application are relatively low. The HSE evaluator notes the sampling intervals are relatively long in the majority of studies limiting their relevance for the ecotoxicology assessment (samples taken at day 0-initiation then first sampling date after initiation ranged from; 8 – 70 days) adding some uncertainty. In addition, the studies where the enantiomeric ratio of cinmethylin was measured and GAP was appropriate, did not detect cinmethylin at a sufficient concentration < 0.01 mg a.s./L after the initial sample on the day of application. Meaning it was not possible to identify changes in enantiomeric ratios.

When considering all plant residue studies the levels are relatively low at the first sampling date after application; oilseed rape range of < 0.01 to 0.065 mg a.s./kg and cereals range of < 0.01 to 0.023 mg a.s./kg. The majority being < 0.01 mg a.s./kg at the first sampling date.

In summary whilst uncertainties have been noted there is some supporting that levels of cinmethylin on plants may be low following application for the proposed uses. In addition, if birds consume cinmethylin it is likely the majority will be excreted based on the hen metabolism study.

#### Consideration of standard risk assessment for cinmethylin

The risk assessment for the proposed uses (see CP dossier, volume 3, section 9) has been summarised below. The worst case scenario (protective of all proposed uses) has been presented for the long-term/reproductive risk assessment. An acceptable risk was demonstrated at screening step. Whilst the toxicity of individual enantiomers and changes to ratios are not known it is possible to conduct a risk assessment in accordance with EFSA guidance for enantiomers which has been considered in the following section.

Table 2.12.7-3: BAS 684 H: Screening step of the long term risk for birds due to the use of BAS 684 03 H for the crop group "cereals" at 1 x 500 g a.s./ha

<b>Screening step (chronic) using reproductive endpoint of 99.1 mg a.s./kg bw/day:</b>							
Reproductive risk assessment screening step	Indicator species	Shortcut value	Daily Dietary Dose (single)	MAF mean	Daily Dietary Dose (Multiple)	TER	Trigger
	Small omnivorous bird	64.8	17.17	1.0	17.17	5.8	5

Risk assessment for birds considering enantiomers following EFSA 2019;17(8):5804:

The risk to birds from changes in enantiomeric composition have been considered further in-line with EFSA journal 2019;17(8):5804. Following the approaches described an uncertainty factor of 2 has been applied to the toxicity endpoint (due to presence of two enantiomers at an initial ratio of 50:50). This is due to the toxicity of individual isomers not being known or the extent of changes in enantiomeric ratios both during the study and in the field.

Using this uncertainty factor there would be a potential risk identified at screening step based on the values in table 2.12.7-3 compared to a trigger value of 5. Therefore, HSE has considered a tier 1 risk assessment below applying an uncertainty factor of 2 to the NOEL endpoint ( $99.1 / 2 = 49.55$ ). The long-term/reproductive risk assessment for birds assessing bare soil at screening step generated a TER of 32.8 (volume 3, CP dossier, section 9, table B.9.2.1-7) hence an uncertainty factor of 2 would also demonstrate an acceptable risk. Similarly, the proposed use on oilseed rape generated a chronic TER of 11.54 at screening step which would also demonstrate an acceptable risk. Therefore, only the proposed use on cereals has been considered below at tier 1.

Table 2.12.7-4: BAS 684 H: Tier 1 of the long term risk for birds due to the use of BAS 684 03 H for the crop group “cereals” at 1 x 500 g a.s./ha at BBCH 10 – 29, using a default ftwa of 0.53 and MAF of 1 (single application). The toxicity endpoint has been adjusted using an uncertainty factor of 2 to allow for enantiomers.

Crop/ Growth stage	Generic focal species	Shortcut value	DDD	Toxicity (mg a.s./kg bw/day)	TER	Trigger
Cereals BBCH 10-29	Large herbivorous bird "goose"	16.2	4.29	49.55	11.54	5
	Small omnivorous bird "lark"	10.9	2.89	49.55	17.15	

Based on the above assessment an acceptable risk for the proposed uses can be concluded when applying an uncertainty factor of 2 to the NOEC in order to allow for unknown toxicity of enantiomers and changes in enantiomeric ratios. In accordance with EFSA journal 2019;17(8):5804 this means an acceptable risk to birds has been demonstrated for the proposed uses. This combined with the other supporting information above (low levels on crop in residue trials and within bird matrices in metabolism study) means further consideration for the proposed uses is not required. However, depending on the proposed GAP this issue and the above risk assessment may need to be re-visited in future applications.

Metabolite M684H005:

The metabolite M684H005 was detected in the residue trials assessing wheat and oilseed rape. Furthermore, for this metabolite there was a change in enantiomeric ratio as shown in the table below.

Table 2.12.7-5: Determination of the diastereomer ratio of M684H005

Matrix	M684H005 Diastereomer 1 [% AR]	M684H005 Diastereomer 2 [% AR]
<b>Cyclohexane-label</b>		
Wheat forage	36	64
Wheat straw	34	66
<b>phenyl-label</b>		
Oilseed rape straw	26	74

Given M684H005 is a major metabolite (> 10 % TRR), residue trials suggesting increased concentration at first sampling point following application for the majority of wheat/oilseed rape trials (see tables 2.12.7-18 to 2.12.7-22) and lack of toxicity data for this metabolite and changes in enantiomeric ratios further consideration is required for birds and mammals.

Further consideration was provided by applicant (BASF DocID 2020/2079734). This included justification that metabolite toxicity is addressed by the active substance, further discussion of toxicology and residue data. Full consideration of the toxicology data is provided in volume 1, section 2.12.3. The metabolite toxicity was considered to be within that of active substance, full consideration provided in the metabolite toxicity to birds and mammals in volume 3 sections B.9.2.1 and B.9.2.2 respectively. The residue consideration of enantiomers is provided in volume 1, section 2.12.5. These sections have been considered further below.

Residue consideration of M684H005 enantiomers (volume 1, section 2.12.5):

The following conclusion was reached by HSE: ‘In wheat forage and straw, compared to the applied parent BAS 684 H, the ratio of the (-):(+)-enantiomer of parent BAS 684 H changed from 51:49 to a diastereomeric ratio for M684H005 (diastereomer 1: diastereomer 2) of 36:64 for wheat forage, and 24:66 for wheat straw.

In oilseed rape straw, compared to the applied parent BAS 684 H, the ratio of the (-):(+)-enantiomer of parent BAS 684 H changed from 48:52 to a diastereomeric ratio for of M684H005 (diastereomer 1: diastereomer 2) of 26:74.

A shift in the diastereomeric ratio of M684H005 towards the later eluting diastereomer (diastereomer 2) was observed in wheat forage, wheat straw and oilseed rape straw. As the parent BAS 684 H consists of two enantiomers and metabolite M684H005 of two corresponding diastereomers, no direct correlation can be made.’

Following discussion with HSE residue specialist it was not possible to confirm whether the changes in ratios were due to degradation or preferential metabolism. Therefore, further consideration is required.

The subsections below have considered the risk to mammals and birds from enantiomers of M684H005.

Risk to wild mammals from enantiomers of M684H005:

The following conclusion was reached by HSE toxicology: ‘Metabolite M684H005 also occurs in plants as two stereoisomers which result from the same stereogenic element of the parent substance. Noting that i) cinmethylin isomers have comparable toxicity and ii) the toxicity of metabolite M684H005 is considered equivalent to and covered by the toxicity data of the parent, consequently, the two isomers of the metabolite M684H005 are also considered toxicologically equivalent.’

As stated above the two enantiomers are considered comparable from toxicology perspective, supporting a similar conclusion for wild mammals. This suggests that any potential changes in ratios may result in comparable toxicity. Furthermore when considering the metabolite in the ecotoxicology risk assessment for mammals there was a wide margin of safety (noting the discussion of toxicity endpoints, metabolism studies and calculation of exposure values is detailed in full in volume 3, section B.9.2.2). As shown in the tables below. Therefore, further consideration of the risk to mammals from enantiomers of M684H005 is not required.

Table 2.12.7-6: Acute risk assessment for mammals for – metabolites in plant food items

Crop + scenario	Generic focal species	DDD		DDD <sup>5</sup> [mg/kg bw/d]	LD <sub>50</sub> [mg a.s./kg bw] <sup>3</sup>	TER	Trigger
		Residue value [mg/kg]	FIR/bw <sup>4</sup>				
M684H005							
Bare soil <sup>1</sup> BBCH 00-09	Small granivorous mammal	4.4	0.17	0.748	>2000	>2673	10
Cereals <sup>1</sup> BBCH 10-29	Small herbivorous mammal	4.4	1.33	5.852		>341	
OSR <sup>3</sup> 10-18	Small herbivorous mammal	1.5	1.33	1.995		>1003	

<sup>1</sup> Maximum residue value for the sum of M684H005 from residue trial data on wheat.

<sup>2</sup> Maximum residue value for the sum of M684H005 from residue trial data on oilseed rape.

<sup>3</sup> Active substance endpoint which is considered to cover the toxicity of M684H005.

<sup>4</sup> From Appendix A of EFSA Bird and Mammal Guidance Document (2009).

<sup>5</sup> DDD = FIR/bw x Residue value.

Table 2.12.7-7: Long-term/reproductive risk assessment for mammals – metabolites in plant food items

Crop + scenario	Generic focal species	DDD		DDD <sup>5</sup>	NOEL [mg a.s./kg bw] <sup>3</sup>	TER	Trigger
		Residue value [mg/kg]	FIR/bw <sup>4</sup>				
M684H005							
Bare soil <sup>1</sup> BBCH 00-09	Small granivorous mammal	4.4	0.17	0.748	58	77.5	5
Cereals <sup>1</sup> BBCH 10-29	Small herbivorous mammal	4.4	1.33	5.852		9.91	
OSR <sup>3</sup> 10-18	Small herbivorous mammal	1.5	1.33	1.995		29.1	

<sup>1</sup> Maximum residue value for the sum of M684H005 from residue trial data on wheat.

<sup>2</sup> Maximum residue value for the sum of M684H005 from residue trial data on oilseed rape.

<sup>3</sup> Active substance endpoint which is considered to cover the toxicity of M684H005.

<sup>4</sup> From Appendix A of EFSA Bird and Mammal Guidance Document (2009).

<sup>5</sup> DDD = FIR/bw x Residue value.

#### **Risk to birds from enantiomers of M684H005:**

When considering the risk to birds, it is unclear whether the toxicology conclusion regarding comparable toxicity of isomers applies. Hence the ecotoxicology assessment of risk to birds from this metabolite has been considered further. To allow for the unknown toxicity of the two enantiomers a default uncertainty factor of 2 has been applied to the toxicity endpoint in accordance with EFSA journal 2019;17(8):5804. The updated risk assessments are shown in the tables below for acute and reproductive risk. For full details of exposure/toxicity endpoints used in metabolite assessment (before application of uncertainty factor) see volume 3 section B.9.2.1.

Table 2.12.7-8: Acute risk assessment for birds for – metabolites in plant food items

Crop + scenario	Generic focal species	DDD		DDD <sup>5</sup> [mg/kg bw/d]	LD <sub>50</sub> [mg a.s./kg bw] <sup>3</sup>	TER	Trigger
		Residue value [mg/kg]	FIR/bw <sup>4</sup>				
M684H005							
Bare soil <sup>1</sup> BBCH 00-09	Small granivorous bird	4.4	0.28	1.232	>1888	1532	10
Cereals <sup>1</sup> BBCH 10-29	Small omnivorous bird	4.4	2.26	9.944		190	
OSR <sup>2</sup> BBCH 10-18	Small omnivorous bird	1.5	2.26	3.39		557	

<sup>1</sup> Maximum residue value for the sum of M684H005 from residue trial data on wheat.

<sup>2</sup> Maximum residue value for the sum of M684H005 from residue trial data on oilseed rape.

<sup>3</sup> Active substance endpoint used as considered to cover toxicity of plant metabolites M684H005, noting this has been divided by 2 to allow for the unknown toxicity of the two enantiomers.

<sup>4</sup> From Appendix A of EFSA Bird and Mammal Guidance Document (2009).

<sup>5</sup> DDD = FIR/bw x Residue value.

Table 2.12.7-9: Long-term/reproductive risk assessment for birds – metabolites in plant food items

Crop + scenario	Generic focal species	DDD		DDD <sup>5</sup>	NOEL [mg a.s./kg bw] <sup>3</sup>	TER	Trigger
		Residue value [mg/kg]	FIR/bw <sup>4</sup>				
M684H005							
Bare soil <sup>1</sup> BBCH 00-09	Small granivorous bird	4.4	0.28	1.232	49.5	40	5
Cereals <sup>1</sup> BBCH 10-29	Small omnivorous bird	4.4	2.26	9.944		5.0*	
OSR <sup>2</sup> BBCH 10-18	Small omnivorous bird	1.5	2.26	3.39		15	

<sup>1</sup> Maximum residue value for the sum of M684H005 from residue trial data on wheat.

<sup>2</sup> Maximum residue value for the sum of M684H005 from residue trial data on oilseed rape.

<sup>3</sup> Active substance endpoint used as considered to cover toxicity of plant metabolites M684H005, noting this has been divided by 2 to allow for the unknown toxicity of the two enantiomers

<sup>4</sup> From Appendix A of EFSA Bird and Mammal Guidance Document (2009).

<sup>5</sup> DDD = FIR/bw x Residue value.

\* To 1 d.p. or 4.98 to 2 d.p.

Based on the above assessment an acceptable acute/reproductive risk to birds from enantiomers of M684H005 can be concluded for the proposed uses.

It was noted that the TER for reproductive risk when considering small omnivorous birds (cereals BBCH 10-29) was marginally below trigger of 5 if considered to 2 d.p. i.e. 4.98. However, this is considered acceptable given a conservative approach has been taken using an uncertainty factor of 2 applied to the toxicity endpoint. In addition, whilst the read across between mammals and birds is unclear, the toxicology conclusion was that the toxicity of M684H005 enantiomers are comparable.

#### **Overall conclusion for birds and mammals (risk from enantiomers of M684H005):**

The risk to birds and mammals from enantiomers of M684H005 is considered acceptable for the proposed uses. It should be noted these conclusions apply to the proposed GAP single application to oilseed rape/cereals hence any changes in future submissions may need further consideration.

#### **1.1.1.-2 Aquatic organisms:**

*‘According to the data presented in the water sediment study (BASF DocID 2016/1119819) some shift of the isomer composition in the racemic product was observed during the study. However, the study duration was 100 days. As described already in the Efate part, there is no conversion of the isomers and the shift of the isomeric ratio at the end of the study related to the slightly different DT<sub>50</sub> of both isomers.*

*The aquatic species however, were either tested in a static short-term exposure or, in case of long-term exposure, flow through or semi-static system (renewal of the active substance, every 2 – 3 days). The maximum static exposure was 14 days. According to the water-sediment study, the shift in the isomeric ratio in the aquatic compartment is negligible (max. 56:44 after 14 days) over the respective time periods.’*

#### **HSE comments:**

The HSE fate evaluator has considered in detail the information provided by the applicant regarding changes in ratios in water and sediment. See volume 1, section 2.8.2 for full details. The following conclusions were reached:

The Applicant investigated the enantiomeric ratio throughout the course of most of the aquatic degradation studies. In the hydrolysis study there was no change from the 50:50 enantiomer ratio at any

pH after 31 days. There was also no significant change in the ratio after 15 days in the direct photolysis study or in the indirect photolysis study. The HSE fate evaluator concludes that chemical degradation of cinmethylin does not alter the enantiomer ratio.

Regarding biological degradation, the Applicant did not explore the enantiomer ratio in relation to ready biodegradability; however, no ready biodegradation was observed. The enantiomer ratio did not change significantly due to aerobic mineralisation. However, large changes in the enantiomer ratio were observed in the water-sediment study, with the ratio shifting towards the (-)-enantiomer. In one system (Berghäuser Altrhein), changes were observed in both the water and sediment portions, with water phase shifting to 60:40 after 14 days, and the ratio in the sediment shifting from 57:43 at 14 DAT to 71:29 at 100 DAT with 30 % and 24 % of the initially applied cinmethylin remaining in the sediment respectively. Enantiomeric shifts were less pronounced in the Ranschgraben system, with ratios observed in the water at approximately 55:45 at 14 DAT. In the sediment, initial ratios of 55:45 at 14 DAT shifted to 67:33 by 100 DAT in both radiolabels.

The HSE fate evaluator concludes that changes in the enantiomeric ratio in aquatic systems are driven by the aerobic degradation, with more rapid degradation of the (+)-enantiomer. In the water-sediment study, the (-)-enantiomer DT<sub>50</sub> (57.9 days) is almost twice as long as the (+)-enantiomer DT<sub>50</sub> (30.0 days).

The changes in enantiomeric ratios are considered to be due to different degradation rates rather than transformation by the fate specialist. Hence, there will not be an increase in concentration of one enantiomer but rather degradation from the initial concentrations. In addition, these changes appear to occur over relatively long time periods compared to aquatic toxicity studies (maximum duration of 14 days for static studies with exception of chronic fish studies- maximum of 35 days with flow through design). The most sensitive endpoint for aquatic organisms was aquatic plants with a study duration of 7 days and water only exposure (Vlechev, 2017a), suggesting based on the fate studies that a significant change in enantiomeric ratios may not have occurred. Therefore, from an ecotoxicology perspective further consideration of enantiomeric ratios for aquatic organisms is not required.

#### 1.1.1.-3 Bees and other non-target arthropods:

Following a request for information from HSE CRD to consider enantiomeric isomer changes the following was provided (shown in italics below).

*'Within the risk estimation for non-target arthropods the relevant exposure route will be via contact to plant/leaf material. In the study Schweda and Forieri, 2017/1186663 carrot plants were treated with cinmethylin at field rate (500g/ha) and harvested after 67 days after treatment. Within this period a shift from 51/49 ((-) isomer/ (+) isomer) to 43/57 (cyclohexane label) (bzw 41/59 (phenyl label). After this period of time the residue level on plant surface is considered to be very low. Even if this slight shift in enantiomers would occur and one of the isomers would contribute exclusively to the toxicity of the mixture, the conclusion of the risk assessment will not be affected at the expected overall residue levels (i.e. by default a DT<sub>50</sub> of 10 days can be assumed and hence an additional worst case safety factor on the toxicity endpoint would be covered in the risk assessment).*

*The same assumptions can be made for the honeybees. The slight shift at this point in time would not affect the risk assessment as the residue levels are expected to be in a very low concentration range. Due to the low mobility of the compound in the plant overall exposure in bee relevant matrices (nectar/pollen) is considered to be low. In any case the risk assessment which is based on worst case initial exposure covers the potential shift in plants with a high margin of safety.'*

#### **HSE comments:**

The shift in enantiomeric ratio observed in the carrot residue trial (table 2.12.7-1) is significant for the environmental risk assessment in accordance with EFSA journal 2019;17(8):5804 guidance i.e. > 10 % trigger.

As described above in the bird section 1.1.1-1, several residue studies were submitted that suggest levels of cinmethylin are likely to be relatively low following application, noting uncertainties were identified in particular the relatively long sampling period from measuring at initiation to the first measurement after

application in the majority of studies. It should be noted that a default DT<sub>50</sub> value of 10 days is not used under SANCO 2002 (bees) risk assessment scheme. Default MAF values are calculated under ESCORT II (non-target arthropod) scheme but the DT<sub>50</sub> value used is not clearly stated. Therefore, this assumption of 10 days has not been incorporated. Furthermore residue DT<sub>50</sub> values specific to the proposed uses were not calculated for cinmethylin. Therefore, a risk assessment following EFSA guidance for enantiomers has been conducted in the following section.

Risk assessment for bees and non-target arthropods considering enantiomers following EFSA 2019;17(8):5804:

The risk to bees and non-target arthropods from changes in enantiomeric composition have been considered further in-line with EFSA journal 2019;17(8):5804. Following the approaches described an uncertainty factor of 2 has been applied to the toxicity endpoint (due to presence of two isomers at an initial ratio of 50:50). This is due to the toxicity of individual isomers not being known or the extent of changes in enantiomeric ratios both during the study and in the field.

Table 2.12.7-10: HQ calculations for honeybees applying uncertainty factor of 2 to toxicity endpoints:

Test substance	Application rate [g a.s./ha]	Endpoint	LD <sub>50</sub> [µg a.s./bee]	Hazard quotient HQ	Trigger
<b>Risk assessment on adult honeybees</b>					
BAS 684 H*	500	48 h oral	> 100.0**	< 5	50
		48 h contact	> 100.0**	< 5	

\* Active substance endpoints are protective of formulation.

\*\* Endpoint corrected using an uncertainty factor of 2.

The calculated HQs are below the trigger value of 50, indicating an acceptable risk to bees for the proposed use.

For non-target arthropods the same approach i.e. an uncertainty factor of 2 to allow for unknown enantiomeric ratios has been applied for the in-field and off-field assessments as shown in the sections below.

In-field assessment:

The in-field tier 1 assessment using the corrected toxicity endpoint is shown below.

Table 2.12.7-11: HQ<sub>in-field</sub> for non-target arthropods exposed to BAS 684 03 H in winter wheat (worst case use) applying uncertainty factor of 2 to toxicity endpoints

Species	LR <sub>50</sub> [L/ha]	PER <sub>in-field</sub> [L/ha]	HQ <sub>in-field</sub>	Trigger value
<i>Aphidius rhopalosiphi</i> Tier I, 2D exposure scenario	0.136 / 2* = 0.068	0.666	<b>9.79</b>	2
<i>Typhlodromus pyri</i> Tier I, 2D exposure scenario	0.764 / 2* = 0.382		1.74	2

\* = Endpoint corrected using an uncertainty factor of 2.

PER = predicted environmental rate.

HQ values shown in **bold** is above the relevant trigger.

Using the corrected toxicity endpoints an acceptable risk has been demonstrated at tier 1 for *T. pyri*. However, further consideration of the risk to *A. rhopalosiphi* is required. A tier II assessment with corrected endpoints has been considered below, along with an additional species in accordance with ESCORT II (see volume 3, section B9 ecotoxicology dossier for full details).

Table 2.12.7-12: Lethal and sublethal effect levels for non-target arthropods exposed to BAS 684 03 H in winter wheat (worst case use) applying uncertainty factor of 2 to toxicity endpoints

Species	50 % M [L/ha]	50 % R [L/ha]	PER <sub>in-field</sub> [L/ha]
<i>Aphidius rhopalosiphi</i> Tier II, 3D exposure scenario	> 0.7 <sup>#</sup> / 2* = 0.35	> 0.7 <sup>#</sup> / 2* = 0.35	0.666
<i>Aleochara bilineata</i> Tier II, 2D exposure scenario	> 1.4 <sup>##</sup> / 2* = 0.7	> 1.4 <sup>##</sup> / 2* = 0.7	0.666

50 % M = concentration with 50 % effects on mortality, 50 % R = concentration with 50 % effects on reproduction. Both endpoints and PER are expressed in terms of L/ha.

PER = predicted environmental rate.

\* = Endpoint corrected using an uncertainty factor of 2.

<sup>#</sup> -5.2 % effects compared to control for reproduction and 13.3 % mortality (7.1 % when corrected for control mortality) at highest test concentration. Negative value indicates greater reproduction than control.

<sup>##</sup> 7.2 % effects compared to control for reproduction and 2.5 % mortality in the highest test concentration.

Based on the reported values, the 50 % effect levels for *A. bilineata* are greater than the in-field PER. Therefore, it is concluded that there is a low in-field risk for this species. For *A. rhopalosiphi* there is a potential risk when applying the uncertainty factor for the proposed use. It is noted that there were less than 50 % effects in terms of mortality and reproduction for *A. rhopalosiphi* at the highest concentration tested (maximum of 13.3 % effects equivalent to 7.1 % based on control corrected mortality). However, an acceptable in-field risk for this species cannot be concluded based on the available data following EFSA enantiomer guidance (journal 2019;17(8):5804).

Following a second request for information further consideration was provided. The applicant proposed adjusting the uncertainty factor to 1.2 based on the highest ratio shift (using available data) from the residue study conducted on carrot leaves (table 2.12.7-1), this was the only trial where the quantity of cinmethylin was sufficient to determine enantiomer ratios. Using the carrot data the highest measured proportion of isomer was 59.4 %. An uncertainty factor in accordance with EFSA journal 2019;17(8):5804 guidance was then calculated by multiplying the highest percentage of isomer by default uncertainty factor of 2 i.e. 59.4/100 x 2 = 1.2. The applicants updated in-field risk assessment for *Aphidius* using the modified uncertainty factor has been shown in the table below.

Table 2.12.7-13: Lethal and sublethal effect levels for non-target arthropods exposed to BAS 684 03 H in winter wheat (worst case use) applying uncertainty factor of 1.2 to toxicity endpoints

Species	50 % M [L/ha]	50 % R [L/ha]	PER <sub>in-field</sub> [L/ha]
<i>Aphidius rhopalosiphi</i> Tier II, 3D exposure scenario	> 0.7 <sup>#</sup> / 1.2* = 0.58	> 0.7 <sup>#</sup> / 1.2* = 0.58	0.666

50 % M = concentration with 50 % effects on mortality, 50 % R = concentration with 50 % effects on reproduction. Both endpoints and PER are expressed in terms of L/ha.

PER = predicted environmental rate.

\* = Endpoint corrected using an uncertainty factor of 1.2.

<sup>#</sup> -5.2 % effects compared to control for reproduction and 13.3 % mortality (7.1 % when corrected for control mortality) at highest test concentration. Negative value indicates greater reproduction than control.

The applicant proposal of using an uncertainty factor of 1.2 to correct the tier II toxicity endpoint is not considered appropriate by the HSE evaluator. This is because the data used to derive the factor is based on carrot data which is not in-line with the proposed GAP. Hence an uncertainty factor of 2 should be used (default value in-line with EFSA journal 2019;17(8):5804). Nonetheless, using either an uncertainty factor of 1.2 or 2 still demonstrates a potential risk (see tables 2.12.7-12 and 2.12.7-13). The applicant provided the following discussion (shown in italics) to justify an acceptable risk:



*‘For A. rhopalosiphi the endpoints corrected by the uncertainty factor are slightly below the  $PER_{in-field}$ . However, there were minor effects in terms of mortality and reproduction for A. rhopalosiphi at the highest concentration tested (7.1% corrected mortality, no effect on reproduction). It is highly unlikely that 50% effects would have been reached at a test rate corresponding to the PER (0.666 L/ha). In addition, the worst-case enantiomeric ratio observed in carrot leaves that was used to calculate the uncertainty factor was measured 67 days after application. The highest residues on leaves that correspond to the  $PER_{in-field}$  occur shortly after application, when a much smaller enantiomeric shift is expected, which would lead to a smaller correction factor. Therefore, the corrected endpoint of >0.58 L/ha can be considered as protective. Assuming a first order exponential decay and a generic  $DT_{50}$  on leaves of 10 days as recommended in the EFSA Birds & Mammals guidance, the estimated residues on leaves will decline from 0.666 L/ha to 0.58 L/ha after 2 days. Therefore, the  $PER_{in-field}$  will reach the level that is shown to be safe for NTAs within a very short timeframe and the potential for recovery is given. An acceptable risk to non-target arthropods is therefore concluded.’*

#### HSE comments:

It is not possible to confirm whether a  $DT_{50}$  value of 10 days is appropriate for cinmethylin due to a lack of data. Furthermore, degradation of the active substance, formation of metabolite and changes in ratios of enantiomers may occur, hence the use of a  $DT_{50}$  for cinmethylin in the enantiomer risk assessment is not considered appropriate.

When considering all plant residue studies (tables 2.12.7-18 to 2.12.7-22) the cinmethylin levels are relatively low at the first sampling date after day 0 (application); oilseed rape range of < 0.01 to 0.062 mg a.s./kg and cereals range of < 0.01 to 0.065 mg a.s./kg. The majority being < 0.01 mg a.s./kg. It should be noted the first sampling dates were variable and not close to application date (range of 8 to 70 days after application). This suggests that levels of cinmethylin and enantiomers will also decrease over time.

The toxicity endpoint is estimated based on toxicity of the formulation as the toxicity of enantiomers is unknown. To allow for this uncertainty the agreed factor of 2 (EFSA journal 2019;17(8):5804) has been Applied. The tier II *Aphidius* toxicity endpoint is based on the highest test concentration where there were no effects on reproduction and 7.1 % mortality (control corrected) i.e. is unbound hence there is a margin of safety built in to this endpoint. Furthermore, it is feasible that a proportion of enantiomers is in the plants (as shown in residue trials), noting the above risk assessment assumes exposure of enantiomers is equivalent to the formulation. Therefore, when considering exposure there is also a margin of safety in the risk assessment.

Given the above, it is considered that the exceedence of the in-field PER compared to the adjusted toxicity endpoint is acceptable (table 2.12.7-13) for the proposed uses. To give further weight to this argument it is likely that residues of cinmethylin and the enantiomers will decline over time and hence decrease to a level where recolonisation of non-target arthropods can occur.

#### Overall conclusion for in-field risk to non-target arthropods:

Based on above an acceptable risk to non-target arthropods has been demonstrated for proposed uses. This includes *Aphidius* based on likely residue levels and potential for recolonisation. However, depending on the proposed GAP the in-field risk assessment may need to be re-visited in future applications.

#### Off-field assessment:

Table 2.12.7-14:  $HQ_{off-field}$  values for non-target arthropods exposed to BAS 684 03 H in winter wheat (worst case use) applying uncertainty factor of 2 to toxicity endpoints

Species	$LR_{50}$ [L/ha]	$PER_{off-field}$ [L/ha]	$HQ_{off-field}$	Trigger value
<i>Aphidius rhopalosiphi</i> , Tier I, 2D exposure scenario	0.136/ 2* = 0.068	0.00184	0.0271	2
<i>Typhlodromus pyri</i> , Tier I, 2D exposure scenario	0.764/ 2* = 0.382		0.0048	2

PER = predicted environmental rate.

\* = Endpoint corrected using an uncertainty factor of 2.

The calculated HQ<sub>off-field</sub> values for *A. rhopalosiphi* and *T. pyri* fall below the trigger value of 2, indicating that the application of BAS 684 03 H to winter wheat and oilseed rape poses a low risk to non-target arthropods in off-field situations following EFSA enantiomer guidance (journal 2019;17(8):5804).

Overall conclusion for bees and non-target arthropods:

An acceptable risk for bees and non-target arthropods has been concluded when considering enantiomeric ratios for the proposed uses. It should be noted these conclusions apply to the proposed GAP single application to oilseed rape/cereals hence any changes in future submissions may need further consideration.

1.1.1.-4 Soil organisms and non-target plants:

*‘BAS 684 H, as racemate, consists of the enantiomer (-) Reg. No. 5925581 and (+) Reg. No. 5925632. Detailed evaluation in soil showed that the DT<sub>50</sub> values of the two enantiomers differed slightly with DT<sub>50</sub> values of 12,8 days and 17,6 days for (-) Reg. No. 5925581 and (+) Reg. No. 5925632, respectively. BAS 684 H has a DT<sub>50</sub> of 15.3 days. While degrading, the difference in DT<sub>50</sub> might lead to a small shift in the 50:50-ratio of the enantiomers compared to the test compound, however the impact on the risk assessment is deemed negligible. Longer half-life could lead to an increase for the (+) enantiomer over time. For all soil organisms the risk assessment is passed with margin of safety and the fact that the change in ratio of the enantiomers would only be relevant at a stage of advanced degradation underlines the negligible impact on the conclusion drawn in the soil risk assessment.*

*For non-target plants it is shown that the herbicidal activity of the (+) enantiomer which degrades somewhat slower is lower than the (-) enantiomer. This suggests that the risk for NTTPs is covered with the current evaluation.’*

**HSE comments:**

The HSE fate evaluator has considered in detail the information provided by the applicant regarding changes in ratios in soil. See volume 1, section 2.8.1 for full details. The following conclusions were reached:

In the aerobic degradation study, a more rapid degradation of the (-)-enantiomer was observed in some soils that led to shifts in the enantiomeric ratio. For example, in the LAD-SCL-PF soil (cinmethylin DT<sub>50</sub> = 43.5 days), the ratio shifted to 23:77 after 120 days, with 9.4 % of cinmethylin remaining. Conversely, in the soil displaying the longest DT<sub>50</sub> (Lufa 2.2; 192.8 days), the ratio measured 46:54 after 120 days, with 40 % of cinmethylin remaining. Overall, there is a 13.1 day difference in the geomean modelling DT<sub>50</sub>s for the aerobic degradation of enantiomers, with the (-)-enantiomer degrading faster.

A similar trend was observed in the aerobic phase of the anaerobic degradation study [see report KCA 7.1.1.2/1], with variable enantiomeric ratios observed by 10 DAT. The Lufa 2.2 soil displayed a slight shift to a ratio of 46:54 with 60.5 % cinmethylin remaining after 10 days, whereas the North Dakota soil exhibited a ratio of 29:71 with 48 % cinmethylin remaining after 10 days. However, all four soils showed little change in the enantiomeric ratio once anaerobic conditions had been established.

In the soil photolysis study [see report KCA 7.1.1.3/1], the enantiomeric ratio also did not display a notable change, shifting to 46:54 after 15 days with 56 % of applied cinmethylin remaining.

The HSE fate evaluator concludes that changes in enantiomeric ratio are driven by the faster degradation of the (-)-enantiomer in aerobic soils. Anaerobic degradation and photolysis do not appear to influence the enantiomeric ratio, consistent with the route of degradation being primarily aerobic degradation.

Similar to the aquatic studies the fate specialist considered the change in ratios driven by degradation rather than transformation meaning concentrations of individual enantiomers are not likely to increase. Conversely, to the aquatic compartment in soil the degradation of the (-) enantiomer was faster than the (+) based on the available data. The HSE evaluator notes that there was a wide margin of safety in the lower tier risk assessment when considering soil-organisms (minimum of 7.4 compared to trigger value of 5) and based on the available fate data

transformation of isomers was not occurring. However, degradation in aerobic soil and subsequent changes in enantiomeric ratio was variable depending on soil type ranging from a slight shift after 10 days in Lufa 2.2 soil and a more rapid significant shift in North Dakota soil with 29:71 over the same time period. The HSE evaluator has summarised the soil types used in the fate and ecotoxicology dossiers in table 2.12.7-17. Based on the reported details a mixture of soil types were used but it was not possible to state that the ecotoxicology studies tested soils were comparable to Lufa 2.2 (where the least degradation occurred based on the available fate studies). Given that the both toxicity of the individual enantiomers to soil organisms and the enantiomeric ratio change in the soil ecotoxicity studies is unknown further consideration is required.

Following a request for information further consideration was provided by the applicant. As previously mentioned the change in ratios appears to be due to degradation rather than increasing concentrations. Furthermore, when considering the available data the largest shift resulted in a ratio of 23:77. In accordance with EFSA enantiomer guidance (journal 2019;17(8):5804) using this ratio would result in an uncertainty factor of 1.54, calculated by highest percentage of isomer multiplied by default uncertainty factor of 2 i.e.  $77/100 \times 2$ . This uncertainty factor has been applied to the soil organism toxicity endpoints in the risk assessment below for the proposed uses using the worst case exposure values. It was noted that even if the default uncertainty factor of 2 was used an acceptable risk would still be demonstrated for the proposed uses.

Table 2.12.7-15 Chronic risk to earthworms and other soil macro-organisms from ‘worst case’ GAP (single application at 500 g a.s./ha to winter cereals).

Test organism	Test substance	Toxicity endpoint# (mg a.s./kg dws)	PECsoil (mg a.s./kg dws)	TER	Trigger
<i>Eisenia fetida</i>	Cinmethylin	41.8	0.667	41	5
<i>Eisenia fetida</i>	BAS 684 03 H	43.6	0.667	42	5
<i>Folsomia candida</i>	BAS 684 03 H	67.0	0.667	65	5
<i>Hypoaspis aculeifer</i>	BAS 684 03 H	102.0	0.667	99	5

# Most conservative value of either NOEC or EC<sub>10</sub>, noting endpoints have been corrected by factor of 2 as  $\log_{10} > 2$ ). In addition an uncertainty factor of 1.54 has been applied.

The risk assessment for soil micro-organisms has been considered below. Noting this assessment would also demonstrate an acceptable risk if the default uncertainty factor of 2 was used in the risk assessment for the proposed uses.

Table 2.12.7-16 Risk to soil micro-organisms from ‘worst case’ GAP (single application at 500 g a.s./ha to winter cereals).

Test substance	Test design	<25 % effects concentration (mg a.s./kg dws)#	PECsoil (mg a.s./kg dws)	Acceptable risk?
Cinmethylin	Nitrogen transformation 28 d	4.66	0.667	Yes
BAS 684 03 H		3.19	0.667	Yes

# An uncertainty factor of 1.54 has been applied to the toxicity endpoint.

Based on the above risk assessments an acceptable risk to soil organisms has been demonstrated for the proposed uses and further consideration from an ecotoxicology perspective is not required.

#### Non-target terrestrial plants:

When considering non-target plants, efficacy studies are available, and the following conclusions were reached by the HSE efficacy evaluator:

The efficacy of the individual isomers was investigated in a 2018 trial (see KCA\_3.2/001, Kraemer, 2018 BASF DocID 2018/1069982). In a greenhouse trial both the R (-) and S (+) enantiomers were tested against the weed species *Apera spica-venti* (APESV) and *Poa annua* (POAAN). In this trial the R (-) enantiomer showed a similar activity as BAS 684 H while the S (+) enantiomer was slightly less efficacious.

As the enantiomer with the slowest degradation rate in soil appears to have less herbicidal activity this suggests the change in ratios is not likely to impact the risk assessment for non-target plants. Therefore, further consideration from an ecotoxicology perspective is not required.

**Overall conclusion (ecotoxicology) for all non-target organism groups:**

An acceptable risk has been demonstrated for the proposed uses when considering enantiomer ratios of cinmethylin and where applicable the metabolite M684H005. It should be noted these conclusions apply to the proposed GAP single application to oilseed rape/cereals hence any changes in future submissions may need further consideration.

The soil types tested in both the fate and ecotoxicology along with properties are detailed in the tables below.

Table 2.12.7-17: Physio-chemical properties of test soils used in fate and ecotoxicology studies.

Soil designation	LUFA 2.2 (fate study: Stewart & Abernethy, 2016)	North Dakota soil (MSL-PF) Fate study: Stewart & Abernethy, 2016	Soil used in chronic cinmethylin Earthworm study 56 days (Friedrich, 2016)	Soil used in chronic product Earthworm study 56 days (Friedrich, 2018)	Soil used in chronic <i>Folsomia candida</i> product study 28 days (Friedrich, 2017)	Soil used in chronic <i>Hypoaspis aculeifer</i> product study 14 days (Schulz, 2017a)	Nitrogen transformation rate cinmethylin study 28 days (Schulz, 2016)	Nitrogen transformation rate cinmethylin study 28 days (Schulz, 2017b)
DIN 4220 particle size distribution (%)								
Sand 0.050 – 2 mm	80	62	50 industrial quartz sand (> 50 % of particles between 0.05 and 0.2 mm)	50 industrial quartz sand (> 50 % of particles between 0.05 and 0.2 mm)	74.7 industrial quartz sand (> 50 % of particles between 0.05 and 0.2 mm)	74.8 industrial quartz sand (> 50 % of particles between 0.05 and 0.2 mm)	52.0 (5.9 % 0.63 – 2.0 mm, 36.9 % 0.2 – 0.63 mm, 9.2 % 0.063 – 0.2 mm)	53.5 (6.0 % 0.63 – 2.0 mm, 37.1 % 0.2 – 0.63 mm, 10.3 % 0.063 – 0.2 mm)
Silt 0.002 – 0.063 mm	11	22	20 % kaolin clay (approx. 0.023 – 0.035 mm)	20 % kaolin clay (approx. 0.023 – 0.035 mm)	20 % kaolin clay (approx. 0.023 – 0.035 mm)	20 % kaolin clay (approx. 0.023 – 0.035 mm)	37.2	35.7
Clay < 0.002 mm	9.0	16	n.r	n.r	n.r	n.r	10.8	10.9
DIN textual class:	Weak loamy sand	Loamy sand	n.r	n.r	n.r	n.r	Loamy sand (DIN 4220)	Loamy sand (DIN 4220)
Total Organic Carbon (%)	1.5	2.1	n.r	n.r	n.r	n.r	1.4	1.49

n.r = not reported.

Table 2.12.7-18: Residues of BAS 684 H, M684H005 and M684H006 in oilseed rape (trials which support the critical GAP are underlined)

Report No. Location (EU-region) Trial No	Commodity/ Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest	Method of treatment	Formulation	Application rate per treatment			No. of treat- ments and last date	Growth stage at last date	Portion analysed	DALA <sup>1</sup>	Residues (mg/kg)		
					kg a.s./hL	Water L/ha	kg a.s./ha					BAS 684 H (cinmethylin)	Sum of M684H005 and M684H006, expressed as M684H005	Total <sup>4</sup>
741157 2017/1219191 67117 Limburgerhof Germany (N) L160024	SO 0495 Oilseed rape Heros	1. 21.03.2016 2. 02.06.-13.06.2016 3. 22.07.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.124	203.8	0.252	1 18.05.2016	18	Plant <sup>2</sup> Plant <sup>2</sup> Rest <sup>3</sup> Seed	0 22 65 65	8.9 <0.01 <0.01 <0.01	0.16 0.32 <0.01 <0.01	9.0 0.20 <0.016 <0.016
741157 2017/1219191 45300 Audeville France (N) L160025	SO 0495 Oilseed rape Mosaik	1. 06.04.2016 2. 20.06.-15.07.2016 3. 08.09.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.125	209	0.261	1 24.05.2016	21	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Rest <sup>3</sup> Seed	0 8 34 107 107	11 0.011 <0.01 <0.01 <0.01	0.049 1.3 <0.01 <0.01 <0.01	11 0.80 <0.016 <0.016 <0.016
741157 2017/1219191 6662 PK Elst The Netherlands (N) L160026	SO 0495 Oilseed rape Royal Pro	1. 11.09.2015 2. not reported 3. 18.07.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.125	203	0.253	1 24.03.2016	18	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Rest <sup>3</sup> Seed	0 11 36 116 116	9.6 0.023 <0.01 <0.01 <0.01	0.017 1.1 0.11 <0.01 <0.01	9.6 0.69 0.077 <0.016 <0.016
741157 2017/1219191 DE695AT Church Broughton United Kingdom (N) L160027	SO 0495 Oilseed rape Picto	1. 02.09.2015 2. 01.05.-16.06.2016 3. 25.07.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.124	220	0.272	1 11.03.2016	18	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Rest <sup>3</sup> Seed	0 25 69 136 136	10 0.022 <0.01 <0.01 <0.01	0.013 1.0 <0.01 <0.01 <0.01	10 0.63 <0.016 <0.016 <0.016
741157 2017/1219191 40052 Baricella Italy (S) L160028	SO 0495 Oilseed rape Pulsar	1. 30.09.2015 2. 02.04.-25.05.2016 3. 16.06.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.125	210	0.263	1 24.02.2016	18	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Rest <sup>3</sup> Seed	0 26 47 113 113	5.4 <0.01 <0.01 <0.01 <0.01	0.012 0.25 <0.01 <0.01 <0.01	5.4 0.16 <0.016 <0.016 <0.016
741157 2017/1219191 57018 Melissachori Greece (S) L160029	SO 0495 Oilseed rape Karun	1. 12.12.2015 2. 30.03.-20.04.2016 3. 23.06.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.125	218	0.272	1 22.02.2016	18	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Rest <sup>3</sup> Seed	0 16 44 122 122	11 0.020 <0.01 <0.01 <0.01	0.037 1.5 0.081 <0.01 <0.01	11 0.93 0.059 <0.016 <0.016

Report No. Location (EU-region) Trial No	Commodity/ Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest	Method of treatment	Formulation	Application rate per treatment			No. of treat- ments and last date	Growth stage at last date	Portion analysed	DALA <sup>1</sup>	Residues (mg/kg)		
					kg a.s./hL	Water L/ha	kg a.s./ha					BAS 684 H (cinmethylin)	Sum of M684H005 and M684H006, expressed as M684H005	Total <sup>4</sup>
741157 2017/1219191 40050 Castello D'Argile Italy (S) L160030	SO 0495 Oilseed rape Excalibur	1. 10.10.2015 2. 04.04.-02.05.2016 3. 23.06.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.125	207	0.258	1 24.02.2016	18	Plant <sup>2</sup>	0	7.6	0.20	7.7
										Plant <sup>2</sup>	29	<0.01	0.41	0.26
										Plant <sup>2</sup>	52	<0.01	<0.01	<0.016
										Rest <sup>3</sup>	121	<0.01	<0.01	<0.016
										Seed	121	<0.01	<0.01	<0.016
741157 2017/1219191 22193 Arascues Spain (S) L160031	SO 0495 Oilseed rape Hydromel	1. 01.10.2015 2. not reported 3. 28.06.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.123	199	0.244	1 10.03.2016	18	Plant <sup>2</sup>	0	6.0	0.10	6.1
										Plant <sup>2</sup>	12	0.062	1.1	0.73
										Plant <sup>2</sup>	32	<0.01	0.067	0.051
										Rest <sup>3</sup>	110	<0.01	<0.01	<0.016
										Seed	110	<0.01	<0.01	<0.016

1 Days after last application

2 Whole plant without roots

3 Rest of plant without roots

4 Sum of BAS 684 H, M684H005 and M684H006, expressed as BAS 684 H. The conversion factor is 0.606, based on molecular weights (274.4 g/mol / 452.54 g/mol).

Table 2.12.7-19: Residues of BAS 684 H, M684H005 and M684H006 in oilseed rape (trials which support the critical GAP are underlined)

Report No. Location (EU-region) Trial No	Commodity/ Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest	Method of treatment	Formulation	Application rate per treatment			No. of treat- ments and last date	Growth stage at last date	Portion analysed	DALA <sup>1</sup>	Residues (mg/kg)		
					kg a.s./hL	Water L/ha	kg a.s./ha					BAS 684 H (cinmethylin)	Sum of M684H005 and M684H006, expressed as M684H005	Total <sup>4</sup>
741158 2017/1219684 27449 Mulsum Germany (N) L170029	SO 0495 Oilseed rape DK Imperial	1. 31.08.2016 2. 18.04.-10.05.2017 3. 05.08.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.126	215	0.270	1 14.03.2017	18	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Rest <sup>3</sup> Seed	0 16 50 144 144	6.8 0.013 <0.01 <0.01 <0.01	0.063 0.60 0.065 <0.01 <0.01	6.8 0.38 0.049 <0.016 <0.016
741158 2017/1219684 6675 AD Valburg The Netherlands (N) L170030	SO 0495 Oilseed rape Pt 211	1. 09.09.2016 2. not reported 3. 19.07.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.127	227	0.288	1 10.03.2017	18	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Rest <sup>3</sup> Seed	0 14 49 131 131	12 0.065 <0.01 <0.01 <0.01	0.075 1.2 0.043 <0.01 <0.01	12 0.79 0.036 <0.016 <0.016
741158 2017/1219684 91150 Mespuits France (N) L170031	SO 0495 Oilseed rape DK Exception	1. 10.09.2016 2. 05.01.-18.05.2017 3. 04.07.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.125	184	0.230	1 03.03.2017	19	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Rest <sup>3</sup> Seed	0 14 40 123 123	9.0 0.018 <0.01 <0.01 <0.01	0.010 0.57 0.015 <0.01 <0.01	9.0 0.36 0.019 <0.016 <0.016
741158 2017/1219684 2476 Pázmánd Hungary (N) L170032	SO 0495 Oilseed rape DK Exquisite	1. 24.10.2016 2. 05.04.-25.04.2017 3. 29.06.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.127	213	0.271	1 17.03.2017	18	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Rest <sup>3</sup> Seed	0 20 35 109 109	9.2 <0.01 <0.01 <0.01 <0.01	0.14 0.50 <0.01 <0.01 <0.01	9.3 0.31 <0.016 <0.016 <0.016
741158 2017/1219684 82290 Barry- d'islemade France (S) L170033	SO 0495 Oilseed rape Trezzor	1. 24.10.2016 2. 05.04.-25.04.2017 3. 29.06.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.125	203	0.253	1 03.03.2017	18	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Rest <sup>3</sup> Seed	0 18 42 118 118	9.8 <0.01 <0.01 <0.01 <0.01	0.018 0.42 0.020 <0.01 <0.01	9.8 0.26 0.022 <0.016 <0.016
741158 2017/1219684 57018 Melissachori Greece (S) L170034	SO 0495 Oilseed rape SY Cassidy	1. 26.09.2016 2. 18.04.-19.05.2017 3. 23.06.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.125	214	0.267	1 20.03.2017	18	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Rest <sup>3</sup> Seed	0 9 37 95 95	8.1 0.025 <0.01 <0.01 <0.01	0.17 1.4 0.17 <0.01 <0.01	8.2 0.87 0.11 <0.016 <0.016



Report No. Location (EU-region) Trial No	Commodity/ Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest	Method of treatment	Formulation	Application rate per treatment			No. of treat- ments and last date	Growth stage at last date	Portion analysed	DALA <sup>1</sup>	Residues (mg/kg)		
					kg a.s./hL	Water L/ha	kg a.s./ha					BAS 684 H (cinmethylin)	Sum of M684H005 and M684H006, expressed as M684H005	Total <sup>4</sup>
741158 2017/1219684 40059 Fossatone di Medicina Italy (S) L170035	SO 0495 Oilseed rape Pulsar	1. 25.10.2016 2. 07.04.-10.05.2017 3. 12.06.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.126	217	0.273	1 02.03.2017	18	Plant <sup>2</sup>	0	9.9	0.33	10
										Plant <sup>2</sup>	19	<0.01	0.23	0.15
										Plant <sup>2</sup>	36	<0.01	0.025	0.025
										Rest <sup>3</sup>	102	<0.01	<0.01	<0.016
										Seed	102	<0.01	<0.01	<0.016
741158 2017/1219684 22193 Arascues Spain (S) L170036	SO 0495 Oilseed rape Hydromel	1. 10.09.2016 2. 20.03.-02.05.2017 3. 19.06.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.125	213	0.266	1 02.03.2017	18	Plant <sup>2</sup>	0	5.7	0.18	5.8
										Plant <sup>2</sup>	12	<0.01	0.81	0.50
										Plant <sup>2</sup>	35	<0.01	0.056	0.044
										Rest <sup>3</sup>	109	<0.01	<0.01	<0.016
										Seed	109	<0.01	<0.01	<0.016

1 Days after last application

2 Whole plant without roots

3 Rest of plant without roots

4 Sum of BAS 684 H, M684H005 and M684H006, expressed as BAS 684 H. The conversion factor is 0.606, based on molecular weights (274.4 g/mol / 452.54 g/mol).

Table 2.12.7-20 Residues of BAS 684 H, M684H005 and M684H006 in wheat (trials which support the critical GAP are underlined)

Report No. Location (EU-region) Trial No	Commodity/ Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest	Method of treatment	Formulation	Application rate per treatment			No. of treatments and last date	Growth stage at last date	Portion analysed	DALA <sup>1</sup>	Residues (mg/kg)			Remarks by residue UK evaluator- see CA, volume 3, B7 residue dossier
					kg a.s./hL	Water L/ha	kg a.s./ha					BAS 684 H (cinmethylin)	Sum of M684H005 and M684H006, expressed as M684H005	Total <sup>3</sup>	
741155 2016/1118116 67117 Limburgerhof Germany (N) L150075	GC 0654 Wheat Kadrij	1. 19.03.2015 2. 08.06.- 24.06.2015 3. 20.07.2015	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.251	200	0.503	1 23.04.2015	29	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Grain Straw	0 43 53 88 88	42 <0.01 <0.01 <0.01 <0.01	1.1 <0.01 <0.01 <0.01 <0.01	43 <0.016 <0.016 <0.016 <0.016	
741155 2016/1118116 6599 AV Ven- Zelderheide The Netherlands (N) L150076	GC 0654 Wheat Tybalt	1. 11.04.2015 2. 26.06.- 11.07.2015 3. 13.08.2015	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.251	192	0.482	1 29.05.2015	29	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Grain Straw	0 17 34 76 76	15 0.023 0.018 <0.01 <0.01	1.0 0.67 0.31 <0.01 <0.01	16 0.43 0.21 <0.016 <0.016	
741155 2016/1118116 51110 Auménancourt France (N) L150077	GC 0654 Wheat Epos	1. 19.03.2015 2. 10.06.- 30.06.2015 3. 29.07.2015	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.251	195	0.490	1 07.05.2015	29	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Grain Straw	0 25 35 83 83	38 <0.01 <0.01 <0.01 <0.01	1.5 0.62 0.092 <0.01 <0.01	39 0.39 0.066 <0.016 <0.016	
741155 2016/1118116 CV35 0JH Kinton United Kingdom (N) L150078	GC 0654 Wheat Tybalt	1. 06.03.2015 2. 10.07.- 23.07.2015 3. 11.09.2015	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.251	203	0.511	1 01.06.2015	29	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Grain Straw	0 32 45 102 102	30 0.026 <0.01 <0.01 <0.01	1.4 0.086 0.041 <0.01 <0.01	31 0.078 0.035 <0.016 <0.016	
741155 2016/1118116 47320 Lafitte-sur- Lot France (S) L150079	GC 0654 Wheat Epos	1. 15.04.2015 2. 25.06.- 07.07.2015 3. 05.08.2015	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.251	211	0.531	1 01.06.2015	29	Plant <sup>2</sup> Plant <sup>2</sup> Plant <sup>2</sup> Grain Straw	0 18 28 65 65	26 0.012 0.016 <0.01 <0.01	0.64 1.2 0.49 <0.01 0.39	26 0.74 0.31 <0.016 0.25	Storage period of samples not supported by the storage stability results.
741155	GC 0654	1. 01.02.2015	Spray	BAS 684 02	0.250	207	0.517	1	29	Plant <sup>2</sup>	0	28	0.23	28	Storage period

Report No. Location (EU-region) Trial No	Commodity/ Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest	Method of treatment	Formulation	Application rate per treatment			No. of treatments and last date	Growth stage at last date	Portion analysed	DALA <sup>1</sup>	Residues (mg/kg)			Remarks by residue UK evaluator- see CA, volume 3, B7 residue dossier
					kg a.s./hL	Water L/ha	kg a.s./ha					BAS 684 H (cinmethylin)	Sum of M684H005 and M684H006, expressed as M684H005	Total <sup>3</sup>	
2016/1118116 61200 Chesotopos Greece (S) L150080	Wheat Maestrale	2. 05.05.- 15.05.2015 3. 16.06.2015	application	H (EC) 750 g/L BAS 684 H				16.04.2015		Plant <sup>2</sup>	14	0.017	0.50	0.32	of samples not supported by the storage stability results.
										Plant <sup>2</sup>	21	<0.01	0.18	0.12	
										Grain	61	<0.01	<0.01	<0.016	
										Straw	61	0.026	0.060	0.062	
741155 2016/1118116 20060 Bellinzago Italy (S) L150081	GC 0654 Wheat Palesio	1. 13.01.2015 2. 03.05.- 13.05.2015 3. 26.06.2015	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.251	204	0.513	1 02.04.2015	29	Plant <sup>2</sup>	0	13	0.40	13	Storage period of samples not supported by the storage stability results.
										Plant <sup>2</sup>	26	0.014	0.47	0.30	
										Plant <sup>2</sup>	36	<0.01	0.54	0.34	
										Grain	85	<0.01	<0.01	<0.016	
741155 2016/1118116 02110 La Gineta Spain (S) L150082	GC 0654 Wheat Mane Nick	1. 22.01.2015 2. 15.05.- 25.05.2015 3. 02.07.2015	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.251	193	0.485	1 10.04.2015	29	Plant <sup>2</sup>	0	25	0.88	26	Storage period of samples not supported by the storage stability results.
										Plant <sup>2</sup>	26	<0.01	0.31	0.20	
										Plant <sup>2</sup>	39	<0.01	0.068	0.051	
										Grain	83	<0.01	<0.01	<0.016	
										Straw	83	<0.01	0.043	0.036	

<sup>1</sup> Days after last application

<sup>2</sup> Whole plant without roots

<sup>3</sup> Sum of BAS 684 H, M684H005 and M684H006, expressed as BAS 684 H. The conversion factor is 0.606, based on molecular weights (274.4 g/mol / 452.54 g/mol).

Table 2.12.7-21: Residues of BAS 684 H, M684H005 and M684H006 in wheat (trials which support the critical GAP are underlined)

Report No. Location (EU-region) Trial No	Commodity/ Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest	Method of treatment	Formulation	Application rate per treatment			No. of treat- ments and last date	Growth stage at last date	Portion analysed	DALA <sup>1</sup>	Residues (mg/kg)		
					kg a.s./hL	Water L/ha	kg a.s./ha					BAS 684 H (cinmethylin)	Sum of M684H005 and M684H006, expressed as M684H005	Total <sup>3</sup>
777105 2017/1198202 67117 Limburgerhof Germany (N) L160032	GC 0654 Wheat Kadrilj	1. 16.03.2016 2. 06.06.-14.06.2016 3. 27.07.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.251	200	0.502	1 04.05.2016	27-29	Plant <sup>2</sup>	0	28	1.5	29
										Plant <sup>2</sup>	28	<0.01	0.088	0.063
										Plant <sup>2</sup>	36	<0.01	0.021	0.023
										Grain	84	<0.01	<0.01	<0.016
										Straw	84	<0.01	<0.01	<0.016
777105 2017/1198202 6580 Vamdrup Denmark (N) L160033	GC 0654 Wheat Lennox	1. 07.04.2016 2. 27.06.-01.07.2016 3. 26.08.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.251	202	0.507	1 01.06.2016	29	Plant <sup>2</sup>	0	22	1.0	23
										Plant <sup>2</sup>	19	<0.01	0.81	0.50
										Plant <sup>2</sup>	28	<0.01	0.11	0.077
										Grain	86	<0.01	<0.01	<0.016
										Straw	86	<0.01	<0.01	<0.016
777105 2017/1198202 60350 Jaulzy France (N) L160034	GC 0654 Wheat Granny	1. 15.03.2016 2. 20.06.-10.07.2016 3. 01.08.-15.08.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.251	207	0.519	1 27.05.2016	29	Plant <sup>2</sup>	0	13	1.5	14
										Plant <sup>2</sup>	18	<0.01	1.1	0.68
										Plant <sup>2</sup>	39	<0.01	0.16	0.11
										Grain	75	<0.01	<0.01	<0.016
										Straw	75	<0.01	<0.01	<0.016
777105 2017/1198202 6221 Saint-Amand Belgium (N) L160035	GC 0654 Wheat Triso	1. 18.03.2016 2. 15.06.-24.06.2016 3. 15.08.-31.08.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.251	204	0.513	1 09.05.2016	29	Plant <sup>2</sup>	0	27	0.50	27
										Plant <sup>2</sup>	30	<0.01	0.056	0.044
										Plant <sup>2</sup>	39	<0.01	0.013	0.018
										Grain	100	<0.01	<0.01	<0.016
										Straw	100	<0.01	<0.01	<0.016
777105 2017/1198202 47320 Bourran France (S) L160036	GC 0654 Wheat Specifik	1. 20.09.2016 2. 12.07.-25.07.2016 3. 03.08.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.252	203	0.511	1 17.06.2016	29	Plant <sup>2</sup>	0	32	0.36	32
										Plant <sup>2</sup>	24	<0.01	<0.01	<0.016
										Plant <sup>2</sup>	31	<0.01	<0.01	<0.016
										Grain	47	<0.01	<0.01	<0.016
										Straw	47	<0.01	<0.01	<0.016
777105 2017/1198202 57020 Apollonia Greece (S) L160037	GC 0654 Wheat Africa	1. 10.11.2015 2. 15.04.-30.04.2016 3. 01.06.-15.06.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.250	202	0.506	1 02.03.2016	29	Plant <sup>2</sup>	0	13	1.2	14
										Plant <sup>2</sup>	37	<0.01	0.24	0.16
										Plant <sup>2</sup>	48	<0.01	0.042	0.035
										Grain	104	<0.01	<0.01	<0.016
										Straw	104	<0.01	<0.01	<0.016

Report No. Location (EU-region) Trial No	Commodity/ Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest	Method of treatment	Formulation	Application rate per treatment			No. of treat- ments and last date	Growth stage at last date	Portion analysed	DALA <sup>1</sup>	Residues (mg/kg)		
					kg a.s./hL	Water L/ha	kg a.s./ha					BAS 684 H (cinmethylin)	Sum of M684H005 and M684H006, expressed as M684H005	Total <sup>3</sup>
777105 2017/1198202 71121 Foggia Italy (S) L160038	GC 0654 Wheat Kadrilj	1. 23.01.2016 2. 25.04.-03.05.2016 3. 28.06.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.251	194	0.487	1 15.03.2016	29	Plant <sup>2</sup>	0	23 <sup>4</sup>	0.55	23
										Plant <sup>2</sup>	33	<0.01	0.023	0.024
										Plant <sup>2</sup>	45	<0.01	<0.01	<0.016
										Grain	105	<0.01	<0.01	<0.016
										Straw	105	<0.01	<0.01	<0.016
777105 2017/1198202 41410 Carmona Spain (S) L160039	GC 0654 Wheat Athoris	1. 24.12.2015 2. 12.04.-04.05.2016 3. 08.06.2016	Spray application	BAS 684 02 H (EC) 750 g/L BAS 684 H	0.251	207	0.519	1 08.03.2016	29	Plant <sup>2</sup>	0	21	0.32	21
										Plant <sup>2</sup>	30	<0.01	0.13	0.089
										Plant <sup>2</sup>	37	<0.01	0.090	0.065
										Grain	92	<0.01	<0.01	<0.016
										Straw	92	<0.01	0.013	0.018

1 Days after last application

2 Whole plant without roots

3 Sum of BAS 684 H, M684H005 and M684H006, expressed as BAS 684 H. The conversion factor is 0.606, based on molecular weights (274.4 g/mol / 452.54 g/mol).

4 Residue of 0.036 mg/kg found in untreated control sample

Table 2.12.7-22: Residues of BAS 684 H, M684H005 and M684H006 in wheat (trials which support the critical GAP are underlined)

Report No. Location (EU-region) Trial No	Commodity/ Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest	Method of treatment	Formulation	Application rate per treatment			No. of treat- ments and last date	Growth stage at last date	Portion analysed	DALA <sup>1</sup>	Residues (mg/kg)		
					kg a.s./hL	Water L/ha	kg a.s./ha					BAS 684 H (cinmethylin)	Sum of M684H005 and M684H006, expressed as M684H005	Total <sup>3</sup>
837496 2017/1202170 46342 Velen-Ramsdorf Germany (N) L170037	GC 0654 Wheat Tybalt	1. 28.03.2017 2. 10.06.-22.06.2017 3. 07.08.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.250	197.1	0.493	1 22.05.2017	29	Plant <sup>2</sup>	0	37	2.1	38
										Plant <sup>2</sup>	15	<0.01	1.4	0.86
										Plant <sup>2</sup>	24	<0.01	1.1	0.68
										Grain	77	<0.01	<0.01	<0.016
										Straw	77	<0.01	0.014	0.018
837496 2017/1202170 6599 Ven Zelderheide The Netherlands (N) L170038	GC 0654 Wheat Tybalt	1. 29.03.2017 2. 11.06.-19.06.2017 3. 07.08.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.250	207.8	0.520	1 23.05.2017	29	Plant <sup>2</sup>	0	12	2.2	13
										Plant <sup>2</sup>	15	0.012	0.57	0.36
										Plant <sup>2</sup>	22	<0.01	0.38	0.24
										Grain	76	<0.01	<0.01	<0.016
										Straw	76	<0.01	<0.01	<0.016
837496 2017/1202170 4542 Nußbach Austria (N) L170039	GC 0654 Wheat Liskamm	1. 10.04.2017 2. 18.06.-30.06.2017 3. 01.08.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.250	202.7	0.507	1 23.05.2017	29	Plant <sup>2</sup>	0	12	4.4	15
										Plant <sup>2</sup>	17	<0.01	1.1	0.68
										Plant <sup>2</sup>	31	<0.01	0.33	0.21
										Grain	68	<0.01	<0.01	<0.016
										Straw	68	<0.01	0.023	0.024
837496 2017/1202170 37340 Ambillou France (N) L170040	GC 0654 Wheat Sculptur	1. 30.03.2017 2. 08.06.-12.06.2017 3. 20.07.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.251	193.3	0.486	1 28.04.2017	29	Plant <sup>2</sup>	0	34	0.16	34
										Plant <sup>2</sup>	26	0.017	0.16	0.11
										Plant <sup>2</sup>	49	<0.01	0.14	0.095
										Grain	83	<0.01	<0.01	<0.016
										Straw	83	<0.01	<0.01	<0.016
837496 2017/1202170 32600 Endoufielle France (S) L170041	GC 0654 Wheat Valbona	1. 03.03.2017 2. 14.05.-23.05.2017 3. 03.08.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.250	195.0	0.488	1 19.04.2017	29	Plant <sup>2</sup>	0	16	0.65	16
										Plant <sup>2</sup>	21	<0.01	0.83	0.51
										Plant <sup>2</sup>	29	<0.01	0.44	0.28
										Grain	99	<0.01	<0.01	<0.016
										Straw	99	<0.01	0.019	0.022
837496 2017/1202170 59300 Platanos Greece (S) L170042	GC 0654 Wheat Africa	1. 20.02.2017 2. 01.07.-15.07.2017 3. 15.08.-20.08.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.250	201.0	0.503	1 12.04.2017	29	Plant <sup>2</sup>	0	30	1.3	31
										Plant <sup>2</sup>	70	<0.01	<0.01	<0.016
										Plant <sup>2</sup>	86	<0.01	<0.01	<0.016
										Grain	126	<0.01	<0.01	<0.016
										Straw	126	<0.01	<0.01	<0.016

Report No. Location (EU-region) Trial No	Commodity/ Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest	Method of treatment	Formulation	Application rate per treatment			No. of treat- ments and last date	Growth stage at last date	Portion analysed	DALA <sup>1</sup>	Residues (mg/kg)		
					kg a.s./hL	Water L/ha	kg a.s./ha					BAS 684 H (cinmethylin)	Sum of M684H005 and M684H006, expressed as M684H005	Total <sup>3</sup>
837496 2017/1202170 44048 Argenta Italy (S) L170043	GC 0654 Wheat Cesare	1. 06.01.2017 2. 03.05.-13.05.2017 3. 23.06.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.250	215.0	0.538	1 07.04.2017	29	Plant <sup>2</sup>	0	18	0.18	18
										Plant <sup>2</sup>	21	<0.01	0.67	0.42
										Plant <sup>2</sup>	31	<0.01	0.38	0.24
										Grain	76	<0.01	<0.01	<0.016
										Straw	76	<0.01	0.069	0.052
837496 2017/1202170 41710 Utrera Spain (S) L170044	GC 0654 Wheat Galera	1. 26.01.2017 2. 20.04.-01.05.2017 3. 01.06.2017	Spray application	BAS 684 03 H (EC) 750 g/L BAS 684 H	0.250	195.0	0.488	1 15.03.2017	29	Plant <sup>2</sup>	0	17	0.25	17
										Plant <sup>2</sup>	21	<0.01	0.73	0.45
										Plant <sup>2</sup>	42	<0.01	0.062	0.048
										Grain	77	<0.01	<0.01	<0.016
										Straw	77	<0.01	0.023	0.024

1 Days after last application

2 Whole plant without roots

3 Sum of BAS 684 H, M684H005 and M684H006, expressed as BAS 684 H. The conversion factor is 0.606, based on molecular weights (274.4 g/mol / 452.54 g/mol)

**2.13. RESIDUE DEFINITIONS****2.13.1. Definition of residues for exposure/risk assessment**

**Food of plant origin:** sum of BAS 684 H, M684H005 and M684H006, expressed as BAS 684 H

**Food of animal origin:** Not applicable

**Soil:** sum of BAS 684 H

**Groundwater:** sum of BAS 684 H

**Surface water:** sum of BAS 684 H, M684H001, M684H003

**Sediment:** sum of BAS 684 H

**Air:** sum of BAS 684 H

**2.13.2. Definition of residues for monitoring**

**Food of plant origin:** BAS 684 H

**Food of animal origin:** BAS 684 H

**Soil:** BAS 684 H

**Groundwater:** BAS 684 H

**Surface water:** BAS 684 H, *M684H001*, *M684H003*

**Sediment:** BAS 684 H

**Air:** BAS 684 H

*Note: metabolites in italics are tentative pending ecotoxicology and toxicology outcomes.*



## **Level 3**

**CINMETHYLIN**

### 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 No 1107/2009

<b>3.1.1.1. Article 4</b>			
		Yes	No
i)	It is considered that Article 4 of Regulation No, 1107/2009 is complied with. Specifically HSE considers that authorisation is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.	Yes	
			It is considered that Article 4 of Regulation No. 1107/2009 is complied with for cinmethylin for uses as a herbicide with residual activity to control the growth of winter annual grasses and several broadleaf weed species (see Volume 1, Level 1, Table 1.5.1 for details of all the representative uses considered).
<b>3.1.1.2. Submission of further information</b>			
		Yes	No
i)	It is considered that a complete dossier has been submitted		No
			It is considered that a sufficiently complete dossier has been submitted in most areas to establish that risks are acceptable and no critical areas of concern are identified with the exception of there currently being an incomplete endocrine disruption (ED) assessment to the current guidance. It should be noted that although the ED section is included in the dossier submission, the evaluation is on-going and will be reviewed at a later date.  Potential mitigation measures (see 3.3.1 below) will be managed or addressed 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		
			<u>Methods:</u> A method for the determination of the relevant impurity Reg No 4539586,(1SR,2RS,4RS)-1-methyl-4-(propan-2-yl)-7-oxabicyclo[2.2.1]heptan-2-ol, in the plant protection product:is required.

	submission of the dossier; or (b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.			<u>Toxicology:</u> Overall, for the EAS modalities cinmethylin is not an ED and its ED potential has been sufficiently investigated. However, in relation to the T modality a conclusion cannot be reached as further information is required. T-mediated activity (in particular UGT and thyroid hormones) has not been sufficiently addressed. Based on scenario 1b of the ECHA/EFSA guidance for the identification of endocrine disruptors in the context of Regulations (EU) 528/2012 and (EC) No 1107/2009, there is an overall indication of adversity. Some information from ToxCast on thyroid activity (direct thyroid MoAs) has been presented and direct thyroid MoAs have been excluded; however, more detailed information is required to substantiate the postulated indirect MoA.				
3.1.1.3. Restrictions on approval								
		Yes	No					
	It is considered that in line with Article 6 of Regulation No 1107/2009 approval should be subject to conditions and restrictions.	Yes		<p>(a) the minimum degree of purity of the active substance; 940 g/kg</p> <p>(b) the nature and maximum content of certain impurities; The following impurities identified in technical cinmethylin are considered to be of toxicological or ecotoxicological relevance and maximum levels have been set:</p> <table><tr><td><b>Reg No 4539586:</b> (1SR,2RS,4RS)-1-methyl-4-(propan-2-yl)-7-oxabicyclo[2.2.1]heptan-2-ol:</td><td><b>Max. 4 g/kg</b></td></tr><tr><td><b>Toluene:</b></td><td><b>Max. 0.5 g/kg</b></td></tr></table> <p>(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</p> <p>(d) type of preparation; n/a</p> <p>(e) manner and conditions of application;</p> <ul style="list-style-type: none"><li>Protective gloves, protective coveralls and face protection (faceshield) when handling the concentrate</li></ul>	<b>Reg No 4539586:</b> (1SR,2RS,4RS)-1-methyl-4-(propan-2-yl)-7-oxabicyclo[2.2.1]heptan-2-ol:	<b>Max. 4 g/kg</b>	<b>Toluene:</b>	<b>Max. 0.5 g/kg</b>
<b>Reg No 4539586:</b> (1SR,2RS,4RS)-1-methyl-4-(propan-2-yl)-7-oxabicyclo[2.2.1]heptan-2-ol:	<b>Max. 4 g/kg</b>							
<b>Toluene:</b>	<b>Max. 0.5 g/kg</b>							

				<ul style="list-style-type: none"> <li>Due to the risk to non-target plants from volatilization a 5 m buffer zone has been proposed.</li> </ul> <p>(f) submission of further confirmatory information), where new requirements are established during the evaluation process or as a result of new scientific and technical knowledge; n/a</p> <p>(g) designation of categories of users, such as professional and non-professional; n/a</p> <p>(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</p> <p>(i) the need to impose risk mitigation measures and monitoring after use; As the risk from spraydrift for the proposed use was not resolved the following label mitigation is required: ‘Extreme care must be taken to avoid spray drift onto non-crop plants outside of the target area.’</p> <p>(j) any other particular conditions that result from the evaluation of information made available in the context of Regulation No 1107. n/a</p>
<b>3.1.1.4. Criteria for the approval of an active substance</b>				
<b>Dossier</b>				
		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).	Yes		Robust ADI, AOEL and ARfD have been established.
	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	Yes		The dossier contains the information necessary to carry out a risk assessment and for enforcement purposes for all the representative uses.

	<p>feed or food crops or leads indirectly to residues in food or feed). In particular it is considered that the dossier:</p> <p>(a) permits any residue of concern to be defined;</p> <p>(b) reliably predicts the residues in food and feed, including succeeding crops</p> <p>(c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing;</p> <p>(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;</p> <p>(e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.</p>			<p>The nature of residues in primary crops, livestock, processed commodities and rotational crops has been sufficiently elucidated for the representative uses.</p> <p>Residue definitions in plant and animal commodities have been determined where necessary.</p> <p>The magnitude of residues in primary crops has been determined in residues trials which are supported by storage stability data and validated analytical methods.</p> <p>Maximum residue levels have been determined for the relevant commodities which are supported by validated analytical methods for monitoring.</p> <p>No chronic or acute consumer intake concerns were identified.</p>
	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.	Yes		For all representative uses/use scenarios of the representative product.
<b>Efficacy</b>				
		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.	Yes		<p>The information provided was sufficient to meet the efficacy requirements for approval of the active substance. The representative product demonstrated control of important weed species of cereals and oilseed rape. At product authorisation it will be important that Member States check that the rates and claims and resistance management is in line with and appropriate to their conditions.</p>
<b>Relevance of metabolites</b>				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.	Yes		Sufficient information provided for the representative uses.
<b>Composition</b>				

		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.	Yes		The proposed specification based on full scale manufacturing is considered supported by the available data. The following impurities identified in technical cinmethylin are considered to be of toxicological or ecotoxicological relevance: <b>Reg No 4539586:</b> (1SR,2RS,4RS)-1-methyl-4-(propan-2-yl)-7-oxabicyclo [2.2.1]heptan-2-ol: <b>Max. 4 g/kg</b> Tolune: Max. 0.5 g/kg
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	-	-	There is currently no FAO Specification for cinmethylin.
	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	-	-	There is currently no FAO Specification for cinmethylin.
<b>Methods of analysis</b>				
		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.	Yes		Acceptable methods have been submitted for the determination of cinmethylin and all significant and relevant impurities in the technical material as manufactured.
	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.	Yes		Acceptable methods have been submitted for the determination of cinmethylin and selected metabolites in various matrices used in support of all areas of the risk assessment  Acceptable methods have been submitted for the determination of cinmethylin and selected metabolites in various matrices for use in post-approval monitoring and control

				A method for the determination of the relevant impurity Reg No 4539586, (1SR,2RS,4RS)-1-methyl-4-(propan-2-yl)-7-oxabicyclo[2.2.1]heptan-2-ol, in the plant protection product is required.
	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.	Yes		
<b>Impact on human health</b>				
<b>Impact on human health - ADI, AOEL, ARfD</b>				
		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.	Yes		<p>An <b>ADI value of 0.08 mg/kg bw/d</b> has been derived from the NOAEL of 7.9 mg/kg bw/d for liver effects from the 12-month dog study.</p> <p>An <b>ARfD value of 0.3 mg/kg bw</b> has been derived from the NOAEL of 30 mg/kg bw/d for maternal toxicity (initial body weight effects) from the rat developmental toxicity study.</p> <p>An <b>AOEL value of 0.06 mg/kg bw/d</b> has been derived from the NOAEL of 7.9 mg/kg bw/d for liver effects from the 12-month dog study.</p> <p>An <b>AAOEL value of 0.21 mg/kg bw/d</b> has been derived from the NOAEL of 30 mg/kg bw/d for maternal toxicity (initial body weight effects) from the rat developmental toxicity study.</p>
<b>Impact on human health – proposed genotoxicity classification</b>				
		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, <b>the substance SHOULD BE classified or proposed for classification</b> , in accordance with the provisions of Regulation (EC) No 1272/2008, <b>as mutagen category 1A or 1B.</b>		No	Overall, it can be concluded that cinmethylin was not genotoxic <i>in vitro</i> or <i>in vivo</i> in a series of investigations that, together, meet the data requirements of Regulation 283/2013. Classification of cinmethylin for mutagenicity is not warranted.

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, <b>the substance SHOULD BE classified or proposed for classification</b> , in accordance with the provisions of Regulation (EC) No 1272/2008, <b>as carcinogen category 1A or 1B</b> .		No	Overall, there is equivocal evidence of carcinogenicity in the female rat but not in the male rat or mice; the evidence is insufficient for classification (see aligned MCL report).
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			Not applicable.
Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, <b>the substance SHOULD BE classified or proposed for classification</b> , in accordance with the provisions of Regulation (EC) No 1272/2008, <b>as toxic for reproduction category 1A or 1B</b> .		No	Cinmethylin has no adverse effects on fertility, reproductive function or development. No classification for reproductive toxicity is required (see aligned MCL report).
ii)				Not applicable.



	<p>Linked to above classification proposal.</p> <p>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.</p>			
<b>Impact on human health – proposed endocrine disrupting properties classification</b>				
		Yes	No	
i)	<p>It is considered that <b>the substance SHOULD BE classified or proposed for classification</b> in accordance with the provisions of Regulation (EC) No 1272/2008, as <b>carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties</b></p>		No	<p>Cinmethylin is not classified for carcinogenicity or reproductive toxicity.</p> <p>Overall, for the EAS modalities cinmethylin is not an ED and its ED potential has been sufficiently investigated. However, in relation to the T modality a conclusion cannot be reached as further information is required</p>
ii)	<p>It is considered that <b>the substance SHOULD BE classified or proposed for classification</b> in accordance with the provisions of Regulation (EC) No 1272/2008, as <b>toxic for reproduction category 2 and</b> in addition HSE considers the substance <b>has toxic effects on the endocrine organs and on that basis shall be considered to have endocrine disrupting properties</b></p>		No	<p>Cinmethylin is not classified for reproductive toxicity.</p> <p>Overall, for the EAS modalities cinmethylin is not an ED and its ED potential has been sufficiently investigated. However, in relation to the T modality a conclusion cannot be reached as further information is required.</p>
iii)	<p>Linked to either i) or ii) immediately above.</p> <p>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.</p>			Not applicable.

<b>Fate and behaviour in the environment</b>				
<b>Persistent organic pollutant (POP)</b>				
		Yes	No	
	It is considered that the active substance <b>FULFILS</b> the criteria of a persistent organic pollutant (POP) as laid out in Regulation No 1107/2009 Annex II Section 3.7.1.		No	<p>A substance is deemed to meet the P criterion in a POP assessment if the DegT<sub>50</sub> is &gt; 2 months in water, &gt; 6 months in sediment or &gt; 6 months in soil.</p> <p>Cinmethylin is not considered persistent in soil as the geomean DegT<sub>50</sub> for cinmethylin in field soils, once surface processes have been eliminated, is 11.1 days. The single longest DegT<sub>50</sub> in a field soil is 53.9 days.</p> <p>Cinmethylin is also not considered persistent in water and sediment. In water/sediment studies, cinmethylin was observed to quickly partition from water to sediment, leading to the assumption that the sediment compartment is the degrading compartment. The whole system geomean DegT<sub>50</sub> was 39.2 days.</p> <p>Cinmethylin does not meet the potential for long range transport criteria as it has a calculated DT<sub>50</sub> in air of 0.167 days, which is below the threshold of 2 days.</p> <p>Based on the above, the HSE evaluator is of the opinion that cinmethylin does not fulfil the P criterion.</p>
<b>Persistent, bioaccumulative and toxic substance (PBT)</b>				
		Yes	No	
	It is considered that the active substance <b>FULFILS</b> the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation No 1107/2009 Annex II Section 3.7.2.		No	<p>Cinmethylin is not considered a PBT substance as none of the three criteria are met.</p> <p><b>Persistence (P)</b> – Cinmethylin is not persistent.</p> <p><b>Bioaccumulation (B)</b> – The active substance does not fulfil the bioaccumulation criterion as the bio concentration factor for aquatic species is ≤ 2000 (Fish, whole body geomean BCF = 100).</p> <p><b>Toxicity (T)</b> – The active substance does not fulfil the toxicity criterion because data indicate that the long-term NOEC for freshwater organisms is &lt;</p>

				0.01 mg/L (Fish NOEC ( <i>Pimephales promelas</i> ) = 0.59 mg/L; Invertebrate NOEC ( <i>Daphnia magna</i> ) = 0.29 mg/L). In addition, the active substance is not classified as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2). The active substance is also not classified as STOT RE 1 or STOT RE 2.
<b>Very persistent and very bioaccumulative substance (vPvB).</b>				
		Yes	No	
	It is considered that the active substance <b>FULFILS</b> the criteria of a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation No 1107/2009 Annex II Section 3.7.3.		No	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, cinmethylin does not fulfil this criterion.
<b>Ecotoxicology</b>				
		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. HSE 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.	Yes		
	It is considered that, on the basis of the assessment of Community or internationally agreed test guidelines, the substance <b>HAS</b> endocrine disrupting properties that may cause adverse effects on non-target organisms.			<u>Ecotoxicology:</u>  It should be noted currently endocrine disruption for the ecotoxicology section is ongoing.  For birds cinmethylin does not meet endocrine disruption criteria. For wild mammals and aquatic organisms a robust conclusion has not been reached as further information is being provided by applicant (see end of sections 2.9.1 and 2.9.2).

	<p>Linked to the consideration of the endocrine properties immediately above.</p> <p>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.</p>			See above comment.
	<p>It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist:</p> <ul style="list-style-type: none"> <li>— will result in a negligible exposure of honeybees, or</li> <li>— has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.</li> </ul>	Yes		Based on available data an acceptable risk to bees was demonstrated for the proposed uses.
<b>Residue definition</b>				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.	Yes		<p>Plant residue definition for risk assessment: sum of BAS 684 H, M684H005 and M684H006, expressed as BAS 684 H</p> <p>Plant residue definition for monitoring: BAS 684 H</p> <p>Animal residue definition for risk assessment: not applicable</p> <p>Animal residue definition for monitoring: BAS 684 H</p> <p>(Sections 2.7.3 and 2.13.1)</p>
<b>Fate and behaviour concerning groundwater</b>				
		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 No 1107/2009.	Yes		As noted at section 2.8.6 above, all metabolites of cinmethylin are predicted to be <0.1 µg/L. No further consideration of groundwater metabolite relevance required.
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### 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		No	<p>It is considered as a result of this evaluation that cinmethylin <b>does not meet the criteria</b> necessary to identify it as a candidate for substitution, as follows:</p> <p>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.</p> <p>It does not meet any of the criteria to be considered as a PBT substance.</p> <p>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).</p> <p>It does not contain a significant proportion of non-active isomers, as both enantiomers showed biological activity on all tested pathogens.</p> <p>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.</p>

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				<p>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</p> <p>It should be noted that the endocrine disruption evaluation is still on-going and therefore has not been concluded as of yet.</p>
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## Proposal – Low risk active substance

Low-risk active substances			
		Yes	No
	<p>It is considered that the active substance <b>shall be considered of low risk</b>.</p> <p>In particular it is considered that the substance <b>should NOT be classified or proposed for classification</b> in accordance with Regulation (EC) No 1272/2008 as at least one of the following:</p> <ul style="list-style-type: none"> <li>— carcinogenic,</li> <li>— mutagenic,</li> <li>— toxic to reproduction,</li> <li>— sensitising chemicals,</li> <li>— very toxic or toxic,</li> <li>— explosive,</li> <li>— corrosive.</li> </ul> <p>In addition it is considered that <b>the substance is NOT</b>:</p> <ul style="list-style-type: none"> <li>— persistent (half-life in soil more than 60 days),</li> <li>— has a bioconcentration factor higher than 100,</li> <li>— is deemed to be an endocrine disrupter, or</li> <li>— has neurotoxic or immunotoxic effects.</li> </ul>		<p>Cinmethylin <b>may not</b> be regarded as low risk because of the proposed toxicological and environmental classification:</p> <p>Skin Sensitisation Category 1: H317 - ‘May cause an allergic skin reaction’  STOT SE Cat. 2 : H371 – ‘May cause damage to the nervous system’  Aquatic Acute Category 1: - ‘H400 very toxic to aquatic life’  Aquatic Chronic Category 1: - ‘H410 very toxic to aquatic life with long lasting effects’</p>

**3.1.3.** 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
3.1.3.1. Identity of the active substance or formulation				
None required.				
3.1.3.2. Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
Data to address the content of the relevant impurity Reg No 4539586,(1SR,2RS,4RS)-1-methyl-4-(propan-2-yl)-7-oxabicyclo[2.2.1]heptan-2-ol, in the plant protection product:is required in the product before and after storage are required.	Relevant to representative product.	X		
3.1.3.3. Data on uses and efficacy				
None required.				
3.1.3.4. Data on handling, storage, transport, packaging and labelling				
Not applicable.				



<b>3.1.3.5. Methods of analysis</b>				
A method for the determination of the relevant impurity Reg No 4539586, (1SR,2RS,4RS)-1-methyl-4-(propan-2-yl)-7-oxabicyclo[2.2.1]heptan-2-ol, in the plant protection product:is required.	Relevant to representative product and therefore all representative uses.	X - Study currently unavailable		
<b>3.1.3.6. Toxicology and metabolism</b>				
Concerning the ED assessment for humans, the following further data and information is being generated by the applicant: <ul style="list-style-type: none"> <li>• <i>In vivo</i> thyroid hormone and enzyme induction study in rats</li> <li>• <i>In vitro</i> comparative enzyme activity study in rat and human hepatocytes</li> <li>• Description of the postulated MoA</li> <li>• Empirical support of the postulated MoA</li> <li>• Conclusion on MoA analysis</li> <li>• A case to address the potential for effects on post-natal neurological development in offspring</li> <li>• A case to address the potential relevance to humans (or lack thereof) of the proposed MoA</li> </ul>	All		X – date not known	
<b>3.1.3.7. Residue data</b>				
None required.				
<b>3.1.3.8. Environmental fate and behaviour</b>				
None required.				

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<b><i>3.1.3.9. Ecotoxicology</i></b>				
It should be noted consideration of endocrine disruption for the ecotoxicology section is ongoing (wild mammals and aquatic organisms).				

### 3.1.4. 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)
Human health consideration of Endocrine Disruption (ED): for the EAS modalities cinmethylin is not an ED and its ED potential has been sufficiently investigated. However, in relation to the T modality a conclusion cannot be reached as further information is required.	Relevant to all uses.
It should be noted consideration of endocrine disruption for the ecotoxicology section is ongoing (wild mammals and aquatic organisms).	Relevant to all uses.

### 3.1.5. 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 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)
Human health consideration of Endocrine Disruption (ED): for the EAS modalities cinmethylin is not an ED and its ED potential has been sufficiently investigated. However, in relation to the T modality a conclusion cannot be reached as further information is required.	Relevant to all uses.

It should be noted consideration of endocrine disruption for the ecotoxicology section is ongoing (wild mammals and aquatic organisms).	Relevant to all uses.
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### 3.1.6. 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		Winter wheat (500 g a.s./ha)	Winter barley (500 g a.s./ha)	Winter oilseed rape (500 g a.s./ha) #
Operator risk	Risk identified			
	Assessment not finalised			
Worker risk	Risk identified			
	Assessment not finalised			
Bystander risk	Risk identified			
	Assessment not finalised			
Consumer risk	Risk identified			
	Assessment not finalised			
Risk to wild non target terrestrial vertebrates	Risk identified			
	Assessment not finalised	X (ED assessment not complete)	X (ED assessment not complete)	X (ED assessment not complete)
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified			
	Assessment not finalised			
Risk to aquatic organisms	Risk identified			
	Assessment not finalised	X (ED assessment not complete)	X (ED assessment not complete)	X (ED assessment not complete)
Groundwater exposure active substance	Legal parametric value breached			
	Assessment not finalised			
Groundwater exposure metabolites	Legal parametric value breached			
	Parametric value of 10µg/L <sup>(a)</sup> breached			
	Assessment not finalised			

Comments/Remarks			
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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

# = Note use on Winter Oilseed Rape is currently not an intended GB use

### 3.1.7. 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
Human health - Carcinogenicity	<p>There is equivocal evidence of carcinogenicity in the female rat (liver carcinomas in female Wistar rats at the top dose of 317 mg/kg bw/d) in a modern study but not in the male rat or mice. See [REDACTED] (2018), DAR Vol. 3 CA B6, section B.6.5.1, Table 6.5-13. In an older study in rats ([REDACTED], 1985) and a new/modern study in mice ([REDACTED], 2018d) cinmethylin demonstrated no carcinogenic potential. An older study in mice ([REDACTED] 1986) was inconclusive due to significant shortcomings. HSE notes that the carcinogenicity response observed is very weak, sex- and species-specific, and occurs in the presence of significant generalised toxicity (effects on body weight, body weight gain and histopathology of thyroid and nasal cavities). In addition, although the liver is a target organ of toxicity in the rat, there was no clear evidence of pre-neoplastic lesions and/or adenomas (Table 6.5-15). It is also noted that the incidence of liver carcinoma was within the extended laboratory HCD range and the Rita database HCD. Considering the totality of the weight-of-evidence, HSE concludes that this equivocal response does not represent a relevant hazard to human health.</p> <p>The opinion of the ECP is sought.</p>
Human health – Developmental toxicity	<p>In a relatively old developmental toxicity study in rats an increased incidence of slight to moderate dilated ventricles of the brain was observed. See Lockry <i>et al.</i> (1984), DAR Vol. 3 CA B6, section B.6.6.2, Table 6.6-47. A statistically-significant increase in the foetal (11.7 % vs 0 % in controls) and litter incidence (28.6 % vs 0 % in controls) of (slight to moderate) lateral ventricles dilation of the brain was observed at the top dose (2,000 mg/kg bw/d, a dose two times higher than the limit dose); incidence of this finding was well above the HCD mean. This does was associated with severe maternal toxicity (deaths, significant reductions in body weights, numerous clinical signs of toxicity and liver effects). Slight to moderate dilation of brain ventricles (as compared to frank hydrocephaly) is considered to be a variation and to represent a developmental delay with no detrimental or irreversible consequences for the foetus. Therefore, HSE deems it is most likely that this abnormality was the secondary consequence of the excessive maternal toxicity occurring at the high dose of 2,000 mg/kg bw/d.</p> <p>The opinion of the ECP is sought.</p>

Human health – Neurotoxicity	<p>In the acute neurotoxicity rat study minimal axonal degeneration of the sciatic nerve was seen at the top dose (2,000 mg/kg bw) in both sexes (more pronounced in females). See [REDACTED]. (2018e), DAR Vol. 3 CA B6, section B.6.7.1, Table 6.7-5. These neuropathology effects were accompanied by alterations in functional observation battery (FOB) and motor activity (MA) parameters (retarded righting response, reduced number of rearings and decreased motor activity) from 1,000 mg/kg bw. These findings occurred in the presence of some generalised toxicity (clinical signs of toxicity and salivation on the day of administration only) from the mid dose (1,000 mg/kg bw) in females and at the top dose (2,000 mg/kg bw) in males.</p> <p>There was no clear evidence of neurotoxicity in the acute toxicity (LD50) studies; however, it should be noted that no specific neurobehavioural or neuropathology investigations are generally performed in these studies. There were no neurotoxic effects of cinmethylin observed following repeated exposure in the new/modern 28- and 90-day oral studies in rats and mice, as well as the 28-day dermal study in rats. It is most likely that the minimal axonal degeneration of the sciatic nerve finding noted at 2,000 mg/kg bw in the rat neurotoxicity study are the acute consequences of high gavage doses of cinmethylin, possibly related to a Cmax, bolus effect. Overall, HSE concludes that cinmethylin is acutely neurotoxic from a dose of 1,000 mg/kg bw.</p> <p>The opinion of the ECP is sought.</p>
Ecotoxicology – chronic mammalian endpoint	<p>HSE determined the ecotoxicology relevant mammalian chronic endpoint as 58 mg a.s./kg b.w./day protective based on adverse effects on body weight gain, see DAR Vol. 3 CP, section B.9.1.3 p8.</p> <p>The following comment was provided by applicant (shown in italics):</p> <p><i>The applicant proposes further discussion on adversity and population relevance of effects on body weight gain for setting the chronic mammalian endpoint.</i></p> <p><i>Impact on body weight gain in the 90-d study in mice at the mid dose (1000 ppm = 285/ mg/kg bw/d (f)) should not be considered an adverse population relevant effect due to following reasons:</i></p> <ul style="list-style-type: none"> <li>- <i>Effects on bwg did not translate into an overall effect on body weight (max. -4.5% at day 21 compared to -3.9% at day 91 in mid dose, following no dose response)</i></li> <li>- <i>Temporary occurrence of impact on bwg (from day 21 to 35, but not earlier or later up 90 d of exposure period) does not indicate adversity</i></li> <li>- <i>If bwg is evaluated on a weekly basis instead from day 0 of exposure period, statistically significant effects are seen only for day 7-14 (see table below for first 4 weeks, further data can be provided)</i></li> <li>- <i>General large variability of body weight gain in mice, with no clear dose response, makes evaluation of effect size difficult (see table below)</i></li> <li>- <i>In a 28-d study in mice (DocID 2014/1162710) the effect was not retrieved at comparable dose levels of 1200 ppm (295.9/254 mg/kg bw/d m/f)</i></li> <li>- <i>Dose level of 1200 ppm (285 mg/kg bw/d) of 90 d study is well above the proposed ecotox endpoint of 80 mg/kg bw/d and thus impact on bwg might be covered</i></li> </ul> <p><i>Example:</i></p>

	<p>Evaluation of bwg in females in the 90d-study on a weekly basis (further evaluation can be provided on request)</p> <p>Summary changes body weights- BW/body weights (g)</p> <p>Sex- female, Phase: In-life</p> <table><tr><th colspan="2"></th><th>0/F 0ppm</th><th>1/F 200ppm</th><th>2/F 1000ppm</th><th>3/F 5000ppm</th></tr><tr><td rowspan="4">D0 - &gt;7</td><td>Mean</td><td>0.7 n</td><td>0.7</td><td>0.8</td><td>0.4</td></tr><tr><td>s.d.</td><td>0.4</td><td>0.4</td><td>0.5</td><td>0.4</td></tr><tr><td>N</td><td>10</td><td>10</td><td>10</td><td>10</td></tr><tr><td>Deviation Vs control (%)</td><td>-</td><td>0.0</td><td>1.2</td><td>-43.1</td></tr><tr><td rowspan="4">D7 - &gt;14</td><td>Mean</td><td>0.6 n</td><td>0.3</td><td>0.1*</td><td>0.2*</td></tr><tr><td>s.d.</td><td>0.4</td><td>0.4</td><td>0.4</td><td>0.4</td></tr><tr><td>N</td><td>10</td><td>10</td><td>10</td><td>10</td></tr><tr><td>Deviation Vs control (%)</td><td>-</td><td>-46.0</td><td>-81.0</td><td>-74.6</td></tr><tr><td rowspan="4">D0 - &gt;21</td><td>Mean</td><td>0.6n</td><td>0.5</td><td>0.2</td><td>0.5</td></tr><tr><td>s.d.</td><td>0.4</td><td>0.5</td><td>0.6</td><td>0.5</td></tr><tr><td>N</td><td>10</td><td>10</td><td>10</td><td>10</td></tr><tr><td>Deviation Vs control (%)</td><td>-</td><td>-14.3</td><td>-62.5</td><td>-7.1</td></tr><tr><td rowspan="4">D0 - &gt;28</td><td>Mean</td><td>0.5n</td><td>0.6</td><td>0.6</td><td>0.6</td></tr><tr><td>s.d.</td><td>0.4</td><td>0.3</td><td>0.3</td><td>0.4</td></tr><tr><td>N</td><td>10</td><td>10</td><td>10</td><td>10</td></tr><tr><td>Deviation Vs control (%)</td><td>-</td><td>13.7</td><td>7.8</td><td>15.7</td></tr></table> <p>Statistic profile = Dunnett test (two-sided), * p&lt; = 0.05, d = day, n=DUNNETT</p> <p>Overall, the applicant is of the opinion that the NOAEL of 80 mg/kg bw/d derived from the 2-generation rat study is the appropriate ecologically relevant endpoint for the wild mammal risk assessment.</p> <p>The opinion of the ECP is sought.</p>			0/F 0ppm	1/F 200ppm	2/F 1000ppm	3/F 5000ppm	D0 - >7	Mean	0.7 n	0.7	0.8	0.4	s.d.	0.4	0.4	0.5	0.4	N	10	10	10	10	Deviation Vs control (%)	-	0.0	1.2	-43.1	D7 - >14	Mean	0.6 n	0.3	0.1*	0.2*	s.d.	0.4	0.4	0.4	0.4	N	10	10	10	10	Deviation Vs control (%)	-	-46.0	-81.0	-74.6	D0 - >21	Mean	0.6n	0.5	0.2	0.5	s.d.	0.4	0.5	0.6	0.5	N	10	10	10	10	Deviation Vs control (%)	-	-14.3	-62.5	-7.1	D0 - >28	Mean	0.5n	0.6	0.6	0.6	s.d.	0.4	0.3	0.3	0.4	N	10	10	10	10	Deviation Vs control (%)	-	13.7	7.8	15.7
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	Deviation Vs control (%)	-	13.7	7.8	15.7																																																																																						
Ecotoxicology – chronic <i>Daphnia</i> endpoint	<p>HSE determined a chronic <i>Daphnia</i> NOEC endpoint of 0.29 mg a.s./L based on the study Rzodeczko, 2017b (for full justification see DAR Vol. 3 CA, section B.9.2.5 p132).</p> <p>The applicant provided several comments and disagrees with the selected endpoint. An example of the key points are shown below in italics:</p> <p><i>‘BASF strongly disagree with setting the NOEC to the lowest test concentration as proposed by HSE. In the chronic <i>Daphnia</i> study, the analytical measurements were conducted according to the scheme proposed by the OECD guideline. BASF <u>expected</u> the concentrations to be maintained within 20% of nominal, which was also the case, except</i></p>																																																																																										

	<p><i>for the last measurement timepoint where recoveries were 73.5-80%. At all other measurement timepoints, the obtained values were within the required range; often above 100% recovery. All concentrations were analysed on seven occasions (three times fresh, four times spent), whereas the lowest and highest test concentrations and control were measured 18 times during the study. The RMS NL recalculated the nominal concentrations to time-weighted average (twa) concentrations and derived an EC<sub>10</sub> value of 2.366 mg a.s./L and a NOEC of 0.615 mg a.s./L (twa). In the EU process, the study is considered fully valid, and the RMS used the derived EC<sub>10</sub> value in the aquatic risk assessment. It should also be noted that it is the biological performance and not the analytical values that set the NOEC. HSE's approach of setting the NOEC at the lowest test concentration is not supported by the data nor by the OECD guideline and would create an unnecessary discrepancy between EU and UK regulatory values.'</i></p> <p>HSE highlighted that in the European process only the RMS has considered this study hence EFSA and other member States (MS) have yet to agree EU endpoints. This is also the case for the GB assessment as the endpoints have not been finalised. Therefore, currently it is not possible to state that there is a discrepancy between EU and GB regulatory values.</p> <p>HSE notes the applicant expected the concentrations to remain stable (within <math>\pm 20</math> % of nominals). However, when considering the aquatic studies that were submitted several demonstrated cinmethylin was not stable (within <math>\pm 20</math> % of nominals). This was also seen on the last sampling occasion in the chronic <i>Daphnia</i> study. Therefore, HSE considers similar or greater declines could have occurred on other occasions for the middle test concentrations if they were fully sampled.</p> <p>Given the decline observed, HSE has determined the endpoint based on a complete analytical dataset (i.e. analysis of fresh and spent media throughout study) to ensure a robust value. HSE does not consider it appropriate to calculate time weighted average concentrations when the analytical data set is not complete and there is evidence the test item was not sufficiently maintained within <math>\pm 20</math> % of nominals.</p> <p>Furthermore, HSE has acknowledged the endpoint derived is conservative.</p> <p>The opinion of the ECP is sought.</p>
Ecotoxicology – acute <i>Chironomus</i> endpoint	<p>HSE determined an acute <i>Chironomus</i> LC<sub>50</sub> endpoint of &gt; 2.06 mg a.s./L based on the study Pearson &amp; Stephenson, 1987 (for full justification see DAR Vol. 3 CA, section B.9.2.4 p116). This endpoint was considered supporting information as the analytical method was not fully validated. The applicant provided several comments. The key points are shown below in italics:</p> <p><i>'The Chironomus acute study is considered by HSE as supporting information. The LC<sub>50</sub> is &gt; 2.09 and &lt; 5 mg/L, so within a factor of 2-3 of the valid acute Daphnia study and thus easily covered by the standard assessment factor of 100 on the Daphnia EC<sub>50</sub>. However, HSE mentions the endpoint from the Chironomus study is used in an "illustrative" assessment. It is not clear to BASF what this means. Is HSE using the supporting information in the risk assessment or not? BASF would prefer the risk assessment to be based on the valid acute Daphnia study.'</i></p>



	<p>HSE notes the valid acute <i>Daphnia</i> endpoint has been used in the quantitative risk assessment for cinmethylin (see table B.9.4-9 of DAR Vol. 3 CP dossier).</p> <p>The <i>Chironomus</i> acute study, whilst not ideal due to a lack of analytical validation, is considered suitable as supporting information by HSE. Given the dose response observed in this study and that it is potentially adverse the endpoint was used to determine whether the valid studies were suitably protective and an acceptable risk could be concluded for the proposed uses.</p> <p>The opinion of the ECP is sought.</p>
Ecotoxicology – aquatic plant endpoints	<p>HSE considered the endpoints for several aquatic plant studies (Rzodeckzo, 2017c; Rzodeczko, 2018a; Rzodeczko, 2017d) as <u>supporting information</u> due to the lack of analytical measurements taken during the study (for full justification see DAR Vol. 3 CA, section B.9.2.7 p153, 158, 162 respectively).</p> <p>The applicant provided several comments. The key points are shown below in italics:</p> <p><i>‘According to the current data requirements for a herbicidal active substance, two algal species and one higher aquatic plant is required. However, BASF conducted four additional macrophyte studies. In the Glyceria study all concentrations and for Myriophyllum the lowest and the two highest concentrations were analysed. For Egeria and Elodea the three highest test concentrations were measured. Comprehensive calculations of measured concentrations and the extrapolation of non-measured concentrations were provided to HSE in September 2019. It should be noted that these calculations are very conservative as the calculations do not include the analytical recovery in sediment (around 10%). BASF kindly requests HSE not to ignore the highly relevant information provided in the four additional macrophyte studies which are of good quality and consider their results in the aquatic risk assessment.’</i></p> <p>HSE has not ignored any of the aquatic plant studies submitted. All have been discussed in detail and considered in the cinmethylin risk assessment (see section B.9.4 of DAR Vol. 3 CP dossier p59). Furthermore, the proposed extrapolation by BASF for non-measured concentrations has been detailed and discussed in relevant parts of section B.9.2.7 of DAR Vol. 3 CA dossier (see above references).</p> <p>HSE does not consider the extrapolations suitable to determine robust endpoints, noting where concentrations were measured, they were not stable i.e. decline beyond <math>\pm 20</math> % of nominals. Hence for these studies the derived endpoints were used as supporting information.</p> <p>HSE requests the opinion of the ECP regarding the additional aquatic plant studies (Rzodeckzo, 2017c; Rzodeczko, 2018a; Rzodeczko, 2017d) and the approach taken in the DAR.</p> <p>The opinion of the ECP is sought.</p>

### 3.2. PROPOSED DECISION

It is proposed that:

**Cinmethylin (BAS 684H) can be approved under Regulation No 1107, *subject to the outstanding issues regarding endocrine disruption being satisfactorily addressed.***

It is considered that the following specific provision should be included in Part B of the approval as an area requiring particular attention when evaluating applications for product authorisation(s):

#### **The risk to aquatic organisms.**

It is considered that it should be specified that conditions of use shall include risk mitigation measures, where appropriate.

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

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

Proposed condition/risk mitigation measure	Relevance in relation to representative use(s)
<u>PPE requirements due to classification of product</u> <ul style="list-style-type: none"> <li>Protective gloves, protective coveralls and face protection (faceshield) when handling the concentrate.</li> </ul>	All proposed uses.
As the risk from spraydrift to non-target plants was not resolved the following label mitigation is proposed:  <b>‘Extreme care must be taken to avoid spray drift onto non-crop plants outside of the target area.’</b>	All proposed uses.
Due to the risk to non-target plants from volatilization a <b>5 m buffer zone</b> has been proposed.	Winter wheat

### 3.4. APPENDICES

#### GUIDANCE DOCUMENTS USED IN THIS ASSESSMENT

##### Identity, Physical chemical properties, method of analysis

- Manual on development and use of FAO and WHO specifications for pesticides, 1st edition, 3<sup>rd</sup> revision; World Health Organisation and Food and Agriculture Organisation of the United Nations, Rome 2016
- Guidance document on significant and non-significant changes of the chemical composition of authorised plant protection products under Regulation (EC) No 1107/2009 of the EU Parliament and Council on placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. SANCO/12638/2011, rev. 2, 20 November 2012
- 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/3030/99 rev. 4, 11 July 2000
- Technical Active Substance and Plant Protection Products: Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex (Section 4) of Regulation (EU) No 283/2013 and Annex (Section 5) of Regulation (EU) No 284/2013. SANCO/3030/99 rev. 5, 22 March 2019
- Guidance document for the generation and evaluation of data on the physical, chemical and technical properties of plant protection products under Regulation (EC) No. 1107/2009 of the EU Parliament and Council on placing plant protection products on the market, Final Draft. HSE, 13 July 2008.
- OECD, 2007, Guidance document on the pesticide residue analytical methods, (ENV/JM/MONO(2007)17), Series on testing and assessment No. 72 and Series on pesticides No. 39
- Residues: Guidance document for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (Part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414. SANCO/3029/99 rev.4, 11/07/200.
- EU Guidance document on pesticide residue analytical methods. SANCO/825/00 rev. 8.1, 16/11/2010.
- Technical Guideline on the Evaluation of Extraction Efficiency of Residue Analytical Methods. SANTE/2017/10632 rev. 3, 22 November 2017

##### Human health

- Guidance of EFSA: Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009: EFSA Journal 2011;9(2):2092.
- Guidance on Dermal Absorption; EFSA Panel on Plant Protection Products and their Residues (PPR). EFSA Journal 2012; 10(4): 2665.
- Guidance on the establishment of the residue definition for dietary risk assessment. EFSA Panel on Plant Protection Products and their Residues (PPR). EFSA Journal 2016;14(12):4549.
- 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.
- 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.

- Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 (EFSA/ECHA, 2018). EFSA Journal, Vol 16, Issue 6, June 2018, e05311 <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311>.

## Exposure

- European Food Safety Authority (2014). Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, EFSA Journal 2014;12(10):3874.

## 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.10.3.
- 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

**Environmental fate and behaviour**

- 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 (2004).
- FOCUS Kinetics “Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration” version 2.0 (2006)
- FOCUS Kinetics “Generic guidance for Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration” Version 1.1 (2014)
- European Commission SANCO/7032/VI/95 rev.5: Storage stability of residue samples (Jul 1997)
- European Commission SANCO/3029/99 rev. 4: Laboratory procedural recovery specimens (Jul 2000)
- OECD 106: Adsorption – desorption using the batch equilibrium method (Jan 2000)
- OECD 111: Hydrolysis as a function of pH (Apr 2004)
- OECD 301B: Ready biodegradability (Jul 1992)
- OECD 307: Aerobic and Anaerobic Transformation in Soil (Apr 2002)
- OECD 308: Aerobic and anaerobic transformation in aquatic sediment systems (Apr 2002)
- OECD 309: Aerobic mineralisation in surface water – simulation biodegradation test (Nov 2004)
- OECD 316: Phototransformation of chemicals in water – direct photolysis (Oct 2008)
- OECD 506: Stability of Pesticide Residues in Stored Commodities (Oct 2007)
- OECD Draft Guideline “Phototransformation of chemicals on soil surfaces” (Jan 2002)
- OECD Principles on Good Laboratory Practice (1998)
- US EPA OPPTS Guidelines 835.4100: Aerobic Soil Metabolism (Oct 2008)
- US EPA OPPTS Guidelines 835.4200: Anaerobic Soil Metabolism (Oct 2008)
- US EPA OPPTS Guidelines 835.2410: photodegradation on soil (Oct 2008)
- US EPA OPPTS Guidelines 835.6100: Terrestrial Field Dissipation (Oct 2008)
- US EPA OPPTS Guidelines 835.1230: Adsorption/Desorption (Nov 2008)
- US EPA OPPTS Guidelines 835.2120: Hydrolysis (Nov 2008)
- US EPA OPPTS Guidelines 835.2240: Photodegradation in water (Nov 2008)
- US EPA OPPTS Guidelines 835.3110: Ready biodegradability (Jan 1998)
- US EPA OPPTS Guidelines 835.4300: Aerobic aquatic metabolism (Oct 2008)
- US EPA OPPTS Guidelines 860.1380: Storage Stability Data (Aug 1996)
- NAFTA Guidance Document for Conducting Terrestrial Field Dissipation Studies Regulatory Directive DIR2006-01 (March 2006)

- International Standard ISO 9439: Water quality – evaluation of ultimate aerobic biodegradability of organic compounds in aqueous medium – CO<sub>2</sub> evolution test (1999)
- BBA (Biologische Bundesanstalt für Land- und Forstwirtschaft) BRD: Richtlinien für die amtliche Prüfung von Pflanzenschutzmitteln, Teil IV, 6-1 (Jul 1990)

### Ecotoxicology

- Birds & Mammals:  
EFSA (2009). Guidance document on risk assessment for birds and mammals. EFSA Journal 2009;7(12):1438
- Aquatic Organisms:  
EFSA (2013). Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013;11(7):3290
- Bees/Soil organisms/Non-target plants:  
SANCO/10329/2002 (rev 2 final). Guidance document on terrestrial ecotoxicology under council directive 91/414/EEC.
- Non-target arthropods:  
ESCORT 2 (Candolfi *et al.*, 2001). Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods.

## 3.5. REFERENCE LIST

### Physical-chemical properties

None.

### Efficacy

None.

### Analytical Methods

None.

### Toxicology

None.

### Residues

None.

### Environmental Fate and Behaviour

None.

### Ecotoxicology

None.