Committee for Risk Assessment
RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at EU level of

thiamethoxam (ISO); 3-(2-chloro-thiazol-5-ylmethyl)-5-methyl[1,3,5]oxadiazinan-4-ylidene-N-nitroamine

EC Number: 428-650-4
CAS Number: 153719-23-4

CLH-O-0000006724-70-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

5 December 2019

European Commission

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

THIAMETHOXAM

Volume 1

Rapporteur Member State: France

Co-Rapporteur Member State: Spain

Version History

When	What
2018-01	Initial RAR-CLH
2018-07-03	RAR-CLH revised after ECHA Accordance Check
2018-07-20	RAR-CLH revised after the 2nd ECHA Accordance Check
2018-08-02	RAR-CLH revised after the 3rd ECHA Accordance Check

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Level 1

THIAMETHOXAM

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 renewal assessment report has been prepared in accordance with Commission Regulation (EC) No 844/2012 and Guidance Document SANCO/2012/11251 rev. 4 in order to evaluate the supplementary dossier submitted by Syngenta Crop Protection AG, and to allow a decision on the renewal of the approval of the active substance Thiamethoxam under Commission Regulation (EC) No 1107/2009.

The harmonised classification and labelling of Thiamethoxam has been considered previously in the EU (ATP01). The existing entry in Annex VI of CLP Regulation (EU) 1272/2008 is:
Acute Tox. 4, H302: Harmful if swallowed
Aquatic Acute 1, H400: Very toxic to aquatic life
Aquatic Chronic 1, H410: Very toxic to aquatic life with long lasting effects

In the framework of the renewal assessment of Thiamethoxam under Regulation (EU) 1107/2009, RMS proposed to reconsidered the current and harmonised classification of the active substance for the **Flammable Solids** and the **Reproductive Toxicity**, and to retain the current classification for environment but to add a **chronic M-factor** of 10 and. Therefore, in this context, a **targeted CLH proposal** is presented in this document for these 3 endpoints using the common agreed template for DAR/RAR/CLH report.

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

According to Commission Regulation (EU) No 686/2012 France was designated Rapporteur Member State (RMS) and Spain assigned as Co-Rapporteur Member State (Co-RMS).

France, as RMS, evaluated the dossier submitted by the applicants and draft the Renewal Assessment Report for all the sections whereas, Spain, as Co-RMS, conducted a pre-peer review of this report. Any deviating views on critical issues between the RMS and the Co-RMS have been reported in Volume 1 Level 3 section 3.1.9.

1.1.3. EU Regulatory history for use in Plant Protection Products

In March 1999, Novartis Crop Protection AG (now Syngenta), submitted an application for the inclusion of the new active substance Thiamethoxam in Annex I of the Directive 91/414/EEC. Spain was designated RMS to carry out the detailed examination of the dossier and report the conclusions to the Commission.

The draft assessment reports was submitted on January 2002 to the Commission and then reviewed by the Member States and the Commission within the Standing Committee on the Food Chain and Animal Health. The review was finalised on 14 July 2006 in the format of the Commission review report (Thiamethoxam SANCO/10390/2002 - rev. final, dated on 14 July 2006). Thiamethoxam was listed in Annex I of Directive 91/414/EEC on 1st February 2007 (Commission Directive 2007/06/EC) with the following specific provisions:
Only uses as insecticide may be authorised.

For the implementation of the uniform principles of Annex VI, the conclusions of the review report on Thiamethoxam, and in particular Appendices I and II thereof, as finalised in the Standing Committee on the Food Chain and Animal Health on 14 July 2006 shall be taken into account.
In this overall assessment Member States:
— must pay particular attention to the potential for groundwater contamination, particularly of the active substance and its metabolites NOA 459602, SYN 501406 and CGA 322704, when the active substance is applied in regions with vulnerable soil and/or climatic conditions,
— must pay particular attention to the protection of aquatic organisms,
— must pay particular attention to the long-term risk to small herbivorous animals if the substance is used for seed treatment.
Conditions of use shall include risk mitigation measures, where appropriate.

In spring 2012, new scientific information on the sub-lethal effects of neonicotinoids on bees was published. The Commission, in accordance with Article 21(2) of Regulation (EC) No 1107/2009, asked the European Food Safety Authority (EFSA), for scientific and technical assistance to assess this new information and to review the risk assessment of neonicotinoids as regards their impact on bees. EFSA presented its conclusions on the risk assessment for bees for thiamethoxam on 16 January 2013. The conclusion of EFSA was reviewed by the Member States and the Commission within the Standing Committee on the Food Chain and Animal Health and finalised on 15 March 2013 in the format of an addendum to the review report on Thiamethoxam (Thiamethoxam, SANCO/10591/2013 rev 2, dated on 15 March 2013). This addendum to the review report has been developed and finalised in support of Commission Implementing Regulation (EU) No 485/2013 of 24 May 2013 amending Implementing Regulation (EU) No 540/2011. Especially, Regulation (EU) No 485/2013 restrictes the uses of Clothianidin, Thiamethoxam and Imidacloprid, and provides for specific risk mitigation measures for the protection of bees and limites the use of the plant protection products containing these active substances to professional users. In particular, the uses as seed treatment and soil treatment of plant protection products containing Clothianidin, Thiamethoxam or Imidacloprid have been prohibited for crops attractive to bees and for cereals except for uses in greenhouses and for winter cereals. Foliar treatments with plant protection products containing these active substances have been prohibited for crops attractive to bees and for cereals with the exception of uses in greenhouses and uses after flowering. Furthermore, the European Commission requested EFSA to provide conclusions concerning an updated risk assessment for bees for Clothianidin, Thiamethoxam and Imidacloprid, taking into account all uses other than seed treatments and granules, including foliar spray uses as mentioned in recital 7 of Commission Implementing Regulation (EU) No 485/2013. EFSA finalised its conclusion on the risk assessment for bees as regards all uses other than seed treatments and granules in July 2015.

Moreover, it was also a specific provision of the EU Regulation 485/2013 that the applicants submit by 31/12/2014 ecotoxicological confirmatory information as regards:

(a) the risk to pollinators other than honey bees;

(b) the risk to honey bees foraging in nectar or pollen in succeeding crops;

(c) the potential uptake via roots to flowering weeds;

(d) the risk to honey bees foraging on insect honey dew;

(e) the potential guttation exposure and the acute and the long-term risk to colony survival and development, and the risk to bee brood resulting from such exposure;

(f) the potential exposure to dust drift following drill and the acute and the long-term risk to colony survival and development, and the risk to bee brood resulting from such exposure;

(g) the acute and long term risk to colony survival and development and the risk to bee brood for honeybees from ingestion of contaminated nectar and pollen.

Spain, as RMS of the active substance, assessed these confirmatory data and sent its report to the Commission and EFSA on November 2015. Then EFSA launched the Peer Review process and published its conclusion on April 2016.

Furthermore according to recital 16 of Regulation (EU) No 485/2013, within two years from the date of entry into force of that Regulation, the European Commission foresees to initiate without undue delay a review of the new scientific information available. For this purpose, with reference to Article 31 of Regulation (EC) No 178/2002 and in accordance with Article 21 of Regulation (EC) No 1107/2009 the European Commission requested EFSA to organise an open call for data in order to collect new scientific information as regards the risk to bees from the neonicotinoid pesticide active substances Clothianidin, Thiamethoxam and Imidacloprid applied as seed treatments and granules in the EU. The European Commission requested EFSA to provide conclusions concerning an updated risk assessment for bees for the three neonicotinoids (namely clothianidin, imidacloprid and thiamethoxam), taking into account:

- the new relevant data collected in the framework of the specific open call for data
- any other new data from studies, research and monitoring activities that are relevant to the uses under consideration
- the EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera, Bombus* spp. and solitary bees)

EFSA also considered the data available from a systematic literature review performed in June 2016, in order to collect all published scientific literature relevant for the current evaluation.
This torough work was reviewed by the EU Member States and EFSA provided its conclusion to the Commission on autumn 2017.

The Commission has then concluded that the further confirmatory information required by Implementing Regulation (EU) No 485/2013 has not been provided, and having also considered the conclusion on the updated risk assessment for bees, the Commission has concluded that further risks to bees cannot be excluded without imposing further restrictions. Bearing in mind the need to ensure a level of safety and protection consistent with the high level of protection of animal health that is sought within the Union, it is appropriate to prohibit all outdoor uses. Therefore, it is appropriate to limit the use of thiamethoxam to permanent greenhouses and to require that the resulting crop stays its entire life cycle within a permanent greenhouse, so that it is not replanted outside. Taking into account the risks for bees from treated seeds, the placing on the market and the use of seeds treated with plant protection products containing thiamethoxam should be subject to the same restrictions as the use of thiamethoxam. It is therefore appropriate to provide that seeds treated with plant protection products containing thiamethoxam shall not be placed on the market or used, except where the seeds are intended to be used only in permanent greenhouses and the resulting crop stays within a permanent greenhouse during its entire life cycle. (Commission Implementing Regulation EU 2018/785, amending Implementing Regulation (EU) No 540/2011 as regards the conditions of approval of the active substance thiamethoxam).

Regarding the consumer safety and according to Article 18(1)b of Regulation (EC) 396/2005, default EU MRLs have been established in 2008 (Commission Regulation (EU) No. 149/2008). On 7 July 2012 the Codex Alimentarius Commission (CAC) adopted Codex maximum residue limits (CXLs) for Thiamethoxam. These CXLs should be included in Regulation (EC) No 396/2005 as MRLs, with the exception of those CXLs which are not safe for a European consumer group and for which the Union presented a reservation to the CAC. According to art.12 of (EC) 396/2005, EFSA has reviewed the existing MRLs for Thiamethoxam (EFSA Journal 2014;12(12):3918) and these MRLs have been adopted under Commission Regulation (Commission Regulation (EU) No. 156/2016).

By Commission Regulation 487/2014/EC, the expiry date of approval of Thiamethoxam, initially on 31 January 2017, was extended to 30 April 2019.

1.1.4. Evaluations carried out under other regulatory contexts

Thiamethoxam is currently under Registration Review at US-EPA (Docket N° EPA-HQ-OPP-2011-0581).
Thiamethoxam was as well evaluated by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 2010 (Toxicology and Residue Evaluation), 2011 and 2012 (Residue Evaluation).

1.2 APPLICANT INFORMATION

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

Name:	Syngenta Crop Protection AG
Address:	Schwarzwaldallee 215 P.O. Box CH-4002 Basel; Switzerland
Contact: Telephone number:	[redacted]
E-mail:	[redacted]

1.2.2 Producer or producers of the active substance

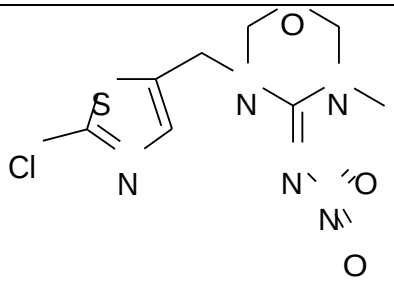
Name:	Syngenta Crop Protection AG
Address:	Schwarzwaldallee 215 P.O. Box CH-4002 Basel; Switzerland
Contact:	[redacted]
Telephone number:	[redacted]
E-mail:	[redacted]

1.2.3 Information relating to the collective provision of dossiers

Not applicable, Syngenta Crop Protection AG is the sole applicant to support the renewal of the active substance Thiamethoxam.

1.3 IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1 Common name proposed or ISO-accepted and synonyms	Thiamethoxam
1.3.2 Chemical name (IUPAC and CA nomenclature)	
IUPAC	(*E*,*Z*)-3-(2-chloro-thiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidene-N-nitroamine
CA	4*H*-1,3,5-Oxadiazin-4-imine, 3-[(2- chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-*N*-nitro-
1.3.3 Producer's development code number	CGA293343
1.3.4 CAS, EEC and CIPAC numbers	
CAS	153719-23-4
EEC	428-650-4
CIPAC	637
1.3.5 Molecular and structural formula, molecular mass	
Molecular formula	$C_8H_{10}ClN_5O_3S$

Structural formula	
Molecular mass	291.7 g mol^{-1}
1.3.6 Method of manufacture (synthesis pathway) of the active substance	Confidential data see vol.4
1.3.7 Specification of purity of the active substance in g/kg	980g/kg
1.3.8 Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1 Additives	Confidential data see vol.4
1.3.8.2 Significant impurities	Confidential data see vol.4
1.3.8.3 Relevant impurities	Not relevant impurities
1.3.9 Analytical profile of batches	Confidential data see vol.4

Thiamethoxam is described as an EZ mixture. It is generally believed that the activation energy for the E-Z interconversion for the C = N bond is low and that an equilibrium mixture is rapidly established at ambient temperature.

1.4 INFORMATION ON THE PLANT PROTECTION PRODUCT: ACTARA 25WG

1.4.1 Applicant	Name: Syngenta Crop Protection AG Address: Schwarzwaldalle 215 P.O. Box CH-4002 Basel; Switzerland Contact: Telepho[redacted] number: [redacted] E-mail: [redacted]
1.4.2 Producer of the plant protection product	Name: Syngenta Crop Protection AG Address: Schwarzwaldalle 215 P.O. Box [redacted] Switzerland Contact: Telephone [redacted] number: [redacted] E-mail:
1.4.3 Trade name or proposed trade name and producer's development code number of the plant protection product	**Trade name:** ACTARA 25 WG **Company code number:** A9584C

1.4.4 Detailed quantitative and qualitative information on the composition of the plant protection product	
1.4.4.1 Composition of the plant protection product	250 g/kg of pure active thiamethoxam
1.4.4.2 Information on the active substances	ISO common name: **Thiamethoxam** CAS No: 153719-23-4 EC No: Not available CIPAC No: 637 ELINCS No: Not available Salt, ester anion or cation present: No
1.4.4.3 Information on safeners, synergists and co-formulants	CONFIDENTIAL information – see Volume 4
1.4.5 Type and code of the plant protection product	Type : Wettable granule [Code : WG]
1.4.6 Function	Insecticide
1.4.7 Field of use envisaged	Agriculture
1.4.8 Effects on harmful organisms	A9584C is a foliar applied insecticide to control a wide spectrum of foliar pests from different orders such as Lepidoptera, Homoptera, Hemiptera, Coleoptera and Thysanoptera and it possesses contact, stomach and systemic activity. The product has shown activity against sucking pests such as aphids, white flies, jassids, chewing pests such as Colorado potato beetle, weevils and leaf miners. The active substance thiamethoxam is taken up by roots and leaves, then translocated translaminarily and acropetally through xylem vessels. Like all neonicotinoid active substances, thiamethoxam targets the postsynaptic acetylcholine receptor. By inhibiting this receptor, thiamethoxam blocks the transmission of nerve impulses in the synaptic area.

1.5 INFORMATION ON THE PLANT PROTECTION PRODUCT: CRUISER 600FS

1.5.1 **Applicant**	Name: Syngenta Crop Protection AG Address: Schwarzwaldalle 215 P.O. Box CH-4002 Basel; Switzerland Contact: Telepho[redacted] number: [redacted] E-mail: [redacted]

1.5.2 Producer of the plant protection product	Name: Syngenta Crop Protection AG Address: Schwarzwaldalle 215 P.O. Box [redacted] Switzerland Contact: Telephone number: [redacted] E-mail: [redacted]
1.5.3 Trade name or proposed trade name and producer's development code number of the plant protection product	**Trade name:** CRUISER **Company code number:** A9765R
1.5.4 Detailed quantitative and qualitative information on the composition of the plant protection product	
1.5.4.1 Composition of the plant protection product	600 g/L of pure active thiamethoxam
1.5.4.2 Information on the active substances	ISO common name: **Thiamethoxam** CAS No: 153719-23-4 EC No: Not available CIPAC No: 637 ELINCS No: Not available Salt, ester anion or cation present: No
1.5.4.3 Information on safeners, synergists and co-formulants	CONFIDENTIAL information – see Volume 4
1.5.5 Type and code of the plant protection product	Type: Flowable concentrate for seed treatment [Code : FS]
1.5.6 Function	Insecticide
1.5.7 Field of use envisaged	Agriculture
1.5.8 Effects on harmful organisms	A9765R is a seed applied insecticide to control Coleoptera (including *Atomaria* spp., *Agriotes* spp.), Diptera, Hemiptera (aphids) and further orders. The active substance thiamethoxam possesses contact, stomach and systemic activity. It is taken up by roots, then translocated translaminarily and acropetally through xylem vessels. Like all neonicotinoid active substances, thiamethoxam targets the postsynaptic acetylcholine receptor. By inhibiting this receptor, thiamethoxam blocks the transmission of nerve impulses in the synaptic area.

1.6 DETAILED USES OF THE PLANT PROTECTION PRODUCT

1.6.1 Details of representative uses

Tradename: ACATRA 25 WG (formulation code A9584C)
Active Substance: Thiamethoxam, formulated as a 250 g/kg WG formulation

1	2	3	4	5	6	7	8	9	10	11	12	13	14
Use-No.	**Member state(s)**	**Crop and/ or situation (crop destination / purpose of crop)**	**F G or I**	**Pests or Group of pests controlled (additionally: developmental stages of the pest or pest group)**	**Application**				**Application rate**			**PHI (days)**	**Remarks:**
					Method / Kind	**Timing / Growth stage of crop & season**	**Max. number a) per use b) per crop/ season**	**Min. interval between applications (days)**	**kg 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/season**	**Water L/ha min / max**		**e.g. safener/synergist per ha e.g. recommended or mandatory tank mixtures**
1	EU	Lettuce	F	*Hyperomyzus lactucae Macrosiphum euphorbiae Myzus persicae Nasonovia ribisnigri* (larval and adult stages)	Foliar spray	BBCH 15-49	1	-	0.2	0.05	300-800	7	1 application per field per year
2	EU	Potato	F	*Leptinotarsa decemlineata* *Aphids* (larval and adult stages)	Foliar spray	BBCH 15-59	1	-	0.08	0.02	200-500	7	1 application per field per year
3	EU	Lettuce	G	*Hyperomyzus lactucae Macrosiphum euphorbiae Myzus persicae Nasonovia ribisnigri* (larval and adult stages)	Foliar spray	BBCH 15-49	1	-	0.2	0.05	300-800	7	1 application per greenhouse per year

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON THIAMETHOXAM (ISO);3-(2-CHLORO-THIAZOL-5-YLMETHYL)-5-METHYL[1,3,5]OXADIAZINAN-4-YLIDENE-N-NITROAMINE

Tradename: CRUISER 600 FS (formulation code A9765R)
Active Substance: Thiamethoxam formulated as a 600 g/L FS

1	2	3	4	5	6	7	8	9	10	11	12	13	14
Use-No.	**Member state(s)**	**Crop and/ or situation** **(crop destination / purpose of crop)**	**F G or I**	**Pests or Group of pests controlled** **(additionally: developmental stages of the pest or pest group)**	**Application**				**Application rate**			**PHI (days)**	**Remarks:** **e.g. safener/synergist per ha** **e.g. recommended or mandatory tank mixtures**
					Method / Kind	**Timing / Growth stage of crop & season**	**Max. number** **a) per use** **b) per crop/ season**	**Min. interval between applications**	**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/season**	**Slurry volume** **min / max**		
1	EU	Sugar beet	F	Pigmy Mangold Beetle (ATOMLI, larval and adult stages), *Agriotes* spp.– wireworms (AGRISP, larval stages), Aphids (APHISP, nymph and adult stages)	Seed treatment	BBCH 00	1 application per crop*	3 years*	75 mL per seed unit	58.5 g as/ha	75-350 mL/seed unit	-	1 seed unit = 100 000 seeds Sowing density = 1.3 units/ha 1 application every 3 years * 1 application per crop to be drilled maximum every 3 years to the same field

1.6.2 Further information on representative uses

For the representative uses, please refer to table above, in 1.5.1. Details of representative uses.

The method of application in lettuce and potatoes is by spray application using a hydraulic tractor-mounted boom sprayer and hand held sprayer, or by handheld lance/spray gun (indoor/greenhouse use in lettuce).

The method of application in sugar beet seed (typically pelleted) can be made with suitable seed treatment equipment, either as the concentrated product (75 ml / seed unit) or diluted with water to provide a slurry, with a maximum slurry volume of 350 ml / seed unit (100 000 seeds).

Minimum waiting periods or other precautions between last application and sowing or planting succeeding crops: No restrictions need to be applied.
Limitations on choice of succeeding crops: No restrictions need to be applied.

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

Not applicable

1.6.4 Overview on authorisations in EU Member States

Authorisations for a range of different formulations have been achieved in Europe. These include different formulation types.

ACTARA 25 WG (A9584C) has been registered in most of the EU Member States: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, France, Germany, Greece, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Romania, Slovenia, Spain and UK.
ACTARA 25 WG (A9584C) has been registered on a range of crops and pests such as the ones mentioned in Volume 3 active substance (B.3.5. Harmful organisms controlled and crops or products protected or treated).

CRUISER 600 FS (A9765R) has been registered in several of the EU Member States: Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Poland, Sweden and UK.
CRUISER 600 FS (A9765R) has been registered on beets and lettuce on a range of pests such as the ones mentioned in Volume 3 active substance (B.3.5. Harmful organisms controlled and crops or products protected or treated).

Level 2

THIAMETHOXAM

2 SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

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

A literature review was carried out for Thiamethoxam and its potential relevant metabolites according to the requirements of the Regulation (EU) No 844/2012 (the AIR3 renewal regulation), which itself refers to Article 8(5) of Regulation (EC) No 1107/2009. The review itself is in accordance with the EFSA Guidance document as published in EFSA Journal 2011; 9(2):2092 and covers the last ten years before the submission of the supplementary dossier (31/10/2015).

The exact search strategy is detailed in the document MCA Section 9, submitted by the applicant in its summary dossier, but a summary of the methodology employed is given below.

1. A very broad search was conducted in 16 scientific source databases for thiamethoxam and its metabolites. For the toxicological review, only metabolite CGA304075 is considered relevant as the only metabolite included in the residue definition for animal commodities, however other metabolites were included in the search criteria for completeness. For more details on the search criteria in each section, please refer to the document MCA Section 9.
2. Duplicates titles from between the data bases were automatically removed from the output.
3. A rapid assessment of the titles was conducted to remove any additional duplicates and any obviously irrelevant titles (where enough information was available from the title alone).
4. A further rapid assessment was conducted using summary abstracts and any clearly irrelevant titles were removed.
5. A detailed assessment of the full-text documents for the remaining titles was conducted using the criteria developed for study relevance in each section.
6. Any relevant papers were highlighted and assessed for reliability according to the criteria described by Klimisch *et al.* (1997).

During the review of the original search, it was noted that the search term 'clothianidin' was not included. As this is a major metabolite of thiamethoxam, a separate search was conducted with this search term to ensure all potentially relevant open literature was reviewed.

An overview of the results, section by section, is summarised in the tables below.

Physical and chemical properties

Data requirement(s) captured in the search	Number of results			
	Number	**Number (Top-Up Search)**	**Clothianidin search**	**Total**
Total number of *summary records* retrieved after *all** searches of peer-reviewed literature (excluding duplicates)	217	10	118	345
Number of *summary records* excluded from the search results after rapid assessment for relevance**	217	10	118	345
Total number of *full-text* documents assessed in detail*	0	0	0	0
Number of *studies* excluded from further consideration after detailed assessment for relevance	0	0	0	0
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	0	0	0	0

*both from bibliographic databases and other sources of peer-reviewed literature
**aligned with EFSA Journal 2011; 9(2):2092: rapid assessment means exclusion of "obviously irrelevant records" based on titles.

All literature references were excluded during the initial rapid assessment. No literature references were assessed in detail or deemed to be relevant to the chemistry endpoints for thiamethoxam and hence have not been discussed further.

Toxicology

Data requirement(s) captured in the search	Number (Initial Search)	Number (Top-Up Search)	Number (Clothianidin search)
Total number of *summary records* retrieved after *all** searches of peer-reviewed literature (excluding duplicates)	862	51	415
Number of *summary records* excluded from the search results after rapid assessment for relevance**	828	50	392
Total number of *full-text* documents assessed in detail*	34	1	23
Number of *studies* excluded from further consideration after detailed assessment for relevance	34	1	23
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	0	0	0

*both from bibliographic databases and other sources of peer-reviewed literature
**aligned with EFSA Journal 2011; 9(2):2092: rapid assessment means exclusion of "obviously irrelevant records" based on titles.

All the 58 full-text documents assessed in details were finally considered as unrelevant for the toxicological endpoints by the applicant.
The RMS has checked the review of literature data submitted by the notifier. While the methodology implemented is considered in line with the EFSA guidance, the relevance criteria seem to be too restrictive. Indeed even if a publication cannot be directly used in quantitative risk assessment, it can provide useful information for hazard identification and exploration of putative modes of action.
Therefore, for 23 of them publications as well as a summary according to the OECD template and their reliability evaluation have been requested and submitted. The summaries when considered relevant were included in the appropriate part of Vol.3CA B.6.

Metabolism and Residue

Data requirement(s) captured in the search	Number			
	Initial Search	Top-Up Search	Additional Search[(a)]	Total
Total number of *summary records* retrieved after *all* [(b)] searches of peer-reviewed literature (excluding duplicates)	1244	83	651	1978
Number of *summary records* excluded from the search results after rapid assessment for relevance[(c)]	1231	83	649	1963
Total number of *full-text* documents assessed in detail [(b)]	13	0	2	15
Number of *studies* excluded from further consideration after detailed assessment for relevance	13	0	2	15
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	0	0	0	0

(a) Additional search for clothianidin as a relevant metabolite
(b) Both from bibliographic databases and other sources of peer-reviewed literature
(c) aligned with EFSA Journal 2011; 9(2):2092: rapid assessment means exclusion of "obviously irrelevant records" based on titles

No literature references were deemed to be relevant to the metabolism and residue endpoints for thiamethoxam and relevant metabolites. No literature references have been discussed further in the submitted supplementary dossier.

Fate and behaviour in the environment

Data requirement(s) captured in the search	Substance	Number (Initial Search)	Number (Top-Up Search)
Total number of *summary records* retrieved after *all* [A)] searches of peer-reviewed literature (excluding duplicates)	Thiamethoxam	1644	87 [D)]
	Clothianidin [C)]	329 [D)]	
Number of *summary records* excluded from the search results after rapid assessment for relevance [B)]	Thiamethoxam	1621	85
	Clothianidin	326	
Total number of *full-text* documents assessed in detail [A)]	Thiamethoxam	23	2
	Clothianidin	3	
Number of *studies* excluded from further consideration after detailed assessment for relevance	Thiamethoxam	22	1
	Clothianidin	3	
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	Thiamethoxam	1	1
	Clothianidin	0	

[A)] Both from bibliographic databases and other sources of peer-reviewed literature
[B)] aligned with EFSA Journal 2011; 9(2):2092: rapid assessment means exclusion of "obviously irrelevant records" based on titles.
[C)] The search for clothianidin was done shortly before submission. Therefore, there is no distinction between initial and top-up search.
[D)] Hits which were already included in a previous search step (i.e. both thiamethoxam searches for clothianidin, initial thiamethoxam search for the thiamethoxam top-up search) were treated as duplicates and excluded.

One literature reference was deemed to be relevant to the fate and behaviour in the environment endpoints for Thiamethoxam and relevant metabolites. This literature reference has been discussed further in the submitted supplementary dossier.

Ecotoxicology

Data requirement(s) captured in the search	Number of results			
	Initial search	Top-up search	Clothianidin search	Total
Total number of *summary records* retrieved after *all** searches of peer-reviewed literature (excluding duplicates)	1819	94	735	2648
Number of *summary records* excluded from the search results after rapid assessment for relevance**	1531	74	673	2278
Total number of *full-text* documents assessed in detail*	288	20	62	370
Number of *studies* excluded from further consideration after detailed assessment for relevance	261	17	52	330
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	27	3	10	40

*both from bibliographic databases and other sources of peer-reviewed literature
**aligned with EFSA Journal 2011; 9(2):2092: rapid assessment means exclusion of "obviously irrelevant records" based on titles.

40 literature references were deemed to be relevant to the ecotoxicological endpoints for Thiamethoxam and relevant metabolites. These literature references have been discussed further in the submitted supplementary dossier.

The outcomes of the review of scientific open literature and these scientific papers are discussed by the RMS in Volumes 3 of the RAR for each section.

2.1 IDENTITY

2.1.1 Summary of identity

The applicant for the renewal of the inclusion of Thiamethoxam in Annex I of the Directive 91/414/EEC is Syngenta.
Syngenta's dossier for the active substance is accompanied by two full dossiers for the plant protection products Actara 25WG and Cruiser 600FS.
The manufacturing process for technical Thiamethoxam is different from the one included in Annex I (DAR 2001). Nevertheless, the active substance can be considered chemically and technically equivalent to the reference source from Novartis in 2001 for Annex I inclusion.
In any case the minimum purity (980 g/kg) complies with the current FAO specifications and technical Thiamethoxam evaluated for inclusion in Directive 91/414/EC.

All relevant information and data concerning the identity of the formulated products Actara 25WG and Cruiser 600FS have been provided. Actara 25WG is a water dispersible granules formulation containing 250g/kg of pure Thiamethoxam. Cruiser 600FS is a flowable concentrate for seed treatment containing 600 g/L of pure Thiamethoxam.

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

2.2.1 Summary of physical and chemical properties of the active substance

Most of tests were performed on the pure active substance (99.7%). The technical material contains 98.0% of active substance.

Table 1: Summary of physico-chemical properties of the active substance

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Pure active substance : slightly cream fine crystalline powder odourless Technical grade active substance : off-white fine powder with a slightly sweet odour	Das, 1995b Das, 1998	Visual Organoleptic
Melting/freezing point	139.1°C	Das, 1995 a	EEC A.1
Boiling point	Thermal decomposition starts at about 147°C (i.e. before the boiling point is reached)	Das, 1997	EEC A.2
Relative density	1.57	Füldner, 1995	EEC A.3
Vapour pressure	Vapour pressure curve in the solid state : ln P [Pa] = - 15400.447 / T [K] + 32.81766 from fit of measurements between 90.5 and 121.0°C vapour pressure at 25°C : $6.6 \cdot 10^{-9}$ Pa (extrapolated)	Geoffroy, 1995	OECD 104 EEC A.4
Surface tension	Re-conducted, in order to provide a guideline compliant study. The surface tension of pure thiamethoxam in water was determined to be in the range: 71.4 mN/m at 21.5 ± 0.5 °C.	O'Connor B., 2014	EEC A.5
Water solubility	The solubility in pure water was determined to be : 4.1 g /L at	Stulz, 1995a	EEC A.6.

Property	Value	Reference	Comment (e.g. measured or estimated)
	25°C. Thiamethoxam has no dissociation within the range pH 2 to pH 12 that means the pH has no effect to the water solubility of the compound in the pH range 4 to 10.		(Flask method)
Partition coefficient n-octanol/water	The octanol/water partition coefficient (P_{OW}) and its logarithm to base 10 (log P_{ow}) were determined to be : P_{OW} : 0.73 ± (0.0029) at 25°C log P_{ow}: -0.13 ± (0.0017) at 25°C	Stulz, 1995b	EEC A.8 (Shake flask method)
Henry's law constant	Henry's law constant at 25°C : $4.7 \cdot 10^{-10}$ Pa · m³ / mol	Burkhard, 1996	calculation
Flash point	Not required thiamethoxam is a solid with a melting point > 40°C		
Flammability	The active substance is classified H228 Flammable solid category 1	Jackson W., 2014	EEC A.10
Explosive properties	The active substance is not classified explosive	Jackson, 2017	UN Test 2(b) : Koenen Test
Self-ignition temperature	The active substance is not auto flammable	Angly, 1998c	EEC A.16
Oxidising properties	The active substance is not classified as an oxidizing solid	Jackson, 2017	UN Test O.1 Test for oxidizing solids
Granulometry	-	-	-
Solubility in organic solvents and identity of relevant degradation products	The solubility in different organic solvents at 25°C was determined to be : acetone: 48g/L ethyl acetate : 7.0 g / L dichloromethane: 110 g / L hexane: < 1 mg L toluene: 680 mg / L methanol: 13 g / L n-octanol: 620 mg / L	Stulz, 1996; Stulz, 1998	CIPAC MT 157.3 (Flask method)
Dissociation constant	Thiamethoxam does not have a dissociation constant within the range 2 to 12	Stulz, 1995c	OECD 112
Viscosity	Not applicable for a solid	-	-
Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity	UV Absorption Characteristics: For the absorption maxima at 255 nm the molar extinction coefficient was determined to be 16800 l / mol · cm in neutral solution. No absorption maximum between 290 nm and 750 nm was observed. Only slightly variations on extinction coefficients were observed at different pH IR (cm^{-1}): 1598 (NO_2 strech. assym. and –C=N- strech. sym.); 1265 (NO_2 strech.) ^{1}H-NMR (δ (ppm)): 7.54 (s, 2H); 5.02 (s, 2H); 4.94 (s, 2H); 4.74 (s, 2H); 2.82 (s, 3H) MS-EI (m/z): (M^+) not detected; 247 (M^+- CH_2OCH_2); 245 (M^+-NO_2)	Birk, 1997	OECD 101

Thiamethoxam is a slightly cream to off-white fine powder with a melting point of 139.1°C. A vapour pressure of $6.6 \cdot 10^{-9}$ Pa was determined at 25°C and the Henry's law constant which largely determines the tendency of a chemical to volatilise from water solution to air was calculated to be $4.7 \cdot 10^{-10}$ Pa ·

m^3 / mol, that means thiamethoxam does not volatilise from water. The solubility in water of the active substance is 4.1 g / L at 25°C. The log P_{ow} is -0.13 at 25°C, indicating only a low potential for bioaccumulation.

Flammability, autoflammability, oxidising and explosive properties do not create critical problems in the production environment or during storage.
The active substance is classified H228 Flammable solid category 1.

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

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

Hazard class not applicable

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

Table 2: Summary table of studies on flammable solids

Method	Results	Remarks	Reference
EEC A.10	From extended testing using a fiberboard base-plate, the test substance propagated combustion over 100 mm in a time of 40 seconds. The enhancement of the burning characteristics is believed to be due to the decomposition of the test substance, the conditions for which are dependent on the physical properties of the substrate. The test substance should be classified as flammable in terms of its burning characteristics.	The active substance is classified H228 Flammable solid category	Jackson W., 2014

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

It was found that there are surfaces on which the substance will propagate combustion very rapidly. The active substance is classified H228 Flammable solid category 1

2.2.1.1.2.2 Comparison with the CLP criteria

EC Test A.10 and UN Test N.1 are almost identical with the exception that the latter has an additional wetted-zone test for substances testing positive, in order to classify them into two hazard categories. Consequently the outcome of UN Test N.1, again with modifications for the use of different substrates, would yield identical results to those already reported. Although not carried out, the wet-zone would not have been sufficient to prevent the propagation of combustion, in which case the substance should be classified as a Flammable Solid, Category 1 under CLP.

2.2.1.1.2.3 Conclusion on classification and labelling for flammable solids

The active substance is classified H228 Flammable solid category 1

RAC evaluation of flammable solids

Summary of the Dossier Submitter's proposal

The DS proposed classification with Flam. Sol. 1 based on an A.10 test they interpreted as positive.

Comments received during public consultation

Comments were received from 2 MSCAs, both in support of the DS's proposal.

Assessment and comparison with the classification criteria

According to the CLP regulation, classification in this hazard class should be based on a result of the UN Test N.1. The EC A.10 test is very similar to the UN Test N.1 except that the former is unable to distinguish between Category 1 and 2 due to lack of wetted zone in the test design.

According to the RAR (draft Renewal Assessment Report under Reg. (EU) No. 1107/2009) Vol. 3 – B.2 (AS), the test was conducted twice. First, thiamethoxam was tested strictly following the EC A.10 method, including the use of a non-combustible base plate made from glass. The result was negative. The second, "extended" test using a fibreboard base plate was positive. The test substance propagated combustion over 100 mm in 40 seconds, which is below the criterion of 45 seconds. RAC notes that both the UN Test N.1 and the EC A.10 test clearly specify that the base plate must be non-combustible. Pyrolysis products from the fibreboard (a wood-based material) are likely to have contributed significantly to the combustion of the test substance in the second test. RAC considers the test using fibreboard to be unsuitable for classification purposes.

Therefore, RAC proposes **no classification** for flammable solids based on the negative result obtained

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

Hazard class not applicable

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

Hazard class not applicable

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

ACTARA 25WG

The appearance of the plant protection product Actara 25 WG is that of light brown free flowing granulate. It is not explosive and has no oxidising properties. It is not flammable and has a relative self-ignition temperature of 120°C. In aqueous solution, it has a pH value of 9.4 at 20°C. The tap density is 0.471 g/cm^3 after 50 taps. There is less than 0.05 % residual material retained on a75 µm sieve and the wettability is 2 seconds. The stability data indicate a shelf life of at least 2 years at ambient temperature. Its technical characteristics are acceptable for a WG formulation.

The attrition test is outside the acceptable limit (<98%), consequently the size of particles of the formulation formed after the attrition test is required and the potential risk of operator must be evaluated.

The formulation is stable after storage 2 years at 20°C in the HDPE packaging.

CRUISER 600FS

The plant protection CRUISER 600FS is a beige liquid with a sweetish odour. It is not explosive and does not have oxidising properties. It is not flammable and auto-ignition was not observed at temperatures up to 450 ºC ± 25°C. The pH of a 1% dilution in water is 6.0 and the pH of the undiluted formulation is 5.5 at 20°C. The relative density was determined to be 1.246 and the surface tension at a concentration of 22% v/v was determined to be 24.6 mN/m at 20.0°C. In a wet sieve test less than 0.01 % residual material was retained on a 75 µm sieve. The diluted formulation does not produces foam, and the formulation exhibits good suspensibility. The formulation has good physical and chemical stability after storage for 7 days at 0°C, two weeks at 54°C. CRUISER 600FS is considered to have acceptable physical and chemical properties for an FS formulation, and there are no particular properties of the formulation, which necessitate any specific handling precautions when transporting, storing or using the product.

The formulation is stable after storage 2 years at 20°C in the HDPE packaging.

2.3 DATA ON APPLICATION AND EFFICACY

2.3.1 Summary of effectiveness

ACTARA 25 WG (A9584C) has been registered in most of the EU Member States: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, France, Germany, Greece, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Romania, Slovenia, Spain and UK.
ACTARA 25 WG (A9584C) has been registered on a range of crops and pests such as the ones mentioned in Volume 3 active substance (B.3.5. Harmful organisms controlled and crops or products protected or treated).

CRUISER 600 FS (A9765R) has been registered in several of the EU Member States: Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Poland, Sweden and UK.
CRUISER 600 FS (A9765R) has been registered on beets and lettuce on a range of pests such as the ones mentioned in Volume 3 active substance (B.3.5. Harmful organisms controlled and crops or products protected or treated).

More detailed consideration will be fully assessed in the context of subsequent applications for products authorization.

2.3.2 Summary of information on the development of resistance

Thiamethoxam is a neonicotinoid insecticide, which is classified by IRAC as a group 4 insecticide, sub-classification: A. Thiamethoxam and other group 4 insecticides act as agonists of the nicotinic acetylcholine receptor (nAChR) and disrupting normal nerve function. Group 4 insecticides include other neonicotinoid insecticides (sub-group A), nicotine (sub-group B), sulfoxaflor (Group C) and flupyradifurone (Group D).

Thiamethoxam and other group 4 insecticides have been globally used as insecticides for over 20 years and there have been a number of reported cases of the development of insecticide resistance in key pests of agriculture.

The Insecticide Resistance Action Committee (IRAC) continuously monitors globally for cases of resistance and according to the database, some cases of resistance have been noted in the literature.

Cases of thiamethoxam resistance indicated on the Arthropod Pesticide Resistance Database for agricultural pests in the world – October 2017
(https://www.pesticideresistance.org/search.php)

Genus Species	Taxonomy (family - order)	Common Name(s)	Cases in the world
Aphis gossypii	Aphididae Hemiptera	Melon and cotton aphid	28
Bemisia tabaci	Aleyrodidae Hemiptera	Sweetpotato whitefly	69
Brevicoryne brassicae	Aphididae Hemiptera	Cabbage aphid	2
Diaphorina citri	Psilidae Hemiptera	Asian citrus psyllid	12
Frankliniella occidentalis	Thripidae Thysanoptera	Western flower thrips	1
Leptinotarsa decemlineata	Chrysomelidae Coleoptera	Colorado potato beetle	2
Myzus persicae	Aphididae Hemiptera	Green peach aphid	4
Nilaparvata lugens	Delphacidae Hemiptera	Brown planthopper	29
Phenacoccus solenopsis	Pseudococcidae Hemiptera	Cotton mealybug	8
Trialeurodes vaporariorum	Aleyrodidae Hemiptera	Greenhouse whitefly	2

According to the applicant, in distinct locations within Europe resistance to group 4 insecticides has been recorded in:

1) the green peach aphid *Myzus persicae* (stone fruits in France, Spain & Italy). From ongoing monitoring activities, there is no evidence of the resistance having spread into other crops;

2) the tobacco whitefly *Bemisia tabaci* and glasshouse whitefly *Trialeurodes vaporariorum* (Protected vegetables and ornamentals in multiple countries) and
3) the damson-hop aphid *Phorodon humuli* (hops in Germany).

More specifically, cases of resistance to neonicotinoids for *Myzus persicae* in Stone fruit orchards are reported by the IRAC Sucking Pest Working Group (*Myzus persicae* neonicotinoid resistance management guidelines for Stone Fruits in Southern Europe, IRAC SPWG, 2016[1]). The results of surveys from 2010 to 2016 confirmed the spread and presence of neonicotinoid-resistant aphids in many of the stone fruit orchards of Southern France, Spain and Italy.

In areas where resistance to thiamethoxam and other class 4 insecticides is known, then the use of thiamethoxam to control those pests is not recommended. However, in areas where resistance to thiamethoxam is not present, thiamethoxam can be used effectively to manage a range of insect pests as a seed treatment, soil or foliar applied insecticide. It is recommended that thiamethoxam is used as part of a resistance management program, using insecticides with different modes of action.
In order to avoid the risk of resistance development for aphids, it could be recommended to avoid applying foliar treatment with a product containing neonicotinoid to a crop that has already received a seed treatment with a product also containing neonicotinoid.

Monitoring of resistance to thiamethoxam should be put in place from the marketing of products, in particular in case of moderate to high risk of resistance (*e.g. Myzus persicae* and *Leptinotarsa decemlineata* in regards to the representative uses).

2.3.3 Summary of adverse effects on treated crops

More detailed consideration will be fully assessed in the context of subsequent applications for products authorization.

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

More detailed consideration will be fully assessed in the context of subsequent applications for products authorization.

2.4 FURTHER INFORMATION

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

See Volumes 3 B-4 for the active substance and the plant protection product.

2.4.2 Summary of procedures for destruction or decontamination

See Volumes 3 B-4 for the active substance and the plant protection product.

2.4.3 Summary of emergency measures in case of an accident

See Volumes 3 B-4 for the active substance and the plant protection product.

[1] http://www.irac-online.org/documents/myzus-persicae-irm-english/?ext=pdf

2.5 METHODS OF ANALYSIS

2.5.1 Methods used for the generation of pre-authorisation data

Analytical method SA-1/2 (Duell B., 2014 and Ebi E, 2014) for the determination of thiamethoxam in technical active substance has been provided and validated according to guidance SANCO3030/99/rev.4.

Analytical methods SB-1/2 (Dull B., 2014 and Dull B., 2015) and SB-101/1 for the determination of thiamethoxam by-products in technical active substance have been provided and validated according to guidance SANCO3030/99/rev.4.

2.5.2 Methods for post control and monitoring purposes

Analytical methods for the determination of the active substance in the plant production product

ACTARA 25WG
Analytical methods AF-1241/1 (Birk R., 1996 and Birk R. 1998) and AF-1241/3 (Düll B., 2003 and Ebi E., 2014) for the determination of Thiamethoxam in the plant production product ACTARA 25 WG have been provided and validated according to guidance SANCO3030/99/rev.4.

CRUISER 600FS
Analytical method AF-1476/1 (Duell B., 2002, Duell B., 2003 and Das R. 2015) for the determination of Thiamethoxam in the plant production product CRUISER 600FS has been provided and validated according to guidance SANCO3030/99/rev.4.

Analytical methods for the determination of Thiamethoxam residues in foodstuff of plant and animal origin

Plant matrices
A QuEChERS multi-residue analytical method (Class T., Richter S., 2012) and its ILV (Austin R., Turner R., 2013) using LC/MS/MS for the determination of Thiamethoxam in crops (high wet, dry, acidic, oily) were provided and fully validated with a limit of quantification of 0.01 mg/kg for thiamethoxam and CGA322704 separately. Confirmatory data were provided on a second mass transition according to SANCO825/00 rev8.1.
The extraction efficiency has been demonstrated.

Animal matrices
A QuEChERS multi-residue analytical method (Class T., Richter S., 2013) and its ILV (Austin R., Turner R., 2013) using LC/MS/MS for the determination of Thiamethoxam in animal matrices (muscle, fat, kidney/liver, milk, eggs and blood) were provided and fully validated with a limit of quantification of 0.01 mg/kg for thiamethoxam and CGA322704. Confirmatory data were provided on a second mass transition according to SANCO825/00 rev8.1.
The extraction efficiency has been demonstrated.

Analytical methods for the determination of Thiamethoxam residues in soil, water and air
An analytical method GRM009.09A (Huang B., 2015 and Bannwarthe M., 2015) using LC/MS/MS for the determination of thiamethoxam residues in soil was provided and fully validated with a limit of quantification of 0.001 mg/kg. Confirmatory data were provided on a second mass transition according to SANCO/825/00 rev. 8.1. No other data is required.

Analytical methods GRM009.10A and its ILV (Lin K., 2015 and Langridge G., 2014 ; Hamberger R., 2015) using LC/MS/MS were provided and fully validated for the determination of Thiamethoxam residues in ground and surface water with a limit of quantification of 0.01 µg/L for thiamethoxam , CGA322704, SYN501406 and NOA459602 in groundwater, 0.01 µg/L for thiamethoxam and CGA322704 in surface water and 0.05 µg/L for SYN501406 and NOA459602 in surface water. Confirmatory data were provided on a second mass transition according to SANCO/825/00 rev.8. No other data is required.

An analytical method REM 179.04 (Tribolet R., 1997) using HPLC/UV for the determination of Thiamethoxam residues in air was provided and fully validated with a LOQ of 0.5 µg/m^3.

Analytical methods for the determination of Thiamethoxam residues in biological fluids and tissues

The analytical method for animal tissues monitoring presented above, QuEChERS (Class, T., Richter S. 2013), was validated in blood and various tissue matrices with a limit of quantification of 0.01 mg/kg for thiamethoxam and CGA322704. It is deemed suitable and sufficiently validated to be used as a method for the analysis of body fluids and tissues.

2.6 EFFECTS ON HUMAN AND ANIMAL HEALTH

The toxicological data package is considered appropriate. The toxicity studies were performed with batches that covered the claimed specification, were carried out under GLP and in compliance with in force guidelines at the time they were performed.

Thiamethoxam is a neonicotinoid with pesticidal mode of action based on nicotinic acetylcholine receptor (nAChR) agonist property. Thiamethoxam as other neonicotinoids has weak affinity for mammalian nAChRs and strong affinity for insect nAChRs. However, metabolism of thiamethoxam could give rise to compounds showing higher affinity for mammalian nAChRs. Therefore Thiamethoxam activity is mainly driven by its metabolism, some of its metabolites being more potent than the parent both in insects (efficacy) and in mammalian (toxicity).
It is also of note that clothianidin, another approved substance currently under review, is a major metabolite of thiamethoxam. Therefore, it is proposed that both substances should be peer-reviewed concurrently for consistency purposes.

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

Table 3: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Rat			
CGA293343: Absorption, distribution and excretion of [Thiazol-2-14C] and [Oxadiazin-4-14C] CGA293343 in the rat. OECD 417 GLP Acceptable	Absorption, distribution and excretion independent of sex, dose, pre-treatment and position of the radiolabel Absorption: >90 % based on urinary excretion within 48h Distribution: Widely distributed in tissues Accumulation: no potential after 7 days, tissue residues very low, highest amounts in liver (0.01-0.04% of the dose). Excretion: Rapid and extensive (> 95% within 24 h), mainly via urine (88-95%) In blood Cmax : 0.18 and 37 ppm for 0.5 and 100 mg/kg respectively Tmax: 1 - 4 hours T1/2: 3-4 hours	Thiamethoxam [Thiazol-2-^{14}C] and [Oxadiazin-4-^{14}C] Single dose: 0.5 mg/kg bw (low dose) 100 mg/kg bw (high dose) Repeated dose: 0.5 mg/kg bw/d Rat Tif:RAIf (SPF) M & F	[redacted],1996 Refer to Annex I. Vol3CA B.6.1.1.1
CGA293343: The metabolism of [Thiazol-2-14C] and [Oxadiazin-4-14C] CGA293343 in the rat OECD 417 GLP Acceptable	Metabolism independent of sex, dose, pre-treatment and position of the radiolabel Major pathway: cleavage of the oxadiazine ring to CGA322704 Minor pathways: reduction of the nitroguanidine group yielding a guanidine derivative, hydrolysis of the guanidine group to the corresponding urea,	Follow up of [redacted],1996	[redacted] 1998 Refer to Annex I. Vol3CA B.6.1.1.1

Method	Results	Remarks	Reference
	demethylation of the guanidine group and substitution of the chlorine of the thiazole ring by glutathione. Metabolism: 20 - 30% of dose Urine metabolites: Thiamethoxam: 69-83% CGA322704: 5-13% CGA265307: 1-2% All other metabolites <1%		
Blood kinetics of CGA293343 and its metabolites Mechanistic study GLP Acceptable	In blood: Tmax total residue : 6 hours Thiamethoxam: major component CGA322704: 3-31% of TRR CGA265307: only traces CGA330050: not detected	Thiamethoxam [Oxadiazin-4-^{14}C] Single dose: 100 mg/kg bw (high dose) Rat Tif:RAIf (SPF) M	[redacted], 2003 Refer to Annex I. Vol3CA B.6.1.1.1
Mouse			
The metabolism of [Thiazol-2-^{14}C] CGA293343 after multiple oral administrations to mice Mechanistic study GLP Acceptable	Absorption: 70% based on urinary excretion Excretion: Rapid and extensive, mainly via urine (70%), faeces (19%) Metabolism: 20 - 30% of dose Urine metabolites: Thiamethoxam: 33-41% CGA322704: 8.12% CGA265307: 9-18% All other metabolites <1%	[Thiazol-2-^{14}C] thiamethoxam Repeated dose (14-d): 100 mg/kg bw (high dose) Mouse MAG Tiflbm:MAG (SPF) M	[redacted], 1998 Refer to Annex I. Vol3CA B.6.1.1.2
The metabolism of [Thiazol-2-^{14}C] CGA293343 after multiple oral administration to mice; further identification of metabolites. Mechanistic study GLP Acceptable	Based on the metabolites identified, the metabolism of thiamethoxam in the mouse proceeds by the same major pathways as in the rat. However quantitative differences are observed.	Follow-up of [redacted], 1998 Identification of metabolites	[redacted], 2000 Refer to Annex I. Vol3CA B.6.1.1.2
CGA293343: Absorption, metabolism, and excretion of [oxadiazin-4-14C] CGA293343 after dietary administration of CGA293343 at four dose levels in the mouse. Mechanistic study GLP Acceptable	Rates and routes of excretion and metabolism not dependent on the dietary exposure level.	[Oxadiazin-4-14C] thiamethoxam Repeated dose (29-d): 0, 100, 500 and 2500 ppm non radiolabelled + 1pulse of [Oxadiazin-4-14C] thiamethoxam at a nominal 10 mg/kg body weight at Day 30 Mouse MAG Tiflbm:MAG (SPF) M	[redacted], 2000 Refer to Annex I. Vol3CA B.6.1.1.2
CGA293343: The metabolism of [Oxadiazin-4-14C] CGA293343 in the mouse after oral administration. Mechanistic study GLP Acceptable	The metabolism of thiamethoxam proceeds predominantly via oxadiazine ring cleavage, dealkylation, hydrolysis, reduction and oxidation reactions. Metabolic pathway of thiamethoxam in the mouse and the rat are similar.	[Oxadiazin-4-14C] thiamethoxam Single dose 0.5 mg/kg bw and 100 mg/kg bw Mouse MAG Tiflbm:MAG (SPF) M and F	[redacted], 2002. Refer to Annex I. Vol3CA B.6.1.1.2
CGA293343: Absorption,	Cmax: 41ppm Tmax : 0.5 hours	[Oxadiazin-4-14C] thiamethoxam	[redacted] 2002a

Method	Results	Remarks	Reference
distribution and excretion of [Oxadiazin-4-14C] CGA293343 in the mouse after oral administration. Mechanistic study GLP Acceptable	T1/2: 4 hours Thiamethoxam : major component in blood CGA322704, CGA265307 CGA330050 also detected	Single dose 100 mg/kg bw Mouse MAG Tiflbm:MAG (SPF) M	Refer to Annex I. Vol3CA B.6.1.1.2
Blood kinetics of CGA 293343 and its metabolites in male mice after oral administration of [Oxadiazin-4-14C] CGA293343 Mechanistic study GLP Acceptable	Absorption: >70 % based on urinary excretion within 48h Distribution: Widely distributed in tissues Excretion: more important in the mouse than in the rat No bile-cannulated animals	[Oxadiazin-4-14C] thiamethoxam Single dose: O.5 and 100 mg/kg bw Mouse MAG Tiflbm:MAG (SPF) M	[redacted], 2003a Refer to Annex I. Vol3CA B.6.1.1.2
See also [redacted], 2002: Comparative metabolism in mice and rats *in vivo*, and in mouse, rat & human liver fractions *in vitro*. 2.6.8.2			
***In vitro* metabolism**			
Thiamethoxam - *In vitro* Rat and Human Liver Microsomal Metabolism. Mechanistic study GLP Acceptable	Thiamethoxam poorly metabolised in both rat and human liver incubates 93% and 96% of [14C]-thiamethoxam remained No qualitative difference between rat and human microsomes M4 4.1% in rat and 1.6% in human microsomes Other metabolites > 1% with both rat and human liver incubates	Thiamethoxam[thiazolyl-2-14C]- and [oxadiazine-4-14C]-radiolabels Rat and human liver microsomes 60 minutes incubation	Paul D, 2017 Refer to Annex I. Vol3CA B.6.1.2.1
See also Green, 2002: Comparative metabolism in mice and rats *in vivo*, and in mouse, rat & human liver fractions *in vitro*. 2.6.8.2			
Data from open literature			
LC-MS/MS method for quantification of thiamethoxam in rat plasma and its toxicokinetics study Klimisch :2 Acceptable	Kinetic parameters (Tmax, TC1/2) obtained consistent with those previously proposed for thiamethoxam while Cmax at 100 mg/kg bw is 2 fold higher than in 1996. [redacted]	Thiamethoxam Purity: 96% Single dose: 100 and 1000 mg/kg bw Rat (SD)	Lin L, 2014 Refer to Annex I. Vol3CA B.6.1.2.2
Unique and common metabolites of thiamethoxam, clothianidin, and dinotefuran in mice. Published paper. Chem. Res. Toxicol. 2006, 19, 1549-1556. Klimisch :2 Acceptable	Structures of 37 metabolites identified in the TMX, TMX-dm, and CLO series, potential contributors in the activation and detoxification pathways. CGA330050 and CGA265307 (TMX-dm and CLO-dm, respectively) detected in the liver and plasma of mice treated with thiamethoxam. Thiamethoxam and some of its metabolites reached the brain	Thiamethoxam and Clothianidin purity not reported Mouse Swiss-Webster mice (albino) M	Ford K, 2006 Refer to Annex I. Vol3CA B.6.1.2.2
Substrate specificity of rabbit aldehyde oxidase for nitroguanidine and nitromethylene neonicotinoid insecticides. Klimisch :2	Aldehyde oxidase is the enzyme involved in nicotinoids nitro-reduction. Contrary to clothianidin, thiamethoxam = poor substrate of AOX.	Thiamethoxam and Clothianidin purity not reported AOX was prepared from rabbit liver cytosol	Dick R, 2006 Refer to Annex I. Vol3CA B.6.1.2.2

Method	Results	Remarks	Reference
Acceptable			
See also Table 44 Swenson			

Thiamethoxam: TMX
CGA322704 = Clothianidin = CLO
CGA265307 = N-desmethyl clothianidin = CLO-dm
CGA330050= N-desmethyl thiamethoxam = TMX-dm

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

Absorption, distribution, metabolism and excretion of thiamethoxam were independent of sex, dose, pre-treatment and position of the radiolabel in both rats and mice.

Absorption:
Thiamethoxam was rapidly absorbed and eliminated in rats and mice. Oral absorption based on urinary excretion within 48 h was > 90% and > 70% in rats and mice respectively.
In rats, blood concentrations peaked at 4-6 hours, followed by rapid elimination. The half-life of elimination of the radioactivity in blood was 3-4 hours.
In mice Tmax was at 0.5 hours after administration and the half-life of elimination of the radioactivity in blood was 4 hours.
Distribution and accumulation:
In both species, thiamethoxam was widely distributed. Distribution to the tissues was generally non-selective, with higher concentrations in liver and blood.
Thiamethoxam showed no potential of accumulation in both species. In rats after 7 days, tissue residues were all very low, with the highest amounts detected in liver (0.01-0.04% of the dose).
Excretion:
In rat approximately 84-95% of the dose was excreted in the urine and 2.5-6% in the faeces within 24 hours while in mice approximately 70% of the dose was excreted in the urine and 19% in the faeces. The majority of excretion was complete by 24 hours post-dosing.
A small amount was detected in expired air (0.2%) in both species.
Metabolism:
Metabolic degradation of thiamethoxam in rats and mice proceeded via the same pathways.
The major reaction involved in the biotransformation of thiamethoxam is cleavage of the oxadiazine ring to the corresponding nitroguanidine compound CGA 322704 (= clothianidin). Minor pathways are reduction of the nitroguanidine group, yielding a hydrazine, followed by either acylation or further reduction to a guanidine derivative, hydrolysis of the guanidine group to the corresponding urea, demethylation of the guanidine group and substitution of the chlorine of the thiazole ring by glutathione. Cleavage between the thiazole and oxadiazine ring occurs to a small extent and is mediated by either glutathione or oxidative dealkylation. The glutathione derivatives are prone to further degradation. Both the thiazole and oxadiazine moieties are susceptible to oxidative attack. These minor pathways proceed to small molecules and ultimately, probably, to carbon dioxide. The small molecules generated may enter the general metabolism.
However quantitative differences among the two species were observed. In rats, about 20–30% of the dose was biotransformed, whereas 70–80% was eliminated as unchanged thiamethoxam. In mice, 30–60% of the dose was biotransformed.

In rats thiamethoxam was the major component detected in blood extracts (82%) followed by CGA 322704 (16%). Only trace amounts of CGA 265307 (0.3%) were found and CGA 330050 was not detected.
In mouse thiamethoxam was the major component detected in blood extracts (78%) within the first 4 hours post-dosing, while CGA265307 was noted to be the major plasma metabolite at 6 hours following dosing (43.3 - 54.5% of radioactivity), indicating rapid metabolism of the parent. CGA322704 was also noted in plasma at a similar concentration (19.5 - 25.6% of radioactivity) as the parent and CGA 330050 was noted at concentration between 4.7 – 12.5% of radioactivity).
A comparative mechanistic study [redacted]2002) showed that the concentrations of CGA265307 were approximately 22-fold greater in mouse plasma than in rat plasma after 1 week of feeding. After 10 weeks feeding, the concentration of CGA265307 in mouse plasma had increased approximately 3.6-fold (suggesting induction of metabolic pathways) whereas that in rat plasma had reduced. As a result, the concentrations of CGA265307 were approximately 140-fold greater in mouse plasma than in rat plasma after 10 week of feeding

The difference between the two species for CGA330050 (N-desethylthiamethoxam) was up to 15-fold over the duration of the study.

In urine of rat , unchanged thiamethoxam accounted for 69-83% , CGA 322704 was the major urinary metabolite accounted for 5-13% of the administrated dose and CGA 265307 accounted for 1- 2%.
In mice, thiamethoxam, CGA 322704 and CGA 265307 accounted for 31-44%, 8-12% and 9-18% of the dose respectively.
The individual contributions of all the numerous other metabolites identified in rats and mice urine did not exceed 1% of the dose.

In vitro comparisons of thiamethoxam metabolism in mouse, rat and human liver microsomal preparations clearly support the significantly higher generation of CGA 330050 and CGA 265307 in mice compared with rats and additionally, demonstrates that human liver microsomes metabolize thiamethoxam in a manner quantitatively similar to and not exceeding that of rats.
The major difference between the metabolism in rats and mice, which may lead to a difference in long term toxicity, is the production of metabolite CGA330050 in mice.
Data from the open literature support the quantitative differences between the two species.

2.6.2 Summary of acute toxicity

The acute oral toxicity of thiamethoxam was evaluated in rats and mice and dermal and inhalation exposure studies were performed in rats. Skin and eye irritancy studies were performed in rabbits, and a skin sensitisation study in guinea pigs. The results are summarized in the table. These studies were previously submitted in the EU and summarized in the Monograph.
Thiamethoxam is of low acute oral toxicity to rats (LD_{50} = 1563mg/kg). Signs of acute thiamethoxam intoxication are tonic or clonic convulsions and ptosis. Thiamethoxam is harmful to mice in acute oral toxicity study (LD_{50} = 783mg/kg).
Thiamethoxam is of low percutaneous toxicity in the rat (LD_{50} = >2000mg/kg) suggesting poor absorption into the systemic circulation by this route.
No serious signs of toxicity occurred following a 4-hour inhalation after nose only exposure to the maximum attainable concentration of 3.72 mg/L respirable particles of thiamethoxam.
Thiamethoxam is not irritant to skin and eyes.
An adjuvant-assisted contact sensitisation study showed thiamethoxam to be a non-sensitizer.
Thiamethoxam elicited an equivocal response in the in vitro 3T3 NRU phototoxicity test. In order to further investigate this finding an EpiDerm phototoxicity test was conducted. While no OECD guideline is available for the later test it has successfully undergone pre-validation by ECVAM in a number of laboratories under blind conditions and the test system is more relevant than that in *in vitro* 3T3 NRU phototoxicity test. In this higher tier assay thiamethoxam gave a negative response, indicating an absence of phototoxic effects. Furthermore no phototoxicity potential has been reported in human.

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

Table 4: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Value LD_{50}**	**Reference**
Acute oral toxicity study OECD Guideline 401 GLP Acceptable	Rat, Crj:CD (SD) strain SPF 5/sex/group	Thiamethoxam technical Batch P.506006 (purity 98.60%) Vehicle: 0.5% w/v aqueous methylcellulose	0, 900, 1500, 2300, 3800 and 6000 mg/kg Single dose (gavage) followed by 14 day observation period.	LD_{50} = 1563 mg/kg in both males and females	[redacted] 1996 Refer to Annex I. Vol3CA B.6.2.1

Acute oral toxicity study	Mice, Crj:CD-1 (ICR) strain SPF	Thiamethoxam technical	0, 500, 700, 100, 1400 and 2000	LD_{50} = 783 mg/kg in males	[redacted] 1996a Refer to Annex I.

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD Guideline 401 GLP Acceptable	5/sex/group	Batch P.506006 (purity 98.60%) Vehicle: 0.5% w/v aqueous methylcellulose	mg/kg Single dose (gavage) followed by 14 day observation period.	LD_{50} = 964 mg/kg in females LD_{50} = 871 mg/kg in both sexes combined	Vol3CA B.6.2.1

Table 5: Summary table of human data on acute oral toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference

From the applicant's detailed records of exposure and poisoning incidences 2003-2014, 2 fatal cases were linked to unclear circumstances with no causal evidence to be linked to exposure to the active ingredient.
The following summary tables of exposure related to thiamethoxam have been compiled[2] for the period 2003-2014. The majority of reported incidents were of very low severity grade[3]

Thiamethoxam exposure type and severity of symptoms

Exposure/severity	None	Minor	Moderate	Severe	Fatal	Total
Occupational	85	242	40	0	1	**368**
Accidental	53	52	20	0	0	**125**
Intentional	25	41	5	5	0	**76**
Uncertain	8	4	16	1	1	**30**
Total	**171**	**339**	**81**	**6**	**2**	**599**

Severity of symptoms and affected area following thiamethoxam exposure

	None	Minor	Moderate	Severe	Fatal	Total
Dermal	35	137	30	2	1	**205**
Eye	5	19	5	0	0	**29**
Ingestion	81	62	10	3	0	**156**
Inhalation	13	106	16	1	0	**136**
Other	0	1	2	0	0	**3**
Unknown	37	14	18	0	1	**70**
Total	**171**	**339**	**81**	**6**	**2**	**599**

Table 6: Summary table of other studies relevant for acute oral toxicity

[2] Countries: Albania, India, Algeria, Argentina, Armenia, Australia, Azerbaijan, Belarus, Belgium, Bosnia-Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Croatia, Cuba, Czech Republic, Denmark, Ecuador, Egypt, El Salvador, Fiji, France, Georgia, Germany, Greece, Guatemala, Hungary, India, Indonesia, Iraq, Ireland, Italy, Japan, Jordan, Kazakhstan, Kenia, Kenya, Korea Republic of, Kosovo, Kuwait, Kyrgyzstan, Lebanon, Lithuania, Macedonia, Malawi, Malaysia, Mauritius, Mexico, Moldova, Morocco, Mozambique, New Zealand, Nicaragua, Oman, Pakistan, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russian Federation, Serbia, Slovakia, Singapore, Slovenia, Spain, Switzerland, Syrian Arab Republic, Taiwan, Tajikistan, Thailand, Turkey, Turkmanistan, Ukraine, United Arab Republic, United Kingdom, USA, Uzbekistan, Venezuela, Vietnam, Yemen, Zimbabwe

[3] **Severity Grades** (Clinical Toxicology Jan 1998, Vol. 36, No. 3: 205–213) :

NONE (0): No symptoms or signs related to poisoning
MINOR (1): Mild, transient and spontaneously resolving symptoms
MODERATE (2): Pronounced or prolonged symptoms
SEVERE (3): Severe or life-threatening symptoms
FATAL (4): Death

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Micronucleus test mouse OECD 474 GLP Acceptable	Thiamethoxam technical Batch P.506006 (purity 98.60%) Solvent Bidistilled water	In the tolerability test: one animal of each sex is treated at 320, 500, 800, 1250 and 2000 mg/kg. Both animals treated with 2000 mg/kg died within 1-3 hours of treatment. All other tested animals survived. In the micronucleus test: The dose level of 1250 mg/kg bw caused death in 7/13 females and this dose was reduced to 1000 mg/kg.	Estimated LD_{50} ≥ 1250 mg/kg in males Estimated LD_{50} ≥ 1000 mg/kg in females	[redacted] 1995a Refer to Annex I. Vol3CA B.6.4.2

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

The acute oral toxicity of thiamethoxam was assessed in a standard guideline study (OECD 401) in Crj:CD (SD) strain SPF rats ([redacted]996). A preliminary acute oral toxicity study test was conducted; three groups of three males and three females were used. These groups had the test article administered at dose levels of 800, 2000 and 5000 mg/kg. 1 animal of each sex in the 2000 mg/kg group and 2 animals of each sex in the 5000 mg/kg group died. Consequently 5 dose levels, 900, 1500, 2300, 3800 and 6000 mg/kg were selected for both sexes in the main study. Six groups, including a control group, were provided and each group consisted of 5 animals per sex.
3 animals of each sex treated at a dose level of 1500 mg/kg were found dead 2 to 6 hours after dosing. 4 animals of each sex treated at a dose level of 2300 mg/kg were found dead between 2 and 4 hours after dosing. At the test doses of 3800 and 6000 mg/kg all test animals in the groups were killed after dosing.

The median lethal dose of thiamethoxam after single oral administration to rats, observed over a period of 14 days, was estimated to be 1563 mg/kg in both sexes (95% CI 1086 – 2174 mg/kg).

The acute oral toxicity of thiamethoxam was assessed in a standard guideline study (OECD 401) in Mice, Crj:CD-1 (ICR) strain ([redacted]996a). Based on the results of a preliminary study, one control group and 5 dose levels, 500, 700, 1000, 1400 and 2000 mg/kg were selected for both sexes (5animals/sex/group) in the main study. No deaths were observed in the 500 mg/kg group in either sex, however, 2 males and 1 female in 700 mg/kg group, 4 males and 3 females in the 1000 mg/kg group, all males and 4 females in the 1400 mg/kg group, and all animals in the 2000 mg/kg group died. The acute oral LD_{50} of thiamethoxam in mice is 783 mg/kg (95% confidence limits 619 – 1000 mg/kg) in males and 964 mg/kg (729 – 1271 mg/kg) in females, and 871 mg/kg (735 – 1028 mg/kg) in both sexes combined.

The applicant has kept detailed records of exposure and poisoning incidences on marketed products for many years. A review of the exposure incidences of thiamethoxam formulations reported between 2003 and 2014 has been conducted.

Health effects observed after exposure to thiamethoxam after occupational, accidental, intentional and uncertain exposure within this 12 years period were almost exclusively of transient nature with minor severity or below. In total 599 cases have been reported in this period. 76 cases (13%) were related to intentional misuse. The other incidents were caused by occupational (368 cases, 61%), accidental (125 cases, 21%) and uncertain (30 cases, 4%) exposure. Exposure happened followed by ingestion in 26% of the cases (156 cases). The majority of reported incidents were of very low severity grade (minor and none). The 3 incidents by ingestion assigned severe severity grade were caused by intentional self-harm.

2.6.2.1.2 Comparison with the CLP criteria regarding acute oral toxicity

In the current Annex VI entry, for Acute Toxicity via the oral route thiamethoxam is classified, Acute Tox. 4* (H302), the asterix indicating that this is a minimum classification.

According to the criteria in CLP Annex I, an oral LD50 >300 but ≤ 2000 mg/kg bodyweight lead to a category 4 classification.
Therefore, based on the results of the acute toxicity studies in rat and mouse and in accordance with CLP criteria,

Acute tox 4 (H302) is confirmed and the asterix should be removed in the current entry.

To facilitate consistent classification of mixtures containing thiamethoxam, a harmonised ATE value is also proposed. According to the CLP regulation, the ATE value for a substance should be derived using the LD_{50} where available. The lowest LD_{50} value in male mice was 783 mg/kg bw and 964 mg/kg bw in female mice.While in rat, the LD_{50} value was 1563 mg/kg bw in both males and females.
Taking these data into account, and in line with table 3.1.2, Annex I of CLP, it is proposed to assign an ATE of 800 mg/kg bw for acute oral toxicity.

2.6.2.1.3 Conclusion on classification and labelling for acute oral toxicity

Acute toxicity (oral), cat. 4 - H302 Harmful if swallowed **ATE value: 800 mg/kg bw**

RAC evaluation of acute oral toxicity

Summary of the Dossier Submitter's proposal

In the current Annex VI entry the substance has a minimum classification with Acute Tox. 4*; H302. Two acute oral toxicity studies are available, one in the rat and one in the mouse. The LD_{50} values from both studies are in the range of $300 < LD_{50} \leq 2\,000$ mg/kg bw, confirming the current classification and allowing removal of the asterisk.

As to the ATE, the DS proposed 800 mg/kg bw, a rounded value based on the lowest LD_{50} of 783 mg/kg bw for male mice and taking into account the other available LD_{50} values, i.e. 964 mg/kg bw for female mice and 1 563 mg/kg bw for rats.

Comments received during public consultation

Comments were received from 3 MSCAs. All 3 MSCAs supported classification in Category 4. 2 MSCAs supported the rounded ATE of 800 mg/kg bw while 1 MSCA preferred the unrounded value of 783 mg/kg bw.

Assessment and comparison with the classification criteria

Both acute oral toxicity studies were conducted according to OECD TG 401 and under GLP. The rat LD_{50} was 1 563 mg/kg bw (the same value for both sexes). The mouse study (strain CD-1) yielded LD_{50} values of 783 mg/kg bw for males, 964 mg/kg bw for females and 871 mg/kg bw for combined sexes. The CLH report also mentions a mouse micronucleus test (strain Tif:MAGf) where 7 out of 13 females died at 1 250 mg/kg bw. All this information is consistent with Category 4.

The Guidance on the application of the CLP criteria generally recommends choosing the lowest ATE in the most sensitive appropriate species tested. RAC agrees with the DS to base the ATE on the lowest available LD_{50} of 783 mg/kg bw (male mice). In previous cases LD_{50} values were usually not rounded for the purpose of ATE setting. On the other hand, RAC notes that rounded values are easier to use and that unrounded values may give an impression of precision that in fact does not exist (the 95 % confidence interval for the LD_{50} in male mice is 619-1 000 mg/kg bw). RAC therefore proposes to classify thiamethoxam as **Acute Tox. 4; H302** with an **ATE** of **780 mg/kg bw**, i.e. to two significant places.

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

Table 7: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Value LD_{50}**	**Reference**
Acute dermal toxicity study OECD Guideline 402 GLP Acceptable	Rat, Crj:CD (SD) strain SPF <u>Preliminary study:</u> 3/sex 2000 mg/kg <u>Main study:</u> 5/sex/group 0 or 2000 mg/kg	Thiamethoxam technical Batch P.506006 (purity 98.60%) Vehicle: distilled water	2000 mg/kg 24 hour application followed by 14 day observation period.	<u>Preliminary study:</u> No death observed. Main study: LD50 > 2000 mg/kg in both sexes No death observed. No systemic or local effect	[redacted] 1996b Refer to Annex I. Vol3CA B.6.2.2

Table 8: Summary table of human data on acute dermal toxicity

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
There is no reliable evidence of systemic adverse effects following dermal exposure to humans				

Table 9: Summary table of other studies relevant for acute dermal toxicity

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

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

The acute dermal toxicity of thiamethoxam was assessed in a standard guideline study (OECD 402) in Crj:CD (SD) strain SPF rats ([redacted], 1996). A preliminary acute dermal toxicity test was conducted, a group of three male and three female were tested at a dose level of 2000 mg/kg. No deaths were observed in either sex therefore a

single dose of 2000 mg/kg CGA 293343 TECH was administered dermally to a group of 5 male and 5 female rats. At the end of the 14 days examination period, no death was observed.

The median lethal dose of thiamethoxam after single dermal application to rats, observed over a period of 14 days, is greater than 2000 mg/kg in both sexes.

2.6.2.2.2 Comparison with the CLP criteria regarding acute dermal toxicity

According to the criteria in CLP Annex I, a dermal LD50 ≥ 2000 mg/kg bodyweight lead to no classification.

2.6.2.2.3 Conclusion on classification and labelling for acute dermal toxicity

Not classified (conclusive but not sufficient for classification)

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

Table 10: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations[1] if any	**Species, strain, sex, no/group**	**Test substance, form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value LC_{50}**	**Reference**
Acute inhalation toxicity study OECD Guideline 403 GLP Acceptable	Rat, Crj:CD (SD) strain SPF 10/sex/group	Thiamethoxam technical Batch P.506006 (purity 98.60%) MMAD: 5.1 µm at 1 hour and 5.6 µm at 3 hours	1.02, 3.72 mg/L (highest technically achievable concentration) 4 hours exposure followed by 14 day observation period.	LC50 > 3.72 mg/L in both sexes	[redacted], 1996 Refer to Annex I. Vol3CA B.6.2.3

Table 11: Summary table of human data on acute inhalation toxicity

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
There is no reliable evidence of systemic adverse effects following inhalation exposure to humans				

Table 12: Summary table of other studies relevant for acute inhalation toxicity

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

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

In an acute inhalation toxicity study assessed in a standard guideline study (OECD 403), groups of young adult SPF Sprague-Dawley (Crj:CD) rats (10 male and 10 female) were exposed by inhalation route to pulverized CGA 293343 TECH (98.60%) in the form of a dust for 4 hours (in a nose only exposure chamber). 2 groups of five male and five female rats were exposed to CGA 293343 TECH at a target formulation concentration of 5 mg/L. Test atmospheres were analysed for particulate concentration. The mean actual atmospheric concentrations of CGA 293343 TECH were 1.02 mg/L (group 1) and 3.72 mg/L (group 2). The mean values of

MMAD and standard deviations of the test substance were 5.1 µm and 2.1 in group 1, and 5.6 µm and 1.8 in group 2. At the end of the 14 days examination period, no death was observed.

The median lethal concentration of thiamethoxam after single inhalation exposure to rats, observed over a period of 14 days, is greater than 3.72 mg/L in both sexes.

2.6.2.3.2 Comparison with the CLP criteria regarding acute inhalation toxicity

According to the criteria in CLP Annex I, a LC50 ≥ 5 mg/L or the maximum attainable concentration lead to no classification.

2.6.2.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Not classified (conclusive but not sufficient for classification)

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

Table 13: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results - Observations and time point of onset[2] - Mean scores/animal - Reversibility	Reference
Skin irritation study OECD 404 GLP Acceptable	Japanese white female rabbits 6 animals	Thiamethoxam technical Batch P.506006 (purity 98.60%)	0.5 g applied 4 hours topical semi-occlusive application. Irritation response assessed at 1 hour, 1, 2 & 3 days after removal of dressings.	No irritant dermal reactions were observed. Mean scores at 24, 48 and 72 hours: Erythema: 0, 0, 0, 0, 0, 0 Oedema: 0, 0, 0, 0, 0, 0	[redacted], 1996 Refer to Annex I. Vol3CA B.6.2.4

Table 14: Summary table of human data on skin corrosion/irritation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
From the French programme « Phyt'attitude »[4] , 28 cases were collected during the time period 1997-2015. 15 cases were excluded as the occurrence of signs and symptoms was considered as non-related to thiamethoxam exposure; another 5 cases were excluded because the individual was exposed to one or more PPP in combination with the thiamethoxam-based PPP. The remaining 8 cases were exposed to thiamethoxam only and the causal relationship between exposure and health outcome was considered plausible or likely. The most frequently reported effects include local signs of irritation of the skin (erythema) and mucous membranes. 4 out of those 8 cases presented skin irritation. Most incidents occurred when operating with treated seeds: big bag opening, seeder filling; operators either did not wear PPE or wore PPE that were not adapted.				

[4] http://www.msa.fr/lfr/sst/phyt-attitude

Table 15: Summary table of other studies relevant for skin corrosion/irritation

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

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

In a primary skin irritation study assessed in a standard guideline study (OECD 404), six 13 week old Japanese white female rabbits were dermally exposed to 0.5g of CGA 293343 TECH (98.6%) for 4 hours to the previously shaved skin of the rabbits' dorsal area. Animals then were observed for up to 72 hours after removal of the test material for signs of erythema oedema. No irritant dermal reactions were observed and the primary dermal irritation index was zero. Thiamethoxam is, therefore, considered to be "not irritant" to rabbit skin.

From the French programme « Phyt'attitude »[2], a vigilance program developed by the Mutualité Sociale Agricole (national insurance company for farmers) based on voluntary event notifications by a network of physicians and self-reporting by users of any case of suspected work-related pesticide injury or illness or poisoning, in 4 cases out the 8 cases for which the causal relationship between exposure and health outcome was considered plausible or likely, irritation of the skin was observed.
Most incidents occurred when operating with treated seeds: big bag opening, seeder filling; operators either did not wear PPE or wore PPE that were not adapted.

2.6.2.4.2 Comparison with the CLP criteria regarding skin corrosion/irritation

Substances are classified if, when applied to the skin of an animal, it produces:

- if destruction of skin tissue (visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours → Classification as skin corrosive – Category 1.
- if at least 4 out of 6 rabbits show a mean score per animal of ≥ 2.3 ≤ 4.0 for erythema/eschar or for oedema → Classification as skin irritant – Category 2;

According to the criteria in CLP Annex I, there was no evidence of skin irritation in any animal, classification as skin corrosive or skin irritant is not applicable.

2.6.2.4.3 Conclusion on classification and labelling for skin corrosion/irritation

Not classified (conclusive but not sufficient for classification)

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

Table 16: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results - Observations and time point of onset[2] - Mean scores/animal - Reversibility	Reference
Eye irritation study	Japanese white female rabbits	Thiamethoxam technical Batch	0.1 g (ground prior to	No irritant eye reactions were observed. Mean scores (24, 48 and 72 hours) for	[redacted], 1996a Refer to Annex I.

OECD Guideline 405 GLP Acceptable	6 animals in the unwashed group 3 animals in the washed group	P.506006 (purity 98.60%)	instillation to left eye). Single exposure.	unwashed group and washed group: Cornea: 0, 0, 0. Iris: 0, 0, 0. Conjunctivae (redness): 0, 0, 0. Conjunctivae (chemosis): 0, 0, 0.	Vol3CA B.6.2.5

Table 17: Summary table of human data on serious eye damage/eye irritation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
From the 8 cases reported in the French programme « Phyt'attitude » where the causal relationship between exposure and health outcome was considered plausible or likely, eye irritation (conjunctivitis and photophobia) was reported after eye contact in 2 cases. Most incidents occurred when operating with treated seeds: big bag opening, seeder filling; operators either did not wear PPE or wore PPE that were not adapted.				

Table 18: Summary table of other studies relevant for serious eye damage/eye irritation

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

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

In a primary eye irritation study assessed in a standard guideline study (OECD 405), 0.1g of CGA 293343 (98.6%) was instilled into the conjunctival sac of the left eye of 6 female rabbits in the unwashed group and in 3 female rabbits for the washed group (washing 2 to 3 min after application). Animals then were observed for 3 days. In the observation of irritation, grade 1 conjunctival redness and conjunctival oedema were observed in the unwashed group but positive effects were not observed. Eye closure and more than normal discharge were observed as other changes. These changes disappeared by 24 hours after application. On the other hand, in the washed group, the same changes as those in the unwashed group were observed except for eye closure. Thiamethoxam is, therefore, considered to be "not irritant" to rabbit eye.
From the French programme « Phyt'attitude »[2], 2 cases of conjunctivitis one of which associated to photophobia were reported after eye contact. Most incidents occurred when operating with treated seeds: big bag opening, seeder filling; operators either did not wear PPE or wore PPE that were not adapted.

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

Substances are classified as irritating to eyes (Category 2) if, when applied to the eye of an animal, it produces:
at least in 2 of 3 tested animals, a positive response of:

- corneal opacity ≥ 1 and/or
- iritis ≥ 1, and/or
- conjunctival redness ≥ 2 and/or
- conjunctival oedema (chemosis) ≥ 2

Calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days.

According to the criteria in CLP Annex I, there was no evidence of eye irritation in any animal, classification as eye irritant is not applicable.

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

Not classified (conclusive but not sufficient for classification)

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

Table 19: Summary table of animal studies on respiratory sensitisation

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

Table 20: Summary table of human data on respiratory sensitisation

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No evidence of respiratory sensitisation in humans from the records of exposure and poisoning incidences.				

Table 21: Summary table of other studies relevant for respiratory sensitisation

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

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

No formally recognized and validated animal tests currently exist for respiratory sensitisation. There was no evidence of respiratory irritation in single dose inhalation studies in rats and there was no indication of sensitisation. There is no reported evidence of respiratory sensitisation in humans.

2.6.2.6.2 Comparison with the CLP criteria regarding respiratory sensitisation

As there are no animal data and no evidence in humans that thiamethoxam exposure can lead to specific respiratory hypersensitivity, classification is not possible.

2.6.2.6.3 Conclusion on classification and labelling for respiratory sensitisation

Not classified (conclusive but not sufficient for classification)

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

Table 22: Summary table of animal studies on skin sensitisation

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
Skin sensitisation irritation study (Maximisation test) OECD 406 GLP Acceptable	Guinea pig, Pirbright White (Tif:DHP) 10 per sex in test group	Thiamethoxam technical Batch P.506006 (purity 98.60%)	Intradermal induction : 1% in physiological saline Epidermal induction application : 30% in vaseline Challenge application : 10% in vaseline	**Induction reactions:** irritation at the application site was seen in all guinea pigs of the test and positive control groups **Challenge reactions:** Epidermal challenge animals in test groups resulted in positive response in 1 male guinea pig after 48 hours, corresponding to a sensitisation rate of 5%. No irritant skin reactions were recorded among control animals. **Positive control:** Positive responses in 17 (8 males. 9 females) of 20 guinea pigs after 24 and 48 hours. **No skin sensitisation**	[redacted] 1996 Refer to Annex I. Vol3CA B.6.2.6

Table 23: Summary table of human data on skin sensitisation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No evidence of skin sensitisation in humans				

Table 24: Summary table of other studies relevant for skin sensitisation

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

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

In a dermal sensitisation study assessed in a standard guideline study (OECD 406), young adult male and female Pirbright White (Tif:DHP) guinea pigs (10/sex) were tested using the Magnusson and Kligman guinea pig maximization test (Magnusson and Kligman, 1980).
Two main procedures were involved in the study; (a) the potential induction of an immune response; (b) a challenge of that response. From the findings of a pilot study the concentrations for use in the main study were selected. On the basis of the results, a 1% w/v preparation of CGA 293343 TECH in physiological saline was used for intradermal induction, a 30% w/v preparation in vaseline was used for the epidermal induction and a 10% w/v preparation in vaseline was used for the challenge.
Epidermal challenge of 10 male and 10 female guinea pigs with CGA 293343 TECH resulted in positive response in 1 male guinea pig after 48 hours, corresponding to a sensitisation rate of 5%. No irritant skin reactions were recorded among control animals.
Epidermal challenge test of 10 male and 10 female guinea pigs with Mercaptobenzothiazole (positive control groups) resulted in positive responses in 17 (8 males and 9 females) of the 20 guinea pigs after 24 and 48 hours, corresponding to a sensitisation rate of 85%.
Thiamethoxam is, therefore, considered to be “not sensitizer”.

2.6.2.7.2 Comparison with the CLP criteria regarding skin sensitisation

Substances are classified as skin sensitizer if, when applied on animal, it produces:

- ≥ 30 % responding at ≤ 0.1 % intradermal induction dose or ≥ 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose → Classification as skin sensitizer – Category 1A.
- ≥ 30 % to < 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose or ≥ 30 % responding at > 1 % intradermal induction dose → Classification as skin sensitizer – Category 1B.

According to the criteria in CLP Annex I, there was no evidence of skin sensitisation, classification as skin sensitizer is not applicable.

2.6.2.7.3 Conclusion on classification and labelling for skin sensitisation

Not classified (conclusive but not sufficient for classification)

2.6.2.8 Phototoxicity

Table 25: Summary table of studies on phototoxicity

Method, guideline, deviations[1] if any	**Test substance**	**Dose levels duration of exposure**	**Results**	**Reference**
Phototoxicity study OECD Guideline 432 GLP Acceptable	Thiamethoxam technical Batch SGO4FE319 (purity 99.4%) BALB/c 3T3 cells	1000; 316; 100; 31.6, 10.0; 3.16; 1.00 and 0.316 µg/mL (dose range finder) 1000; 681.29; 464.16; 316.23, 215.44; 146.78; 100.00 and 68.13 µg/mL (main experiment I and II) Treated for 1 h with different concentrations of the test solution at 37 ± 1°C and a further 50 min in absence and in presence of a non-cytotoxic dose of UVA light.	**In the dose range finder experiment:** A phototoxic effect was observed. With irradiation the viability of the cells was reduced to 67.8% and without irradiation to 93.8%. Therefore, the PIF could not be calculated and the MPE was determined: MPE = 0.151 (indicates phototoxicity, slightly exceeds the cut-off value) **In the first main experiment:** EC_{50} value for the - UVA could be determined. No cytotoxic effect up to the highest concentration tested. With irradiation, the viability of the cells was reduced to 50.2%. The EC_{50}-value of thiamethoxam technical in the + UVA experiment could not be calculated. Therefore, the PIF could not be derived and the MPE was determined: MPE = 0.218 (indicates phototoxicity, but general damage to the cell was reported) **In the second main experiment:** No EC_{50} value for the - UVA and for the + UVA could be determined. No cytotoxic effect up to the highest concentration of tested. The MPE was determined: MPE: = -0.051 (indicates no phototoxicity) **The results of the 3T3-NRU phototoxicity assay are contradictory and must be considered as inconclusive.**	Gehrke, 2015 Refer to Annex I. Vol3CA B.6.2.7
Phototoxicity study Epiderm Phototoxicity:	Thiamethoxam technical Batch SGO4FE319	0, 0.01, 0.0316, 0.1, 0.316, 1 % Vehicle: water	No cytotoxic effects were observed, either in absence or in presence of UVA light. No concentration related change in viability between +UVA and –UVA	Gehrke, 2016 Refer to Annex I. Vol3CA B.6.2.7

ECVAM 121 GLP Acceptable	(purity 99.4%) Human skin model EpiDerm™ (MatTek)	Treated overnight with different concentrations of the test solution at 37 ± 1°C and further 60 min in absence and in presence of a non-cytotoxic dose of UVA light.	cultures was observed, and the maximum difference in viability between –UVA and +UVA cultures was 17.13%, below the 30% value defined by ECVAM as the threshold for positivity. **Thiamethoxam technical was therefore determined to be non-phototoxic under the conditions of this EpiDerm™ phototoxicity assay.**	

Table 26: Summary table of human data on phototoxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No evidence of phototoxicity in humans				

Table 27: Summary table of other studies relevant for phototoxicity

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

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

Table 28: Summary table of evidence for aspiration hazard

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Not applicable, thiamethoxam is a powder				

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

Not applicable.

2.6.2.9.2 Comparison with the CLP criteria regarding aspiration hazard

Liquid substances and mixtures have to be classified which contain hydrocarbons to ≥ 10% and which show a kinematic viscosity of < 20.5 cSt (mm²/sec).

Thiamethoxam is a slightly cream fine crystalline powder.

2.6.2.9.3 Conclusion on classification and labelling for aspiration hazard

Not classified

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

Table 29: Summary table of animal studies on STOT SE (specific target organ toxicity-single exposure)

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
Acute oral neurotoxicity study OECD Guideline 424 GLP Acceptable Rat, Sprague-Dawley Crl:CD®BR 10/ sex/group	Thiamethoxam technical Batch 9600110 (purity 98.7%) 0, 100, 500 and 1500 mg/kg Single oral (gavage) dose Vehicle: 0.5% w/v aqueous methylcellulose	**At 100 mg/kg bw** No differences from control. **From 500 mg/kg bw:** Neurotoxicity (effects observed 2-3 hours after dosing): - Decreased locomotor activity (males and females) - Decreased rectal temperature (males and females) - Increased forelimb grip strength (males only). **At 1500 mg/kg bw:** General toxicity: - Mortality (3/10 females: 2 on Day1 and 1 on Day2) - Decreased BWG (males) Neurotoxicity (effects observed 2-3 hours after dosing): - Impaired respiration, tremors - Longer latency to first step in the open field, crouched-over posture, gait impairment, hypo-arousal, decreased number of rears, uncoordinated landing during the righting reflex test. - Increased average input stimulus value in the auditory startle response test (males only) No treatment–related histopathological findings **NOAEL neurotoxicity: 100 mg/kg bw** **NOAEL general toxicity: 500 mg/kg bw**	[redacted], 1997 Refer to Annex I. Vol3CA B.6.7.1.1

Table 30: Summary table of human data on STOT SE (specific target organ toxicity-single exposure)

Type of data/report	**Test substance**	**Route of exposure Relevant information about the study (as applicable)**	**Observations**	**Reference**
Headache has been reported as a systemic effect among the 8 cases collected by « Phyt'attitude ».				

Table 31: Summary table of other studies relevant for STOT SE (specific target organ toxicity-single exposure)

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

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

An acute guidelined neurotoxicity study of thiamethoxam has been evaluated in the rat ([redacted], 1997). Thiamethoxam induced effects on functional observational battery and locomotor activity parameters from 500 mg/kg onwards. These effects occurred at the time of peak systemic exposure, and were not associated with neuro-histopathological alterations. At the top dose level (1500 mg/kg bw), 3 females out of 10 died and a decreased body weight gain was observed in males.

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

Specific target organ toxicity (single exposure) is defined as specific, non-lethal target organ toxicity arising from a single exposure to a substance or mixture. All significant health effects that can impair function, reversible and irreversible, immediate and/or delayed effects are considered.

Specific target organ toxicity – single exposure, Category 1 and 2
Categories 1 and 2 for non lethal 'significant and/or severe toxic effects' are the basis for classification with the category reflecting the dose level required to cause the effect.
For category 1 and 2, it must be taken not to classify for STOT-SE for effects which are not yet lethal at a certain dose, but would lead to lethality within the numeric classification criteria. In other words, if lethality would occur at relevant doses then a classification for acute toxicity would take precedence and STOT-SE would not be assigned.

In the acute neurotoxicity study effects were seen from 500 mg/kg bw onwards. At 1500 mg/kg bw, neurotoxic effects were more severe inducing 3 deaths in females which may warrant classification cat.2 (guidance value for acute oral toxicity study in rat $2000 \geq C > 300$).
However, according to the EChA guidance, care should be taken not to assign each class (i.e.: STOT-SE and acute toxicity), for the same effect, in other words a double classification for the same effect has to be avoided.
Since thiamethoxam is already classified for acute oral toxicity cat.4 H302 (DL50 of 1563 mg/kg in both sexes), classification for STOT SE is not triggered.

Specific target organ toxicity – single exposure, Category 3
Category 3 covers 'transient effects' occurring after single exposure, specifically respiratory tract irritation and narcotic effects.
The available acute studies do not provide any indication that thiamethoxam meets the classification criteria for specific target-organ toxicity category 3 following a single exposure.

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

Not classified (conclusive but not sufficient for classification)

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

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

Table 32: Summary table of animal studies on repeated dose toxicity (short-term and long-term toxicity) STOT RE (specific target organ toxicity - repeated exposure)

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
Oral studies			
Rat			
28-days range finding oral toxicity study OECD 407 GLP Partially fulfilled Acceptable Rat, Tif:RAIf (SPF), hybrids of RII/1 x RII/2 (Sprague-Dawley derived) 5/sex/group	Thiamethoxam technical Batch KGL4654/12 (purity > 95%) 0, 100, 1000, 2500, 10000 ppm ♂: 8.0, 81.7, 198.6, 710.6 mg/kg bw/day ♀: 8.7, 89.3, 210.6, 762.6 mg/kg bw/day Continuous in the diet for 28 days.	**<u>At 100 ppm :</u>** No differences from control. **<u>From 1000 ppm :</u>** Increased cholesterol level (♂) *Increased kidney toxicity ♂:* - *Increased kidney weight* - *hyaline change to the tubular epithelium* - *Hyperplasia of the pelvic epithelium (in one animal of each sex). Many of the affected male animals also showed one or more further kidney lesions, focal calcification, pelvic dilatation, renal cyst, basophilic proliferation, lymphohistiocytic infiltration or an acute tubular lesion* **<u>From 2500 ppm :</u>** Centrilobular hypertrophy (♂/♀) Increased incidence of thyroid follicular hypertrophy (♀) **<u>At 10000 ppm :</u>** Reduction of body weight gain by 29% and food consumption (22%) (♂) Increased cholesterol level (♀) Increased ASAT activity and decreased total protein and albumin levels (♂) Increased liver weight (♂/♀) In the adrenal cortex, fatty change mainly of the zona fasciculate (♂/♀) In the thyroid gland, hypertrophy of the follicular epithelium fasciculate (♂/♀) ***The observed kidney toxicity in male rats is due to α2μ-globulin nephropathy which is considered not relevant for humans.*** **NOAEL: 1000 ppm equivalent to 81.7 mg/kg bw/day (males) and 89.3 mg/kg bw/day (females)**	[redacted] 1995 Refer to Annex I. Vol3CA B.6.3.1
90-days range finding oral toxicity study	Thiamethoxam technical	**<u>At 25 ppm :</u>** No differences from control.	[redacted] 1996

Method, guideline, deviations[1]if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
OECD 408 GLP Acceptable Rat, Tif:RAIf (SPF), hybrids of RII/1 x RII/2 (Sprague-Dawley derived) 10/sex/group	Batch KI-4654/18 (purity 98.4%) 0, 25, 250, 1250, 2500, 5000 ppm ♂: 1.74, 17.6, 84.9, 168, 329 mg/kg bw/day ♀: 1.88, 19.2, 92.5, 182, 359 mg/kg bw/day Continuous in the diet for 90 days.	**<u>From 250 ppm :</u>** Decreased lymphocyte counts (♀) *Kidney (♂): Hyaline change in the tubular epithelium, acute and chronic tubular lesions, increased incidence of tubular basophilic proliferation. Increased incidence of pelvic dilatation, epithelial hyperplasia, tubular cast formation.* **<u>From 1250 ppm :</u>** Reduction of body weight gain and food consumption (♂) Adrenal : fatty change in the adrenal cortex (♂) **<u>From 2500 ppm :</u>** Reduction of body weight gain and food consumption (♂) Increased of the relative weights of the liver and kidneys (♂) A minimal to moderate centrilobular hypertrophy and an increased incidence of lymphohistiocytic infiltration of the parenchyma (♂/♀), increased incidence of cholangiofibrosis of bile ducts (males) Haemosiderosis (♀) Adrenal : fatty change in the adrenal cortex (♀) **<u>At 5000 ppm :</u>** Reduction of body weight gain (30%), bw and food consumption (♂) *Increased creatinine levels and kidney weight (♂22%)* Adrenal: Increased relative weight (♂) Liver: minimal to moderate centrilobular hypertrophy , lymph histiocytic infiltration of the parenchyma (♂/♀), cholangiofibrosis of bile ducts (males) minimal pigmentation of Kupffer cells (♀) Extramedullary haemopoiesis (♂), haemosiderosis (♂) ***The observed kidney toxicity in male rats is due to α2μ-globulin nephropathy which is considered not relevant for humans.*** **NOAEL: 250 ppm in males equivalent to 17.6 mg/kg bw/day** **NOAEL: 25 ppm in females equivalent to 1.88 mg/kg bw/day**	Refer to Annex I. Vol3CA B.6.3.2
Mice			
90-days range finding oral toxicity study OECD 408 GLP Acceptable Mice, Tif:MAGf	Thiamethoxam technical Batch KI-4654/18 (purity 98.4%) 0, 10, 100, 1250,	**At 10 ppm :** No differences from control. **From 100 ppm :** Hepatocellular hypertrophy (♂) **At 1250 ppm :** Minimal elevation in platelets numbers (♀)	[redacted], 1996a Refer to Annex I. Vol3CA B.6.3.2

Method, guideline, deviations[1]if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
(SPF), hybrids of NIH x MAG 10/sex/group	3500, 7000 ppm ♂:0, 1.41, 14.3, 176, 543, 1335 mg/kg bw/day ♀: 0, 2.01, 19.2, 231, 626, 1163 mg/kg bw/day Continuous in the diet for 90 days.	Liver: Increased liver weight (♀) Minimal to marked hypertrophy of centrilobular hypertrophy, minimal pigmentation of Kupffer cells, minimal lymphocytic infiltration of the parenchyma in liver (♂/♀) Decreased of kidney weights (♂) **From 3500 ppm :** Slight reduction of body weight gain (males), slight reduction of food consumption (females). Minimal elevation in platelets numbers (♀) Decreased of kidney weights (♂) Ovary: decreased weights and atrophy (reduced numbers of corpora lutea) Spleen: decreased weight (♀) **At 7000 ppm :** Restricted to transient respiratory sounds, without dyspnea (males and females) Reduction of bwg and bw (♂33%/♀15%) Liver: moderate necrosis of single hepatocytes (♂33%/♀15%) Slight anaemia (♂) **NOAEL: 10 ppm in males equivalent to 1.41 mg/kg bw/day** **NOAEL: 100 ppm in females equivalent to 19.2 mg/kg bw/day**	
Dog			
28-days range finding oral toxicity study OECD 409 GLP Partially fulfilled Acceptable Dog, Pedigree Beagle 2/sex/group	Thiamethoxam technical Batch KI-4654/18 (purity 98.4%) 0, 300, 1000, 3000 ppm ♂: 10.0, 31.6, 47.7 mg/kg bw/day ♀: 10.7, 32.6, 43.0 mg/kg bw/day Continuous in the diet for 28 days.	**<u>At 300 and 1000 ppm :</u>** No differences from control. **<u>At 3000 ppm :</u>** Body weight loss and decreased food consumption (♂/♀) Leucopoenia (♂/♀), slightly elevated red blood cell count, haemoglobin level and haematocrit (♂) Slight increase of plasma levels of urea and creatinine (♂/♀) Thymus: Markedly reduction of weight and atrophy (♂/♀) Liver: minimal pigment accumulation in hepatic Kupffer cells, Spleen: minimal to moderate atrophy of the white pulp **NOAEL: 1000 ppm equivalent to 31.6 mg/kg bw/day (males) and 32.6 mg/kg bw/day (females)**	[redacted], 1996 Refer to Annex I. Vol3CA B.6.3.1
90-days oral toxicity study OECD 409 GLP Acceptable	Thiamethoxam technical Batch P.506006 (purity 98.6%)	**<u>At 50 ppm and 250 ppm :</u>** No differences from control. **<u>From 1000 ppm :</u>** Slight anaemia, associated with a tendency to hypochromasia,	[redacted], 1996 Refer to Annex I.

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
Dog, Pedigree Beagle 4/sex/group	0, 50, 250, 1000, 2500/2000 ppm ♂: 1.58, 8.23, 32.0, 54.8 mg/kg bw/day ♀: 1.80, 9.27, 33.9, 50.5 mg/kg bw/day Continuous in the diet for 90 days.	anisochromasia and microcytosis) (♀) Lower plasma Ca^{++} concentration and ALAT activity, minimally reduced plasma albumin levels (♂/♀) Prolonged prothrombin times (♂/♀) **At 2500/2000 ppm :** Lost of weight during the first 2 weeks of the study and therefore, the concentration was reduced to 2000 ppm. Reduce bwg (♀83%/♂36%) and bw (♀26%/♂6%), decrease of food consumption (♂/♀) Reduced white cell counts (total, neutrophils, monocytes and lymphocytes (♀) Reduce monocyte counts (♂) Ovary: decrease weights with histological correlates (immature). Testis: decreased weights , minimal to marked reduction in spermatogenesis and an increased incidence of spermatic giant cells occurred in the testes (all males) and moderate tubular atrophy (one male) **NOAEL: 250 ppm equivalent to 8.23 mg/kg bw/day (males) and 9.27 mg/kg bw/day (females)**	Vol3CA B.6.3.2
1-year oral toxicity study OECD 452 GLP Acceptable Dog, Pedigree Beagle 4/sex/group	Thiamethoxam technical Batch P.506006 (purity 98.6%) 0, 25, 150, 750, 1500 ppm ♂: 0.70, 4.05, 21.0, 42.0 mg/kg bw/day ♀: 0.79, 4.49, 24.6, 45.1 mg/kg bw/day Continuous in the diet for 1 year.	**At 25 and 150 ppm :** No differences from control. **At 150 ppm :** No differences from control. **From 750 ppm :** Increased plasma creatinine and tendency to higher plasma urea levels (♂/♀) Testis: Higher incidence of tubular atrophy ~~**At 1500 ppm :**~~ Reduce of body weight gain (♂) but final body weight not affected Minimally lower albumin levels and albumin/globulin ratios (♀) Testis: Decrease in absolute (-16%) and relative (–15%) testis weights (due mainly from 2 animals) **NOAEL: 150 ppm equivalent to 4.05 mg/kg bw/day (males) and 4.49 mg/kg bw/day (females)**	[redacted], 1998 Refer to Annex I. Vol3CA B.6.3.3
Dermal studies			
28-days dermal toxicity study OECD 410 GLP Acceptable Rat, Tif:RAIf (SPF), hybrids of RII/1 x	Thiamethoxam technical Batch P.506006 (purity 98.6%) 0, 20, 60, 250, 1000	**At 20 and 60 mg/kg bw/day:** No differences from control. **From 250 mg/kg bw/day:** Decreased body weight gain (♀) Slight increased glucose, triglycerides and alkaline	[redacted], 1996 Refer to Annex I. Vol3CA B.6.3.4

Method, guideline, deviations[1]if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
RII/2 (Sprague-Dawley derived) 5/sex/group	mg/kg bw/day Vehicle : 0.5% w/v carboxymethylcellulose in 0.1% w/v aqueous polysorbate 80 Topical application under occlusive dressing for 6 hours/day, 5 days/week, for 4 weeks	phosphatase levels (♀) Liver: minimal inflammatory cell infiltration and necrosis of single hepatocytes (♀) **At 1000 mg/kg bw/day:** Decreased body weight gain (♂) Kidneys: minimal tubular lesions (♂/♀) Adrenals glands: minimal inflammatory cell infiltration (♀) **NOAEL: 250 mg/kg bw/day in males** **NOAEL: 60 mg/kg bw/day in females**	

Table 33: Summary table of human data on repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

Type of data/report	**Test substance**	**Route of exposure** **Relevant information about the study (as applicable)**	**Observations**	**Reference**
No evidence of adverse health effects in humans				

Table 34: Summary table of other studies relevant for repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
Long term and carcinogenicity studies see Table 42				
Generational studies see Tables 46-49-52				
Developmental toxicity studies see Table 49				
Neurotoxicity studies see Table 55				
Immunotoxicity studies see 2.6.8.2				

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

The oral toxicity of thiamethoxam was evaluated in mice, rats and dogs, administered via the diet. Four-week range-finding studies followed by 13-week toxicity studies in rats and dogs, and a 52-week toxicity study in dogs, were performed. A 13-week dietary range-finding study was also performed in mice. The percutaneous toxicity of thiamethoxam was evaluated in a 4-week study in rats.

The liver and kidneys were identified as the main target organs. Treatment for 13 weeks induces liver hypertrophy, inflammatory cell infiltration and pigmentation of Kupffer cells in both rodent species. In rat, liver effects were observed from 2500 ppm (eq. to168/182 mg/kg bw/day in M/F).

In mice, single cell necrosis occurs in parallel with these alterations from 1250 ppm (eq. to 176/231 mg/kg bw/day in M/F). The long-term sequelae of the hepatic changes in mice are discussed in 2.6.5. Dogs were generally refractory to hepatotoxicity, but at high dosage, minimal pigmentation of Kupffer cells occurred.

Effects on the kidneys occur in rats. In the male, nephrotoxicity is characterised by tubular epithelial hyaline droplet accumulation, acute and chronic tubular lesions, basophilic proliferation and cast formation. In the female at high dose, morphological alterations are confined to chronic tubular lesions and enhanced nephrocalcinosis. The pattern of effects in male rat kidneys suggested α2µ-globulin nephropathy which was objectivised by immunohistochemical studies. This mode of action is considered of non-human relevance. Therefore, no-observed-(adverse)-effect-levels determined in rat studies are based, where applicable, on the conclusion that α2µ-globulin nephropathy-induced effects are specific to the male rat and thus not relevant to human risk assessment.

Other alterations, occurring in one species only, at high dose levels were fatty changes in the adrenal cortex, enhanced hemosiderosis or extramedullary hematopoiesis in the spleen. Decreased lymphocyte count was observed in rat females.

In the 90-d dog study, decreased testicular weights and a reduction in spermatogenesis associated were noted. Atrophy of the seminiferous tubules was found in the 1-year dog study at minimally to moderately toxic dose levels and this effect is further discussed in 2.6.8.3 (ED section).

Table 35: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days

Study reference	**Effective dose (mg/kg/day)**	**Length of exposure**	**Extrapolated effective dose when extrapolated to 90-day exposure***	**Classification supported by the study**
Rat				
[redacted], 1995	198.6/210.6	28 days	66.2/70.2	No (only slight effect on cholesterol)
[redacted], 1996 and 1998	19.2♀ /84.9♂	90 days	19.2♀ /84.9♂	No Effect on lymphocyte count in females not reproduced in longer study.
[redacted] 1998	(95.4♂/216.4♀) No effect	90 days Neurotoxicity	>(95.4♂/216.4♀)	No No effect
[redacted] (1998b)	155♀	2 years	1200	No
(1998)	1.8/2.4	2G : effect on F1	1.8/2.4	No Effects on testis : classification for reproductive toxicity Effect on thymus weight in females: no histopathological findings and not reproduced in [redacted] study
(2004a)	3.0	2G : effect on F1	3.0	No Effects on sperm : classification for reproductive toxicity
(1996a)	200 750	GD 6-15	33.3	No Effects on bw gain
A, 2003a, 2007 [redacted]	298.7	DNT From GD7 to PND22 in diet (36 days)	119.32	No
Mouse				
[redacted], 2011	2025.8	28-day Immunotoxicity	675.3	No

Study reference	Effective dose (mg/kg/day)	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure*	Classification supported by the study
[redacted], 1996	176/231	90 days	176/231	No
n (1998a)	63.8/87.6	18-month	375.3/515.3	No
Dog				
[redacted],1996	47.7/43.0	28 days dog	15.9/14.3	No Range finding study 2 animals
[redacted], 1996	32.0/33.9	90 days dog	32.0/33.9	No Effect on testis considered for classification for reproduction
[redacted], 1998	21.0/24.6	1 year dog	84/98.4	No Effect on testis considered for classification for reproduction
Rabbit				
(1996b)	150	GD 7-19	33.3	No Effects considered for classification for reproduction
Dermal exposure rat				
1996	250♀/1000♂	28 days dermal	41.7/166.7	No Severity of effects not triggering classification.

* For practical purposes, for toxicity studies of greater or lesser duration than 90 days extrapolation of equivalent effective dose for a 90-day duration have been calculated using Haber's rule in order to compare them to guidance values for 90-day studies (i.e.: 10 mg/kg bw/d in a 90-day oral rodent study for category 1 and at dose levels 10> ≤100 mg/kg bw/d in a 90-day oral rodent study for category 2). It is acknowledged that guidance values for 28-day are available (also using Haber/s rule), however this is not the case for chronic studies or developmental toxicity studies).

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

According to the CLP criteria, substances should be classified for repeated dose toxicity if significant adverse effects, which indicate functional impairment, occur at dose levels ≤10 mg/kg bw/d in a 90-day oral rodent study for category 1 and at dose levels10> ≤100 mg/kg bw/d in a 90-day oral rodent study for category 2.
Such effects may include significant consistent and adverse changes in clinical biochemistry, haematology, or urinalysis parameters; significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination; or morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction. In contrast, adaptive responses that are not considered toxicologically relevant do not warrant classification.

Liver effects:

Liver effects were observed in the three species, the most sensitive species being the mouse due to quantitative difference in metabolism which is further discussed in the section dedicated to long term toxicity/carcinogenicity. The mode of action was considered on non-relevance for human safety (see 2.6.5).
Furthermore even in the mouse, effects on liver of severity which would trigger classification are only at doses above the regulatory threshold for STOT RE cat.2.

Kidney effects:

Kidney effects on male rats are observed at doses that would trigger STOT RE classification. However, the underlying mode of action (i.e.: α2μ-globulin nephropathy) is well supported by the submitted data (immunohistochemical studies). This mode of action is considered of non-human relevance. Therefore, those effects are not taken into account for STOT RE classification.

Immune system:

Immunotoxic potential of thiamethoxam has been investigated in a guidelined 28-d immunotoxicity study in mice in which thiamethoxam did not impact humoral immunity or innate immunity (lack of effects on both AFC assay and NKC assay) up to a dose level of 2025.8 mg/kg bw/d. In few studies decreased total leucocyte counts and/or lymphocyte counts were noted. However, those findings were not observed after longer exposure. The only potential immunotoxic findings not associated to systemic toxicity were decreased absolute thymus weight in females F1 in the first 2-generation study. However, it was not associated to histopathological findings and not reproduced in the second 2-generation study (see also 2.6.8.2). A weight of the evidence evaluation of the available data does not indicate consistent evidence of adverse effects of thiamethoxam on the immune system. Classification for STOR RE in not warranted.

Central nervous system:

No neurotoxicity or neuropathological findings were observed in a guidelined sub-chronic neurotoxicity study up to the higher dose tested of 1500/3000 ppm in males/females (eq. to 95 mg/kg bw/day and 216 mg/kg bw/day respectively). Classification for STOT SE is therefore not triggered (see 2.6.7).

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

Not classified (conclusive but not sufficient for classification)

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

Table 36: Summary table of genotoxicity/germ cell mutagenicity tests *in vitro*

Method, guideline, deviations[1] if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
Bacterial gene mutation assay OECD 471 GLP Acceptable	Thiamethoxam technical Batch P.506006 (purity 98.60%) Solvent Dimethylsulfoxide (DMSO)	S. typhimurium strains TA 98, TA 100, TA102, TA 1535, TA 1537; E. coli WP2 uvr A S. typhimurium & E. coli: 312.5, 625, 1250, 2500 and 5000 µg/plate with and without metabolic activation.	not mutagenic with and without metabolic activation in S. typhimurium and E. coli	[redacted], 1995 Refer to Annex I. Vol3CA B.6.4.1
Bacterial gene mutation assay OECD 471 GLP Acceptable	Thiamethoxam technical Batch P.506006 (purity 98.60%) Solvent Dimethylsulfoxide (DMSO)	312.5, 625, 1250, 2500 and 5000 µg/plate with metabolic activation (induced or non-induced mouse liver).	not mutagenic with metabolic activation (induced or non-induced mouse liver) in *Salmonella typhimurium*	[redacted], 1999 Refer to Annex I. Vol3CA B.6.4.1
Mammalian cytogenetic test Chromosome aberrations OECD 473 GLP Acceptable	Thiamethoxam technical Batch P.506006 (purity 98.60%) Solvent Dimethylsulfoxide (DMSO)	Chinese hamster ovary cells (ATTC CCL 61) 283.75 to 2270.0 µg/ml without metabolic activation; 1135.0 to 4540.0 µg/ml with metabolic activation	not clastogenic with and without metabolic activation	Zeugin, 1996 Refer to Annex I. Vol3CA B.6.4.1

Method, guideline, deviations[1] if any	**Test substance**	**Relevant information about the study including rationale for dose selection (as applicable)**	**Observations /Results**	**Reference**
Mammalian gene mutation assay OECD 476 GLP Acceptable	Thiamethoxam technical Batch P.506006 (purity 98.60%) Solvent Dimethylsulfoxide (DMSO)	Chinese hamster V79 cells 61.67 to 2220.0 µg/ml without metabolic activation; 123.33 to 3330.0 µg/ml with metabolic activation	not mutagenic with and without metabolic activation	Ogorek, 1996 Refer to Annex I. Vol3CA B.6.4.1
Unscheduled DNA repair OECD 482 GLP Acceptable	Thiamethoxam technical Batch P.506006 (purity 98.60%) Solvent Dimethylsulfoxide (DMSO)	Rat hepatocytes 13.01 to 1665 µg/ml culture medium	no induction of unscheduled DNA synthesis	Ogorek, 1996a Refer to Annex I. Vol3CA B.6.4.1
Unscheduled DNA repair OECD 482 GLP Acceptable	Thiamethoxam technical Batch P.506006 (purity 98.60%) Solvent Dimethylsulfoxide (DMSO)	Mouse hepatocytes 7.3, 14.6, 29.3, 58.6, 117.2 and 235 µg/ml culture medium	no induction of unscheduled DNA synthesis	Ogorek, 2000 Refer to Annex I. Vol3CA B.6.4.1
Evaluation of high-throughput genotoxicity assays used in profiling the US EPA ToxCastTM chemicals. Klimisch : 2	Thiamethoxam	3 high-throughput screening (HTS) genotoxicity assays—GreenScreen HC GADD45a-GFP (Gentronix Ltd.), CellCiphr p53 (Cellumen Inc.) and CellSensor p53RE-bla (Invitrogen Corp.)	No evidence of genotoxicity in GreenScreen HC, Invitrogen p53RE-bla HCT-116, or the CellCiphr Cytotox Panel	Knight A, Little S, Houck K, Dix D, Judson R, Richard A, McCarroll N, Akerman G, Yang C, Birrell L and Walmsley R, 2009a Refer to Annex I. Vol3CA B.6.4.1

Table 37: Summary table of genotoxicity/mutagenicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations[1] if any	**Test substance**	**Relevant information about the study (as applicable)**	**Observations/Results**	**Reference**
Micronucleus test OECD 474 GLP Acceptable	Thiamethoxam technical Batch P.506006 (purity 98.60%) Solvent Bidistilled water	5 male and 5 female (Tif: MAGf, SPF) mice per group and time point 312.5, 625 and 1000 mg/kg (all males and in females sacrificed 16 hours post-application) 312.5, 625 and 1250 mg/kg bw (females of the 24 and 48 hours groups)	not clastogenic or aneugenic	[redacted] 1995a Refer to Annex I. Vol3CA B.6.4.2

Table 38: Summary table of human data relevant for genotoxicity / germ cell mutagenicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
There are no human relevant data				

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

The mutagenic potential of thiamethoxam was investigated in five test systems representing 3 fundamental organisation levels of the genetic material. The test battery was designed to evaluate *in vitro* point mutations in prokaryotic and eukaryotic cells, *in vitro* and *in vivo* clastogenic potential in somatic cells, and DNA damaging potential measured as unscheduled DNA synthesis. The *in vitro* point mutation and clastogenicity studies were performed both with and without a metabolic activation system to investigate the effect of metabolites of thiamethoxam on the test systems. Additionally, the mutagenic potential of thiamethoxam was investigated in an Ames test using microsomal S9 activation system from mice pre-treated (induced) with thiamethoxam. Furthermore, upon a specific request of the regulatory authorities in Japan, an autoradiographic DNA repair study (UDS) was conducted *in vitro* with mouse hepatocytes. None of the studies revealed any genotoxic effects of thiamethoxam at the DNA level, the gene level or the chromosome level of organization, either with or without metabolic activation (standard or from thiamethoxam induced mice). Since there is no evidence of genotoxicity it is concluded that an *in vivo* study in germ cells is not necessary.

Since phototoxicity test was negative, no photomutagenicity test is required. Furthermore photomutagenicity testing is not required for the time being, unless further guidance is provided (technical report EFSA 25 July 2016).

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

The classification criteria for germ cell mutagenicity takes into account test results from mutagenicity or genotoxicity tests *in vitro* and from studies with mammalian somatic and germ cells *in vivo*. The overall body of toxicological data coming from a number of *in vitro* and *in vivo* assays indicates that there is no concern.

Based on the CLP criteria thiamethoxam does not require classification and labelling for germ cell mutagenicity.

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

Not classified (conclusive but not sufficient for classification)

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

Table 39: Summary table of animal studies on long-term toxicity and carcinogenicity

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
Toxicity and carcinogenicity dietary study in rat OECD Guideline 453 GLP Acceptable Rat, Sprague-Dawley Tif: RAIf, SPF 70/sex/group	Thiamethoxam technical BatchP.50600 (Purity 98.6%) ♂/♀: 0/0, 10/10, 30/30,500/1000, 1500/3000 ppm ♂: 0.41, 1.29, 21.0, 63.0 mg/kg bw/day ♀: 0.48,1.56, 50.3, 155 mg/kg bw/dy Continuous in the diet for 104 weeks.	***Non-neoplastic findings*** **Target organs:** Males: kidney Females: liver and spleen No treatment related effects on survival **At 10 and 30 ppm: (♂/♀: 0.41/0.48 and 1.29/1.56 mg/kg bw/day):** No difference from controls. **At 500/1000 ppm(♂/♀: 21 / 50.3 mg/kg bw/day):** Males: α2μ-globulin mediated chronic nephropathy in the proximal tubules Females: no treatment related effects. **At 1000/3000 ppm (♂/♀: 63 / 155 mg/kg bw/day):** Males: α2μ-globulin mediated chronic nephropathy in the proximal tubules Females: - Decreased body weight gain (↓12.6%). - Foci of hepatic cellular alteration - Increased incidence of splenic hemosiderosis ***The observed kidney toxicity in male rats is due to α2μ-globulin nephropathy which is considered not relevant for humans.*** **NOAEL males: 63 mg/kg bw/day** ***NOAEL kidney effects in males: 0.41 mg/kg bw (not relevant for human risk assessment)*** **NOAEL female: 50.3 mg/kg bw/day** ***Neoplastic findings*** No treatment related neoplastic findings. **NOAEL for carcinogenicity: 1500 ppm (equivalent to 63 mg/kg/day for males) and 3000 ppm (equivalent to 155 mg/kg/day in females)**	[redacted] 1997 & 1998a Refer to Annex I. Vol3CA B.6.5.1
Toxicity and carcinogenicity dietary study in mouse OECD Guideline 453 GLP Acceptable Mouse Tif:MAGf (SPF)	Thiamethoxam technical BatchP.50600 (Purity 98.6%) ♂/♀: 0, 5, 20, 500, 1250 and 2500 ppm ♂: 0.65,2.63, 63.8, 162, 354	***Non-neoplastic findings*** **Target organs:** Males and females: liver, spleen, stomach No treatment related effects on survival **At 5 and 20 ppm (♂/♀: 0.65/0.89 and 2.63/3.68 mg/kg bw/day):** No difference from controls.	[redacted] 1998 Refer to Annex I. Vol3CA B.6.5.2

<table>
<tr><th>Method, guideline, deviations[1] if any, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results
- NOAEL/LOAEL
- target tissue/organ
- critical effects at the LOAEL</th><th>Reference</th></tr>
<tr><td>60/sex/group</td><td>mg/kg bw/day

♀: 0.89, 3.68, 87.6, 215, 479 mg/kg bw/day

Continuous in the diet for 78 weeks.</td><td>
<u>From 500 mg/kg bw/day</u> (♂/♀: 63.8 / 87.6 mg/kg bw/day):
<u>In both sexes:</u> alterations in the liver (hypertrophy, pigment deposition, mitotic activity, Kupffer cell hyperplasia and single cell necrosis)

<u>From 1250 mg/kg bw/day</u> (♂/♀: 162 / 215 mg/kg bw/day):
<u>In both sexes:</u> Increased absolute and relative liver weight

<u>At 2500 mg/kg bw/day</u> (♂/♀: 354 / 479 mg/kg bw/day):
<u>In both sexes:</u>
- Decreased body weight gain (↓ 18% / 14% in ♂/♀)
- Splenic extramedullary hematopoiesis
- Gastric mucosal epithelial hyperplasia

NOAEL for chronic toxicity: 20 ppm (equivalent to 2.63/3.68 mg/kg bw/day in ♂/♀)

Neoplastic findings
<u>From 500 mg/kg bw/day</u> (♂/♀: 63.8 / 87.6 mg/kg bw/day):
<u>In both sexes:</u> Increased incidence of hepatocellular adenomas.
<u>From 1250 mg/kg bw/day</u> (♂/♀: 162 / 215 mg/kg bw/day):
<u>Females:</u> Increase incidence of hepatocellular adenocarcinomas
<u>At 2500 mg/kg bw/day</u> (♂/♀: 354 / 479 mg/kg bw/day):
<u>Males:</u> Increase incidence of hepatocellular adenocarcinomas

<table>
<tr><th>Dose Level [ppm]</th><th colspan="6">Males</th><th colspan="6">Females</th></tr>
<tr><th></th><th>0</th><th>5</th><th>20</th><th>500</th><th>1250</th><th>2500</th><th>0</th><th>5</th><th>20</th><th>500</th><th>1250</th><th>2500</th></tr>
<tr><td>Liver - no. examined</td><td>50</td><td>50</td><td>50</td><td>50</td><td>50</td><td>50</td><td>50</td><td>50</td><td>50</td><td>50</td><td>50</td><td>50</td></tr>
<tr><td>hepatocellular adenocarcinoma (%)</td><td>6</td><td>6</td><td>4</td><td>8</td><td>8</td><td>32*</td><td>-</td><td>-</td><td>-</td><td>-</td><td>4*</td><td>6*</td></tr>
<tr><td>At least 1 hepatocellular adenoma (%)</td><td>18</td><td>10</td><td>16</td><td>34*</td><td>42*</td><td>78*</td><td>-</td><td>-</td><td>-</td><td>10*</td><td>16*</td><td>56*</td></tr>
</table>

*p ≤ 0.05 in bold exceeding HCD range
NOAEL for carcinogenicity: 20 ppm (equivalent to 2.63/3.68 mg/kg bw/day in ♂/♀.
</td><td></td></tr>
</table>

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
		Plausible mode of action of non relevance for human risk assessment has been established	

Table 40: Summary table of human data on long-term toxicity and carcinogenicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No evidence of carcinogenicity in humans				

Table 41: Summary table of other studies relevant for long-term toxicity and carcinogenicity

Type of study/data Test substance	NOEL	LOEL	Observations	Reference
Submitted mechanistic studies				
In vivo liver biochemical parameters; Male and female mice; 14-days feeding 0, 100, 500, 2500ppm Thiamethoxam	100ppm	500ppm	Moderate induction of liver phase I and II xenobiotic-metabolising enzymes.	[redacted] (1998) Syngenta File No. CGA293343/0719 Study submitted in original EU review. Refer to Annex I. Vol3CA B.6.8.2.2.1
In vivo hepatic cell proliferation; Male and female mice; up to 59 days feeding 0, 100, 500, 2500ppm Thiamethoxam	NOEL (proliferation) 100ppm (males), 500ppm (females) NOEL (Glycogenesis / fatty change) <100ppm (males), 500ppm (females)	LOEL (proliferation) 500ppm (males), 2500ppm (females) LOEL (Glycogenesis / fatty change) 100ppm (males), 2500ppm (females)	2500ppm: Hepatic glycogenosis and fatty change after 3+ days treatment; Inc. liver weight at 2500ppm after 7+ days treatment; Hepatic necrosis/apoptosis after 27+ days treatment; Hepatic deposition of lipogenic pigment after 59 days treatment; Inc. hepatocyte proliferation after 3+ days treatment.	[redacted] (1998) Syngenta File No. CGA293343/0718 Study submitted in original EU review. Refer to Annex I. Vol3CA B.6.8.2.2.1
In vivo hepatic cell proliferation; Male rats; 28-days feeding 0, 10000ppm Thiamethoxam	>10000ppm ≅ 710.6mg/kg bw/day	-	No effect on hepatocyte proliferation detected	[redacted] (1995) Syngenta File No. CGA293343/0005 Study submitted in original EU review. Refer to Annex I. Vol3CA B.6.8.2.2.1

Type of study/data **Test substance**	**NOEL**	**LOEL**	**Observations**	**Reference**
In vitro cytotoxicity; Rat / mouse hepatocytes; 0, 10 - 5000µM (9 concentrations) Thiamethoxam	>5000µM (rat) >5000µM (mouse)	-	No cytotoxicity detected in either species	Bouis (1997) Syngenta File No. CGA293343/0383 Study submitted in original EU review. Refer to Annex I. Vol3CA B.6.8.2.2.1

Type of study/data **Test substance**	**NOEL**	**LOEL**	**Observations**	**Reference**
In vivo acute hepatic cell damage; Male mice; 500 mg/kg Thiamethoxam	<500 mg/kg		Cytoplasmic condensation of mostly periportal hepatocytes at 6 hours, suppression of hepatocellular mitotic activity at 24 hours after dosing	[redacted] (1999) Syngenta File No. CGA293343/1168 Study submitted in original EU review. Refer to Annex I. Vol3CA B.6.8.2.2.1
Changes in plasma cholesterol levels during dietary feeding studies Investigation of HMG-CoA-reductase activity Mice 0, 50, 200, 500, 1250, 2500, 5000ppm up to 50 weeks Thiamethoxam	200ppm for cholesterol reduction.	Reduction in plasma cholesterol in mice at 500ppm & above.	Sustained & dose dependent reduction in plasma cholesterol in mice but not in rats. Neither thiamethoxam nor its metabolites (CGA265307 and CGA330050) inhibit the HMG-CoA-reductase. ("Statins MoA")	[redacted] (2003) Syngenta File No. CGA293343/1799 Study not previously submitted to EU. Refer to Annex I. Vol3CA B.6.8.2.2.1
Comparative hepatotoxicity in weanling & adult mice 0, 500, 1250, 2500ppm 7 days Thiamethoxam	adults <500ppm weanlings 500ppm	adults 500ppm weanlings 1250ppm	Reduction in plasma cholesterol in adults at 500ppm & above, in weanlings at 1250ppm & above. Internal dose in weanlings approx 2x adults. Weanlings seem less sensitive to the hepatic effects of thiamethoxam.	[redacted] (2003a) Syngenta File No. CGA293343/1800 Study not previously submitted to EU. Refer to Annex I. Vol3CA B.6.8.2.2.1
Hepatic cell proliferation & apoptosis in male mice fed thiamethoxam for up to 50 weeks 0, 50, 200, 500, 1250, 2500, 5000ppm Thiamethoxam	200ppm	500ppm	General toxicity at 2500 & 5000ppm. Time & dose related hepatotoxicity; increased ASAT & ALAT at 1250ppm & above, increased apoptosis & necrosis at 500ppm & above. Increased cell proliferation at 1250ppm & above.	[redacted] (2003) Syngenta File No. CGA293343/1804 Study not previously submitted to EU. Refer to Annex I. Vol3CA B.6.8.2.2.1
Comparative toxicity of thiamethoxam and metabolites in 2 strains of mouse up to 20 weeks 2500ppm thiamethoxam 2000ppm CGA 322704 500ppm CGA 265307	n/a	n/a	In contrast to the effects of thiamethoxam, CGA 322704 & CGA 265307 had no significant effects on liver. Both strains responded similarly.	[redacted] (2003) Syngenta File No. CGA293343/1831 Study not previously submitted to EU. Refer to Annex I. Vol3CA B.6.8.2.2.1
Sub-lobular assessment of hepatic cell proliferation	200ppm	500ppm	Thiamethoxam induces increases in hepatocellular	[redacted] (2003) Syngenta File No.

Type of study/data Test substance	NOEL	LOEL	Observations	Reference
0, 200, 500, 1250ppm Thiamethoxam			labelling at 500 & 1250ppm	CGA293343/1811 Study not previously submitted to EU. Refer to Annex I. Vol3CA B.6.8.2.2.1
Hepatotoxicity of metabolites Mice 500, 1000ppm CGA 330050 up to 10 weeks Rats 0, 1000, 3000ppm 1 week	n/a	n/a	Thiamethoxam and CGA 330050 induced significant hepatic effects. Metabolite CGA 330050 has a key role in the mechanism of thiamethoxam hepatotoxicity. No liver effect in rat.	[redacted] (2003b) Syngenta File No. CGA293343/1807 Study not previously submitted to EU. Refer to Annex I. Vol3CA B.6.8.2.2.1
The role of nitric oxide in mouse hepatotoxicity 2000 ppm CGA265307 for 7 Days IP of 10 µL/kg carbon tetrachloride in corn oil (10 mL/kg)	n/a	n/a	CGA 265307 inhibits nitric oxide synthase. This inhibition of the normal protective effect of NO exacerbates the liver toxicity induced by CGA 330050.	[redacted] (2003c) Syngenta File No. CGA293343/1603 Study not previously submitted to EU. Refer to Annex I. Vol3CA B.6.8.2.2.1
Hepatic cell proliferation & apoptosis in female rats fed thiamethoxam for up to 50 weeks 1000, 3000ppm thiamethoxam	>3000ppm	no effects	No toxicologically significant changes – in particular, no effects on the liver.	[redacted] (2003a) Syngenta File No. CGA293343/1834 Study not previously submitted to EU. Refer to Annex I. Vol3CA B.6.8.2.2.1
Biochemical parameters in rat liver after 1 & 10 weeks 1000, 3000ppm thiamethoxam	n/a	n/a	No remarkable inducing effect on xenobiotic metabolising enzymes. No effect on hepatic glutathione concentration or on activity of γ-glutamylcysteine synthetase.	[redacted] (2003) Syngenta File No. CGA293343/1787 Study not previously submitted to EU. Refer to Annex I. Vol3CA B.6.8.2.2.1
Comparative metabolism in mice and rats *in vivo*, and in mouse, rat & human liver fractions *in vitro*.	n/a	n/a	Production of key metabolites *in vivo* much higher in mice than rats. Induction of metabolism in mice over time, whereas reduction seen	[redacted] (2002) Syngenta File No. CGA293343/1798 Study not

Type of study/data Test substance	NOEL	LOEL	Observations	Reference
			in rats. Results in plasma concentrations of CGA 265307 in mice after 10 weeks that are 108-fold higher than in rats. A similar difference is seen *in vitro*, with rate conversions in mouse liver being much higher than rat liver fractions. The rate conversions in human liver were even lower than in rat liver, indicating that human metabolism of thiamethoxam to the key metabolites would be minimal.	previously submitted to EU. Refer to Annex I. Vol3CA B.6.8.2.2.1
Metabolism in rats and mice in dietary feeding studies 50 week mouse; 500, 1250,2500ppm thiamethoxam 50 week rat; 1000, 3000ppm thiamethoxam 20 week mouse; 2500ppm thiamethoxam, 200ppm CGA 322704, 500ppm CGA 265307 1 week mouse; 1000ppm CGA 330050	n/a	n/a	Following administration of thiamethoxam, the plasma concentrations of parent were similar in rats & mice, but the concentrations of CGA 322704, CGA 265307 & CGA 330050 were much higher in mice than rats, with evidence for induction of metabolism in mice, but not rats. Following administration of CGA 322704 to mice, the only major metabolite detected was CGA 265307. As CGA 3222704 is not carcinogenic in the mouse, CGA 265307 is unlikely to be responsible for the carcinogenicity of thiamethoxam in the mouse.	[redacted] (2003d) Syngenta File No. CGA293343/1801 Study not previously submitted to EU. Refer to Annex I. Vol3CA B.6.8.2.2.1
In vivo hepatic cell apoptosis; Male mice; up to 59 days, feeding 0, 100, 500, 2500ppm; 9 month feeding 0, 2500ppm	100 ppm ≅ 15.8mg/kg bw/day	500ppm	Increase in apoptotic activity after 59 days, still present after 9 months (data only at 2500ppm)	[redacted] (1999) Syngenta File No. CGA293343/1152 Study not previously submitted to EU. Refer to Annex I. Vol3CA B.6.8.2.2.1
From literature search for the purpose of thiamethoxam renewal-2017				
Thiamethoxam induced mouse liver tumors and their relevance to humans Part 1: Mode of action studies in the mouse.	n/a	n/a	Thiamethoxam hepatotoxicity and hepato-carcinogenicity in mice result of its metabolism to CGA330050. Metabolite CGA265307 exacerbates the toxicity of CGA330050 in thiamethoxam treated mice.	Green (2005) Published paper. Refer to Annex I. Vol3CA B.6.8.2.2.2

Type of study/data Test substance	NOEL	LOEL	Observations	Reference
Thiamethoxam induced mouse liver tumors and their relevance to humans Part 2: Species differences in response.	n/a	n/a	Thiamethoxam is unlikely to pose a hazard to humans exposed to this chemical at the low concentrations found in the environment or during its use as an insecticide.	Green (2005a) Published paper. Refer to Annex I. Vol3CA B.6.8.2.2.2
Case Study: Weight of Evidence Evaluation of the Human Health Relevance of Thiamethoxam-Related Mouse Liver Tumors.	n/a	n/a	MoA for thiamethoxam-induced mouse liver tumors described. The postulated MoA found to fulfil the Hill criteria The coherent and extensive database demonstrates a clear depiction of the MoA for mouse liver tumorigenesis and also allows for the conclusion on its non-relevance to human.	Pastoor (2005) Published paper.
Neonicotinoid formaldehyde generators: Possible mechanism of mouse-specific hepatotoxicity/hepatocarcinogenicity of thiamethoxam. Thiamethoxam (TMX) Clothianidin (CLO) *In vivo* Mouse Swiss-Webster M 15–25 mg/kg, 1–3 doses 45 min apart *In vitro* liver microsomes for species comparison studies : mouse, rat, human	The oxadiazinane moiety of TMX provides a slow release reservoir for the production of HCHO and potentially N-methylols as candidate hepatotoxicants and hepatocarcinogens with higher yields in mice than rats or humans. *In vitro*: relative amount of HCHO liberated was closely correlated with the relative CLO yield and Mouse yielded significantly more HCHO from TMX and TMX-dm compared to rat or human. However, an attempt by the authors to detect elevated HCHO levels in liver tissues of mice intraperitoneally treated with thiamethoxam showed no differences in liver HCHO concentrations between mice treated with thiamethoxam and control animals. Furthermore, all attempts to detect N-methylol and N-formamide intermediates *in vitro* were unsuccessful. The data demonstrate that thiamethoxam metabolites CGA330050 and CGA265307 form at significantly higher levels during thiamethoxam metabolism with mouse microsomes than with rat or human microsomes, adding further weight to the significant quantitative species differences in metabolic formation of these metabolites.			Swenson (2013) Published paper. Refer to Annex I. Vol3CA B.6.8.2.2.2
Using nuclear receptor activity to stratify hepatocarcinogens.	n/a	n/a	Based on ToxCast project, TMX has no activity on nuclear receptors: CAR, PXR, AhR, PPAR, LXR, RXR and steroid receptors SR.	Shah (2011) Published paper. Refer to Annex I. Vol3CA B.6.8.2.2.2

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

Two long-term toxicity and carcinogenicity studies were performed, one in rat and the other one in mice. The main target organs were the liver in mice and female rats and the kidneys in male rats. Minor splenic histopathological changes occurred in both rats and mice (hemosiderosis and extramedullary haematopoiesis respectively).

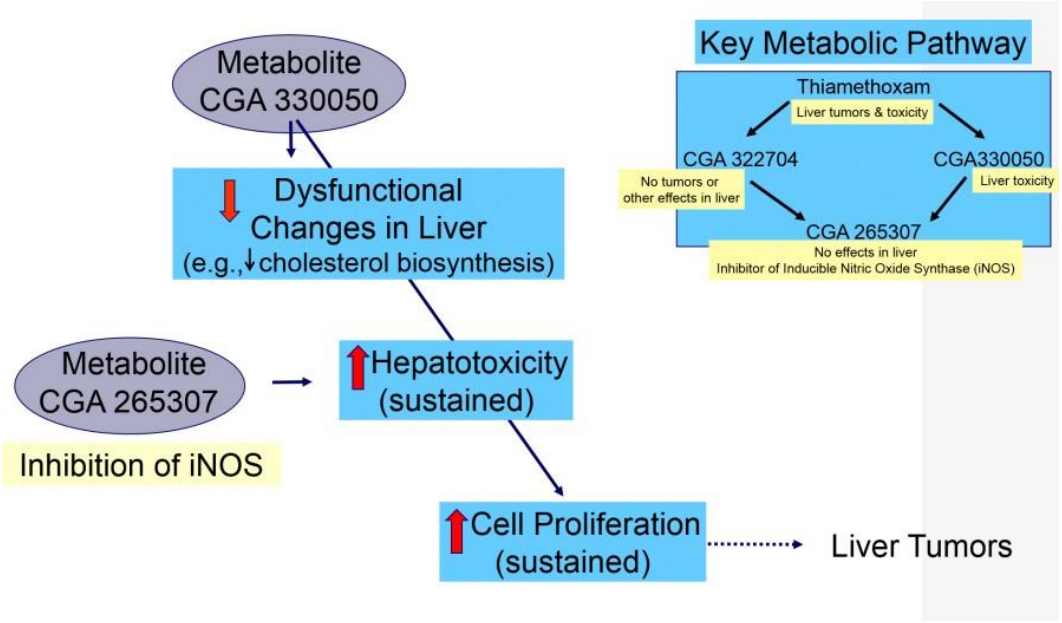
In the male rat the principal finding was an increased incidence of renal tubular regenerative lesions. These

lesions are considered to represent the sequelae of α2μ-globulin mediated nephropathy, specific to sexually mature male rats, and not indicative of a human health hazard. The overall NOAEL of relevance to human risk assessment is the female NOAEL of 1000 ppm (50.3 mg/kg bw/day) based on decreased body weight gain, focal cellular alteration in the liver and increased severity of splenic hemosiderosis at 3000 ppm.

Based on no excess tumours occurring at any dose level, there was no indication of a carcinogenic potential in rats and the NOAEL for carcinogenicity was set at the highest dose level 1500 ppm (equivalent to 63 mg/kg/day for males and 3000 ppm (equivalent to 155 mg/kg/day) in females.

In mice, the NOAEL established for chronic toxicity and carcinogenicity was 20 ppm (2.63-3.68 mg/kg bw/day male and female respectively), based on the occurrence of non-neoplastic (hypertrophy, pigment deposition, mitotic activity, Kupffer cell hyperplasia and single cell necrosis) and neoplastic alterations in the liver at 500 ppm (63.8-87.6 mg/kg bw/day males and females, respectively).

A number of studies were submitted to support a proposed underlying mode of action for liver carcinogenicity observed in mice. A plausible mode of action has been established which is considered to have no relevance to human.
The applicant has proposed the following mode of action:



Proposed MoA by the applicant

Thiamethoxam metabolism has been extensively studied *in vivo* in rat and mouse and *in vitro* comparison in mouse, rat and human microsomes showing increased metabolism of thiamethoxam in the mouse compared to rat (*in vitro* and in *vivo data*) and human (*in vitro* data).
Notably, the rate of metabolism through CGA 330050 is much higher in the mouse than in the rat suggesting that the thiamethoxam → CGA 330050 → CGA 265307 pathway accounts for the hepatotoxic effects that lead to liver tumours in mice.

While decreased in plasma cholesterol levels was the earliest and most significant change observed from dose levels of 500 ppm thiamethoxam onwards, the causality between this key event and the downstream one (hepatotoxicity) has not been demonstrated. Furthermore contrary to statin drugs, thiamethoxam does not inhibit HMG-CoA-reductase ([redacted], 2003a).

The effects reported to support the proposed key event "increased sustained hepatotoxicity" in the numerous mechanistic studies generated reflect cytotoxicity. Indeed both histopathological findings (hepatocellular necrosis and apoptosis, inflammatory cell infiltration) and plasma chemistry changes (increased ALT and AST) are strongly indicative of liver cytotoxicity.
The numerous dietary studies of up to 50 weeks duration conducted with thiamethoxam and its major metabolites support the key event liver cytotoxicity induced by thiamethoxam and by its metabolite desmethyl-

thiamethoxam (CGA 330050) contrary to clothianidin (CGA 322704) and desmethyl-clothianidin (CGA 265307) ([redacted], 2003a; [redacted], 2003, [redacted] 2003b, [redacted] 2003d).
The key events "increased cell proliferation" is also supported by the submitted data.

Therefore, RMS is of the opinion that the underlaying MoA of the liver tumours in mice is likely to be cytotoxicity and subsequent regenerative hyperplasia.
Cytotoxicity is a generally accepted MoA and has been defined for a number of nongenotoxic rodent carcinogens. A liver cytotoxicant would produce continual hepatocyte death, leading to persistent regenerative growth. Such growth results in more opportunities for "spontaneous" DNA mutations, allowing mutated cells to accumulate and proliferate, and giving rise to preneoplastic foci and, ultimately, to tumors via further clonal expansion (Holsapple, 2006).

Postulated Mode of action (RMS proposal):

- **Metabolic activation-generation of hepatocyte cytotoxicant metabolite(s)**
- **Sustained liver cytotoxicity**
- **Regenerative hyperplasia**
- **Clonal expansion of aberrant cells/foci of cellular alteration**
- **Liver tumours**

As mentioned before, based on the data available it is obvious that metabolism plays a key role in carcinogenicity potential of thiamethoxam in mice liver. Based on the generated data Green et al considered that the main driver of liver hepatotoxicity is desmethyl-thiamethoxam (CGA 330050) and that desmethyl-clothianidin (CGA265307) exacerbates desmethyl-thiamethoxam liver cytotoxicity by inhibition of nitric oxide synthase.

On the other hand, in a published study, Swenson T and Casida J have investigated an alternative hypothesis. The liver toxicity of thiamethoxam (TMX) and desmethyl-thiamethoxam (TMX-dm) would be driven by CYP-mediated oxidative oxadiazinane ring cleavage leading to formaldehyde (HCHO) and N-methylol intermediates considered being the ultimate hepatotoxicants and hepatocarcinogens.

However, while *in vitro* release of HCHO during thiamethoxam metabolism by mouse microsomes was demonstrated, an attempt by the authors to detect elevated HCHO levels in liver tissues of mice intraperitoneally treated with thiamethoxam showed no differences in liver HCHO concentrations between mice treated with thiamethoxam and control animals. Furthermore, all attempts to detect N-methylol and N-formamide intermediates *in vitro* were unsuccessful.

Although some uncertainty remains whether liver cytotoxicity is driven by HCHO and N-methylol intermediates formation resulting from oxidative oxadiazinane ring cleavage or by desmethyl-thiamethoxam itself, both submitted mechanistic studies and the publication from Swenson and Casida support that CYP-mediated oxidative metabolism of thiamethoxam accounts for the hepatotoxic effects that lead to liver tumours in mice.

Nevertheless, the ultimate effect of thiamethoxam treatment of mice is to induce cytotoxicity, which leads to regenerative proliferation and ultimately the development of tumours.

Throughout the database, a good dose-concordance and a temporal concordance between the causal key events, associative events and the apical outcome (liver tumours) were observed in both male and female mice. The available data permitted to adequately rule out alternative MoAs (i.e., genotoxicity, peroxisome proliferation, AhR induction, CAR and/or PXR induction, estrogenic stimulation, statins, infections, iron/copper overload, and increased apoptosis).

In summary RMS is of the opinion that the available data provide enough evidence to support the postulated MoA (liver tumours induced through sustained cytotoxicity and subsequent regenerative hyperplasia) to be the underlying MoA of liver tumours observed in mice.

Human relevance of the plausible mode of action

As described in a recent extension of the IPCS Mode of action Framework (Boobis et al., 2006), in order to address the relevance of the plausible MoA to human assessment of the qualitative and quantitative differences between the mouse and human for each of the key events should be performed.

The initial key event is metabolic activation of thiamethoxam. Whereas mouse, rat and human are clearly qualitatively capable of CYP-mediated oxidative metabolism, kinetic studies have shown that there are huge quantitative differences between species.

The ADME studies show that the rat excretes 73% of an administered dose as unchanged thiamethoxam, whereas the mouse excretes only 39% into the urine as thiamethoxam. The increased metabolism of thiamethoxam in the mouse is reflected in urine as significantly greater amounts of metabolite desmethyl-clothianidin (CGA 265307), 19% of the dose in mouse urine, but only 1.9% in rat urine. The urinary excretion of clothianidin (CGA 322704) is similar in both species, suggesting that the route to CGA 265307 via desmethyl-thiamethoxam (CGA 330050) is much more important in the mouse ([redacted], 1998; [redacted], 2002a, 2002b, 2002c, 2002d; [redacted] 2000). CGA 330050 is not excreted to any significant extent in urine but is observed, together with thiamethoxam and the other major metabolites in plasma.

Cross-Species Comparison of Thiamethoxam Metabolic Conversion Rates

Metabolic pathway	**Relative rate – Mouse:Rat**
Thiamethoxam to CGA 265307 via CGA 322704	54:1
Thiamethoxam to CGA 265307 via CGA 330050	87:1
	Relative rate – Mouse:Human
Thiamethoxam to CGA 265307 via CGA 322704	371:1
Thiamethoxam to CGA 265307 via CGA 330050	238:1

In vitro investigation of thiamethoxam metabolism in mouse, rat and human liver fractions [redacted], 2002) show that the flux of thiamethoxam to desmethyl-clothianidin (CGA265307) is 54-87 times greater in the mouse than the rat and 238-371 times greater than human microsomal preparations

The data presented by Swenson and Casida (2013) demonstrate also that thiamethoxam metabolites CGA330050 and CGA265307 form at significantly higher levels during thiamethoxam metabolism with mouse microsomes than with rat or human microsomes, adding further weight to the significant quantitative species differences in metabolic formation of these metabolites.

Based on all the available data, it can be concluded that the metabolic activation of thiamethoxam is quantitatively inadequate for cytotoxicity to occur in rats and no tumours are produced in rats treated with thiamethoxam at dose levels up to 1500ppm during 24 months.
Likewise, in human cells the metabolic activation of thiamethoxam appears to be quantitatively far much lower than in mouse cells.
The table below shows that the progression of key events cannot occur in rats and humans because of insufficient metabolic rate to generate enough amount of hepatocyte cytotoxicant.
Therefore, thiamethoxam is not expected to cause hepatic tumours in humans for the same reasons it does not cause tumors in rats in long-term studies.
Consequently it is highly unlikely that humans would have a carcinogenic response to exposure to thiamethoxam.

Concordance of key events across species

Key Event	**Mouse**	**Rat**	**Human**
Metabolic activation (CYP-mediated oxidation) **Metabolic rate to induce sufficient amount of**	Yes	Yes	Yes*

hepatocyte cytotoxicant(s)	Yes	No	No*
Sustained liver cytotoxicity	Yes	No	*In vivo* data not available
Regenerative hyperplasia	Yes	No	*In vivo* data not available
Clonal expansion of aberrant cells	Yes	No	*In vivo* data not available
Liver tumours	Yes	No	**Unlikely**

*Based on *in vitro* data

In summary RMS is of the opinion that the available data provide enough evidence to support the postulated MoA (liver tumours induced through sustained cytotoxicity and subsequent regenerative hyperplasia induced by hepatocyte cytotoxicant metabolite) to be the underlying MoA of liver tumours observed in mice.
Human relevance of the mode of action can reasonably be excluded on the basis of marked quantitative differences in metabolism between mice and humans.

The same conclusion was reached by US-EPA: Thiamethoxam is "not likely to be carcinogenic to humans" based on species differences in metabolism (Environmental Protection Agency, 2007; Pastoor et al., 2005) and JMPR: "On the basis of the absence of genotoxicity *in vivo*, the absence of carcinogenicity in rats and the mode of action by which liver tumours arise in mice, the Meeting concluded that thiamethoxam is unlikely to pose a carcinogenic risk at human dietary exposure levels" (JMPR, 2010).

2.6.5.2 Comparison with the CLP criteria regarding carcinogenicity

Table 42: Compilation of factors to be taken into consideration in the hazard assessment

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
Mouse Tif:MAGf (SPF)	Hepatocellular adenoma Males Statistically significant increase: 34%, 42% and 78% at 500, 1250 and 2500 ppm respectively HCD Range 10-34% Females Statistically significant increase: 10%, 16% and 56% at 500, 1250 and 2500 ppm respectively HCD Range 0-8%	No	Yes	No	Both	At 2500 ppm decreased body weight gain (↓ 18% / 14% in ♂/♀)	Oral diet	MoA, liver tumours induced through sustained cytotoxicity and subsequent regenerative hyperplasia induced by hepatocyte cytotoxicant metabolite not relevant to humans MoA, not relevant to humans on the basis of marked quantitative differences in metabolism between mice and humans
	Hepatocellular carcinoma males 32% in male mice at 2500 ppm HCD Range 0-16% Females Statistically significant increase: 4%, 6% and 56% at 1250 and 2500 ppm respectively HCD 0-2%	No	n/a	No	Both	At 2500 ppm decreased body weight gain (↓ 18% / 14% in ♂/♀)	Oral diet	

Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence, or Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence.
The classification in Category 1A and 1B is based on strength of evidence together with additional considerations. Such evidence may be derived from: – human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or – animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.

There is no available human data showing thiamethoxam has carcinogenic potential for humans.
Cat 1A not triggered.

Since the evidence of carcinogenicity is restricted to a single experiment, in one species (mouse) and concerned only liver tumours, there is no sufficient evidence of carcinogenicity triggering Cat 1.B.

Based on the results in the 18-month study, thiamethoxam may trigger Cat.2 for carcinogenicity.
A number of studies were submitted to support the mode of action for liver carcinogenicity observed in mice. A plausible mode of action has been established which is considered to have no relevance to human according to the weight of evidence framework as outlined by IPCS (see above).
Indeed, the submitted mechanistic data as well as published data from an independent team demonstrated that the liver tumours observed in mice are induced through sustained cytotoxicity and subsequent regenerative hyperplasia induced by hepatocyte cytotoxicant metabolite.
Human relevance of the mode of action can reasonably be excluded on the basis of marked quantitative differences in metabolism between mice and humans.

2.6.5.3 Conclusion on classification and labelling for carcinogenicity

Not classified (conclusive but not sufficient for classification)

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

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

Table 43: Summary table of animal studies on adverse effects on sexual function and fertility – generational studies

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for sexual function and fertility, parents)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
2-generation reproduction study OECD Guideline 416 (1981) GLP Acceptable Rat, Sprague-Dawley Tif: RAIf, SPF 30/sex/group	Thiamethoxam technical Batch P.50600 (purity 98.6%) 0, 10, 30, 1000, 2500ppm (♂: 0, 0.6, 1.8, 61 or 158 mg/kg bw/day, ♀: 0, 0.8, 2.4, 79 or 202 mg/kg bw/day) In the diet	**<u>At 10 ppm (♂/♀): 0.6/0.8 mg/kg bw/day</u>** No difference from controls. **<u>From 30 ppm (♂/♀): 1.8/2.4 mg/kg bw/day</u>** **Paternal toxicity :** No effect **Maternal toxicity :** No effect **Sexual function and fertility:** increased incidence and severity of tubular atrophy observed in testes of F1 males (no effect in F0 males). **<u>From 1000 ppm (♂/♀): 61/79 mg/kg bw/day</u>** **Paternal toxicity:** *increased incidence of hyaline change in renal tubules (F0 and F1 males) not relevant for human risk assessment.* **Maternal toxicity :** No effect **<u>At 2500 ppm (♂/♀): 158/202 mg/kg bw/day</u>** **Paternal toxicity**: transient reduced food consumption and slight decreased body weight gain of F0 weeks 1-6 (10%). In F1 lower body weights at selection remained lower than controls thereafter. **Maternal toxicity :** No effect **Sexual function and fertility:** Statistically significant decrease of F1 abs testis weight (no effect in F0 males). **Paternal NOAEL: 1000 ppm (eq. to: 61 mg/kg bw/day)** ***NOAEL kidney effects in males : 30ppm eq.to: 1.8 mg/kg bw (not relevant for human risk assessment)*** **Maternal NOAEL : 10 ppm (eq. to: 0.6 mg/kg bw/day)** **Sexual function and fertility NOAEL: 10 ppm (eq. to: 0.6 mg/kg bw/day)**	(1998) Refer to Annex I. Vol3CA B.6.6.1.1

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for sexual function and fertility, parents)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
2-generation reproduction study OECD Guideline 416 (2001) GLP Acceptable Rat, Sprague-Dawley Tif: RAIf, SPF 26/sex/group	Thiamethoxam technical Batch P.50600 (purity 98.6%) 0, 20, 50, 1000, 2500ppm (♂: 0, 1.2, 3, 61.7 or 155.6 mg/kg bw/day, ♀: 0, 1.7, 4.3, 84.4 or 208.8 mg/kg bw/day) In the diet	**<u>At 20 ppm (♂/♀): 1.2/1.7 mg/kg bw/day</u>** No difference from controls. **<u>From 50 ppm (♂/♀): 3.0/ 4.3 mg/kg bw/day</u>** **Paternal toxicity :** No effect **Maternal toxicity :** No effect **Sexual function and fertility:** significant reduced number of sperm cells in F1 males (no effect in F0 males). **<u>From 1000 ppm (♂/♀): 61.7/84.4 mg/kg bw/day</u>** **Paternal toxicity:** *increased incidence of hyaline change in renal tubules (F0 and F1 males) not relevant for human risk assessment.* **Maternal toxicity :** No effect **Sexual function and fertility:** dose-related increase in epididymal and testes weights in F1 males (no effect in F0 males). **<u>At 2500 ppm (♂/♀): 155.6/208.8 mg/kg bw/day</u>** **Paternal toxicity:** reduced food consumption and decreased body weight gain F0 males. **Maternal toxicity :** No effect **Sexual function and fertility**: increased incidence of germ cell loss/disorganisation and Sertoli cell vacuolation in F1 males. F1 sperm velocity parameters statistically significantly lower. Delayed preputial separation. **Paternal NOAEL: 1000 ppm (eq. to: 61.7 mg/kg bw/day)** ***NOAEL kidney effects in males : 50 ppm eq.to: 3 mg/kg bw (not relevant for human risk assessment)*** **Maternal NOAEL: 2500 ppm (eq. to: 208.8 mg/kg bw/day)** **Sexual function and fertility NOAEL: 20 ppm (eq. to: 1.2 mg/kg bw/day)**	(2004) Refer to Annex I. Vol3CA B.6.6.1.2
Developmental Neurotoxicity Study OECD Guideline 426	Thiamethoxam technical Batch P. 506006 (Purity: 98.8%)	**<u>At 50 ppm (4.3 mg/kg bw per day) and 400 ppm (34.5 mg/kg bw per day):</u>** No difference from controls. **<u>At 4000 ppm (298.7 mg/kg bw/day):</u>** **Maternal toxicity:**	[redacted], 2003 & 2006 Refer to Annex I. Vol3CA B.6.7.1.3

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for sexual function and fertility, parents)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
GLP Acceptable Rat, Wistar Alpk:APrSD 30 time-mated females/group	0, 50, 400 or 4000 ppm (0, 4.3, 34.5 or 298.7 mg/kg bw/day) From GD7 to PND22 in diet	Decreased BW gain (↓12% during gestation) and food consumption **Sexual function and fertility NOAEL:** Delayed sexual maturation in F1 males **Maternal NOAEL: 400 ppm (34.5 mg/kg bw per day)** **Sexual function and fertility NOAEL: 400 ppm (34.5 mg/kg bw/day)**	
90-days oral toxicity study OECD 409 GLP Acceptable Dog, Pedigree Beagle 4/sex/group	Thiamethoxam technical Batch P.506006 (purity 98.6%) 0, 50, 250, 1000, 2500/2000 ppm ♂: 1.58, 8.23, 32.0, 54.8 mg/kg bw/day ♀: 1.80, 9.27, 33.9, 50.5 mg/kg bw/day Continuous in the diet for 90 days.	**<u>At 50 ppm and 250 ppm :</u>** No differences from control. **<u>From 1000 ppm :</u>** **Sexual function and fertility:** no effect **Other toxic effects:** Slight anaemia, associated with a tendency to hypochromasia, anisochromasia and microcytosis (♀) Lower plasma Ca^{++} concentration and ALAT activity, minimally reduced plasma albumin levels (♂/♀) Prolonged prothrombin times (♂/♀) **<u>At 2500/2000 ppm :</u>** **Sexual function and fertility:** Ovary: decrease weights with histological correlates (immature). Testis: decreased weights , minimal to marked reduction in spermatogenesis, increased incidence of spermatic giant cells occurred in the testes (all males) and moderate tubular atrophy (one male) **Other toxic effects:** Lost of weight during the first 2 weeks of the study and therefore, the concentration was reduced to 2000 ppm. Reduce bwg (♀83%/♂36%) and bw (♀26%/♂6%), decrease of food consumption (♂/♀) Reduced white cell counts (total, neutrophils, monocytes and lymphocytes) (♀) Reduce monocyte counts (♂) **NOAEL: 250 ppm equivalent to 8.23 mg/kg bw/day (males) and 9.27 mg/kg bw/day (females)**	[redacted], 1996 Refer to Annex I. Vol3CA B.6.3.2
1-year oral toxicity study OECD 452 GLP Acceptable Dog, Pedigree	Thiamethoxam technical Batch P.506006 (purity 98.6%)	**<u>At 25 and 150 ppm :</u>** No differences from control. **<u>At 150 ppm :</u>** No differences from control.	[redacted], 1998 Refer to Annex I. Vol3CA B.6.3.3

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for sexual function and fertility, parents)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
Beagle 4/sex/group	0, 25, 150, 750, 1500 ppm ♂: 0.70, 4.05, 21.0, 42.0 mg/kg bw/day ♀: 0.79, 4.49, 24.6, 45.1 mg/kg bw/day Continuous in the diet for 1 year.	**<u>From 750 ppm :</u>** **Sexual function and fertility:** Testis: Higher incidence of tubular atrophy **Other toxic effects:** Increased plasma creatinine and tendency to higher plasma urea levels (♂/♀) **<u>At 1500 ppm :</u>** **Sexual function and fertility:** Testis: Decrease in absolute (-16%) and relative (–15%) testis weights (due mainly from 2 animals) **Other toxic effects:** Reduce of body weight gain (♂) but final body weight not affected Minimally lower albumin levels and albumin/globulin ratios (♀) **NOAEL: 150 ppm equivalent to 4.05 mg/kg bw/day (males) and 4.49 mg/kg bw/day (females)**	

Table 44: Summary table of human data on adverse effects on sexual function and fertility

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

Table 45: Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
See also 2.6.8.3				

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

The potential for thiamethoxam to affect sexual function and fertility was assessed in two multigeneration studies in the rat.

In the 2-generation studies in the rat, testicular effects were observed in the F1 males but not in parental males.

1) First guidelined 2-generation study OECD 416 (1981) (refer to Vol3CA B.6.6.1.1)

No clinical sign or death was observed in rats administrated 0, 10, 30, 1000 or 2500 ppm of thiamethoxam.

Body weight and food consumption:

No effect on body weight or food consumption was observed in females of both generations.

Body weight gain of top dose F0 males was slightly reduced weeks 1-6 and body weights were reduced weeks 5-9. The top dose F1 males had lower body weights at selection which remained lower than controls thereafter but weight gain was similar to that of the control group. There were no other effects on body weight. F0 males treated with2500 ppm showed transiently reduced food consumption during weeks 5 and 6 of the first pre-mating treatment period only. There were no other effects on food consumption.

Body weight development and food consumption in - F_0 generation

Day	Time point	Parameter/Dose Level	0 ppm	10 ppm	30 ppm	1000 ppm	2500 ppm
Males							
1	Treatment start	Mean body weight (g)	199.5	198.8	198.2	199.2	196.8
68	End 1st premating	Mean body weight (g)	460.7	454.6	453.6	450.1	430.8
		Cumulative body weight gain[a]	261.2	255.8	255.4	250.9	234.0
		Body weight gain % of control		-2.1	-2.2	-3.9	**-10.4**
190	End 2nd postmating	Mean body weight (g)	578.1	566.9	562.3	557.2	546.5
		Cumulative body weight gain	378.6	368.1	364.1	358.0	349.7
		Body weight gain % of control		-2.8	-3.8	-5.4	-7.6
1	Treatment start	Food consumption	19.3	20.2	20.8*	19.0	19.4
29-36	5 week premating		26.6	25.1*	25.6	25.2	24.6**
36-43	6 week premating		26.8	25.6	25.6	25.3	24.8**
190	End 2nd postmating		25.9	25.6	25.8	25.4	26.7
Females							
1	Treatment start	Mean body weight (g)	154.5	153.7	153.5	152.7	154.2
68	End 1st premating	Mean body weight (g)	265.4	271.1	272.5	267.4	266.4
		Cumulative body weight gain	110.9	117.4	119.0	114.7	112.2
		Body weight gain % of control		+5.9	+7.3	+3.4	+1.2
211	End 2nd lactation	Mean body weight (g)	348.4	357.3	349.8	346.3	348.5
		Cumulative body weight gain	193.9	203.6	196.3	193.6	194.3
		Body weight gain % of control		+5.0	+1.2	-0.2	+0.2
1-8	Treatment start	Food consumption	13.0	14.3*	14.6**	12.8	13.9
68	End 1st premating		15.9	16.3	16.3	16.3	15.7
211	End 2nd lactation		67.5	67.7	67.4	69.3	64.6

[a] Body weights and body weight gains in grams; (*)= p≤0.05 (**)=p≤0.01

Body weight development - F_1 parental animals

Day	Time point	Parameter/ Dose Level	0 ppm	10 ppm	30 ppm	1000 ppm	2500 ppm
			Males				
134	Start premating	Mean body weight[a]	162.0	153.2	163.3	161.6	147.8
204	End 1st premating	Mean body weight	470.2	469.5	456.9	453.6	437.9*
		Cumulative body weight gain[a]	308.2	316.3	293.6	292.0	290.1
		Body weight gain % of control		+2.6	-4.7	-5.3	-5.9
323	End 2nd postmating	Mean body weight	603.8	612.2	598.2	588.8	589.2
		Cumulative body weight gain	441.8	459.0	434.9	427.2	441.4
		Body weight gain % of control		+3.9	-1.6	-3.3	-0.1
			Females				
134	Start premating	Mean body weight	146.5	134.3	141.7	142.3	134.7
204	End 1st premating	Mean body weight	294.1	281.4	284.4	288.9	279.0
		Cumulative body weight gain	147.6	147.1	142.7	146.6	144.3
		Body weight gain % of control		-0.3	-3.3	-0.7	-2.2
334	End 2nd lactation	Mean body weight	372.5	357.2	358.7	371.3	369.0
		Cumulative body weight gain	226.0	222.9	217.0	229.0	234.3
		Body weight gain % of control		-1.4	-4.0	+1.3	+3.7

[a] Body weights and body weight gains in grams; * $p \leq 0.05$, ANOVA + Dunnett

Reproductive performance: For both generations and all matings, there were no effects on the number of animals mating, the number of females becoming pregnant or on the mean pre-coital time. The mean duration of gestation was approximately 22 days in all groups.

Investigations *post mortem:*

- *Organ weights*

F0: There were no effects on absolute and relative organ weights at any dose level.

F1: Absolute testis weights were statistically significantly lower than concurrent control for the F1 males at 2500ppm but not relative weights.

Testes/Ovaries - F_1 parental animals

		Males					Females				
Organ[a] Dose Level (ppm)		**0**	**10**	**30**	**1000**	**2500**	**0**	**10**	**30**	**1000**	**2500**
Carcass	absolute[a]	582	593	578	575	573	350	335	341	342	339
Testes/Ovaries	absolute[b]	4.48	4.42	4.24	4.41	4.08*	0.23	0.20**	0.22	0.22	0.23
	relative	77.36	75.31	74.09	77.30	72.43	6.67	6.11	6.37	6.43	6.77

[a] All absolute weights in grams; [b]Relative organ weights are organ weight % of body weight x 100;
* $p \leq 0.05$, ** $p \leq 0.01$, ANOVA + Dunnett

- *Microscopic examination:*

Kidney

Increased incidences of minimal to marked hyaline change (eosinophilic droplets in the cytoplasm of renal tubular epithelium and occasionally within the tubular lumen) in renal tubules were present in male F0 and F1 animals treated with 1000 ppm and 2500 ppm and in one (1/30) F1 female treated with 2500 ppm. Minimal to marked renal tubular cast was found in F1 males at 1000 ppm and in males of both generations at 2500 ppm in slightly increased incidences.

Incidence of selected microscopic kidney findings in F0 and F1 males

Kidney finding	Dietary concentration of CGA293343 technical (ppm)									
	0	**10**	**30**	**1000**	**2500**	**0**	**10**	**30**	**1000**	**2500**
	F0 Males					F1 Males				
Hyaline change	1/30	2/30	3/30	16/30	25/30	3/30	5/30	3/30	24/30	28/30
grade 1	1	2	3	12	1	3	4	3	4	1

grade 2	-	-	-	4	17	-	1	-	16	12
grade 3	-	-	-	-	7	-	-	-	4	12
grade 4	-	-	-	-	-	-	-	-	-	3
average grade	1.0	1.0	1.0	1.3	2.2	1.0	1.2	1.0	2.0	2.6
Tubular cast	22/30	20/30	19/30	23/30	28/30	21/30	20/30	21/30	27/30	29/30
grade 1	8	12	10	15	10	7	5	11	11	6
grade 2	14	6	8	7	17	9	13	7	15	13
grade 3	-	2	1	1	-	5	2	3	1	9
grade 4	-	-	-		1	-	-	-	-	1
average grade	1.6	1.5	1.5	1.4	1.7	1.9	1.9	1.6	1.6	2.2

Testes

Histopathological examination revealed an increase of the incidence of testes tubular atrophy in all F1 treated animals 8/30(10 ppm), 15/30(30 ppm), 24/30(1000 ppm) and 14/30 (2500 ppm). According to the study author, there was no evidence of a dose-related occurrence.

However, a further evaluation of those effects was performed by a Pathology Working Group (PWG/), this report was not mentioned in the previous EU peer-review under Directive 91/414/EEC and Directive 67/548/EC. It has been submitted upon request of the RMS for the re appraisal.

The PWG review was conducted in accordance with EPA Pesticide Regulation (PR) Notice 94-5 (EPA, August 24, 1994) which sets forth a procedure to be followed for submission of pathology re-reads to the Agency.

The PWG examined coded slides without knowledge of treatment group from the F1 generation in this study as well as controls from 5 reference studies, performed at the same laboratory.

The PWG considered the changes that were present in the sections of testes examined to represent a continuum and that therefore the separation between minute focal tubular change and diffuse tubular atrophy was inappropriate since they were not two distinctly different entities. A grading system was agreed between pathologists and gave the following results. The results of the PWG review of the testes from the F1 generation males are presented in Table below and those from controls from 5 reference studies in the next Table.

Incidence and severity of testicular Tubular atrophy diagnosed by the PWG in F1 generation male rats

Dose	0 ppm	10 ppm	30 ppm	1000 ppm	2500 ppm
No. Exam.	30	30	30	30	30
Grade 1	6	7	9	8	10
Grade 2	0	3	4	8	5
Grade 3	0	0	0	1	1
Grade 4	0	0	0	2	1
Grade 5	0	0	0	2	1
Overall Incidence	6	10	13*	21**	18*
%Incidence	20%	33%	43%	70%	60%
Ave. Grade	1.0	1.3	1.3	2.1	1.8

*P 0.05; **P 0.01 (one sided Fisher Exact Test)

Incidence and severity of testicular Tubular atrophy diagnosed by the PWG in untreated F1 animals of five two-generation studies

Study number	951041 F1	951031 F1	943045 F1	923152 F1	923179 F1
No. Exam.	30	30	30	30	30
Grade 1	5	9	1	2	3
Grade 2	1	2	1	2	2
Grade 3	0	0	0	0	0
Grade 4	1	0	0	0	0
Grade 5	2	0	0	0	3

Overall Incidence	9	11	3	4	8
%Incidence	30%	36.7%	10%	13.3%	26.7%
Ave. Grade	2.3	1.2	2.7	1.5	2.8

Contrary to the study author and the former reviewer, the PWG considered the increased incidence of tubular atrophy in F1 animals at the 1000 and 2500 ppm groups to be associated with the dietary administration of CGA-293343 Technical. Based upon the historical control data, findings at the 30 ppm level were considered equivocal while the 10 ppm dose group represented the "No Effect Level".

Sperm analysis:

Main study:
Sperm motility in F0 & F1 males of most treatment groups was reduced significantly when compared to controls. Investigations concluded that standardisation of the method might have been flawed. In the absence of concomitant changes in other sperm parameters, evidence of impaired mating and a lack of dose-response relationship, the toxicological relevance of the result for sperm motility was considered questionable.

Sperm motility main study (%)

Generation	Dietary concentration of CGA293343 technical (ppm)				
	0	**10**	**30**	**1000**	**2500**
F0	73	55*	51**	56*	55*
F1	65	53*	55	60	53*

* Statistically significant difference from control group mean, $p<0.05$

One technical flaw considered to have contributed to the variability between samples was poor standardization of the interval between sacrifice and sperm evaluation. A flaw probably accounting for the significant differences among groups was the conduct of sperm evaluations in group order rather than in randomised order.

Therefore an additional sperm analysis study was performed in which procedural changes were implemented to reduce and standardize the time for sperm collection, to refine the technique for opening the cauda epididymis, and to randomise the order in which sperm evaluations were performed to minimize inter-day bias. The results of the sperm analysis study showed no effect of treatment on any sperm parameters, suggesting that the apparent reductions in sperm motility were not an effect of treatment.

Additional sperm analysis study:
There were no effects on the proportion of motile sperm cells within the cauda epididymis fluid, the proportion of morphologically abnormal sperm, the number of spermatids per gram of testis or the number of sperm cells per mg cauda epididymis fluid.

Sperm parameters (sperm analysis study)

	Dietary concentration of CGA293343 technical (ppm)				
Dose Level	**0**	**10**	**30**	**1000**	**2500**
Total spermatids ($x10^6$ /g testis)	59.6	58.2	55.0	57.5	55.8
Percent abnormal sperm	12.2	11.7	11.6	12.2	11.0
Percent motile sperm cells	73.0	76	73	74	74

No statistically significant differences from control group means

It should be noted that this supplementary study performed under improved and upgraded technical conditions to evaluate potential sperm effects was conducted only on F0 animals.

CONCLUSION:

As regard sexual function and fertility, reproductive performance was not affected by treatment. However, from 30 ppm onwards an increased incidence and severity of seminiferous tubule atrophy in F1 were observed. Absolute testis weights were statistically significantly lower than concurrent control for the top dose F1 males. Equivocal results in sperm motility (decreased at all doses tested, with no apparent dose-relationship) were not reproduced in a separate study on sperm parameters performed under improved and upgraded technical conditions. It should however be noted that only F0 animals were investigated in this additional study, whereas seminiferous tubule atrophy was observed in F1 in the main study.

As regard other toxic effects, no adverse effect was noted in females of both generations at any dose levels. Increased incidence of hyaline change in renal tubules in F0 and F1 males was observed from 1000 ppm related to α2μ-globulin nephropathy. Body weight gain of top dose F0 males was slightly reduced between weeks 1 and week 6 (10%) associated with transient reduced food consumption during weeks 5 and 6.

2) Second guidelined 2-generation study, OECD 416 (2001) (refer to Vol3CA B.6.6.1.2)

There was no effect of thiamethoxam on the incidence of mortality or on the clinical condition of the F0 or F1 parent animals or the F1 satellite males (14 F1 / group were selected to generate histological data on the testis only).

Body weight, food consumption: Body weight gain in F0 males was statistically significantly decreased (6.7% between week 1 and week 28) associated with reduced food consumption at the beginning of the treatment.

Intergroup comparison of F0 male body weights (g) (selected time points; adjusted mean values)

	Dietary Concentration of Thiamethoxam (ppm)				
week	**0**	**20**	**50**	**1000**	**2500**
2	219.6	221.6	221.1	217.9	215.9*
4	297.5	302.3	301.5	290.4*	282.8**
10	399.6	408.0	405.4	391.9	374.5**
20	478.5	490.6	484.1	471.7	450.0**
28	514.6	523.0	520.6	504.3	479.9**

* Statistically significant difference from control group mean, p<0.05 (Student's t-test, 2-sided)
** Statistically significant difference from control group mean, p<0.01 (Student's t-test, 2-sided)

Intergroup comparison of F0 male food consumption and food utilization (selected time points)

Food consumption (g/rat/day)	**Dietary Concentration of Thiamethoxam (ppm)**				
week	**0**	**20**	**50**	**1000**	**2500**
1	22.6	21.8	22.8	21.6	20.7**
2	25.1	24.5	25.0	23.9	23.4**
7	25.5	25.3	26.4	25.5	24.2*
10	24.4	24.3	24.8	23.7	23.4
26	22.6	21.7	22.5	21.6	21.6
Overall food utilization (g growth/100g food)					
(weeks 1-4)	23.11	23.88	23.39	22.25	21.61**
(weeks 1-10)	14.02	14.35	14.01	13.53	13.26*

* Statistically significant difference from control group mean, p<0.05 (Student's t-test, 2-sided)
** Statistically significant difference from control group mean, p<0.01 (Student's t-test, 2-sided)

Reproductive performance: There was no effect of thiamethoxam on oestrus cyclicity, pre-coital interval, and duration of gestation or on the success of mating. There was no effect on reproductive performance.

Puberty onset: there was no effect on the mean day of age vaginal opening occurred. However a slight delayed preputial separation (1 day) was observed at high dose level while not statistically significant in the absence of concurrent effect on body weight at preputial separation.

Developmental landmarks F1

	Dose level of Thiamethoxam (ppm)					HCD CTL/RR0942	HCD CTL/RR0943
	0	**20**	**50**	**1000**	**2500**		
Day of preputial separation	47.7	47.3	47.2	46.7	48.7	47.1	47.2
BW at preputial separation	173.7	175.8	169.3	170.9	177.7	178.7	181.7
Day of vaginal opening	38.6	37.3	37.2	37.4	38.9	37.7	37.4
BW at vaginal opening	106.5	104.7	102.6	101.9	107.6	109.7	107.5

Investigations *post mortem:*

- *Organ weights*

For the F0 males, kidney weights adjusted for body weight were statistically significantly greater in the 2500 ppm group in comparison with the control group.

There was a dose-related increase in epididymal and testes weights in F1 males (both absolute and relative weights) given 1000 ppm or 2500 ppm (testes weights at the two higher dose levels were outside the historical control range). The mean epididymal weight obtained in the second control study (CTL/RR0943) was equal to that in the high dose males. However the terminal F1males body weight was higher in the control study and when the organs to BW ratios are compared, the values in the two high dose levels exceeded the HCD range.

Organ weight (adjusted for final bodyweight) - males

	Dietary Concentration of Thiamethoxam (ppm)					HCD CTL/RR0942	HCD CTL/RR0943
Organ	**0**	**20**	**50**	**1000**	**2500**	**0**	**0**
F0							
Terminal BW	551.2	520.2	536.7	505.1	482.6	501.1	531.8
Kidney	3.00	3.03	3.01	2.95	3.11*	2.89	3.04
Epididymis	1.638	1.545	1.619	1.582	1.674	1.549	1.755
F1							
Terminal BW	464.2	477.4	469.0	467.3	458.3	469.1	483
Kidney	2.83	2.88	2.85	2.81	2.85	2.88	2.99
Epididymis *adj for bw*	1.584	1.617	1.615	1.656*	1.668*	1.572	1.668
Epididymis *absolute*	*1.580*	*1.627*	*1.616*	*1.656*	*1.659**		
Organ to BW ratio	*0.345*	*0.343*	*0.348*	*0.356*	*0.364*	*0.332*	*0.347*
Testes *adj for bw*	3.90	4.12*	4.01	4.13*	4.21**	4.01	4.01
Testes *absolute*	*3.89*	*4.15**	*4.02*	*4.13**	*4.19***		
Organ to BW ratio	*0.85*	*0.87*	*0.87*	*0.87*	*0.92*	*0.85*	*0.83*

* Statistically significant difference from control group mean, p<0.05 (Student's t-test, 2-sided)
** Statistically significant difference from control group mean, p<0.01 (Student's t-test, 2-sided)

- *Microscopic examination:*

Treatment-related histological change was seen in the kidneys of the F0 and F1 males given 1000 or 2500 ppm. The histological change was consistent with α-2μ globulin nephropathy seen previously in rats treated with thiamethoxam.

An increased incidence of germ cell loss/disorganisation +/- Sertoli cell vacuolation was observed in F1 males given 2500 ppm. The severity was considered low with few tubules affected.

For the main study only one testis by animal was available for histopathology examination and so it was not possible to determine whether the changes were unilateral or bilateral.
From the satellite group, there was evidence to show that effects were treatment-related since the lesion was bilateral.

Incidence of F1 Males with Testicular Tubules showing Germ Cell Loss/Disorganisation +/- Sertoli Cell Vacuolation

	Dose level of Thiamethoxam (ppm)				
	0	**20**	**50**	**1000**	**2500**
Total number of F1 Males (main study + satellites)	40 (26+14)	40 (26+14)	40 (26+14)	40 (26+14)	40 (26+14)
Main study: uni/bilateral status unknown	3/26	1/26	1/26	3/26	15/26
Satellites: unilateral	1/14	4/14	2/14	3/14	0/14
Satellites: bilateral	1/14	0/14	0/14	1/14	5/14
Total incidence	5/40	5/40	3/40	7/40	20/40

No changes were detected in any other tissue from F0 or F1 animals that could be attributed to treatment with thiamethoxam.

Sperm analysis:
Sperm count:
For the F0 males, there was no effect on the number of sperm in the right cauda epididymis but for the F1 males given 2500 ppm, the total number of sperm and the number of sperm per gram of right cauda epididymis were statistically significantly higher than in the control group and slightly higher the historical range of values. Although possibly treatment-related, the higher number of sperm in right cauda epididymis was considered not to be an adverse finding.

The number of sperm cells in the right testis was significantly lower in the F1 males given 50, 1000 or 2000 ppm and the values at 50 ppm were below the historical control range A clear dose-response relationship was not observed; however, the decrease in sperm count is considered to be treatment-related in view of the pattern of testicular effects observed in the two 2-generation studies as well as in dog studies.

Sperm number (millions) – F1 males

	Total number of sperm (million)			
	per testis	**per g testis**	**per cauda epididymis**	**per g cauda**
0	87 ± 22	52 ± 14	153 ± 38	505 ± 94
20	93 ± 23	52 ± 12	153 ± 37	523 ± 136
50	70 ± 19**	42 ± 10**	163 ± 53	532 ± 153
1000	63 ± 16**	36 ± 9**	168 ± 49	546 ± 173
2500	74 ± 18*	43 ± 10**	192 ± 37**	620 ± 122**
CTL/RR0942	85 ± 16	48 ± 8	137 ± 51	479 ± 135
CTL/RR0943	69 ± 18	42 ± 10	170 ± 61	545 ± 170

* Statistically significant difference from control group mean, p<0.05 (Student's t-test, 2-sided)
** Statistically significant difference from control group mean, p<0.01 (Student's t-test, 2-sided)

Sperm motility: There was no effect of treatment on sperm motility.

Sperm velocity: For the F0 males, there was no effect of thiamethoxam on straight line, curvilinear or average path velocities. For the F1 males given 2500 ppm, the straight line, curvilinear and average path were statistically significantly lower in comparison with the control group but within the historical control range.

Sperm velocity (µm/s) – F1 males

ppm	**Straight line velocity**	**Curvilinear velocity**	**Average path velocity**
0	71.6 ± 5.6	305.0 ± 16.7	123.9 ± 7.5
20	71.8 ± 6.0	297.2 ± 19.5	122.1 ± 7.5
50	72.3 ± 5.2	302.4 ± 17.1	123.1 ± 7.8

1000	71.3 ± 7.4	297.7 ± 21.1	120.4 ± 7.9
2500	68.1 ± 5.4*	291.9 ± 14.7**	117.2 ± 6.1**
CTL/RR0942	64.9	277.9 ± 20.1	112.6 ± 8.6
CTL/RR0943	73.7	306.2 ± 17.1	124.0 ± 8.0

* Statistically significant difference from control group mean, p<0.05 (Student's t-test, 2-sided)
** Statistically significant difference from control group mean, p<0.01 (Student's t-test, 2-sided)

Sperm morphology:
Morphological examination of the sperm did not reveal any abnormalities in either generation.

CONCLUSION:

As regard_sexual function and fertility, reproductive performance was not affected by treatment. However, significant reductions in the number of sperm cells in the right testes of F1 males were observed from 50 ppm (3 mg/kg/day). In top dose F1 males, a delayed preputial separation was also observed, an increased incidence of germ cell loss/disorganisation and Sertoli cell vacuolation as well as a decrease in sperm velocity were noted at termination.

As regard other toxic effects, no adverse effect was noted in females of both generations at any dose levels. Increased incidence of hyaline change in renal tubules in F0 and F1 males was observed from 1000 ppm related to α2μ-globulin nephropathy. Body weight gain F0 males was statistically significantly decreased (6.7%) between week 1 and week 28) associated with reduced food consumption at the beginning of the treatment.

Delayed preputial separation was also observed in the developmental neurotoxicity study.

3) Guidelined Developmental neurotoxicity study OECD (426) (Refer to Annex I Vol3CA B.6.7.1.3)

Sexual function and fertility:

Preputial separation was delayed by an average of 1.5 days relative to the controls in the 4000 ppm males and the bodyweight on the day of preputial separation was lower than controls in this group. The slight delayed preputial separation observed in high dose males may be secondary to decreased body weight. However, in the absence of other investigations (hormonal levels, sperm parameters…), the involvement of another mechanism cannot be excluded. Furthermore a slight delay in preputial separation was also observed in a 2-generation study at 2500 ppm without any effect on the weight at preputial separation.

There was no treatment related effect on the day of vaginal opening in females.

Intergroup comparison of Preputial separation and vaginal opening

	Dose level of TMX (ppm)			
Observation	**0**	**50**	**400**	**4000**
Day of preputial separation	**44.9**	**45.6**	**45.1**	**46.4****
Bodyweight at landmark	**230.2**	**233.0**	**230.5**	**220.7****
Day of vaginal opening	**36.6**	**37.7**	**37.0**	**37.4**
Bodyweight at landmark	**136.0**	**140.3**	**136.4**	**129.2**

** Statistically significant difference from control group mean, p<0.01

Other toxic effects:
Dams' bodyweights: The bodyweights of the dams fed 4000ppm TMX were statistically significantly lower than controls on days 15 and 22 of gestation by 4-5% (equivalent to approximately 18% lower bodyweight gain from days 7-22 of gestation). This lower bodyweight was maintained from days 1 to 22 *postpartum* although there was no effect of treatment on *postpartum* weight gain.

There were no treatment related effects in dams fed 50 or 400ppm TMX.

Intergroup comparison of bodyweights during gestation and lactation (selected time points; adjusted mean values shown for day 8 onwards)

	Dose level of TMX (ppm)			
	0(Control)	**50**	**400**	**4000**
Body weight during gestation				
GD1	262.0	259.1	261.9	257.9
GD7	294.5	292.6	296.4	290.6
GD15	335.3	335.1	334.4	320.7**
GD22	417.0	415.6	417.8	394.9**
Body weight gain during gestation				
1-22	155.0	156.5	155.9	137.0 (↓12%)
Body weight during lactation				
LD1	314.6	313.1	313.2	291.7**
LD8	333.9	328.5	332.2	323.7**
LD15	369.1	362.5	362.0	344.9**
LD22	373.7	368.0	368.3	360.7**
LD29	353.1	350.2	353.2	352.4

* Statistically significant difference from control group mean, p<0.05 (Student's t-test, 2-sided)

** Statistically significant difference from control group mean, p<0.01 (Student's t-test, 2-sided)

Offspring bodyweights: Bodyweights of the selected F1 males and females in the 4000 ppm group were statistically significantly lower than the control group on day 5 (by approximately 12%) and remained lower than controls throughout the study (maximum effect on day 18 of 13%). The effects on growth during early, mid and late lactation, in male and female pups exposed to 4000 ppm TMX, are shown in the table below.

There was no effect of maternal treatment with 50 or 400 ppm TMX on the bodyweight of the selected F1 animals.

Intergroup comparison of F1 bodyweights (Selected time points; mean and adjusted mean by analysis of covariance on day 5 mean bodyweights)

		Dose level of TMX (ppm)							
		Males				Females			
Day		0	50	400	4000	0	50	400	4000
5	Mean	10	9.8	9.9	8.8**	9.6	9.3	9.3	8.4**
12	Mean	24.5	24.3	24.3	21.3**	24.0	23.4	23.3	20.6**
	Adjusted mean	*24.1*	*24.1*	*24.0*	*22.0***	*23.5*	*23.2*	*23.1*	*21.3***
18	Mean	40.3	39.3	39.4	34.3**	39.2	38.0	37.5*	33.3**
	Adjusted mean	*40.0*	*39.2*	*39.0*	*34.8***	*38.8*	*37.8*	*37.4**	*33.9***
29	Mean	96.4	94.5	94.9	85.6**	89.6	88.1	86.9	80.2**
	Adjusted mean	*95.4*	*94.0*	*94.3*	*87.5***	*88.4*	*87.6*	*86.5*	*82.0***

36	Mean	154.2	152.8	153.5	137.8**	134.5	133.4	131.7	122.6**
	Adjusted mean	*152.6*	*152.1*	*152.4*	*141.0***	*132.7*	*132.7*	*131.2*	*125.4***
43	Mean	221.2	209.9	211.6	191.4**	168.7	166.3	164.9	155.0**
	Adjusted mean	*210.2*	*209.0*	*210.2*	*195.3***	*166.4*	*165.4*	*164.3*	*158.3***
50	Mean	329.9	325.0	328.6	302.9**	197.2	192.6	191.1	181.5**
	Adjusted mean	*327.2*	*323.8*	*326.7*	*308.3***	*195.0*	*191.8*	*190.5*	*184.7***
63	Mean	368.1	361.6	365.4	337.4**	228.5	221.0	219.9	212.3*
	Adjusted mean	*365.0*	*360.2*	*363.5*	*343.2***	*225.9*	*220.1*	*219.2*	*216.1**

* Statistically significant difference from control group mean, p<0.05 (Student's t-test, 2-sided)

** Statistically significant difference from control group mean, p<0.01 (Student's t-test, 2-sided)

CONCLUSION:

Delayed preputial separation was observed at the highest dose level in the presence of reduced body weight gain in dams during gestation and offspring decreased body weight (#10% compared to controls)

Testicular effects were also observed in the 90-d and 1-year dog studies.

4) Guidelined 90-d dog study OECD 409 (1981) (Refer to Annex I Vol3CA B.6.3.2)

Sexual function and fertility:

Organ weights:

Testis and ovary weights were reduced at 2500/2000 ppm and histological correlates were identified. Slightly reduced heart, liver and kidney weights in females at 2500/2000 ppm and increased thyroid weights in males at 50, 1000 and 2500/2000 ppm were not associated with histological changes and were considered incidental to treatment with thiamethoxam.

Intergroup comparison of organ weight changes

	Dietary Concentration of CGA293343 tech (ppm)									
	Males					**Females**				
	0	**50**	**250**	**1000**	**2500 / 2000**	**0**	**50**	**250**	**1000**	**2500 / 2000**
Carcass weight *[kg]*	10.68	11.05	10.54	10.93	9.905 (-6%)	9.705	9.195	9.530	9.575	7.135* (-26%)
Testes/Ovaries										
- absolute [g][a]	16.54	14.76	14.60	15.59	9.38* (-43%)	0.835	0.663	0.696	0.712	0.543* (-35%)
- relative [% body weight x 100]	1.545	1.336	1.384	1.439	0.929*- (-40%)	0.087	0.072	0.073	0.074	0.076 (-13%)

Microscopic findings: A minimal to marked reduction in spermatogenesis and an increased incidence of spermatic giant cells occurred in the testes of all males at 2500/2000 ppm. One male also showed moderate tubular atrophy. Body weight in males was slightly affected with reduced final body weight by 6% compared to controls. Therefore a direct compound-related effect on testes cannot be ruled out. Furthermore, in the 1-year dog study, the body weight was not affected by the treatment, but effects on testes were also observed.

An immature stage of ovarian development occurred in three females at 2500/2000 ppm. The maturity of the uterus in two of these animals reflected the immature stage of ovarian development. These effects in females were most likely secondary to the general delay in both growth and development. Indeed the body weight gain

was reduced by 83% and the body weight by 26% compared to the control at the end of study. Furthermore in the 1-year dog study, female body weight was not affected up to 1500 ppm (highest dose level) and such effects were not observed at any dose levels.

Intergroup comparison of histopathological findings

Organ and finding	Dietary Concentration of CGA293343 tech (ppm)									
	Males					Females				
	0	50	250	1000	2500 / 2000	0	50	250	1000	2500 / 2000
Testes – number examined	**4**	**4**	**4**	**4**	**4**					
Tubular atrophy	0	0	0	0	1					
Spermatogenesis reduced	0	1	0	0	4					
Spermatic giant cells	1	1	0	1	4					
Uterus – number examined						**4**	**4**	**4**	**4**	**4**
Immature						0	0	0	0	2
Ovary – number examined						**4**	**4**	**4**	**4**	**4**
Immature						0	0	0	0	3

Other toxic effects:
Prolonged thromboplastin times, slightly reduced plasma calcium ions and changes in blood chemistry were observed in both sexes as well as a slight anaemia in females from 1000 ppm onwards

Bodyweight and weight gain: Seven animals at 2500 ppm lost weight during the first 2 weeks of the study and, therefore, the concentration was reduced to 2000 ppm. Subsequently, three of these animals showed markedly decreased weight gain. The weight gain of the remaining animals was unaffected by treatment. There was no effect on weight gain at dose levels up to 1000 ppm.

Intergroup comparison of mean body weight (g) -selected time points

	Dietary Concentration of CGA293343 tech (ppm)									
	Males					Females				
	0	50	250	1000	2500 / 2000	0	50	250	1000	2500 / 2000
Week -1	8.325	8.375	8.625	8.650	8.725	7.525	7.250	7.450	7.575	7.275
Week 2	8.950	9.050	9.200	9.250	8.725	8.150	7.750	8.125	8.150	6.875
Week 3	9.175	9.325	9.425	9.550	8.675	8.425	7.950	8.300	8.300	6.575*
Week 13	11.28	11.65	11.38	11.58	10.60 (↓6%)	10.43	9.775	10.25	10.65	7.750*(↓26%)

* $p \leq 0.05$ (Wilcoxon)

Intergroup comparison of cumulative body weight gain (kg) -selected time points

	Dietary Concentration of CGA293343 tech (ppm)									
	Males					Females				
	0	50	250	1000	2500 / 2000	0	50	250	1000	2500 / 2000
Week 2	0.625	0.675	0.575	0.600	0.00 (↓100%)	0.625	0.500	0.675	0.575	-0.40*(↓164%)
Week 3	0.850	0.950	0.800	0.900	-0.05 (↓106%)	0.900	0.700	0.850	0.725	-0.70*-(↓178%)
Week 13	2.950	3.275	2.750	2.925	1.875 (↓36%)	2.900	2.525	2.800	3.075	0.475*(↓83%)

* $p \leq 0.05$ (Wilcoxon); - :negative trend (Jonckheere)

CONCLUSION: At the highest dose level, testis weights were reduced and histological correlates were identified (minimal to marked reduction in spermatogenesis and an increased incidence of spermatic giant cells), one male also showed moderate tubular atrophy. At the same dose level, body weight was slightly affected with reduced final body weight by 6% compared to controls. Therefore a direct compound-related effect on testes

cannot be ruled out. On the contrary, effects on ovary and uterus observed at the top dose are considered most likely to be secondary to the general delay in both growth and development (decreased body weight gain by 83% and the body weight by 26% compared to the control at the end of study). Furthermore in the 1-year dog study, such were not observed at any dose levels.

5) <u>Guidelined 1-year dog study OECD 452 (1981)</u> (Refer Annex I Vol3CA B.6.3.3)

Sexual function and fertility:

Organ weights:
Analysis of absolute and relative organ weights indicated a decrease in absolute (-16%) and relative (-15%) testis weights in 1500 ppm animals. Lower ovary weights in females at 750 and 1500 ppm did not have histopathological correlates and are therefore considered incidental.

Organ weight changes

Organ	**Dose level (ppm)**	**Males**					**Females**				
		0	**25**	**150**	**750**	**1500**	**0**	**25**	**150**	**750**	**1500**
Carcass (kg)	absolute	11.46	11.43	11.80	10.95	11.17	10.56	10.27	10.38	9.61	10.46
Testes/Ovaries	absolute	19.07	20.48	19.83	20.65	16.06	1.51	1.10	1.66	1.06	1.03

- : negative trend ($p \leq 0.01$, Jonckheere) [a]: (g); [b] : % body weight x 10

Microscopic findings:

Histopathological examination of tissues/organs revealed a higher incidence of tubular atrophy in the testes at 750 and 1500 ppm; as this observation was also made in control animals. In control and low dose animals affected the change was only seen unilaterally in a small group of tubuli whereas a larger number of tubuli were affected in animals at 750 and 1500 ppm, and tubular atrophy was present bilaterally in both affected animals of the high dose group and one animal at 750 ppm. At 1500 ppm, the observation correlated with reduced testis weights in two animals.

Incidence of histopathology findings in testes

		Males				
Dose Level [ppm]		0	25	150	750	1500
Testes	No. exam.	4	4	4	4	4
tubular atrophy		1	1	1	2	2
spermatid giant cells		2	1	1	-	1
inflammatory cell infiltration		-	-	1	-	-

Other toxic effects:
Increased plasma creatinine and urea levels were observed in both sexes from 750 ppm onwards. At 1500 ppm, decreased prothrombin time was observed in sexes as well as minimally lower albumin levels and albumin/globulin ratios in females.

Bodyweight and weight gain:

The overall body weight gain of males at 1500ppm was reduced by 26% during the study compared to controls but this decrease may be more a consequence of the higher initial bodyweight in top dose males (380 g more) than a treatment -related effect indeed, the final body weight was not affected (1% higher than controls). Other male groups were unaffected by treatment. Transient body weight loss occurred in females at 1500ppm at study start, but body weight subsequently increased and overall weight gain was comparable to the controls.

Intergroup comparison of mean body weight selected time points

Weight	Dietary Concentration of CGA 293343 tech. (ppm)									
	Males					Females				
week	0	25	150	750	1500	0	25	150	750	1500
week –1	11.30	11.28	11.63	11.18	11.68	9.675	9.400	9.875	9.925	9.800
week 13	11.65	11.50	11.80	11.35	11.83	10.58	10.23	10.58	9.975	10.43
week 26	11.88	11.85	12.03	11.75	12.00	10.63	10.55	10.75	10.00	10.73
week 39	12.28	12.33	12.58	12.05	11.98	11.13	11.03	11.38	10.30	11.28
week 52	12.25	12.40	12.75	12.18	12.38	11.30	11.15	11.33	10.48	11.55
Week 52 % of control value		-1.2	+4	-0.6	+1		-1.3	+0.3	-7.3	+2.2

Mean body weights at start and cumulative body weight gains (kg)

	Dietary Concentration of CGA 293343 tech. (ppm)									
	Males					Females				
week	0	25	150	750	1500	0	25	150	750	1500
Weight week –1	11.30	11.28	11.63	11.18	11.68	9.675	9.400	9.875	9.925	9.800
Gain at week 13	0.350	0.225	0.175	0.175	0.150	0.900	0.825	0.800	0.050	0.625
Gain at week 26	0.575	0.575	0.400	0.575	0.325	0.950	1.150	0.875	0.075	0.925
Gain at week 39	0.975	1.050	0.950	0.875	0.300	1.450	1.625	1.500	0.375	1.475
Gain at week 52	0.950	1.125	1.125	1.000	0.700 (-26%)	1.625	1.750	1.450	0.550 (-66%)	1.750

CONCLUSION: Increased incidence of tubular atrophy was observed from 750 ppm onwards associated with s decreased testes weights at 1500 ppm. while decreased bw gain was observed in top dose males compared to controls, this decrease may be more a consequence of the higher initial bodyweight in top dose males (380 g more) than a treatment -related effect since the final body weight was not affected (1% higher than controls).

Overall summary:

Below, effects on sexual function/fertility and co-occurring other toxic effects observed in the available studies are summarised in a parallel dose response-table in order to assess transparently the severity of the effects on sexual function and fertility along with general toxicity.

In the 2-generations studies, effects on testes were observed in F1 generation but not in F0 generation. In the first study, there was an increased incidence and severity of testicular tubular atrophy in F1 males from 30 ppm (1.8 mg/kg bw/day) onwards while in the second study significant reduced number of sperm cells was observed in F1 males from 50 ppm (3.0 mg/kg bw/day) onwards. At the top dose level, slight delayed preputial separation, increased incidence of germ cell loss/disorganisation, Sertoli cell vacuolation and decreased sperm velocity parameters were also observed in F1 males. General toxicity was limited to renal effects (α-2µ globulin nephropathy) in males from 1000 ppm onwards and slight effect on male bodyweight gain at the highest dose (2500 ppm). No adverse effect on female adults was highlighted in both the two 2-generation studies.
Delayed male puberty was also observed in the DNT study in presence of moderate maternal toxicity (18% decreased body weight gain during gestation).
In F1 generation testicular tubular atrophy, reduced in number of sperm cells and delayed puberty observed in the absence of an overt general toxicity and as such are not considered secondary to non-specific marked systemic toxicity.
While no correlated effects in fertility parameters were observed in both of the 2-generation studies, it is noteworthy that sperm count in rodents must be drastically reduced before an effect on fertility is seen (OECD, ENV/JM/MONO(2008)16). Therefore, effects on reproductive system of the F1 generation are considered adverse.

Testicular affects was also observed in dogs in the 90-d and 1-year studies. While, decreased body weight gain was observed at the same dose level in the 90-d study, final body weight was slightly affected. In the 1-year dog study increased incidence of tubular atrophy was observed from the mid-dose onwards and reduced body weight gain was observed only at the high dose levels with no impact on final body weight. Therefore those effects cannot be ruled out as secondary to severe general toxicity.

Study type	**Effects on sexual function and fertility:**	**General toxicity**	**Reference**
2-generation OECD 416 0, 10, 30, 1000, 2500ppm (♂: 0, 0.6, 1.8, 61 or 158 mg/kg bw/day, ♀: 0, 0.8, 2.4, 79 or 202 mg/kg bw/day)	From 30 ppm **Testis:** Increased incidence and severity of testicular tubular atrophy in F1 males. At 2500 ppm **Testis:** Statistically significant decrease of F1 absolute testis weight.	At 10 and 30 ppm : No effect From 1000 ppm Increased incidence of hyaline change in renal tubules (F0 and F1 males). At 2500 ppm Reduced food consumption and decreased body weight gain (≤ 10%) of F0 and F1 males during first premating period	[redacted] (1998)
2-generation OECD 416 0, 20, 50, 1000, 2500ppm (♂: 0, 1.2, 3, 61.7 or 155.6 mg/kg bw/day, ♀: 0, 1.7, 4.3, 84.4 or 208.8 mg/kg bw/day)	From 50 ppm **Testis:** **S**ignificant reduced number of sperm cells in F1 males From 1000 ppm **Testis:** Dose-related increase in epididymal and testes weights in F1 males At 2500 ppm Slight delayed preputial separation (1 day). **Testis:** Increased incidence of germ cell loss/disorganisation and Sertoli cell vacuolation in F1 males. F1 sperm velocity parameters statistically significantly lower.	At 20 and 50 ppm : No effect From 1000 ppm Increased incidence of hyaline change in renal tubules (F0 and F1 males) At 2500 ppm Reduced food consumption and decreased body weight gain F0 males (↓6.7% between week 1 and week 28). No effect on terminal bw in F1 males	[redacted] (2004a)
Developmental Neurotoxicity Study in Rats OECD 426 (Level 4, *in vivo*) 0, 50, 400 or 4000 ppm (0, 4.3, 35.5 or 298.7 mg/kg bw/day) GD7 to PND22	At 4000 ppm Delayed balano- preputial separation (1.5 day)	At 4000 ppm: **Dams:** Decreased BW gain (↓12% during gestation) and food consumption **Offspring :** Decreased pup BW at birth (8%) Bw remained lower than controls throughout the study (maximum effect 13% on day 18)	[redacted], (1996b)
90-days oral study in dogs OECD 409 (Level 4, in vivo) 0, 50, 250, 1000 and 2500/2000 ppm	At 2500/2000 ppm **Ovary:** stat reduced absolute and relative weights Immature stage of ovarian development in 3 / 4 females **Uterus:** Immature stage of uterus in 2 / 4 females **Testis:** Tubular atrophy, reduced spermatogenesis and presence of spermatic giant cells. Statistically	At 2500/2000 ppm In females: Reduced bwg by 83% and bw by 26% In males: reduced bwg 36% but bw slightly affected with reduced final body weight by 6% compared to controls	[redacted]. (1996b)

	significant reduced absolute and relative weights.		
12-month oral study in dogs OECD 452 (Level 4, in vivo) 0, 25, 150, 750 and 1500 ppm	From 750 ppm: **Testis:** increased incidence and severity of tubular atrophy At 1500 ppm: **Testis:** reduced absolute and relative weights	From 750 ppm: Increased plasma creatinine and urea levels in both sexes**.** No effect on bw at any dose level	[redacted]. (1998)

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

In the classification system, reproductive toxicity is subdivided under two main headings: Adverse effects on sexual function and fertility and Adverse effects on development of the offspring.

Adverse effects on sexual function and fertility
Any effect of substances that has the potential to interfere with sexual function and fertility: This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

There is no available human data showing thiamethoxam has reproductive toxicity in humans.
Cat 1A is therefore not triggered.

In repeat dose studies in rat and mice, no effect on reproductive organs was observed.
Tubular atrophy in testis was observed in the 90-d and 1-year dog studies in the presence of slight general toxicity.
In the two multigenerational studies, no effect on F0 reproductive system was observed. Mating, fertility, gestation, survival indexes and reproductive performance remained unaffected by treatment with thiamethoxam even at the highest dose level that induced slight general toxicity in both generations. Sperm parameters were not affected in F0 males.
However, in both of the 2-generation studies in rat, testicular effects were observed in the F1 males in the absence of general toxicity (testicular atrophy in the first study and decreased sperm cells in the second one). At the top dose level, in presence of slight general toxicity, delayed preputial separation, increased incidence of germ cell loss/disorganization, Sertoli cell vacuolation and decreased sperm velocity parameters were also observed in F1 males.

Since fertility and reproductive performance were not impacted by treatment with thiamethoxam, the effects observed in rat offspring are considered to provide some evidence of an effect on reproductive system, but not sufficient to place the substance in category 1B.

Furthermore, as effects on postnatal reproductive development observed in rat offspring (testicular atrophy, decreased sperm cells and delayed balano-preputial separation observed in F1 generation) could be considered as effects on fertility as well as effects on development, no specification (f or d) is proposed.

Thiamethoxam needs to be classified as Reproductive toxicant Cat. 2 H361 according to Regulation (EC) 1272/2008.

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

Table 46: Summary table of animal studies on adverse effects on development

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL (for parent, offspring and for developmental effects) - target tissue/organ - critical effects at the LOAEL**	**Reference**
Developmental toxicity study in rat OECD Guideline 414 (1981) GLP Acceptable Rat, Sprague-Dawley Tif: RAIf, SPF 24/group	Thiamethoxam technical Batch P.50600 (purity 98.6%) 0, 5, 30, 200, 750 mg/kg bw/day Gavage GD 6-15	**At 5 and 30 mg/kg bw/day** No difference from control. **From 200 mg/kg bw/day** **Dams:** Decreased corrected BW gain and food consumption. **Foetus:** No differences from control. **At 750 mg/kg bw/day** **Dams:** Corrected bw loss day GD7-GD11, piloerection, hypoactivity, regurgitation of test material **Foetus:** Decreased fetal weight, delayed ossification, increased incidence of skeletal anomalies (asymmetrically shaped sternebrae 6 and irregular ossification of the occipital bone). **Maternal NOAEL: 30 mg/kg bw/day** **Developmental NOAEL: 200 mg/kg bw/day**	(1996) Refer to Annex I. Vol3CA B.6.6.2.1
Developmental toxicity study in rabbit OECD Guideline 414 (1981) GLP Acceptable Rabbit, Russian Chbb:HM 19/group	Thiamethoxam technical Batch P.50600 (purity 98.6%) 0, 5, 15, 50, 150 mg/kg bw/day Gavage GD 7-19	**At 5 and 15 mg/kg bw/day** No difference from control. **From 50 mg/kg bw/day** **Dams:** Decreased BW gain and food consumption. **Foetus:** No treatment related effect **At 150 mg/kg bw/day** **Dams:** 3 deaths, bw loss and hemorrhagic uterine contents, hemorrhagic discharge in the perineal area. **Foetus:** Increased post implantation loss, decreased fetal weight, delayed ossification, increased incidence of skeletal variations. **Maternal NOAEL: 15 mg/kg bw/day** **Developmental NOAEL : 50 mg/kg bw/day**	(1996a Refer to Annex I. Vol3CA B.6.6.2.2
Developmental Neurotoxicity Study OECD Guideline 426	Thiamethoxam technical Batch P. 506006 (Purity: 98.8%)	**At 50 ppm (4.3 mg/kg bw per day) and 400 ppm (34.5 mg/kg bw per day):** No difference from control.	, 2003 & 2006 Refer to Annex I. Vol3CA B.6.7.1.3

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL (for parent, offspring and for developmental effects) - target tissue/organ - critical effects at the LOAEL**	**Reference**
GLP Acceptable Rat, Wistar Alpk:APrSD 30 time-mated females/group	0, 50, 400 or 4000 ppm (0, 4.3, 34.5 or 298.7 mg/kg bw/day) From GD7 to PND22 in diet	**At 4000 ppm (298.7 mg/kg bw/day):** Maternal toxicity: Decreased BW gain (↓12% during gestation) and food consumption **Maternal NOAEL: 400 ppm (34.5 mg/kg bw per day)** Developmental toxicity : - Decreased pup BW at birth and decreased BW gain in males and females. - Delayed sexual maturation in males - Neurotoxicity Decreased absolute brain weight. Morphometric changes: At Day 12: ↓length and width of the cerebellum in males At Day 63: ↓in Level 3-5 measurements in males and in Level 4-5 in females **Developmental NOAEL (general toxicity and neurotoxicity): 400 ppm (34.5 mg/kg bw/day)**	
2-generation reproduction study OECD Guideline 416 (1981) GLP Acceptable Rat, Sprague-Dawley Tif: RAIf, SPF 30/sex/group	Thiamethoxam technical Batch P.50600 (purity 98.6%) 0, 10, 30, 1000, 2500ppm (♂: 0, 0.6, 1.8, 61 or 158 mg/kg bw/day, ♀: 0, 0.8, 2.4, 79 or 202 mg/kg bw/day) In the diet	**At 10 ppm (♂/♀): 0.6/0.8 mg/kg bw/day** No difference from controls. **From 30 ppm (♂/♀): 1.8/2.4 mg/kg bw/day** **Paternal toxicity :** No effect **Maternal toxicity :** No effect **Development:** increased incidence and severity of tubular atrophy observed in testes of F1 males (no effect in F0 males). **From 1000 ppm (♂/♀): 61/79 mg/kg bw/day** **Paternal toxicity:** *increased incidence of hyaline change in renal tubules (F0 and F1 males) not relevant for human risk assessment.* **Maternal toxicity :** No effect **Development: :** reduced body weight gain of F2a and F2b pups during late lactation **At 2500 ppm (♂/♀): 158/202 mg/kg bw/day** **Paternal toxicity**: transient reduced food consumption and slight decreased body weight gain of F0 weeks 1-6 (10%). In F1 lower body weights at selection remained lower than controls thereafter. **Maternal toxicity :** No effect **Development:** reduced body weight gain of	(1998) Refer to Annex I. Vol3CA B.6.6.1.1

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for parent, offspring and for developmental effects)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
		F1a and F1b during late lactation. Statistically significant decrease of F1 abs testis weight (no effect in F0 males). **Paternal NOAEL: 1000 ppm (eq. to: 61 mg/kg bw/day)** ***NOAEL kidney effects in males : 30ppm eq.to: 1.8 mg/kg bw (not relevant for human risk assessment)*** **Maternal NOAEL : 10 ppm (eq. to: 0.6 mg/kg bw/day)** **Developmental NOAEL: 10 ppm (eq. to: 0.6 mg/kg bw/day)**	
2-generation reproduction study OECD Guideline 416 (2001) GLP Acceptable Rat, Sprague-Dawley Tif: RAIf, SPF 26/sex/group	Thiamethoxam technical Batch P.50600 (purity 98.6%) 0, 20, 50, 1000, 2500ppm (♂: 0, 1.2, 3, 61.7 or 155.6 mg/kg bw/day, ♀: 0, 1.7, 4.3, 84.4 or 208.8 mg/kg bw/day) In the diet	~~**At 20 ppm (♂/♀): 1.2/1.7 mg/kg bw/day**~~ No difference from controls. **From 50 ppm (♂/♀): 3.0/ 4.3 mg/kg bw/day** **Paternal toxicity :** No effect **Maternal toxicity :** No effect **Development:** significant reduced number of sperm cells in F1 males (no effect in F0 males). **From 1000 ppm (♂/♀): 61.7/84.4 mg/kg bw/day** **Paternal toxicity:** *increased incidence of hyaline change in renal tubules (F0 and F1 males) not relevant for human risk assessment.* **Maternal toxicity :** No effect **Development:** dose-related increase in epididymal and testes weights in F1 males (no effect in F0 males). **At 2500 ppm (♂/♀): 155.6/208.8 mg/kg bw/day** **Paternal toxicity:** reduced food consumption and decreased body weight gain F0 males. **Maternal toxicity :** No effect **Sexual function and fertility**: reduced total litter weight of the F1A pups. Delayed preputial separation. Increased incidence of germ cell loss/disorganisation and Sertoli cell vacuolation in F1 males. F1 sperm velocity parameters statistically significantly lower. **Paternal NOAEL: 1000 ppm (eq. to: 61.7**	(2004) Refer to Annex I. Vol3CA B.6.6.1.2

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for parent, offspring and for developmental effects)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
		mg/kg bw/day) ***NOAEL kidney effects in males : 50 ppm eq.to: 3 mg/kg bw (not relevant for human risk assessment)*** **Maternal NOAEL: 2500 ppm (eq. to: 208.8 mg/kg bw/day)** **Developmental NOAEL: 20 ppm (eq. to: 1.2 mg/kg bw/day)**	

Table 47: Summary table of human data on adverse effects on development

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

Table 48: Summary table of other studies relevant for developmental toxicity

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

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

Studies on developmental toxicity/teratogenicity of thiamethoxam after oral administration by gavage were conducted in rats and rabbits. Furthermore effects on developmental toxicity were also identified in the available DNT and 2-generation studies.

1) **Guidelined rat oral teratogenicity OECD 414 (1981)** (refer to Vol3CA B.6.6.2.1)

In the teratogenicity study in rats reduced net BW gain and food consumption were observed in dams from 200 mg/kg bw/day, but signs of embryo-foetal toxicity (reduced foetal weight and interference with ossification) were only present at the highest dose tested. The maternal NOAEL was set at 30 mg/kg bw/day and the developmental NOAEL was 200 mg/kg bw/day.

Maternal toxicity:
At the highest dose, 17 dams had transient hypoactive behaviour and piloerection one hour after treatment start and lasting up to 4 days in a few animals.

Body weight and food consumption

Intergroup comparison of body weight gain (g) – selected time points

Days	Dose level (mg/kg bw/day)				
	0 (control)	5	30	200	750
6-11	25.6	25.2	25.4	18.5**	-1.0**
6-16	63.4	62.0	63.8	53.4**	33.9**
6-21	135.8	133.8	134.6	128.5	110.3**
Net change	36.8	40.1	36.3	25.9*	20.0**

* Statistically significant difference from control group mean, p<0.05

** Statistically significant difference from control group mean, p<0.01

Net change = carcass weight minus day 6 body weight

Intergroup comparison of food consumption (g/animal/day) – selected time points

Days	Dose level (mg/kg bw/day)				
	0 (control)	5	30	200	750
6-11	23.4	24.0	23.4	19.9**	10.8**
11-16	25.6	25.7	25.7	23.9	21.1**
16-21	25.9	27.3	25.9	26.3	28.8**

** Statistically significant difference from control group mean, p<0.01

Developmental Toxicity:

Pre & post-implantation losses, live litter size and sex ratios were similar in all groups.

At 750 mg/kg bw/day, mean foetal body weights were significantly lower than controls. At the same dose level, delayed ossification was observed resulting to increased incidence of asymmetrically shaped sternebra 6 and irregular ossification of the occipital bone increased incidence of poor ossification of sternebra 5, absent ossification of metatarsal 1, shortened rib 13, absent ossification of the proximal phalanx of anterior digits 2 & 5, poor or absent ossification of the distal or proximal phalanx of posterior digits 1 – 5.

Fetal body weight

Observation	Dose level (mg/kg bw/day)				
	0 (control)	5	30	200	750
Mean foetal body weight (g)	5.3	5.3	5.2	5.2	4.8**
Mean male foetal body weight (g)	5.4	5.4	5.3	5.3	4.9**
Mean female foetal body weight (g)	5.1	5.2	5.1	5.1	4.7**

** Statistically significant difference from control group mean, p<0.01

Selected foetal skeletal anomalies

Observations	Dose level (mg/kg bw/day)					HCD 1988-1995
Dose level [mg/kg b.w.]	**0**	**5**	**30**	**200**	**750**	
Litters evaluated	21	22	22	22	21	
Fetuses evaluated	154	150	158	166	150	
Fetal incidences Litter incidences	23 (14.9%) 9 (42.9%)	14 (9.3%) 10 (45.5%)	16 (10.1%) 9(40.9%)	12 (7.2%) 9(40.9%)	40 (26.7%) 17(81%)	
asymmetric sternebra 6						
Fetal incidences	4 (2.6%)	3 (2.0%)	2 (1.3%)	3 (1.8%)	11 (7.3%)	0.0-1.9%
Litter incidences	4 (19.0%)	2 (9.1%)	2 (9.1%)	3 (13.6%)	8 (38.1%)	0.0-12.5%
irregular /absent ossification of occipital bone						
Fetal incidences	3 (1.9%)	0 (0%)	2 (1.3%)	2 (1.2%)	12 (8.0%)*	0.0-4.2%
Litter incidences	2(9.5%)	0 (0%)	2 (9.1%)	1(4.5%)	7 (33.3%)	0.0-13.6%

* $p \leq 0.05$,

Skeletal variations

Dose level [mg/kg b.w.]	0	5	30	200	750
Litters evaluated	21	22	22	22	21
Fetuses evaluated	154	150	158	166	150
poor ossification of sternebra 5					
Fetal incidences	0(0%)	0(0%)	1 (0.6%)	0(0%)	10** (6.7%)
Litter incidences	0(0%)	0(0%)	1 (4.5%)	0(0%)	6* (28.6%)
absent ossification of metatarsal 1					
Fetal incidences	15(9.7%)	31*(20.7%)	24 (15.2%)	16(9.6%)	51** (34.0%)
Litter incidences	8(31.1%)	12(54.5%)	10 (45.5%)	7(31.8%)	19 (90.5%)
shortened 13th rib					
Fetal incidences	13(8.4%)	5(3.3%)	4* (2.5%)	21(12.7%)	27* (18%)
Litter incidences	7(33.3%)	3(13.6%)	4 (18.2%)	13(51.1%)	11 (52.4%)
Absent ossification of proximal phalanx anterior digit-2					
Fetal incidences	8(5.2%)	12(8.0%)	7 (4.4%)	6(3.6%)	27** (18%)
Litter incidences	6(28.6%)	6(27.3%)	3 (13.6%)	3 (13.6%)	12 (57.1%)
Absent ossification of proximal phalanx anterior digit-5					
Fetal incidences	15 (9.7%)	19 (12.7%)	11 (7.0%)	15 (9%)	41** (27.3%)
Litter incidences	9(42.9%)	10(45.5%)	6 (27.3%)	9(40.9%)	16 (76.2%)
Poor ossification distal phalanx posterior digit-1					
Fetal incidences	2 (1.3%)	1(0.7%)	4 (2.5%)	2(1.2%)	9* (6.0%)
Litter incidences	2(9.5%)	1(4.5%)	2 (9.1%)	2 (9.1%)	4(19%)
Absent ossification of proximal phalanx posterior digit-2					
Fetal incidences	61 (39.6%)	66(44.0%)	65(41.1%)	69(41.6%)	118** (78.7%)
Litter incidences	18(85.7%)	19(86.4%)	20 (90.9%)	19 (86.4%)	21(100%)
Poor ossification distal phalanx posterior digit-2					
Fetal incidences	2 (1.3%)	1(0.7%)	4(2.5%)	3(1.8%)	9* (6.0%)
Litter incidences	2(9.5%)	1(4.5%)	2 (9.1%)	3 (13.6%)	5(23.8%)
Absent ossification of proximal phalanx posterior digit-3					
Fetal incidences	46 (29.9%)	56(37.3%)	48(30.4%)	57(34.3%)	96** (64.0%)
Litter incidences	16(76.2%)	17(77.3%)	16 (72.7%)	17(77.3%)	21(100%)
Poor ossification distal phalanx posterior digit-3					
Fetal incidences	2 (1.3%)	1(0.7%)	4 (2.5%)	2(1.2%)	10* (6.7%)
Litter incidences	2(9.5%)	1(4.5%)	2 (9.1%)	2 (9.1%)	5(23.8%)
Absent ossification of proximal phalanx posterior digit-4					
Fetal incidences	46 (29.9%)	53(35.3%)	52 (32.9%)	66(39.8%)	97** (64.7%)
Litter incidences	16(76.2%)	16(72.73%)	17 (77.3%)	18(81.8%)	21(100%)
Poor ossification distal phalanx posterior digit-4					
Fetal incidences	2 (1.3%)	1(0.7%)	4 (2.5%)	2(1.2%)	10* (6.7%)
Litter incidences	2(9.5%)	1(4.5%)	2 (9.1%)	2 (9.1%)	5(23.8%)
Absent ossification of proximal phalanx posterior digit-5					
Fetal incidences	92 (59.7%)	85(56.7%)	100 (63.3%)	94(56.6%)	138** (92%)
Litter incidences	19(90.5%)	20(90.9%)	21 (95.5%)	21 (95.5%)	21(100%)

* = $p<0.05$, ** = $p \leq 0.01$

CONCLUSION: Maternal toxicity consisting of 30% and 46% decrease of corrected body weight gain was seen at 200 and 750 mg/kg bw/day respectively associated with decreased food consumption. At the highest dose level only, developmental toxicity consisted of reduced foetal weight and delayed ossification with increased incidence of foetal skeletal anomalies and variations consistent with delayed development resulting from or secondary to, significant maternal toxicity.

2) Guidelined rabbit oral teratogenicity OECD 414 (1981) (refer to Vol3CA B.6.6.2.2)

In the rabbits study, reduction in body weight gain was noted from 50 mg/kg bw/day onwards. At the highest dose level, severe maternal toxicity was observed consisting of marked weight loss, clinical signs and 3 deaths. At this dose level, signs of embryotoxicity were also seen consisting of reduced foetal weight, elevated post-implantation loss and interference with the ossification. The maternal NOAEL was set at 15 mg/kg bw/day and the developmental NOAEL at 50 mg/kg bw/day.

Maternal toxicity:

At the highest dose level, one death occurred as well as two other dams killed moribund. Bloody discharge in the perineal area was detected in a total of 13/19 dams in the high dose group between days 14 and 23.

Intergroup comparison of body weight gain (g) – selected time points

Days	Dose level (mg/kg bw/day)				
	0 (control)	**5**	**15**	**50**	**150**
7-12	-26	-23	-17	-30	-105**
12-16	57	69	73	47	38
16-20	21	-2	-17**	3	-6
7-19	51	61	40	17	-67**
7-29	114	144	167	134	38
Net change	-112	-159	-150	-160	-172

** Statistically significant difference from control group mean, p<0.01

Net change = carcass weight minus day 7 body weight

Intergroup comparison of food consumption (g/animal/day) – selected time points

Days	Dose level (mg/kg bw/day)				
	0 (control)	**5**	**15**	**50**	**150**
	N = 15	19	19	18	12
7-12	88.7	92.4	88.5	69.2**	21.4**
12-16	86.7	91.2	79.1	64.2**	38.5**
16-20	96.3	95.9	88.5	80.6	56.8**
20-24	96.3	99.2	93.1	100.9	125.1*
24-29	93.4	96.8	100.3	103.3	121.6*

* Statistically significant difference from control group mean, p<0.05

** Statistically significant difference from control group mean, p<0.01

Developmental Toxicity:

There was a higher post-implantation loss at the high dose due to an increase in early resorptions. Increased numbers of post-implantation losses in 3 high dose dams resulted from total resorption and were considered treatment-related.

There was no evidence of teratogenicity.

At the top dose, decreased fetal weight was observed as well as interference with ossification resulting to increased incidence of skeletal variations.

Caesarean section observations

Observation	Dose level (mg/kg bw/day)				
	0 (control)	**5**	**15**	**50**	**150**
Number of females inseminated	19	19	19	19	19
Number not pregnant	4	0	0	0	1
Number pregnant, premature deaths	0	0	0	0	3
Number pregnant at term	15	19	19	19	15
Number with total resorption at term	0	0	0	1	3
Number with live foetuses at term	15	19	19	18	12
Gravid uterus weight (g)	226	303	316	294	210
Mean number of corpora lutea	6.7	7.2	7.2	6.9	7.1

Mean number of implantation sites	4.7	5.4	5.9	5.4	5.4
% Pre-implantation loss	32.6	23.1	17.5	23.7	25.1
Mean number live foetuses	3.7	5.1	5.4	4.6	3.0
Mean number early resorptions	1.0	0.3	0.5	0.6	2.4
Mean number late resorptions	0.0	0.0	0.1	0.2	0.0
% post implantation loss	21.0	6.3	9.9	16.3	45.6
Total number viable foetuses - males	31	48	46	46	22
Total number viable foetuses - females	24	49	56	40	23
% Males	56.4	49.5	45.1	53.5	48.9
Mean foetal body weight (g)	44.0	41.5	41.7	42.1	37.5**
Mean male foetal body weight (g)	44.4	41.7	43.0	42.2	38.8**
Mean female foetal body weight (g)	41.8	40.9	40.8	41.1	36.6*

* Statistically significant difference from control group mean, $p<0.05$

** Statistically significant difference from control group mean, $p<0.01$

Incidence of selected foetal skeletal anomalies and variations

Dose level [mg/kg bw]	0	5	15	50	150
Fetuses evaluated	55	97	102	88	45
Litters evaluated	15	19	19	18	12
Skeletal anomalies:					
Fetal incidence	8 (14.5%)	9 (9.3%)	7 (6.9%)	5 (5.7%)	11(24.4%)
Litter incidence	4(26.7%)	7(36.8%)	6(31.6%)	5(27.8%)	6 (50%)
Fused sternebrae 3 and 4					
Fetal incidence	0 (0%)	0 (0%)	2 (2.0%)	1 (1.1%)	5*(11.1%)
Litter incidence	0 (0%)	0 (0%)	1(5.3%)	1 (5.6%)	3 (25%)
Historical control mean (range)%#					
Fetal incidence	2.7% (0-9.2%)				
Litter incidence	13.3% (0-33.3%)				
Skeletal variations:					
Fetal incidence	39(70.9%)	76(78.4%)	81(79.4%)	70(79.5%)	34(75.6%)
Litter incidence	15(100%)	19(100%)	19(100%)	18(100%)	11(91.7%)
Absent ossification of the medial phalanx (anterior digit-5)					
Fetal incidence	0 (0%)	1 (1.0%)	0 (0%)	0 (0%)	4* (8.9%)
Litter incidence	0 (0%)	1(5.3%)	0 (0%)	0 (0%)	3 (25%)
Historical control mean (range)%					
Fetal incidence	1.5(0-9.2%)				
Litter incidence	6.5(0-26.7%)				

* $p \leq 0.05$; ** $p \leq 0.01$ #: HCD same strain in the same laboratory 1990-1995

CONCLUSION: In dams, reduced weight gain and food consumption were observed from 50 mg/kg bw/day. Additionally, at 150 mg/kg morbidity (3), vaginal bloody discharge, reduced body weight gain and food consumption and uterine contents haemorrhagic were recorded in dams.

Fetal toxicity was only observed at 150 mg/kg bw/day including reduced fetal weights, an increase number of post-implantation loss, delayed ossification and increased incidence of skeletal anomalies and variations.

3) Guidelined Developmental neurotoxicity study OECD (426) (Refer to Annex I Vol3CA B.6.7.1.3)

In the developmental neurotoxicity study, the maternal toxicity was observed at the top dose consisting of reduced body weight gain (↓12%) and food consumption observed at 4000 ppm (298.7 mg/kg bw/day) during gestation (refer to 2.6.1.1).

At the same dose level, both general and neurodevelopmental toxicity were seen: decreased F1 body weight at birth and body weight gain in male, delayed sexual maturation in males (refer to 2.6.1.1), reduced absolute brain weight and morphometric changes in males and females observed at 4000 ppm (298.7 mg/kg bw/day).

The morphometric changes consisted of decreased length and width of the cerebellum in males on day 12, and significant decreases in Level 3-5 measurements in males and in Level 4-5 measurements in females on day 63.

F1 bodyweights; mean and adjusted mean at day 5, by analysis of covariance on day 1 mean bodyweights)

		Dose level of TMX (ppm)							
		Males				**Females**			
Day		**0**	**50**	**400**	**4000**	**0**	**50**	**400**	**4000**
1	mean	6.1	5.9	6.0	5.7*	5.8	5.6	5.6	5.3**
5	mean	10.1	9.9	9.8	8.9**	9.5	9.3	9.3	8.4**
5	Adjusted mean	9.8	9.8	9.7	9.3**	9.3	9.3	9.2	8.9*

* Statistically significant difference from control group mean, p<0.05 (Student's t-test, 2-sided)

** Statistically significant difference from control group mean, p<0.01 (Student's t-test, 2-sided)

The bodyweights of male and female pups born of dams fed 4000 ppm TMX were statistically significantly lower than controls on day 12 (by approximately 12-15%) and on day 63 (by approximately 6-9%). However since brain weight is relatively insensitive to body weight change, the decreased absolute brain weight observed on Day 12 and Day 63 cannot be disregarded as only secondary to decreased bodyweight.

According to OPPTS 870.6300 (1998) "A change in brain weight is considered to be a biologically significant effect. This is true regardless of changes in body weight, because brain weight is generally protected during undernutrition or weight loss, unlike many other organs or tissues. It is inappropriate to express brain weight changes as a ratio of body weight and thereby dismiss changes in absolute brain weight."

Intergroup comparison of brain weights - F1 animals

	Dose level of TMX (ppm)							
	Males				**Females**			
	0	**50**	**400**	**4000**	**0**	**50**	**400**	**4000**
	Day 12 fixed brain							
Terminal BW(g) (%decrease)	23.5±1.3	24.8±1.5	24.8±1.7	20.7±1.6 (12%)	24.0±2.7	22.9±2.4	23.0±.2.5	20.5±1.9 (15%)
Brain weight(g) (%decrease)	1.15±0.04	1.16±0.04	1.13±0.04	1.10±0.05* (4%)	1.11±0.05	1.09±0.05	1.10±0.04	1.06±0.04* (5%)
Brain weight adjusted to BW	1.15	1.14	1.12	1.13	1.10	1.08	1.10	1.09
Brain-to-BW ratio (%)	4.90	4.68	4.59	5.34	4.68	4.76	4.83	5.23
	Day 63 fixed brain							
Terminal BW(g) (%decrease)	372.3±18.8	361.1±28.2	370.8±20.8	346.8±22.8 (7%)	233.4119.8	221.8±21.2	222.5=16.3	218.7=14.1 (6%)
Brain weight(g) (%decrease)	2.07±0.09	2.02±0.06	2.04±0.07	1.99±0.09* (4%)	1.90±0.09	1.89±0.07	1.86±0.07	1.86±0.08 (2%)
Brain weight adjusted to BW	2.06	2.02	2.03	2.01	1.88	1.90	1.87	1.87
Brain-to-BW ratio (%)	0.56	0.56	0.55	0.58	0.82	0.86	0.84	0.85
	Day 63 Post-perfusion							
Terminal BW(g) (%decrease)	369.4±19.5	363.53±2.2	355.4±26.6	341.6±11.2 (8%)	227.6±17.0	220.3±17.9	217.6±13.5	206.6±19.9 (9%)
Brain weight(g) (%decrease)	2.03±0.12	2.01±0.15	2.00±0.08	1.93±0.07* (5%)	1.89±0.10	1.89±0.07	1.82±0.06* (4%)	1.80±0.08* (5%)
Brain weight adjusted to BW	1.99	1.99	2.01	1.97	1.87	1.88	1.82	1.82
Brain-to-BW ratio (%)	0.55	0.55	0.57	0.56	0.83	0.86	0.84	0.88

* Statistically significant difference from control group mean, $p<0.05$ (Student's t-test, 2-sided)

Selected brain morphometry findings with low and intermediate dose investigated at day 12

Parameters		**Control**	**50 ppm**	**400 ppm**	**4000 ppm**	**HCD range**
Males Day 12						
Level 4						
Corpus Callosum Thickness (mm)	Mean ± SD	0.57±0.11	0.53±0.06 (↓7%)	0.58±0.05	0.55±0.06 (↓4%)	0.58±0.09 to 0.687±0.12
	Adjusted Mean	0.58	0.54	0.59	0.53	
Thalamus – Width (mm)	Mean ± SD	7.54±0.43	7.22±0.22 (↓4%)	7.49±0.23	7.37±0.47 (↓3.2%)	7.48 ± 0.36 to 8.35 ± 0.57
	Adjusted Mean	7.53	7.11*	7.40	7.55	
Cerebellum						
Cerebellum Length (mm)	Mean ± SD	4.41±0.32	4.22±0.15	4.22±0.32	4.11±0.29* (↓6.8%)	3.71± 0.31 to 4.45 ± 0.14
	Adjusted Mean	4.40	4.11*	4.09**	4.34	
Thickness of Molecular Layer (µm) PPF	Mean ± SD	63.8±9.0	61.0±6.9 (↓6%)	63.6±4.4 (↓4%)	56.0±6.1** (↓12%)	45.41± 10.8 to 79.9 ± 12.8
	Adjusted Mean	63.7	59.2	61.7	59.5	

The morphological changes were not associated with neuro-histopathological finding or change in functional or neurobehavioral parameters. However, it should be noted that the Y-maze for learning and memory assessment is a low sensitivity assay of behavioural change unless associated with appropriate difficulty tasks, which was not the case in the present study.

Moreover, at termination the same neuroanatomic regions were affected for both males and females (i.e.: dorsal cortex, thalamus and hippocampus) and the morphometric changes went in the same direction (consistent pattern of decreased morphometric measurements).
Furthermore neuroanatomic location makes biological sense. Indeed, thiamethoxam is a neonicotinoid with pesticidal mode of action based on nicotinic acetylcholine receptor (nAChR) agonist property.
The nAChRs are expressed in several brain structures such as cerebellum, hippocampus, entorhinal cortex, basal ganglia and thalamus (Court et al., 2000).
Moreover, α4β2 nAChR (high expression of α4 subunit in human foetal brain) is believed to play a morphogenic role during central nervous system development, while α7 nAChR subtype is believed to regulate neuronal growth, differentiation, synaptogenesis during brain development (EFSA Journal 2013;11(12):3471).

Selected brain morphometry findings with low and intermediate dose investigated at day 63

Parameters		Control	50 ppm	400 ppm	4000 ppm	HCD range
Males Day 63						
Level 3						
Dorsal Cortex 1 - Thickness	Mean ± SD	1.58 ± 0.12	1.35 ± 0.11** (↓15%)	1.37 ± 0.12** (↓13%)	1.40 ± 0.11** (↓11%)	1.22 ± 0.11 to 1.53 ± 0.11
	Adjusted Mean	1.58	1.35**	1.37**	1.40**	
Dorsal Cortex 2 - Thickness	Mean ± SD	1.88 ± 0.1.1	1.87±0.10	1.87±0.10	1.74 ±0.16 (↓7%)	1.48 ±0.19 to 1.77 ± 0.11
	Adjusted Mean	1.90	1.88	1.87	1.72**	
Piriform Cortex - Thickness	Mean ± SD	1.52 ± 0.18	1.51 ± 0.06	1.49 ± 0.03	1.38± 0.12** (↓9%)	1.05 ±0.11 to 1.38 ± 0.09
	Adjusted Mean	1.52	1.51	1.49	1.38**	
Level 4						
Dorsal Cortex - Thickness	Mean ± SD	1.53 ± 0.16	1.46 ± 0.08 (↓5%)	1.46 ± 0.08 (↓5%)	1.36 ± 0.09** (↓11%)	1.11± 0.17 to 1.53 ± 0.16
	Adjusted Mean	1.53	1.46	1.46	1.36**	
Corpus Callosum - Thickness	Mean ± SD	0.46 ± 0.06	0.41 ± 0.04 (↓11%)	0.44 ± 0.04 (↓11%)	0.37 ± 0.09** (↓20%)	0.31±0.08 to 0.46 ± 0.11
	Adjusted Mean	0.45	0.41	0.44	0.38*	
Thalamus - Height	Mean ± SD	5.64 ± 0.46	5.37 ± 0.24	5.55 ± 0.28	5.02 ± 0.47** (↓11%)	5.03±0.26 to 5.42 ± 0.34
	Adjusted Mean	5.61	5.35	5.55	5.07**	
Thalamus - Width	Mean ± SD	8.98 ± 0.55	8.73±0.34	8.58±0.22* (↓4%)	8.39 ± 0.31** (↓7%)	7.48±0.36 to 8.37 ± 0.38
	Adjusted Mean	8.94	8.70	8.58*	8.46*	
Thalamus/Cortex – Overall width	Mean ± SD	14.82 ± 0.66	14.14±0.69* (↓5%)	14.18±0.44* (↓4%)	14.08 ± 0.60* (↓5%)	14.2±0.5 to 14.7± 0.6
	Adjusted Mean	14.81	14.12*	14.18*	14.12	
Hippocampus – Width Dentate Gyrus	Mean ± SD	0.64 ± 0.05	0.61 ± 0.05 (↓5%)	0.61 ± 0.03 (↓5%)	0.58 ± 0.05** (↓9%)	0.54 ± 0.05 to 0.64± 0.07
	Adjusted Mean	0.64	0.60	0.61	0.59*	
Level 5						
Dorsal Cortex - Thickness	Mean ± SD	1.40±0.07	1.43±0.10	1.42±0.07	1.32±0.12 * (↓6%)	1.19 ± 0.1 to 1.39 ± 0.13
	Adjusted Mean	1.40	1.42	1.42	1.33	
Thalamus - width	Mean ± SD	8.11 ± 0.51	8.04 ± 0.26	7.93 ± 0.18	7.49 ± 0.39** (↓8%)	7.41 ± 0.39 to 7.98 ± 0.25
	Adjusted Mean	8.10	8.03	7.93	7.51**	
Hippocampus width overall	Mean ± SD	1.55 ± 0.12	1.54 ± 0.10	1.61 ± 0.07	1.45 ± 0.15* (↓6%)	1.55 ± 0.12 to 1.55 ± 0.12
	Adjusted Mean	1.56	1.54	1.61	1.45*	
Females Day 63						
Level 3						
Dorsal Cortex 1 - Thickness	Mean ± SD	1.51 ± 0.10	1.50 ± 0.10	1.48 ± 0.09	1.46 ± 0.09	1.22 ± 0.10 to 1.46 ± 0.11
	Adjusted Mean	1.54	1.51	1.48	1.41*	
Dorsal Cortex 2 - Thickness	Mean ± SD	1.78 ± 0.13	1.64 ± 0.12** (↓8%)	1.71 ± 0.13	1.71 ± 0.11	1.47 ± 0.06 to 1.73 ± 0.12

	Adjusted Mean	1.79	1.64**	1.71	1.70	
Piriform Cortex - Thickness	Mean ± SD	1.41 ± 0.14	1.41 ± 0.03	1.39 ± 0.05	1.40± 0.14	1.09 ± 0.12 to 1.37 ± 0.15
	Adjusted Mean	1.41	1.41	1.39	1.41	
Level 4						
Dorsal Cortex - Thickness	Mean ± SD	1.41 ± 0.12	1.42 ± 0.04	1.41 ± 0.05	1.29 ± 0.11** (↓9%)	1.16 ± 0.09 to 1.43 ± 0.09
	Adjusted Mean	1.41	1.42	1.41	1.30*	
Corpus Callosum - Thickness	Mean ± SD	0.39 ± 0.08	0.40 ± 0.04	0.39 ± 0.05	0.42 ± 0.09	0.30 ± 0.05 to 0.45 ± 0.10
	Adjusted Mean	0.39	0.40	0.39	0.43	
Thalamus - Height	Mean ± SD	5.27 ± 0.38	5.60 ± 0.24 (↑6%)	5.40 ± 0.46	5.40 ± 0.46	4.88 ± 0.43 to 5.42 ± 0.12
	Adjusted Mean	5.19	5.59*	5.40	5.25	
Thalamus - Width	Mean ± SD	8.46 ± 0.27	8.51 ± 0.26	8.73 ± 0.20* (↑3%)	8.01 ± 0.32** (↓5%)	8.19 ± 0.48 to 8.71 ± 0.40
	Adjusted Mean	8.44	8.50	8.73*	8.04**	
Thalamus/Cortex – Overall width	Mean ± SD	14.49 ± 0.50	14.41 ± 0.59	14.72 ± 0.72	13.5 ± 0.53** (↓7%)	13.6 ± 0.8 to 14.6 ± 0.2
	Adjusted Mean	14.44	14.40	14.73	13.55**	
Hippocampus – Width Dentate Gyrus	Mean ± SD	0.61 ± 0.06	0.59 ± 0.02	0.60 ± 0.02	0.58 ± 0.07	0.49 ± 0.04 to 0.62 ± 0.02
	Adjusted Mean	0.60	0.59	0.61	0.59	
Level 5						
Dorsal Cortex - Thickness	Mean ± SD	1.41 ± 0.06	1.39 ± 0.07	1.35 ± 0.07	1.33 ± 0.08** (↓6%)	1.19 ± 0.09 to 1.34 ± 0.07
	Adjusted Mean	1.40	1.39	1.35	1.33	
Thalamus - width	Mean ± SD	7.88 ± 0.34	7.65±0.32	7.74 ± 0.41	7.18 ± 0.31** (↓8%)	7.18 ± 0.35 to 7.72 ± 0.36
	Adjusted Mean	7.86	7.64	7.74	7.31**	
Hippocampus width overall	Mean ± SD	1.55 ± 0.08	1.50 ± 0.03	1.55 ±0.04	1.46 ± 0.08** (↓6%)	1.34 ± 0.06 to 71.58 ± 0.09
	Adjusted Mean	1.53	1.50	1.55	1.48	

* Statistically significant difference from control group mean, p<0.05 (Student's t-test, 2-sided)

** Statistically significant difference from control group mean, p<0.01 (Student's t-test, 2-sided)

Adjusted mean: bw as covariate.

Grey data: low-dose and mid-dose data analysed in the supplemental study (2007)

HCD: Historical control data from 11 studies (10/2001 and 10/2004). Concurrent control from this study not included as part of the range.

CONCLUSION: While the maternal and the offspring NOAELs were set at the same dose, it is considered that young animals exhibited increased susceptibility compared to adults since findings in the pups (reduced brain weight and significant changes in brain morphometric measurements) were more severe than those in the dams (decreased body weight gain and food consumption).

4) **First guidelined 2-generation study OECD 416 (1981)** (refer to Vol3CA B.6.6.1.1)

In this study, reduced body weight gain of F2a and F2b pups during late lactation was observed from 1000 ppm onwards and in all generations at 2500 ppm (see table in 2.6.6.3.1) while effects on body weight gain in adults was limited to F0 males at 2500 ppm (see table in 2.6.6.1.1).

Effects on reproductive postnatal development were also noted in F1 males (increased incidence and severity of tubular atrophy) from 30 ppm onwards which are summarised in 2.6.6.1.1.

5) **Second guidelined 2-generation study OECD 416 2001)** (refer to Vol3CA B.6.6.1.1)

In this study, reduced total litter weight of the F1A pups during late lactation was observed at the top dose (2500 ppm) (see table in 2.6.6.3.1). At the same dose level reduced food consumption and decreased body weight gain F0 males was noted (see table in 2.6.6.1.1).

Effects on reproductive postnatal development were also noted in F1 males (significant reduced number of sperm cells from 50 ppm, related increase in epididymal and testes weights from 1000 ppm, delayed preputial separation, increased incidence of germ cell loss/disorganisation and Sertoli cell vacuolation and lower sperm velocity parameters at 2500 ppm) which are summarised in 2.6.6.1.1.

Overall summary:

Below, effects on development and concurrent maternal toxicity/parental toxicity in the available studies are summarised in a parallel dose response-table in order to assess transparently the severity of the effects and the potential influence of maternal toxicity on developmental outcomes.

Study type (OECD Level, *in vivo* or *in vitro*)	**Developmental toxicity**	**Maternal/parental toxicity**	**Conclusion**	**Reference**
Rat oral teratogenicity study OECD 414 (Level 4, *in vivo*) 0, 5, 30, 200 and 750 mg/kg bw/day GD 6-15	**<u>At 750 mg/kg bw/day</u>** Decreased fetal weight, delayed ossification, increased incidence of skeletal anomalies	**<u>From 200 mg/kg bw/day</u>** **Dams:** Decreased corrected BW gain and food consumption. **<u>At 750 mg/kg bw/day</u>** **Dams:** Net bw loss day GD7-GD11, piloerection, hypoactivity, regurgitation of test material	**Developmental toxicity concomitant with severe maternal toxicity**	[redacted], (1996a)
Rabbit oral teratogenicity study OECD 414 (Level 4, *in vivo*) 0, 5, 15, 50 and 150 mg/kg bw/day GD 7-19	**<u>At 150 mg/kg bw/day</u>** Increased post implantation loss, decreased fetal weight, delayed ossification, increased incidence of skeletal anomalies.	**<u>At 50 mg/kg bw/day</u>** **Dams:** Decreased BW gain and food consumption. **<u>At 150 mg/kg bw/day</u>** **Dams:** 3 deaths, bw loss and hemorrhagic uterine contents, hemorrhagic discharge in the perineal area.	**Developmental toxicity concomitant with severe maternal toxicity**	[redacted], (1996b)
Developmental Neurotoxicity Study in Rats OECD 426 (Level 4, *in vivo*) 0, 50, 400 or 4000 ppm (0, 4.3, 35.5 or 298.7 mg/kg bw/day) GD7 to PND22	**<u>At 4000 ppm</u>** Decreased pup BW at birth (8%) Bw remained lower than controls throughout the study (maximum effect 13% on day 18) Decreased absolute brain weight + morphometric changes Delayed balano- preputial separation	**<u>At 4000 ppm:</u>** **Dams:** Decreased BW gain (↓12% during gestation) and food consumption	**Developmental toxicity concomitant with moderate maternal toxicity**	[redacted] 2003 & 2006
2-generation OECD 416 (Level 5, *in vivo*) 0, 10, 30, 1000, 2500ppm (♂: 0, 0.6, 1.8, 61 or 158 mg/kg bw/day, ♀: 0, 0.8, 2.4, 79 or	**<u>From 30 ppm</u>** **Testis:** Increased incidence and severity of testicular tubular atrophy in F1 males. **<u>From 1000 ppm</u>** Reduced body weight gain of F2a and F2b pups during	**From 1000 ppm** ——————— Increased incidence of hyaline change in renal tubules (F0 and F1 males).	**Toxicity on reproductive postnatal development in the absence of parental toxicity**	[redacted] (1998)

202 mg/kg bw/day)	late lactation and decreased **At 2500 ppm** Reduced body weight gain of F1a and F1b pups during late lactation and decreased body weight at weaning (# 10% compared to control). **Testis:** Statistically significant decrease of F1 absolute testis weight.	**At 2500 ppm** Reduced body weight gain of F1a and F1b pups during late lactation and decreased body weight at weaning (# 10% compared to control). Reduced food consumption and decreased body weight gain (≤ 10%) of F0 In F1 lower body weights at selection remained lower than controls thereafter. **NB: no severe general toxicity**		
2-generation OECD 416 (Level 5, *in vivo*) 0, 20, 50, 1000, 2500ppm (♂: 0, 1.2, 3, 61.7 or 155.6 mg/kg bw/day, ♀: 0, 1.7, 4.3, 84.4 or 208.8 mg/kg bw/day)	**From 50 ppm** **Testis: S**ignificant reduced number of sperm cells in F1 males **From 1000 ppm** **Testis:** Dose-related increase in epididymal and testes weights in F1 males **At 2500 ppm** Reduced total litter weight of the F1A pups Slight delayed preputial separation. **Testis:** Increased incidence of germ cell loss/disorganisation and Sertoli cell vacuolation in F1 males. F1 sperm velocity parameters statistically significantly lower.	**From 1000 ppm** Increased incidence of hyaline change in renal tubules (F0 and F1 males) **At 2500 ppm** Reduced food consumption and decreased body weight gain F0 males. No effect on terminal bw in F1 males	**Toxicity on reproductive postnatal development in the absence of parental toxicity**	[redacted] (2004a)

2.6.6.2.2 Comparison with the CLP criteria regarding adverse effects on development

In the classification system, reproductive toxicity is subdivided under two main headings: Adverse effects on sexual function and fertility and Adverse effects on development of the offspring.

Adverse effects on development of the offspring:
Developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

1) Death of developing organism was only observed at the top dose of the rabbit developmental study manifesting as increased of post implantation losses in the presence of severe maternal toxicity.

2) Structural abnormalities: no teratogenic effect was noted in both rat and rabbit developmental studies.
However in the DNT study brain effects were observed in offspring at the highest dose level in the presence of moderate maternal toxicity. There is therefore an increased qualitative susceptibility of developing organism since the effects in the pups (reduced brain weight and significant changes in brain morphometric measurements) are considered more severe than effects in the dams (decreased body weight gain and food consumption) observed at the same dose.

3) Altered growth: reduced foetal weight and delayed ossification were observed in both rat and rabbit developmental toxicity studies but only at maternally toxic dose levels revealing no increased susceptibility of developing organisms.
On the other hand, there is evidence of increased quantitative susceptibility for pups in the two multigeneration studies. Indeed, reduced bodyweights are observed in the pups during late lactation at high dose levels while no effect on weight and no toxicological findings were noted in the dams at any dose levels.

4) Effects on reproductive postnatal development were also observed in males in the two multigeneration studies. The reproductive effects in F1 males (increased incidence of testicular tubular atrophy in first study and sperm abnormalities in the second one) were noted at dose levels with no concurrent parental toxicity.
Delayed male puberty in rat progeny was observed in the 2-generation study and in the DNT study.

There is no available human data that thiamethoxam could induce developmental toxicity.
Cat 1A is therefore not triggered.

From the developmental toxicity studies it can be concluded that thiamethoxam shows no teratogenic potential in rats and rabbits. It is foetotoxic only at marked maternally toxic doses. Indeed in rat, lower fetal weight (↓9%), delayed ossifications and increased incidence of skeletal anomalies and variations were only observed at the top dose level (750 mg/kg bw/d) consisting of a 46% decrease of corrected body weight gain and transient neurotoxic effects in dams.
In rabbit, fetal toxicity was only observed at the highest dose level of 150 mg/kg bw/day including reduced fetal weights (15%), an increase number of post-implantation loss, delayed ossification and increased incidence of skeletal anomalies and variations. At this dose level, a marked maternal toxicity was noted 3 deaths, bloody discharge in the perineal in a total of 13/19 dams, marked body weight loss between days 7 and 12 and during the whole treatment period.
Since effects on prenatal development were observed only at marked maternal toxicity, classification category 1B seems not warranted.

However, there is evidence of increased qualitative susceptibility of developing organisms in the multigeneration studies (i.e.: effects on male post-natal reproductive development in the absence of maternal toxicity) and in the developmental neurotoxicity study (effects on brain weight and morphometric changes in the presence of moderate maternal toxicity).

Since the effects observed on postnatal reproductive development in F1 males testicular atrophy, decreased sperm cells and delayed balano-preputial separation observed in F1 generation) fall within both classification criteria for fertility or developmental toxicity, no specification (f or d) is proposed**.**

Thiamethoxam needs to be classified as Reproductive toxicant Cat. 2 H361 according to Regulation (EC) 1272/2008.

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

Table 49: Summary table of animal studies on effects on or via lactation

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
2-generation reproduction study OECD Guideline 416 (1981) GLP Acceptable Rat, Sprague-Dawley Tif: RAIf, SPF 30/sex/group	Thiamethoxam technical Batch P.50600 (purity 98.6%) 0, 10, 30, 1000, 2500ppm (♂: 0, 0.6, 1.8, 61 or 158 mg/kg bw/day, ♀: 0, 0.8, 2.4, 79 or 202 mg/kg bw/day) In the diet	**<u>At 10 ppm (♂/♀): 0.6/0.8 mg/kg bw/day</u>** No difference from controls. **<u>From 30 ppm (♂/♀): 1.8/2.4 mg/kg bw/day</u>** **Paternal toxicity :** No effect **Maternal toxicity :** No effect **Toxicity on or *via* lactation:** No effect **<u>From 1000 ppm (♂/♀): 61/79 mg/kg bw/day</u>** **Paternal toxicity:** *increased incidence of hyaline change in renal tubules (F0 and F1 males) not relevant for human risk assessment.* **Maternal toxicity :** No effect **Toxicity on or *via* lactation:** reduced body weight gain of F2a and F2b pups during late lactation **<u>At 2500 ppm (♂/♀): 158/202 mg/kg bw/day</u>** **Paternal toxicity**: transient reduced food consumption and slight decreased body weight gain of F0 weeks 1-6 (10%). In F1 lower body weights at selection remained lower than controls thereafter. **Maternal toxicity :** No effect **Toxicity on or *via* lactation:** reduced body weight gain of F1a and F1b during late lactation. **Paternal NOAEL: 1000 ppm (eq. to: 61 mg/kg bw/day)** ***NOAEL kidney effects in males : 30ppm eq.to: 1.8 mg/kg bw (not relevant for human risk assessment)*** **Maternal NOAEL : 10 ppm (eq. to: 0.6 mg/kg bw/day)** **Toxicity on or *via* lactation NOAEL: 30 ppm (eq. to: 1.8 mg/kg bw/day)**	(1998) Refer to Annex I. Vol3CA B.6.6.1.1.

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
2-generation reproduction study OECD Guideline 416 (2001) GLP Acceptable Rat, Sprague-Dawley Tif: RAIf, SPF 26/sex/group	Thiamethoxam technical Batch P.50600 (purity 98.6%) 0, 20, 50, 1000, 2500ppm (♂: 0, 1.2, 3, 61.7 or 155.6 mg/kg bw/day, ♀: 0, 1.7, 4.3, 84.4 or 208.8 mg/kg bw/day) In the diet	**At 20 ppm (♂/♀): 1.2/1.7 mg/kg bw/day** No difference from controls. **From 50 ppm (♂/♀): 3.0/ 4.3 mg/kg bw/day** **Paternal toxicity :** No effect **Maternal toxicity :** No effect **Toxicity on or via lactation:** No effect **From 1000 ppm (♂/♀): 61.7/84.4 mg/kg bw/day** **Paternal toxicity:** *increased incidence of hyaline change in renal tubules (F0 and F1 males) not relevant for human risk assessment.* **Maternal toxicity :** No effect **Toxicity on or *via* lactation:** No effect **At 2500 ppm (♂/♀): 155.6/208.8 mg/kg bw/day** **Paternal toxicity:** reduced food consumption and decreased body weight gain F0 males. **Maternal toxicity :** No effect **Toxicity on or via lactation:** No effect **Toxicity on or *via* lactation:** reduced total litter weight of the F1A during late lactation. **Paternal NOAEL: 1000 ppm (eq. to: 61.7 mg/kg bw/day)** ***NOAEL kidney effects in males : 50 ppm eq.to: 3 mg/kg bw (not relevant for human risk assessment)*** **Maternal NOAEL: 2500 ppm (eq. to: 208.8 mg/kg bw/day)** **Toxicity on or *via* lactation NOAEL: 1000 ppm (eq. to: 61.7 mg/kg bw/day)**	(2004 Refer to Annex I. Vol3CA B.6.6.1.2

Table 50: Summary table of human data on effects on or via lactation

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

Table 51: Summary table of other studies relevant for effects on or via lactation

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

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

1) First guidelined 2-generation study OECD 416 (1981) (refer to Vol3CA B.6.6.1.1)

In the first 2-generation study (Doubovetzky ,1998), reduced body weight gain during late lactation period was observed from 1000 ppm in F2a and F2b pups and at 2500 ppm in of F1a and F1b pups in the absence of maternal toxicity.

Litter data – selected parameters

Generation / litter	Parameter	Dietary concentration of CGA293343 technical (ppm)				
		0	10	30	1000	2500
F1a	Number of litters Mean	25	28	27	23	27
	litter size at birth	13.6	13.0	13.1	13.0	11.4
	Live birth index	99.4	98.6	99.2	99.7	98.4
	Viability index (days 0-4)	96.2	96.1	98.3	99.0	98.4
	Pup weight (g) day 0 (m+f)	6.2	5.9	6.1	6.1	6.1
	Pup weight (g) day 14 (m+f)	30.5	29.8	30.7	29.8	28.9
	Pup weight (g) day 14 (m)	31.2	30	30.9	30.3	29.1*
	Pup weight (g) day 14 (f)	29.9	29.5	30.6	29.3	28.7
	Pup weight (g) day 21 (m+f)	53.1	50.9	52.5	51.4	48.6**
	Pup weight (g) day 21 (m)	54.5	51.7	53.5	52.6	49.1**
	Pup weight (g) day21 (f)	51.9	50.2	51.6	50.3	47.9**
F1b	Number of litters Mean	24	26	27	22	27
	litter size at birth	13.8	13.7	13.2	13.3	12.1
	Live birth index	99.7	98.6	98.9	96.1	99.1
	Viability index (days 0-4)	94.3	97.7	97.8	98.3	95.7
	Pup weight (g) day 0 (m+f)	6.1	6.0	6.2	5.9	6.1
	Pup weight (g) day 14 (m+f)	30.5	30.5	30.3	30.9	28.4*
	Pup weight (g) day 14 (m)	31.2	31.4	30.7	31.2	29.1*
	Pup weight (g) day 14 (f)	29.9	29.9	29.9	30.6	27.7*
	Pup weight (g) day 21 (m+f)	52.6	51.8	51.8	52.9	47.3**
	Pup weight (g) day 21 (m)	53.6	53.8	52.9	54	48.9**
	Pup weight (g) day21 (f)	51.7	50.2	50.7	51.7	46.1**
F2a	Number of litters	28	27	25	26	27
	Mean litter size at birth	13.8	13.3	13.6	13.6	13.0
	Live birth index	99.7	98.4	98.0	98.6	100.0
	Viability index (days 0-4)	97.4	96.6	96.8	99.2	97.7
	Pup weight (g) day 0 (m+f)	6.3	6.2	6.0	6.1	6.1
	Pup weight (g) day 14 (m+f)	31.5	30.5	30.2	30.0	28.9**
	Pup weight (g) day 14 (m)	31.7	30.7	30.4	30.4	29.5
	Pup weight (g) day 14 (f)	31.3	30.0	29.9	29.4*	28.4**

	Pup weight (g) day 21 (m+f)	54.4	52.1	51.9	51.3*	48.7**
	Pup weight (g) day 21 (m)	55.4	52.9	52.9	52.4	49.9**
	Pup weight (g) day21 (f)	53.4	51.0	51.0	50.0*	47.6**
F2b	Number of litters	28	25	21	28	25
	Mean litter size at birth	14.1	13.8	14.1	13.8	13.9
	Live birth index	99.7	96.1	98.3	99.5	98.6
	Viability index (days 0-4)	97.0	94.8	98.6	93.5	95.1
	Pup weight (g) day 0 (m+f)	6.3	6.1	6.1	6.0	6.2
	Pup weight (g) day 14 (f)	31.6	31.3	31.2	29.3	30.0
	Pup weight (g) day 21 (m+f)	56.5	55.1	54.8	52.0*	52.0*
	Pup weight (g) day 21 (m)	57.8	55.9	55.5	51.6	52.7**
	Pup weight (g) day21 (f)	55.1	54.1	54.1	50.9*	51.3

* Statistically significant difference from control group mean, p<0.05

** Statistically significant difference from control group mean, p<0.01

2) Second guidelined 2-generation study, OECD 416 (2001) (refer to Vol3CA B.6.6.1.2)

In the second 2-generation study ([redacted], 2004), total litter weight was reduced at 2500 during late lactation period in both F1A without concurrent maternal toxicity.

Intergroup comparison of litter sizes, pup survival and total litter weight (excluding whole litter losses)

	Dose level of Thiamethoxam (ppm)				
	0	**20**	**50**	**1000**	**2500**
F1A					
Litter size Day 1	12.9	12.3	12.3	12.5	12.2
Total litter weight at Day 1 (g)	65.4	63.3	65.5	69.7	66.2
Litter size Day 15	12.7	11.1	11.9	12.4	11.4
% of pup survival at Day 15	98.6	91.9*	96	99.1	95.2
Total litter weight at Day 15 (g)	281.2	257.0	261.1	271.8	244.9**
Litter size Day 22	12.7	11.1	11.9	12.4	11.3
% of pup survival at Day 22	98.6	91.9*	96	99.1	94.6
Total litter weight at Day 22 (g)	450.7	418.0	422.9	437.2	397.4*
F2A					
Litter size Day 1	11.9	11.6	12.0	11.0	11.9
Total litter weight at Day 1 (g)	60.0	59.2	63.2	61.7	92.0
Litter size Day 15	11.3	10.2	11.8	10.9	11.0
% of pup survival at Day 15	95.8	86.5*	98.1	99.3	93.4
Total litter weight at Day 15 (g)	266.2	248.2	271.0	260.3	247.0
Litter size Day 22	11.3	10.2	11.7	10.9	11.0
% of pup survival at Day 22	95.8	86.5*	97.7	99.3	93.4
Total litter weight at Day 22 (g)	431.5	409.9	438.7	426.6	400.6

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

The classification is intended to indicate when a substance may cause harm due to its effects on or *via* lactation and is independent of consideration of the reproductive or developmental toxicity of the substance.

The effects on pup bodyweight were observed only during late lactation period when pups begin eating diet therefore they are not considered to be linked to lactation.

There were no effects to warrant classification of thiamethoxam for effects on or *via* lactation.

2.6.6.4 Conclusion on classification and labelling for reproductive toxicity

Proposal for classification: Repr. cat2 H361

Suspected of damaging fertility or the unborn child

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Reproductive toxicity of thiamethoxam had been investigated in two 2-generation studies in the rat, in two prenatal developmental toxicity (PNDT) studies, one in the rat and one in the rabbit, and in a developmental neurotoxicity study (DNT) in the rat. Information on effects on reproductive organs was also obtained from repeat dose toxicity studies in rats, mice and dogs.

The DS proposed a classification for reproductive toxicity without sub-categorisation based on the following findings:

- Testicular tubular atrophy in the 90-day and 1-year dog studies, occurring in the absence (1-year study) and presence (90-day study) of slight general toxicity.
- Testicular tubular atrophy (dose-dependent increase in the incidence and severity) in F1 males of the first 2-generation study (1998), occurring in the absence of general toxicity.
- Delayed preputial separation, significantly increased incidence of germ cell loss/disorganization and Sertoli cell vacuolation, significantly reduced testicular sperm count at 3 doses and reduced sperm velocity in F1 males of the second 2-generation study (2004), occurring in the presence of slight general toxicity (increased incidence of hyaline change in renal tubules, no effect on terminal bw in F1). Preputial separation was delayed also in the DNT study.
- Effects on brain weight and morphometric changes in the offspring in the DNT study, occurring in the presence of moderate maternal toxicity (reduced maternal bw gain of 12 %).

The DS did not consider the observed effects sufficient for classification in Category 1B because fertility and reproductive performance were not affected in the available studies. The other effects on prenatal development (mainly variations) were only observed at doses causing marked maternal toxicity whereas the delayed preputial separation and brain effects were observed in either the absence or presence of only slight maternal toxicity.

The DS proposed not to specify 'f' or 'd' as the effects in F1 males such as testicular atrophy, reduced sperm count and delayed preputial separation were considered to fall within classification criteria for both fertility and developmental toxicity. Thus, the classification proposal was Repr. 2; H361.

The DS proposed no classification for effects on or via lactation. The only potentially relevant effect was reduced pup body weight during late lactation (PND 14 and 21) in generational studies. However, as pups already begin eating the diet in this period, the body weight reduction was not considered to be linked to lactation.

Comments received during public consultation

Comments were received from 5 MSCAs and 1 manufacturer.

One MSCA supported Category 2 without specification for fertility or development and no classification for effects on or via lactation. The MSCA pointed out the lack of maternal toxicity at the top dose in the 2-generation studies and questioned the top dose selection, explaining that an effect on female reproductive function cannot be excluded.

Another MSCA supported Category 2 but proposed to specify 'development' in the hazard statement since fertility and reproductive performance were not affected and the reduction in sperm count in one of the generational studies was not clearly dose dependent. As to the brain effects in the DNT study, the MSCA mentioned that most of the changes in morphometric measurements were within the historical control range.

Two other MSCAs supported classification "at least" in Category 2, one of them specifically indicating a need for a discussion about Category 1B, due to effects on several parameters related to male reproduction in two species starting in some cases from relatively low doses.

One MSCA expressed preference for Category 1B, additionally pointing out effects on ovaries, both in a 90-day mouse study and in a 90-day dog study. The MSCA was of the opinion that effects on reproduction in general were observed from rather low doses in several species in both sexes and in the absence of other toxic effects.

Regarding the ovarian findings, the DS replied that reduced weight, atrophy and reduced numbers of corpora lutea were indeed observed from 3 500 ppm (626 mg/kg bw/d) with concomitant general toxicity. However, no such effects were observed in an 18-month study at doses up to 2 500 ppm (479 mg/kg bw/d).

As to classification, the DS maintained their proposal for Category 2, reiterating that reproductive performance was not affected.

Industry proposed no classification and provided detailed analysis of the available studies. Their main arguments for no classification are summarised as follows:

- Sperm parameters (2-generation study, 1998, F1 generation): The decrease in testicular sperm count was not dose-related, with only one value being outside the historical control range. Thus, the testicular sperm counts are likely to reflect normal biological variation. Although sperm velocities were reduced at the top dose, the values remained well within the historical control range.
- Delayed preputial separation (developmental neurotoxicity study; 2-generation study, 2004): A delay by at least 2 days in the absence of body weight reduction is generally considered toxicologically significant. The developmental neurotoxicity study reported a delay by 1.5 days in conjunction with a significant reduction in body weight. Based on the small magnitude of delay associated with the bodyweight effects, this effect is considered to be of no toxicological relevance. The second 2-generation study reported a delay by only 1 day without statistical significance.
- Histopathological findings in the testes of rats (2-generation study, 1998, F1 generation; 2-generation study, 2004, F1 generation): The increased incidence of germ cell loss/disorganisation +/− Sertoli cell vacuolation in the second study was of low severity, with approximately 0.4 % of tubules affected at the top dose, and did not lead to reduction in testicular weight. The testicular atrophy was minimal to mild in both studies, barely exceeded background variability and had no effect

on reproductive function or spermatogenesis. Thus, the histopathological findings were not considered adverse.

- Testicular findings in dogs (90-day study; 1-year study): Dogs were sexually immature at the start of the studies and systemic toxicity caused an overall developmental delay, leading to lower testicular weight and immature histopathological appearance of the testes.
- Effects on brain weight and brain morphometric measurements (developmental neurotoxicity study): These findings are secondary to lower pup bodyweights at birth, which are in turn secondary to reduced maternal food consumption (fc reduced by up to 15 %). The relevance of body weight for the assessment of brain weight is apparent from scatter graphs on the brain weight vs body weight. While the adult brain is relatively insensitive to changes in body weight, published literature indicates that the developing brain is affected by deficits in maternal nutrition, food consumption and body weight. There were no histopathological changes in the brain and no changes in the investigated functional and neurobehavioural parameters.

The DS gave a detailed response to industry's comment, and retained their original classification proposal.

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

Two 2-generation studies are available for thiamethoxam, both conducted according to OECD TG 416 and under GLP. Both studies were performed in the same rat strain and with the same batch of the test substance but in different laboratories. The more recent study (2004) was conducted according to the current (2001) version of OECD TG 416. The older study (1998) followed the older (1981) version and therefore did not investigate some parameters, such as puberty onset, required by the current test guideline.

In addition, certain findings from the developmental neurotoxicity study in rats (GLP, OECD TG 426) and repeated dose studies in dogs and mice are also considered in the assessment.

<u>2-generation study in the rat (1998)</u>

The top dose was 2 500 ppm (ca. 160/200 mg/kg bw/d in m/f, respectively). Parental toxicity at the top dose was limited to mild effects on body weight and food consumption in males (bw reduced by up to 8 % as compared to controls). Treated males also showed increased incidence of hyaline change in renal tubules related to α2u-globulin nephropathy. No general/parental toxicity was observed in top dose females. According to the study report, the top dose selection was based on a 90-day study and on a 1-generation range-finding study.

In the 90-day rat study a dose of 5 000 ppm caused body weight reduction by 19 % as compared to controls and renal lesions in males but no general toxicity in females. In the 1-generation range-finding study, males were exposed for 4 weeks (2-week premating, 2-week mating and post-mating periods) and females for ca. 7 weeks (2 weeks premating, 3 weeks gestation, 2 weeks lactation) to dietary concentrations of up to 4000 ppm. Terminal body weights of males and females were reduced by 5% and 6% respectively compared to controls at the top dose. It is noted that the exposure duration in this range-finding study was considerably shorter than that in the full 2-generation study.

The top dose selection in the main study is considered acceptable for males given the marked body weight reduction at 5000 ppm in the 90-day study. However, RAC is of the opinion that a dose higher than 2500 ppm would have been well-tolerated by females. Therefore, this 2-generation study may not provide sufficient information about the potential of the substance to cause adverse effects on female sexual function and fertility and adverse developmental effects on the offspring.

The study design included two matings per generation and a 10 weeks premating period. Selected F1a young animals were used to produce F2a and F2b offspring. No effect on reproductive performance was observed in any generation. There was no effect on sperm parameters in P males (no reliable data are available for F1 males). A 9 % reduction in absolute testes weight and increased incidence of testicular tubular atrophy were seen in F1 generation. Detailed results are presented in the table below (for testicular tubular atrophy the table shows the data from re-examination by the Pathology Working Group).

2-generation study (1998): testes weight and incidence of testicular tubular atrophy in F1 males

Dose (ppm)	**0**	**10**	**30**	**1 000**	**2 500**
Dose (mg/kg bw/d)	0	0.6	1.8	61	158
Terminal bw (g)	582	593	578	575	573
Testes weight, absolute (g)	4.48	4.42	4.24	4.41	4.08*
No. of animals examined	30	30	30	30	30
Incidence of testicular tubular atrophy, total	6	10	13*	21**	18*
– grade 1	6	7	9	8	10
– grade 2		3	4	8	5
– grade 3				1	1
– grade 4				2	1
– grade 5				2	1

* statistically significant difference from control, $p \leq 0.05$

For comparison, incidence of testicular tubular atrophy in controls of 5 reference studies performed by the same laboratory and examined by the same Pathology Working Group ranged from 3 to 11 out of 30 males (average grade 1.2 to 2.8). This shows that control values are exceeded in terms of incidence but not necessarily in terms of severity from 1 000 ppm. The dose-response relationship is not very clear and obscured by the large interval between 30 ppm and 1 000 ppm. However, when testicular weights are taken into account, the effect is likely to be most pronounced at the top dose.

2-generation study in the rat (2004)

This study employed the same top dose as the first 2-generation study (1998), i.e. 2 500 ppm. General toxicity in top dose males was similar to that in the first study: a reduction in body weight (by up to 10%, only in the F0 generation) and increased incidence of hyaline change in renal tubules. No toxicity was observed in females. Due to low dosing, this study is not considered sufficiently informative about the reprotoxic potential of the substance in females and about adverse developmental effects on the offspring.

No effect on reproductive performance was observed in either generation. A number of

findings in F1 generation related to male reproductive organs were discussed in the CLH report and are summarised in the table below: delayed preputial separation, increased testicular and epididymal weight, increased incidence of germ cell loss/disorganisation and Sertoli cell vacuolation, reduced testicular sperm count, increased epididymal sperm count and reduced sperm velocity. No effect on these parameters was observed in the P generation.

The germ cell loss/disorganisation in the 2004 study is likely to represent the same entity as testicular tubular atrophy in the 1998 study because germ cell loss/disorganisation is one of the key features of testicular tubular degeneration/atrophy (Creasy *et al.*, 2012) and the strain and the top dose were identical in both studies.

The table also shows results of two control studies (RR0942, denoted HCD 1; RR0943, denoted HCD 2) run in parallel with the main study in order to provide information on the background variability of the strain used since the Tif:RAIf strain was not frequently used by the performing laboratory.

2-generation study (2004): findings related to reproductive organs in F1 males

Dose (ppm)	**0**	**20**	**50**	**1 000**	**2 500**	**HCD 1**	**HCD 2**
Dose (mg/kg bw/d)	0	1.2	3.0	62	156		
Day of preputial separation; (±SD)	47.7 (±2.9)	47.3 (±2.0)	47.2 (±3.6)	46.7 (±2.3)	48.7 (±1.9)	47.1	47.2
Body weight at PS (g)	174	176	169	171	178	179	182
Body weight on PND 22 (g)	36.8	38.7	38.5	36.9	35.8		
Terminal bw (g)	464	477	469	467	458	469	483
Testes weight, abs. (g); (±SD)	3.89 (±0.29)	4.15* (±0.32)	4.02 (±0.39)	4.13* (±0.33)	4.19** (±0.46)	4.01	4.01
Epididymides weight, abs. (g); (±SD)	1.58 (±0.12)	1.63 (±0.13)	1.62 (±0.14)	1.66 (±0.14)	1.66* (±0.18)	1.63	1.67
No. of animals examined, main study	26	26	26	26	26		
Incidence of germ cell loss/disorganization, with or w/o Sertoli cell vacuolation (only one testis examined)[b]	3 (2 ±, 1 +)	1 (1 +)	1 (1 ±)	3 (3 ±)	15** (14 ±, 1 ++)		
No. of animals examined, satellites	14	14	14	14	14		
Incidence of germ cell loss/disorganization, with or w/o Sertoli cell vacuolation, unilateral[b]	1 (1 ±)	4 (3 ±, 1 +)	2 (2 ±)	3 (3 ±)	0		
Incidence of germ cell loss/disorganization, with or w/o Sertoli	1	0	0	1	5 (4 ±,		

cell vacuolation, bilateral[b]	(1 +)			(1 ±)	1 +)		
Testicular sperm count, per testis (millions); (±SD)	87 (±22)	93 (±23)	70** (±19)	63** (±16)	74* (±18)	Range[a]: 69–103	
Epididymal sperm count, per cauda epid. (millions); (±SD)	153 (±38)	153 (±37)	163 (±53)	168 (±49)	192** (±37)	Range[a]: 137–170	
Sperm velocity: straight line velocity (µm/s); (±SD)	71.6 (±5.6)	71.8 (±6.0)	72.3 (±5.2)	71.3 (±7.4)	67.6* (±6.0)	Range[a]: 64.9–76.7	
Sperm velocity: curvilinear velocity (µm/s); ±SD	305 (±17)	297 (±20)	302 (±17)	298 (±21)	290** (±18)	Range[a]: 278–316	
Sperm velocity: average path velocity (µm/s); ±SD	124 (±8)	122 (±8)	123 (±8)	120 (±8)	116** (±8)	Range[a]: 113–131	

Statistically significant difference from control: *, p≤0.05; **, p≤0.01

[a] The range includes the controls from both generations of the current study (i.e. including the P and F1 generation) and both generations of the two additional control studies (HCD 1 and HCD 2). Individual control mean values are provided under 'Supplemental information'.

[b] Severity grades: ±, minimal; +, slight; ++, moderate

While there are a number of findings related to male reproductive organs and sperm parameters in the F1 generation, the main evidence for a treatment-related effect comes from the histopathology, namely from the statistically significantly increased incidence of germ cell loss at the top dose of 2 500 ppm. The severity was mostly 'minimal' and, on average, 10 tubules per section were affected per affected animal (study report, Appendix H), which represents a relatively small portion (in the order of 0.4 % according to the study report) of the tubular cross sections examined. The changes in sperm parameters were still within normal variation. The delay in puberty onset in males was slight and not statistically significant, so its relation to treatment would be debatable should this finding be considered in isolation. The testicular and epididymal weights were only slightly increased.

Developmental neurotoxicity study in the rat

The animals were dosed from GD 7 to LD 22, the top dose was 4 000 ppm (equivalent to ca. 300 mg/kg bw/d during gestation). Maternal toxicity was limited to body weight reduction by 5-10 % compared to controls (–5%, –7%, –8%, –10% and –6% on GD 15 (unadjusted), LD 1, 8, 15 and 22, respectively). The top dose was chosen on the basis of a preliminary study, where a dose of 5 000 ppm was reported to cause maternal toxicity (not further specified in the study report of the main study) and reduced pup weight at birth and afterwards.

The only finding related to sexual function and fertility was a statistically significant delay in preputial separation by approx. 1 day. The delay was associated with reduced body weight (by ca. 10 %), so the finding may at least partly be attributed to a general developmental delay. However, some contribution of a specific MoA cannot be excluded considering the delay of approx. 1 day at 2 500 ppm in the 2-generation study (2004) observed in the absence of an effect on body weight. There was no effect on vaginal

opening.

Developmental neurotoxicity study: preputial separation				
Dose (ppm)	**0**	**50**	**400**	**4 000**
Dose (mg/kg bw/d)	0	4.3	35	299
Day of PS; (±SD)	44.9 (±0.9)	45.6* (±0.8)	45.1 (±0.9)	46.4** (±1.3)
Body weight on PND 1 (g)	6.1	5.9	6.0	5.7**
Body weight on PND 43 (g)	212	210	212	191
Body weight on PND 50 (g)	275	269	273	249
Body weight at PS (g)	230	233	231	221**

Statistically significant difference from control: *, p ≤ 0.05; **, p ≤ 0.01

90-day dog study

The top dose of 2 500 ppm had to be reduced after 2 weeks to 2 000 ppm (51 mg/kg bw/day in females) due to body weight loss especially in females. Still, females showed a marked body weight reduction compared to controls until the end of the study (terminal bw 26 % lower than in controls, cumulative bw gain 0.5 kg vs 2.9 kg in controls), indicating that the top dose was in excess of MTD for this sex. The toxicity in males was less pronounced but not negligible (cumulative bw gain 1.9 kg vs 3.0 kg in controls).

The animals were 5 to 7 months old at the beginning of the study. The age of the animals at the end of the study was 8 to 10 months, which is approximately the age when Beagle dogs normally reach sexual maturity.

3 out of 4 top dose females were found to have immature ovaries (bilateral). The 1 non-affected animal was that with the highest body weight gain (1.5 kg). RAC considers the immaturity of ovaries in this study as a secondary non-specific consequence of developmental delay caused by severe general toxicity, and as such not relevant for classification for reproductive toxicity. No changes in the ovary were observed at 1500 ppm in a 1-year study in the absence of significant general toxicity.

90-day dog study: ovarian findings					
Dose (ppm)	**0**	**50**	**250**	**1 000**	**2 500/2 000**
Dose (mg/kg bw/d)	0	1.8	9.3	34	51
No. of animals examined	4	4	4	4	4
Initial body weight (kg)	7.5	7.3	7.5	7.6	7.3
Terminal body weight (kg)	10.4	9.8	10.3	10.7	7.8*
Body weight gain (kg) [individual data]	2.9	2.5	2.8	3.1	0.5* [-0.4; -0.2; 1.0; 1.5]
Ovarian weight, abs. (g)	0.84	0.66	0.70	0.71	0.54*
Ovarian weight, rel. (‰)	0.087	0.072	0.073	0.074	0.076
Immature ovary	0	0	0	0	3
Immature uterus	0	0	0	0	2

* Statistically significant difference from control, p<0.05

All top dose males showed reduced spermatogenesis and spermatic giant cells, and testicular weight was reduced by 43%. These findings may be indicative of immaturity (cf. Goedken *et al.*, 2008; Creasy *et al.*, 2012) although some contribution of direct testicular toxicity cannot be excluded as a slight increase in testicular atrophy was also observed in a 1-year study. As to the mode of action behind the delayed puberty onset, general developmental delay is considered by RAC plausible (body weight gain was reduced by 36%), but a direct effect on puberty onset cannot be excluded given the slight delay in preputial separation seen in F1 rats (2-generation study, 2004; developmental neurotoxicity study).

90-day dog study: testicular findings					
Dose (ppm)	**0**	**50**	**250**	**1 000**	**2 500/2 000**
Dose (mg/kg bw/d)	0	1.6	8.2	32	55
No. of animals examined	4	4	4	4	4
Initial body weight (kg)	8.3	8.4	8.6	8.7	8.7
Terminal body weight (kg)	11.3	11.7	11.4	11.6	10.6
Body weight gain (kg)	3.0	3.3	2.8	2.9	1.9
Testicular weight, abs. (g)	16.5	14.8	14.6	15.6	9.4*
Tubular atrophy	0	0	0	0	1 (1 ++)
Spermatogenesis reduced	0	1 (1 +)	0	0	4 (1 +, 2 ++, 1 +++)
Spermatic giant cells	1 (1 +)	1 (1 ++)	0	1 (1 +)	4 (3 +, 1 ++)

* Statistically significant difference from control, $p<0.05$

Severity scores: +, minimal (slight); ++, moderate; +++, marked

1-year dog study

No remarkable effect on body weight was observed at the top dose of 1 500 ppm (42/45 mg/kg bw/d m/f). Males showed a slightly increased incidence and severity of tubular atrophy from 750 ppm (see the table below). Testicular weight was statistically non-significantly reduced by 16 % at the top dose. There was no correlation between testicular weights and histopathological findings at the level of individual animal data.

1-year dog study: histopathological findings in the testes					
Dose (ppm)	**0**	**25**	**150**	**750**	**1 500**
Dose (mg/kg bw/d)	0	0.7	4.1	21	42
No. of animals examined	4	4	4	4	4
Testicular weight, abs. (g)	19.1	20.5	19.8	20.7	16.1
Tubular atrophy (severity grade, 1-5)	1 (1)	1 (1)	1 (3)	2 (2,2)	2 (2,2)

Severity grades: 1, minimal; 2, slight; 3, moderate

90-day mouse study

Increased incidence of ovarian atrophy manifested by reduced number of corpora lutea was observed from 3500 ppm (626 mg/kg bw/d) in this study. The severity at 3500 ppm was mostly slight but a more pronounced effect was observed at the top dose of 7000 ppm (1160 mg/kg bw/d), see the table below. Absolute ovarian weight was reduced by 20% and 44% at 3500 and 7000 ppm, respectively. There was no general toxicity at 3500 ppm and the body weight was reduced only about 10% as compared to controls at the top dose. No effect on ovaries was observed in an 18-month mouse study at 2 500 ppm (479 mg/kg bw/d).

90-day mouse study: ovarian findings						
Dose (ppm)	**0**	**10**	**100**	**1 250**	**3 500**	**7 000**
Dose (mg/kg bw/d)	0	2.0	19	231	626	1 160
No. of animals examined	10	10	10	10	10	10
Body weight week 13 (g)	31.8	30.4	30.6	31.1	30.5	29.2
Body weight gain (g)	6.1	5.4	4.9	5.6	4.9	3.8
Carcass weight (g)	30.1	30.8	30.6	31.9	30.3	25.6*
Ovaries weight absolute (mg)	48.1	50.1	41.3	43.2	38.7	31.6*,t–
Ovaries weight relative (‰)	1.60	1.63	1.35	1.35	1.29t–	1.24t–
Ovarian atrophy	0	0	1 (1 +)	1 (1 +)	5 (4 +, 1 ++)	10 (6 +, 4 ++)

* statistically significant difference from controls (Lepage's test, $p < 0.01$)

t– statistically significant negative trend from the control group to the respective dose group (Jonckheere's test, $p < 0.01$)

Severity scores: +, minimal (slight); ++, moderate

Conclusion on classification for fertility and sexual function

Findings related to fertility were observed in all three species investigated: rat, mouse and dog. RAC is of the opinion that the testicular tubular atrophy in F1 rats of the 2-generation study (1998), germ cell loss/disorganisation in F1 rats of the 2-generation study (2004) and the testicular tubular atrophy in the 90-day mouse study are sufficient to collectively trigger classification in Category 2 for adverse effects on fertility and sexual function. The slight increase in testicular tubular atrophy in the 1-year dog study is considered by RAC as additional supportive evidence for classification.

RAC acknowledges that the potential of the substance to adversely affect female sexual function and fertility has not been sufficiently investigated due to low dosing in the 2-generation studies.

Adverse effects on development

Two PNDT studies are available, one in the rat and one in the rabbit. Both have been conducted under GLP and according to OECD TG 414 and both are negative regarding developmental toxicity. Likewise, no developmental effects were observed in the two

generational studies discussed in the fertility section. However, the developmental neurotoxicity study reported some effects on brain weight and morphometry that are considered relevant for classification.

Rat PNDT study

Maternal toxicity at the top dose of 750 mg/kg bw/d consisted of clinical signs (hypoactivity, piloerection, regurgitation of the test substance), reduced food consumption (by 35 % over the dosing period) and moribund condition (1 animal was killed for humane reasons). Developmental toxicity at this dose was limited to reduced foetal weight (by 9 %) and reduced ossification. No developmental toxicity was apparent at the lower dose of 200 mg/kg bw/d.

Rabbit PNDT study

The top dose of 150 mg/kg bw/d induced severe maternal toxicity including 3 deaths (1 spontaneous, 2 animals killed moribund) and markedly reduced food consumption (by 58 % during the dosing period). Developmental toxicity at the top dose consisted of increased post-implantation loss (46 % vs 21 %), reduced foetal body weight (by 15 %) and increased incidence of fused sternebrae 3 and 4 (5 foetuses vs 0 in the control). Developmental effects at the top dose are not considered relevant for classification as maternal mortality exceeded 10 % and there was no increase in malformations. No developmental effects were observed at the lower dose of 50 mg/kg bw/d.

Developmental neurotoxicity study in the rat

Statistically significant reductions in brain weight and size of some brain regions were observed at the top dose of 4 000 ppm (299 mg/kg bw/day) in the presence body weight reductions. The table below summarizes the body and brain weight data together with selected morphometry parameters.

Developmental neurotoxicity study: absolute brain weight and selected morphometry parameters (in brackets % reduction compared to control)

Dose (ppm)	**0**	**50**	**400**	**4 000**	**HCD[a]**
Dose (mg/kg bw/d)	0	4.3	35	299	
PND 12, males					
Terminal body weight (g)	23.5	24.8	24.8	20.7 (-12%)	
Brain weight (g)	1.15	1.16	1.13	1.10* (-4%)	1.03–1.16 Mean 1.11
PND 12, females					
Terminal body weight (g)	24.0	22.9	23.0	20.5 (-15%)	
Brain weight (g)	1.11	1.09	1.10	1.06* (-5%)	1.01–1.12 Mean 1.08
PND 63, males					
Terminal body weight (g)	369	364	355	342 (-8%)	342–382 Mean 359
Brain weight (g), post-perfusion	2.03	2.01	2.00	1.93* (-5%)	1.89–2.11 Mean 1.99
Dorsal cortex thickness, level 4 (mm)	1.53			1.36** (-11%)	1.11–1.53 Mean 1.36

Dorsal cortex thickness, level 5 (mm)	1.40			1.32 (-6%)	1.19–1.41 Mean 1.32
Thalamus width, level 4 (mm)	8.98			8.39** (-7%)	8.27–8.86 Mean 8.59
Thalamus width, level 5 (mm)	8.11	8.04	7.93	7.49** (-8%)	7.41–7.98 Mean 7.78
Hippocampus width overall, level 5 (mm)	1.55	1.54	1.61	1.45* (-6%)	1.31–1.54 Mean 1.47
PND 63, females					
Terminal body weight (g)	228	220	218	207 (-9%)	205–232 Mean 218
Brain weight (g), post-perfusion	1.89	1.89	1.82*	1.80* (-5%)	1.75–1.92 Mean 1.82
Dorsal cortex thickness, level 4 (mm)	1.41			1.29 (-9%)	1.16–1.43 Mean 1.33
Dorsal cortex thickness, level 5 (mm)	1.41	1.39	1.35	1.33** (-6%)	1.19–1.34 Mean 1.29
Thalamus width, level 4 (mm)	8.46	8.51	8.73*	8.01** (-5%)	8.19–8.71 Mean 8.41
Thalamus width, level 5 (mm)	7.88	7.65	7.74	7.28** (-8%)	7.18–7.72 Mean 7.57
Hippocampus width overall, level 5 (mm)	1.55			1.46* (-6%)	1.34–1.58 Mean 1.46

Statistically significant difference from control: *, $p \leq 0.05$; **, $p \leq 0.01$

Missing morphometry values for 50 ppm and 400 ppm: Not analysed in the main study, analysed in a supplemental study and were processed several years after the main study. As variations between groups processed early (high-dose and control) versus those processed later (low-dose and mid-dose) could reflect a processing artefact, the values from the supplemental study are not included in the table.

[a] 11 studies conducted by the same laboratory in the same strain within 3 years of the present study (the present study started 03/2002, the HCD covers studies starting 10/2001–10/2004); the current study not included.
The ranges are ranges of control means per study (i.e. range for 11 mean values), the mean is a mean of means from the individual studies.

As to brain weights, scatter plots of the historical control data provided by industry during the public consultation (see 'Supplemental information') indicate a correlation between body weight and brain weight on PND 12. The regression equations predict a brain weight reduction of 4 % for top dose males and 5 % for top dose females, which are exactly the values observed in the study. Thus, the observed reductions in brain weight at the top dose on PND 12 can be attributed to reduced body weight.

The correlation between brain weight and body weight on PND 63 is apparently weaker. If the correlation is taken as significant (statistical significance of the slope is not reported in the position paper), the observed reductions are slightly larger than the predicted reductions (males: predicted 3 %, observed 5 %; females: predicted 2 %, observed 5 %), which suggests a contribution of a direct effect on the brain. The brain weights at the top dose are still within the HCD range. This does not mean that the statistically significant brain weight reductions at the top dose are not treatment-related, but indicates a relatively low magnitude of the effect.

While there seems to be a weak correlation between brain weight and body weight on PND 63, there is no correlation between morphometry measurements and body weight on PND 63 (based on a limited analysis of the individual data from the current study and HCD means). Therefore, the observed differences in morphometry have to be taken as such, indicating a direct effect on the brain. The top dose values were mostly within the HCD range (where applicable).

No effects were found on histopathological examination or in functional and neurobehavioural tests (FOB, motor activity, auditory startle, Y-shaped water maze with one escape ladder). However, these tests may not be sufficiently sensitive for detection of subtle but adverse changes in brain function. Specifically, the Y-maze test in its basic setup (no alteration of arms) is not a very difficult task for rats and thus not very sensitive (cf. discussion of T-maze in the OECD guidance document no. 43). The study report does mention alteration of arms.

Conclusion on classification for development

RAC considers the changes in brain morphometry and brain weight observed following pre- and early postnatal exposure of rats in the developmental neurotoxicity study to constitute limited evidence of developmental toxicity, **warranting classification in Category 2**.

Classification for developmental toxicity is further supported by testicular findings in F1 rats in both 2-generation studies (discussed in the fertility section); no such effects were seen in F0 males, so the testicular tubular atrophy / germ cell loss/disorganization in F1 males is apparently a result of prenatal and/or early postnatal exposure.

Adverse effects on or via lactation

The first 2-generation study (1998) reported reductions in pup body weight by less than 11%, mostly towards the end of the lactation period when the pups already feed on maternal diet. No significant effect on pup body weight was found in the second 2-generation study (2004) using the same top dose (2 500 ppm, 156 mg/kg bw/day).

In the DNT study the pup body weight at 4 000 ppm (299 mg/kg bw/day) was reduced by 8 %, 12 %, 13 % and 15 % on PND 1, 5, 12 and 18, respectively. The magnitude of body weight reduction corresponding to the lactation period (ca. 6 %) is not considered sufficient for classification.

Overall, RAC agrees with the DS that classification for adverse effects on or via lactation is not warranted.

Overall conclusion on reproductive toxicity

RAC concludes to classify thiamethoxam with **Repr. 2; H361fd** mainly based on (1) testicular tubular atrophy / germ cell loss/disorganisation in F1 rats, (2) ovarian atrophy in mice and (3) reduced size of certain brain regions (changes in weight and morphometry) in rat offspring exposed *in utero* and during the early postnatal period. The effects on sexual function and fertility are supported by testicular effects seen in dogs.

RAC is of the view that **due to the low dosing in the 2-generation studies the potential of the substance to adversely affect female sexual function and fertility has not been fully investigated**.

Supplemental information - In depth analyses by RAC

1-generation range-finding study to the first 2-generation study (1998)

In this study, Tif:RAIf rats (15/sex/dose) were administered thiamethoxam at dietary concentrations of 0, 1000, 2000 and 4000 ppm. The top dose was equivalent to 241/275 mg/kg bw/d (m/f) during premating, 346 mg/kg bw/d during gestation and 651 mg/kg bw/d during lactation. Pre-mating exposure period was 2 weeks for both sexes. Males were terminated after 4 weeks of exposure (2 weeks pre-mating, 2 weeks mating and post-mating), dams and pups were sacrificed on lactation day 14.

Terminal body weights of the top dose males and females were reduced by 5% and 6%, respectively, compared to controls. There were no significant clinical observations and no effect on mating index, fertility index, pre-coital interval, gestation index, duration of gestation, post-implantation loss, litter size, pup weight at birth or pup survival. Pup weight at termination (LD 14) was reduced by 10% (not statistically significant).

Historical control data for the second 2-generation study (2004)

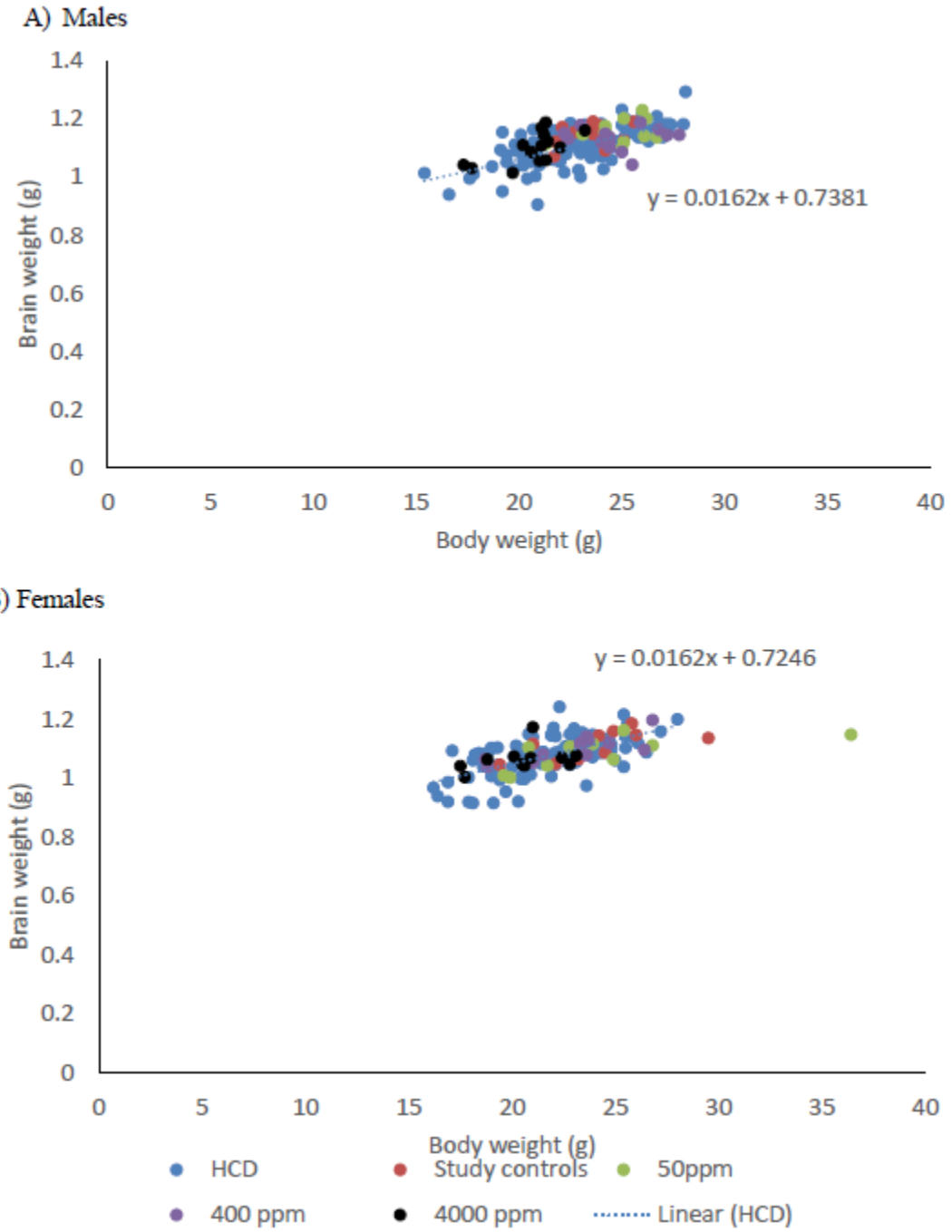
The table below shows control means for several parameters in the current 2-generation study (2004) and the two additional control studies.

Historical control data for 2-generation study (2004)						
Parameter	**Current study** (July 2002)		**HCD 1** (July 2002)		**HCD 2** (August 2002)	
	P	**F1**	**P**	**F1**	**P**	**F1**
Terminal bw (g)	551	464	501	469	532	483
Testes weight (g)	4.18	3.89	4.11	4.01	4.33	4.01
Epididymides weight (g)	1.66	1.58	1.55	1.63	1.76	1.67
Testicular sperm count, per testis (million)	98	87	93	85	103	69
Epididymal sperm count, per cauda (million)	148	153	146	137	154	170
Straight line velocity (µm/s)	76.7	71.6	75.2	64.9	72.7	73.7
Curvilinear velocity (µm/s)	316	305	280	278	302	306
Average path velocity (µm/s)	131	124	119	113	125	124

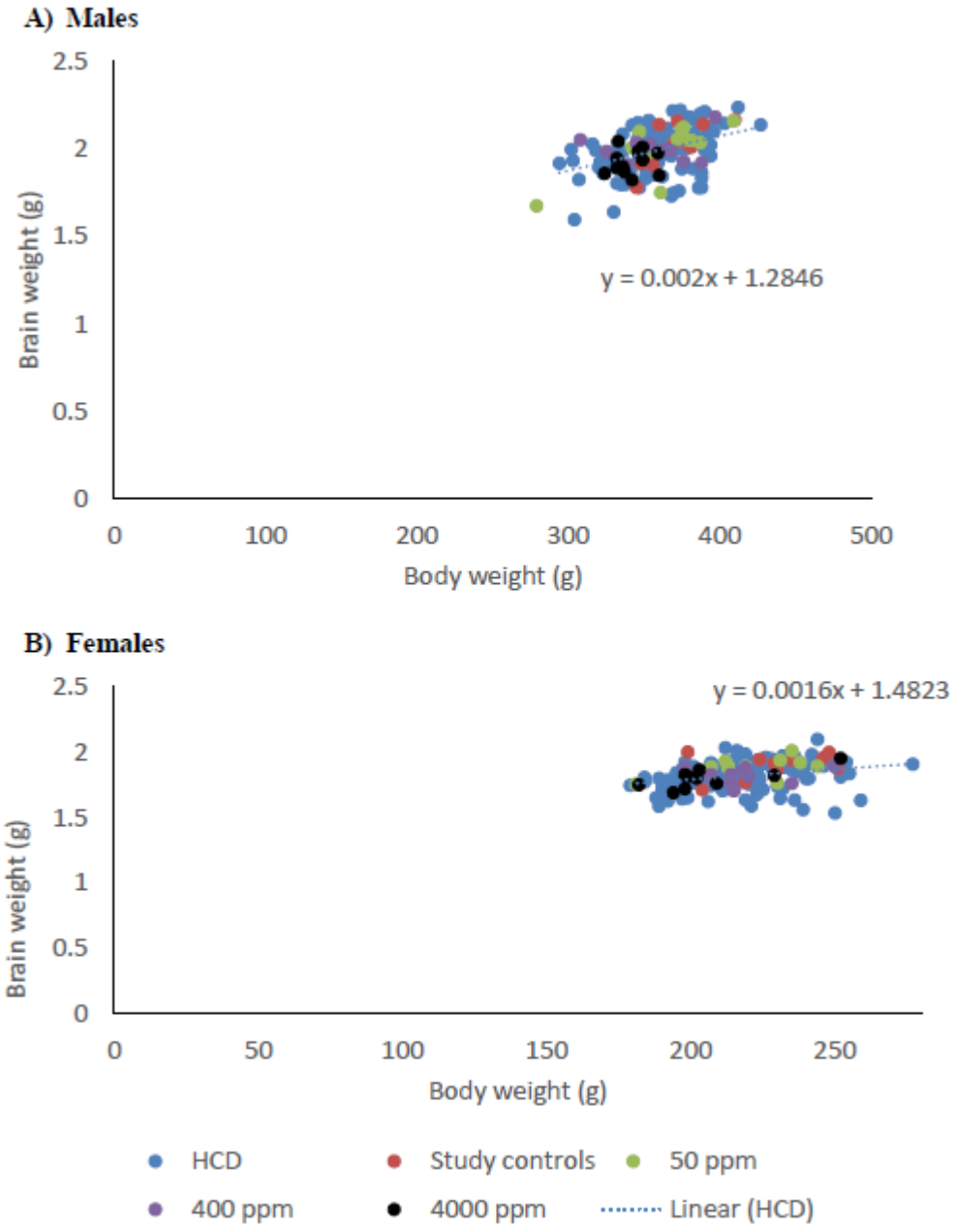
Relationship between body weight and brain weight

The following graphs were provided by industry during the public consultation. Brain weight data are plotted against body weight data for historical controls (11 studies) and the current study.

HCD: Brain weight vs body weight on PND 12



HCD: Brain weight vs body weight on PND 63 (post perfusion)



The effects observed on reproductive postnatal development in F1 males trigger both classification for fertility and developmental toxicity, therefore no specification (f or d) is proposed.
Co-RMS agrees with RMS proposal for classification Repr. Cat2 H361.

2.6.7 Summary of neurotoxicity

Table 52: Summary table of animal studies on neurotoxicity

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results: - NOAEL/LOAEL - target tissue/organ -critical effect at LOAEL**	**Reference**
Acute oral neurotoxicity study OECD Guideline 424 GLP Acceptable Rat, Sprague-Dawley Crl:CD®BR 10/ sex/group	Thiamethoxam technical Batch 9600110 (purity 98.7%) 0, 100, 500 and 1500 mg/kg Single oral (gavage) dose Vehicle: 0.5% w/v aqueous methylcellulose	**<u>At 100 mg/kg bw</u>** No differences from control. **<u>From 500 mg/kg bw:</u>** <u>Neurotoxicity</u> (effects observed 2-3 hours after dosing): - Decreased locomotor activity (males and females) - Decreased rectal temperature (males and females) - Increased forelimb grip strength (males only). **<u>At 1500 mg/kg bw:</u>** <u>General toxicity:</u> - Mortality (3/10 females 2 on Day1 and 1 on Day2) - Decreased BWG (males) <u>Neurotoxicity</u> (effects observed 2-3 hours after dosing): - Impaired respiration, tremors - longer latency to first step in the open field, crouched-over posture, gait impairment, hypo-arousal, decreased number of rears, uncoordinated landing during the righting reflex test. - Increased average input stimulus value in the auditory startle response test (males only) No treatment –related histopathological findings **NOAEL neurotoxicity: 100 mg/kg bw** **NOAEL general toxicity: 500 mg/kg bw**	[redacted], 1997 Refer to Annex I. Vol3CA B.6.7.1.1
13-Week dietary subchronic neurotoxicity OECD Guideline 424 GLP Acceptable Rat, Sprague-Dawley Crl:CD®BR 10/ sex/group	Thiamethoxam technical Batch 9600110 (purity 98.7%) ♂/♀: 0/0,10/10, 30/30, 500/1000 or 1500/3000 ppm (♂: 0, 0.7, 1.9, 31.8 or 95.4 mg/kg bw/day,	No difference from controls. **NOAEL General toxicity and neurotoxicity : highest tested dose** **males: 95.4 mg/kg bw/day (1500ppm)** **females: 216.4 mg/kg bw/ day (3000ppm)**	, 1998 Refer to Annex I. Vol3CA B.6.7.1.2

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results: - NOAEL/LOAEL - target tissue/organ -critical effect at LOAEL**	**Reference**
	♀: 0, 0.7, 2.1, 73.2 or 216.4 mg/kg bw/day) Continuous in the diet for 13 weeks.		
Developmental Neurotoxicity Study OECD Guideline 426 GLP Acceptable Rat, Wistar Alpk:APrSD 30 time-mated females/group	Thiamethoxam technical Batch P. 506006 (Purity: 98.8%) 0, 50, 400 or 4000 ppm (0, 4.3, 34.5 or 298.7 mg/kg bw/day) From GD7 to PND22 in diet	**<u>At 50 ppm (4.3 mg/kg bw per day) and 400 ppm (34.5 mg/kg bw per day):</u>** No difference from controls. **<u>At 4000 ppm (298.7 mg/kg bw/day):</u>** <u>Maternal toxicity:</u> Decreased BW gain (↓12% during gestation) and food consumption **Maternal NOAEL: 400 ppm (34.5 mg/kg bw per day)** <u>Offspring toxicity :</u> - Decreased pup BW at birth and decreased BW gain in males and females. - Delayed sexual maturation in males - Neurotoxicity Decreased absolute brain weight. Morphometric changes: At Day 12: ↓length and width of the cerebellum in males At Day 63: ↓in Level 3-5 measurements in males and in Level 4-5 in females **Offspring NOAEL (general toxicity and neurotoxicity): 400 ppm (34.5 mg/kg bw/day)**	[redacted], 2003 & 2006 Refer to Annex I. Vol3CA B.6.7.1.3
From open literature			

Behavioral and biochemical effects of neonicotinoid thiamethoxam on the cholinergic system in rats Non-Guideline (research study) Non-GLP Klimisch: 2 Rat:Wistar 9 males/group	Thiamethoxam Purity : 99.7% Vehicle: 0.9% saline solution 0, 25, 50 and 100 mg/kg bw/d **subcutaneous injection** 7 days	**<u>At 25 mg/kg bw/day :</u>** No difference from controls. **<u>From 50 mg/kg bw/day :</u>** - Decreased time in the open arms of elevated plus-maze. - Decreased AChE activity in the hippocampus when measured 2 hours after final dose. - Decreased AChE activity in the cortex and the striatum when measured 2 hours after final dose and or 7 days after final dose - Decreased of hippocampal high affinity choline uptake (HACU) **<u>At 100 mg/kg bw/day :</u>** - Decreased AChE activity in the hippocampus when measured 7 days after final dose. **NOAEL neurotoxicity: 25 mg/kg bw/day** **NOAEL general toxicity: 100 mg/kg bw/day** (systemic toxicity poorly reported)	Rodrigues K, 2010 Refer to Annex I. Vol3CA B.6.7.1.4.1

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results: - NOAEL/LOAEL - target tissue/organ -critical effect at LOAEL**	**Reference**
Effects of the neonicotinoids thiamethoxam and clothianidin *on in vivo* dopamine release in rat striatum. Non-Guideline (research study) Non-GLP Klimisch: 2 Rat: Sprague Dawley 5 females/group	Thiamethoxam Purity : 99.7% Clothianidin Purity : 99.9% Vehicle: Perfusion fluid (Ringer), at a final DMSO concentration of 2.5%. **Intrastriatal infusion** 60 min infusion TMX (1, 5 and 10 mM) and CLO (1, 2, 3.5 and 5 mM)	Intrastriatel infusion of CLO and TMX increased dopamine (DA) release in striatum **TMX at 10 nM** **CLO from 2 nM onwards**	Machado de Oliveira I., 2010. Refer to Annex I. Vol3CA B.6.7.1.4.2

In an acute guidelined neurotoxicity study, thiamethoxam induced effects on functional observational battery and locomotor activity parameters from 500 mg/kg onwards. These effects occurred at the time of peak systemic exposure, and were not associated with neuro-histopathological alterations. There was no neurotoxicity or neuropathological findings observed in a guidelined sub-chronic neurotoxicity study up to the higher dose tested of 1500/3000 ppm in males/females (eq. to 95 mg/kg bw/day and 216 mg/kg bw/day respectively).
Meanwhile, in published literature, two papers reported effects of thiamethoxam on the central nervous system in rats. While the routes of exposure (i.e.: subcutaneous injection and intrastriatal infusion) are not representative of exposure to pesticides, those research studies investigated several parameters not performed in the regulatory studies. They both suggested that thiamethoxam acted as a nicotinic agonist in CNS by stimulating presynaptic nAChRs and modulating the release of other neurotransmitters (serotonin and dopamine in Rodrigues K, 2010 and Machado de Oliveira I., 2010, respectively).

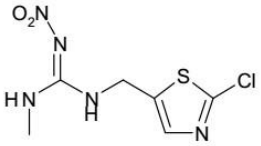
In the developmental neurotoxicity study, the maternal NOAEL was set at 400 ppm (34.51 mg/kg bw/day) based on reduced body weight gain and food consumption observed at 4000 ppm (298.7 mg/kg bw/day).
The offspring NOAEL for both general and neurodevelopmental toxicity, was also set at 400 ppm (34.5 mg/kg bw/day) based on decreased body weight and body weight gain in male and female F1 offspring, delayed sexual maturation in males, reduced absolute brain weight and morphometric changes in males and females observed at 4000 ppm (298.7 mg/kg bw/day).
The morphometric changes consisted of decreased length and width of the cerebellum in males on day 12, and significant decreases in Level 3-5 measurements in males and in Level 4-5 measurements in females on day 63.
While the maternal and the offspring NOAELs were set at the same dose, it is considered that young animals exhibited increased susceptibility compared to adults since findings in the pups (reduced brain weight and significant changes in brain morphometric measurements) were more severe than those in the dams (decreased body weight gain and food consumption).

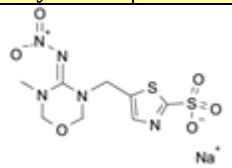
2.6.8 Summary of other toxicological studies

2.6.8.1 Toxicity studies of metabolites and impurities

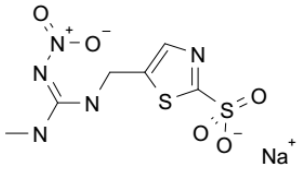
Groundwater metabolites:
The relevance of thiamethoxam environmental metabolites CGA322704, NOA459602, CGA282149 and SYN501406 has been considered. A complete toxicological assessment is available for thiamethoxam. CGA322704 is a major mammalian metabolite of thiamethoxam and as such, its toxicity has been assessed in the regulatory studies on thiamethoxam parent. In addition, a complete toxicological assessment is available in the form of published EU endpoints for CGA322704 as the plant protection active substance clothianidin.
Neither thiamethoxam nor clothianidin are **currently** classified as 'Toxic', and they have no classification for either carcinogenicity or reproductive toxicity.
The available toxicity data of CGA322704, NOA459602, CGA282149 and SYN501406 are summarised in the table below.
It should be noted that if the classification proposal for reproductive toxicity is agreed, the reprotoxic profile of groundwater metabolites should be addressed in order to assess their relevance according to Sanco/221/2000 –rev.10- final 25 February 2003.

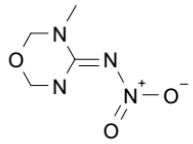
See also level 2.11 for relevance assessment

Type of study/data	Test substance, dose levels duration of exposure	Relevant information about the study (as applicable), Observations	Reference
Studies on metabolite CGA 322704 (Clothianidin) 			
Acute oral toxicity study OECD 401 GLP Acceptable	CGA 322704 Batch RV-2793/6 (purity 99%) Rat, Hanlbm: Wistar 5/sex/group Sighting phase : 1500, 2000 mg/kg bw Single dose followed by 14 day observation period. Vehicle: 0.5% carboxymethylcellulose 0.1% aqueous polysorbate 80	**<u>Main phase at 2000 mg/kg bw:</u>** No deaths observed. **$LD_{50} \geq 2000$ mg/kg bw in both sexes**	[redacted], 1998 Refer to Annex I. Vol3CA B.6.8.1.1.1
Bacterial gene mutation assay OECD 471 GLP Acceptable	CGA 322704 Batch RV-2793/6 (purity 99%) Solvent Dimethylsulfoxide (DMSO) S. typhimurium strains TA 98, TA 100, TA 102, TA 1535, TA 1537; E. coli WP2, WP2 uvr A *S. typhimurium* & *E. coli*: 5 concentrations in the range of 312.5 to 5000 µg/plate with and without metabolic activation.	Not mutagenic with and without metabolic activation in *S. typhimurium* and *E. coli*	Deparade, 1998 Refer to Annex I. Vol3CA B.6.8.1.1.1
Clothianidin is an approved active substance Genotoxicity: *in vitro* clastogenic at cytotoxic dose, negative in Ames, HPRT *in vitro* negative in mouse bone marrow and liver UDS ADI = 0.097 mg/kg bw/day ARfD = 0.1 mg/kg bw Since clothianidin is currently being reassessed under Regulation EC n°1107/2009, the above mentioned end points may be challenged during peer-review process.			06/41/EC
Acute Tox. 4 - H302			Regulation EC n° 1272/2008
Studies on metabolite NOA 459602			

Type of study/data	Test substance, dose levels duration of exposure	Relevant information about the study (as applicable), Observations	Reference
			
Acute oral toxicity study OECD 420 GLP Acceptable	NOA 459602 Batch KI 6510/10 (purity 99%) Rat, Alpk:APfSD (Wistar-derived) 5/sex/group (main phase) Sighting phase : 500, 2000 mg/kg bw Main phase : 2000 mg/kg bw Single dose followed by 14 day observation period. Vehicle: 1% carboxymethylcellulose in water	**Sighting phase :** One female per group tested at 500 or 2000 mg/kg : no deaths observed **Main phase at 2000 mg/kg bw:** No deaths observed. **LD_{50} ≥ 2000 mg/kg bw in both sexes**	[redacted] 2002 Refer to Annex I. Vol3CA B.6.8.1.1.2
Bacterial gene mutation assay OECD 471 GLP Acceptable	NOA 459602 Batch KI 6510/10 (purity 99%) Solvent Dimethylsulfoxide (DMSO) S. typhimurium strains TA 98, TA 100, TA 1535, TA 1537; E. coli WP2, WP2 uvr A S. typhimurium & E. coli: 100, 200, 500, 1000, 2500 and 5000 µg/plate with and without metabolic activation.	Not mutagenic with and without metabolic activation in *S. typhimurium* and *E. coli*	Callander R D, 2002 Refer to Annex I. Vol3CA B.6.8.1.1.2
Mammalian gene mutation assay OECD 476 GLP Acceptable	NOA 459602 Batch KI 6510/10 (purity 99%) Solvent Dimethylsulfoxide (DMSO) Mouse lymphoma L5178Y cells 125, 250, 500, 1000, 2000, 3593 µg/mL with and without metabolic activation.	Not mutagenic with and without metabolic activation	[redacted] 2002 Refer to Annex I. Vol3CA B.6.8.1.1.2
Mammalian cytogenetic test Chromosome aberrations OECD 473 GLP Acceptable	NOA 459602 Batch KI 6510/10 (purity 99%) Solvent Dimethylsulfoxide (DMSO) Human lymphocytes. 250, 2000, 3593 µg/mL with and without metabolic activation.	Not clastogenic with and without metabolic activation for 3h exposure Clastogenic without S9 for 20 h exposure	[redacted] 2002 Refer to Annex I. Vol3CA B.6.8.1.1.2
Micronucleus test mouse OECD 474 GLP Acceptable	NOA 459602 (Metabolite of CGA 293343) Batch KI 6510/10 (purity 99%) Solvent 0.5% carboxymethylcellulose in 0.1% polysorbate 80 5 CD-1 mice per group and time point Mice treated at 2000 mg/kg and sacrificed 24 and 48 hours post-application	Not clastogenic in the *in vivo* mouse bone marrow micronucleus test	[redacted] 2002a Refer to Annex I. Vol3CA B.6.8.1.1.2
A proof of exposure study after single dose oral administratio	NOA 459602 (Metabolite of CGA 293343) Batch KI 6510/10 (purity 99%) Solvent 0.1 % Tween 80 in 0.5 % carboxymethylcellulose	The highest concentration of NOA459602 was measured in 1 hour post-dose samples and slowly decreased up to 4 hour post-dose and reached the lower limit of quantification in the blood samples 24 hours post-dose. Exposure of the bone marrow to the test item	[redacted], 2016 Refer to Annex I. Vol3CA

Type of study/data	Test substance, dose levels duration of exposure	Relevant information about the study (as applicable), Observations	Reference
n of NOA459602 in the mouse. GLP Acceptable	3 Mice Hsd ICR:CD1 (Harlan) treated with a single oral dose of 2000 mg/kg bw and sacrificed at day 1. Blood sampling at 1, 4 and 24h after dosing	was assessed indirectly by demonstrating the presence of NOA459602 in the blood.	B.6.8.1.1.2
The *in vitro* Blood Cell Partitioning of NOA459602 in mouse. GLP Acceptable	NOA 459602 (Metabolite of CGA 293343) Batch KI 6510/10 (purity 99%) 3 male CD-1 mice blood incubated for 120 minutes at nominal concentrations of 0.4, 4 and 8 µg/mL.	Plasma/blood cell partitioning data in male mouse blood were comparable at all the concentrations investigated. A minimal association with red blood cells was observed which indicates NOA459602 is preferentially distributed in the plasma under the experimental conditions employed	Sayer R, Noctor J, 2017 Refer to Annex I. Vol3CA B.6.8.1.1.2
Unscheduled DNA repair OECD 486 GLP Acceptable	NOA 459602 (Metabolite of CGA 293343) Batch KI 6510/10 (purity 99%) Solvent 1% CMC 3 male Rat Alpk:APfSD per group treated with a single oral dose of 2000 mg/kg bw and sacrificed 16h (expt 1) or 2 hours (expt 2) post-application	No induction of unscheduled DNA synthesis	[redacted] 2002a Refer to Annex I. Vol3CA B.6.8.1.1.2
28-days oral toxicity study OECD 407 GLP Acceptable	NOA 459602 (Metabolite of CGA 293343) Batch KI 6510/10 (purity 99%) Rat, Alpk:AP SD (Wistar-derived) 5/sex/group 150, 1500, 15000 ppm (♂: 0, 15.7, 161.2 or 1658.8 mg/kg bw/day, ♀: 0, 16.3, 164.5 or 1623.7 mg/kg bw/day) Continuous in the diet for 28 days.	**At 150 ppm :** No differences from control. **From 1500 ppm :** Males: increased motor activity **At 15000 ppm :** Males: Decrease in plasma alkaline phosphatase activity (21%) Lower absolute and adjusted epididymides weight (13%and 11%) Increased hindlimb grip strength Females: Decrease in plasma bilirubin (37%) Lower adjusted brain weight (7%) Females **NOAEL: 150 ppm equivalent to 15.7 mg/kg bw/day (males) and 1500 ppm equivalent to 164.5 mg/kg bw/day (females)**	[redacted], 2002 Refer to Annex I. Vol3CA B.6.8.1.1.2
90-days oral toxicity study OECD 408 GLP Acceptable	NOA 459602 (Metabolite of CGA 293343) Batch KI6510/010 and KI6510/021* (purity 99%/99%*) Rat, Alpk:AP SD (Wistar-derived) 12/sex/group 150, 1500, 15000 ppm (♂: 0, 12.5, 124 or 1242 mg/kg bw/day, ♀: 0, 13.9, 140 or 1450 mg/kg bw/day) Continuous in the diet for 90 days.	**At 150 ppm :** No differences from control. **At 1500 ppm :** No differences from control. **At 15000 ppm :** Males: no differences from control. Females: decreased motor activity **NOAEL: and 1500 equivalent to 140 mg/kg bw/day (females) and 15000 ppm equivalent to 1242 mg/kg bw/day (males)**	[redacted] 2003a Refer to Annex I. Vol3CA B.6.8.1.1.2
Studies on SYN 501406 metabolite			

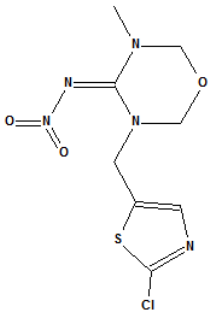
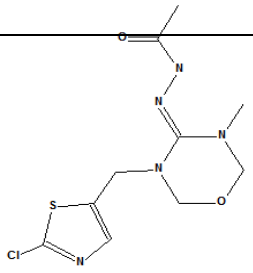
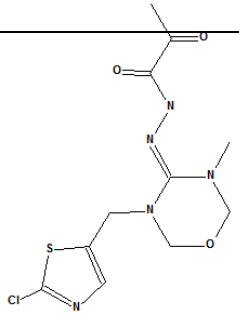
Type of study/data	Test substance, dose levels duration of exposure	Relevant information about the study (as applicable), Observations	Reference
			
Acute oral toxicity study OECD 425 GLP Acceptable	SYN501406 Batch MLA-502/12 K 12 (purity 88% (10% of inorganic material (H2O,NaHCO3 + NaHCO3) and 2% organic impurities)) Rat, Alpk:APfSD (Wistar-derived) 5 female/group 2000 mg/kg Single dose followed by 14 day observation period. Vehicle: Deionised water	**<u>At 2000 mg/kg:</u>** No deaths observed. **$LD_{50} \geq 2000$ mg/kg**	[redacted], 2002 Refer to Annex I. Vol3CA B.6.8.1.1.3
Bacterial gene mutation assay OECD 471 GLP Acceptable	SYN501406 Batch MLA-502/12 K 12 (purity 88% (10% of inorganic material (H2O,NaHCO3 + NaHCO3) and 2% organic impurities)) Solvent Dimethylsulfoxide (DMSO) S. typhimurium strains TA 98, TA 100, TA 1535, TA 1537; E. coli WP2, WP2 uvr A S. typhimurium & E. coli: 100, 200, 500, 1000, 2500 and 5000 µg/plate with and without metabolic activation.	Not mutagenic with and without metabolic activation in S. typhimurium and E. coli	Callander R, 2003 Refer to Annex I. Vol3CA B.6.8.1.1.3
Mammalian gene mutation assay OECD 476 GLP Acceptable	SYN501406 Batch CRI-5276 (purity 98 % (± 2 %) SYN501406 [based on C6H8N5O5S2Na . 0.03 NaCl . 0.9 Na2CO3 . 1.0 NaHCO3 . 2.3 H2O] 58% SYN501406 [based on C6H8N5O5S2Na]) Solvent Deionised water Mouse lymphoma L5178Y cells 171.3, 342.5, 685, 1370, 2740, 5480 µg/mL with and without metabolic activation.	Not mutagenic with and without metabolic activation	Wollny H, 2009 Refer to Annex I. Vol3CA B.6.8.1.1.3
Mammalian cytogenetic test Chromosome aberrations OECD 473 GLP Acceptable	SYN501406 Batch CRI-5276 (purity 98 % (± 2 %) SYN501406 [based on C6H8N5O5S2Na . 0.03 NaCl . 0.9 Na2CO3 . 1.0 NaHCO3 . 2.3 H2O] 58% SYN501406 [based on C6H8N5O5S2Na]) Solvent Deionised water Human lymphocytes. 1786.1, 3125.7, 5470.0 µg/mL with and without metabolic activation.	Not clastogenic with and without metabolic activation	Bohnenberger S, 2009 Refer to Annex I. Vol3CA B.6.8.1.1.3
Studies on metabolite CGA 282149			

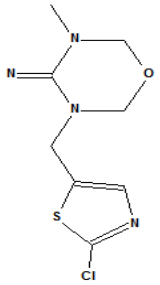
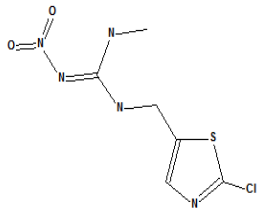
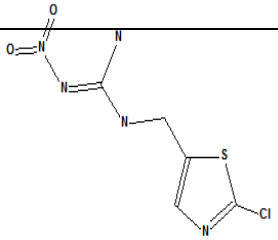
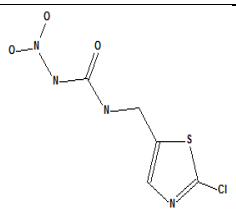
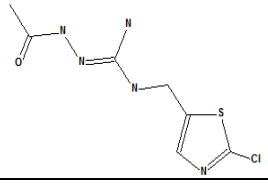
Type of study/data	Test substance, dose levels duration of exposure	Relevant information about the study (as applicable), Observations	Reference
			
Acute oral toxicity study OECD 401 GLP Acceptable	CA2343A (Intermediate of CGA 293343) Batch P.503005 (purity 96.7%) Rat, Tif:RAI f (SPF) 5/sex/group 1000 or 2000 mg/kg bw Single dose followed by 14 day observation period. Vehicle: 0.5% w/v carboxymethyl cellulose in 0.1% w/v aqueous polysorbate 80	**<u>At 1000 mg/kg bw:</u>** No deaths observed. **<u>At 2000 mg/kg bw:</u>** 3/5 males and all the females were found dead within 7 hours following administration. **LD_{50} > 1000 mg/kg bw and < 2000 mg/kg bw**	[redacted], 1995 Refer to Annex I. Vol3CA B.6.8.1.1.4
Bacterial gene mutation assay OECD 471 GLP Acceptable	CA2343A (Intermediate of CGA 293343) Batch P.503005 (purity 96.7%) Solvent Dimethylsulfoxide (DMSO) S. typhimurium strains TA 98, TA 100, TA 102, A 1535, TA 1537; E. coli WP2 uvr A S. typhimurium & E. coli: 312, 625, 1250, 2500 and 5000 µg/plate with and without metabolic activation.	Not mutagenic with and without metabolic activation in S. typhimurium and E. coli	Hertner T, 1995 Refer to Annex I. Vol3CA B.6.8.1.1.4
Mammalian cytogenetic test Chromosome aberrations OECD 473 GLP Acceptable	CA2343A (Intermediate of CGA 293343) Batch P.503005 (purity 96.7%) Solvent Deionised water Chinese hamster ovary (CHO) cells Original Experiment: 312.5, 625.0, 1250.0, 2500.0, 5000 µg/mL with and without metabolic activation. Confirmatory Experiment : 625.0, 937.5, 1250.0, 1875.0, 2500.0 µg/mL with and without metabolic activation.	Clastogenic with metabolic activation but not clastogenic without metabolic activation	Ogorek B, 1996c Refer to Annex I. Vol3CA B.6.8.1.1.4
Micronucleus test mouse OECD 474 GLP Acceptable	CA2343A (Intermediate of CGA 293343) Batch P.503005 (purity 96.7%) Solvent 0.5% CMC 5 Tif: MAGf(SPF) mice per group/sex and time point Mice treated at 2000 mg/kg and sacrificed 16, 24 and 48 hours post-application Preliminary study : 500, 800, 1200 mg/kg Main study : 62.5, 125, 250, 500 mg/kg	Not clastogenic in the *in vivo* mouse bone marrow micronucleus test	[redacted], 1997 Refer to Annex I. Vol3CA B.6.8.1.1.4
Oral (Gavage) Proof of Exposure Study in the Mouse GLP Acceptable	CGA282149 (intermediate of CGA293343) Batch MES 398/1 (purity 99%) Solvent 0.5% CMC 3 male Mice Crl:CD-1 treated with a single oral dose of 62.5 mg/kg bw and sacrificed at day 1. Blood sampling at 1, 4 and 24h after dosing	Exposure to CGA282149 was confirmed in all three animals, by presence of the test item in circulating blood and plasma at 1 and 4 hours after dosing.	[redacted], 2017 Refer to Annex I. Vol3CA B.6.8.1.1.4
Unscheduled	CA2343A (Intermediate of CGA	No induction of unscheduled DNA synthesis	[redacted],

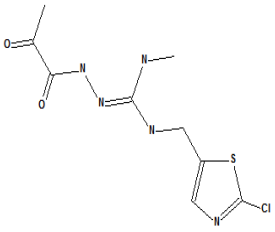
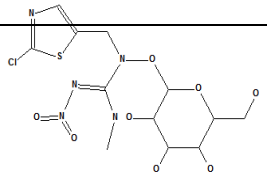
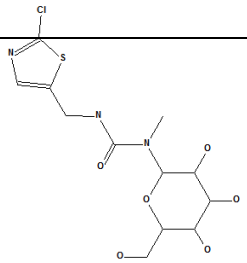
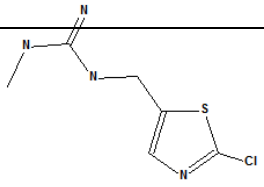
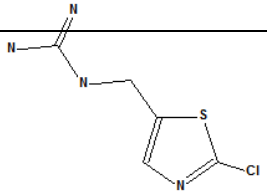
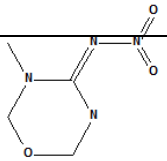
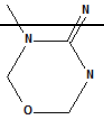
Type of study/data	Test substance, dose levels duration of exposure	Relevant information about the study (as applicable), Observations	Reference
DNA repair OECD 486 GLP Acceptable	293343) Batch P.503005 (purity 96.7%) Solvent 0.5% CMC 4 male Rat Wistar Hanlbm: WIST (SPF) per group treated with a single oral dose and sacrificed 16h (expt 1) or 2 hours (expt 2) post-application Preliminary study : 1000, 1500, 2000 mg/kg Main study : 1250, 312.5 mg/kg	*in vivo*	2001 Refer to Annex I. Vol3CA B.6.8.1.1.4

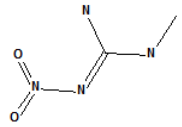
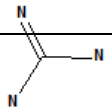
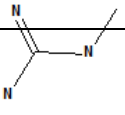
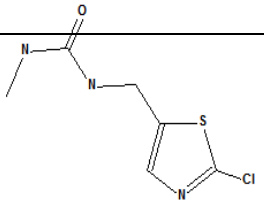
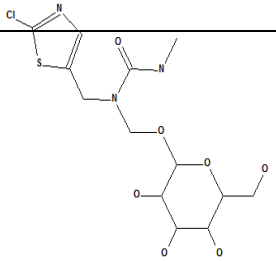
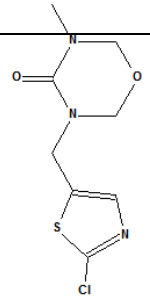
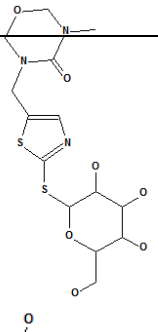
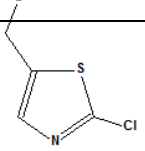
Residue in food and feed:

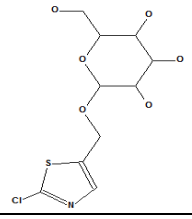
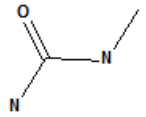
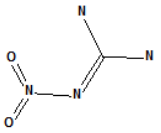
Several metabolites were identified (refer to residue section). Depending on the level they are retrieved in foodstuff, their genotoxic potential and their toxicological profile have to be addressed. No specific data has been submitted and therefore a data gap is set.

Common name	Chemical name	Chemical structure	Compound found in	Toxicological data
CGA 293343, thiamethoxam CAS No. 153719-23-4	3-(2-chloro-thiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidene-N-nitroamine		Crop (Lettuce, cucumber, pear, tobacco, potato, rice, maize) Animal (rat, lean meat, (poultry), fat and skin (poultry), egg, muscle (ruminant), fat (ruminant), kidney (ruminant), milk) Soil Water	
N5	acetic acid [3-(2-chloro-thiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidene]-hydrazide		Ruminant (kidney)	Genotoxicity: Data gap General toxicity: Data gap
L14	2-oxo-propionic acid[3-(2-chloro-thiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidene]-hydrazide		Rat (minor) Ruminant (liver, kidney)	Genotoxicity: Data gap General toxicity: Data gap

Common name	Chemical name	Chemical structure	Compound found in	Toxicological data
NOA407475 I3 CAS No. 868542-26-1	3-(2-chloro-thiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidene amine		Crop (lettuce, cucumber, potato folliage, maize fodder) Rotation (radish tops) Ruminant (liver) Rat (minor) Aqueous photolysis, soil photolysis, aerobic soil, anaerobic soil, water-sediment systems, paddy soil	Genotoxicity: Data gap General toxicity: Data gap
CGA322704, clothianidin CAS No. 205510-53-8	N-(2-chloro-thiazol-5-ylmethyl)-N'-methyl-N''-nitro-guanidine		Crop (lettuce, pear, tobacco, potato, rice, maize), Rat (major) Poultry (fat and skin, liver, egg) Ruminant (muscle, fat, milk) Hydrolysis, aqueous photolysis, soil photolysis, soil aerobic, soil anaerobic	ADI = 0.097 mg/kg bw ARfD = 0.1 mg/kg bw Since clothianidin is currently being reassessed under Regulation EC n°1107/2009, the above mentioned end points may be challenged during peer-review process.
CGA265307, CLO-dm TZNG CAS No. 135018-15-4	N-(2-chloro-thiazol-5-ylmethyl)-N'-nitro-guanidine		Crop (lettuce) Rotation (cereals husks, radish tops) Poultry (lean meat, fat and skin, liver, egg) Ruminant (milk) Rat (minor) Mouse (major) Soil aerobic	Major metabolite of clothianidin in rat Refence dose of clothianidin
NOA404617 CAS No. 902493-08-7	N-(2-chloro-thiazol-5-ylmethyl)-N'-nitro-urea		Rat (minor) Poultry (egg) Hydrolysis, soil photolysis, anaerobic soil, water-sediment systems, OECD 309	Genotoxicity: Data gap General toxicity: Data gap
MU3	acetic acid {amino-[(2-chloro-thiazol-5-ylmethyl)-amino]-methylene}-hydrazide		Rat (minor) Poultry (lean meat, fat and skin, liver)	Genotoxicity: Data gap General toxicity: Data gap

Common name	Chemical name	Chemical structure	Compound found in	Toxicological data
MU12	2-oxo-propionic acid{[(2-chloro-thiazol-5-ylmethyl)-amino]-methylamino-methylene}-hydrazide		Goat (muscle, kidney)	Genotoxicity: Data gap General toxicity: Data gap
CGA322704-hydroxyl-amine-glucoside	(N-(2-chloro-thiazol-5-ylmethyl)-N'-methyl-N''-nitro-guanidine)-N-Glucose conjugate		Leaf (pear leaf and potato folliage)	Genotoxicity: Data gap General toxicity: Data gap
CGA353968-N-glucoside conjugate	(1-(2-chloro-thiazol-5-ylmethyl)-3-methyl-urea)-N-sugar conjugate		Leaf (lettuce, cucumber, tobacco) Potato (tuber)	Genotoxicity: Data gap General toxicity: Data gap
NOA421275 I7	N-(2-chloro-thiazol-5-ylmethyl)-N'-methyl-guanidine		Crop (lettuce, potato folliage, maize fodder) Rotation (cereal straw) Poultry (lean meat, liver) Ruminant (fat, liver, kidney) Rat (minor)	Genotoxicity: Data gap General toxicity: Data gap
NOA421276	N-(2-chloro-thiazol-5-ylmethyl)-guanidine		Rat (minor) Ruminant (muscle, fat, liver, kidney)	Genotoxicity: Data gap General toxicity: Data gap
CGA282149 CAS No. 153719-38-1	2H-1,3,5-oxadiazin-4-amine,3,6-dihydro-3-methyl-N-nitro		Crop (potato) Rat (minor) Soil photolysis, soil aerobic	Genotoxicity: negative Acute oral tox : General toxicity: LD50 > 1000 mg/kg and < 2000 mg/kg Data gap for repeated toxicity
CGA353042 CAS No. 915125-06-3	3-methyl-[1,3,5]oxadiazina n-4-yliden-amine		Crop (lettuce, potato folliage) Rat (minor) Aqueous photolysis, soil photolysis	Genotoxicity: Data gap General toxicity: Data gap

Common name	Chemical name	Chemical structure	Compound found in	Toxicological data
NOA405217 CAS No. 4245-76-5	N-methyl-N'-nitro guanidine		Crop (lettuce) Rotation (cereal straw and husks) Rat (minor) Aerobic soil	Genotoxicity: Data gap General toxicity: Data gap
NOA436944	Guanidine		Crop (potato folliage)	Genotoxicity: Data gap General toxicity: Data gap
CGA382191 I5 CAS No. 21770-81-0	1-N-methyl-guanidine		Crop (lettuce)	Genotoxicity: Data gap General toxicity: Data gap
CGA353968	1-(2-chloro-thiazol-5-ylmethyl)-3-methyl-urea		Crop (lettuce)	Genotoxicity: Data gap General toxicity: Data gap
CGA 353968-O-glucoside conjugate	1-(2-chloro-thiazol-5-ylmethyl)-1-hydroxymethyl-3-methyl-urea)-O-glucoside		Crop (lettuce)	Genotoxicity: Data gap General toxicity: Data gap
CGA355190	3-(2-chloro-thiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-one		Crop (lettuce)	Genotoxicity: Data gap General toxicity: Data gap
CGA355190-S-Glucose conjugate	3-(2-mercapto-thiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-one)-S-Glucoside		Crop (lettuce)	Genotoxicity: Data gap General toxicity: Data gap
CGA349208	(2-chloro-thiazol-5-yl)-methanol		Crop (lettuce)	Genotoxicity: Data gap General toxicity: Data gap

Common name	Chemical name	Chemical structure	Compound found in	Toxicological data
CGA349208-O-Glucose conjugate	((2-chloro-thiazol-5-yl)-methanol)-O-glucoside		Crop (lettuce)	Genotoxicity: Data gap General toxicity: Data gap
CGA204261	1-methyl urea		Crop (lettuce)	Genotoxicity: Data gap General toxicity: Data gap
NOA424255	N-nitro guanidine		Crop (lettuce)	Genotoxicity: Data gap General toxicity: Data gap

2.6.8.2 Supplementary studies on the active substance

- **Mechanistic studies on kidney effects in the rat**

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Non-guideline investigative study Acceptable Rat, Tif:RAIf (SPF) 5/sex/group	Thiamethoxam technical Batch: KGL4654/12 (purity > 95%) 0, 2500 and 10000 ppm In diet	Retrospective immunohistochemical assessment of the nature of hyaline accumulation in kidneys of male animals of the 28-d rat study • H&E (Hematoxylin & Eosin) • immunohistochemistry/haematoxylin • $\alpha_{2\mu}$ -globulin immunohistochemistry without primary antibody	Increased accumulation of α2μ-globulin in the kidney in males at 2500 ppm, as characterised by immunohistochemistry.	[redacted] (2000) Refer to Annex I. Vol3CA B.6.8.2.1
Non-guideline investigative study Acceptable Rat, Tif:RAIf (SPF) 5/sex/group	Thiamethoxam technical Batch: KI-4654/18 (purity > 98.4%) 0 and 5000 ppm In diet	Retrospective immunohistochemical assessment of the nature of hyaline accumulation in kidneys of male animals of the 90-d rat study Same procedure as above	Increased accumulation of $\alpha_{2\mu}$-globulin in the kidney in males at 5000 ppm, as characterised by immunohistochemistry.	[redacted] (2000a) Refer to Annex I. Vol3CA B.6.8.2.1

Non-guideline investigative study Acceptable Rat, Tif:RAIf (SPF) males: 6-9/group females: 5/group	Thiamethoxam technical BatchP.50600 (purity 98.6%) Males: 0 and 1500 ppm Females 0 and 3000 ppm Continuous in the diet for 52 weeks.	Retrospective immunohistochemical assessment of the nature of hyaline accumulation in kidneys of male animals of chronic rat study after 12 months ([redacted], 1998) Same procedure as above	Increased accumulation of $\alpha_{2\mu}$-globulin in the kidney in males at 5000 ppm, as characterised by immunohistochemistry.	[redacted] (2000b) Refer to Annex I. Vol3CA B.6.8.2.1
Non-guideline investigative study Acceptable Rat, Tif:RAIf (SPF) males: 10/group females: 5-10/group	Thiamethoxam technical BatchP.50600 (purity 98.6%) Males: 0 and 1500 ppm Females 0 and 3000 ppm Continuous in the diet for 52 weeks.	Retrospective immunohistochemical assessment of the nature of hyaline accumulation in kidneys of male animals of the chronic rat study after 24 months ([redacted], 1998) Same procedure as above	Increased accumulation of $\alpha_{2\mu}$-globulin in the kidney in males at 5000 ppm, as characterised by immunohistochemistry.	[redacted] (2000c) Refer to Annex I. Vol3CA B.6.8.2.1

Thiamethoxam induces kidney toxicity in male in rats consistently in the repeated dose studies. The proposed underlying mode of action is that the observed kidney toxicity in male rats is due to α2μ-globulin nephropathy.
In order to support this hypothesis, the applicant has proposed a weight of evidence analysis of the thiamethoxam data set against the MoA as postulated by IARC (1999) and using the IPCS/ILSI FRAMEWORK for the evaluation of the human health relevance of a hypothesized mode of action. Reduced catabolism of α2μ-globulin in hyaline droplets due to xenobiotic conjugation is a well-documented mechanism and has been demonstrated to occur in male rats treated with a range of compounds.
The regulatory studies together with specific retrospective immunohistochemical assessments of α2μ-globulin in kidneys support the propose mode of action. The 'triad' of lesions indicating the presence of α2μ-globulin nephropathy were present in male rats consistently in the repeated dose studies. The biology plausibility, the time and dose concordance were demonstrated.
Neither hyaline droplets nor other typical histopathological changes were identified in female rats and mice of both sexes.
Although, some uncertainty remains (thiamethoxam conjugation to α2μ-globulin was not investigated and no staining for α2μ-globulin was determined below 1500ppm), RMS is of the opinion that the weight of evidence analysis of the available data set supports a mode of action via α2μ-globulin accumulation for kidney lesions observed in male rats exposed to thiamethoxam.

- **<u>Supplementary data on liver effects in repeat dose studies in the mouse.</u>**

See table 44.

The numerous submitted mechanistic studies support the proposed underlying mode of action of liver tumors observed in mice (i.e.: liver tumours induced through sustained cytotoxicity and subsequent regenerative hyperplasia induced by hepatocyte cytotoxicant metabolite).
Indeed, the submitted mechanistic data as well as published data from an independent team demonstrated that the liver tumours observed in mice are induced through sustained cytotoxicity and subsequent regenerative hyperplasia induced by hepatocyte cytotoxicant metabolite.
Throughout the database, a good dose-concordance and a temporal concordance between the causal key events, associative events and the apical outcome (liver tumours) were observed in both male and female mice. The available data also permitted to adequately rule out alternative MoAs (i.e., genotoxicity, peroxisome proliferation, AhR induction, CAR and/or PXR induction, estrogenic stimulation, statins, infections, iron/copper

overload, and increased apoptosis).
Mechanistic data along with data from the open literature permit also conclude that this mode of action is of low relevance for human on the basis of marked quantitative differences in metabolism between mice and humans.

- **Immunotoxicity**

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL (for sexual function and fertility, parents) - target tissue/organ - critical effects at the LOAEL**	**Reference**
Immunotoxicity Study OPPTS 870.7800 (1998) GLP Mice females B6C3F1 10/group	Thiamethoxam technical Batch: SGO7K699E (purity > 95%) TMX: 0, 100, 1250 or 5000 ppm in diet 28 day (0, 37.2, 447.8 or 2025.8 mg/kg bw/day) **Subset** **AFC Assay** Positive control: Cyclophosphamide **Subset** **NKC assay** Positive control: Anti asialo GM1	**At 100 ppm (37.2 mg/kg bw/day):** No treatment related effect **At 1250 ppm (447.8 mg/kg bw/day):** General toxicity: Increased relative liver weight in AFC group (10.3%) **From 5000 ppm (2025.8 mg/kg bw/day):** General toxicity: Decreased bw gain 69.6% and 83.3% in AFC and NKC groups. Increased relative liver weight in AFC and NKC groups Immunotoxicity: Decreased spleen weight in both AFC and NKC groups Decreased spleen cellularity Decreased thymus weight in NKC group At any dose level: no suppression of the humoral (AFC) or innate (NKC) components of the immune system. **NOAEL immunotoxicity : 1250 ppm (eq. to: 447.8 mg/kg bw/day)** **NOAEL general toxicity: 1250 ppm (eq. to: 447.8 mg/kg bw/day)**	[redacted], 2011 Refer to Annex I. Vol3CA B.6.8.2.3
Study on the impact of lead acetate pollutant on immunotoxicity produced by thiamethoxam pesticide Non-Guideline (research study) Non-GLP Klimisch: 3 Mice Albino (strain not reported) 6/group	Thiamethoxam Purity : not stated Vehicle: corn oil 0, 43.5, 87.1mg/kg bw/d 29 days gavage Other groups : lead acetate alone or co-exposure to lead acetate and thiamethoxam	Alterations on both humoral immunity and cell mediated immune response from 43.5mg/kg bw/d onwards. **Limitations:** parameters of general systemic toxicity not investigated/reported, lack of positive control, only two dose tested, results poorly reported (e.g.: numerical data available for plasmatic globulins), lack of historical control data.	, 2014. Refer to Annex I. [redacted] B.6.8.2.3

The occurrence of α_7 nAChR in non-neuronal cells as T-lymphocytes or endothelial cells suggests that target-cell populations of the neonicotinoids may also include those of the immune system (EFSA Journal 2013;11(12):3471). Immunotoxic potential of thiamethoxam has been investigated in a guidelined 28-d immunotoxicity study in mice in which thiamethoxam did not impact humoral immunity or innate immunity (lack of effects on both AFC assay and NKC assay) up to a dose level of 2025.8 mg/kg bw/d. Decreased spleen and thymus weights as well as decreased spleen cellularity were observed at the top dose level in the presence of marked general toxicity (decreased body weight gain of 70-80%).

The NOAEL for both general systemic toxicity and immunotoxicity was set at 447.8 mg/kg/day.

Contradictory results were obtained in a non-guidelined 28-day study in mice in which thiamethoxam induced alterations on both humoral immunity and cell mediated immune response from 43.5mg/kg bw/d onwards. The difference in the way of administration gavage in the published study versus diet in the regulatory study may explain the conflicting results. However this publication has numerous limitations: parameters of general systemic toxicity not investigated/reported, lack of positive control, only two dose tested, results poorly reported (e.g.: numerical data available for plasmatic globulins), lack of historical control data. Those caveats compromise the reliability of this study. Furthermore, the review of parameters related to immune function conducted on the existing toxicity database for thiamethoxam does not highlight evidence of adverse effects on immune system. Indeed, some effects on immune organs weights were observed but generally in the presence of general toxicity and without correlated histopathological findings.

In few studies decreased total leucocyte counts and/or lymphocyte counts were noted. However, those findings were not observed after longer exposure. The only potential immunotoxic findings not associated to systemic toxicity were decreased absolute thymus weight in females F1 in the first 2-generation study. However, further investigations did not show histopathological differences compared to control in particular the cortex/medulla or cortex/whole-organ ratios were not affected. A subsequent microscopical evaluation of the spleen, axillary, mesenteric and popliteal lymph nodes of all F1 female rats was performed in order to clarify if the effects on thymus weights are accompanied by other changes in lymphoid organs which did not identify any changes in morphology due to treatment. In particular, T cell compartments of those different organs were of similar morphology in control and treated animals. Furthermore in the second 2-generation study, no effect of thymus or any other immune organs were observed.

2.6.8.3 Endocrine disrupting properties

Interim criteria:

- Thiamethoxam is not currently classified as carcinogenic category 2 nor as toxic for reproduction category 2, in accordance with the provisions of Regulation (EC) No 1272/2008 and therefore, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties are not met.
- In the case of proposal for reproductive classification Repr. Cat.2 H361 is agreed, since thiamethoxam also induces effects on endocrine organs, it will satisfy the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties.

In the report "Screening of available evidence on chemical substances for the identification of endocrine disruptors according to different options in the context of an Impact Assessment"[5] mandated by the European Commission, thiamethoxam was:

- **unclassified in option 2**. *For option 2, the WHO/IPCS definition is used to identify endocrine disruptors.*

- **classified as Cat. II in option 3 according to path of decision tree number 3a.** *For option 3, the WHO/IPCS definition was used to identify endocrine disruptors, but the substances were allocated in one of the three different categories based on the different weight of evidence for fulfilling the WHO/IPCS definition. These categories are the following: endocrine disruptor (Category I), Suspected Endocrine Disruptor (Category II) and Endocrine active substance (Category III).*
  "Cat I" under "Option 3" was equivalent to categorization as "ED" under "Option 2", whilst all the other categories were considered as "Unclassified" under "Option 2".
  Path 3a describes the pathway leading to Category II where there is strong evidence of EATS-specific adverse effect data but there are neither in vivo mechanistic nor in vitro data available, either because no studies were performed (lack of data) or because the available mechanistic data include negative results.

- **unclassified in option 4.** *Option 4 introduces a "potency cut-off" value to characterize EDs identified from "Options 2 and 3".*

Assessment:

Specific parameters of estrogenic, androgenic, thyroid and steroidogenesis (EATS) pathways as well as parameters sensitive to but not diagnostic of EATS were altered in several studies of the core dossier and are summarised in the table Vol.3CA B.6.8.3-1.

Adversity of the effects:

- Testicular atrophy, reduced sperm count and delayed male puberty in rat progeny in 2-generation studies and delayed male puberty observed in the DNT study: No correlated effects in fertility parameters were observed in the two 2-generation studies. However, sperm count in rodents must be drastically reduced before an effect on fertility is seen (OECD, ENV/JM/MONO(2008)16).

Therefore, as regard potential endocrine disruption in human health those effects are considered adverse.

- Testicular affects in dogs: effects are observed in the 90-d and 1-year studies. While, decreased body weight gain was observed at the same dose level in the 90-d study, final body weight was slightly affected. In the 1-year dog study increased incidence of tubular atrophy was observed from the mid-dose onwards and reduced body weight gain was observed only at the high dose levels with no impact on final body weight. Therefore those effects cannot be ruled out as secondary to severe general toxicity.

Therefore, as regard potential endocrine disruption in human health those effects are considered adverse.

- Effects on ovary observed both in the mice 90-d (decreased weight and reduced numbers of corpora lutea) and in dog 90-d study (decreased weight and immature ovary): effects were observed only with concomitant marked general toxicity. They are therefore considered of lower concern.

- As regard effects on parameters sensitive to but not diagnostic of EATS, adrenal glands were affected in several studies only in the presence concomitant marked general toxicity. They are therefore considered of low concern.

[5] Screening of available evidence on chemical substances for the identification of endocrine disruptors according to different options in the context of an Impact Assessment. Specific Contract SANTE/2015 /E 3/SI/SI/SI2.7062182 http://ec.europa.eu/health/endocrine_disruptors/docs/2016_impact_assessment_study_en.pdf

The effects on testes observed both in dog (90-d and 1-y studies) and in rat progeny in two 2-generation studies as well as the delay in balano-preputial separation are considered as adverse health effects in intact organisms. Indeed, these effects were observed in the absence of an overt general toxicity and as such are not considered secondary to non-specific marked systemic toxicity. It should also be noted that effects on sperm and testis are also reported for clothianidin, a major metabolite of thiamethoxam.

Underlying mode of action of action:

- No mechanistic studies have been submitted. No hormonal measurement has been performed in any of the available toxicological studies and no investigating studies on the putative modes of action involved in testicular effects have been generated

- Only *in vitro* data from TOXCAST program are available.

Thiamethoxam was tested in a number of high throughput *in vitro* assays aimed at identification of potential endocrine activity and was negative in all assays investigated binding, agonism or antagonism of estrogen, androgen and thyroid receptors EDSP21 Dashboard (https://actor.epa.gov/edsp21/ August 2017). Clothianidin was also negative in EDSP21 programm.

Thiamethoxam was also negative in TOX21-Aromatase-inhibition and in the two other assays exploring CYP19 (NVS-ADME-hCYP19A1 and NVS-ADME-hCYP19A1-Activator). In the 2 last one, only one concentration was tested.

As mentioned before thiamethoxam activity is mainly driven by its metabolism, some of its metabolites being more potent than the parent both in insects (efficacy) and in mammalian (toxicity). The metabolic competence of cell systems used in high throughput in *vitro* assays performed with thiamethoxam may not be sufficient to adequately investigate metabolites activity along with the parent.

The underlying mode of action of testicular effects and delayed male puberty induced by exposure to thiamethoxam may involve more complex inter-organs relationship that cannot be investigated in *in vitro* systems. For instance, some agonists of nicotinic acetylcholine receptors may act by an agonist effect on central (neuronal) nicotinic acetylcholine receptors (nAChRs) inducing the release of dopamine and disrupting the hypothalamic-pituitary-testicular axis.
Nicotine treatment was also reported to produce degenerative changes in the germ cells and inhibits the androgen production acting primarily at the level of hypothalamic pituitary axis to inhibit the release of gonadotropins. An alternative mechanism pathway could be that the modulation of the extent of testicular lipid peroxidation through free radicals generation (Jana *et al.*, 2010).
Involvement of oxidative stress was also suggested for clothianidin-mediated sperm effects in developing male rats (Bal R *et al*., 2012) and mice exposed during pre-natal and early post-natal periods (Yanai S *et al.*, 2017)
Anyway, no hormonal measurement has been performed in any of the available toxicological studies and no investigating studies on the putative modes of action involved in testicular effects have been generated for thiamethoxam.

In the absence of specific data, demonstrating alternative non-endocrine MoA(s) or showing that the adversity of the effects is not human relevant, it cannot be excluded that the testicular effects and the delayed male puberty could be plausibly linked to endocrine activity.

At the time this report was written, the agreed regulatory criteria were not published and the dedicated guidance document was not available.
In light of those uncertainties, it is considered that the endocrine disruption potential of thiamethoxam should be discussed at an expert meeting.

Since clothianidin is a major metabolite in rat and also induces effects on reproduction, it is proposed to discuss this point for the both substances concurrently.

2.6.9 Summary of medical data and information

Detail records of exposure an and poisoning incidences on marketed products

The applicant has kept detailed records of exposure and poisoning incidences on marketed products for many years. A review of the exposure incidences of thiamethoxam formulations reported between 2003 and 2014 has been conducted and is presented in the tables below.
Health effects observed after exposure to thiamethoxam after occupational, accidental, intentional and uncertain exposure within this 12 years period were almost exclusively of transient nature with minor severity or below.

In total 599 cases have been reported in this period. 76 cases (13%) were related to intentional misuse. The other incidents were caused by occupational (368 cases, 61%), accidental (125 cases, 21%) and uncertain (30 cases, 4%) exposure.

Exposure happened predominantly via the dermal route (34%) followed by ingestion (26%), inhalation (23%) the eyes (5%) and other and unknown routes (13%). For the remaining 14% no exposure route was reported.

The majority of reported incidents were of very low severity grade[6] (minor and none), representing 85% of all reported incidents. Incidents assigned to fatal and severe severity grade representing 0.3 and 1.0% of all reports received respectively.

Highest severity grades with fatal outcome, reported for 2 cases, are linked to unclear circumstances with no causal evidence to be linked to exposure to the active ingredient. Incidents leading to severity grade severe (6 cases) were almost exclusively caused by intentional self-harm (5 cases). For the remaining incident with severe outcome no exposure reason was reported.

Occupational exposure predominantly happened via the dermal route (29% of all reported incident cases, 47% of all occupational cases), were causing mainly temporary health effects of minor severity grade or less.

Case incidents reporting in the occupational setting
The French programme « Phyt'attitude »[7] is a vigilance programme developed by the Mutualité Sociale Agricole (national insurance company for farmers); it is based on voluntary event notifications by a network of physicians and self-reporting by users of any case of suspected work-related pesticide injury or illness or poisoning.
Twenty eight cases were collected during the time period 1997-2015; fifteen cases were excluded as the occurrence of signs and symptoms was considered as non-related to thiamethoxam exposure; another 5 cases were excluded because the individual was exposed to one or more PPP in combination with the thiamethoxam-based PPP.
The remaining eight cases were exposed to thiamethoxam only and the causal relationship between exposure and health outcome was considered plausible or likely.

The most frequently reported effects include local signs of irritation of the skin and mucous membranes: erythema, throat and upper airways irritation, epistaxis, dry mucous membranes, chest discomfort. Conjunctivitis and photophobia were also reported after eye contact. Headache has been reported as a systemic effect.

Most incidents occurred when operating with treated seeds: big bag opening, seeder filling; operators either did not wear PPE or wore PPE that were not adapted.

Epidemiological studies
The company has performed no epidemiological study.
No relevant public literature reporting on specific epidemiological investigations on health effects on the general population due to exposure to thiamethoxam has been captured in the submitted literature review.

2.6.10 Toxicological end points for risk assessment (reference values)

[6] **Severity Grades** (Clinical Toxicology Jan 1998, Vol. 36, No. 3: 205–213) :

NONE (0):	No symptoms or signs related to poisoning
MINOR (1):	Mild, transient and spontaneously resolving symptoms
MODERATE (2):	Pronounced or prolonged symptoms
SEVERE (3):	Severe or life-threatening symptoms
FATAL (4):	Death

[7] http://www.msa.fr/lfr/sst/phyt-attitude

Table 53: Overview of relevant studies for derivation of reference values for risk assessment

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
Rat, Sprague-Dawley Crl:CD®BR Males and females	**Acute oral neurotoxicity study** OECD Guideline 424 GLP Single oral (gavage) dose	Thiamethoxam technical Batch 9600110 (purity 98.7%) 0, 100, 500 and 1500 mg/kg Vehicle: 0.5% w/v aqueous methylcellulose	**From 500 mg/kg bw:** Neurotoxicity (effects observed 2-3 hours after dosing): Decreased locomotor activity Decreased rectal temperature Increased forelimb grip strength (males only).	100 mg/kg bw	500 mg/kg bw	Table [redacted], 1997
Mice B6C3F1 females	**Immunotoxicity Study** OPPTS 870.7800 (1998) GLP 28-day diet	Thiamethoxam technical Batch: SGO7K699E (Purity > 95%) 0, 100, 1250 or 5000 ppm in diet 28 day (0, 37.2, 447.8 or 2025.8 mg/kg bw/day)	**At 5000 ppm (2025.8 mg/kg bw/day)** Decreased bw gain Decreased spleen weight in both AFC and NKC groups Decreased spleen cellularity Decreased thymus weight in NKC group	1250 ppm (447.8 mg/kg bw/day)	5000 ppm (2025.8 mg/kg bw/day)	2.6.8.2 [redacted], 2011
Rat, Tif:RAIf (SPF), hybrids of RII/1 x RII/2 (Sprague-Dawley derived)	**90-days range finding oral toxicity study** OECD 408 GLP Continuous in the diet for 90 days.	Thiamethoxam technical Batch KI-4654/18 (purity 98.4%) 0, 25, 250, 1250, 2500, 5000 ppm ♂: 0, 1.74, 17.6, 84.9, 168, 329 mg/kg bw/day ♀: 0, 1.88, 19.2, 92.5, 182, 359 mg/kg bw/day	**From 250 ppm :** Decreased lymphocyte counts (♀)	25 ppm (1.88 mg/kg bw/day)	250 ppm (19.2 mg/kg bw/day	Table 35 [redacted], 1996
Rat, Sprague-Dawley Crl:CD®BR	**13-Week dietary subchronic neurotoxicity** OECD Guideline 424 GLP Continuous in the diet for	Thiamethoxam technical Batch 9600110 (purity 98.7%) ♂/♀: 0/0,10/10,	No effect at any dose levels.	1500 ppm (95.4 mg/kg bw/day in males)	-	Table 55 [redacted], 1998

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
	13 weeks.	30/30, 500/1000 or 1500/3000 ppm (♂: 0, 0.7, 1.9, 31.8 or 95.4 mg/kg bw/day, ♀: 0, 0.7, 2.1, 73.2 or 216.4 mg/kg bw/day)				
Mice, Tif:MAGf (SPF), hybrids of NIH x MAG	**90-days range finding oral toxicity study** OECD 408 GLP Continuous in the diet for 90 days.	Thiamethoxam technical Batch KI-4654/18 (purity 98.4%) 0, 10, 100, 1250, 3500, 7000 ppm ♂: 1.41, 14.3, 176, 543, 1335 mg/kg bw/day ♀: 2.01, 19.2, 231, 626, 1163 mg/kg bw/day	**From 100 ppm :** Hepatocellular hypertrophy (♂)	10 ppm (1.41 mg/kg bw/day in males)	100 ppm (14.3 mg/kg bw/day in males)	Table 35 [redacted], 1996
Dog, Pedigree Beagle 4/sex/group	**90-days oral toxicity study** OECD 409 GLP Continuous in the diet for 90 days.	Thiamethoxam technical Batch P.506006 (purity 98.6%) 0, 50, 250, 1000, 2500/2000 ppm ♂: 1.58, 8.23, 32.0, 54.8 mg/kg bw/day ♀: 1.80, 9.27, 33.9, 50.5 mg/kg bw/day	**From 1000 ppm :** Slight anaemia, associated with a tendency to hypochromasia, anisochromasia and microcytosis) (♀) Lower plasma Ca^{++} concentration and ALAT activity, minimally reduced plasma albumin levels (♂/♀) Prolonged prothrombin times (♂/♀)	250 ppm (8.23/9.27 mg/kg bw/day in males/females)	1000 ppm (32/33.9 mg/kg bw/day in males/females)	Table 31 [redacted], 1996
Dog, Pedigree Beagle 4/sex/group	**1-year oral toxicity study** OECD 452 GLP Continuous in the diet for 1 year.	Thiamethoxam technical Batch P.506006 (purity 98.6%) 0, 25, 150, 750, 1500 ppm ♂: 0.70, 4.05, 21.0, 42.0 mg/kg bw/day ♀: 0.79, 4.49, 24.6, 45.1 mg/kg bw/day	**From 750 ppm :** Increased plasma creatinine and tendency to higher plasma urea levels (♂/♀) Testis: Higher incidence of tubular atrophy	150 ppm (4.05 mg/kg bw/day males)	750 ppm (4.05 mg/kg bw/day males)	Table 35 [redacted], 1998

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
Rat, Sprague-Dawley Tif: RAIf, SPF	**Toxicity and carcinogenicity dietary study in rat** OECD Guideline 453 GLP Acceptable Continuous in the diet for 104 weeks.	Thiamethoxam technical BatchP.50600 (purity 98.6%) ♂/♀: 0/0, 10/10, 30/30,500/1000, 1500/3000 ppm ♂: 0.41, 1.29, 21.0, 63.0 mg/kg bw/day ♀: 0.48,1.56, 50.3, 155 mg/kg bw/day	**<u>At 3000 ppm</u> (♀: 155 mg/kg bw/day):** <u>Females:</u> Decreased body weight gain (↓12.6%). Foci of hepatic cellular alteration Increased incidence of splenic hemosiderosis No Neoplastic findings	1000 ppm (50.3 mg/kg bw/day in females)	3000 ppm (155 mg/kg bw/day in females)	Table 42 [redacted] 1998a
Mouse Tif:MAGf (SPF) 60/sex/group	**Toxicity and carcinogenicity dietary study in mouse** OECD Guideline 453 GLP Continuous in the diet for 78 weeks.	Thiamethoxam technical BatchP.50600 (purity 98.6%) ♂/♀: 0, 5, 20, 500, 1250 and 2500 ppm ♂: 0.65,2.63, 63.8, 162, 354 mg/kg bw/day ♀: 0.89, 3.68, 87.6, 215, 479 mg/kg bw/day	**<u>From 500 mg/kg bw/day</u> (♂/♀: 63.8 / 87.6 mg/kg bw/day):** <u>In both sexes:</u> alterations in the liver (hypertrophy, pigment deposition, mitotic activity, Kupffer cell hyperplasia and single cell necrosis) ***Neoplastic findings:*** **<u>From 500 mg/kg bw/day</u>** Increased incidence of hepatocellular adenomas in both sexes. **<u>From 1250 mg/kg bw/day</u>** <u>Females:</u> Increase incidence of hepatocellular adenocarcinomas **<u>At 2500 mg/kg bw/day</u>** Increase incidence of hepatocellular adenocarcinomas in males	20 ppm (2.63/3.68 mg/kg bw/day in males/females)	500 ppm (63.6/87.6 mg/kg bw/day in males/females)	Table 42 [redacted] 1998

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
Rat, Sprague-Dawley Tif: RAIf, SPF	**2-generation reproduction study** OECD Guideline 416 (1981) GLP Continuously in the diet	Thiamethoxam technical Batch P.50600 (purity 98.6%) 0, 10, 30, 1000, 2500ppm (♂: 0, 0.6, 1.8, 61 or 158 mg/kg bw/day, ♀: 0, 0.8, 2.4, 79 or 202 mg/kg bw/day)	**From 30 ppm (♂/♀): 1.8/2.4 mg/kg bw/day** **Offspring and Reproduction:** increased incidence and severity of tubular atrophy observed in testes of F1 males. Decreased thymus absolute weight in F1 females. **At 2500 ppm (♂/♀): 158/202 mg/kg bw/day** **Parents:** reduced food consumption and decreased body weight gain of F0 and F1 males.	Offspring and reproduction: 30 ppm (1.8 mg/kg bw/day in males) Parental: 1000 ppm (61 mg/kg bw/day in males)	Offspring and reproduction 1000 ppm (61mg/kg bw/day in males) Parental: 2500 ppm (158 mg/kg bw/day in males)	Table 46 [redacted] 1998
Rat, Sprague-Dawley Tif: RAIf, SPF	**2-generation reproduction study** OECD Guideline 416 (2001) GLP Continuously in the diet	Thiamethoxam technical Batch P.50600 (purity 98.6%) 0, 20, 50, 1000, 2500ppm (♂: 0, 1.2, 3, 61.7 or 155.6 mg/kg bw/day, ♀: 0, 1.7, 4.3, 84.4 or 208.8 mg/kg bw/day)	**From 50 ppm (♂/♀): 3.0/ 4.3 mg/kg bw/day** **Parents:** No treatment related effect **Offspring and Reproduction:** significant reduced number of sperm cells in F1 males **At 2500 ppm (♂/♀) 155.6/208.8 mg/kg bw/day** **Parents:** reduced food consumption and decreased body weight gain F0 males.	Offspring and reproduction: 20 ppm (1.2 mg/kg bw/day in males) Parental: 1000 ppm (6.7 mg/kg bw/day in males)	Offspring and reproduction 50 ppm (3 mg/kg bw/day in males) Parental: 2500 ppm (155.6 mg/kg bw/day in males)	Table 46 [redacted] 2004
Rat, Sprague-Dawley Tif: RAIf, SPF	**Developmental toxicity study in rat** OECD Guideline 414 (1981) GLP Gavage GD 6-15	Thiamethoxam technical Batch P.50600 (purity 98.6%) 0, 5, 30, 200, 750 mg/kg bw/day	**From 200 mg/kg bw/day** **Dams:** Decreased BW gain and food consumption. **At 750 mg/kg bw/day** **Foetus:** Decreased fetal weight, delayed ossification, increased incidence of skeletal anomalies (asymmetrically shaped	Maternal: 30 mg/kg bw/day	Maternal: 200 mg/kg bw/day	Table 49 [redacted] 1996

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
			sternebrae6 and irregular ossification of the occipital bone).	Developmental: 200 mg/kg bw/day	Developmental: 750 mg/kg bw/day	
Rabbit, Russian Chbb:HM 19/group	**Developmental toxicity study in rabbit** OECD Guideline 414 (1981) GLP Gavage GD 7-19	Thiamethoxam technical Batch P.50600 (purity 98.6%) 0, 5, 15, 50, 150 mg/kg bw/day	**From 50 mg/kg bw/day** **Dams:** Decreased BW gain and food consumption. **At 150 mg/kg bw/day** **Foetus:** Increased post implantation loss, decreased foetal weight, delayed ossification, increased incidence of skeletal anomalies.	Maternal: 15 mg/kg bw/day	Maternal: 50 mg/kg bw/day	Table 49 [redacted] (1996a)
				Developmental: 50 mg/kg bw/day	Developmental: 150 mg/kg bw/day	

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
Rat, Wistar Alpk:APrSD	**Developmental Neurotoxicity Study** OECD Guideline 426 GLP From GD7 to PND22 in diet	Thiamethoxam technical Batch P. 506006 (Purity: 98.8%) 0, 50, 400 or 4000 ppm (0, 4.3, 34.5 or 298.7 mg/kg bw/day)	**<u>At 4000 ppm (298.7 mg/kg bw/day):</u>** <u>Maternal toxicity:</u> Decreased BW gain (↓12% during gestation) and food consumption <u>Offspring toxicity :</u> Decreased pup BW at birth and decreased BW gain in males and females. Delayed sexual maturation in males Neurotoxicity: Decreased absolute brain weight. Morphometric changes: At Day 12: ↓length and width of the cerebellum in males At Day 63: ↓in Level 3-5 measurements in males and in Level 4-5 in females	Maternal: 400 ppm (34.5 mg/kg bw/day) Developmental: 400 ppm (34.5 mg/kg bw/day)	Maternal: 4000 ppm (298.7 mg/kg bw/day) Developmental: 400 ppm (298.7 mg/kg bw/day)	Table 49 [redacted] 2003 & 2006

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

For the first EU approval of thiamethoxam, the ADI was established at 0.026 mg/kg bw/day based on the NOAEL in the 18 month mouse study (20 ppm equivalent to 2.6 mg/kg bw/d) and application of a 100-fold assessment factor.

Based on the re-evaluation of the two 2-generation studies, the overall NOAEL for offspring and reproduction is proposed to be set at 10 ppm equivalent to 0.6 mg/kg bw/day.
This NOAEL is the lowest of all the toxicological studies and is therefore proposed as the point of departure for the ADI setting. A safety factor of 100 for inter- and intra-species variation should apply.
Co-RMS agrees with RMS proposal.

ADI thiamethoxam = 0.6 mg/kg bw/day /100 = **0.006 mg/kg bw/day**

The applicant has proposed an ADI of 0.041 mg/kg bw/day based on the 1-year dog study.

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

For the first EU approval of thiamethoxam, the ARfD was established at 0.05 mg/kg bw/day based on the developmental NOAEL of 50 mg/kg in the rabbit developmental study and applying a 100-fold safety factor.

A DNT study has been submitted for the purpose of thiamethoxam renewal. The developmental NOAEL in this study was established at 400 ppm equivalent to 34.5 mg/kg bw/day, based on decreased body weight and body weight gain in males and females, delayed sexual maturation in males, reduced absolute brain weight and morphometric changes in males and females observed at 4000 ppm (equivalent to 298.7 mg/kg bw/day).
Since effect on brain can result from a single exposure during organogenesis, it is proposed to use this NOAEL as point of departure for the ARfD setting. A safety factor of 100 for inter- and intra-species variation will provide a sufficient margin of 853 to the LOAEL.
Co-RMS agrees with RMS proposal.

ARfD thiamethoxam = 34.5 mg/kg bw/day /100 = **0.35 mg/kg bw**

The applicant has proposed an ARfD of 1 mg/kg bw based on the acute neurotoxicity in rat.

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

For the first EU approval of thiamethoxam, the AOEL was established at 0.08 mg/kg bw/day based on the NOAEL in the 90-day dog study (250 ppm equivalent to 8.23/9.27 mg/kg bw/day in males/females) and application of a 100-fold assessment factor.

The same point of departure as for the ADI setting is proposed: The overall NOAEL for offspring and reproduction is proposed to be set at 10 ppm (equivalent to 0.6 mg/kg bw/day). A safety factor of 100 for inter- and intra-species variation should apply.

Since the oral absorption is higher than 80% based on the ADME studies, no correction factor is needed according to the Guidance document on AOEL setting (SANCO 7531 - rev.10).
Co-RMS agrees with RMS proposal.

AOEL thiamethoxam = 0.6 mg/kg bw /100 = **0.006 mg/kg bw/day**

The applicant has proposed an AOEL of 0.08 mg/kg bw/day based on the 90-day dog study.

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

For the setting of the AAOEL, the RMS proposes to use the same point of departure as for the ARfD, the developmental NOAEL in the DNT study of 400 ppm equivalent to 34.5 mg/kg bw/day. A safety factor of 100 for inter- and intra-species variation should apply.
Since the oral absorption is higher than 80% based on the ADME studies (even at high dose level), no correction factor is needed according to the Guidance document on AOEL setting (SANCO 7531 - rev.10)
Co-RMS agrees with RMS proposal.

AAOEL thiamethoxam = 34.5 mg/kg bw /100 = **0.35 mg/kg bw**

The applicant has proposed not to set any AAOEL in the absence of guidelinefor AAOEL setting.

2.6.11 Summary of product exposure and risk assessment

2.6.11.1 ACTARA 25 WG (A9584C)

Acute toxicity
Acute toxicity studies were conducted with A9584C. Summaries of these studies are presented below.

Table 2.6.11.1-1 Summary of acute toxicity

Parameter	Species	Result	Classification according to Regulation (EC) No.1272/2008	Reference
Acute oral LD50	Rat	LD_{50} >5000 mg/kg bw	None	[redacted] 1996a
Acute oral LD50	Mice	LD_{50} = 4215 mg/kg	-	[redacted], 1998
Acute dermal LD50	Rat	LD_{50} >5000 mg/kg bw	None	[redacted], 1996b
Acute inhalation	Rat	LC_{50} > 5.29 g/m³ for both sexes	None	[redacted] 1996
Acute skin irritation	Rabbit	Not Irritating	None	[redacted], 1996c
Acute eye irritation	Rabbit	Not irritating	H318	[redacted] 1996d
Skin sensitisation	Guinea Pigs	Not a sensitiser	None	[redacted] 1996e

Classification for human health

According to CLP Regulation (EC) No.1272/2008, the formulation should be labelled as follows taking account also of the current classification of the active substance and co-formulants:

- Serious eye damage cat. 1 H318: "Causes serious eye damage"

Classification **Repr. Cat. 2 H361** is proposed by the RMS for thiamethoxam (see level 2.6.6).
According to CLP Regulation (EC) No.1272/2008, the formulation should be labelled as follows taking account also of the **proposed** classification of the active substance and co-formulants:

- Serious eye damage cat. 1 H318: "Causes serious eye damage"
- **Repr. Cat. 2 H361: "Suspected of damaging fertility or the unborn child".**

Dermal absorption

The dermal absorption of thiamethoxam from A9584C was investigated with *in vitro* human skin study. In accordance with the EFSA guidance on dermal absorption (2012), the following dermal absorption values have been used for risk assessments:
- 4% for the concentrate
- 75% for field dilutions

Risk assessment

A9584C is a water dispersible granule (WG), the proposed representative use is as an insecticide on lettuce (field and greenhouse) and on potato (field). Applications of formulation will be achieved via a tractor mounted boom sprayer hydraulic nozzle in field and with a hand-held in greenhouse.

- ***Operator***

In field:
According to the German model, for tractor-mounted/boom sprayer application in field, there is no unacceptable risk anticipated for operator wearing PPE (gloves during mixing/loading and application).
According to AOEM model, there is no unacceptable longer term risk and acute risk anticipated for operator wearing PPE (gloves during mixing/loading and application).
According to the UK-POEM model, for tractor-mounted/boom sprayer application in field, there is unacceptable risk anticipated for operator wearing PPE (gloves during mixing/loading and application).

In greenhouse:
According to the Southern Greenhouse model (ECPA), for hand-held sprayer application in greenhouse, there is no unacceptable risk anticipated for operator not wearing PPE (work clothing). According to the EUROPOEM model, for hand-held sprayer application in greenhouse, there is no unacceptable risk anticipated for operator wearing PPE (gloves and coverall during mixing/loading and application).
According to AOEM model, there is unacceptable longer term risk and acute risk anticipated for operator wearing PPE (gloves during mixing/loading and application).
According to the UK-POEM model, for hand-held sprayer application in field, there is unacceptable risk anticipated for operator wearing PPE (gloves during mixing/loading and application and impermeable coverall during application).

- ***Bystander***

According to EUROPOEM II model, there is no unacceptable risk anticipated for bystander incidentally exposed to A9584C.
According to BfR model, there is no unacceptable risk anticipated for an adult and a child bystander incidentally exposed to A9584C.
According to AOEM model, there is no unacceptable risk anticipated for an adult and a child bystander incidentally exposed to A9584C.

- ***Resident***

According to BfR model, there is no unacceptable risk anticipated for an adult and a child resident exposed to A9584C.
According to AOEM model, for an application on lettuce, there is no unacceptable risk anticipated for an adult but these is unacceptable risk anticipated for a child resident exposed to A9584C with and without risk mitigation measures.
Considering the updated Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873), a default value of 50% should be chosen for the diluted formulation; these is no unacceptable risk anticipated for an adult and a child resident exposed to A9584C for an application on lettuce.

According to AOEM model, for an application on potato, there is no unacceptable risk anticipated for an adult and a child resident exposed to A9584C.

- ***Worker***

According to EUROPOEM II model, for an application on lettuce (greenhouse and field), there is an unacceptable risk anticipated for a worker wearing PPE (gloves), when re-entering crops treated with A9584C ; for an application on potato, there is no unacceptable risk anticipated for a worker wearing PPE (gloves), when re-entering crops treated with A9584C.
Considering the updated Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873), a default value of 50% should be chosen for the diluted formulation; these is no unacceptable risk anticipated for a worker wearing PPE (gloves), when re-entering lettuce crops treated with A9584C with an application on lettuce.

According to BfR model, for an application on lettuce (greenhouse and field), there is unacceptable risk anticipated for a worker wearing PPE (protective gloves), when re-entering crops treated with A9584C ; for an application on potato, there is no unacceptable risk anticipated for a worker without PPE, when re-entering crops treated with A9584C.
Considering the updated Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873), a default value of 50% should be chosen for the diluted formulation; these is no unacceptable risk anticipated for a worker wearing PPE (gloves), when re-entering lettuce crops treated with A9584C.

According to AOEM model, for an application on lettuce (greenhouse and field), there is an unacceptable risk anticipated for a worker wearing PPE (gloves), when re-entering crops treated with A9584C ; for an application on potato, there is no unacceptable risk anticipated for a worker without PPE, when re-entering crops treated with A9584C.
Considering the updated Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873), a default value of 50% should be chosen for the diluted formulation; these is no unacceptable risk anticipated for a worker wearing PPE (gloves), when re-entering lettuce crops treated with A9584C.

2.6.11.2 CRUISER 600FS (A9765R)

Acute toxicity

Acute toxicity studies were conducted with A9765R. Summaries of these studies are presented below.

Table 2.6.11.2-1 Summary of acute toxicity

Parameter	Species	Result	Classification according to Regulation (EC) No.1272/2008	Reference
Acute oral LD50	Rat	LD50 = 5000 mg/kg	Not acceptable	[redacted] 2011
Acute oral	calculation	ATE = 3216 mg/kg bw	None	
Acute dermal LD50	Rat	LD50 > 5000 mg/kg	None	[redacted] 2011
Acute inhalation	Rat	N/A	N/A	
Acute skin irritation	Rabbit	Not Irritating	None	[redacted], 2011a
Acute eye irritation	Rabbit	Mild Irritant	None	2011 ,
Skin sensitisation	Guinea Pigs	Not a sensitizer	None	2011a

* - Study not required, see **M-CP section 7.1.3**.

Classification for human health

According to CLP Regulation (EC) No.1272/2008, the formulation should be labelled as follows taking account also of the current classification of the active substance and co-formulants:

- No classification for human health

Additional labelling phrases: EUH208 Contains 1,2-benzisothiazol-3(2H)-one. May produce an allergic reaction.
Classification **Repr. Cat. 2 H361** is proposed by the RMS for thiamethoxam (see level 2.6.6).
According to CLP Regulation (EC) No.1272/2008, the formulation should be labelled as follows taking account also of the **proposed** classification of the active substance and co-formulants:

- **Repr. Cat. 2 H361: "Suspected of damaging fertility or the unborn child".**

Additional labelling phrases: EUH208 Contains 1,2-benzisothiazol-3(2H)-one. May produce an allergic reaction.

Dermal absorption

The dermal absorption of thiamethoxam from A9765R was investigated with *in vitro* human skin study. In accordance with the EFSA guidance on dermal absorption (2012), the following dermal absorption value has been used for risk assessments:
- 0.1% for the concentrate
- Not applicable for field dilutions (seed treatment)

Risk assessment

A9765R is a flowable concentrate (FS), the proposed representative use is as an insecticide for sugar beet seed treatment.

- ***Operator***

Estimates of operator exposure have been made for thiamethoxam, using a Seed-TROPEX Group sponsored operator exposure study on the treatment of sugar beet seeds in two treatment facilities in France (Determination of operator exposure to imidacloprid during treatment of sugar beet seeds with IMPRIMO® in France. Marcenac F, 2006)
This study is considered to be representative of the specialised treatment of sugar beet seeds. Exposure to thiamethoxam of operators treating sugar beet seed with A9765R is calculated on the basis of this study.

According to the field study extrapolation, there is no unacceptable risk anticipated for operator during the mixing/loading process for seed coating with protective coverall, gloves.

There is no unacceptable risk anticipated for operator during the seed coating process assuming a **low level of PPE** (one layer of work clothing during the whole work shift, as well as protective coverall and gloves during cleaning are worn) or assuming a **high-level of PPE** (one layer of work clothing, as well as protective coverall and gloves are worn throughout the whole work shift).

- ***Bystander***

Bystander exposure to A9765R has not been evaluated as part of an EU review for proposed critical use rate/crop. In industrial seed treatment facilities the incidental presence of bystanders can be excluded by technical management measures.
During the sowing, A9765R is applied in the sowing row; no drift is expected.
If occurring, exposure of bystanders would be of short duration and normally lower than that of seed treatment operators who are occupationally exposed all day long. Therefore, it is concluded that there is no undue risk of exposure to the bystander after incidental short-term exposure to A9765R.

- ***Resident***

Resident exposure to A9765R has not been evaluated as part of an EU review for proposed critical use rate/crop. The presence of resident in the industrial seed treatment facilities can be excluded. Furthermore during the sowing, A9765R is applied in the sowing row; no drift is expected.
Resident exposure estimation is considered not relevant.

- ***Worker***

Estimates of potential sower exposure have been made for thiamethoxam using a Seed-TROPEX Group sponsored operator exposure study on the loading and sowing of treated maize seeds on farms in Italy and Germany (Determination of operator exposure to imidacloprid during loading/sowing of GAUCHO® treated maize seeds under realistic field conditions in Germany and Italy. Zietz E, 2007).

The extrapolation data from the maize seed study is not judged as the most acceptable for sugar beet seeds. Maize and sugar beet are not entirely comparable regarding the sowing system, the size of the seeds, the process of coating, the packaging (boxes for sugar beet, bags for maize), the quantities of seeds sown per hectare.
The type of technique could be comparable to the loading and sowing of maize seeds. Seeds are sown in rows and the sowing machine is equipped with one sowing unit per row. Each sowing unit has a separate seed tank in which the seeds are loaded. However, usually the seed separation in the sowing unit during sowing of sugar beet seeds is only mechanical which is different from the pneumatic system during maize seed sowing. The pneumatic system should be representing a worst case compared to the mechanical system with regards to dust emission during seed sowing. Furthermore sugar beet seeds are covered with a final protective film coating (which minimizes the abrasion of coating material from the seed) unlike the maize seeds in the study which were not coated with a surface layer. Therefore, the data generated during loading and sowing of maize seeds could be considering as a conservative data base for the estimation of operator exposure during loading and sowing of pelleted sugar beet seeds.

According to the field study extrapolation, there is no unacceptable risk anticipated for the sower during loading and sowing with protective gloves when handling treated seeds or contaminated surfaces.

2.7 RESIDUE

2.7.1 Summary of storage stability of residues

2.7.1.1 Thiamethoxam

Storage stability of thiamethoxam (CGA293343) under freezing conditions has been investigated in the category of high water content commodities (apple fruit, tomato fruit), high starch content commodities (maize grain, potato tuber) and high oil content commodities (rapeseed). Although not essential in context of representative uses on lettuce, sugar beet and potatoes in the context of this renewal procedure, additional studies were provided to investigate the categories of a high acid content matrix (orange) and a high protein content matrix (dry beans).

In commodities of animal origin, storage stability of thiamethoxam (CGA293343) in freezing conditions has also been investigated formerly in beef muscle, beef liver, milk and eggs.

Table 2.7.1.1-1: Overview of storage stability of **thiamethoxam** under freezing conditions

Thiamethoxam (CGA293343)				
PLANT COMMODITIES				
Category	**Commodity**	**Maximum Storage Period**	**T(°C)**	**Report Reference**
High water content	Apple fruit	24 months	-18°C	KCA6.1/01,Mair.P, 1998j
	Tomato fruit	32 days[1]		
High starch content	Maize grain	24 months		
	Potato tuber	24 months		
High oil content	Rapeseed	results not reliable[2]		
High acid content	Orange fruit	results not reliable[3]	-18°C	KCA6.1/05,Graham.P, 2015
High protein content	Dry beans	24 months		
ANIMAL COMMODITIES				
Category	**Commodity**	**Maximum Storage Period**	**T(°C)**	**Report Reference**
Animal Meat	Bovine muscle	16 months	-20°C	KCA6.1/04,Grunenwald.M.C, 2000
Animal Liver	Bovine Liver	16 months		
Milk	Cow's Milk	results not reliable[4]		
Eggs	Poultry eggs	16 months		
Fat	-	-	-	Not available[5]

[1] significant degradation of 36% at storage duration of 102 days (circa 3 months) and 31-43% at 188 days (circa 6 months) (as bolded in volume 3-B7.1.1.1).

[2] significant degradation of 30-37% at storage duration of 32 and 102 days (as bolded in volume 3-B7.1.1.1).
[3] analytical method not fully validated in oranges (HPLC-MS/MS 179.06) (cf. volume 3-B7.1.2.1)
[4] significant degradation of 49% at storage duration of 85 days (as bolded in volume 3-B7.1.1.2).
[4,5] to be noted that the log Pow for thiamethoxam is of -0.13 ±(0.0017) at 25°C (cf. LOEP).

Discussion/conclusion about thiamethoxam

About tomato which belongs to the group of matrixes with high water content (OECD Guideline 506), it can be underlined that this matrix is not necessarily the most relevant representative of this category since pH close to 4 can be found in literature[8] for this commodity. Tomato would consequently not be an abnormal candidate representing acid matrixes. This assumption in relation with presumed instability in tomato or acid matrixes could not be completely confirmed nor contradicted. Effectively, no abnormal degradation was observed following a storage period of 24 months (as detailed in volume 3-B7.1.2.1) in orange but unfortunately the analytical method provided to support this additional study in orange fruit (analytical method HPLC-MS/MS 179.06) was not fully validated. However, it can also be noted that no significant degradation of thiamethoxam could be observed in acid and harsh conditions simulating pasteurization process (pH4, 90°C, 20min), boiling and sterilization (cf. volume 3-B7.5.1.).

Finally, concerning available storage stability data for thiamethoxam under freezing conditions:

Additional information/studies will be required depending on future extensions of uses:

- inside the group of high water content matrixes to resolve the discrepancy observed in tomato, currently a representative of high water content matrixes.

- inside the group of high acid content matrixes to resolve analytical validation of the method 179.06 in matrix of high acid content (see section 2 analytical methods).

- inside the group of high lipid content matrixes since despite its low log P_{ow}, residues of thiamethoxam could be found in fat from results available in animal metabolism studies.

- which involve consideration of the level of residues in milk and/or high fat content commodities of animal origin.

But when only focusing on the representative uses for the renewal on lettuce, potato and sugar beet :

- the use on lettuce, is covered by high water content matrixes, which are considered stable up to 24 months under freezing storage conditions.

- the uses on potato and sugar beet, are covered by high starch content matrixes, which are considered stable up to 24 months under freezing storage conditions.

- when needed (i.e. following significant intake calculation of animal dietary burden), thiamethoxam is considered stable up to 16 months in meat, liver and eggs under freezing storage conditions.

2.7.1.2 Metabolite CGA 322704 (a.k.a clothianidin)

Storage stability of the metabolite CGA 322704 (a.k.a clothianidin) under freezing conditions has been investigated in the category of high water content commodities (apple fruit, tomato fruit), high starch content (maize grain, potato tuber) and high oil content (rapeseed). Although not essential in the context of intended uses on lettuce, sugar beet and potatoes in the context of this renewal procedure, additional studies were provided to investigate the storage stability in categories of high acid content (orange) and high protein content matrixes (dry beans).

In matrixes of animal origin, storage stability of the metabolite CGA 322704 (a.k.a clothianidin) under

[8] As an example, a pH below 4.6 is mentionned in the codex document for processed tomatoes : *ww.fao.org/input/download/standards/237/CXS_057f.pdf*

freezing conditions have also been investigated formerly in beef muscle, beef liver, milk and eggs.

Table 2.7.1.2-2: Overview of storage stability of **CGA 3227040 (a.k.a clothianidin)** under freezing conditions

Metabolite CGA 322704 (a.k.a clothianidin)				
PLANT COMMODITIES				
Category	**Commodity**	**Maximum Storage Period**	**T(°C)**	**Report Reference**
High water content	Apple fruit	24 months	-18°C	KCA6.1/01,Mair.P, 1998j
	Tomato fruit	results not reliable [6]		
High starch content	Maize grain	24 months		
	Potato tuber	24 months		
High oil content	Rapeseed	results not reliable[7]		
High acid content	Orange fruit	results not reliable[8]	-18°C	KCA6.1/05,Graham.P, 2015
High protein content	Dry beans	24 months		
ANIMAL COMMODITIES				
Category	**Commodity**	**Maximum Storage Period**	**T(°C)**	**Report Reference**
Animal Meat	Bovine muscle	16 months	-20°C	KCA6.1/04,Grunenwald.M.C, 2000
Animal Liver	Bovine Liver	16 months		
Milk	Cow's Milk	16 months		
Eggs	Poultry eggs	16 months		
Fat	-	-	-	Not available[9]

[6] significant degradation of 52% at storage duration of 29 days and 45-58% at 184 days (circa 6 months) (as bolded in volume 3-B7.1.1.1)

[7] significant degradation of 39-42% at storage duration of 29 days (as bolded in volume 3-B7.1.1.1).

[8] analytical method not fully validated in oranges (HPLC-MS/MS 179.06) (cf. volume 3-B7.1.2.1).

[9] to be noted that the log P_{ow} of the clothianidin (CGA322704) is 0.893 at 25°C (cf. LOEP)

Discussion/conclusion about the metabolite CGA322704 (a.k.a clothianidin)

About tomato which belongs to the group of matrixes with high water content (OCDE Guideline 506), it can be underlined that this matrix is not necessarily the most relevant representative of this category since pH close to 4 can be found in literature[9] for this commodity. Tomato would consequently not be an abnormal candidate representing acid matrixes. This assumption in relation with presumed instability in tomato or acid matrixes could not be completely confirmed nor contradicted. Effectively, no abnormal degradation was observed following a storage period of 24 months (as detailed in volume 3-B7.1.2.1) in orange but unfortunately the analytical method provided to support this additional study in orange fruit (analytical method HPLC-MS/MS 179.06) was not fully validated. However, it can be also noted that no significant degradation of thiamethoxam could be observed in acid and harsh conditions simulating pasteurization process (pH4, 90°C, 20min), boiling and sterilization (cf. volume 3-B7.5.1.).

Finally, concerning available storage stability data for CGA322704 (a.k.a clothianidin) under freezing conditions:

Additional information/studies will be required depending on future extensions of uses:

- inside the group of high water content matrixes to resolve the discrepancy observed in tomato, currently a representative of high water content matrixes.

- inside the group of high acid content matrixes to resolve validation of analytical method in matrixes of high acid content (see section 2 analytical methods).

[9] As an example, a pH below 4.6 is mentioned in the codex document for processed tomatoes : *ww.fao.org/input/download/standards/237/CXS_057f.pdf*

- inside the group of high lipid content matrixes since despite its low log P_{ow}, residues of CGA322704could be found in fat from results in animal metabolism studies.

- which involve consideration of the level of residues in high fat content commodities of animal origin.

But when only focusing on the representative uses for the renewal on lettuce, potato and sugar beet :

- the use on lettuce, is covered by high water content matrixes, which are considered stable up to 24 months under freezing storage conditions.

- the uses on potato and sugar beet, are covered by high starch content matrixes, which are considered stable up to 24 months under freezing storage conditions.

- when needed (i.e. following significant intake calculation of animal dietary burden), metabolite CGA 322704 (a.k.a clothianidin) is considered stable up to 16 months in meat, liver and eggs under freezing storage conditions.

Additional RMS comment: discussions/conclusions above concerning the metabolite CGA 322704 (a.k.a clothianidin) should be also confronted with corresponding conclusions from the concomitant assessment for the renewal of the active substance clothianidin.

2.7.1.3 Metabolite CGA 365307

Storage stability of the metabolite CGA 265307 under freezing conditions has been investigated formerly in commodities of animal origin. No additional studies were provided in the context of this renewal for thiamethoxam.

Table 2.7.1.3-3: Overview of storage stability of CGA 265307 in commodities of animal origin

Metabolite CGA 265307				
ANIMAL COMMODITIES				
Category	**Commodity**	**Maximum Storage Period**	**T(°C)**	**Report Reference**
Animal Meat	Bovine muscle	16 months	-20°C	KCA6.1/04,Grunenwald.M.C, 2000
Animal Liver	Bovine Liver	16 months		
Milk	Cow's Milk	16 months		
Eggs	Poultry eggs	16 months		
Fat	-	-	-	Not available

Finally, about available storage stability for CGA 265307 under freezing conditions:

- when needed (i.e. following significant intake calculation of animal dietary burden), CGA 265307 is considered stable up to 16 months in meat, liver, milk and eggs under freezing storage conditions.

2.7.1.4 Limitations/restrictions/discussion

Pending final outcome on the toxicity of several significant metabolites identified in metabolism of plants and/or livestock (as listed in the LOEP and in Volume 1in section 2.7.3) and since several of these metabolites could also be identified as relevant in the context of the concomitant renewal dossier assessment of the active substance clothianidin, **additional information on storage stability under freezing conditions may be required, in accordance with the final residue definitions that will be adopted.**

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

2.7.2.1 Metabolism in plants

Cereals

In the initial DAR the metabolism of thiamethoxam was investigated in seven different crops, representative of four crop group categories, i.e. fruit crops (pear, cucumber), root crops (potato), leafy crops (lettuce, tobacco) and cereal crops (maize and rice) using respectively [oxadiazin-4-^{14}C] and [thiazol-2-^{14}C] radiolabelled moieties of thiamethoxam (CGA 293343).

Table 2.7.2.1-1 Study design overview (**maize)**

Crop	Label position	Formulation	Type of treatment	Application details			Sampling	Ref.
				Growth stage at applic.	Rate per application	n		
Maize	thiamethoxam-[oxadiazin-4-^{14}C]	70WS A-9567 A	seed treatment	BBCH 00	488g a.s/100kg seeds eq. to 145g a.s/ha (0.3 quintal treated seeds/ha)	1	33 DAS whole tops 124 DAS whole tops forage stage 166 DAS mature plant : grain, fodder 34% dry, 3 soils cores 0-10/10-20/20-30cm	Sandmeier, 1996a, Sandmeier, 1997a, Sandmeier, 1996b, Sandmeier, 1997b
		25WG	soil application	BBCH 12	485g a.s/ha	1	89 DAT whole tops 152 DAT i.e. 166DAS mature plant at harvest: grain, fodder 41% dry matter	
		experimental solution in DMSO in growth chamber	stem injection	BBCH 16	1.26 mg a.s/plant	2	78 DAT i.e. 105 DAS whole plant	
		experimental solution in DMSO in Erlenmeyer flask	cell culture	Log phase of growth (3 days)	10^{-4} M	1	3; 10; 19; 33 DAT aliquot solution	
	thiamethoxam-[thiazol-2-^{14}C]	70WS A-9567 A	seed treatment	BBCH 00	461g a.s./100kg seeds eq. to 145g a.s/ha	1	14 DAS top, root, seeds 33 DAS whole tops 124 DAS forage stage 166 DAS mature plant : grain, fodder 39% dry, 3 soils cores 0-10/10-20/20-30 cm	
		25WG	soil application	BBCH 12	488g a.s/ha	1	89 DAT whole tops 152 DAT i.e. 166 DAS mature plants harvested : grain, fodder 43% dry matter	
		experimental solution in DMSO in growth chamber	stem injection	BBCH 16	1.26 mg a.s/plant	2	78 DAT (i.e. 105 DAS) : whole plants	
		experimental solution in DMSO in Erlenmeyer flask	cell culture	Log phase of growth (3 days)	10^{-4} M	1	3; 33 DAT aliquot solution	

DAT: days after treatment; DAS: days after seedling; WS: water dispersible powder; WG: wettable granule ; DMSO: dimethylsulfoxyde

Table 2.7.2.1-2 Study design overview **(rice)**

Crop	Label position	Formulation	Type of treatment	Application details			Sampling	Ref.
				Growth stage at applic.	Rate per application	n		
Rice	thiamethoxam-[oxadiazin-4-^{14}C]	GR 2% Granules J-92/04 or A-9593/695A	soil treatment	BBCH 12-13 2-3 leaf stage	1.5g a.s/seedling box i.e 200 seedling box/ha eq. to 300g a.s/ha (0.3 quintal treated seeds/ha)	1	1 DAT, 34 DAR (25% maturity), 71 DAT (50% maturity), 126 DAT	, Krauss
	thiamethoxam-[thiazol-2-^{14}C]					1	1 DAT, 34 DAT (25% maturity), 71 DAT (50% maturity), 127 DAT	, Krauss
	thiamethoxam-[oxadiazin-4-^{14}C]	WP 25 FL950357 or A-9584/705A	foliar treatment	foliar treat. 1st applic. 48 DATr i.e after BBCH 12-13 2nd applic. 98 DATr i.e 21 days before harvest	25g a.s./ha	2	49 and 99 DATr + harvest, 120 DATr i.e 21 DAT	Krauss, 1997d
	thiamethoxam-[thiazol-2-^{14}C]					2	48 and 98 DATr + harvest, 119 DATr i.e 21 DAT	Krauss, 1997c

DATr : days after transplantation ; DAT: days after treatment ; WP: wettable powder

No representative use in the context of this renewal belongs to the group of cereals.

Fruiting/vegetable group

Table 2.7.2.1-3 Study design overview **(pear)**

Crop	Label position on the thiamethoxam	Formulation	Type of treatment	Application details			Sampling	Ref.
				Growth stage at applic.	Rate per application	n		
Pear	[thiazol-2-^{14}C]	50 WP	foliar	15 days before mature fruit harvest 13 days interval between application	150 g a.s/ha	2	Fruit harvested at normal maturity (15 DAT) and leaf were taken after the 2nd applic. at fruit harvest and 28 days after fruit harvest	Capps, 1999
	[oxadiazin-4-^{14}C]							
	[thiazol-2-^{14}C]				1500 g a.s/ha	2		
	[oxadiazin-4-^{14}C]							

DAT: days after treatment; WP: wettable powder

Table 2.7.2.1-4 Study design overview **(cucumber)**

Crop	Label position on the thiamethoxam	Formulation	Type of treatment	Application details			Sampling	Ref.
				Growth stage at applic.	Rate per application	n		
Cucumber	[thiazol-2-^{14}C]	50 WP	Experiment n°1 Foliar	1st application BBCH 69-71 (54 DAS) 2nd application (64 DAS)	50 g a.s./ha	2	leaves 14 DALA fruits 0, 14 DALA	Capps T., Carlin T. 1999
	[oxadiazin-4-^{14}C]							
	[thiazol-2-^{14}C]		Experiment n°2 1st application: soil drench 2nd application foliar	1st application BBCH 11 (15 DAS) 2nd application BBCH 70 (57 DAS)	1500 g a.s./ha + 500 g a.s./ha	2	Fruits, leaves prior 2ndapplic & 15 DALA	
	[oxadiazin-4-^{14}C]							

DAS: days after seedling; DALA: days after last application

No representative use in the context of this renewal belongs to the group of fruiting/vegetable.

Group of roots and tubers

Table 2.7.2.1-5 Study design overview **(potato)**

Crop	Label position	Formulation	Type of treatment	Application details			Sampling	Ref.
				Growth stage at applic.	Rate per application	n		
Potato	^{14}C-oxadiazin-thiamethoxam	70 WS CRUISER 70WS red colored	Seed treatment	BBCH 00 seed treatment using paintbrush and allowed to dry 9 potatoes/m² 621g potatoes /m2	7.5 g a.s./100kg of tubers i.e.465.8 g a.s/ha	1	84 DAP Immature tuber, foliage 106 DAP mature tuber, foliage Soil	Capps, 1999
	^{14}C-thiazol-thiamethoxam					1		
	^{14}C-oxadiazin-thiamethoxam				37.5 g a.s./100kg of tubers i.e.2329 g a.s/ha	1		
	^{14}C-thiazol-thiamethoxam					1		

Metabolism studies performed on potato were performed with seed treatment. This mode of application covers the representative use on sugar beet.

Metabolism studies assessed in the frame of the first approval dossier and described above on potatoes would be interpreted as 23X and 116X rates compared to the intended rate on potatoes in the context of the renewal.

Nevertheless, it has to be underlined that the representative use on potatoes in frame of the renewal concerns a foliar application of 20 g a.s/ha whereas the metabolism study was performed with a seed treatment. **Comparability between these 2 different modes of applications could be discussed, however a rationale based on the residue trials was added as RMS comment in section 2.7.4.2.**

Group of leafy crops

Table 2.7.2.1-6 Study design overview **(lettuce)**

Crop	Label position	Formulation	Type of treatment	Application details			Sampling	Ref.
				Growth stage at applic.	Rate per application	n		
Lettuce	^{14}C-oxadiazin-thiamethoxam	25 WG A-9584 C	Foliar treatment	application 64, 71, 78 DAS 7 days interval	53-54	3	0,3,7,14 DALA heads, soil core	Sandmeier, 1999
					527-533	3	14 DALA heads, soil core	
	^{14}C-thiazol-thiamethoxam				51-52	3	0,3,7,14 DALA heads, soil core	
					499-510	3	14 DALA heads, soil core	

DAS: days after seedling ; DALA: days after last application

Studies realized and described above on lettuce would be interpreted as 3.2X and 32X rates when cumulating all applications compared with intended rate on lettuce for the renewal (only 1 x 50 g a.s/ha as stated in the table of GAP) . Furthermore the same mode of application (foliar treatment) is at stake.

Nevertheless, when focusing on the overview of residue results in volume 1 section 2.7.4.1 (summary of residue trials in lettuce) one can observe that the number of applications (within the interval of 7-15 days between applications) has no influence on the level of analysed residues.

Therefore, studies realized and described above on lettuce would be finally interpreted as 1X and 10X rates in comparison with intended rate on lettuce for renewal and this point would be of significant importance when identifying the relevant metabolites to consider in the residue definition for lettuce.

Table 2.7.2.1-7 Study design overview **(tobacco)**

Crop	Label position	Formulation	Type of treatment	Application details			Sampling	Ref.
				GS at application	Rate g a.s/ha	n		
Tobacco	^{14}C-oxadiazin-thiamethoxam	25 WP	in furrow	1st applic. at transplant.	148 g a.s./ha	2	14, 28, 42 DALA i.e. 1st, 2nd and 3rd priming	**Capps, 1999 , Peffer,1999**
			foliar	2st applic. 121 DAFA i.e. 14 days before 1st priming	65 g a.s./ha			
	^{14}C-thiazol-thiamethoxam		in furrow	1st applic. at transplant.	144 g a.s./ha	2		
			foliar	2st applic. 71 DAFA i.e. 14 days before 1st priming	65 g a.s./ha			
	^{14}C-oxadiazin-thiamethoxam		in furrow	1 applic at transplant.	208 g a.s./ha	1	140, 154, 168 DALA i.e. 1st, 2nd and 3rd priming	
	^{14}C-thiazol-thiamethoxam				200 g a.s./ha	1	84, 98, 112 DALA i.e. 1st, 2nd and 3rd priming	
	^{14}C-oxadiazin-thiamethoxam		in furrow	1st applic. at transplant.	1515 g a.s./ha	2	14, 28, 42 DALA i.e. 1st, 2nd and 3rd priming	
			foliar	2st applic 121 DAFA, i.e. 14 days before 1st priming	641 g a.s./ha			
	^{14}C-thiazol-thiamethoxam		in furrow	1st applic at transplant.	1418 g a.s./ha	2		
			foliar	2st applic 71 DAFA, i.e. 14 days before 1st priming	658 g a.s./ha			

DAFA: days after first application; DALA: days after last application

Limitations/restrictions/discussion

Primary crop metabolism of thiamethoxam was investigated during the first approval dossier on various crops following:

- foliar application on rice, pear, cucumber, lettuce

- seed treatment on maize and potato

- soil application on maize, rice and tobacco

- soil and foliar application on cucumber and tobacco

hereby covering 4 different crop groups (i.e. cereals, fruiting vegetables, leafy crops and root and tuber vegetables.

These metabolism studies were of good quality, according to GLP and following current in force guidelines realized at normal or exaggerated rates. Effectively, it has to be noted that the study on lettuce has been performed close to the GAP (3 applications instead of 1) but it can be observed, taking also into account corresponding residues trials on lettuce (cf. volume 1 section 2.7.4.1 summary

of residue trials in lettuce) that the number of applications (within the interval of 7-15 days between application) would not significantly influence the level of analyzed residues for this crop. The metabolism study available on lettuce is therefore considered as a good indicator of the real behaviour of the residue at normal rate intended on lettuce in the context of this renewal.

Concerning the representative metabolism study available for the roots crops category, it should be noted that only a seed treatment is available instead of a foliar treatment as intended for the use on potato in the context of the renewal and that **the comparability between these 2 different modes of applications may be disputable.**

To this purpose, the following rational was provided by the applicant SYNGENTA:

Notifier Response:

The foliar application of thiamethoxam to potatoes is not a new mode of application – it was presented and previously evaluated in the original Annex 1 inclusion document.

OECD Guidance 501 indicates that if comparable metabolism can be demonstrated across at least 3 of the 5 representative crops then the use pattern can be extended to all crop groups. Syngenta has submitted multiple studies that included foliar application to pears, leaf lettuce, rice, cucurbits, and tobacco. Comparable metabolism was demonstrated in fruits, leafy crops, and cereals/grass crops thus the foliar use pattern can effectively be extended to all crop groups, including potatoes (root /tuber vegetables). It therefore follows that the pathway would be the same or similar and so the current residue definition would apply also to foliar application to potatoes.

The purpose of metabolism studies is to demonstrate whether the metabolism across crops follow the same pathways. From the range of studies previously evaluated in the original Annex 1 inclusion, this has been clearly demonstrated. Quantitative levels of metabolites would not be expected to be the same in all commodities because of differences in use patterns, plant physiology, PHIs etc. As highlighted in the original DAR, "as only thiamethoxam and CGA322704 are common to all edible parts of plants, it was concluded that including both compounds would adequately reflect the residue situation in thiamethoxam treated samples"

All identified plant and animal metabolites are either 1) covered by the toxicological evaluation based on their occurrence in rat and mouse metabolism, 2) believed to occur as short-lived metabolic intermediates in the animal metabolism or 3) they may be regarded as quantitatively non-significant, based on the amounts at which they occur in crops grown under Good Agricultural Practice, in relation to the relevant trigger values. Consequently, it is therefore considered that the current residue definitions are suitable to both evaluate any potential risk to consumers and provide suitable monitoring data.

Effectively, the metabolic pathway from these different metabolism studies might be considered to be rather similar but on the other hand the quantification and ranking of metabolites according to their residue levels rather depend on the mode of application (e.g. soil vs. foliar) or inner the same metabolism group (e.g. lettuce vs. tobacco) as detailed in the tables below:

Table 2.7.2.1-8 List of identified residues in **maize grain** (%TRR in decreasing order)

Mature grain (TRR in %)			
Residues	**Seed treatment 35 [T] – 75 [O]**	**Residues**	**Soil application 39 [T] –74 [O]**
thiamethoxam, CGA 293343	**15.1**	clothianidin, CGA 322704	**15.8**
clothianidin, CGA 322704	**9.6**	thiamethoxam, CGA 293343	**15.1**
to be noted a rather low level of extracted radioactivity in grain [T] for both seed or soil treatment		NOA405217	4.1
		NOA407475	*2.5*
		CGA265307	2.2
		NOA421275	1.9
		CGA353968	1.2
		CGA330050 & CGA349208	0.7
		CGA355190	0.4

Table 2.7.2.1-9 List of identified residues in **maize fodder** (%TRR in decreasing order)

Maize fodder (TRR in %)			
Residues	**Seed treatment 51 [T] – 69 [O]**	**Residues**	**Soil application 58 [T] – 66 [O]**
NOA421275	**10.4**	NOA421275	**9.5**
NOA407475	**8.5**	NOA407475	7.7
thiamethoxam CGA 293343	4.3	thiamethoxam CGA 293343	5.3
clothianidin, CGA 322704	4.3	clothianidin, CGA 322704	3.9
CGA382191	3.2	CGA382191	3.8
CGA353042	3.2	CGA353042	3.8
NOA405217	1.0	NOA405217	0.8
CGA265307	1.0	CGA330050 & CGA349208	0.8
CGA330050 & CGA349208	0.8	CGA265307	0.5
CGA355190	0.5	CGA353968	0.5
		CGA355190	0.4

Table 2.7.2.1-10 list of identified residues in **rice grain** (%TRR in decreasing order)

Granular treatment max 7% [T] or 10% [O] TRR was extractable		**Foliar treatment** max 14% [T] or 37% [O] TRR was extractable	
Residues	**Max % TRR**	**Residues**	**Max % TRR**
clothianidin, CGA 322704	2.3	thiamethoxam	**12.8**
CGA204261	1.4	clothianidin, CGA 322704	**10.6**
CGA353968	1.0	CGA353968	2.6
thiamethoxam, CGA293343	0.4	CGA204261	0.9
CGA353968 desmethyl	0.4	CGA355190	0.7
NOA407475	0.3	CGA265307	0.5
CGA349208	0.3	NOA407475	0.3
CGA359683	0.3	CGA349208	0.3
CGA265307	0.2	NOA404617	0.3
To be noted difficulties to extract residue in cereal grain			

Table 2.7.2.1-11 list of identified residues in **rice straw** (%TRR in decreasing order)

Granular treatment max 71% [T] or 84% [O] TRR extractable		**Foliar treatment** max 87% [T] or 87% [O] TRR extractable	
Name	**Max % TRR**	**Name**	**Max % TRR**
thiamethoxam	**27.4**	thiamethoxam	**53.0**
clothianidin, CGA 322704	7.8	clothianidin, CGA 322704	**11.4**
NOA407475	5.9	CGA265307	5.2
CGA204261	4.0	NOA407475	4.0
CGA355190	4.0	CGA355190	3.2
CGA353968	3.8	CGA353968	1.8
CGA265307	3.2	NOA404617	0.9
NOA405217	2.5	CGA349208	0.7
CGA353968 desmethyl	2.1	CGA353968 desmethyl	0.4
NOA404617	1.6	NOA405217	0.35
NOA421275	1.3		
NOA424255	0.8		
CGA330050	0.7		
CGA349208	0.4		
CGA382191	<0.1		

Table 2.7.2.1-12 List of identified residues in **pear fruit or leaves** (%TRR in decreasing order)

Pear fruit max 91% [T] or 100% [O] TRR extractable.		**Pear leave** max 73% [O] or 74% [T] TRR extractable.	
Residues	**Max % TRR**	**Residues**	**Max % TRR**
thiamethoxam, CGA 293343	**33.4**	CGA322704-hydroxyl-amine-glucoside	**23.9**
clothianidin, CGA 322704	**24.3**	thiamethoxam, CGA 293343	**18.2**
CGA353968	8.4	NOA407475	7.4
CGA265307	4.8	CGA355190	4.8
NOA407475	4.6	clothianidin, CGA 322704	4.75
CGA353968-desmethyl	3.0	CGA353968-desmethyl	3.9
CGA355190	2.8	1-methyl guanidine	3.9
CGA349208	1.9	CGA265307	3.8
NOA405217	1.8	CGA353968	3.5

1-methyl guanidine	1.6	NOA405217	2.4
NOA421275	1.2	CGA349208	0.1
CGA322704-hydroxyl-amine-glucoside	1.1		

Table 2.7.2.1-13 List of identified residues in **potato tuber** (in decreasing order, **at 23X or specified**)

Immature tubers, 84 DAP max 76% [T] or 92% [O] TRR eq. to max 0.20 [O] or 0.25 [T] mg/kg extractable			**Mature tubers**, 106 DAP max 75% [T] or 85% [O] TRR eq.to max 0.11 [O] or 0.17 [T] mg/kg extractable		
Residues	**max in %TRR**	**max in µg/kg (ppb)**	**Residues**	**max in %TRR**	**max in µg/kg (ppb)**
thiamethoxam, CGA 293343	**28**	60	thiamethoxam, CGA 293343	**13** **24** (115X)	30
Clothianidin, CGA 322704	**13**	30	clothianidin, CGA 322704	6.2	14
CGA282149	**10**	20	CGA353968 -N-glucoside conjugate	6 **9.7** (115X)	13
CGA322704 -hydroxylamine glucoside	6.0	20	CGA282149	6.3 6.5 (115X)	<10 56 (115X)
CGA340575	4.8	10	CGA340575	4.4	<10
NOA405217	4.7	12	CGA349208	3.4	<10
CGA349208	3.5	11	NOA421275	3.1	<10
CGA353968 -N-glucoside conjugate	3.2 8.2(115X)	10	CGA265307	3	<10
CGA265307	3	10	CGA353968	3	<10
CGA353968	3.1	<10	NOA407475	2.5 2.7 (115X)	<10
NOA421275	2.7	<10	CGA322704 -hydroxylamine-glucoside	2.2	<10
NOA407475	2.4	<10	NOA405217	0.7	<10
			CGA353968-desmethyl	0.3	<10

Table 2.7.2.1-14 List of identified molecules in **tobacco** (%TRR in decreasing order incl. sub proj. 1 & 2 & 3)

Composite foliage Sub proj. 1 & 2	TRR % 70[T] 87[O]	**Composite cured foliage** Sub proj. 3	TRR % 67[O] 70[T]	**Pyrolysis Composite cured foliage** Sub proj. 3	TRR % 81[O] 83[T]
thiamethoxam, CGA293343	**24.5**	NOA407475	**18.5**	CO2	**71**
NOA407475	**16.0**	clothianidin, CGA322704	**11.0**	CGA265307	6.8
CGA353968-N-glucoside conjugate	**13.2**	CGA353968	9.3	CGA355190	6.1
CGA353042	7.4	thiamethoxam, CGA293343	8.6	CGA349208	3.9
CGA353968	6.9	CGA353042	8.6	CGA353968	2.8
NOA408445	6.6	NOA408445	7.6	NOA407475	2.2
CGA382191	6.4	CGA382191	7.5	clothianidin, GA322704	1.9
NOA421275	5.7	CGA353968-N-glucoside conjugate	5.8	CGA382191	1.5
clothianidin, CGA322704	4.2	CGA265307	5.5	methyl Isocyanate	1.2
NOA405217	4.0	NOA421275	5.2	thiamethoxam, CGA293343	1.1
CGA353968-desmethyl	3.7	NOA436944	3.4	CGA353042	0.8
CGA355190	3.3	NOA405217	2.9	NOA405217	0.6
NOA436944	2.4	CGA353968-desmethyl	2.7	CGA353968-desmethyl	0.4
CGA265307	1.0	CGA355190	2.2	NOA421275	0.3
		CGA349208	0.8	NOA436944	0.3

Table 2.7.2.1-15 List of identified residues in **lettuce** (%TRR in decreasing order) (3 x 50 g as/ha) **(bolded : ≥10%TRR or ≥10ppb)**

Lettuce 0 day	%[1]	ppb[1]	**Lettuce 3 day**	%[1]	ppb[1]	**Lettuce 7 day**	%[1]	ppb[1]	**Lettuce 14 day**	%[1]	ppb[1]
	97 - 98	1740 -1980		93 - 97	1020 – 1500		90 - 97	630 - 720		83 - 89	570 - 690
thiamethoxam,CGA293343	**83**	**1550**	**thiamethoxam,CGA293343**	**70.4**	**1060**	**thiamethoxam,CGA293343**	**55.4**	**410**	**thiamethoxam,CGA293343**	**41.9**	**260**
NOA405217	2.5	**49**	NOA405217	3.7	**55**	NOA405217	**6.8**	**52**	NOA405217	**7.9**	**54**
CGA353042	2.3	**46**	CGA353042	3.3	**49**	NOA407475	5.0	**32**	CGA353042	**6.6**	**46**
NOA407475	2.1	**37**	**clothianidin, CGA322704**	3.3	**49**	CGA353042	4.6	**35**	NOA407475	6.2	**36**
clothianidin, CGA322704	2.1	**41**	NOA407475	3.2	**37**	**clothianidin, CGA322704**	3.8	**29**	**clothianidin, CGA322704**	5.8	**39**
CGA355190	1.8	**31**	CGA355190	3.1	**44**	CGA349208-O-gluc-conj.	3.4	**21**	CGA382191	3.8	**26**
CGA353968	1.4	**25**	CGA349208-O-gluc-conj	2.2	**23**	CGA353968-N-gluc-conj.	2.7	**17**	CGA349208-O-gluc-conj.	3.8	**22**
CGA349208-O- gluc-conj.	1.3	**22**	CGA353968	2.1	**26**	CGA355190	2.6	**17**	CGA353968-N-gluc-conj.	3.3	**19**
CGA 353968-O-gluc-conj.	0.8	**15**	CGA355190-S-gluc-conj.	1.5	**15**	CGA353968	2.4	**15**	CGA355190-S-gluc-conj.	3.0	**17**
CGA355190-S- gluc-conj.	0.8	**14**	CGA 353968-O-gluc-conj.	1.5	**15**	CGA382191	2.2	**17**	CGA353968	2.5	**18**
CGA382191	0.7	**13**	CGA353968-N-gluc-conj.	1.4	**14**	CGA355190-S-gluc-conj.	2.2	**14**	CGA 353968-O-gluc-conj.	2.5	**15**
CGA353968-N-gluc-conj.	0.6	**11**	NOA421275	1.1	**11**	CGA 353968-O-gluc-conj.	2.2	**14**	NOA421275	2.2	**12**
NOA421275	0.6	**10**	CGA382191	1.0	**15**	NOA421275	1.6	**10**	CGA204261	1.5	**11**
NOA424255	0.3	6	CGA204261	0.4	7	CGA204261	1.1	8	NOA424255	1.5	**10**
CGA204261	0.3	5	NOA424255	0.3	4	NOA424255	0.7	6	CGA359683	1.0	6
CGA359683	0.3	4	CGA359683	0.3	3	CGA265307	0.4	11	CGA353968-desmethyl	0.9	7
CGA265307	0.2	4	CGA265307	0.3	5	CGA353968-desmethyl	0.5	4	CGA355190	0.9	6
CGA353968-desmethyl	0.1	3	CGA353968-desmethyl	0.3	3	CGA359683	0.4	3	CGA265307	0.7	5

In table 2.7.2.1-15 above thiamethoxam and metabolite CGA322704 (a.k.a clothianidin) have been bolded in manner to highlight metabolites that are also observed at significant levels between these 2 molecules and since currently only thiamethoxam and metabolite CGA322704 (a.k.a clothianidin) are included in the residue definition for plants and consequently analyzed in residue trials realized on lettuce (see volume 3-B7.3.1 and volume 1 section 2.7.4.1)). No other metabolites have been analysed for in the residue trials and **no information concerning the toxicity relevance of these metabolites NOA 405217, CGA 353042 and NOA 407475 nor equivalence as "thiamethoxam-like" or "clothianidin–like" were provided.**

It has to be noted that within the intended PHI of 7 days for lettuce and at later PHIs, several metabolites were found above 10ppb. There is currently no information to qualify their respective toxicities.

In addition several of these metabolites could be identified as relevant and/or as "clothianidin-like" in the context of assessment the concomitant renewal dossier of the active substance clothianidin. According to RMS a harmonized approach and conclusion should be drawn for both renewal dossiers concerning the final outcome of these metabolites.

Another useful way to get a good overview and to identify relevant metabolites from available metabolism studies is presented below (in table 2.7.2.1-16 to 2.7.2.1-21) : cell appears in green when the residue label represent below 5% of the TRR or below 5ppb and changes progressively into red when close to 10% of the TRR or 10ppb or above.

Table 2.7.2.1.-16 Overview of identified residues (**all results in leaves - %TRR**)

OVERVIEW OF IDENTIFIED RESIDUES IN LEAVES (%TRR)																		
MODE OF APPLICATION	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**FS**	**FS**	**FS**	**FS**	**FS**	**SOIL**	**SOIL**	**SOIL +F**	**SOIL +F**	**SOIL +F**
CROP/PART OF CROP/DOSE RATE	**CUCUMBER**	**PEAR**	**PEAR**	**LETTUCE**	**LETTUCE**	**LETTUCE**	**LETTUCE**	**LETTUCE**	**POTATO**	**POTATO**	**POTATO**	**POTATO**	**MAIZE**	**MAIZE**	**TOBACCO**	**TOBACCO**	**TOBACCO**	**CUCUMBER**
5% 10%	2X	6X	60X	PHI 0 - 3,2X	PHI 3 - 3,2X	PHI 7 - 3,2X	PHI 14 - 3,2X	PHI 14 - 31X	immature 23X	mature 23X	immature 116X	mature 116X	fodder 3X	fodder 10X	4,2X	4,3X	43X	40X
Residues - %TRR extractable	53-61	n.a	73-74	92-95	86-92	82-86	74-81	76-90	76-80	64-69	79-87	66-85	47-68	52-66	64-67	59-66	68-77	54-61
guanidine	A complete work-up of the 2X cucumber leaves was not conducted (to low amount of radioactivity)	A complete work-up of the 6X pear leaves was not conducted (to low amount of radioactivity)							8,4	13,2	6,5	14,7			0,5	2,4	0,9	
CGA204261, methyl urea				0,3	0,4	1,1	1,5	0,8										
CGA265307			3,8	0,2	0,3	0,4	0,7	0,5	0,8	0,6	0,9	0,3	1	0,5	0,7	0,7	1	2,3
CGA282149																		
CGA322704, clothianidin			4,8	2,1	3,3	3,8	5,8	4,5	3,3	1,4	3,6	0,8	4,3	3,9	4,2	3,5	3,1	3,2
CGA322704-hydroxyl-amine-glucoside			23,9						16,6		20	4,5						3,4
CGA322704 and its conjugates (calc. sum)			28,7	2,1	3,3	3,8	5,8	4,5	19,9	1,4	23,6	5,3	4,3	3,9	4,2	3,5	3,1	6,6
CGA330050													0,8	0,8				
CGA340575										0,2	0,7	0,3						
CGA349208			0,1							0,5			0,8	0,8				
CGA349208-O-Glucose conjugate				1,3	2,2	3,4	3,8	2,4										
CGA349208 and its conjugates (calc. sum)			0,1	1,3	2,2	3,4	3,8	2,4		0,5			0,8	0,8				
CGA353042				2,3	3,3	4,6	6,6	4,3	1,2	9,4	0,7	12,1	3,2	3,8	7,4	7,4	7	
CGA353968-desmethyl			3,9	0,1	0,3	0,5	0,9	0,4	1,1		1	0,3			2,7	1,7	3,7	2,5
CGA353968			3,5	1,4	2,1	2,4	2,5	3,6	2	0,8	3	1,1		0,5	4,1	5,6	6,9	5,6
CGA353968-N-glucoside conjugate			-	0,6	1,4	2,7	3,3	1,8	2,5	4,8	12,6	1,5			10,2	13,2		18,6
CGA353968-O-glucoside conjugate			-	0,8	1,5	2,2	2,5	1,6										
CGA353968 and its conjugates (calc. sum)				2,8	5	7,3	8,3	7	4,5	5,6	15,6	2,6		0,5	14,3	18,8	6,9	24,2
CGA355190			4,8	1,8	3,1	2,6	0,9	1,7	0,8	0,5	1,1	0,4	0,5	0,4	1,7	2,2	3,3	6,4
CGA355190-S-Glucose conjugate				0,8	1,5	2,2	3	2,4										
CGA355190 and its conjugates (calc. sum)			4,8	2,6	4,6	4,8	3,9	4,1	0,8	0,5	1,1	0,4	0,5	0,4	1,7	2,2	3,3	6,4
CGA359683				0,3	0,3	0,4	1	1,2										
CGA382191, N-methyl guanidine			3,9	0,7	1	2,2	3,8	2,2	2,4		1,7	4,7	3,2	3,8	5,7	6,4	3,6	
NOA404617																		
NOA405217, methyl nitro guanidine			2,4	2,5	3,7	6,8	7,9	4,5	1,9	1,6	1,3	0,7	1	0,8	3,9	4	3,2	
NOA407475			7,4	2,1	3,2	5	6,2	6,1	8,6	10,1	17	14,4	8,5	7,7	16	13	8,8	22,2
NOA408445															6,5	6,6		
NOA421275				0,6	1,1	1,6	2,2	1,5	9	11,3	11,9	11,6	10,4	9,5	5,7	5,7	3,8	0,7
NOA421276									0,7	1,7	0,6	1,3						
NOA424255, nitro guanidine				0,3	0,3	0,7	1,5	0,6										
NOA436944																		
Parent : thiamethoxam, CGA293343			18	82,7	70,4	55,4	41,9	60,1	8,9	3,3	13,8	2,6	4,3	5,3	18,2	15,3	24,5	16,9

Bolded: summed conjugated forms (in italics) which were considered belonging to the same parent molecule.
Cells in grey: not representative uses in the context of the renewal
Mode of application: F=Foliar, FS= seed treatment, Soil = soil treatment, Soil+F: combined 2 modes of applications.

Table 2.7.2.1-17 Overview of identified residues (**all results in leaves - ppb**)

OVERVIEW OF IDENTIFIED RESIDUES IN LEAVES (PPB)																			
MODE OF APPLICATION	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**FS**	**FS**	**FS**	**FS**	**FS**	**SOIL**	**SOIL**	**SOIL +F**	**SOIL +F**	**SOIL +F**
CROP/PART OF CROP/DOSE RATE	**CUCUMBER**	**PEAR**	**PEAR**	**LETTUCE**	**LETTUCE**	**LETTUCE**	**LETTUCE**	**LETTUCE**	**POTATO**	**POTATO**	**POTATO**	**POTATO**	**MAIZE**	**MAIZE**	**TOBACCO**	**TOBACCO**	**TOBACCO**	**CUCUMBER**
5ppb 10ppb	2X	6X	60X	PHI 0 - 3,2X	PHI 3 - 3,2X	PHI 7 - 3,2X	PHI 14 - 3,2X	PHI 14 - 31X	immature 23X	mature 23X	immature 116X	mature 116X	fodder 3X	fodder 10X	4,2X	4,3X	43X	40X
	53-61	n.a	73-74	92-95	86-92	82-86	74-81	76-90	76-80	64-69	79-87	66-85	47-68	52-66	64-67	59-66	68-77	54-61
guanidine	A complete work-up of the 2X cucumber leaves was not conducted (to low amount of radioactivity)	A complete work-up of the 6X pear leaves was not conducted (to low amount of radioactivity)							806	1181	1719	5465						
CGA204261, methyl urea				5	7	8	11	41										
CGA265307			15850	4	5	11	5	26	58	43	362	111	3	5	5	12	242	308
CGA282149																		
CGA322704, clothianidin			19830	41	49	29	39	226	245	990	1416	333	15	38	46	50	667	438
CGA322704-hydroxyl-amine-glucoside			99920						1204		5286	1673						463
CGA322704 and its conjugates (calc. sum)			1E+05	41	49	29	39	226	1449	990	6702	2006	15	38	46	50	667	901
CGA330050													3	7				
CGA340575										18	185	112						
CGA349208			400							39			3	7				
CGA349208-O-Glucose conjugate				22	23	21	22	119										
CGA349208 and its conjugates (calc. sum)			400	22	23	21	22	119		39			3	7				
CGA353042				46	49	35	46	218	83	841	185	4498	8	40	52	102	935	
CGA353968-desmethyl			16180	3	3	4	7	22	79		254	112			19	31	490	346
CGA353968			15880	25	26	15	18	179	151	72	1265	443		5	49	103	1757	766
CGA353968-N-glucoside conjugate				11	14	17	19	92	121	348	3330	558			129	243		2553
CGA353968-O-glucoside conjugate				15	15	14	15	79										
CGA353968 and its conjugates (calc. sum)			15880	51	55	46	52	350	272	420	4595	1001		5	178	346	1757	3319
CGA355190			21560	31	44	17	6	86	66	39	291	66	2	4	22	33	504	886
CGA355190-S-Glucose conjugate				14	15	14	17	118										
CGA355190 and its conjugates (calc. sum)			21560	45	59	31	23	204	66	39	291	66	2	4	22	33	504	886
CGA359683				4	3	3	6	59										
CGA382191, N-methyl guanidine			17570	13	15	17	26	109	171		450	1747	10	10	41	89	486	
NOA404617																		
NOA405217, methyl nitro guanidine			10810	49	55	52	54	227	138	143	344	275	2	8	28	55	427	
NOA407475			33380	37	37	32	36	303	628	805	7161	15350	25	71	202	238	2231	2550
NOA408445															82	121		
NOA421275				10	11	10	12	76	658	1011	4660	4877	36	90	72	105	509	82
NOA421276									51	152	159	483						
NOA424255, nitro guanidine				6	4	6	10	29										
NOA436944															4	33	124	
Parent : thiamethoxam, CGA293343			75280	1548	1057	411	263	3043	662	250	5777	1061	15	47	229	281	4545	2308

Bolded: summed conjugated forms (in italic) which were considered belonging to the same parent molecule.
Cells in grey: not representative uses in the context of the renewal
Mode of application: F=Foliar, FS= seed treatment, Soil = soil treatment, Soil+F: combined 2 modes of applications.

Table 2.7.2.1-18 Overview of identified residues (**in matrix that may enter into the animal ration and processed ones from tobacco – %TRR**)

OVERVIEW OF IDENTIFIED RESIDUES THAT MAY ENTER INTO THE ANIMAL RATION (%TRR)													PROCESSED (%TRR)					
MODE OF APPLICATION	F	F	F	FS	FS	FS	FS	FS	SOIL	SOIL	SOIL	SOIL	SOIL	SOIL+F		SOIL	SOIL+F	
CROP/PART OF CROP/DOSE RATE	RICE	RICE	RICE	POTATO	POTATO	POTATO	POTATO	MAIZE	MAIZE	RICE	RICE	RICE	TOBACCO	TOBACCO	TOBACCO	TOBACCO	TOBACCO	TOBACCO
5% 10%	husk - 1X	straw - 6X	grain - 6X	immature 23X	mature 23X	immature 116X	mature 116X	fodder 3X	fodder 10X	husk - 6X	straw - 1X	grain - 1X	cured - 4,2X	cured - 4,3X	cured - 43X	cured + pyrolysed 4,2X	cured + pyrolysed 4,3X	cured + pyrolysed 43X
Residues - %TRR extractable	49-65	80-82	14-36	68-90	68-86	76-92	75-85	47-68	52-66	86-88	63-77	7-8	49-64	58-64	58-100	78-80	64-73	68-79
guanidine				0,9		1,4							1	3,4	2	0,3	0,2	0,2
CGA204261, methyl urea	4,3		0,9							0,1	4	1,4						
CGA265307	1,1	5,2	0,5	3	3	1,7	1,7	1	0,5	0,7	3,2	0,2	5	5,5	2,2	6,8	4,4	4,4
CGA282149				10	6,3	8,8	6,5											
CGA322704, clothianidin	17,2	11,4	10,6	13,3	6,2	8,4	5,2	4,3	3,9	6,3	7,8	2,3	11	8,9	10,6	1,9	1,1	1,9
CGA322704-hydroxyl-amine-glucoside				6,1	2,2	3,4	1,7											
CGA322704 and its conjugates (calc. sum)	17,2	11,4	10,6	19,4	8,4	11,8	6,9	4,3	3,9	6,3	7,8	2,3	11	8,9	10,6	1,9	1,1	1,9
CGA330050								0,8	0,8		0,7							
CGA340575				4,8	4,4	2,2	1,6											
CGA349208		0,7	0,3	3,5	3,4	3,2	3,7	0,8	0,8	0,5	0,4	0,3	0,8		0,8	0,8	2,1	3,9
CGA349208-O-Glucose conjugate																		
CGA349208 and its conjugates (calc. sum)		0,7	0,3	3,5	3,4	3,2	3,7	0,8	0,8	0,5	0,4	0,3	0,8		0,8	0,8	2,1	3,9
CGA353042				0,5		1,4		3,2	3,8				5,2	8,6	6,9	0,8	0,4	0,5
CGA353968-desmethyl	1,8	0,4				0,3	0,3				2,1	0,4	2,2	2,7	2,6	0,4	0,2	0,2
CGA353968	2,6	1,8	2,6	3,1	3	2,6	1,6		0,5	0,9	3,8	1	8,7	7	9,3	1,9	2,8	2,4
CGA353968-N-glucoside conjugate				3,2	6	8,2	9,7						5	5,8	3,8			
CGA353968-O-glucoside conjugate																		
CGA353968 and its conjugates (calc. sum)	2,6	1,8	2,6	6,3	9	10,8	11,3		0,5	0,9	3,8	1	13,7	12,8	13,1	1,9	2,8	2,4
CGA355190	1,6	3,2	0,7					0,5	0,4	4,4	4		2,2	1,4	1,8	1,8	0,7	6,1
CGA355190-S-Glucose conjugate																		
CGA355190 and its conjugates (calc. sum)	1,6	3,2	0,7					0,5	0,4	4,4	4		2,2	1,4	1,8	1,8	0,7	6,1
CGA359683												0,3						
CGA382191, N-methyl guanidine				0,5				3,2	3,8		*0,1*		4,7	7,5	6,5	1,5	0,9	0,8
NOA404617	*1*	0,9	0,3							0,4	1,6							
NOA405217, methyl nitro guanidine		0,35		4,7	0,7	3,9	0,4	1	0,8		2,5		1,4	2,9	1,8	0,6	0,1	0,5
NOA407475	3	4	0,3	2,4	2,5	1,4	2,7	8,5	7,7	3	5,9	0,3	18,5	18,2	15,2	2,2	1,8	1,1
NOA408445													5,2	7,6	5,1			
NOA421275	*1*			2,7	3,1		2,1	10,4	9,5		1,3		5,2	5,1	3,8	0,3	0,1	0,1
NOA421276						1,4												
NOA424255, nitro guanidine											0,8							
NOA436944																		
Parent : thiamethoxam, CGA293343	21,7	53	12,8	27,6	13,1	37	24,2	4,3	5,3	70,8	27,4	0,4	3,5	4,6	8,6	0,7	0,7	0,7

Bolded: summed conjugated forms (in italic) which were considered belonging to the same parent molecule.
Cells in grey: not representative uses in the context of the renewal
Mode of application: F=Foliar, FS= seed treatment, Soil = soil treatment, Soil+F : combined 2 modes of applications.

Table 2.7.2.1-19 Overview of identified residues **(in matrix that may enter into the animal ration and processed ones from tobacco – ppb)**

OVERVIEW OF IDENTIFIED RESIDUES THAT MAY ENTER INTO THE ANIMAL RATION (PPB)													PROCESSED (PPB)					
MODE OF APPLICATION	F	F	F	FS	FS	FS	FS	FS	SOIL	SOIL	SOIL	SOIL	SOIL	SOIL+F		SOIL	SOIL+F	
CROP/PART OF CROP/DOSE RATE	RICE	RICE	RICE	POTATO	POTATO	POTATO	POTATO	MAIZE	MAIZE	RICE	RICE	RICE	TOBACCO	TOBACCO	TOBACCO	TOBACCO	TOBACCO	TOBACCO
5ppb 10ppb	husk - 1X	straw - 6X	grain - 6X	immature 23X	mature 23X	immature 116X	mature 116X	fodder 3X	fodder 10X	husk - 6X	straw - 1X	grain - 1X	cured - 4,2X	cured - 4,3X	cured - 43X	cured + pyrolysed 4,2X	cured + pyrolysed 4,3X	cured + pyrolysed 43X
Residues - %TRR extractable	49-65	80-82	14-36	68-90	68-86	76-92	75-85	47-68	52-66	86-88	63-77	7-8	49-64	58-64	58-100	78-80	64-73	68-79
guanidine				2		14												
CGA204261, methyl urea	23		*1*							*1*	114	3						
CGA265307	7	58	*1*	10	6	17	15	3	5	8	87	*1*	516	736	3514	710	586	7115
CGA282149				22	6	88	56											
CGA322704, clothianidin	90	115	3	29	14	86	45	15	38	60	220	4	1148	1185	17376	106	144	3155
CGA322704-hydroxyl-amine-glucoside				20	5	39	14											
CGA322704 and its conjugates (calc. sum)	90	115	3	49	19	125	59	15	38	60	220	4	1148	1185	17376	106	144	3155
CGA330050								3	7		20							
CGA340575				10	6	23	14											
CGA349208		7	1	11	7	37	32	3	7	6	12	1	80		1275	82	284	6301
CGA349208-O-Glucose conjugate																		
CGA349208 and its conjugates (calc. sum)		7	1	11	7	37	32	3	7	6	12	1	80		1275	82	284	6301
CGA353042				1		14		8	40				571	1359	11099	83	69	723
CGA353968-desmethyl	12	2		-	-	3	3				60	1	240	431	4188	41	26	340
CGA353968	17	19	*1*	6	5	27	17		5	10	108	2	900	1102	15137	193	377	3965
CGA353968-N-glucoside conjugate				10	13	92	83						524	772	6205			
CGA353968-O-glucoside conjugate																		
CGA353968 and its conjugates (calc. sum)	17	19	1	16	18	119	100		5	10	108	2	1424	1874	21342	193	377	3965
CGA355190	11	34	*1*					2	4	51	113		233	226	2991	192	102	10113
CGA355190-S-Glucose conjugate																		
CGA355190 and its conjugates (calc. sum)	11	34	*1*					2	4	51	113		233	226	2991	192	102	10113
CGA359683												*1*						
CGA382191, N-methyl guanidine				1				10	10		*1*		521	1182	10508	172	133	1378
NOA404617	*1*	9	*1*							5	48							
NOA405217, methyl nitro guanidine		4		12	40	1	3	2	8		72		149	459	2865	72	15	741
NOA407475	16	43	*1*	8	3	14	23	25	71	31	167	1	1927	2427	25336	229	238	1735
NOA408445													536	1018	8376			
NOA421275	*1*			6	4		18	36	90		33		541	681	5429	35	8	127
NOA421276						14												
NOA424255, nitro guanidine											23							
NOA436944													110	536	3188	32	30	331
Parent : thiamethoxam, CGA293343	144	570	3	59	29	378	207	15	47	821	778	*1*	392	723	13937	81	112	1828

Bolded : summed conjugated forms (in italic) which were considered belonging to the same parent molecule.
Cells in grey : not representative uses in the context of the renewal
Mode of application : F=Foliar, FS= seed treatment, Soil = soil treatment, Soil+F : combined 2 modes of applications.

Table 2.7.2.1-20 Overview of identified residues **(in matrix that may enter into the food for human - %TRR)**

OVERVIEW OF IDENTTIFIED RESIDUES THAT MAY ENTER INTO THE HUMAN RATION (%TRR)																				
MODE OF APPLICATION	**F**	**F**	**F**	**F**	**F**	**SOIL+F**	**F**	**F**	**F**	**F**	**F**	**FS**	**FS**	**FS**	**FS**	**FS**	**SOIL**	**SOIL**	**SOIL**
CROP/PART OF CROP/DOSE RATE	**RICE**	**RICE**	**PEAR**	**PEAR**	**CUCUMBER**	**CUCUMBER**	**LETTUCE**	**LETTUCE**	**LETTUCE**	**LETTUCE**	**LETTUCE**	**POTATO**	**POTATO**	**POTATO**	**POTATO**	**MAIZE**	**MAIZE**	**RICE**	**RICE**
5% 10%	grain - 1X	husk - 1X	mature fruit - 6X	mature fruit - 60X	mature fruit - 2X	mature fruit - 40X	PHI 0 - 3,2X	PHI 3 - 3,2X	PHI 7 - 3,2X	PHI 14 - 3,2X	PHI 14 - 31X	mature tubber - 23X	immature tubber - 116X	immature tubber - 23X	mature tubber - 116X	grain - 3X	grain - 10X	grain - 6X	husk - 6X
Residues - %TRR extractable	14-36	86-88	83-102	91-103	75-94	80-86	92-95	86-92	82-86	74-81	76-90	68-86	76-92	68-90	75-85	39-71	43-77	7-8	49-65
guanidine													1,4	0,9					
CGA204261, methyl urea	0,9	0,1					0,3	0,4	1,1	1,5	0,8							1,4	4,3
CGA265307	0,5	0,7	4,8	3,5			0,2	0,3	0,4	0,7	0,5	3	1,7	3	1,7		2,2	0,2	1,1
CGA282149												6,3	8,8	10	6,5				
CGA322704, clothianidin	10,6	6,3	24	19	1,3	1,5	2,1	3,2	3,8	5,8	4,5	6,2	8,4	13,3	5,2	9,6	15,8	2,3	17,2
CGA322704-hydroxyl-amine-glucoside			1,1	1,1								2,2	3,4	6,1	1,7				
CGA322704 and its conjugates (calc. sum)	10,6	6,3	25,1	20,1	1,3	1,5	2,1	3,2	3,8	5,8	4,5	8,4	11,8	19,4	6,9	9,6	15,8	2,3	17,2
CGA330050																	0,7		
CGA340575												4,4	2,2	4,8	1,6				
CGA349208	0,3	0,5	1,9									3,4	3,2	3,5	3,7		0,7	0,3	
CGA349208-O-Glucose conjugate							1,3	2,2	3,4	3,8	2,4								
CGA349208 and its conjugates (calc. sum)	0,3	0,5	1,9				1,3	2,2	3,4	3,8	2,4	3,4	3,2	3,5	3,7		0,7	0,3	
CGA353042							2,3	3,3	4,6	6,6	4,3		1,4	0,5					
CGA353968-desmethyl			1,8	3			0,1	0,3	0,5	0,9	0,4		0,3		0,3			0,4	1,8
CGA353968	2,6	0,9	6	8,4	1	1,1	1,4	2,1	2,4	2,5	3,6	3	2,6	3,1	1,6		1,2	1	2,6
CGA353968-N-glucoside conjugate							0,6	1,4	2,7	3,3	1,8	6	8,2	3,2	9,7				
CGA353968-O-glucoside conjugate							0,8	1,5	2,2	2,5	1,6								
CGA353968 and its conjugates (calc. sum)	2,6	0,9	6	8,4	1	1,1	2,8	5	7,3	8,3	7	9	10,8	6,3	11,3		1,2	1	2,6
CGA355190	0,7	4,4	1,1	2,8	0,4	1,4	1,8	3,1	2,6	0,9	1,7						0,4		1,6
CGA355190-S-Glucose conjugate							0,8	1,5	2,2	3	2,4								
CGA355190 and its conjugates (calc. sum)	0,7	4,4	1,1	2,8	0,4	1,4	2,6	4,6	4,8	3,9	4,1						0,4		1,6
CGA359683							0,3	0,3	0,4	1	1,2							0,3	
CGA382191, N-methyl guanidine				1,6			0,7	1	2,2	3,8	2,2			0,5					
NOA404617	0,3	0,4																	*1*
NOA405217, methyl nitro guanidine				1,8			2,5	3,7	6,8	7,9	4,5	0,7	3,9	4,7	0,4		4,1		
NOA407475	0,3	3	4,6	2	30	19,5	2,1	2,4	5	6,2	6,1	2,5	1,4	2,4	2,7		2,5	0,3	3
NOA408445																			
NOA421275			1,2				0,6	1,1	1,6	2,2	1,5	3,1		2,7	2,1		1,9		*1*
NOA421276													1,4						
NOA424255, nitro guanidine							0,3	0,3	0,7	1,5	0,6								
NOA436944																			
Parent : thiamethoxam, CGA293343	12,8	70,8	29,3	33,4	15,9	13,5	82,7	70,4	55,4	41,9	60,1	13,1	37	27,6	24,2	15,1	15,1	0,4	21,7

Bolded : summed conjugated forms (in italic) which were considered belonging to the same parent molecule.
Cells in grey: not representative uses in the context of the renewal
Mode of application: F=Foliar, FS= seed treatment, Soil = soil treatment, Soil+F : combined 2 modes of applications.

Table 2.7.2.1-21 Overview of identified residues **(in matrix that may enter into the food for human - ppb)**

OVERVIEW OF IDENTTIFIED RESIDUES THAT MAY ENTER INTO THE HUMAN RATION (PPB)																			
MODE OF APPLICATION	**F**	**F**	**F**	**F**	**F**	**SOIL+F**	**F**	**F**	**F**	**F**	**F**	**FS**	**FS**	**FS**	**FS**	**FS**	**SOIL**	**SOIL**	**SOIL**
CROP/PART OF CROP/DOSE RATE	**RICE**	**RICE**	**PEAR**	**PEAR**	**CUCUMBER**	**CUCUMBER**	**LETTUCE**	**LETTUCE**	**LETTUCE**	**LETTUCE**	**LETTUCE**	**POTATO**	**POTATO**	**POTATO**	**POTATO**	**MAIZE**	**MAIZE**	**RICE**	**RICE**
5ppb 10ppb	grain - 1X	husk - 1X	mature fruit - 6X	mature fruit - 60X	mature fruit - 2X	mature fruit - 40X	PHI 0 - 3,2X	PHI 3 - 3,2X	PHI 7 - 3,2X	PHI 14 - 3,2X	PHI 14 - 31X	mature tubber - 23X	immature tubber - 116X	immature tubber - 23X	mature tubber - 116X	grain - 3X	grain - 10X	grain - 6X	husk - 6X
Residues - %TRR extractable	14-36	86-88	83-102	91-103	75-94	80-86	92-95	86-92	82-86	74-81	76-90	68-86	76-92	68-90	75-85	39-71	43-77	7-8	49-65
guanidine													14	2					
CGA204261, methyl urea	*1*	*1*					5	7	8	11	41							3	23
CGA265307	*1*	8	23	238			4	5	11	5	26	6	17	10	15		1	*1*	7
CGA282149												6	88	22	56				
CGA322704, clothianidin	3	60	134	1409		5	41	49	29	39	226	14	86	29	45	2	7	4	90
CGA322704-hydroxyl-amine-glucoside			8	75								5	39	20	14				
CGA322704 and its conjugates (calc. sum)	3	60	142	1484		5	41	49	29	39	226	19	125	49	59	2	7	4	90
CGA330050	1																1	1	
CGA340575												6	23	10	14				
CGA349208	1	6	9									7	37	11	32		1	1	
CGA349208-O-Glucose conjugate							22	23	21	22	119								
CGA349208 and its conjugates (calc. sum)	1	6	9				22	23	21	22	119	7	37	11	32		1	1	
CGA353042							46	49	35	46	218		14	1					
CGA353968-desmethyl			13	212			3	3	4	7	22	-	3	-	3			1	12
CGA353968	*1*	10	42	594		4	25	26	15	18	179	5	27	6	17		*1*	2	17
CGA353968-N-glucoside conjugate							11	14	17	19	92	13	92	10	83				
CGA353968-O-glucoside conjugate							15	15	14	15	79								
CGA353968 and its conjugates (calc. sum)	*1*	10	42	594		4	51	55	46	52	350	18	119	16	100		*1*	2	17
CGA355190	*1*	51	8	198		4	31	44	17	6	86						1		11
CGA355190-S-Glucose conjugate							14	15	14	17	118								
CGA355190 and its conjugates (calc. sum)	*1*	51	8	198		4	45	59	31	23	204						1		11
CGA359683							4	3	3	6	59							*1*	
CGA382191, N-methyl guanidine				113			13	15	17	26	109			1			2		
NOA404617	*1*	5					49	55	52	54	227								*1*
NOA405217, methyl nitro guanidine				127								40	1	12	3		2		
NOA407475	*1*	31	32	141	9	58	37	37	32	36	303	3	14	8	23		2	1	16
NOA408445																			
NOA421275			8				10	11	10	12	76	4	-	6	18		1		*1*
NOA421276													14						
NOA424255, nitro guanidine							6	4	6	10	29								
NOA436944																			
Parent : thiamethoxam, CGA293343	3	821	196	2274	6	44	1548	1057	411	263	3043	29	378	59	207	2	6	*1*	144

Bolded: summed conjugated forms (in italic) which were considered belonging to the same parent molecule.
Cell in grey: uses not at stake in context of renewal
Mode of application: F=Foliar, FS= seed treatment, Soil = soil treatment, Soil+F: combined 2 modes of applications.

Metabolism studies conducted with [oxadiazin-4-^{14}C] or [thiazol-2-^{14}C]-thiamethoxam show a similar pathway but different ranking of metabolites according to their residue levels, depending on the mode of application or inner the same representative metabolism group. In terms of chemical structures several of these metabolites might be grouped and considered as "thiamethoxam-like" or "clothianidin-like" but structural activity in this sense is not so obvious without additional information concerning toxicity (see volume 1 summary of other toxicological studies 1.1.1.4 Toxicity studies of metabolites and impurities).

In addition several of these metabolites could also be identified as relevant and/or perhaps as "clothianidin-like" in terms of their toxicity in the context of the concomitant assessment for the renewal of the active substance clothianidin.

2.7.2.2 Metabolism in rotational crops

Bare ground application with ^{14}C-thiazol- and ^{14}C-oxadiazin- thiamethoxam at a rate of 207 g a.s/ha and 200 g a.s/ha, respectively, were performed to investigate the amounts and nature of pesticide residues in rotational crops. The plant back intervals and rotational crops were as follows: 29 days (lettuce, radish, spring wheat), 104 days (spring wheat), 119 days (lettuce, radish), 180 days (winter wheat) and 362 days (lettuce, radish, spring wheat).

Table 2.7.2.2-1 Study design overview **(rotations)**

Crop group	Crop	Label position	PBI	Application and sampling details				Sampling	Ref.
				Method	Rate g a.s./ha	Harvest Intervals DAT	Remarks		
Leafy vegetables	lettuce	thiamethoxam-[thiazol-2-^{14}C]	29, 119 and 362	Soil treatment	207	89, 180 and 425	Radish, spring and winter wheat were sowed directly onto the plot. Lettuce was transplanted as 20 days old seedlings.	3 soil cores 0-30 cm	Sandmeier, 1997c
Root and tuber vegetables	Radish		29, 119 and 362			89, 180 and 425			
Cereals	spring wheat		29, 104 and 362			89, 124, 180, 250 474 and 492			
	winter wheat		180			250, 425 and 474			
Leafy vegetables	Lettuce	thiamethoxam-[oxadiazin-4-^{14}C]	29, 119 and 362	Soil treatment	200	89, 180 and 425	Radish, spring and winter wheat were sowed directly onto the plot. Lettuce was transplanted as 20 days old seedlings.	soil cores 0-30 cm	Sandmeier, 1997b
Root and tuber vegetables	Radish		29, 119 and 362			89, 180 and 425			
Cereals	Spring wheat		29, 104 and 362			89, 124, 180, 250 474 and 492			
	winter wheat		180			250, 425 and 474			

An overview of identified residues is presented below with the same methodology (as for plant metabolism) with:

A=1st plant back interval, 29 DAT: assessing circumstance of crop failure situation

B=2nd plant back interval, 119 DAT: reflecting a typical rotation after harvest of the primary crop

B"=3rd plant back interval, 180 DAT: reflecting a typical rotation after harvest of the primary crop with winter variety

C=4th plantation, 362 DAT: reflecting crops rotated the following year

Table 2.7.2.2-2 Overview of identified residues **(in lettuce after rotation)**

Plant part/timing		Sub-Proj.	Metabolite Fractions (ppb)										unres	subtot	Sox.	Extracted	NE
			I1	I3	I5	I7	I11	I12	I14	I16	**I18**	I20					
				NOA 407475	CGA 382191	NOA 421275			NOA 407217	CGA 322704	CGA 293343	Hypothetic*					
Lettuce	A	[O]	1,3	1,7	1,6	1,8	1,6		3,8	4	8,5		7	31,4	0,6	34	4,9
		[T]	1,3	1,6		2,9	3,5	2,6		4,2	7,5		3,8	27,4	0,5	35	6,1
	B	[O]	5,8							1,6	1,5	0,3	0,7	9,9		12	2,3
		[T]	4,4							2,1	2,4		1,1	9,9		13	3,2
	C	[O]	total 8														n.a
		[T]	total 4														n.a
			Metabolite Fractions (%)										unres	subtot	Sox.	Extracted	NE
			I1	I3	I5	I7	I11	I12	I14	I16	**I18**	I20					
Lettuce	A	[O]	3,8	5	4,8	5,4	4,7		11,2	11,9	25,1		20,5	92,4	1,9	94,3	14,5
		[T]	3,8	4,5		8,2	9,9	7,5		12,1	21,3		10,8	78,1	1,5	79,6	17,3
	B	[O]	48,41							13,7	12,2	2,6	5,8	82,7		82,7	19,2
		[T]	33,61							16	18,3		8,1	76		76	24,9

Table 2.7.2.2-3 Overview of identified residues **(in radish after rotation)**

Plant part/timing		Sub-Proj	Metabolite Fractions (ppb)														unres	subtot	Sox.	Extracted	NE
			I1	I3	I5	I7	I11	I12	I14	I15	I15a[7]	I16	I16a	**I18**	I20	I21					
				NOA 407475	CGA 382191	NOA 421275			NOA 407217	CGA 265307	CGA 353968 desmethyl	CGA 322704	CGA 353968	CGA 293343	Hypothetic*	CGA 355190					
Radish (tops)	**A**	**[O]**	4,2	7,1	4,9	5,8		0,9	2,2	6,9	1,4	11,9		18,8		1	8	73,1	1,7	77	6
		[T]	5,9	7,8		7,3	5,8	5,9		10,5	2,3	7,9	6	23	1,2	1	8,3	93	1,9	116	10,9
	B	**[O]**	7,21 (I1 to I14)							0,3		0,7		1,1			0,3	9,7		11	1,7
		[T]	total 9																		2,6
	C	**[O]**	total 8																		n.a
		[T]	total 9																		n.a
Roots	**A**	**[O]**	total 5																		n.a
		[T]	total 7																		n.a
	B	**[O]**	total 2																		n.a
		[T]	total 2																		n.a
	C	**[O]**	total 2																		n.a
		[T]	total 3																		n.a
			Metabolite Fractions (%)														unres	subtot	Sox.	Extracted	NE
			I1	I3	I5	I7	I11	I12	I14	I15	I15a	I16	I16a	**I18**	I20	I21					
Radish tops	A	**[O]**	5,5	9,2	6,4	7,5		1,2	2,8	8,9	1,8	15,52		24,4		1,3	10,4	94,9	2,2	97,1	7,8
		[T]	5,1	6,7		6,3	5	5,1		9,1	2	6,8	5,2	19,8	1	0,9	7,1	80,1	1,6	81,7	9,4
	B	**[O]**	65,2 (I1 to I14)							2,9		6,5		9,7			2,8	87,1		87,1	15,8
		[T]	81,5																		23,1

Table 2.7.2.2-4 Overview of identified residues **(in grain after rotation)**

Plant part/timing		Sub-Proj	Metabolite Fractions (ppb)						unres	subtot	Sox.	Extracted	NE
			I1 or precised	I15	I15a[7]	I16	**I18**	I20					
				CGA 265307	CGA 353968 desmethyl	CGA 322704	CGA 293343	Hypothetic*					
Grain	A	[O]	7,5 (I1 to I14)	1,5		0,7	0,2		0,3	10,1	1,7	20	8,2
		[T]	9,2 (I1 to I14)	2,1		1,1	0,1	0,1	0,5	13,1	0,9	29	18,9
	B	[O]	2,8	1,5	0,8	0,3		0,1	7,3	12,8	2,1	85	70
		[T]	4,4	1,7		0,3			4,3	10,7	2,8	147	131,3
	B"	[O]	total 6										n.a
		[T]	total 5										n.a
	C	[O]	total 7										n.a
		[T]	total 4										n.a
			Metabolite Fractions (%)						unres	subtot	Sox.	Extracted	NE
			I1 or precised	I15	I15a	I16	**I18**	I20					
Grain	A	[O]	37,41 (I1 to I14)	7,3		3,3	1		1,4	50,4	8,5	58,9	41,1
		[T]	31,71 (I1 to I14)	7,4		3,8	0,3	0,3	1,8	45,3	3,1	48,4	65,1
	B	[O]	3,3	1,8	0,9	0,3		0,2	8,6	15,1	2,5	17,6	**82,3**
		[T]	3	1,2		0,2			3	7,4	1,9	9,3	**89,3**

Note: as for cereals in primary crop plant metabolism studies (section 2.7.2.1): low extraction yield in grain.

Table 2.7.2.2-5 Overview of identified residues **(in husk after rotation)**

Plant part/timing	Sub-Proj		Metabolite Fractions (ppb)															unres	subtot	Sox.	Extracted	NE
			I_1	I_3	I_5	I_7	I_{11}	I_{12}	I_{14}	I_{14a}	I_{15}	I_{15a}[7]	I_{16}	I_{17}	**I_{18}**	I_{20}	I_{21}					
				NOA 407475	CGA382191	NOA 421275			NOA 407217		CGA265307	CGA353968 desmethyl	CGA322704		CGA293343	Hypothetic*	CGA355190					
Husks	A	[O]	12,9	19,7	30,8	20,6	13,2	13,5	18,5	11,7	42,9	9,1	61,4		9,7		4,7	25	293,7	17,2	390	91,3
		[T]	12,7	4,3		20,5	17,2	21,3		3,8	53,4		55,2	3	18,5	2,5	3,3	37,7	253,6	15,7	365	97,5
	B	[O]	9,6		12,5	8,1		13,6	27,1		17,7	2,2	12,3		3,9	1,3		22,9	131,2	7	180	47,9
		[T]	8			5,3		7			12,5	1,6	7,8		1	1		19,9	64,1	6	131	65,4
	B"	[O]	41,61								3		1,5			0,3		1,3	47,7	3,4	69	19,7
		[T]	24,81								3,4		1,8			0,5		1,5	31,9	1,9	52	17,3
	C	[O]	36,71								3,1		2,2			0,4		1,2	43,5	3,8	72	24,5
		[T]	24,21								3,9		3,1					1,8	32,9	2,7	58	23,7
			Metabolite Fractions (%)															unres	subtot	Sox.	Extracted	NE
			I_1	I_3	I_5	I_7	I_{11}	I_{12}	I_{14}	I_{14a}	I_{15}	I_{15a}	I_{16}	I_{17}	**I_{18}**	I_{20}	I_{21}					
Husks	A	[O]	3,3	5	7,9	5,3	3,4	3,5	4,7	3	11	2,3	15,7		2,5		1,2	6,4	75,2	4,4	79,6	23,4
		[T]	3,5	1,2		5,6	4,7	5,8		1	14,6		15,1	0,8	5,1	0,7	0,9	10,3	69,5	4,3	73,6	26,7
	B	[O]	5,3		6,9	4,5		7,6	15,1		9,8	1,2	6,9		2,2	0,7		12,7	72,9	3,9	76,8	26,6
		[T]	6,1			4		5,4			9,6	1,2	5,9		0,7	0,8		15,2	48,9	4,6	53,5	49,9
	B"	[O]	60,31								4,3		2,2			0,5		1,9	69,2	4,9	74,1	28,5
		[T]	47,61								6,5		3,4			0,9		2,8	61,2	3,6	64,8	33,2
	C	[O]	50,91								4,3		3,1			0,5		1,7	60,5	5,3	65,8	34
		[T]	41,71								6,7		5,4					3	56,8	4,7	61,5	40,8

Table 2.7.2.2-6 Overview of identified residues **(in whole plant immature after rotation)**

Plant part/timing	Sub-Proj		Metabolite Fractions (ppb)															unres	subtot	Sox.	Extracted	NE
			I_1	I_{3a}	I_3	I_5	I_7	I_{11}	I_{12}	I_{14}	I_{14a}	I_{15}	I_{15a}[7]	I_{16}	**I_{18}**	I_{20}						
					NOA 407475	CGA 382191	NOA 421275			NOA 407217		CGA 265307	CGA353968 desmethyl	CGA 322704	CGA 293343	Hypothetic*						
Spring Wheat whole tops 50% mature	A	[O]	4		4,2	4,9	8,7	4,3	3,5	3,3		2,2	1,2	5,1	3,7			4,4	49,9	7,7	67	15,7
		[T]	6,3		7		23,2	11,7	5,2		2,1	4,2	1,4	11,2	4,9			9,9	87,1	6,3	112	10,5
	B	[O]	4,4	3,1		3,8	5	4,3	1,7	2,5	0,5	2,1	1	7,5	1,1	0,5		7,4	44,9	2,9	56	8,9
		[T]	2,5	0,5			2,8	2,5	1,5		0,7	1,4	0,6	5,5		0,4		5,8	24,2	2	30	5,9
Winter Wheat whole tops fall cutting	B"	[O]	9,71									0,6		4,5	0,4	0,8		1,1	17,1		23	5,1
		[T]	4,01									0,6		4,4	0,2			0,9	10,1		14	3,6
Spring Wheat whole tops 50% mature	C	[O]	23,81									1,1		0,9		0,2		0,5	26,6	1,8	35	6
		[T]	12,21									0,7		0,8		0,2		0,5	14,5	1	19	4,7
			Metabolite Fractions (%)															unres	subtot	Sox.	Extracted	NE
			I_1	I_{3a}	I_3	I_5	I_7	I_{11}	I_{12}	I_{14}	I_{14a}	I_{15}	I_{15a}	I_{16}	**I_{18}**	I_{20}						
Spring Wheat whole tops 50% mature	A	[O]	6		6,3	7,4	13,1	6,5	5,2	5		3,3	1,9	7,6	5,5			6,6	74,4	11,5	85,9	23,5
		[T]	5,6		6,3		20,7	10,4	4,7		1,9	3,7	1,2	10	4,4			8,9	77,8	5,6	83,4	9,4
	B	[O]	7,9	5,4		6,7	9	7,7	3	4,5	1	3,7	1,7	13,5	2	0,9		13,1	80,1	5,1	85,2	15,9
		[T]	8,3		1,6		9,3	8,5	5		2,3	4,7	2	18,4		1,2		19,4	80,7	6,8	87,5	19,6
Winter Wheat whole tops fall cutting	B"	[O]	42,21									2,7		19,7	1,6	3,4		4,8	74,4		74,4	22,3
		[T]	28,91									4,1		31,2	1,6			6,1	71,9		71,9	25,8
Spring Wheat wholetops50%	C	[O]	68,01									3,1		2,5		0,7		1,5	75,8	5,1	80,9	17
		[T]	64,31									3,8		4,3		1,1		2,8	76,3	5,3	81,6	24,5

Table 2.7.2.2-7 Overview of identified residues **(in straw after rotation)**

Plant part/timing	Sub-Proj		Metabolite Fractions (ppb)																	unres	subtot	Sox.	Extracted	NE
			I_1	I_2	I_3	I_4	I_5	I_7	I_{11}	I_{12}	I_{14}	I_{14a}	I_{15}	$I_{15'a}$	I_{16}	I_{16a}	I_{17}	**I_{18}**	I_{20}					
					NOA 407475	CGA 353042	CGA 382191	NOA 421275			NOA 407217		CGA 265307	CGA 353968 desmethyl	CGA 322704	CGA 353968		CGA 293343	Hypothetic*					
Spring Wheat straw	A	[O]	20,2		4,1	6,2	43,1	40,8	22,63	25,54	24,6	14,9	34,8	14,6	23,1	4,4		9,6		43,5	332,1	38	520	146,1
		[T]	21,1	18,4	22,8			65,8	52,73	29,4		6,1	38,2	23,7	43,52		13,6	38,2		65	438,6	24,8	753	227,4
	B	[O]	5,8	5,6	2,9		12,5	11,4	10,9	6,4	23,1		13,6	3,2	13,4			3,4	1,2	19,7	133,3	8,2	233	84,8
		[T]	5,1					8,3	10,1	3,7			12,8	2,8	10,2		1,8	6,9	1	26,3	89,1	11,9	172	74,8
Winter Wheat straw	B"	[O]	29,41										1,8		1,8			0,2	0,3	0,9	34,5	2,5	57	21
		[T]	21,91										1,7		1,9				0,4	1,3	27,2	2,4	51	22
Spring Wheat straw	C	[O]	34,01										2,6		2,2				0,4	1,3	40,5	2,9	80	32,3
		[T]	32,31										3,5		4,4				0,7	1,7	42,5	2,6	82	36,2
			Metabolite Fractions (%)																	unres	subtot	Sox.	Extracted	NE
			I_1	I_2	I_3	I_4	I_5	I_7	I_{11}	I_{12}	I_{14}	I_{14a}	I_{15}	I_{15a}	I_{16}	I_{16a}	I_{17}	**I_{18}**	I_{20}					
Spring Wheat straw	A	[O]	3,9		0,8	1,2	8,3	7,8	4,3	4,9	4,7	2,9	6,7	2,8	4,5	0,8		1,9		8,4	63,9	7,3	71,2	28,1
		[T]	2,8	2,4	3			8,7	7,03	3,9		0,8	5,1	3,1	5,82		1,8	5,1		8,6	58,1	3,3	61,4	30,2
	B	[O]	2,5	2,4	1,3		5,3	4,9	4,7	2,8	9,9		5,8	1,4	5,8			1,5	0,5	8,5	57,3	3,5	60,8	36,4
		[T]	3					4,8	5,9	2,1			7,4	1,6	5,9		1,1	4	0,6	15,3	51,8	6,9	58,6	43,5
Winter Wheat straw	B"	[O]	51,61										3,2		3,2			0,3	0,5	1,6	60,4	4,3	64,7	36,9
		[T]	42,91										3,4		3,8				0,8	2,5	53,4	4,8	58,2	43,2
Spring Wheat straw	C	[O]	42,51										3,3		2,8				0,5	1,6	50,7	3,6	54,3	40,4
		[T]	39,31										4,3		5,4				0,8	2	51,8	3,2	55	44,1

Table 2.7.2.2-8 Overview of identified residues **(in soil after rotation)**

Soil layer	DAT	Sub-Proj.	Metabolite Fractions (ppb)								unres	subtot	Sox.	Extracted	NE
			I_{10}	I_{14}	I_{15}	I_{16}	I_{17}	**I_{18}**	I_{20}	I_{21}					
				NOA 407217	CGA 265307	CGA 322704		CGA 293343	Hypothetic*	CGA 355190					
0-10cm	29	[O]				4		102,3		4	4,1	114,4	-	147	41,5
		[T]				4,9		106,7	2,7	5,9	5,3	125,5	-	143	17,6
	63	[T]				8		101	1,6	3,8	6,7	121,1	-	134	17,2
	89	[T]	0,9		0,4	8,4	0,6	45,2	1,1	2,2	1,6	60,4	-	72	14,4
0-10cm	119	[O]	2,4	1,5	1	13,9	1	32,7	2	1,5	2,8	58,8	-	79	22,1
		[T]	2,6		0,9	14,7	1,6	42,6	1	1,9	2,9	68,2	-	86	21,5
0-10cm	180	[O]	0,9	1,5	1,9	19,8	0,7	13	1,6	0,7	1,3	41,4	-	74	32,9
		[T]	0,9		1,4	16,2	0,7	12,4	0,9	0,5	2	35	-	55	21,4
10-20cm		[O]	2,1	2,1	0,8	7,2	0,4	3,1	0,7		0,9	17,3	-	23	6
0-10cm	362	[O]		0,8	1,3	14,2	0,5	7,6	1,1	0,5	1,6	27,6	-	50	22,3
		[T]	0,2		1,1	13,1	0,3	6	0,8	0,3	1,1	22,9	-	41	17,7
0-10cm	492	[T]			1,3	10,3	0,1	2,4	0,4	0,2	1	15,7	-	29	13,9
10-20cm		[T]			0,7	4,5		0,1	<0,1		0,3	5,6	-	7	1,9
			Metabolite Fractions (%)								unres	subtot	Sox.	Extracted	NE
			I_{10}	I_{14}	I_{15}	I_{16}	I_{17}	**I_{18}**	I_{20}	I_{21}					
0-10cm	29	[O]				2,7		69,6		2,7	2,8	77,8	-	77,8	28,2
		[T]				3,4		74,6	1,9	4,1	3,7	87,7	-	87,7	12,3
	63	[T]				6		75,4	1,2	2,8	5	90,4	-	90,4	12,8
	89	[T]	1,2		0,6	11,7	0,8	62,9	1,5	3	2,2	83,9	-	83,9	20
0-10cm	119	[O]	3	1,9	1,3	17,6	1,3	41,4	2,5	1,9	3,6	74,5	-	74,5	28
		[T]	3		1	17	1,8	49,3	1,1	2,2	3,4	78,8	-	78,8	24,9
0-10cm	180	[O]	1,2	2	2,5	26,7	1	17,5	2,2	0,9	1,8	55,8	-	55,8	44,4
		[T]	1,6		2,5	29,7	1,2	22,6	1,6	1	3,6	63,8	-	63,8	39,1
10-20cm		[O]	9	9,1	3,3	31,5	1,6	13,4	3,1		4	75	-	75	25,9
0-10cm	362	[O]		1,5	2,5	28,3	0,9	15,2	2,2	0,9	3,2	54,7	-	54,7	44,5
		[T]	0,5		2,7	32	0,8	14,6	2	0,8	2,7	56,1	-	56,1	43,2
0-10cm	492	[T]			4,4	35,8	0,5	8,4	1,5	0,6	3,4	54,6	-	54,6	48,5
10-20cm		[T]			9,9	62,3		1,8	0,5		4,8	79,3	-	79,3	26,3

Hypothetic*: suspected to be a coelution of CGA349208+CGA330050 after cochromatographed in same conditions with corresponding standards.

Qualitative metabolite pattern in rotational crops is similar to the pattern found previously in plants primary crop metabolism studies. Metabolites found above 10% in relative concentrations:

- after plant back interval of 29 DAT assessing a circumstance of crop failure situation **(A)**

- CGA 293343 (parent), CGA 322704 (clothianidin), NOA 407217 in leafy crops
- CGA 322704 (clothianidin) , CGA 265307 in cereals husks
- CGA 322704 (clothianidin) , NOA 421275 in cereals immature stage
- CGA 293343 (parent) in soil

- after plant back interval of 119-180 DAT reflecting a typical rotation after harvest of the primary crop **(B)** and **(B")**

- CGA 293343 (parent), CGA 322704 (clothianidin) in leafy crops
- NOA 407217, CGA 265307 in cereals husks
- CGA 322704 (clothianidin) in cereals immature stage
- NOA 407217 in cereals straw
- CGA 293343 (parent) and CGA 322704 (clothianidin) in soil

- after plant back interval of 362 DAT reflecting a crops rotated the following year **(C)**

- Parent and CGA322704 below 10% but main representation of unextracted radioactivity (90% in cereal grain, ca 50-80% in husk, cereal immature stage and straw)

The residue that may be found in edible parts of succeeding crops is the same residue that arises from direct application to the crop but unidentified portion significantly increases with time (especially in cereal grains). However it should be noted that as already indicated in plant metabolism primary crop studies, residues from grain are not efficiently extracted.

It is concluded, that the metabolic pathway after rotation is rather similar than in primary crop plant metabolism (except one minor amount of CGA 265307 i.e. demethylated CGA 322704 also observed in animal metabolism but not previously found in plant metabolism).

Uptake of radioactive material in succeeding crops clearly indicates the systemic behaviour of thiamethoxam, however the concentration of determined metabolites is rather low in crops after one year of rotation and following an exaggerated application rate of 200 g a.s/ha (i.e. 3.4X rate in comparison with the maximal intended rate of 58.5 g a.s/ha intended on sugar beet in this renewal context).

In addition and to rely with predicted environmental concentration (PEC) calculated from the environmental section (available results on the parent thiamethoxam, CGA322704 (a.k.a clothianidin) , metabolites CGA355190 and CGA282149), based on the critical intended rate on sugar beet of 1 x 58.5 g a.s/ha as a seed treatment (i.e. without crop interception)

Table 2.7.2.2-9 Overview and comparison with PEC soil

		Environmental section							
		thiamethoxam		CGA 322704 a.k.a clothianidin		CGA 355190		CGA 282149	
$PEC_{(s)\ 5cm}$ (calc. mg/kg soil[1]) Initial		0.078		0.024		0.015		0.003	
Short term	24h	0.078		0.024		n.a		n.a	
	2d	0.078		0.024					
	4d	0.077		0.024					
Long term	7d	0.076		0.023		n.a		n.a	
	28d	0.071		0.020					
	50d	0.065		0.017					
	100d	0.054		0.014					
Plateau concentration		0.093 mg/kg after 13 yrs		0.029 mg/kg After 4 years		n.a		n.a	
Level in soil		**Residue section** (level in soil, max. observed in table 2.7.2.3-8)							
		thiamethoxam		CGA 322704 a.k.a clothianidin		CGA 355190		CGA 282149	
		200 g a.s/ha	58.5 g a.s/ha calc.	200 g a.s/ha	58.5 g a.s/ha calc.	200 g a.s/ha	58.5 g a.s/ha calc.	200 g a.s/ha	58.5 g a.s/ha calc.
analysed (mg/kg soil)									
A (circa 30 days)		0.107	**0.031**	0.005	**0.001**	0.006	**0.002**	Not found	-
B (119 days)		0.043	**0.013**	0.015	**0.004**	0.002	**<0.001**	Not found	-
B" (180 days)		0.013	**0.004**	0.020	**0.006**	0.0007	**0.002**	Not found	-
C (365 days)		0.008	**0.002**	0.014	**0.004**	0.0005	**0.001**	Not found	-

[1] calculated with critical rate with treated sugar beet seeds (i.e. 58.5 g a.s./ha) , depth of soil layer of 5cm and soil bulk density of 1.5 g/cm^3, no plant interception and 1 applic. every third year

Results from radiolabelled study are consistent and are lower than the theoretical predicted plateau concentration in soil ($PEC_{soil\text{-}5cm}$). In consequence, the study covers the representative critical GAP (seed treatment, sugar beet).

To be added also that as stated in the table of intended GAPs, the use of thiamethoxam is limited to 1 application every 1 year (for lettuce and potato) or to 3 years (for sugar beet). It is thus considered that under these conditions, no significant residues are expected in rotational crops.

In addition and to avoid discrepancies, this assessment should be also confronted with corresponding conclusions from the concomitant assessment for the renewal of the active substance clothianidin.

2.7.2.3 Metabolism in livestock

The metabolism of thiamethoxam was investigated in the frame of the first approval dossier in poultry (laying hens) and ruminant (lactating goats), using respectively [oxadiazin-4-^{14}C] and [thiazol-2-^{14}C] radiolabelled moieties of thiamethoxam.

Table 2.7.2.3-1 Study design overview **(laying hens)**

Group	Species	Label position	No of animals	Rate (mg/kg bw/d)	Duration (days)	Commodity	Time	Ref.
Laying poultry	Laying hens	thiamethoxam-[thiazol-2-^{14}C]	5	111.7 ppm in feed or 7.9 mg/kg bw/d	4	eggs	Daily for 4 days	Ruembeli R., 1998
						excreta		
						blood	immediately prior to the sacrifice	
						tissues	6 hours after the last dose	
						bile		
						gizzard		
		thiamethoxam-[oxadiazin-4-^{14}C]	5	97.6 ppm in feed	4	Same procedure as for thiazol moiety		Lutringer C.,

Table 2.7.2.3-2 Study design overview **(lactating ruminants)**

Group	Species	Label position	No of animals	Rate (mg/kg bw/d)	Duration (days)	Commodity	Time	Ref.
Lactating ruminant	Lactating goats	thiamethoxam-[thiazol-2-^{14}C]	2	170.9 mg/capsule/day = 100.6 ppm in feed or 3.8 mg/kg bw	4	urine	Daily for 4 days	Ruembeli R., 1998
						faeces		
						milk		
						blood	Immediately prior to the sacrifice	
						tissues	6 hours after the last dose	
						bile		
						gastro intestinal tract		
		thiamethoxam-[oxadiazin-4-14C]	2	170.9 mg/capsule/day = 111.9 ppm in feed or 4.2mg/kg bw	4	Same procedure as for thiazol moiety		Lutringer C., 1998a,

Detailed results are presented in volume 3 but an overview of identified residues is presented below with the same coloring methodology as for plant and rotation metabolism studies.

Table 2.7.2.3-4 Overview of identified residues in commodities of animal origin (%TRR)

	In laying hens							In lactating goats						
	Lean meat	fat+skin	liver	liver (mild extr.+MW)	egg white	egg yolg	whole eggs (calc.)	muscle	fat	liver	liver (mild extr.+MW)	kidney	kidney (mild extr.+MW)	milk
Residues - %TRR extractable	68-85	87-95	30-48	71-93	86-91	93-93	90-92	90-94	91-93	74-86	81-83	81-83	84-90	95-96
CGA265307	8,4	57,4	14,9	19,9	47,2	58,9	52,3	3,2	3,1	2,2	3,8	0,2	0,9	17,7
CGA309335										2,7	2,7			
CGA322704, aka clothianidin	3,2	9,2	3,2	38,5	24,8	23,2	24	9,4	12,2	0,6	7,2	2	2,6	44,6
CGA 353968										1,3	1,3	1,9	1,9	
CGA355190	2,4	5,6			4,2		2,1			2,6	2,6	2,5	2,5	
CGA359683										0,6	0,6	1,5	1,5	
L9			1,9	1,9										
L14								5,6		23	25,1	9,8	9,8	
MU3	38,7	8,3	21,9	21,9										
MU12								10,9	4,6	5,9	5,9	9,3	9,3	
N1												0,2		
N5										3,6	3,6	11,8	11,8	
NOA402988			1,3	1,3										
NOA404617		1,8	0,2	0,8	14,6		7,3		0,2	0,2	0,2	4,1	4,1	
NOA405217	1	1,4	0,2	0,4	1,2	0,7	1	1,4	1,7	0,5	0,5	1,6	1,6	2,8
NOA407475	0,8	0,3				6,1	3,1	1,5		10,7	10,7	5,3	5,3	
NOA421275	10,7	3,4	3,3	12,7		1,3	0,6	5,6	13,3	10,1	13,2	17,5	19,8	
NOA421276								14,6	23,3	20,4	22,3	10,9	13,2	
8U-CGA353968-desmethyl	4,8	4,5	1,2	1,2	2,4	0,9	1,4	2,9	2,7	1,4	1,4	1,4	1,4	2,8
Parent : thiamethoxam, CGA 293343	21,1	14,8	0,2	0,2	5	11,3	8,3	53,6	51,9	1	1,1	22,3	22,3	36,8

Limitations/restrictions/discussion

If similar metabolites can be found in both species to draw a similar metabolic pathway, several differences can be noticed.

In excreta

The major metabolite eliminated via urine in goats is the metabolite CGA322704 (a.ka clothianidin), CGA 265307 following by the parent when in faeces NOA421275 is observed. In excreta from hens, main metabolites found in significant amounts are CGA 265307 following by the metabolite CGA322704 (a.k.a clothianidin). This is slightly different than in rat since thiamethoxam was found as the major metabolite eliminated via urine and faeces.

In commodities of animal origin

Several significant differences between ruminants and poultry can also be noticed in the list below :

For example in ruminants the metabolism seems more extensive with additional relevant metabolites as NOA 421275, NOA 421276, L14, MU12, NOA407475 and N5 for which toxicity relevance should be determined.

And in poultry the toxicity relevance of MU3, NOA 404617 and NOA 421275 (also in ruminants) should also be determined.

It has also to be noted that thiamethoxam does not appear in liver when MU3 or poultry and L14 in ruminant would be identified as a good markers for the residue definition for monitoring. These situations were considered in residue definitions proposed in section 2.7.3

Finally, the study duration in laying hens did not allow to reach a plateau concentration of the residue levels in eggs. In milk this information is available from a feeding study in lactating cow (plateau in milk around 7 to 14 days).

Table 2.7.2.3-5 List of identified and significant residues in commodities of animal origin (ranking in decreasing order per matrix) - Highlighted in orange : metabolites found in both poultry and ruminant inner the same matrix or products

Poultry		% TRR	Ruminant		% TRR
lean meat	Thiamethoxam	53.6	meat	Thiamethoxam	53.6
	MU3	38.7		NOA421276	14.6
	NOA421275 (a.k.aTMG)	10.7		MU12	10.9
	CGA265307	8.4		CGA322704 (a.k.a clothianidin)	9.4
fat + skin	CGA265307	57.4	fat	Thiamethoxam	51.9
	Thiamethoxam	14.8		NOA421276	23.3
	CGA322704 (a.k.a clothianidin)	9.2		NOA421275 (a.k.a TMG)	13.3
	MU3	8.3		CGA322704 a.k.a clothianidin	12.2
liver	CGA322704 (a.k.a clothianidin)	38.5	liver	L14	25.1
	MU3	21.9		NOA421276	22.3
	CGA265307	19.9		NOA 421275 (a.k.a TMG)	13.2
	NOA421275 (a.k.a TMG)	12.7		NOA 407475	10.7
			kidney	Thiamethoxam	22.3
				NOA 421275 (a.k.a TMG)	19.8
				NOA421276	13.2
				N5	11.8
				L14	9.8
				MU12	9.3
Products					
eggs	CGA265307	58.9	milk	CGA322704 a.k.a clothianidin	44.6
	CGA322704 a.k.a clothianidin	24.8		Thiamethoxam	36.8
	NOA404617	14.6		CGA265307	17.7
	Thiamethoxam	11.3			

The metabolite pattern in ruminant was slightly more complex with additional metabolites indicating a more extensive metabolism than in hen.

In addition and to avoid discrepancies, this assessment should be also confronted with corresponding conclusions from the concomitant assessment for the renewal of the active substance clothianidin.

The proposed metabolic pathway of thiamethoxam in hens and lactating goats are showed in following Figures (metabolic map built with MSS Livestock Composer - METAPATH software).

Figure 2.7.2.3-6 Metabolic pathway of thiamethoxam (CGA293343) **(laying hens)**

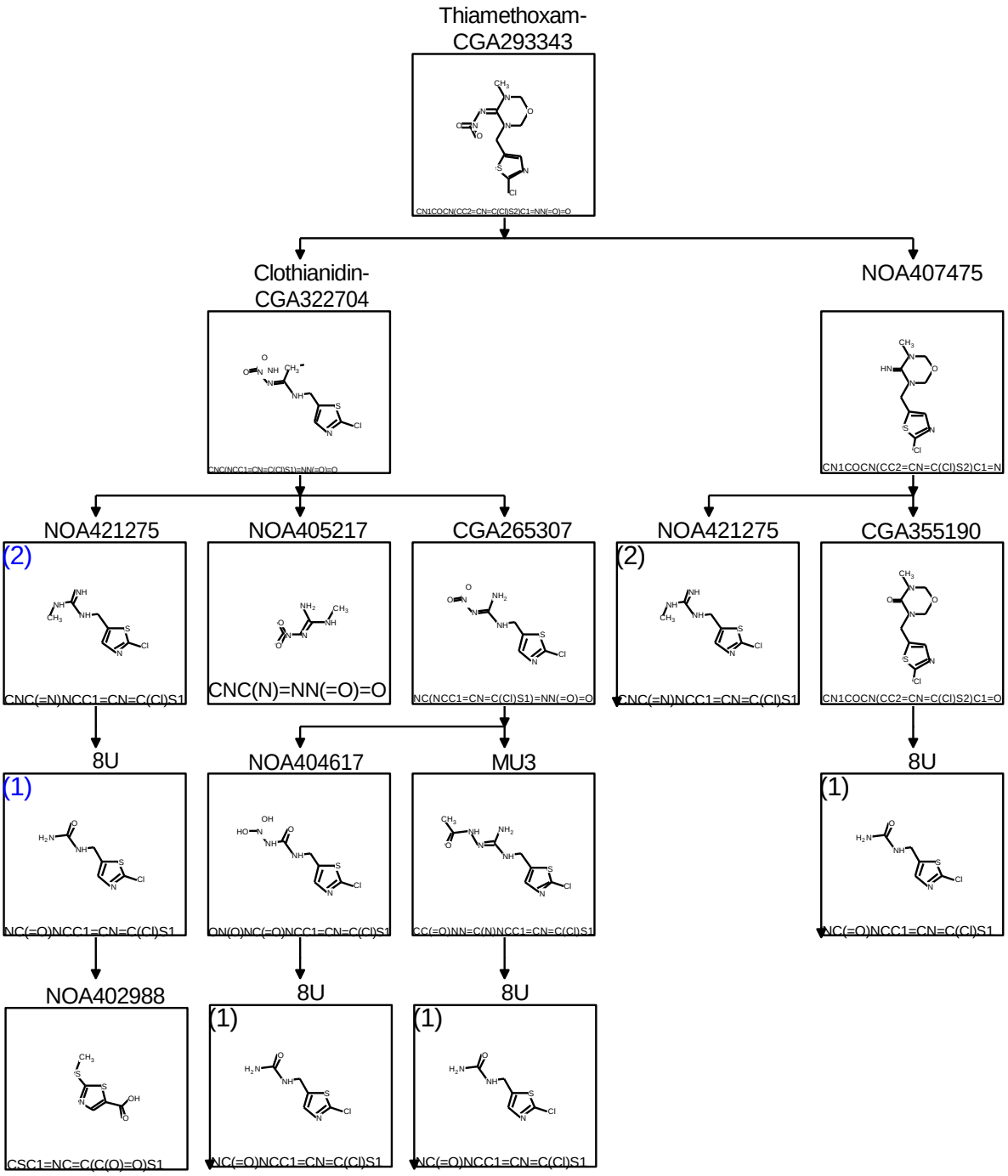
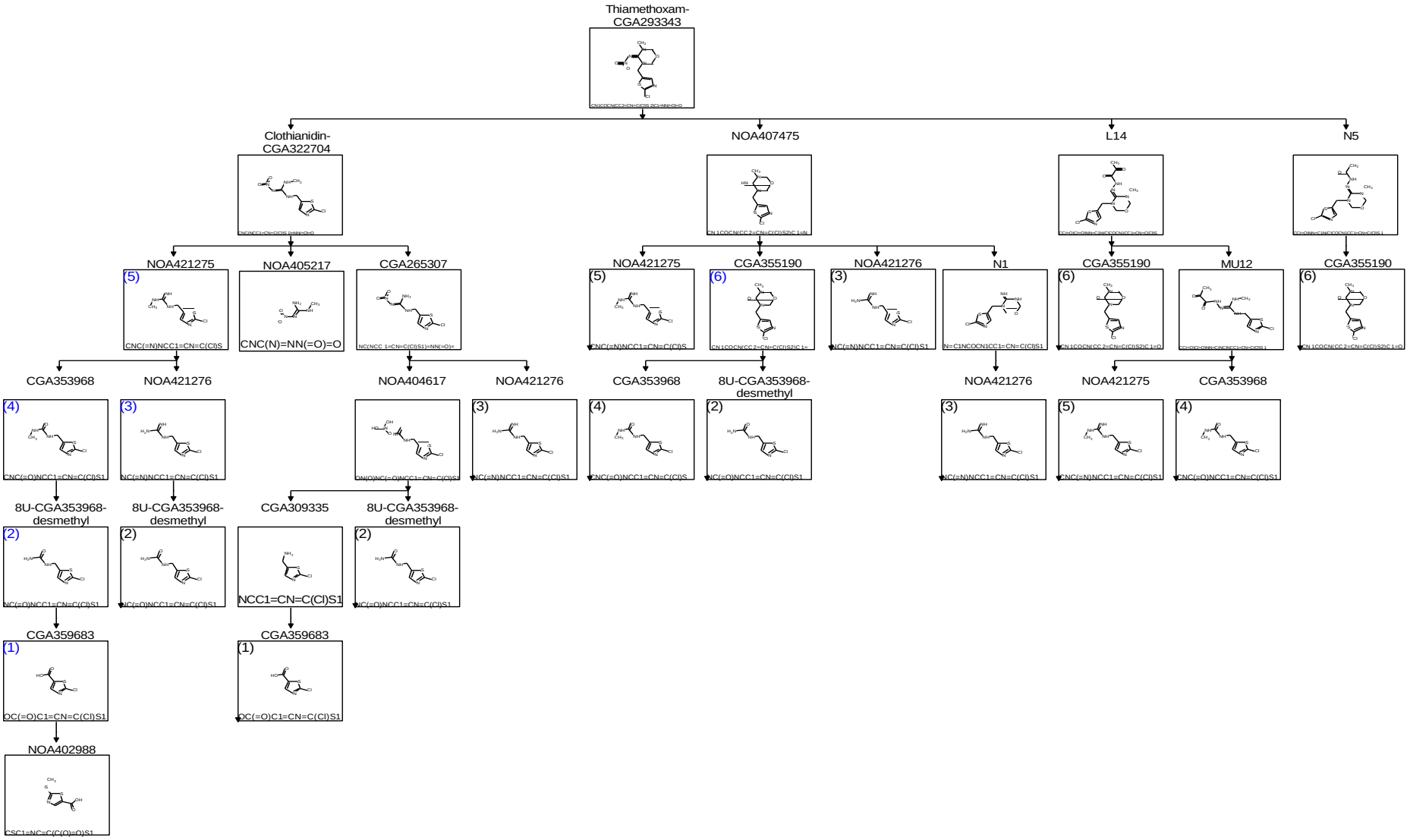


Figure 7.2.2.3-7 Metabolic pathway of thiamethoxam (CGA293343) **(lactating goats)**



2.7.3 Definition of the residue

2.7.3.1 Residue definition in plants

Approach proposed by RMS to establish the risk assessment residue definitions for plant and animal commodities:

The proposal of a residue definition based on the assessment of the metabolism of thiamethoxam is challenged by a particular situation. On one hand abundant information to handle the behaviour of the residues is available: as an example for plants, numerous metabolism studies on different crop groups categories which furthermore include different modes of applications (foliar, seed treatment, soil treatment, and sometimes combined applications on soil + foliar)). But on the other hand, this situation is counterbalanced by a lack of information concerning the toxicity of the metabolites at stake.

Furthermore, it should be underlined that one of thiamethoxam's metabolites is clothianidin, which is also an active substance under renewal process for approval, is currently evaluated by Germany as RMS. Consequently clothianidin is *de facto* included in the residue definition and it was necessary to rank all identified metabolites in relation with both thiamethoxam and clothianidin to get a suitable overview of their respective relevance with the former residue definitions.

After all, in manner to carry on the assessment of thiamethoxam pending information about the toxicity of identified metabolites but also to avoid any inconsistency with the final RAR of clothianidin and perhaps expecting additional information about the toxicity and exposure of common metabolites, a very conservative approach is proposed here.

As an example concerning intended use on lettuce: when identified metabolites appeared at levels below 10% of the TRR, it was considered relevant to shed light on these metabolites since their amounts in mg/kg within the 1X rate in comparison with the intended rate on lettuce were found above the limit of quantification and furthermore comprised for several of them between the level of clothianidin and thiamethoxam (both molecules currently in force for the residue definition).

Therefore more information about the toxicity and relevance of these metabolites would be awaited.

Another point concerns identified metabolites comprised between the LOQ and the residue level of clothianidin or thiamethoxam: it was also considered important to discuss their potential inclusion in the residue definition pending information about their relative toxicity and perhaps discuss the possibility to gather several of them as "thiamethoxam-like" or "clothianidin-like" in manner to allow a conversion factor. If this grouping is relevant from a toxicological point of view, then adding the radioactivity can lead to >10% of the TRR in some cases.

Finally, due to the high number of available studies and the important list of metabolites identified, RMS was at this stage not able to propose an overall residue definition covering all plant groups and all modes of applications.

In conclusion, one should bear in mind that the proposed residue definitions in this RAR and corresponding to an exhaustive list of identified metabolites should be firstly interpreted as a pragmatic tool for the attention of the future peer review to help in discussions, most probably in favour of a more concise residue definition, after an overview of available data from both the RAR of thiamethoxam and clothianidin and relevance of these metabolites in terms of toxicity.

Table 2.7.3.1-1 Overview of relevant residues identified

PLANTS	Metabolism							Rotation				Ground water
Mode of application	**F**	**SOIL+F**	**F**	**SOIL+F**	**FS**	**SOIL+F**	**SOIL+FS**	**Soil**	**Soil**	**Soil**	**Soil**	**soil**
Overview of relevant residues in residue definition for RA	Lettuce	Cucumber	Pear	Tobacco	Potatoe	Rice	Maize	Leafy	Cereals*	Roots	Pulses and oilseeds	Environment section
CGA 204261	X										no studies	
CGA 265307									X	X		
CGA 282149					X							X
CGA 322704 (a.k.a clothianidin, a.k.a TI-435)	X		X	X	X	X	X	X	X			
CGA 322704-hydroxyl-amine-glucoside (a.k.a THMN-Glc formerly Ni-UK-5)			X		X							
CGA 322704 (a.k.a clothianidin, a.k.a TI-435) and conjugates (calc. sum)	X		X	X	X	X	X	X	X			
CGA 349208-O-gluc-conj	X											
CGA 353042	X				X							X
CGA 353968 (a.k.a TZMU)	X											
CGA 353968-N-glucoside conjugate	X	X		X	X							
CGA 353968-O-glucoside conjugate	X											
CGA 353968 (a.k.a TZMU) and its conjugates (calc. sum)	X	X		X	X							
CGA 355190 and CGA 355190-S-gluc-conj (calc. sum)	X											X
CGA 382191	X											
NOA 405217 (a.k.a MNG)	X							X	X			
NOA 407475	X	X			X		X			X		
NOA 421275 (a.k.a TMG)	X				X		X		X			
NOA 424255 (a.k.a NTG)	X											
NOA 436944					X							
NOA 459602												X
SYN 501604												X
Thiamethoxam (a.k.a CGA 293343)	X	X	X	X	X	X	X	X				

Boded : result of the sum of conjugates (in italic) from a same molecule
X : residue found in a commodity that may enter in human food or animal ration.
Highlighted in orange: residue found in a commodity that may enter in human food.
Highlighted in grey: residue found in a commodity that may enter in animal ration only.
Highlighted in blue: residue found relevant in ground water (information from environmental section).
* to be noted low extraction yield and low identification in grain.

Notes

- a second name may appear (with the mention a.k.a = also known as) since several chemical structures could be linked with the same chemical structure identified in the former monograph of the clothianidin.

- several metabolites can be found in both ground water (see section 2.7.8.2) and

- potatoes: CGA 282149

- lettuce: CGA 355190 and CGA 353042

Table 2.7.3.1-2 Resulting proposal for residue definition in plants (alphanumeric order)

Plant residue definition for monitoring (RD-Mo)	
Respectively (pending toxicological consideration):	
	thiamethoxam, clothianidin, respectively
Plant residue definition for risk assessment (RD-RA)	
Respectively (pending toxicological consideration):	
Lettuce (foliar application)	CGA204261 CGA265307 CGA322704 (a.k.a clothianidin or TI-435) and its conjugates CGA349208 and its conjugates CGA353042 CGA353968 and its conjugates CGA355190 and its conjugates CGA382191 NOA405217 (a.k.a MNG) NOA407475 NOA421275 (a.k.a TMG) NOA424255 (a.k.a NTG) Thiamethoxam (CGA293343)
Cucumber (soil and foliar application)	NOA407475 Thiamethoxam (CGA293343)
Pear (foliar application)	CGA322704 (a.k.a clothianidin or TI-435) and its conjugates Thiamethoxam (CGA293343)
Tobacco *(soil and foliar application)* *Not relevant for RA*	*CGA322704 (a.k.a clothianidin or TI-435) and its conjugates* *CGA353968 and its conjugates* *Thiamethoxam (CGA293343)*
Potato (seed treatment)	CGA282149 CGA322704 (a.k.a clothianidin or TI-435) CGA353968 and its conjugates Thiamethoxam (CGA293343)
Rice (soil and foliar treatment)	CGA322704 (a.k.a clothianidin or TI-435) and its conjugates Thiamethoxam (CGA293343) But with high uncertainty: insufficient extraction rate in grain.
Maize (soil and foliar treatment)	CGA322704 (a.k.a clothianidin or TI-435) and its conjugates Thiamethoxam (CGA293343) But with high uncertainty: insufficient extraction rate in grain.
Conversion factor (monitoring to risk assessment)	Available residue trials show only residue analysis of thiamethoxam and metabolite CGA322704 (a.k.a clothianidin). Thus, pending information on the toxicity of each metabolite (including clothianidin under renewal process) proposed in the residue definitions and their respective levels in residue trials, no conversion factor can be proposed.

In terms of chemical structures several of these metabolites could perhaps be grouped and considered as "thiamethoxam-like" or "clothianidin-like" but at this time considerations based on structural/activity remain unstated (see volume 1 summary of other toxicological studies 1.1.1.4 Toxicity studies of metabolites and impurities).

In addition and to avoid discrepancies, this assessment should be also confronted with corresponding conclusions from the concomitant assessment for the renewal of the active substance clothianidin assessment.

2.7.3.2 Residue definition in livestock

The same methodology as for residue definition in plants was proposed in commodities of animal origin pending conclusions from the concomitant assessment for the renewal of the active substance clothianidin.
To be noted also that for the monitoring definition, thiamethoxam is not systematically proposed when not found significant (absent) in the corresponding commodity.

Table 2.7.3.2-1 Overview of relevant residues identified in commodities of animal origin

ANIMAL	Metabolism								
ANIMAL	Poultry				Ruminant				
Overview of relevant residues in residue d	Lean Meat	Fat + Skin	Liver	Whole eggs (calc.)	Muscle	Fat	Liver	Kidney	milk
CGA 265307	X	X	X	X					X
CGA 322704 (a.k.a clothianidin, a.k.a TI-435)		X	X	X	X	X			X
L14							X	X	
MU3	X	X	X						
MU12					X			X	
N5								X	
NOA 404617				X					
NOA 407475							X		
NOA 421275 (a.k.a TMG)	X		X			X	X	X	
NOA 421276					X	X	X	X	
Thiamethoxam (a.k.a CGA 293343)	X	X		X	X	X		X	X

X: residue found in a commodity that may enter in human food.

Table 2.7.3.2-2 Resulting proposal for residue definition in commodities of animal origin (alphanumeric order)

Animal residue definition for monitoring (RD-Mo)	
Respectively (pending toxicological data on most of metabolites):	
Poultry	Thiamethoxam, clothianidin, CGA265307, MU03, NOA421275
Ruminant	Thiamethoxam, clothianidin, CGA265307, NOA421276, NOA421275
Animal residue definition for risk assessment (RD-RA)	
Respectively (pending toxicological data on most of metabolites):	
Poultry	
Lean meat	CGA265307 MU3 NOA421275 (a.k.a TMG) Thiamethoxam (CGA293343)
Fat + skin	CGA265307 CGA322704 (a.k.a clothianidin or TI-435) MU3 Thiamethoxam (CGA293343)
Liver	CGA265307 CGA322704 (a.k.a clothianidin or TI-435) NOA421275 (a.k.a TMG) MU3
Egg	CGA265307 CGA322704 (a.k.a clothianidin or TI-435) NOA404617 Thiamethoxam (CGA293343)
Ruminant	
Muscle	CGA322704 (a.k.a clothianidin or TI-435) MU12 NOA421276 Thiamethoxam (CGA293343)
Fat	CGA322704 (a.k.a clothianidin or TI-435) NOA421275 (a.k.a TMG) NOA421276 Thiamethoxam (CGA293343)
Liver	L14 NOA 407475 NOA 421275 (a.k.a TMG) NOA421276
Kidney	L14 MU12 N5 NOA 421275 (a.k.a TMG) NOA 421276 Thiamethoxam (CGA293343)
Milk	CGA265307 CGA322704 (a.k.a clothianidin or TI-435) Thiamethoxam (CGA293343)
Conversion factor (monitoring to risk assessment)	Feeding studies are available on laying hens and dairy cattle but only with results on thiamethoxam and clothianidin respectively. Pending information on the toxicity of each metabolite proposed in the residue definition for risk assessment (including clothianidin under renewal process), no conversion factor can be proposed.

Fat solubility	No The log P_{OW} for thiamethoxam (CGA293343) is -0.13 ±(0.0017) at 25°C and 0.893 for clothianidin (CGA322704). Thiamethoxam and clothianidin (CGA322704) are not considered fat soluble. Nevertheless to be toned down since : Thiamethoxam and clothianidin were not observed above the LOQ of 0.01 mg/kg in ruminant fat (feeding study with 0.787 mg thiamethoxam/kg bw/day (eq.to 187N compared with DB_{calc} of 0.0042 mg/kg bw/day) **but in milk** following 0.079 mg thiamethoxam/kg bw/day (eq.to 19N compared with DB_{calc} of 0.0042 mg/kg bw/day). Moreover thiamethoxam, clothianidin and other metabolites can be found in fat (see residue definition) and **fat solubility of each metabolite proposed in the residue definition should be stated.**

In term of chemical structures several of these metabolites could perhaps be grouped and considered as "thiamethoxam-likes" or "clothianidin-likes" but at this time considerations based on structural/activity remain unstated (see volume 1 summary of other toxicological studies 1.1.1.4 Toxicity studies of metabolites and impurities).

In addition and to avoid discrepancies, this assessment should be also confronted with corresponding conclusions from the concomitant assessment for the renewal of the active substance clothianidin assessment.

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

2.7.4.1 Lettuce

Thiamethoxam is intended as foliar treatment for indoor and outdoor uses with WG25 (formulation code A9584C, 250 g thiamethoxam/kg WG) on lettuce and the representative critical GAPs are reported in the table below.

Table 2.7.4.1-1 Critical GAP **(lettuce)**

Crop	Region	Outdoor/ Protected	Application	Number of applications	Rate (g a.s/ha)	BBCH at last application/ PHI
GAP for the first inclusion of thiamethoxam in Annex I						
Lettuce	EU (North and South)	Outdoor	Foliar spray	1-3 7 days interval	50	PHI 7 days
GAP in the framework of renewal AIRIII						
Lettuce	EU (North and South)	Outdoor	Foliar spray	1 : per field per year	50	BBCH 15-49 /PHI 7 days
Lettuce	EU (North and South)	Indoor	Foliar spray	1 : per greenhouse per year	50	BBCH 15-49 /PHI 7 days

Lettuce is considered as a major crop in northern and southern parts of Europe. Residue trials assessed in the initial DAR were performed with 3-4 applications instead of only one as intended for renewal. A new data package was provided outdoor and indoor with 1 application including species of lettuce qualified as "open leaf varieties".

More residues would be expected with more than one application but it can be concluded that this is not the case since trials realized with more than one application do not show results with higher residue levels (trials with more than 1 application (marked in orange) are also presented in the table below as indicative.

The residue data package from the initial DAR and new trials with more than one application were not considered since a new complete data package was provided covering North, South and indoor uses with only 1 application.

Table 2.7.4.1-2 Overview of available residue trials on lettuce **(outdoor – former trials)**

Outdoor (trials from initial DAR)							
North		n applic.	open leaf	South		n applic.	open leaf
T	C			T	C		
<0.02	<0.02	4	n.a	<0.02	<0.02	3	n.a
<0.02	<0.02	3	n.a	<0.02	<0.02	3	n.a
0.02	<0.02	4	n.a	0.03	<0.02	3	n.a
0.03	<0.02	3	n.a	0.05	<0.02	3	n.a
0.04	<0.02	3	n.a	0.05	<0.02	3	n.a
0.07	<0.02	4	n.a	0.05	<0.02	3	n.a
				0.07	<0.02	3	n.a
				0.28	0.03	3	n.a

Table 2.7.4.1-3 Overview of available residue trials on lettuce **(outdoor – new trials)**

Outdoor (new trials)							
North		n applic.	Open Leaf	South		n applic.	Open Leaf
T	C			T	C		
0.02	<0.02	3	Yes	0.03	<0.01	1	Yes
0.03	<0.02	3	Yes	0.08	<0.02	3	n.a
0.05	<0.01	1	Yes	0.11	0.01	1	Yes
0.06	<0.02	3	Yes	0.16	<0.02	3	n.a
0.07	<0.02	3	Yes	0.16	0.01	1	Yes
0.14*	<0.02	3	Yes	0.17	<0.01	1	Yes
0.15	<0.01	1	Yes	0.26	0.01	1	Yes
0.16	<0.01	1	Yes	0.31	0.01	1	Yes
0.21	0.01	1	Yes	0.37	0.02	1	Yes
0.22	<0.02	3	Yes	0.44	0.01	1	Yes
0.23	<0.01	1	Yes				
0.24	<0.01	1	Yes				
0.37	0.01	1	Yes				
2.05	0.05	1	Yes				

Table 2.7.4.1-4 Overview of available residue trials on lettuce **(indoor – new trials)**

Indoor (new trials)				
North		n applic.	South	open Leaf
T	C		N/S	
0.18	<0.01	1	S	Yes
0.22	<0.01	1	S	Yes
0.25	0.02	1	N	Yes
0.54	0.01	1	S	Yes
0.70	<0.01	1	S	Yes
1.04	<0.01	1	N	Yes
1.71	0.02	1	N	Yes
2.02	<0.01	1	N	Yes

* blank contaminated with 0.05 mg/kg of thiamethoxam, no previous treatment with thiamethoxam
In orange values not considered in the data package

RMS comment : the metabolism study on lettuce (cf. table 2.7.2.1-15) shows that additional

metabolites were observed at significant residue level, and especially at levels comprised between those found for thiamethoxam and metabolite CGA322704 (a.k.a clothianidin) and which were not analysed in residue trials. No information concerning the toxicity relevance of these metabolites NOA405217, CGA353042 and NOA 407475 and/or equivalence as "thiamethoxam–like" or "clothianidin-like" were provided.

Moreover, within the intended PHI of 7 days for lettuce and at higher PHI, several other metabolites were found above 10ppb. There is currently no information to qualify their respective toxicities.

In addition several of these metabolites could also be identified as relevant and/or as "clothianidin like" in terms of their toxicity and should be also confronted with corresponding conclusions from the concomitant assessment for the renewal of the active substance clothianidin.

Consequently, pending a final overview as detailed above, as the residue definition cannot be set pending toxicology data on the metabolites, the estimation of the level of the residues in lettuce with intended GAP is considered as not finalized concerning risk assessment

2.7.4.2 Potato

Thiamethoxam is intended as foliar treatment for outdoor use with WG25 (formulation code A9584C, 250 g thiamethoxam/kg WG) on potato and the representative critical GAP is reported in the table below.

Table 2.7.4.2-1 Critical GAP **(potato)**

Crop	Region	Outdoor/ Protected	Application	Number of applications	Rate (g as/ha)	BBCH at last application/ PHI
GAP for the first inclusion of thiamethoxam in Annex I						
Potato	EU (North and South)	Outdoor	Foliar spray	1-4 7 days interval	20	PHI 7 days
Potato	EU South	Outdoor	Seed treatment	1	7.5 g a.s/100kg eq. to 135 g as/ha	Based on 1800 kgs tubers/ha
GAP in the framework of renewal AIRIII						
Potato	EU (North and South)	Outdoor	Foliar spray	1 : per field per year	20	BBCH 15-49 /PHI 7 days

Potato is considered as a major crop in northern and southern parts of Europe. Residue trials from the initial DAR were performed with 4 applications instead of only one as intended for renewal. Only 1 new trial was provided in the context of the renewal dossier with also 4 applications instead of 1.

Nevertheless, despite a higher number of applications, the residues remain below the LOQ of 0.02 mg/kg and submitted data package can be considered as a worst case.

Table 2.7.4.2-2 Overview of available residue trials on potatoes **(outdoor – former trials)**

Outdoor (former trials)						Outdoor (new trials)					
North		n	South		n	North		n	South		n
T	C	applic.	T	C	applic.	T	C	applic.	T	C	applic.
<0.02	<0.02	4	<0.02	<0.02	4	-	-	-	<0.02	<0.02	4
<0.02	<0.02	4	<0.02	<0.02	4						
<0.02	<0.02	4	<0.02	<0.02	4						
			<0.02	<0.02	4						
			<0.02	<0.02	4						

	<0.02	<0.02	4	
	<0.02	<0.02	4	
	<0.02	<0.02	4	
	<0.02	<0.02	4	

RMS comment: as stated in section 2.7.2.1 related to the metabolism in potatoes after a seed treatment instead of foliar treatment: the question of comparability between these 2 different modes of applications can be toned down since residue levels show a non-residue situation (<LOQ of 0.02 mg/kg) for both thiamethoxam and metabolite CGA 322704 (a.k.a clothianidin) in tubers following a foliar treatment.

2.7.4.3 Sugar beetSugar beet

Thiamethoxam is intended as seed treatment for outdoor use with CRUISER FS (formulation code A9765R, 600 g thiamethoxam/L FS) formulation on sugar beet and the representative critical GAP is reported in the table below.

Table 2.7.4.3-1 Critical GAP **(sugar beet)**

Crop	Region	outdoor/ protected	Application	Number of applications	Rate (g as/ha)	BBCH at last application/ PHI
GAP for the first inclusion of thiamethoxam in Annex I						
Sugar beet	EU (North and South)	Outdoor	Seed treatment	1	78 based on a max of 1.3 unit seeds/ha[a]	BBCH00
GAP in framework of the renewal AIRIII						
Sugar beet	EU (North and South)	Outdoor	Seed treatment	1 every 3 years[b]	58,5 based on a max of 1.3 unit seeds/ha[a]	BBCH 00

[a] 1seed unit = 100 000 seeds, sowing density = 1.3 units/ha
[b] 1 application per crop to be drilled maximum every 3 years to the same field

Sugar beet is considered as a major crop in northern and southern parts of Europe. No new trials were provided in the context of the renewal assessment. Residue trials in the frame of the first DAR were performed with higher application rate of 1 to 3X above the intended one in the context of the renewal dossier.
Nevertheless, despite a higher application rate, the residues remain below the LOQ of 0.02 mg/kg and the data package from the initial DAR can be considered as a worst case.

Table 2.7.4.3-2 Overview of available residue trials on sugar beet **(outdoor – former trials)**

Outdoor (former trials)						Outdoor (new trials)			
North		Rate compared to 58.5 g a.s/ha	South		Rate compared to 58.5 g a.s/ha	North		South	
T	C		T	C		T	C	T	C
<0.02	<0.02	1X	<0.02	<0.02	1.5X	-	-	-	-
<0.02	<0.02	1X	<0.02	<0.02	2.3X				
<0.02	<0.02	2.3X	<0.02	<0.02	2.8X				
<0.02	<0.02	1.5X	<0.02	<0.02	1X				
<0.02	<0.02	1.3X	<0.02	<0.02	2X				
<0.02	<0.02	1X	<0.02	<0.02	2X				
<0.02	<0.02	1X	<0.02	<0.02	3X				
<0.02	<0.02	1X							
<0.02	<0.02	1.7X							
<0.02	<0.02	1X							

2.7.4.4 Overview of the available residue trials data and MRL calculation

Table 2.7.4.4-1 Overview of the available residues trials data and MRL calculation

Crop	Region/ Indoor (a)	Residue levels (mg/kg) observed in the supervised residue trials relevant to the supported GAPs (b)	Recommendations/comments (OECD calculations)	**MRL** proposals (mg/kg)	**HR** (mg/kg) (c)	**STMR** (mg/kg) (d)
Residue definition for monitoring and enforcement (Mo): not applicable see dedicated section 2.7.3 **Residue definition for risk assessment (RA): not applicable see dedicated section 2.7.3**						
Lettuce	NEU outdoor	Thiamethoxam : 0.05; 0.15; 0.16; 0.21; 0.23; 0.24; 0.37; 2.05 Clothianidin : <0.01 x 5 ; 0.01 x 2 ; 0.05	Trials performed with intended GAP and open leaf varieties of lettuce	3 0.06	**2.05** 0.05	0.22 0.015
	SEU outdoor	Thiamethoxam : 0.03; 0.11; 0.16; 0.17; 0.26; 0.31; 0.37; 0.44 Clothianidin : <0.01 x 2 ; 5 x 0.01 ; 0.02	Trials performed with intended GAP and open leaf varieties of lettuce	0.8 0.04	0.44 0.02	0.15 0.01
	Indoor	Thiamethoxam : 0.18; 0.22; 0.25; 0.54; 0.70; 1.04 ; 1.71; 2.02 Clothianidin : <0.01 x 5 ; 0.01 ; 0.02 x 2	Trials performed with intended GAP and open leaf varieties of lettuce	**4** 0.04	2.02 0.02	**0.62** 0.01
Potatoes	NEU outdoor	Thiamethoxam : <0.02 x 3 Clothianidin : <0.02 x 3	Trials with 4 applications instead of 1	0.02* 0.02*	0.02* 0.02*	0.02* 0.02*
	SEU outdoor	Thiamethoxam : <0.02 x 10 Clothianidin : <0.02 x 10	Trials with 4 applications instead of 1	**0.02*** **0.02***	0.02* 0.02*	0.02* 0.02*
Sugar beet	NEU outdoor	Thiamethoxam : <0.02 x 10 Clothianidin : <0.02 x 10	Trials with 1-2.3X rate instead of 20 g a.s/ha	**0.02*** **0.02***	0.02* 0.02*	0.02* 0.02*
	SEU outdoor	Thiamethoxam : <0.02 x 7 Clothianidin : <0.02 x 7	Trials with 1-3X rate instead of 20 g a.s/ha	0.02* 0.02*	0.02* 0.02*	0.02* 0.02*

Lettuce : MRL in force for thiamethoxam is 5 mg/kg under Reg. (EU) 2017/671 ; MRL in force for clothianidin is 0.1 mg/kg under Reg. (EU) 2017/671
Potato : MRL in force for thiamethoxam is 0.07 mg/kg under Reg. (EU) 2017/671 ; MRL in force for clothianidin is 0.03 mg/kg under Reg. (EU) 2017/671
Sugar beet : MRL in force for thiamethoxam is 0.02* mg/kg under Reg. (EU) 2017/671 ; MRL in force for clothianidin is 0.02* mg/kg under Reg. (EU) 2017/671 (a)**NEU** or **SEU** for northern or southern **outdoor** trials in EU member states (**N+SEU** if both zones), **Indoor** for glasshouse/protected crops, **Country** if non-EU location.
(b)Residue levels in trials conducted according to GAP reported in ascending order (*e.g.* 3x <0.01, 0.01, 6x 0.02, 0.04, 0.08, 3x 0.10, 2x 0.15, 0.17). When residue definition for monitoring and risk ssessment differs, use **Mo/RA** to differentiate data expressed according to the residue definition for **Mo**nitoring and **R**isk **A**ssessment.
(c) **HR**: Highest residue. When residue definition for monitoring and risk assessment differs, HR according to residue definition for monitoring reported in brackets (HR_{Mo}).
(d) **STMR:** Supervised Trials Median Residue. When residue definition for monitoring and risk assessment differs, STMR according to definition for monitoring reported in brackets ($STMR_{Mo}$).

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

Crops assessed in the context of renewal assessment of thiamethoxam can be fed to livestock (as potatoes, sugar beet roots and foliage). The median and maximum dietary burdens were therefore calculated for different groups of livestock using the OECD Guidance documents n° 64/32 and 73. The input values for all relevant commodities are summarized in table 2.7.5-1 below.

The available study presented to cover the root crop category may be accepted for sugar beet which is also intended as a seed treatment. However, the acceptability of this study is disputable concerning potato which is intended with a foliar treatment (as stated in the section 2.7.2.1. Nevertheless,
- since thiamethoxam and clothianidin were found as the most significant compounds following a 23X rate as a seed treatment in the metabolism study (cf. table 2.7.2.1-13).
- since following 4 foliar applications, residue trials on potato did not show any measurable residues of thiamethoxam nor metabolite CGA322704 (a.k.a clothianidin) in tubers (cf. table 2.7.4.2-2)

It could assumed that no other metabolite would be in significant and above thiamethoxam and its metabolite (CGA322704 a.k.a clothianidin) (i.e. > LOQ). Thus only thiamethoxam and its metabolite (CGA322704 a.k.a clothianidin) were considered relevant in the dietary burden calculation.

Table 2.7.5-1 : Input values for the dietary burden calculation (thiamethoxam)(DB model 2017)

Commodity	Median dietary burden		Maximum dietary burden	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Risk assessment residue definition: see dedicated section 2.7.3				
Forages				
Beet, sugar (tops)	0.02*	STMR x (PF=1.0)	0.02*	HR x (PF=1.0)
Roots and tubers				
Potato (culls)	0.02*	STMR x (PF=1.0)	0.02*	HR x (PF=1.0)
By-products				
Beet, sugar (dried pulp)	0.02*	STMR x (PF=1.0)	0.02*	STMR x (PF=1.0)
Beet, sugar (ensiled pulp)	0.02*	STMR x (PF=1.0)	0.02*	STMR x (PF=1.0)
Beet sugar (molasses)	0.02*	STMR x (PF=1.0)	0.02*	STMR x (PF=1.0)
Potato (process waste)	0.02*	STMR x (PF=1.0)	0.02*	STMR x (PF=1.0)
Potato (dried pulp)	0.02*	STMR x (PF=1.0)	0.02*	STMR x (PF=1.0)

Table 2.7.5-2 : Input values for the dietary burden calculation (metabolite CGA322704 a.k.a clothianidin)

Commodity	Median dietary burden		Maximum dietary burden	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Risk assessment residue definition: see dedicated section 2.7.3				
Forages				
Beet, sugar (tops)	0.02*	STMR x (PF=1.0)	0.02*	HR x (PF=1.0)
Roots and tubers				
Potato (culls)	0.02*	STMR x (PF=1.0)	0.02*	HR x (PF=1.0)
By-products				
Beet, sugar (dried pulp)	0.02*	STMR x (PF=1.0)	0.02*	STMR x (PF=1.0)
Beet, sugar (ensiled pulp)	0.02*	STMR x (PF=1.0)	0.02*	STMR x (PF=1.0)
Beet sugar (molasses)	0.02*	STMR x (PF=1.0)	0.02*	STMR x (PF=1.0)
Potato (process waste)	0.02*	STMR x (PF=1.0)	0.02*	STMR x (PF=1.0)
Potato (dried pulp)	0.02*	STMR x (PF=1.0)	0.02*	STMR x (PF=1.0)

Calculation results are reported in the table 2.7.5-2.

Table 2.7.5-2 : Results for dietary burden calculation

Animal burden calculation — **thiamethoxam**

According to: "OECD Guidance Document, Series on testing and assessment No 64 and Series on pesticides No 32" and "OECD Guidance Document on Residues in livestock, Series on Pesticides No 73"

Maximum Intake	Cattle						Sheep					
	Beef (500 kg / 12 kg)			Dairy (650 kg / 25 kg)			Ram/Ewe (75 kg / 2,5 kg)			Lamb (40 kg / 1,7 kg)		
(mg/kg bw/d)	**0,003**	mg/kg bw/d	%	**0,004**	mg/kg bw/d	%	**0,004**	mg/kg bw/d	%	**0,003**	mg/kg bw/d	%
Contributor 1	Potato	process wast	40	Beet, sugar	ensiled pulp	40	Potato	process wast	40	Potato	process wast	20
Contributor 2	Potato	culls	30	Potato	culls	30	Potato	culls	30	Potato	culls	20
Contributor 3	Beet, sugar	tops	20	Beet, sugar	tops	30	Beet, sugar	tops	20	Beet, sugar	tops	20
Contributor 4												
Median intake	0,0027	mg/kg bw/d		0,0042	mg/kg bw/d		0,0038	mg/kg bw/d		0,0030	mg/kg bw/d	

Maximum Intake	Swine					
	Breeding (260 kg / 6 kg)			Finishing (100 kg / 3 kg)		
(mg/kg bw/d)	**0,002**	mg/kg bw/d	%	**0,002**	mg/kg bw/d	%
Contributor 1	Potato	process wast	20	Potato	culls	50
Contributor 2	Potato	culls	50	Beet, sugar	dried pulp	20
Contributor 3	Beet, sugar	tops	10			
Contributor 4						
Median intake	0,002	mg/kg bw/d		0,002	mg/kg bw/d	

Intakes >0.004 mg/kg bw/d are highlighted

Maximum Intake	Poultry								
	Broiler (1,7 kg / 0,12 kg)			Layer (1,9 kg / 0,13 kg)			Turkey (7 kg / 0,5 kg)		
(mg/kg bw/d)	**0,001**	mg/kg bw/d	%	**0,001**	mg/kg bw/d	%	**0,001**	mg/kg bw/d	%
Contributor 1	Potato	culls	10	Potato	culls	10	Potato	culls	20
Contributor 2	Potato	dried pulp	20	Beet, sugar	tops	5			
Contributor 3				Potato	dried pulp	15			
Contributor 4									
Median intake	0,001	mg/kg bw		0,001	mg/kg bw		0,001	mg/kg bw	

Animal burden calculation — **clothianidin**

According to: "OECD Guidance Document, Series on testing and assessment No 64 and Series on pesticides No 32" and "OECD Guidance Document on Residues in livestock, Series on Pesticides No 73"

Maximum Intake	Cattle						Sheep					
	Beef (500 kg / 12 kg)			Dairy (650 kg / 25 kg)			Ram/Ewe (75 kg / 2,5 kg)			Lamb (40 kg / 1,7 kg)		
(mg/kg bw/d)	**0,003**	mg/kg bw/d	%	**0,004**	mg/kg bw/d	%	**0,004**	mg/kg bw/d	%	**0,003**	mg/kg bw/d	%
Contributor 1	Potato	process wast	40	Beet, sugar	ensiled pulp	40	Potato	process wast	40	Potato	process wast	20
Contributor 2	Potato	culls	30	Potato	culls	30	Potato	culls	30	Potato	culls	20
Contributor 3	Beet, sugar	tops	20	Beet, sugar	tops	30	Beet, sugar	tops	20	Beet, sugar	tops	20
Contributor 4												
Median intake	0,0027	mg/kg bw/d		0,0042	mg/kg bw/d		0,0038	mg/kg bw/d		0,0030	mg/kg bw/d	

Maximum Intake	Swine					
	Breeding (260 kg / 6 kg)			Finishing (100 kg / 3 kg)		
(mg/kg bw/d)	**0,002**	mg/kg bw/d	%	**0,002**	mg/kg bw/d	%
Contributor 1	Potato	process wast	20	Potato	culls	50
Contributor 2	Potato	culls	50	Beet, sugar	dried pulp	20
Contributor 3	Beet, sugar	tops	10			
Contributor 4						
Median intake	0,002	mg/kg bw/d		0,002	mg/kg bw/d	

Intakes >0.004 mg/kg bw/d are highlighted

Maximum Intake	Poultry								
	Broiler (1,7 kg / 0,12 kg)			Layer (1,9 kg / 0,13 kg)			Turkey (7 kg / 0,5 kg)		
(mg/kg bw/d)	**0,001**	mg/kg bw/d	%	**0,001**	mg/kg bw/d	%	**0,001**	mg/kg bw/d	%
Contributor 1	Potato	culls	10	Potato	culls	10	Potato	culls	20
Contributor 2	Potato	dried pulp	20	Beet, sugar	tops	5			
Contributor 3				Potato	dried pulp	15			
Contributor 4									
Median intake	0,001	mg/kg bw		0,001	mg/kg bw		0,001	mg/kg bw	

There is no significant intakes for ruminants, pigs and poultries (exceeding the trigger value of 0.004 mg/kg bw/d) except for dairy cow which is slightly above 0.004 mg/kg bw/day but only related to a contribution of residues levels at the LOQ of 0.02 mg/kg which is considered as an artefact of the model.

Feeding studies are thus not considered as relevant, related to the representative uses. .

However, the ruminant study which was formerly presented in the context of the first inclusion of thiamethoxam is nevertheless presented in volume 3-B7.4.2.1 which would be related to conclusions on clothianidin renewal assessment.

2.7.6 Summary of effects of processing

2.7.6.1 Nature of the residue

In processing procedures, pasteurization and boiling show that thiamethoxam and clothianidin are hydrolytically stable (100%) and no degradation products will be formed. Only in the process of sterilization a marginal unknown radioactive fraction of 0.4-2% was found. Identification of this fraction was not realized and remains below the desired goal for identification and characterization of at least 90% of the remaining TRR.

Table 2.7.6-1 Distribution of radioactivity after different hydrolysis process

Standard hydrolysis experiments	Thiamethoxam	CGA322704 (a.k.a clothianidin)
20 min, 90°C, pH 4	100	100
60 min, 100°C, pH 5	100	100
20 min, 120°C, pH 6	98-98.5	99.7-100

2.7.6.1 Magnitude of the residue in processed commodities

For the representative uses (potato, sugar beet and lettuce), no dedicated processing studies were presented. Residues results in raw commodities presented in sections 2.7.4.2 for potatoes and 2.7.4.3 for sugar beet are below the LOQ of 0.02 mg/kg for both thiamethoxam and clothianidin (CGA322704). In addition and as detailed in Weber study (see volume 3-B.7.3.2.2.7), residues in processed potatoes (boiled potato, peeled potato, crisp and French fries: 1 trial following 4 x 25 g a.s/ha on potatoes) do not show any concentration of the residues in processed commodities and remain below the LOQ of 0.02 mg/kg and consequently no processing factor can be proposed.

Concerning lettuce, a residue situation was observed in residue trials but the only process applicable to lettuce can be washing which would act in favor of a dilution of the residues based on the high solubility of thiamethoxam and clothianidin in water (log P_{OW} for thiamethoxam (CGA293343) is -0.13 ±(0.0017) at 25°C and 0.893 for clothianidin (CGA322704) and solubility in water of 4.1 g/L (25°C) and 0.3 g/L (20°C) and respectively.

For these reasons and based on representative uses, processing studies are not deemed necessary.

Nevertheless high uncertainty remains about any additional uses since no information was provided about other metabolites proposed in the residue definition for which information on the toxicity may be awaited.

2.7.7 Summary of residues in rotational crops

Magnitude of residue

In addition to information available from metabolism in rotational crops (cf. section 2.7.2.2), the magnitude of the residues in rotational crops was presented in the context of this renewal.
Four studies were presented (cf. volume 3-B7.6.3) : 4 field trials (2 trials realized in the North and 2 in the South) were conducted to investigate the magnitude of residues of thiamethoxam and its metabolite CGA322704 (a.k.a clothianidin) in rotated crops.

- 1 soil application of 200 g a.s/ha which is equivalent to:
  - ✓ Sugar beet: 1x 58.5 g/ha; 3.4X

- ✓ Lettuce: 1x 50 g/ha; 4X
- ✓ Potato: 1x 20g/ha; 10X

- 3 plant back interval (PBI) of 28-31, 58-64, 341-367 days
- no residue of parent thiamethoxam (<0.02 mg/kg)
- residue situation for CGA322704 (a.k.a clothianidin) comprised between : <0.02 – 0.06 mg/kg.

It has to be reminded from the metabolism studies (primary crops and rotation, sections 2.7.2.1 & 2.7.2.2) that significant difficulties to extract all the residues where noticed in cereal grains. Nevertheless, as stated in the table of intended GAPs the use of thiamethoxam is limited to only 1 application every 3 years on sugar beet and only one application per year on lettuce and potato. It is thus considered that under these conditions, no significant residues would be expected in rotational crops.

2.7.8 Summary of other studies

2.7.8.1 Residues in honey

According to EFSA guidance[10], representative crops for renewal seem to be of low attractivity to honey bees (potatoes and sugar beet). Concerning lettuce, since the crop is harvested before flowering stage (BBCH 49 = before principal growth stage 5: inflorescence emergence), this crop is also out of consideration for its honey bee attractivity. This point concerning attractivity to honey bees is also more detailed in ecotoxicological section.

Moreover, as detailed in section 2.7.10.1 and 2.7.10.2 the current MRL is set at 0.05* mg/kg in honey for thiamethoxam and clothianidin respectively (cf. Reg. (EU) 2017/671) but according to considerations above a **default MRL at the LOQ of 0.01* mg/kg would be more relevant.**

2.7.8.2 Additional contribution to the consumer intakes through drinking water resulting from groundwater metabolite(s) expected to be present above 0.75µg/L

PEC_{gw} for the metabolites CGA 353042 and CGA 355190 are below 0.1 µg/L in all scenarios and crops assessed. (maximal respective values of < 0.001 µg/L and 0.078 µg/L).

Also, metabolite CGA 353042 and CGA 355190 were identified in metabolism study on lettuce (cf. table 2.7.2.1-15 and table 2.7.3.1-1 since furthermore it was comprised between the level of thiamethoxam and metabolite CGA 322704 (a.k.a clothianidin) for metabolite CGA 353042 and above 10ppb for metabolite CGA355190 with similar conditions than intended GAP.

PECgw for CGA 282149 and SYN 501604 remain below 0.75 µg/L (maximal respective values of 0.237 µg/L and 0.284 µg/L).

Finally metabolite CGA 282149 was found at the limit of 10% of the TRR in metabolism study on potatoes (seed treatment) (cf. table 2.7.2.1-13)

PECgw for NOA459602 is in the range of 0.1<10 µg/L (maximal value of 2.10 µg/L)

Nevertheless with undetermined toxicity for these metabolites, the risk assessment for the consumer cannot be finalized.

2.7.8.3 Review of open scientific literature

No relevant literature references were deemed to be relevant by the notifier in relation to the metabolism and residue endpoints for thiamethoxam and relevant metabolites (see volume 3-B7.8).

[10] EFSA guidance on risk assessment on bees - EFSA Journal 2013;11(7):3295 – Appendix D Attractiveness of agricultural crops to honey bees and bumble bees for the collection of nectar and/or pollen page 107/268. https://www.efsa.europa.eu/fr/efsajournal/pub/3295

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

In the initial DAR, toxicological reference values were only determined for thiamethoxam. Since this time, both thiamethoxam and metabolite CGA322704 (a.k.a clothianidin) were considered for risk assessment respectively with their respective toxicological reference values (as an example in context of Reasoned opinion on the review of the existing maximum residue levels (MRLs) according to Article 12 of Regulation (EC) No 396/2005 (EFSA2014).

In framework of this renewal, new reference values were proposed for thiamethoxam but pending conclusions from the concomitant assessment for the renewal of the active substance clothianidin, only the former toxicological reference values from the initial DAR of clothianidin could be used.

Table 2.7.9-1 : Overview of toxicological reference values

thiamethoxam					
Source	Year	Value	Study relied upon	Safety factor	Source
Former ADI	EC	2006	0.026 mg/kg bw/d	18 month study on mouse	100
Former ARfD	EC	2006	0.5 mg/kg bw	rabbit developmental	100
New proposed ARfD	FR	2017	0.35 mg/kg bw	rat, developmental neurotoxicity	100
CGA 322704 (a.k.a clothianidin)					
Source	Year	Value	Study relied upon	Safety factor	Source
ADI pending renewal assessment	EC	2005	0.097 mg/kg bw/d	2 year rat	100
ARfD pending renewal assessment	EC	2005	0.1 mg/kg bw	rat and rabbit developmental	100

Consumer risk assessment was performed using the revision 2 of the EFSA PRIMo (Pesticide Residue Intake Model). For the chronic and acute intake assessment the proposed MRL and HR derived from residue trials were considered.

Table 2.7.9-1 : Input values for the consumer risk assessment

Thiamethoxam				
Commodity	Chronic risk assessment		Acute risk assessment	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
211000 - Potatoes	0.02*	Calculated MRL	0.02*	HR
251020 - Lettuce	4	Calculated MRL	2.05	HR
900010 - Sugar beet (root)	0.02*	Calculated MRL	0.02*	HR
Metabolite CGA322704 (a.k.a clothianidin)				
211000 - Potatoes	0.02*	Calculated MRL	0.02*	HR
251020 - Lettuce	0.06	Calculated MRL	0.05	HR
900010 - Sugar beet (root)	0.02*	Calculated MRL	0.02*	HR

Table 2.7.9-2: TMDI calculation linked to EU representative uses for thiamethoxam

thiamethoxam

Prepare workbook for refined calculations

Undo refined calculations

Status of the active substance:	renewal	Code no.	
LOQ (mg/kg bw):	0,02	proposed LOQ:	
Toxicological end points			
ADI (mg/kg bw/day):	0,006	ARfD (mg/kg bw):	0,35
Source of ADI:	renewal	Source of ARfD:	renewal
Year of evaluation:	2017	Year of evaluation:	2017

Explain choice of toxicological reference values.

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

The pTMRLs have been submitted to EFSA in September 2006.

Chronic risk assessment

	TMDI (range) in % of ADI minimum - maximum
	1 36
No of diets exceeding ADI:	---

Highest calculated TMDI values in % of ADI	MS Diet	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	pTMRLs at LOQ (in % of ADI)
36,0	ES adult	35,7	Lettuce	0,3	Potatoes			0,3
28,4	ES child	27,8	Lettuce	0,6	Potatoes			0,6
26,5	WHO regional European diet	25,1	Lettuce	1,3	Potatoes	0,0	Sugar beet (root)	1,3
25,4	IT adult	25,2	Lettuce	0,2	Potatoes			0,2
25,0	WHO Cluster diet B	23,9	Lettuce	0,9	Potatoes	0,2	Sugar beet (root)	1,1
21,1	WHO Cluster diet F	20,0	Lettuce	1,1	Potatoes	0,0	Sugar beet (root)	1,1
19,7	IT kids/toddler	19,4	Lettuce	0,3	Potatoes			0,3
11,1	UK vegetarian	9,4	Lettuce	1,3	Sugar beet (root)	0,5	Potatoes	1,7
10,2	DK child	9,4	Lettuce	0,8	Potatoes			0,8
10,2	UK Toddler	7,6	Sugar beet (root)	1,4	Lettuce	1,2	Potatoes	8,8
9,6	UK Adult	7,8	Lettuce	1,3	Sugar beet (root)	0,5	Potatoes	1,8
8,9	NL general	8,0	Lettuce	0,9	Potatoes			0,9
8,5	NL child	6,5	Lettuce	2,0	Potatoes			2,0
7,4	WHO cluster diet E	6,1	Lettuce	1,3	Potatoes	0,0	Sugar beet (root)	1,3
6,5	FR all population	6,1	Lettuce	0,4	Potatoes			0,4
6,4	IE adult	5,7	Lettuce	0,8	Potatoes			0,8
5,6	FI adult	5,2	Lettuce	0,4	Potatoes			0,4
5,3	LT adult	4,2	Lettuce	1,1	Potatoes			1,1
5,0	DE child	4,1	Lettuce	0,9	Potatoes			0,9
4,4	UK Infant	3,4	Sugar beet (root)	1,1	Potatoes			4,4
2,0	PL general population	1,1	Potatoes	0,9	Lettuce			1,1
1,8	PT General population	1,8	Potatoes					1,8
1,7	FR toddler	1,7	Potatoes					1,7
1,6	WHO cluster diet D	1,4	Potatoes	0,2	Lettuce	0,0	Sugar beet (root)	1,4
1,4	SE general population 90th percentile	1,4	Potatoes					1,4
1,4	FR infant	1,4	Potatoes					1,4
0,5	DK adult	0,5	Potatoes					0,5

Conclusion:

The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI.

A long-term intake of residues of thiamethoxam is unlikely to present a public health concern.

Table 2.7.9-4: TMDI calculation linked to EU representative uses (CGA322704 a.k.a clothianidin)

clothianidin

Prepare workbook for refined calculations

Undo refined calculations

Status of the active substance:	renewal	Code no.	
LOQ (mg/kg bw):	0,02	proposed LOQ:	
Toxicological end points			
ADI (mg/kg bw/day):	0,097	ARfD (mg/kg bw):	0,1
Source of ADI:	1st inclusion	Source of ARfD:	1st inclusion
Year of evaluation:	2006	Year of evaluation:	2006

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

Chronic risk assessment

TMDI (range) in % of ADI minimum - maximum: 1

No of diets exceeding ADI: ---

Highest calculated TMDI values in % of ADI	MS Diet	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	pTMRLs at LOQ (in % of ADI)
0,5	UK Toddler	0,5	Sugar beet (root)	0,1	Potatoes	0,0	Lettuce	0,5
0,3	UK Infant	0,2	Sugar beet (root)	0,1	Potatoes			0,3
0,1	NL child	0,1	Potatoes	0,0	Lettuce			0,1
0,1	UK Adult	0,1	Sugar beet (root)	0,0	Potatoes	0,0	Lettuce	0,1
0,1	UK vegetarian	0,1	Sugar beet (root)	0,0	Potatoes	0,0	Lettuce	0,1
0,1	PT General population	0,1	Potatoes					0,1
0,1	WHO regional European diet	0,1	Potatoes	0,0	Lettuce	0,0	Sugar beet (root)	0,1
0,1	FR toddler	0,1	Potatoes					0,1
0,1	WHO Cluster diet B	0,1	Potatoes	0,0	Lettuce	0,0	Sugar beet (root)	0,1
0,1	WHO Cluster diet F	0,1	Potatoes	0,0	Lettuce	0,0	Sugar beet (root)	0,1
0,1	WHO cluster diet E	0,1	Potatoes	0,0	Lettuce	0,0	Sugar beet (root)	0,1
0,1	SE general population 90th percentile	0,1	Potatoes					0,1
0,1	FR infant	0,1	Potatoes					0,1
0,1	WHO cluster diet D	0,1	Potatoes	0,0	Lettuce	0,0	Sugar beet (root)	0,1
0,1	PL general population	0,1	Potatoes	0,0	Lettuce			0,1
0,1	LT adult	0,1	Potatoes	0,0	Lettuce			0,1
0,1	NL general	0,1	Potatoes	0,0	Lettuce			0,1
0,1	ES child	0,0	Potatoes	0,0	Lettuce			0,0
0,1	DK child	0,1	Potatoes	0,0	Lettuce			0,1
0,1	DE child	0,1	Potatoes	0,0	Lettuce			0,1
0,1	IE adult	0,0	Potatoes	0,0	Lettuce			0,0
0,1	ES adult	0,0	Lettuce	0,0	Potatoes			0,0
0,0	IT kids/toddler	0,0	Potatoes	0,0	Lettuce			0,0
0,0	IT adult	0,0	Lettuce	0,0	Potatoes			0,0
0,0	FI adult	0,0	Potatoes	0,0	Lettuce			0,0
0,0	DK adult	0,0	Potatoes					0,0
0,0	FR all population	0,0	Potatoes	0,0	Lettuce			0,0

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

Table 2.7.9-5: IESTI calculation linked to EU representative uses (thiamethoxam)

Acute risk assessment /children

The acute risk assessment is based on the ARfD.
For each commodity the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical consumption. If no data on the unit weight was available from that MS an average European unit weight was used for the IESTI calculation.
In the **IESTI 1** calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002), for lettuce a variability factor of 5 was used.
In the **IESTI 2** calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce the calculation was performed with a variability factor of 3.
Threshold MRL is the calculated residue level which would leads to an exposure equivalent to 100 % of the ARfD.

Unprocessed commodities

No of commodities for which ARfD/ADI is exceeded (IESTI 1):		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 2):**		---
IESTI 1	***)**	****)**	**IESTI 2**	***)**	****)**
Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)
15,8	Lettuce	2,05 / -	9,5	Lettuce	2,05 / -
0,9	Potatoes	0,02 / -	0,6	Potatoes	0,02 / -
0,4	Sugar beet (root)	0,02 / -	0,4	Sugar beet (root)	0,02 / -

No of critical MRLs (IESTI 1) ---

Acute risk assessment / adults / general population

No of commodities for which ARfD/ADI is exceeded (IESTI 1):		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 2):**		---
IESTI 1	***)**	****)**	**IESTI 2**	***)**	****)**
Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)
6,4	Lettuce	2,05 / -	3,9	Lettuce	2,05 / -
0,2	Potatoes	0,02 / -	0,1	Sugar beet (root)	0,02 / -
0,1	Sugar beet (root)	0,02 / -	0,1	Potatoes	0,02 / -

No of critical MRLs (IESTI 2) ---

Processed commodities

No of commodities for which ARfD/ADI is exceeded:		---	**No of commodities for which ARfD/ADI is exceeded:**		---
		*****)**			*****)**
Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)
0,1	Potato puree (flakes)	0,02 / -	0,0	Potato uree (flakes)	0,02 / -
0,0	Fried potatoes	0,02 / -	0,0	Fried potatoes	0,02 / -

*) The results of the IESTI calculations are reported for at least 5 commodities. If the ARfD is exceeded for more than 5 commodities, all IESTI values > 90% of ARfD are reported.
**) pTMRL: provisional temporary MRL
***) pTMRL: provisional temporary MRL for unprocessed commodity

Conclusion:
For thiamethoxam IESTI 1 and IESTI 2 were calculated for food commodities for which pTMRLs were submitted and for which consumption data are available.
No exceedance of the ARfD/ADI was identified for any unprocessed commodity.

For processed commodities, no exceedance of the ARfD/ADI was identified.

Table 2.7.9-6: IESTI calculation linked to EU representative uses (CGA322704 a.k.a clothianidin)

Acute risk assessment /children						Acute risk assessment / adults / general population					
The acute risk assessment is based on the ARfD.											
For each commodity the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical consumption. If no data on the unit weight was available from that MS an average European unit weight was used for the IESTI calculation.											
In the **IESTI 1** calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002), for lettuce a variability factor of 5 was used. In the **IESTI 2** calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce the calculation was performed with a variabilty factor of 3.											
Threshold MRL is the calculated residue level which would leads to an exposure equivalent to 100 % of the ARfD.											
Unprocessed commodities	**No of commodities for which ARfD/ADI is exceeded (IESTI 1):**		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 2):**		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 1):**		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 2):**	---
	IESTI 1	***)**	****)**	**IESTI 2**	***)**	****)**	**IESTI 1**	***)**	****)**	**IESTI 2**	***)**	****)**
	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)
	3,1	Potatoes	0,02 / -	2,2	Potatoes	0,02 / -	0,6	Potatoes	0,02 / -	0,5	Sugar beet (root)	0,02 / -
	1,3	Lettuce	0,05 / -	1,3	Sugar beet (root)	0,02 / -	0,5	Lettuce	0,05 / -	0,5	Potatoes	0,02 / -
	1,3	Sugar beet (root)	0,02 / -	0,8	Lettuce	0,05 / -	0,5	Sugar beet (root)	0,02 / -	0,3	Lettuce	0,05 / -
	No of critical MRLs (IESTI 1)		---			**No of critical MRLs (IESTI 2)**			---			
Processed commodities	**No of commodities for which ARfD/ADI isexceeded:**		---			**No of commodities for which ARfD/ADI is exceeded:**			---			
			*****)**						*****)**			
	Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)				Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)			
	0,3	Potato puree (flakes)	0,02 / -				0,0	Potato uree (flakes)	0,02 / -			
	0,0	Fried potatoes	0,02 / -				0,0	Fried potatoes	0,02 / -			
*) The results of the IESTI calculations are reported for at least 5 commodities. If the ARfD is exceeded for more than 5 commodities, all IESTI values > 90% of ARfD are reported. **) pTMRL: provisional temporary MRL ***) pTMRL: provisional temporary MRL for unprocessed commodity												
Conclusion: For clothianidin IESTI 1 and IESTI 2 were calculated for food commodities for which pTMRLs were submitted and for which consumption data are available. No exceedance of the ARfD/ADI was identified for any unprocessed commodity. For processed commodities, no exceedance of the ARfD/ADI was identified.												

RMS comment: assessment for the consumer is considered as not finalized pending additional information about the toxicity of relevant metabolites found in plants (e.g. lettuce) and also should be confronted with toxicological data and toxicological reference values from the concomitant assessment for the renewal of the active substance clothianidin.

2.7.10 Proposed MRLs and compliance with existing MRLs

2.7.10.1 Thiamethoxam

Table 2.7.10.1-1 Proposed and existing MRL for thiamethoxam

Crops	Proposed MRLs based on intended use	MRL according to Reg. (EU) 2017/671
	mg/kg	mg/kg
0211000 - Potatoes	**0.02***	0.07
0251020 - Lettuce	**4.0**	5.0
0900010 - Sugar beet (root)	**0.02***	0.02*
1000000 - Products of animal origin – terrestrial animals	**Default MRLs of 0.01***	swine, bovine, sheep, goat, equine and other farmed terrestrial animals
		muscle : 0.02
		fat tissue : 0.01*
		liver : 0.01*
		kidney : 0.01*
		edible offal (other than liver and kidney) : 0.02
		others : 0.01*
		milk : 0.05
		poultry including eggs : 0.01*
		honey and other apiculture products: 0.05*

2.7.10.2 CGA 322704 (a.k.a clothianidin)

Table 2.7.10.2-2 Proposed and existing MRL for metabolite CGA 322704 (a.k.a clothianidin)

Important remark: this situation where a metabolite is also an active substance is rather uncommon. Consequently proposed value below are not really MRLs but provided as information pending concomitant assessment and conclusions for the renewal of the active substance clothianidin		
Crops	Proposed levels of metabolite CGA322704 (a.k.a clothianidin) based on representative uses proposed with the renewal assessment of thiamethoxam	MRL in force for clothianidin according to Reg. (EU) 2017/671
	mg/kg	mg/kg
0211000 - Potatoes	**0.02***	0.03
0251020 - Lettuce	**0.06**	0.1
0900010 - Sugar beet (root)	**0.02***	0.02*
1000000 - Products of animal origin – terrestrial animals	**Default MRLs of 0.01***	swine, bovine, sheep, goat, equine and other farmed terrestrial animals
		muscle : 0.02*
		fat tissue : 0.01*
		liver : 0.2
		kidney : 0.02*
		edible offal (other than liver and kidney) : 0.2
		others : 0.01*
		milk : 0.02
		poultry including eggs : 0.01* liver and edible offal (other than liver and kidney) : 0.1
		honey and other apiculture products : 0.05*

2.7.11 Proposed import tolerances and compliance with existing import tolerances

Not relevant.

2.8 FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1 Summary of fate and behaviour in soil

2.8.1.1 Soil route of degradation

- Degradation route of thiamethoxam in soil under aerobic conditions:

The fate and behaviour of thiamethoxam in soils was investigated using both [^{14}C]-thiazol labelled and [^{14}C]-guanidine labelled test substance in standard laboratory studies.
The degradation route of thiamethoxam was studied in 14 soils in dark aerobic conditions in laboratory. Some metabolites were identified: CGA322704 (or clothianidin), exceeding 10% of the Applied Radioactivity (AR) in nine soils (maximum observed 35.6% AR after 90 days) and still increasing at the end of the study in some soils; CGA355190 which exceeded 10% AR in at least one soil (maximum observed 23.1% AR after 180 days) and still increasing at the end of the study in some soils and CGA282149 which exceeded 5% AR in two succeeding samples (maximum 6.9% AR after 180 days) and still increasing at the end of the study in another soil. Two transient minor (not exceeding 5% AR) metabolites CGA353968 and NOA459602 were also observed in few soils.
By the end of the aerobic soil incubations in laboratory, levels of evolved carbon dioxide and unextracted residues had reached maxima of 39% AR and 44% AR respectively; there were no significant differences between the radiolabels.

- Degradation route of thiamethoxam in soil under anaerobic conditions:

The soil degradation of thiamethoxam under anaerobic conditions was also investigated in laboratory. The studies were conducted with a preliminary aerobic incubation before flooding the test soil samples. Two unique metabolites were identified and formed at levels above 5% AR during the anaerobic incubation: NOA407475 with a maximal occurrence level of 13% AR and NOA404617 with a maximal occurrence level of 7% AR. Both metabolites were still increasing at the end of the studies. Evolved carbon dioxide reached a maximum value of 12.7% AR at 120 DAT. Non extractable residues reached a maximum of 51.9% AR at 120 DAT.

- Degradation route of thiamethoxam in soil, photolysis:

In a soil photodegradation study in laboratory, thiamethoxam degraded more rapidly than under dark conditions, indicating that photodegradation may accelerate the degradation process of the active substance. One major unique metabolite CGA353042 was observed up to 13.3% AR at the end of the study. Other minor unidentified degradation products were observed; none of these individually exceeded 5 % AR during the test. Degradation in the dark control was considerably slower with negligible degradation observed over the study period.

2.8.1.2 Soil rates of degradation

Soil degradation rates of thiamethoxam (n=18) were investigated in aerobic conditions in laboratory. They were calculated according to FOCUS Kinetic guidance document (FOCUS, 2006). A summary of degradation rates for thiamethoxam is provided below. The active substance can be considered as persistent. Degradation rates are not pH-dependent.

Table 2.8.1.2-1: Normalized laboratory soil DT50 values of thiamethoxam in soil for modeling purposes

Study	Soil name	Kinetic	Normalized DT_{50} values at 20°C and pF2 (days)
Schwartz (1998a)	Sandy Loam	SFO	305.2
	Sandy Loam	SFO	242.9
Dixon (1998a)	Sandy Loam	SFO	336.3
	Sandy Loam	SFO	283.8
Adam (1999a)	Loamy Sand	SFO	234.4
Cruz (1998)	Clay loam	SFO	149
Hein and Dorn (2001a)	Loamy Sand	SFO	167.6
Adam (1996)	Lomay sand	SFO	188.1
	Sandy loam	SFO	150.3
	Sandy Loam	SFO	79.5
	Loamy Sand	SFO	135
Phaff (1997a)	Silty Loam	SFO	73.6
	Silty Loam	SFO	117.9
	Silty Loam	SFO	34.3
Herrchen (2015)	Loam	SFO	33.5
	Sandy Silt Loam	SFO	143
	Sandy Loam	SFO	60.3
	Silt Loam	SFO	92.6
Geometric mean (n=18)			**129**
pH dependence			**No**

Metabolite CGA322704 (clothianidin) is considered persistent in soil, with normalized DT_{50} values ranging from 44.7 to 264.7 days (geomean: 108.5 days, 15 soils).
Metabolites CGA355190, CGA282149, NOA459602, SYN501406 and CGA353042 are not considered persistent in soil with normalized DT_{50} values ranging from 15.6 to 91.5 days for CGA355190 (geomean: 47.2 days, 4 soils), from 21.6 to 233 days for CGA282149 (geomean: 30.2 days, 4 soils), from 27 to 116 days for NOA459602 (geomean: 46.3 days, n=3), from 16.6 to 36.8 days for SYN501406 (geomean: 25.3 days, 6 soils) and from 5.55 to 43.8 days for CGA353042 (geomean: 15.8 days, 3 soils).
No pH-dependence was identified for any metabolite.

In addition, field dissipation studies with application of thiamethoxam by spray or by seed treatment were performed in 11 European and 3 North-American sites. Metabolite CGA322704 (clothianidin) was also looked for during these studies. These studies have been assessed according to EFSA guidance (EFSA, 2014) as proposed by the notifier.

Several studies were discarded by the notifier for obvious reasons: multiple applications, cropped soils, no climate data available, etc. RMS agrees with this proposal. Then, the majority of the remaining studies were not considered acceptable for RMS for modelings purposes according to the EFSA guidance criteria: high variability observed in the data sets, too important surface phenomenon (systemicity, photo-degradation, etc.) or no climate data robust enough for normalization. For more details, please refer to Volume 3 B.8.1.1.1.2.1.

Therefore, the corresponding $DissT_{50}$ values can only be used for persistence trigger endpoints. The values range from 6.83 to 192 days, confirming that thiamethoxam is persistent in soil as indicated in laboratory conditions. It should be noticed that the refined PECgw and PECsw calculations based on field DT_{50} values proposed by the applicant for the active substance were not considered acceptable by RMS. This proposal had a significant impact on risk assessments.

2.8.1.3 Soil mobility

Adsorption of thiamethoxam was measured in a batch equilibrium study on 18 soils. Adsorption constant was determined according to Freundlich isotherm and Kfoc values ranged between 32 and 177 mL/g (geometric mean: 54.1 mL/g). According to McCall classification, thiamethoxam is considered as highly mobile. No pH dependence was identified.

Adsorption of thiamethoxam metabolites CGA322704 (clothianidin), CGA355190, CGA282149, NOA404617, NOA459602, SYN501406, NOA407475 and CGA353042 was also determined in batch adsorption experiments in 5 to 10 soils. According to McCall classification, CGA322704 is highly mobile (Kfoc from 63 to 205 mL/g; geometric mean: 111 mL/g). CGA355190 is very highly mobile (Kfoc from 38 to 188 mL/g; geometric mean: 79.6 mL/g). CGA282149 is very highly mobile (Kfoc from 10 to 64 mL/g; geometric mean: 20.5 mL/g). NOA404617 is very highly mobile (Kfoc from 11 to 73 mL/g; geometric mean: 28.7 mL/g). NOA459602 is very highly mobile (Kfoc from 1.50 to 8.90 mL/g; geometric mean: 3.62 mL/g). SYN501406 is very highly mobile (Kfoc from 2.80 to 8.60 mL/g; geometric mean: 4.28 mL/g). NOA407475 is lowly mobile (Kfoc from 433 to 1550 mL/g; geometric mean: 659 mL/g). CGA353042 is moderately mobile (Kfoc from 255 to 1425 mL/g; geometric mean: 402 mL/g). No pH dependence was identified for any metabolite.

Mobility of thiamethoxam was further investigated in a column leaching study and in an aged column leaching study. The active substance is mobile in soil columns eluted with 200 mm water and 1.6 – 59.2 % of the AR can be recovered in leachates. Only parent compound was detected in the leachates.
Furthermore, four lysimeter studies were provided for thiamethoxam. Results from these lysimeter studies showed that concentrations of thiamethoxam were below to trigger value of 0.1 µg/L/year. Metabolites CGA322704 (<0.1 µg/L/year), NOA459602 (up to 0.33 µg/L/year) and SYN501406 (up to 0.097 µg/L/year) were also detected in the leachates. No other unknown fraction or metabolite exceeded 0.1 µg/L/year. Both metabolites NOA459602 and SYN501406 were considered in groundwater risk assessments.

2.8.2 Summary of fate and behaviour in water and sediment [equivalent to section 11.1 of the CLH report template]

Thiamethoxam and its metabolite CGA322704 (clothianidin) were stable to abiotic hydrolysis at 20°C and at pH 5 and 7. At pH 9, CGA322704 is also stable at 20°C. Thiamethoxam degradation at pH 9 can be considered fast with DT_{50} values between 4.2 and 8.3 days at 25°C. Several metabolites were observed: CGA355190 reaching 59.5% AR at 30 days, NOA404617 reaching 27.9% AR after 30 days, CGA309335 reaching 9.1% AR after 30 days.

Thiamethoxam degrades by photolysis, mainly forming CGA353042 (up to 65.8% AR after 30 days in pH 5 buffer, guanidine ^{14}C labelled study) and CGA355190 (up to 9% AR after 21 days).

Thiamethoxam was not considered readily biodegradable under the conditions of the available 28-day ready biodegradability test. In addition, results from hydrolysis and aerobic mineralization studies show that thiamethoxam is not degraded in the aquatic environment to a level > 70 % within a 28-day period. As a consequence, thiamethoxam is considered not rapidly degradable.

Thiamethoxam was not rapidly degraded in the available aerobic mineralization study, with best-fit DT_{50} ranging between 87 and 96 days. Two metabolites were formed: CGA355190 reached a maximum of 36.56 % after 61 days and metabolite NOA404617 reached a maximum of 8.8% after 61 days.
Chemical hydrolysis was determined to be the major route of degradation for thiamethoxam in sediment amended natural water. Only < 1.7 % AR was mineralized to carbon dioxide.

The route and rate of degradation of thiamethoxam has been investigated in water-sediment systems with three different systems under laboratory conditions. The maximal amount of thiamethoxam observed on sediment was 36.6% AR after 8 days. Several metabolites were observed in whole water-sediment systems: CGA355190 (max 8.9% AR after 100 d), NOA407475 (max. 47.4% AR after 42 d) and NOA404617 (max. 8% AR after 48 d). Non extractable residues and mineralization reached respectively a maximum of 22.2-51.3% AR after 80-100 days and 11.96% AR after 100 days.

According to available data and previous comments, no DT_{50} values have been considered as reliable and robust enough in water-sediment systems for the active substance thiamethoxam and its metabolites CGA322704, NOA407475, NOA404617 and CGA355190. **Consequently, a data gap has been identified.**

- Impact of water treatment procedures:

Information on the effect of water treatment processes on the nature of residues when surface water is abstracted for drinking water are needed according to Article 4(3) of Regulation (EC) No 1107/2009 which requires that 'it shall have no immediate or delayed harmful effects on human health, including that of vulnerable groups, or animal health,….through drinking water (taking into account substances resulting from water treatment)'.

The statement provided by the applicant is not considered robust enough by RMS. **As a consequence, a data gap has been identified.**

2.8.2.1 Rapid degradability of organic substances

Table 2.8.2.1-1: Summary of relevant information on rapid degradability

Method	Results	Key or Supportive study	Remarks	Reference
Ready biodegradability OECD 301/B	After 29 days: Biodegradation = 7%	Key study	-	Grade, R. (1996) (See Vol. 3 B.8.2.2.1)

2.8.2.1.1 Ready biodegradability

The ready biodegradability of thiamethoxam was determined in (Grade, 1996), according to OECD guideline 301/B. In this study, carbon dioxide formation was measured over 29 days at 22°C.

An inoculum control and a procedure control as well as toxicity controls were incubated for 21 days in diffuse light at 22°C. An activated sludge from the sewage treatment plant of CH-4153 Reinach was used as the inoculum. The preparation was carried out according to the method described in the guideline.

As a procedure control, the reference item sodium benzoate was tested. The toxicity control contained both test material and the reference item sodium benzoate. At each sampling day the CO_2, trapped in the scrubbers, was measured as inorganic carbon with a carbon analyzer (Shimadzu TOC-500). The biodegradation was calculated on the basis of the theoretical carbon content of the test substance and the quantities of inorganic carbon determined on the days of measurement in the absorbers.

Biodegradation in sludge exposed to the test item
The quantities of inorganic carbon produced from the test item thiamethoxam in the test media was in the range of the inoculum controls throughout the study period of 29 days. Consequently, thiamethoxam was not biodegradable under the test conditions within 29 days.

Biodegradation of the reference item in the procedure controls
In the procedural controls, the reference item was degraded by an average of 84% by Exposure Day 21, thus confirming suitability of the activated sludge.

Biodegradation in the toxicity control
In the toxicity control containing both the test item thiamethoxam and the reference item, the quantities of inorganic carbon produced over the 29 day exposure period was similar to the two procedure controls, containing only the reference item.

2.8.2.1.2 BOD5/COD

No data available.

2.8.2.2 Other convincing scientific evidence

Table 2.8.2.1-1: Summary of other relevant information

Method	Results	Key or Supportive study	Remarks	Reference
Hydrolysis OECD 111	Thiamethoxam is stable at pH 5 and 7 at 25°C. It is degraded at pH 9 (25°C), with a DT50 of 4.2 days.	Key study	-	Clark A. (1998c) (See Vol. 3 B.8.2.1.1, study 1)
Hydrolysis OECD 111	Thiamethoxam is stable at pH 5 and 7 at 25°C. It is degraded at pH 9 (25°C), with a DT50 of 8.4 days.	Key study	-	Lowery E. (1996) (See Vol. 3 B.8.2.1.1, study 2)
Hydrolysis OECD 311	Thiamethoxam is stable at pH 4, 5, 7 and 9 at 20°C.	Key study	-	Ulbrich (1999) (See Vol. 3 B.8.2.1.1, study 3)
Photolysis US-EPA 161-2	At pH 5, 25°C, thiamathoxam is degraded under irradiation with a DT50 of 3.1 days.	Key study	No major deviation from OECD 316	Schwartz B. (1998b) (See Vol. 3 B.8.2.1.2, study 1)
Photolysis US-EPA 161-2	At pH 5, 25°C, thiamathoxam is degraded under irradiation with a DT50 of 2.3 days.	Key study	No major deviation from OECD 316	Sparrow K. (1997c) (See Vol. 3 B.8.2.1.2, study 2)
Aerobic mineralisation OECD 309	Best-fit DT50 ranged between 87-96 days. Mineralization is < 1.7% AR.	Key study	-	Hüben, M. (2015a) (See Vol. 3 B.8.2.2.2, study 1)
Degradation in water/sediment systems No guideline	After 100 days, thiamethoxame amounts to 6.2-13.6% AR in the water phase, 9.8-12.2% AR in the sediment phase and 15.9-25.1% AR in total system. Maximum amount in sediment: 36.6% AR after 8 d. Mineralization: 6.0-9.3% AR after 100 days. DT50 were not validated.	Key study	No guideline followed but no major deviation from OECD 308	Adam, D. (1998a&b) (See Vol. 3 B.8.2.2.3, studies 1& 2) Kinetic analysis in Ford, S. (2015h) (See Vol. 3 B.8.2.2.3, study 7)
Degradation in water/sediment systems OECD 308	After 100 days, thiamethoxame amounts to 6.8-10.6% AR in the water phase, 6.6% AR in the sediment phase and 13.4-17.1% AR in total system. Maximum amount in sediment: 18.6% AR after 7 d. Mineralization: 12.0% AR after 100 days. DT50 were not validated.	Key study	-	Kang, S. (2015a) (See Vol. 3 B.8.2.2.3, study 6) Kinetic analysis in Ford, S. (2015h) (See Vol. 3 B.8.2.2.3, study 7)

2.8.2.2.1 Aquatic simulation tests

Aerobic mineralization study, Results from Hüben, M. (2015a) – Please refer to Vol. 3 B.8.2.2.2, study 1 for detailed summary and assessment

Thiamethoxam was not rapidly degraded in the available aerobic mineralization study, with best-fit DT_{50} ranging between 87 and 96 days. Two metabolites were formed: CGA355190 reached a maximum of 36.56 % after 61 days and metabolite NOA404617 reached a maximum of 8.8% after 61 days.
Chemical hydrolysis was determined to be the major route of degradation for thiamethoxam in sediment amended natural water. Only < 1.7 % AR was mineralized to carbon dioxide.

Route of degradation in water/sediment systems, Results from Adam, D. (1998a&b), Kang, S. (2015a) and Ford, S. (2015h) – Please refer to Vol. 3 B.8.2.2.3 for detailed summary and assessment

The route and rate of degradation of thiamethoxam has been investigated in water-sediment systems with three different systems under laboratory conditions. The maximal amount of thiamethoxam observed on sediment

was 36.6% AR after 8 days. Several metabolites were observed in whole water-sediment systems: CGA355190 (max 8.9% AR after 100 d), NOA407475 (max. 47.4% AR after 42 d) and NOA404617 (max. 8% AR after 48 d). Non extractable residues and mineralization reached respectively a maximum of 22.2-51.3% AR after 80-100 days and 11.96% AR after 100 days.
No DT_{50} values have been considered as reliable and robust enough in water-sediment systems for the active substance thiamethoxam and its metabolites CGA322704, NOA407475, NOA404617 and CGA355190. **Consequently, a data gap has been identified.**

2.8.2.2.2 Field investigations and monitoring data (if relevant for C&L)

No data available.

2.8.2.2.3 Inherent and enhanced ready biodegradability tests

Please refer to 2.8.2.1.1.

2.8.2.2.4 Soil and sediment degradation data

Please refer to 2.8.1 for soil degradation and to 2.8.2 for sediment degradation (water/sediment systems).

2.8.2.2.5 Hydrolysis

Results from Clark A. (1998c), Lowery E. (1996) and Ulbrich (1999) – Please refer to Vol. 3 B.8.2.1.1 for detailed summary and assessment

Thiamethoxam was stable to abiotic hydrolysis at 20°C and at pH 5 and 7. Thiamethoxam degradation at pH 9 can be considered fast with DT_{50} values between 4.2 and 8.3 days at 25°C. Several metabolites were observed: CGA355190 reaching 59.5% AR at 30 days, NOA404617 reaching 27.9% AR after 30 days, CGA309335 reaching 9.1% AR after 30 days.

2.8.2.2.6 Photochemical degradation

Results from Clark A. (1998c), Lowery E. (1996) and Ulbrich (1999) – Please refer to Vol. 3 B.8.2.1.2 for detailed summary and assessment

Thiamethoxam degrades by photolysis (DT50 2.3-3.1 days at pH 5, 25°C), mainly forming CGA353042 (up to 65.8% AR after 30 days in pH 5 buffer, guanidine ^{14}C labelled study) and CGA355190 (up to 9% AR after 21 days).

2.8.2.2.7 Other / Weight of evidence

No additional data available.

2.8.3 Summary of fate and behaviour in air

The vapour pressure of thiamethoxam is low (6.6×10^{-9} Pa at 25°C) indicating no concern for short-range transport according to the FOCUS Air guidance document (FOCUS, 2008). This was confirmed by experimental laboratory studies in which volatilization was negligible.

Atmospheric half-life of thiamethoxam is of 0.5 to 2.5 hours, indicating no concern for long-range transport.

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

Monitoring studies with thiamethoxam and its metabolites CGA322704 (clothianidin), NOA459602 and SYN501406 in groundwater were conducted in 7 European sites. Only the soil characterizations are available for now for a majority of studies since samplings are ongoing. The final reports of these studies are not available yet.

Publically available groundwater monitoring data were checked for analyses and findings of thiamethoxam and its metabolite CGA322704 (clothianidin). No data were made available for both compounds in surface water. Data for thiamethoxam in groundwater were found for Austria, Czech Republic, France, Denmark, Estonia, Germany, Italy, Slovenia and Sweden. Data for CGA322704 in groundwater were found for Austria, France, Denmark, Germany and Sweden.

The French dataset is the most complete, with several years of results, and a significant number of wells and analysis. The data provide a picture of the groundwater contamination by thiamethoxam and CGA322704 (clothianidin). For thiamethoxam, over a total of 17212 analyses between 2010 and 2017, no detection was above 0.1 µg/L. For CGA322704 (clothianidin), over a total of 2845 analyses between 2014 and 2017, no detection s above 0.1 µg/L. However no further interpretation can be made particularly because no information on the use of pesticides in the areas around the sampling sites is available and the vulnerability of the sites is unknown. In addition, the selected wells are not systematically the same from one year to the next.

2.8.5 Definition of the residues in the environment requiring further assessment

The following residue definition for risk assessment is proposed:

Soil: Thiamethoxam, CGA322704 (clothianidin), CGA355190, CGA282149, CGA353042.

Surface water: Thiamethoxam, CGA322704 (clothianidin), CGA355190, CGA282149, CGA353042, NOA407475, NOA404617.

Sediment: Thiamethoxam, CGA322704 (clothianidin), CGA355190, CGA282149, CGA353042, NOA407475, NOA404617.

Ground water: Thiamethoxam, CGA322704 (clothianidin), CGA355190, CGA282149, NOA459602, SYN501406, CGA353042

Air: Thiamethoxam

2.8.6 Summary of exposure calculations and product assessment

Soil

$PECs_{soil}$ were calculated for thiamethoxam and its major or minor non-transient soil metabolites CGA322704 (clothianidin), CGA355190, CGA282149 and CGA353042 (photo-product, not relevant for seed treatment).

PECsoil were calculated for the intended uses of ACTARA and CRUISER for thiamethoxam and its metabolites according to FOCUS recommendations. For each compound, the longest best-fit non-normalised DT_{50} was used.

Since thiamethoxam and its metabolite CGA322704 (clothianidin) are considered as persistent in soil, a PECplateau was also calculated for these 2 compounds.

PECsoil and PECplateau are available in Volumes 3 B.8 (CP) under B.8.2.

Groundwater

PECgw were calculated for the intended uses of ACTARA for thiamethoxam and its metabolites CGA322704 (clothianidin), CGA355190, CGA282149, NOA459206, SYN501406 and CGA353042 according to FOCUS recommendations. PECgw were calculated for the intended use of CRUISER for thiamethoxam and the same metabolites except the photo-product CGA353042 since no photo-degradation is expected for seed treatment.
The models FOCUS PELMO 5.5.3 and FOCUS PEARL 4.4.4 were used.
Annual applications of ACTARA were considered instead of one application every third year for CRUISER.
It should be noticed that the applicant provided 2 Tiers of PECgw calculations for thiamethoxam and its metabolite CGA322704 (clothianidin): Tier 1 based on soil DT_{50} determined in laboratory for the active substance and its metabolite and Tier 2 based on soil DT_{50} determined in field dissipation studies. As explained previously, the field studies have not been considered acceptable by RMS and cannot be used in modelings. Therefore, PECgw calculations provided in Tier 1 (lab. $DegT_{50}$) have only been considered in order to finalize the groundwater risk assessment.
It should be noticed that no PECgw calculations were provided for the second crop cycle of lettuce. **Therefore, the intended use on lettuce has been restricted to applications in spring/summer.**

- For one application of ACTARA on lettuce every year, the PECgw based on Tier 1 calculations (lab. $DegT_{50}$) are reported in the following table.

PECgw	Thiamethoxam	CGA322704 (Clothianidin)	CGA355190	CGA282149	NOA459602	SYN501406	CGA353042
Number of scenarios > 0,1 µg/L	7/7	5/7	0	5/7	7/7	7/7	0
Min (µg/L)	0,536	0,032	0.012	0,065	0,670	0,100	< 0.001
Max (µg/L)	2,42	0,207	0.078	0,237	2,10	0,284	< 0.001

The metabolites CGA282149, NOA459602 and SYN501406 are considered not relevant according to guidance document SANCO/221/2000. Further calculations were performed by RMS to refine the groundwater risk assessment for the active substance. Considering one application every third year, the PECgw values for thiamethoxam are under the regulatory threshold of 0.1 µg/L for one European representative scenario (min. PECgw: 0.031 µg/L; max. PECgw: 0.431 µg/L).
An unacceptable risk of groundwater contamination can be excluded for thiamethoxam for one application of ACTARA on lettuce every third year.

- For one application of ACTARA on potatoes every year, the PECgw based on Tier 1 calculations (lab. $DegT_{50}$) are reported in the following table.

PECgw	Thiamethoxam	CGA322704 (Clothianidin)	CGA355190	CGA282149	NOA459602	SYN501406	CGA353042
Number of scenarios > 0,1 µg/L	9/9	0	0	1/9	9/9	4/9	0
Min (µg/L)	0.170	0.001	0.004	0.025	0.257	0.043	< 0.001
Max (µg/L)	0.926	0.071	0.028	0.104	0.841	0.130	< 0.001

The metabolites CGA282149, NOA459602 and SYN501406 are considered not relevant according to guidance document SANCO/221/2000. Further calculations were performed by RMS to refine the groundwater risk assessment for the active substance. Considering one application every other year, the PECgw values for thiamethoxam are under the regulatory threshold of 0.1 µg/L for two European representative scenarios (min. PECgw: 0.036 µg/L; max. PECgw: 0.285 µg/L).
An unacceptable risk of groundwater contamination can be excluded for thiamethoxam for one application of ACTARA on potatoes every other year.

- For one application of CRUISER on sugar beet (seed treatment) every third year, the PECgw based on Tier 1 calculations (lab. $DegT_{50}$) are reported in the following table.

PECgw	Thiamethoxam	CGA322704 (Clothianidin)	CGA355190	CGA282149	NOA459602	SYN501406
Number of scenarios > 0,1 µg/L	9/9	3/9	0	4/9	9/9	7/9
Min (µg/L)	0.532	0.038	0.013	0.060	0.390	0.062
Max (µg/L)	1.45	0.137	0.043	0.144	1.17	0.285

The metabolites CGA282149, NOA459602 and SYN501406 are considered not relevant according to guidance document SANCO/221/2000.
Based on the available data, an unacceptable risk of groundwater contamination cannot be excluded for thiamethoxam for one application of CRUISER on sugar beet (seed treatment) every third year (PECgw of thiamethoxam > 0.1 µg/L in all scenarios).

PECgw calculations are available in Volumes 3 B.8 (CP) under B.8.3.

Surface water

- *Field uses*

PECsw and PECsed for the intended uses of ACTARA and CRUISER were calculated for thiamethoxam and its metabolites according to FOCUS recommendations, considering the entry routes spray drift, drainage and runoff for ACTARA. No spray drift has been considered for the intended use of CRUISER on sugar beet by seed treatment.

FOCUS Step 1-2 calculations were performed for thiamethoxam and its metabolites CGA322704 (clothianidin), CGA355190, CGA282149, NOA407475, NOA404617 and CGA353042 using the tool STEPS1-2 in FOCUS version 3.2.

Further calculations were performed in FOCUS Step 3 for thiamethoxam and its major soil metabolite CGA322704 (clothianidin) using the software package SWASH version 5.3 including FOCUS-PRZM version 4.3.1, FOCUS-MACRO version 5.5.4 and FOCUS-TOXSWA version 4.4. It should be noticed that the applicant provided refined PECsw calculations (Tier 2) for thiamethoxam and its metabolite CGA322704: Tier 1 based on soil DT_{50} determined in laboratory for the active substance and its metabolite and Tier 2 based on soil DT_{50} determined in field dissipation studies. As explained previously, the field studies have not been considered acceptable by RMS and cannot be used in modelings. Therefore, only the PECsw calculations provided in Tier 1 have been considered in order to finalize the risk assessment for aquatic organisms.

In addition, mitigation measures were implemented in Step 4 for the intended uses of ACTARA for thiamethoxam and its metabolite CGA322704 (clothianidin) using SWAN version 4.0.1. No spray buffer zones of 20 meters were used to reduce spray drift. Vegetated filter strips of 20 meters were used to reduce run-off.

- *Glasshouse use on lettuce (ACTARA)*

PECsw for the intended use of ACTARA were calculated for thiamethoxam considering an overall emission of 0.1% of the application rate.

PECsw calculations are available in Volumes 3 B.8 (CP) under B.8.5.

2.9 EFFECTS ON NON-TARGET SPECIES

2.9.1 Summary of effects on birds and other terrestrial vertebrates

Table 2.9.1-1: Summary of toxicity endpoints used in risk assessment for birds

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Acute oral	Thiamethoxam	Bobwhite quail	LD_{50} = 1 552 mg a.s./kg bw	Geometric mean = **506 mg a.s./kg bw** [e]	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); Geometric mean calculated according to EFSA 2009	[redacted], 1996a [a] CGA293343/0046
		Mallard duck	LD_{50} = 576 mg a.s./kg bw (to be considered with reserve, due to regurgitation)		Agreed EU endpoint; (SANCO/10390/2002 – rev. final 2006) **Change proposed in this dossier: 14-d NOEL (mortality and regurgitation) = 125 mg a.s./kg (14-d LD50 > 125 mg a.s./kg)**	[redacted], 1996b [a] CGA293343/0044
		House sparrow	LD_{50} = 786 mg a.s./kg bw		US data requirement, included for completeness; Geometric mean calculated according to EFSA 2009	[redacted], 2012 [b, c] CGA293343_11575

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
		Canary	LD_{50} = 431 mg a.s./kg bw		US data requirement, included for completeness; Geometric mean calculated according to EFSA 2009	[redacted] 2015 [b, c] CGA293343_52867
	CGA322704	Bobwhite quail	LD_{50} > 2 000 mg/kg bw	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	[redacted], 1998 [a] CGA322704/0017
	CGA322704	Japanese quail	LD_{50} = 430 mg a.s./kg bw	-	Study not submitted by the notifier in the current dossier. Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005) reported by RMS for completeness	Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final
	A9584C	Japanese quail	LD_{50} >2 000 mg formulation/kg bw (equivalent to > 500 mg a.s./kg bw)	LD_{50} = 3 776 mg formulation/kg bw (equivalent to 944 mg a.s./kg bw)	Brazil data requirement, included for completeness; Extrapolated according to EFSA 2009	[redacted], 1997 [d] CGA293343/0624
Short term dietary	Thiamethoxam	Bobwhite quail	LD_{50} >5 200 mg a.s./kg feed (equivalent to >2 503 mg a.s./kg bw/day)	--	(SANCO/10390/2002 – rev. final 2006) Not a required endpoint as not lower than the acute LD_{50}	[redacted], 1996c [a] CGA293343/0047
		Mallard duck	LD_{50} >5 200 mg a.s./kg feed (equivalent to >2 503 mg a.s./kg bw/day)	--	(SANCO/10390/2002 – rev. final 2006) Not a required endpoint as not lower than the acute LD_{50}	[redacted], 1996d [a] CGA293343/0045
Sub-chronic and reproductive	Thiamethoxam	Bobwhite quail	NOEC = 900 mg a.s./kg feed	--	Change NOEC = 300 mg a.s./kg feed (**equivalent to 24.1 mg a.s./kg bw/day**)	[redacted], 1998 [a] CGA293343/0653
		Mallard duck	NOEC = 300 mg a.s./kg feed (equivalent to 29.4 mg a.s./kg bw/day)	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	[redacted], 1998 [a] CGA293343/0889

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
	CGA322704	Bobwhite quail	NOEC = 56.8 mg a.s./kg bw	-	Study not submitted by the notifier in the current dossier. Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005) reported by RMS for completeness	Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final

Endpoints in **bold** represent the endpoint used in the risk assessment.
[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2
[b] Study was not included in or has been performed since EU registration
[c] Study summary provided in volume 3 CA B.9
[d] Study summary provided in volume 3 CP B.9
[e] The geometric mean has been calculated using the bobwhite quail, house sparrow, Mallard duck and canary endpoints. Further details are provided in volume 3 CA B.9.

An acute oral toxicity study on A9584C was conducted with the Japanese quail. The acute LD_{50} for A9584C is >2000 mg/kg bodyweight (nominally equivalent to >500 mg a.s./kg bodyweight). Since there is no evidence that the formulation is expected to be significantly more toxic than the active ingredient, it is appropriate to assess the risk using toxicity data for the active ingredient.

Table 2.9.1-2: Summary of toxicity endpoints used in risk assessment for mammals

Thiamethoxam

Test type	Organism	Current Endpoint	Endpoint retained by RMS in Toxicological section	Endpoint retained by RMS for ecotoxicological section (see explanation in text part under volumes 3 CP)	Reference (author, date, Syngenta File No.)
Acute oral	Rat	LD_{50} = 1 563 mg a.s./kg bw	LD_{50} = 1 563 mg a.s./kg bw	LD_{50} = 1 563 mg a.s./kg bw	[redacted], 1996a [a] CGA293343/0054
	Mouse	**LD_{50} = 783 mg a.s./kg bw**	**LD_{50} = 783 mg a.s./kg bw**	**LD_{50} = 783 mg a.s./kg bw**	[redacted], 1996b [a] CGA293343/0055

Dietary 2-generation reproduction study	Rat	NOEAEL = 46 mg a.s./kg bw/day	Parental NOAEL = 61 mg a.s./kg bw/day Offspring NOAEL = 0.6 mg a.s./kg bw/day Reproductive NOAEL = 0.6 mg a.s./kg bw/day The parental systemic toxicity NOAEL was 30 ppm in males (1.8 mg/kg bw/day) based on increased incidence of hyaline change in renal tubules in F0 and F1 males observed from 1000 ppm and the highest dose tested 2500 ppm (202 mg/kg bw/day) in females.	Reproductive NOAEL = 10 ppm 0.6/0.8 mg/kg bw/day in males/females	[redacted], 1998 [a] CGA293343/0626

Test type	Organism	Current Endpoint	Endpoint retained by RMS in Toxicological section	Endpoint retained by RMS for ecotoxicological section (see explanation in text part under volumes 3 CP)	Reference (author, date, Syngenta File No.)
			Since α2μ-globulin nephropathy is considered not relevant for humans, the parental systemic toxicity NOAEL of relevance to human risk assessment is 1000 ppm (61 mg/kg bw/day) based on reduced food consumption and decreased body weight gain of F0 and F1 males. The reproductive NOAEL was 10 ppm (0.6 mg/kg bw/day) based on increased incidence and severity of tubular atrophy observed in testes of the F1 males. The offspring NOAEL was 10 ppm (0.6 mg/kg bw/day) based on increased incidence and severity of tubular atrophy observed in testes of the F1 males.		

	Rat	NOEAEL = 62 mg a.s./kg bw/day	Parental NOAEL = 61.7 mg a.s./kg bw/day Offspring NOAEL = 1.2 mg a.s./kg bw/day Reproductive NOAEL = 1.2 mg a.s./kg bw/day The parental systemic toxicity NOAEL was 50 ppm in males (3 mg/kg bw/day) based on increased incidence of hyaline change in renal tubules in F0 and F1 males and no systemic toxicity was observed in females up to the highest dose tested 2500 ppm (208.8 mg/kg bw/day). Since α2μ-globulin nephropathy is considered not relevant for humans, the parental systemic toxicity NOAEL of relevance to human risk assessment is 1000 ppm (61.7 mg/kg bw/day) based on decreased body weight and reduced food consumption and increased adrenal weight of F0 males.	Reproductive NOAEL = 20 ppm (1.2/1.7 mg/kg bw/day in males/females)	[redacted], 2004 [b] CGA293343/1925

Test type	Organism	Current Endpoint	Endpoint retained by RMS in Toxicological section	Endpoint retained by RMS for ecotoxicological section (see explanation in text part under volumes 3 CP)	Reference (author, date, Syngenta File No.)
			The reproductive NOAEL was 20 ppm (1.2/1.7 mg/kg bw/day in males/females) based on significant reductions in the number of sperm cells in the right testes of F1 males from 50 ppm (3 mg/kg/day). The offspring NOAEL was 20 ppm (1.2/1.7 mg/kg bw/day in males/females) based on significant reductions in the number of sperm cells in the right testes of F1 males from 50 ppm (3 mg/kg/day).		

Endpoints in **bold** represent the endpoint used in the risk assessment.
NOEL = No Observed Effect Level; NOAEL = No Observed Adverse Effect Level; NOEAEL = No Oberseved Ecological Adverse Effect Level
[a] Thiamethoxam Monograph, B6: Toxicology and Metabolism, March 2001_v.2
[b] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, January 2005

Reproductive endpoints retained in Toxicological section from thiamethoxam in rat 2-generation reproduction studies.

Study type / duration	Reference (author, date, Syngenta File No.)	Reproductive (mg a.s./kg bw/day)	
		NOAEL	LOAEL
Rat – dietary two-generation reproduction	[redacted], 1998 CGA293343/0626	0.6/0.8 mg/kg bw/day (♂/♀)	1.8/2.4 mg/kg bw/day (♂/♀)
Rat – dietary two-generation reproduction	[redacted], 2004 CGA293343/1925	1.2/1.7 (♂/♀)	3.0/ 4.3 mg/kg bw/day (♂/♀)

As recommended in EFSA Guidance Document 2009, the highest NOAEL in either 2 generation rat study (1.2/1.7 (♂/♀)) which is not above the lowest LOAEL (1.8/2.4 mg/kg bw/day (♂/♀), is retained for risk assessment in ecotoxicoloical section. The NOAEL retained is therefore 1.2 mg/kg bw/day.

A9584C

Test type	Test substance	Test species	Current Endpoint	Proposed endpoint in this document	Comment	Reference (author, date, Syngenta File No.)
		Rat	LD_{50} > 5 000 mg formulation/kg bw	--	No change	1996a CGA293343/0050

Acute oral	A9584C	Mouse	LD_{50} = 4 153 mg formulation/kg bw	--	No change	1998 CGA293343/0758

Thiamethoxam metabolites

Test type	Test substance	Test species	Current Endpoint	Proposed endpoint in this document	Comment	Reference (author, date, Syngenta File No.)
Acute oral	CGA322704	Rat	LD_{50} >2 000 mg/kg bw	--	No change	[redacted] 1998 [a] CGA322704/0013
	CGA322704	Mouse	LD_{50} = 389 mg/kg bw	--	Study not submitted by the notifier in the current dossier. Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005) reported by RMS for completeness	(Clothianidin SANCO/10533/05 - Final 18 January 2005)
Subchrionic and reproductive	CGA322704	Rat	NOAEL = 32.7 mg a.s./kg bw	--	Study not submitted by the notifier in the current dossier. Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005) reported by RMS for completeness	(Clothianidin SANCO/10533/05 - Final 18 January 2005)
Acute oral	NOA407475	Rat	1 000 > LD_{50} > 500 mg/kg bw	--	No change	[redacted], 1998 [a] NOA407475/0002

[a] Thiamethoxam Monograph, B6: Toxicology and Metabolism, March 2001_v.2

2.9.2 Summary of effects on aquatic organisms [section 11.5 of the CLH report]

2.9.2.1 Bioaccumulation [equivalent to section 11.4 of the CLH report template]

2.9.2.1.1 Estimated bioaccumulation

The experimentally derived Log Kow of Thiamethoxam is -0.13 at 25°C (see 2.9.2.1.2). For classification and labelling purposes a substance with Log Kow <4 may be considered unlikely to bioaccumulate in aquatic organisms. Therefore, Thiamethoxam has a low potential for biocaccumulation.

2.9.2.1.2 Measured partition coefficient and bioaccumulation test data

Property	Value	Reference	Comment (e.g. measured or estimated)
Partition coefficient n-octanol/water	The octanol/water partition coefficient (P_{OW}) and its logarithm to base 10 ($\log P_{ow}$) were determined to be : P_{OW}: 0.73 ± (0.0029) at 25°C $\log P_{ow}$: -0.13 ± (0.0017) at 25°C	Stulz, 1995b	EEC A.8 (Shake flask method)

2.9.2.2 Acute aquatic hazard [equivalent to section 11.5 of the CLH report template]

2.9.2.2.1 Acute (short-term) toxicity to fish

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Acute toxicity	Thiamethoxam	*Oncorhynchus mykiss*	**96 hr LC_{50} >125 mg a.s./L**	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	[redacted], 1996 [a] CGA293343/0036
			96 hr LC_{50} >100 mg a.s./L	--	No change [h]	[redacted], 1997a [a] CGA293343/0388
		Lepomis macrochirus	96 hr LC_{50} >114 mg a.s./L	--	No change [h]	[redacted], 1996 [a] CGA293343/0145
		Cyprinodon variegatus	96 hr LC_{50} >111 mg a.s./L	--	No change [h]	[redacted] 1997a [a] CGA293343/0208
		Cyprinus carpio	96 hr LC_{50} >120 mg a.s./L	--	No change [h]	[redacted], 2003 [b] CGA293343/1835
	CGA322704	*Oncorhynchus mykiss*	**96 hr LC_{50} >100 mg/L**	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	[redacted] 1997b [a] CGA322704/0009
	CGA322704	*Oncorhynchus mykiss*	**96 hr LC_{50} >104.2 mg/L**	--	Study not submitted by the notifier in the current dossier. Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005) reported by RMS for completeness	Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005)
	CGA355190	*Oncorhynchus mykiss*	**96 hr LC_{50} >100 mg/L**	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	[redacted] 1998 [a] CGA355190/0002
	NOA407475	*Oncorhynchus mykiss*	**96 hr LC_{50} >100 mg/L**	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	[redacted], 1998a [a] NOA407475/0010
	CGA282149	*Oncorhynchus mykiss*	--	**96 hr LC_{50} >100 mg/L**	Conducted on a metabolite; included for completeness	[redacted], 1996 [d, e] CA2343/0025
	NOA459602	*Oncorhynchus mykiss*	96 hr LC_{50} >120 mg/L	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	[redacted], 2002a [c] NOA459602/0016
	A9584C	*Oncorhynchus mykiss*	**96 hr LC_{50} >100 mg formulation/L**	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	[redacted] 1998 [a] CGA293343/0500
		Xenopus laevis	--	48 hr LC_{50} = 149.7 mg formulation/L	CN data requirement; included for completeness	[redacted], 2008 [d, f] A9584C_10158

Endpoints in **bold** represent endpoints used in the risk assessment.

[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2

[b] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, January 2005

[c] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, January 2004
[d] Study was not included in or has been performed since EU registration
[e] Study summary provided in Volume 3 CA. B.9
[f] Study summary provided in Volume 3 CP B.9
[h] No study summary provided in Volume 3 CA B.9 as endpoints not used in the risk assessment

2.9.2.2.2 Acute (short-term) toxicity to aquatic invertebrates

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Acute toxicity	Thiamethoxam	*Daphnia magna*	48 hr EC_{50} > 100 mg a.s./L	--	No change	Neumann, 1996 [a] CGA293343/0043
		Asellus aquaticus	**48 hr EC_{50} = 0.084 mg a.s./L**	--	No change	Ashwell and Dark, 2002 [b] CGA293343/1608
			--	48 hr EC_{50} > 0.32 mg a.s./L	Supportive of the risk assessment	Pickervance et al., 2003 [c, d] CGA293343/1698
		Crangonyx pseudogracilis	48 hr EC_{50} = 0.42 mg a.s./L	--	No change	Ashwell and Dark, 2002 [b] CGA293343/1608
			--	48 hr EC_{50} = 1.49 mg a.s./L	Supportive of the risk assessment	Pickervance et al., 2003 [c, d] CGA293343/1698
		Copepoda	48 hr EC_{50} > 100 mg a.s./L	--	No change	Ashwell and Dark, 2002 [b] CGA293343/1608
		Daphnia pulex	24 hr EC_{50} > 100 mg a.s./L	--	No change	Knauer, 2000c [a] CGA293343/1274
		Gammarus sp.	48 hr EC_{50} > 2.8 mg a.s./L	--	No change	Knauer, 2000b [a] CGA293343/1229
		Mysidopsis bahia	96 hr EC_{50} = 6.9 mg a.s./L	--	No change	Drottar and Swigert, 1997b [a] CGA293343/0207
		Ostracoda	48 hr EC_{50} = 0.18 mg a.s./L	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Knauer, 2000d [a] CGA293343/1273
		Procambarus clarkii	--	96 hr EC_{50} = 2.3 mg a.s./L	Supportive of the risk assessment	Sayers, 2008 [c, d] CGA293343_11533
		Thamnocephalus platyurus	24 hr EC_{50} > 100 mg a.s./L	--	No change	Knauer, 2000c [a] CGA293343/1274
		Chironomus riparius	48 hr EC_{50} = 35 µg a.s./L	--	No change	Mank and Krueger, 1998 [a] CGA293343/1273 CGA293343/0890
			48 hr EC_{50} = 0.045 mg a.s./L	--	No change	Ashwell and Dark, 2002 [b] CGA293343/1608
			--	48 hr EC_{50} = 0.071 mg a.s./L	Supportive of the risk assessment	Pickervance et al., 2003 [c, d] CGA293343/1698
		Chironomus dilutus	--	**10 d EC_{50} = 2 mg a.s./kg (mm)**	US data requirement; included for completeness	Bradley, 2015 [c, d] CGA293343/52661
		Chaoborus cristallinus	48 hr EC_{50} = 7.3 mg a.s./L	--	No change	Ashwell and Dark, 2002 [b] CGA293343/1608

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Acute toxicity	Thiamethoxam	*Chaoborus sp.*	48 hr EC_{50} = 5.5 mg a.s./L	--	No change	Knauer, 2000d [a] CGA293343/1273
		Cloeon dipterum	48 hr EC_{50} = 0.021 mg a.s./L	--	No change	Ashwell and Dark, 2002 [b] CGA293343/1608
			--	48 hr EC_{50} = 0.044 mg a.s./L	Supportive of the risk assessment	Pickervance et al., 2003 [c, d] CGA293343/1698
		Cloeon sp	**48 hr EC_{50} = 0.014 mg a.s./L**	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Knauer, 2000 [a] CGA293343/1228
		Coengrionidae	48 hr EC_{50} = 0.98 mg a.s./L	--	No change	Ashwell and Dark, 2002 [b] CGA293343/1608
		Dytiscidae	48 hr EC_{50} = 0.069 mg a.s./L	--	No change	Ashwell and Dark, 2002 [b] CGA293343/1608
			--	48 hr EC_{50} = 0.047 mg a.s./L	Supportive of the risk assessment	Pickervance et al., 2003 [c, d] CGA293343/1698
		Crassostrea virginica	96 hr EC_{50} > 119 mg a.s./L	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Drottar and Swigert, 1997c [a] CGA293343/0209
		Lymnea stagnalis	48 hr EC_{50} >100 mg a.s./L	--	No change	Knauer, 2000d [a] CGA293343/1273
			48 hr EC_{50} > 100 mg a.s./L	--	No change	Ashwell and Dark, 2002 [b] CGA293343/1608
		Radix peregra	48 hr EC_{50} >100 mg a.s./L	--	No change	Knauer, 2000d [a] CGA293343/1273
		Brachionus calyciforus	24 hr EC_{50} > 100 mg a.s./L	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Knauer, 2000c [a] CGA293343/1274
		Erpobdellidae sp.	48 hr EC_{50} = 100 mg a.s./L	--	No change	Ashwell and Dark, 2002 [b] CGA293343/1608
		Lumbriculus sp.	48 hr EC_{50} = 7.7 mg a.s./L	--	No change	Ashwell and Dark, 2002 [b] CGA293343/1608
		Planariidae	48 hr EC_{50} > 100 mg a.s./L	--	No change	
	CGA322704	*Daphnia magna*	48 hr EC_{50} > 100 mg/L	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Neumann, 1997a [a] CGA322704/0008

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
		Daphnia magna	48 hr EC_{50} > 40 mg/L	--	Study not submitted by the notifier in the current dossier. Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005) reported by RMS for completeness	Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005)
		Asellus aquaticus	--	48 hr EC_{50} = 0.067 mg/L	Supportive of the risk assessment	Pickervance et al., 2003 [c, d] CGA293343/1698
		Chironomus riparius	--	48 hr EC_{50} = 0.014 mg/L		
		Cloeon dipterum	--	48 hr EC_{50} = 0.012 mg/L		
		Crangonyx pseudogracilis	--	**48 hr EC_{50} = 0.014 mg/L**		
		Dytiscidae	--	**48 hr EC_{50} = 0.007 mg/L**		
		Chironomus riparius	--	48 hr EC_{50} = 0.029 mg/L	Study not submitted by the notifier in the current dossier. Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005) reported by RMS for completeness	Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005)
Acute toxicity	CGA355190	*Daphnia magna*	**48 hr EC_{50} > 100 mg/L**	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Maetzler, 1998a [a] CGA355190/0003
		Chironomus riparius	--	**48 hr EC_{50} = 4.1 mg/L**	Data requirement	Sayers, 2007 [c, d] CGA355190_10000
	NOA407475	*Daphnia magna*	**48 hr EC_{50} = 82.9 mg/L**	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Seyfried, 1998b [a] NOA407475/0011
	NOA459602	*Daphnia magna*	48 hr EC_{50} > 120 mg/L	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Wallace, 2002 [e] NOA459602/0017
	NOA404617	*Chironomus riparius*	--	**48 hr EC_{50} >110 mg/L**	Data requirement	Sayers, 2007 [c, d] NOA404617_10000
	CGA282149	*Daphnia magna*	--	**48 hr EC_{50} > 100 mg/L**	Conducted on a metabolite; included for completeness	Neumann, 1996 [c, d] CA2343/0026
		Chironomus riparius	--	**48 hr EC_{50} > 100 mg/L**	Data requirement	Hengsberger and Hartel, 2015 [c, d] CA2343_10010

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
	NOA421275	*Chironomus riparius*	--	48 hr EC_{50} >100 mg/L	Conducted on a metabolite; included for completeness	Schmidt, 2003 [c, d] NOA421275/0001
	A9765R	*Chironomus riparius*	--	**48 hr EC_{50} = 0.205 mg formulation/ L**	Data requirement	Eckenstein, 2014 [c, f] A9765R_10081
	A9584C	*Daphnia magna*	**48 hr EC_{50} > 100 mg formulation/ L**	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Rufli, 1998 [a] CGA293343/0516
		Chironomus riparius	--	**48 hr EC_{50} = 0.154 mg formulation/ L**	Data requirement	Pfeifle et al., 2005 [c, f] CGA293343/2175

Endpoints in **bold** represent endpoints used in the risk assessment.
[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2
[b] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, January 2005
[c] Study was not included in or has been performed since EU registration
[d] Study summary provided in Volume 3CA B.9
[e] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, January 2004
[f] Study summary provided in Volume 3 CP B.9

2.9.2.2.3 Acute (short-term) toxicity to algae or aquatic plants

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Algal toxicity	Thiamethoxam	*Selenastrum capricornutum* [a]	72 hr E_rC_{50} > 81.8 mg a.s./L 72 hr NOErC = 81.8 mg a.s./L	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Grade, 1996a [b] CGA293343/0035
			72 hr E_rC_{50} > 100 mg a.s./L 72 hr NOErC =100 mg a.s./L	--	No change	Grade, 1998a [b] CGA293343/0580
		Navicula pelliculosa	--	96 hr E_rC_{50} > 98 mg a.s./L 96 hr NOErC = 98mg a.s./L	US data requirement; included for completeness This study is not considered fully acceptable and reliable for the risk assessment**. No impact on risk assessment as this study was not required.	Staggs, 2014 [c] CGA293343_52048

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
		Skeletonema costatum	--	96 hr E_rC_{50} > 99 mg a.s./L 96 hr NOErC = 99mg a.s./L	US data requirement; included for completeness This study is not considered fully acceptable and reliable for the risk assessment**. No impact on risk assessment as this study was not required.	Staggs, 2014a [c] CGA293343_52060
		Anabaena flos-aquae	--	96 hr E_rC_{50} > 97 mg a.s./L 96 hr NOErC = 47 mg a.s./L	US data requirement; included for completeness This study is not considered fully acceptable and reliable for the risk assessment**. No impact on risk assessment as this study was not required.	Staggs, 2014b [c] CGA293343_52044
	CGA322704	*Selenastrum capricornutum* [a]	**72 hr E_rC_{50} > 100 mg/L** **72 hr NOE_rC = 50 mg/L**	--	No change	Grade, 1997 [b] CGA322704/0007
	CGA355190	*Selenastrum subspicatum*	**72 hr E_rC_{50} > 100 mg/L** **72 hr NOE_rC = 100 mg/L**	--	No change	Maetzler, 1998 [b] CGA355190/0004
	NOA407475	*Selenastrum subspicatum*	**E_rC_{50} = 33.8 mg/L** **E_rC_{10} = 7.7 mg/L**	--	No change	Seyfried, 1998c [b] NOA407475/0009
	NOA459602	*Selenastrum capricornutum* [a]	72 hr E_rC_{50} > 120 mg/L **72 hr NOE_rC = 60 mg/L**	--	No change	Wallace, 2002 [d] NOA459602/0018
	CGA282149	*Selenastrum capricornutum* [a]	--	**E_rC_{50} > 12.8 mg/L*** **E_rC_{10} = 6.914 mg/L**	Conducted on a metabolite; included for completeness	Grade, 1996 [c] CA2343/0011
	A9584C	*Selenastrum capricornutum* [a]	**E_rC_{50} > 100 mg formulation/L** **E_rC_{10} = 58.26 mg formulation/L**	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Grade, 1998 [b] CGA293343/0466

Aquatic plant toxicity	Thiamethoxam	*Lemna gibba*	**7 d E_rC_{50} > 90.2 mg a.s./L** **7 d NOE_rC = 90.2 mg a.s./L**	--	No change	Grade, 1998c [b] CGA293343/0595

Endpoints in **bold** represent endpoints used in the risk assessment.

[a] Now known as *Raphidocelis subcapitata*
[b] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2
[c] Study has been performed since EU registration; Study summary provided in Volume 3 CA B.9
[d] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, January 2004
* 33.4% effect at this highest tested concentration of 12.8 mg/L
** One of the validity criteria was not met (The mean coefficient of variation of the daily growth rates in the control cultures was >35% over 96 hours (must be ≤ 35%).

2.9.2.2.4 Acute (short-term) toxicity to other aquatic organisms

No data on other aquatic organisms

2.9.2.3 Long-term aquatic hazard [equivalent to section 11.6 of the CLH report template]

2.9.2.3.1 Chronic toxicity to fish

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Chronic toxicity	Thiamethoxam	*Oncorhynchus mykiss*	28 d NOEC = 100 mg a.s./L	--	No change [h]	, 1997c [a] CGA293343/0296
Early life stage	Thiamethoxam	*Oncorhynchus mykiss*	88 d NOEC = 20 mg a.s./L	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change [h]	[redacted], 1997 [a] CGA293343/0205
	Thiamethoxam	*Cyprinodon variegatus*	--	**28 d NOEC = 1.7 mg a.s./L**	US data requirement; included for completeness	, 2015 [d, g] CGA293343_52670
	CGA282149	*Pimephales promelas*	--	**32 d NOEC = 115 mg/L**	NONS data requirement for intermediates; included for completeness	[redacted], 2001 [d, g] CA2343/0056
	CGA322704	*Pimephales promelas*	28 d NOEC = 20 mg/L	--	Study not submitted by the notifier in the current dossier. Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005) reported by RMS for completeness	Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final

Endpoints in **bold** represent endpoints used in the risk assessment.
[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2
[d] Study was not included in or has been performed since EU registration
[g] Study summary provided in Volume 3 CA B.9
[h] No study summary provided in Volume 3 CA B.9 as endpoints not used in the risk assessment

2.9.2.3.2 Chronic toxicity to aquatic invertebrates

Test type	Test item	Test species	Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Chronic toxicity	Thiamethoxam	*Daphnia magna*	21 d NOEC = 100 mg a.s./L	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Neumann, 1997b [a] CGA293343/0323
		Mysidopsis bahia	--	**28 d NOEC = 0.56 mg a.s./L**	US data requirement; included for completeness	Sayers, 2015 [b, c] CGA293343/52672
		Chironomus riparius	**30 d NOEC = 0.1 mg a.s./kg sediment (initial nominal)**	30 d EC_{10}= 0.085 mg a.s./kg dry sediment (initial nominal) **30 day EC_{10} = 0.0072 mg a.s./kg dry sediment (geomean measured)**	**30 d NOEC = 0.1 mg a.s./kg sediment** corresponding to the Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); Change: EC_{10} calculated, endpoint also expressed in term of geomean in volume 3 CA B.9 **30 day EC_{10} = 0.0072 mg a.s./kg dry sediment (geomean measured)**	Grade, 1998b [a] CGA293343/0720
			30 d NOEC = 0.01 mg a.s./L (initial nominal)	**30 d NOEC = 0.01 mg a.s./L (initial nominal)** **30 day NOEC (emergence rate and development rate) = 0.0027 mg a.s./L (geomean measured).**	**30 d NOEC = 0.01 mg a.s./L** corresponding to the Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); Change: Endpoint also expressed in term of geomean in volume 3 CA B.9 **30 day NOEC (emergence rate and development rate) = 0.0027 mg a.s./L (geomean measured).**	
		Chaoborus sp.	--	34 d EC10 = 0.06 mg a.s./L (initial nominal)	Supportive of the risk assessment Endpoint also expressed in term of geomean in volume 3 CA B.9 34 d EC10 = 0.03 mg a.s./L (geomean measured).	Grade, 2002 [b, c] CGA293343/1568
	CGA322704	*Daphnia magna*	21 d NOEC = 0.12 mg/L	--	Study not submitted by the notifier in the current dossier. Agreed EU endpoint (Clothianidin	Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final

Test type	Test item	Test species	Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
					SANCO/10533/05 - Final 18 January 2005) reported by RMS for completeness	18 January 2005)
	CGA322704	*Chironomus riparius*	**28 d NOEC = 0.015 mg/kg sediment (nominal)** **28 d NOEC = 0.0055 mg/kg sediment (geomean measured)**	--	**28 d NOEC = 0.015 mg/kg sediment (nominal)** Change: Endpoint also expressed in term of geomean in volume 3 CA B.9 **28 d NOEC = 0.0055 mg/kg sediment (geomean measured)**	Grade, 1998 [a] CGA322704/0021
			28 d NOEC = 0.00067 mg/L (nominal)	--	28 d NOEC = 0.00067 mg/L, corresponding to the agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); Change: Endpoint also expressed in term of geomean in volume 3 CA B.9 **28 d NOEC = 0.00018 mg/L (geomean measured)**	Smyth et al., 2004 [d] CGA322704/0042
	CGA322704	*Chironomus riparius*	**28 d EC_{15} = 0.0007 mg/L**	--	Study not submitted by the notifier in the current dossier. Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005) reported by RMS for completeness	Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005)
	NOA407475	*Chironomus riparius*	**28 d NOEC = 1 mg/kg sediment**	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Grade, 2000 [a] NOA407475/0014
	NOA459602	*Chironomus riparius*	24 d NOEC = 50 mg/L	--	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); No change	Grade, 2002 [e] NOA459602/0009
	CGA353042	*Chironomus riparius*	**26 d NOEC = 100 mg/L**	--	Change: Endpoint also expressed in term of geomean in volume 3 CA B.9	Schmidt, 2003 [d] CGA353042/0004

Test type	Test item	Test species	Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
					26 d NOEC = 43.5 mg/L (geomean measured)	
	CGA282149	*Daphnia magna*	--	**21 d NOEC = 56 mg/L**	NONS data requirement for intermediates; included for completeness	Daniel, 2001 [b, c] CA2343/0050
	SYN501406	*Chironomus riparius*	--	28 d NOEC = 1.1 mg/L	Conducted on a metabolite; included for completeness	Maynard et al., 2003 [b, c] SYN501406/0003

Endpoints in **bold** represent endpoints used in the risk assessment.
[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2
[b] Study has been performed since or not included in EU registration
[c] Study summary provided in Volume 3 CA B.9
[d] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, January 2005
[e] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, January 2004

Higher Tier studies (Outdoor freshwater mesocosm)

Test type	Test item	Current endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Outdoor freshwater mesocosm	Thiamethoxam	NOEC = 30 µg a.s./L NOEAEC = 100 µg a.s./L	NOEC = 30 µg a.s./L (nom) NOEC = 3.7 µg a.s./L (mm)	Change in endpoint due to statistical re-evaluation Change: Endpoint also expressed in term of geomean in volume 3 CA B.9 (no NOAEC can be derived)	Ashwell et al., 2003 [a] CGA293343/1851
	Thiamethoxam	--	Cloeon dipterum NOEC = 0.3 µg a.s./L (nom)	New study	Hommen et al., 2016 c A9584C_11124
	CGA322704	EAC = 3.1 µg/L (NOEC = 1 µg/L) (NOEAEC = 10 µg/L)	NOEC = 1 µg/L (nom) NOEAEC = 3.2 µg/L (nom)	MDD criteria taxa of Brock et al. (2015) for a reliable analysis (category 1) for 5 potentially sensitive populations: 3 crustaceans (*Daphnia pulex*, *Copepod nauplii* and *Cyclopoid copepods*) and 2 insect species (*Cricotopus spec.* male and *Orthocladiinae* female)	Memmert, 2001 [b] CGA322704_10070
	CGA322704	--	NOEC = 0.5 µg/L (nom) NOEAEC = 1 µg/L (nom)	MDD criteria taxa of Brock et al. (2015) for a reliable analysis (category 1) for 8 potentially sensitive populations: 3 crustaceans (Asellus aquaticus Asellidae juveniles Gammarus pulex) and 5 insect species (Chaoborus sp., Chironomini, Tanytarsini, Plea sp., Ephemeroptera) However, an uncertainty remains concerning effects and recovery (abundance and emergence) of the known sensitive Ephemeroptera, particularly species Cloeon dipterum and Caenis sp	Hartgers and Roessink, 2015 [c] CGA322704_10054

[a] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, January 2005

[b] This study was previously reviewed (Clothianidin SANCO/10533/05, 18 January 2005); however a study summary is provided in Volume 3 CA B.9.

[c] Study has been performed since EU registration; Study summary provided in Volume 3 CA B.9

2.9.2.3.3 Chronic toxicity to algae or aquatic plants

See 2.9.2.2.3

2.9.2.3.4 Chronic toxicity to other aquatic organisms

No data on other aquatic organisms

2.9.2.4 Comparison with the CLP criteria

2.9.2.4.1 Acute aquatic hazard

Summary of information on acute aquatic toxicity relevant for classification

Method*	Species	Test material	Results	Remarks	Reference
OECD No. 203 (1992) 92/69/EEC C.1 FIFRA No. 72-1 (1989)	Rainbow trout (*Oncorhynchus mykiss*)	thiamethoxam	96 hr LC50 >125 mg/L (mm)	-	, 1996 CGA293343/0036
No guideline available, so based on: OECD No. 202	*Asellus aquaticus*	thiamethoxam	48 hr EC_{50} = 0.084 (nom)	-	Ashwell and Dark, 2002 CGA293343/1608
No guideline available, so based on: OECD No. 202 (1984) 92/69/EEC Part C.2 (1992) OPPTS 850.1010 (1996) EPA 540/9-86-141 FIFRA No.: 72-2	*Cloeon sp.*	thiamethoxam	48 hr $EC_{50=}$ 0.014 (nom)[1]	-	Knauer, 2000 CGA293343/1228
OECD No. 201 (1984) 92/69/EEC Part C.3 (1992)	*Selenastrum capricornutum*	thiamethoxam	72 hr E_rC_{50} >81.8 mg/L (mm)	-	Grade, 1996a **CGA293343/0035**
ASTM 1415-91 FIFRA No. 122-2 and 123-2 OECD 1996 Draft guideline for the Anabeana toxicity test OPPTS Draft proposal April 1996	*Lemna gibba*	thiamethoxam	7d E_rC_{50} >90.2 mg/L (mm)	-	Grade, 1998c **CGA293343/0595**

** When the guidance followed differs from guidance in force, differences have been listed and reliability and validity of the study has been assessed (see volume 3.CA B.9 for more details)*

[1] *Acute M-factor = 10*

Based on these results the most sensitive species group are aquatic invertebrates with an EC_{50} = 0.014 mg/L. On this basis, the following classification for thiamethoxam is proposed:
Aquatic Acute 1 H400 (Very toxic to aquatic life); as the lowest L(E)C50 is between 0.01 and 0.1 mg/L the associated M-factor is 10.

Summary of the relevant study used for acute environmental hazards is presented below:

	Summary for previously evaluated study submitted for purposes of renewal
Report:	*KIIA 8.2.4 Knauer K (2000). Acute toxicity test of CGA293343 tech. to the Ephemeroptera Cloeon sp. under static conditions. Report number 2002613, Novertis Crop Protection AG, Basel, Switzerland. (Syngenta File No. CGA293343/1228)*

Guidelines

No guideline available, so based on;

OECD Guidelines for Testing of Chemicals, Section 2 - Effects on Biotic Systems, Method 202: *Daphnia* sp., Acute Immobilisation Test (1984)

Official Journal of the European Communities, Dir 92/69/EEC, O.J. L383A, Part C.2: Acute toxicity for Daphnia (1992)

US EPA Ecological Effects Test Guidelines, OPPTS 850.1010: Aquatic Invertebrate Acute Toxicity Test, Freshwater Daphnids (1996)

US EPA Pesticide Assessment Guidelines, FIFRA Subdivision E, Hazard Evaluation: Wildlife and Aquatic Organisms. EPA 540/9-86-141, Guideline No.: 72-2.

GLP: Yes

Executive Summary

The acute toxicity of CGA293343 to nymphs of the ephereropteran *Cloeon* sp. was determined under static conditions. Nymphs were exposed to a range of nominal concentrations of 3.1, 6.3, 13, 25, 50 and 100 µg a.s./L, alongside a dilution water control. Based on nominal concentrations, the 48-hour EC_{50} was 14 µg a.s./L.

Materials

Test Material	CGA293343
Lot/Batch #:	P.506006
Purity:	98.6%
Description:	Beige powder
Stability of test compound:	Stable under standard conditions
Reanalysis/Expiry date:	August 2001.
Treatments	
Test concentrations:	Dilution water control and nominal concentrations of 3.1, 6.3, 13, 25, 50 and 100 µg/L
Solvent:	None
Positive control:	Not stated
Analysis of test concentrations:	Yes, analysis of CGA293343 at 0 and 48 hours using HPLC analysis with UV detection at 250 nm.
Test organisms	
Species:	*Cloeon* sp.
Source:	Field collected from Novartis Crop Protection AG's aquatic ecosystem, Stein, Switzerland
Feeding:	None during the test
Culture medium:	Pond water filtered to 90 µm and ultrasonicated for around 3 minutes.
Test design	
Test vessels:	250 mL glass beakers containing 200 mL
Test medium:	Same as culture medium
Replication:	4 replicates per treatment & control, each containing 5 *Cloeon* nymphs
Exposure regime:	Static
Acclimation:	Acclimated to test conditions for at least 20 hours
Duration:	48 hours.
Environmental conditions	
Test temperature:	18.9 – 19.0°C
pH range:	8.2 to 8.5
Dissolved oxygen:	87 to 96% saturation value
Total hardness of dilution water:	Not stated
Lighting:	Fluorescent light, 16 hours light and 8 hours dark, with 30 minute dawn and dusk periods.

Study Design and Methods

Experimental dates: 6th to 9th June, 2000

A stock solution with a nominal concentration of 10 mg a.s./L was prepared by dissolving 10.1 mg of the test item completely in 1000 mL of dilution water by stirring. Using this stock solution, the nominal test concentrations as stated above were prepared by dilution of requisite volumes of stock solution with dilution water. The control consisted of dilution water only. Test solutions were added to the test vessels and the *Cloeon* added.

Immobility of the ephemera was determined by visual observations after 24 and 48 hours of exposure. Organisms unable to swim within 15 seconds after gentle agitation of the test beaker were considered to be immobile.

The test was conducted in a climate controlled chamber.

The pH and dissolved oxygen were measured at the start and end of the test for each test concentration and the control. The temperature was measured in the control at the start and end of the test.

The test concentrations were verified by chemical analysis of CGA293343 at 0 and 48 hours using high performance liquid chromatography with ultra violet detection.

Results and Discussion

At the start of the test, the measured concentrations were in the range 92 to 104% of the nominal values and at the end of the test were in the range 86 to 100% (see table below). The limit of quantification in this study was 0.5 µg/L. Nominal concentrations were used for the calculation and reporting of results.

Table 8.2.4.2-10: Analytical results

Nominal concentrations (µg a.s./L)	% of nominal measured at 0 hours	% of nominal measured at 48 hours	Mean measured concentrations (µg a.s./L)
0 (control)	<LOQ	<LOQ	<LOQ
3.1	98	100	3.1
6.3	104	100	6.4
13	92	86	12
25	100	97	25
50	97	96	48
100	93	91	92

The median effect concentration (EC_{50}) was defined as the concentration resulting in 50% immobilisation of the *Cloeon* sp. in the time period specified and was calculated by the Probit method at 24 and 48 hours. Immobility data and estimated EC_{50} values are shown in the table below.

Table 8.2.4.2-11: Effects of CGA293343 on *Cloeon* sp. following exposure for 48-hours in a static test

Nominal concentration	Immobilised *Cloeon* sp. after 24 hours		Immobilised *Cloeon* sp. after 48 hours	
(µg a.s./L)	Number	%	Number	%
0 (control)	0	0	0	0
3.1	0	0	0	0
6.3	0	0	0	0
13	6	30	10	50
25	12	60	18	90
50	20	100	20	100
100	20	100	20	100
EC_{50} µg/L	19		14	
95% Confidence limits	16 - 23		11 - 17	
NOEC	n.d.		n.d.	

n.d. = not determined

There was no immobility observed in the dilution water control, hence the validity criterion of $\leq$ 10% immobility in the control was met.

Conclusions

Based on nominal concentrations, the 48-hour EC_{50} for CGA293343 to *Cloeon* sp. was 14 µg a.s./L. The 48-hour NOEC was not determined.

There is no agreed testing guideline for non-standard test species; however this study complies with the current reliability and validity criteria for the acute toxicity testing with *Daphnia magna*. Therefore this study is still reliable and valid for use in the risk assessment.

Reference	Guidance followed	Current guidance in force	Differences from guidance in force	Critical assessment
Knauer, 2000 CGA293343/1228	Based on: OECD No. 202 92/69/EEC Part C.2 OPPTS 850.1010 FIFRA No.: 72-2	None. But could generally follow OECD No. 202 (acute *Daphnia*)	The following is not reported: 1. Aeration of test system 2. Covering of test vessels The following deviations are noted: 1. *Cloeon sp.* collected from pond (unknown age) 2. Acclimation period only at least 20 hours 3. Pond water used as test medium 4. Water hardness >250 mg/L $CaCO_3$ (366 mg/L) 5. Temperature only measured in the control vessels	Even if conditions of the study were not fully reported and there are deviations from the recommended test design, the validity criteria were met: 1. Mortality in the control was ≤ 10% (0%) 2. DO ≥ 3 mg/L (87-96% saturation) The study is reliable and the endpoint can be used in the risk assessment.

This study is still considered acceptable and reliable for the risk assessment. 48-hour EC50 = 14 µg a.s./L (nominal).

2.9.2.4.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Summary of information on long-term aquatic toxicity relevant for classification

Method*	Species	Test material	Results	Remarks	Reference
OECD Guidelines for Testing of Chemicals, Section 2 - Effects on Biotic Systems, Method 210 (draft): Fish, Early-Life Stage Toxicity Test (2013) US EPA Ecological Effects Test Guidelines, OCSPP 850.1400 (public draft): Fish Early Life-Stage Toxicity Test, Freshwater and Marine (1996)	Sheepshead minnow (*Cyprinodon variegatus*)	thiamethoxam	28 d NOEC= 1.7 mg/L (mm)	-	**CGA293343_52670**
U.S EPA 540/9-82-024 (1982), U.S EPA 540/9-86-138 (1986), ASTM Standard E1241-88 (1988).	Oncorhynchus mykiss	thiamethoxam	88 d NOEC = 20 mg/L (mm)	-	, 1997 CGA293343/0205
OECD Guideline No. 202 (1984), Revised draft OECD guideline 202 Part II (1996) , FIFRA Guideline No 72-4 (1989)	Daphnia magna	thiamethoxam	21 d NOEC = 100 mg/L (nom)	-	Neumann, 1997b **CGA293343/0323**

US EPA Ecological Effects Test Guidelines, OCSPP 850.1350: Mysid Chronic Toxicity Test (1996)	*Mysidopsis habia*	thiamethoxam	28 d NOEC = 0.560 mg/L (nom)	-	Sayers, 2015 **CGA293343/52672**
OECD Proposal for Toxicity Test with Chironomidae, November (1997) Proposal for a BBA-Guideline: Effects of Plant Protection Products on the Development of Sediment-Dwelling Larvae of Chironomus riparius in a Water-Sediment System (1995)	*Chironomus riparius*	thiamethoxam	30 d NOEC = 0.0027 mg/L (mm)[1]	-	Grade, 1998b **CGA293343/0720**
OECD No. 201 (1984) 92/69/EEC Part C.3 (1992)	*Selenastrum capricornutum*	thiamethoxam	72 hr NOE_rC = 81.8 mg/L (mm)	-	Grade, 1996a **CGA293343/0035**
ASTM 1415-91 FIFRA No. 122-2 and 123-2 OECD 1996 Draft guideline for the Anabeana toxicity test OPPTS Draft proposal April 1996	*Lemna gibba*	thiamethoxam	7d NOE_rC = 90.2 mg/L (mm)	-	Grade, 1998c **CGA293343/0595**

** When the guidance followed differs from guidance in force, differences have been listed and reliability and validity of the study has been assessed (see volume 3.CA B.9 for more details)*
[1] chronic M-factor = 10

Based on these results the most sensitive species group are aquatic invertebrates with a NOEC = 0.0027 mg/L. On this basis, the following classification for thiamethoxam is proposed:
Aquatic Chronic 1 H410 (Very toxic to aquatic life); as the lowest NOEC is between 0.001 and 0.01 mg/L and considering that thiamethoxam is a non-rapidly degradable component (see 2.8.2) and has a low potential for bioaccumulation (see 2.9.2.1), the associated M-factor is 10.

Summary of the relevant studies used for long-term environmental hazards is presented below:

	Summary for previously evaluated study submitted for purposes of renewal
Report:	*KIIA 8.2.7 Grade R (1998b) Toxicity test of CGA293343 tech. on sediment-dwelling Chironomus riparius (syn. Chironomus thummi) under static conditions, Report Number 972552, Novartis Crop Protection AG, Basel, Switzerland. (Syngenta File No. CGA293343/0720)*

Guidelines

OECD Guidelines for the Testing of Chemicals, Proposal for Toxicity Test with Chironomidae, November (1997).

Proposal for a BBA-Guideline: Effects of Plant Protection Products on the Development of Sediment-Dwelling Larvae of *Chironomus riparius* in a Water-Sediment System (1995).

GLP: Yes

Executive Summary

The effects of CGA293343 on the development of *Chironomus riparius* were determined using two test scenarios:

Scenario A – Test item applied via water column

Scenario B – Test item applied via sediment (on treated sand).

For Scenario A, organisms were exposed to nominal concentrations of 1.25, 2.5, 5, 10, 20 and 40 µg a.s./L, alongside a dilution water control.

For Scenario B, organisms were exposed to nominal concentrations of 12.5, 25, 50, 100, 200 and 400 µg a.s./kg dry sediment, alongside aged sediment controls with and without acetone.

For Scenario A, based on nominal concentrations of CGA293343 the 30 day EC_{50} for emergence rate was 11.4 µg a.s./L, and for development rate the 30 day EC_{50} was >10 µg a.s./L. The 30 day NOEC for emergence ratio was 10 µg a.s./L, and for development rate the 30 day NOEC was 10 µg a.s./L.

For Scenario B, based on nominal concentrations of CGA293343 the 30 day EC_{50} for emergence rate was 110 µg a.s./kg dry sediment, and for development rate the 30 day EC_{50} was >100 µg a.s./kg dry sediment. The 30 day NOEC for emergence rate was 100 µg a.s./kg dry sediment, and for development rate the 30 day NOEC was 100 µg a.s./kg dry sediment.

Materials

Test Material	CGA293343
Batch No.	P.506006
Purity:	98.6%
Description:	Beige powder
Stability of test compound:	Stable under standard conditions
Reanalysis/expiry date:	06/1999
Density:	Not stated.
Treatments	
Test concentrations:	Scenario A - 1.25, 2.5, 5, 10, 20 and 40 µg a.s./L, alongside a dilution water control. Scenario B - 12.5, 25, 50, 100, 200 and 400 µg a.s./kg dry sediment, alongside aged sediment controls with and without acetone.
Solvent:	Scenario A – None Scenario B – Acetone
Analysis of test concentrations:	Based on measurements of CGA293343 in the water on days 0 and 30 for Scenario A Based on measurements of CGA293343 in the sediment on days 0, 7 and 30 for Scenario B.
Test organism	
Species:	*Chironomus riparius*, first instar
Source:	Continuous laboratory cultures originally obtained from Dr. F. Heimbach, Bayer AG, Leverkusen
Feeding:	Fish food (Tetramin) suspension (2g Tetramin in 40 ml medium); equivalent to about 1.0 mg fish food per larva per day on days 0 and 1, doubled to 2 mg fish food par larva per day on the remaining feeding days (see below).
Test design	
Test medium:	Elendt M4
Artificial Sediment:	10% sphagnum peat 20% kaolin clay

	68% industrial sand (>50% of the particles between 50 and 200µm)
	Calcium carbonate (to adjust the pH)
	The organic carbon content of the final sediment mixture was 3 - 4%
Test vessels:	Scenario A - 1 L tall-form glass beakers 9 cm diameter, covered with parafilm and containing 86 g of wet sediment (1.6 - 2 cm layer) and 536 mL (8 cm layer) of test medium. Gentle aeration applied.
	Scenario B - 1 L tall-form glass beakers 9 cm diameter, covered with parafilm and containing 120 g of wet sediment and 510 mL of test medium. Separation of sediment ingredients avoided when adding water by placing styropore layer on sediment before pouring water. Styropore removed, and then gentle aeration applied.
Replication:	Scenario A – 12 days before application of the test item, three replicate test and control replicate vessels were prepared (water and sediment added) and gently aerated. Three replicate test vessels per treatment and control. Then 20 larvae added randomly per vessel 24-h before application of test item to water column. Aeration halted for this period, until test item applied 24-h after larvae added and aeration re-started. Test system kept in temperature controlled room.
	Scenario B – Artificial sediment was conditioned in flowing water for 13 days before application of the test item (spiked onto sand using acetone as a solvent). Three replicate test and control replicate vessels were then prepared (water and sediment added) about 20 hours before test start and gently aerated. Then 20 larvae added randomly per vessel and the aeration halted for 24-h. Aeration then re-started. Test system kept in temperature controlled room.
Duration:	30 days

Environmental conditions

Scenario A	
Test temperature:	
	19.7 to 21.4°C
pH range of overlying water:	7.7 to 9.2
Dissolved oxygen of overlying water:	95 to 110% saturation value
Total hardness :	272 mg/L as $CaCO_3$
Conductivity:	701 µS/cm
Lighting:	16 hours fluorescent light (800 - 1000 lux) and 8 hours dark with 30 minute dawn and dusk transition periods
Scenario B	
Test temperature:	19.7 to 21.4°C
pH range of overlying water:	7.7 to 8.4
Dissolved oxygen of overlying water:	78 to 104% saturation value
Total hardness :	297 mg/L as $CaCO_3$
Conductivity:	720 µS/cm
Lighting:	16 hours fluorescent light (800 - 1000 lux) and 8 hours dark, with 30 minute dawn and dusk transition periods

Study Design and Methods

Experimental dates: 24 February to 5 May, 1998.

Scenario A - A solution was prepared by dissolving 70.0 mg of test material in 1000 mL of M4 medium to give a nominal concentration of 70 mg/L. From this, six stock solutions (one per treatment) were prepared by making appropriate aliquots of the 70 mg/L solution up to 1000 mL with M4 medium. Then appropriate volumes of each stock solution were added to the appropriate treatment replicates to produce the test dilutions. A dilution water control was also prepared.

Scenario B – A solution was prepared by dissolving 20.01 mg of test material in 100 mL of acetone to give a nominal concentration of 200 mg/L. Six stock solutions (one per treatment) were prepared by making appropriate aliquots of the 200 mg/L solution up to 25 mL with acetone. Then appropriate volumes of each stock solution were added to 15.5 g sand, mixed and the solvent evaporated off. Each batch of spiked sand was then mixed with 760.6 g (dry weight) of aged sediment for about 30 minutes to produce the spiked sediment for the six test treatments. A solvent control was also prepared in the same manner as the test treatments, using acetone and sand, along with a negative control using sand alone.

Larvae of *Chironomus riparius* were exposed for 30 days to the test item in 1-L tall-form beakers filled with sediment and test medium spiked via the water column (Scenario A) or via the sediment (Scenario B). The larvae were randomly distributed amongst the test vessels. Throughout the test the larvae were fed daily and from day one the vessels were gently aerated.

For both scenarios, food (see above) was supplied on days 0, 1, 3, 7, 8, 10, 13, 15, 17, 20, 22, 24, 27 and 29.

Visual assessments of behaviour, mortalities and emergence were made daily (except on days 4, 5, 12, 19, 25 and 26) for both scenarios. Emerged adults were removed from the test vessels when seen, recorded and sexed before being discarded.

The emergence and development rates, and the gender ratio were calculated from the total numbers of emerged male and female adults, and from the time to emergence.

On day 7 a sacrificial replicate at each treatment and control, set up at the same time as the three test replicates, was sieved to remove the larvae. After drying at 60^{o}C the larvae were weighed.

The pH and dissolved oxygen were measured in each test vessel on different days. Water temperature was recorded continuously. The hardness and conductivity of the batches of M4 medium were measured after preparation.

For Scenario A, sacrificial replicates were used to determine the concentration of test material for the overlying water in the 40 and 20 µg a.s./L treatments, and in the sediment at 40 µg a.s./L, on days 0, 7 and 30. Analysis of the sediment at 20 µg a.s./L was performed on day 30.

For Scenario B, sacrificial replicates were used to determine the concentration of test material for the overlying water in the 400 and 200 µg a.s./kg dry sediment treatments, and in the sediment at 400 µg a.s./kg dry sediment, on days 0, 7 and 30. Analysis of the sediment at 200 µg a.s./kg dry sediment was performed on day 30.

A HPLC method was used to analyse the test material.

Results and Discussion

Scenario A - The initial measured concentrations of test material in the water were 93% of nominal at 40 µg a.s./L and 82% of nominal at 20 µg a.s./L. At seven days these values were 68% and 56% respectively, and by the end of the test were <LOD. The measured concentrations of test material in the sediment were <LOD throughout the test at 40 µg a.s./L, and by the end of the test at 20 µg a.s./L (see table below).

Scenario B - The initial measured concentrations of test material in the water were 21% of nominal at 400 µg a.s./kg dry sediment and 22% of nominal at 200 µg a.s./kg dry sediment. At seven days these values were 35% and 45% respectively, and by the end of the test 25% and 41% respectively. The initial measured concentrations of test material in the sediment were 66% of nominal at 400 µg a.s./kg dry sediment. At 7 days this was 38% of nominal, and by ythe end of the test <LOD. At 200 µg a.s./kg dry sediment the analysed concentration was <LOD at the end of the test (see table below).

Table 8.2.5.3-1: Analytical results for Scenario A

Nominal concentrations (µg a.s./L or µg a.s./kg dry sediment)	% of nominal measured in the water			Geomean measured concentration in water %	% of nominal measured in sediment			Geomean measured concentration in sediment %
	Day 0	Day 7	Day 30		Day 0	Day 7	Day 30	
Scenario A (Test item applied via water column)								
20	**82**	**56**	**0***	**28.3**	-	-	0	-
40	**93**	**68**	**0****	**25.1**	0	0	0	0
Scenario B (Test item applied via sediment (on treated sand))								
200	22	45	41	34.4	-	-	0	-
400	21	35	25	26.4	66	38	0***	8.5%

* 5 % if LOD is considered.
** 2.5 % if LOD is considered
*** 0.25 % if LOD is considered

The Limit of determination (LOD) for sediment and water analysis was 1 µg a.s./kg and for water 1 µg a.s./L.

Biological results are based on nominal concentrations of CGA293343 in the spiked water for Scenario A and in the spiked sediment for Scenario B. There were no indications of different sensitivities of sexes for either exposure scenario, therefore male and female results were pooled for statistical analysis.

The effects of CGA293343 on *C. riparius* emergence rate and development rate for both scenarios are given in the tables below:

Table 8.2.5.3-2: Effects of CGA293343 on emergence and development of *Chironomus riparius* after 30 days exposure for Scenario A

Nominal concentrations (□g a.s./L)	Mean number emerged	Mean emergence rate	Mean gender rate	Mean development rate/vessel	Day to first hatch
Control	17.7	0.88	0.40	0.09	13
1.25	17.7	0.88	0.45	0.08	13
2.50	18.0	0.90	0.52	0.07	13
5.00	19.0	0.95	0.53	0.08	13
10.0	16.7	0.83	0.54	0.07	13
20.0	0	0	0	0	-
40.0	0	0	0	0	-

Table 8.2.5.3-3: Effects of CGA293343 on emergence and development of *Chironomus riparius* after 30 days exposure for Scenario B

Nominal concentrations (□g a.s./kg dry sediment)	Mean number emerged	Mean emergence rate	Mean gender rate	Mean development rate/vessel	Day to first hatch
Control	17.0	0.85	0.40	0.07	14
Solvent control	17.7	0.88	0.51	0.07	13
12.5	18.0	0.90	0.56	0.07	14
25	15.0	0.75	0.52	0.07	14
50	16.3	0.82	0.63	0.07	14
100	15.3	0.77	0.55	0.07	13
200	0	0	0	0	-

400	0	0	0	0	-

For both scenarios the EC_{50} (defined as the test concentration that results in 50% reduction of effect relative to the control and calculated using the Probit method) for emergence rate and development rate are tabulated below, along with the NOECs and LOECs identified using Dunnett's test:

Table 8.2.5.3-4: Summary of the effects of CGA293343 on emergence and development of *Chironomus riparius* after 30 days exposure for Scenario A

Endpoint	EC_{50} (µg a.s./L)	95% Confidence limits (µg a.s./L)	NOEC (µg a.s./L)	LOEC (µg a.s./L)
Emergence rate	11.4	n.d.	10	20
Development rate (sexes pooled)	>10	n.d.	10	n.d.

n.d. = not determined

Table 8.2.5.3-5: Summary of the effects of CGA293343 on emergence and development of *Chironomus riparius* after 30 days exposure for Scenario B

Endpoint	EC_{50} (µg a.s./kg sediment)	95% Confidence limits (µg a.s./kg sediment)	NOEC (µg a.s./kg sediment)	LOEC (µg a.s./kg sediment)
Emergence rate	114	n.d.	100	200
Development rate (sexes pooled)	>100	n.d.	100	n.d.

n.d. = not determined

Growth measurements (dry weights) of larvae from sacrificial vessels on day 7 are tabulated below for both scenarios:

Table 8.2.5.3-6: Summary of the effects of CGA293343 on growth *Chironomus riparius* after 7 days exposure for Scenario A

Concentration (µg a.s./L)	Average dry weight of larvae (mg)	No. larvae found
0 (control)	0.59	19
1.25	0.69	19
2.5	0.33	14
5.0	0.78	19
10	0.45	20
20	0.20	19
40	0.35	15

Table 8.2.5.3-7: Summary of the effects of CGA293343 on growth *Chironomus riparius* after 7 days exposure for Scenario B

Concentration (µg a.s./kg dry sediment)	Average dry weight of larvae (mg)	No. larvae found
0 (control)	0.25	15
0 (solvent control)	0.24	18
12.5	0.22	11
25	0.38	15
50	0.29	10
100	0.32	14
200	0.48	12

400	0.25	15

As several larvae were destroyed during the sieving procedure on day 7 no statistical analysis of these data was performed.

The test is considered valid as, for both scenarios, control emergence was >80% and the larval mean development time was ≤ 23 days post exposure.

Conclusions

Based on nominal concentrations of CGA293343, the 30 day EC_{50} for emergence rate was 11.4 µg a.s./L when exposed via the water column (Scenario A), and 114 µg a.s./kg dry sediment when exposed via the sediment (Scenario B). For development rate the 30 day EC_{50} was >10 µg a.s./L when exposed via the water column (Scenario A), and 100 µg a.s./kg of dry sediment when exposed via the sediment (Scenario B).

The 30 day NOECs for emergence rate and development rate were 10 µg a.s./L (Scenario A), and 100 µg a.s./kg dry sediment (Scenario B).

This study complies with most of the current reliability criteria for toxicity testing with *Chironomus riparius*; there are minor exceedances in pH and temperature. Despite some test conditions not being reported and minor deviations from the recommended test design, the study is still reliable and valid for use in the risk assessment.

Reference	Guidance followed	Current guidance in force	Differences from guidance in force	Critical assessment
Grade, 1998b CGA293343/0720	OECD Proposal for Toxicity Test with Chironomidae, November (1997) Proposal for a BBA-Guideline: Effects of Plant Protection Products on the Development of Sediment-Dwelling Larvae of Chironomus riparius in a Water-Sediment System (1995)	OECD No. 218 and 219	The following is not reported: 1. Reference test The following deviations are noted: 1. Water temp varied by >1°C (19.7-21.4 °C) 2. Sediment contained 10% peat (4-5% recommended) 3. Equilibrium period for sediment less than the recommended minimum (20hrs; 48hrs recommended) 4. Only 3 replicates (4 recommended)	Conditions of the study were not fully reported and there are deviations from the recommended test design. Most of the validity criteria were met: 1. Emergence must be at least 70% at the end of the test in the controls (>85%) 2. Emergence to adults from control vessels should occur between 12 and 23 days (<23 days) 3. DO should be at least 60% of the air saturation value (>78%) 4. pH of overlying water should be in the 6-9 range in all test vessels (pH 7.7-9.2) 5. Water temperature should not differ by more than 1.0°C (19.7-21.4°C; 1.6°C difference) The minor exceedances in pH and temperature do not impact the reliability of the study. The study is reliable and the endpoint can be used in the risk assessment.

In accordance with **Commission Regulation (EU) No 283/2013**, estimation of EC_{10} and EC_{20} values was attempted for Grade, 1998b (CGA293343/0720) in the following report:

	Submitted for purposes of renewal due to change in data requirements:
Report:	K-CA 8.2.5.3/01 Taylor, S., Majdanik, V. (2015a) Thiamethoxam - Toxicity of CGA293343 tech. on sediment-dwelling *Chironomus riparius* (syn. *Chironomus thummi*) under static conditions. Statistical Re-analysis. Report Number: CEA.1389. Cambridge Environmental Assessments, Battlegate Road, Boxworth, Cambridgeshire, CB23 4NN, UK. (Syngenta File No: CGA293343_11756)

Executive Summary

Report number 972552 (Grade, 1998b; CGA293343/0720) did not provide estimates of the EC_{10} and EC_{20} for the response variables of emergence rate or development rate of thiamethoxam to *Chironomus riparius* in a water-sediment system. In Exposure Scenario A, chironomids were exposed via spiked water and in Exposure Scenario B, chironomids were exposed using spiked sediment. Consequently the data generated in this study have been re-analyzed in order to provide these values.

Statistical analyses of the available data for development rate revealed that no reliable EC_x values were able to be calculated for either Exposure Scenario, nor for emergence rate of Exposure Scenario A. The EC_x for Exposure Scenario B were reliably calculated.

Statistical Analysis

Probit analysis with linear maximum likelihood regression was used to determine the concentration response function. Chi² was used as a goodness of fit measure. All computations were carried out in ToxRat Professional version 2.10 (ToxRat Solutions GmbH, 2001-2010).

Results

Emergence Rate

No clear treatment related effects were observed in Exposure Scenario A and as a result no EC_{10} or EC_{20} values were reliably determined. In Exposure Scenario B there was a significant difference between treatment and controls ($p(F) = 0.010$), therefore the EC_{10} or EC_{20} values and the 95% and 99% confidence limits were reliably determined.

EC_{10} and EC_{20} Estimates

Parameter	EC_{10} (mg/kg)	EC_{20} (mg/kg)
Exposure Scenario B	0.085 (0.045-0.108)	0.098 (0.061-0.123)

CL: Confidence Limits
n.d.: Not Determined

Development Rate

No clear treatment related effects were observed in Exposure Scenario A and B, and as a result no EC_{10} or EC_{20} values were reliably determined.

Conclusion

For the study results on chronic effects of thiamethoxam on *Chironomus riparius* statistical analyses of the available data for development rate revealed that no reliable EC_x values could be calculated for either exposure scenario. Additionally, reliable ECx values could not be calculated for emergence rate of exposure scenario A. The EC_x for exposure scenario B were reliably calculated.

This study is still considered acceptable and reliable for the risk assessment.

Test item applied via water column (Scenario A):

30 day NOEC (emergence rate and development rate) = 10 µg a.s./L (initial nominal).

30 day NOEC (emergence rate and development rate) = 2.7 µg a.s./L (geomean measured).

Relevant OECD test guidelines, such as OECD 218, 219 prefers to express the endpoint as measured initial, without particular consideration of the potential disappearance of the test item from the system that may occur by the end of the study. The initial test concentrations in the water were above 80 % of the nominal. However, the concentrations were not maintained throughout the test (within ± 20 % of the initial) including the final sampling. In the same time, the active substance was not measured in the sediment phase throughout the test (0% measured in sediment) indicating that Thiamethoxam did not partition to sediment. As concentrations in water were not maintained throughout the test and no partition to sediment occurred, then such endpoint expressed in term of nominal (initial) should be used in risk assessment, ensuring that the exposure in the study is sufficiently representative (worst case) of the predicted exposure profile. If it is not demonstrated that the exposure in the study is sufficiently representative (worst case) of the predicted exposure profile, then the endpoint should be expressed in term of mean measured (geomean in case of static conditions, in **line with the recommendations of OECD 23).**

Test item applied via sediment (Scenario B):

30 day EC_{10} (emergence rate) = 85 µg a.s./kg dry sediment (initial nominal); 30 day NOEC (development rate) = 100 µg a.s./kg dry sediment. (initial nominal)

30 day EC_{10} (emergence rate) = 7.2 µg a.s./kg dry sediment (geomean measured); 30 day NOEC (development rate) = 8.5 µg a.s./kg dry sediment. (geomean measured)

The initial test concentration in the sediment was below 80 % (66%) of the nominal. In the same time, the active substance was measured in the water phase at the beginning (21%) indicating that Thiamethoxam did partition from sediment to water phase from the beginning of the test. It can be noted that the sum of the % in the two compartments (water and sediment) is 87% indicating that the initial test concentrations in the sediment (before release in the water compartment) would be above 80 % of the nominal. However, the concentrations in sediment were not maintained throughout the test (within ± 20 % of the initial) including the final sampling. In the same time, the active substance was measured in the water phase throughout the test indicating that Thiamethoxam may have partitioned to water phase. As concentrations in sediment were not maintained throughout the test, then such endpoint expressed in term of nominal (initial) in sediment should be used in risk assessment, ensuring that the exposure in sediment in the study is sufficiently representative (worst case) of the predicted exposure profile. If it is not demonstrated that the exposure in sediment in the study is sufficiently representative (worst case) of the predicted exposure profile in sediment, then the endpoint should be expressed in term of mean measured (geomean in case of static conditions, in **line with the recommendations of OECD 23).**

2.9.2.5 Conclusion on classification and labelling for environmental hazards

Based on these results the most sensitive species group are aquatic invertebrates with an EC_{50} = 0.014 mg/L and a NOEC = 0.0027 mg/L. On this basis, the following classification for thiamethoxam is proposed:
Aquatic Acute 1 H400 (Very toxic to aquatic life); as the lowest L(E)C50 is between 0.01 and 0.1 mg/L the associated M-factor is 10.
Aquatic Chronic 1 H410 (Very toxic to aquatic life); as the lowest NOEC is between 0.001 and 0.01 mg/L and considering that thiamethoxam is a non-rapidly degradable component (see 2.8.2) and has a low potential for bioaccumulation (see 2.9.2.1), the associated M-factor is 10.

Aquatic acute1 H400 (Acute M-factor = 10)

Aquatic chronic 1 H410 (Chronic M-factor = 10)

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Thiamethoxam is an insecticidal active substance used in Europe on various crops. Thiamethoxam has an existing entry in Annex VI of CLP with harmonised classification for environment as Aquatic Acute 1; H400, Aquatic Chronic 1; H410, with a generic M-factor of 10.

Overall, the dossier submitter (DS) concluded that thiamethoxam is 'not rapidly degradable', has low potential for bioaccumulation and proposed classification based on results from the most sensitive species group aquatic invertebrates:

Aquatic Acute 1 with an M-factor of 10, based on the lowest 48h EC_{50} value for invertebrates (*Cloeon sp.)* of 0.014 mg/L; and

Aquatic Chronic 1 with an M-factor 10, based on the lowest 30d NOEC value for invertebrates (*hironomus riparius*) of 0.0027 mg/L.

Degradation

Two studies have been conducted in order to investigate the hydrolytic stability of thiamethoxam (CGA293343) in sterile aqueous buffer solutions (pH 1, 5, 7 and 9) at different temperatures (25, 40, and 60°C). One additional study had also been conducted to investigate the hydrolytic stability of thiamethoxam's major soil metabolite CGA322704 (clothianidin). All three studies were in compliance with GLP, however some deviations from OECD guidelines were indicated by the DS related to the temperature (test performed at 60°C instead of 50°C) and to the pH (pH value of 5 was used instead of 4). Nevertheless, the DS considered that no significant impact on the study outcomes is expected and that the studies are still valid and acceptable.

Both studies, (OECD TG 111, Clark A., 1998c and OECD TG 111, Lowery E., 1996) indicated that thiamethoxam is stable at pH 1, 5 and 7 at 25°C (experimental). However, at pH 9 (25°C) thiamethoxam degraded with a DT_{50} of 4.2-8.4 days (respectively). At pH 9 (20°C), thiamethoxam degraded with a DT_{50} of 7.3-15.6 days (calculated).

The study with the major soil metabolite (OECD TG 111, Ulbrich, 1999) indicated that CGA322704 (clothianidin) is stable at pH 4, 5, 7 and 9 in the dark at 20°C under sterile conditions.

Two studies have been provided by the DS in order to estimate the photodegradation of thiamethoxam. Both were in compliance with GLP and follow US EPA 161-2 guidelines although no major deviations from equivalent guideline OECD TG 316 were observed by the DS and the studies were considered as acceptable.

The first study (Schwartz B., 1998b), showed a first order kinetic degradation for thiamethoxam in aqueous buffers solutions at pH 5, under photolytic conditions. A half-life of 3.1 days was calculated. In a non-irradiated control or hydrolytic conditions at pH

5, thiamethoxam did not significantly degrade.

In the second study (Sparrow K., 1997c), the half-life of thiamethoxam under photolytic conditions was 2.3 days. Thiamethoxam also did not significantly degrade under non-irradiated control or hydrolytic conditions at pH 5.

In a ready biodegradation study following OECD TG 301B, biodegradation of thiamethoxam was observed with 7% mineralisation by day 29 (Grade R, 1996). Therefore, thiamethoxam was considered as "not readily biodegradable".

According to an aerobic mineralization study (OECD TG 309, Hüben, 2015a), the mineralization rate and the rate and route of degradation of thiamethoxam was investigated in Heiminghausen natural lake water amended with 0.01 g/L suspended sediment. The mineralization was low (< 1.6% AR) in all systems tested. No adsorption on suspended sediments was observed. The best-fit DT_{50} range for thiamethoxam in natural sediment amended lake water was 87 to 96 days. There were no significant observed differences between the degradation rate of the low and the high dosed systems. Two metabolites were formed: CGA355190 reached a maximum of 36.56% after 61 days and metabolite NOA404617 reached a maximum of 8.8 % after 61 days.

The fate and behaviour of thiamethoxam in the aquatic environment has been investigated in two water/sediment studies (Adam, 1998a&b). No guideline was followed in both studies. However, only minor deviations from OECD TG 308 guidelines were observed. The two systems used in the studies had very similar pH values and sediment textures. The OECD guideline recommends that both textures should have silt contents different from at least 20%. However, the DS consider that no significant impact on the results is expected and that the studies are still valid and acceptable. In support of these studies, an additional study following OECD TG 308 has been conducted in order to determine the degradation behaviour of thiamethoxam in a water/sediment system, with a water and sediment pH < 7, under aerobic conditions (Kang, 2015). Kinetic analysis was also performed according to FOCUS kinetics guidance (Ford S., 2015h). The maximal amount of thiamethoxam observed in sediment was 36.6% AR after 8 days. The active substance mineralization was low: max. 12% AR after 100 days. Several metabolites were observed in whole water-sediment systems: CGA355190 (max 8.9% AR after 100 d), NOA407475 (max. 47.4% AR after 42 d) and NOA404617 (max. 8% AR after 48 d). Non-extractable residues and mineralization reached respectively a maximum of 22.2-51.3 % AR after 80-100 days and 11.96% AR after 100 days. No DT_{50} values have been considered as reliable and robust enough in water-sediment systems for the active substance thiamethoxam and its metabolites.

Overall, due to the results summarised above, the DS consider that thiamethoxam is not readily biodegradable and not degraded in the aquatic environment to a level > 70 % within a 28-day period. As a consequence, thiamethoxam was considered as not rapidly degradable, according to the CLP criteria.

Aquatic Bioaccumulation

No experimentally derived BCF was available. The experimentally derived Log K_{ow} of thiamethoxam was -0.13 at 25°C (Stulz, 1995b). For classification and labelling purposes a substance with Log K_{ow} < 4 may be considered unlikely to bioaccumulate in aquatic organisms. Therefore, DS concluded that thiamethoxam has a low potential for bioaccumulation.

Aquatic Toxicity

The relevant and most representative information for classification according to DS are summarised in the following tables and sections. All data refers to thiamethoxam as the test substance.

Acute Aquatic toxicity

Test organism	Guideline, test method	Short-term result (endpoint)	Reference
Oncorhynchus Mykiss	OECD TG 203 (1992) 92/69/EEC C.1 FIFRA No. 72-1 (1989) / GLP	96h LC_{50} > 125 mg/L (mm)	Anonymous (1996a)
Asellus aquaticus	Not stated / GLP (generally could follow OECD TG 202)	48h EC_{50} = 0.084 mg/L (nom)	Ashwell and Dark (2002)
Cloeon sp.	No guideline available, so based on: OECD TG 202 (1984) 92/69/EEC Part C.2 (1992) OPPTS 850.1010 (1996) EPA 540/9-86-141 FIFRA No.: 72-2	48h EC_{50} = 0.014 mg/L (nom)	Knauer (2000)
Selenastrum capricornutum	OECD TG 201, 92/69/EEC Part C.3 (1992) / GLP	72h E_rC_{50} > 81.8 mg/L (mm)	Grade (1996a)
Lemna gibba	ASTM 1415-91 FIFRA No. 122-2 and 123-2 OECD 1996 Draft guideline for the Anabeana toxicity test OPPTS Draft proposal April 1996, GLP	7d E_rC_{50} > 90.2 mg/L (mm)	Grade (1998c)

All available studies were considered acceptable and reliable by the Rapporteur Member State for the risk assessment and are therefore used by the DS for classification, even if conditions of these studies do not fully comply with the current guidance or if there is no agreed testing guideline for non-standard test species, for example *Asellus aquaticus* or *Cloeon sp*. However, these studies comply with the current reliability and validity criteria for acute toxicity testing with *Daphnia magna*. Therefore, these studies were considered reliable and valid, and therefore relevant for classification by the DS.

Overall, based on these results the DS considered that the most sensitive group is aquatic invertebrates with an EC_{50} of 0.014 mg/L for *Cloeon sp.* and propose classification as Aquatic Acute 1, M=10.

Chronic Aquatic Toxicity

Test organism	Guideline, test method	Long-term result (endpoint)	Reference
Sheepshead minnow (Cyprinodon variegatus)	OECD Guidelines for Testing of Chemicals, Section 2 - Effects on Biotic Systems, Method 210 (draft): Fish, Early-Life Stage Toxicity Test (2013) US EPA Ecological Effects Test Guidelines, OCSPP	28d NOEC = 1.7 mg/L (mm)	Anonymous (2015)

	850.1400 (public draft): Fish Early Life-Stage Toxicity Test, Freshwater and Marine (1996) / GLP		
Oncorhynchus mykiss	U.S EPA 540/9-82-024 (1982), U.S EPA 540/9-86-138 (1986), ASTM Standard E1241-88 (1988) / GLP	88d NOEC = 20 mg/L (mm)	Anonymous (1997)
Daphnia magna	OECD TG 202 (1984), Revised draft OECD guideline 202 Part II (1996), FIFRA Guideline No 72-4 (1989) / GLP	21d NOEC = 100 mg/L (nom)	Neumann (1997b)
Mysidopsis bahia	US EPA Ecological Effects Test Guidelines, OCSPP 850.1350: Mysid Chronic Toxicity Test (1996)/ GLP	28d NOEC = 0.560 mg/L (nom)	Sayers (2015)
Chironomus riparius	OECD Proposal for Toxicity Test with Chironomidae, November (1997) Proposal for a BBA Guideline: Effects of Plant Protection Products on the Development of Sediment-Dwelling Larvae of Chironomus riparius in a Water-Sediment System (1995) / GLP	30d NOEC = 0.0027 mg/L (mm)	Grade (1998b)
Selenastrum capricornutum	OECD TG 201 (1984) 92/69/EEC Part C.3 (1992) /GLP	72h NOE_rC = 81.8 mg/L (mm)	Grade (1996a)
Lemna gibba	ASTM 1415-91 FIFRA No. 122-2 and 123-2 OECD 1996 Draft guideline for the Anabeana toxicity test OPPTS Draft proposal April 1996 / GLP	7d NOE_rC = 90.2 mg/L (mm)	Grade (1998c)

All provided studies comply with the current reliability criteria and were considered as acceptable and reliable by the RMS for the risk assessment even if conditions of these studies do not fully comply with the current guidance. Any minor deviations from the guideline do not affect the reliability of the studies. They are therefore used by the DS for classification.

Overall, the DS considers that the most sensitive group is aquatic invertebrates with an NOEC = 0.0027 mg/L for *Chironomus riparius* and propose classification Aquatic Chronic 1, M=10 considering that thiamethoxam is not rapidly degradable.

Comments received during public consultation

Three MSs submitted comments on the environmental part of the DS's proposals. One of them agreed that thiamethoxam is "not readily biodegradable", however they pointed out that in the substance approval process under the biocidal product regulation, further information is available regarding degradation in soil and in water/sediment systems. In response, the DS noted that CLH report has been based on the data

submitted in the frame of the EU PPP renewal dossier for thiamethoxam. During public consultation no additional data on degradation was provided. Consequently, RAC has evaluated available data which was provided in the dossier.

The second MS supported Aquatic Chronic 1 with M factor of 10. However, they mentioned that the surrogate approach using acute endpoints in the range 0.01 to 0.1 mg/L (including the most acutely sensitive endpoint and acute toxicity to *Chironomus* endpoint) should be noted. In response, the DS noted that the surrogate approach would also support the Aquatic Chronic 1, M=10 proposal.

The third MS supported the conclusion that thiamethoxam is considered not readily biodegradable and unlikely to have a potential for bioaccumulation, for classification purposes. They also agreed that the most sensitive group is invertebrates and that the key data for aquatic acute classification is from a non-guideline study using a species of mayfly, *Cloeon dipterum* with an EC_{50} of 0.014 mg/L. For aquatic chronic classification, the MS pointed out that the lowest value is from a study performed with midge larvae, *Chironomus riparius* with a NOEC value of 0.0027 mg/L. However, they indicated that the proposed NOEC is based on the measured geometric mean. Hence, the mean measured concentrations declined below the level of detection during the test and the concentrations of the test medium were analysed only three times during the test. Therefore, the actual NOEC is lower than that based on nominal concentrations. The DS agreed that the actual NOEC would be lower than that based on nominal concentrations and therefore expressed the endpoint in terms of geomean measured concentrations. The DS also pointed out that surrogate approach would lead to the same classification and M-factor.

Assessment and comparison with the classification criteria

Degradation

In addition to the studies assessed in the CLH report, one more study on the photodegradation of thiamethoxam and one study with the major soil metabolite of thiamethoxam were included in the dossier (RAR Vol. 3 B8). These studies were not assessed in the CLH report by the DS but were taken into account by RAC as supplemental information. The photodegradation study was done in compliance with GLP and no major deviations from OECD TG 316 were observed. The results from the soil degradation study with thiamethoxam (Zetzsch C., 1997) showed that half-lives estimated for different seasons vary between 0.8 days in summer and 8 days in winter with an annual half-life of 1.2 days at 40°N and of 1.6 days at 50°N, respectively. The study with the metabolite (Rüdel, 1998) indicated that the half-life for major soil metabolite CGA322704 (clothianidin) referring to direct photolysis in natural sunlight for Northern latitude 52°N vary between 7.2 hours in summer and 8.5 days in winter.

Regarding photolysis, test results thiamethoxam seems to be primarily degraded with half-life <16 days, however information on photochemical degradation is difficult to use for classification purposes. The actual degree of photochemical degradation in the aquatic environment depends on local conditions (e.g. water depth, suspended solids, turbidity as well as seasonal influences). Photolytic degradation also led to formation of at least 22 - 25 components including clothianidin, which seems to be more toxic than the parent substance and meets the criteria for classification as hazardous to the aquatic environment (clothianidin has a current entry in Annex VI to the CLP regulation as Aquatic Acute 1 and Aquatic Chronic 1, M=10). Consequently, primary degradation via photolysis cannot be used to conclude that thiamethoxam is rapidly degradable.

Hence, RAC considers that thiamethoxam is not readily biodegradable and there is not sufficient information to show that thiamethoxam is ultimately degraded to a level > 70 % within 28 days (equivalent to a half-life < 16 days) or transformed to non-classifiable products.

In conclusion, RAC agrees with the DS that thiamethoxam should be considered as not rapidly degradable.

Aquatic Bioaccumulation

The experimentally derived Log K_{ow} of thiamethoxam -0.13 at 25 °C is well below the CLP trigger of ≥ 4. Therefore, RAC agrees with the DS's conclusion that thiamethoxam has a low potential for bioaccumulation.

Aquatic Toxicity

RAC notes that there are reliable acute and chronic aquatic toxicity data for thiamethoxam and its metabolites for fish, aquatic invertebrates and algae included in the CLH dossier. However, as thiamethoxam is an insecticide, invertebrates are expected to be the most sensitive group for both acute and chronic toxicity. All relevant metabolites with exception of the major soil metabolite CGA322704 (clothianidin) are less toxic and are not considered as relevant in the further evaluation on classification. Although, RAC recognises that metabolite CGA322704 (clothianidin) is more acutely and chronically toxic than the parent substance. However, as clothianidin occurred in soil and not in aqueous media, RAC considers that clothianidin is not relevant for aquatic hazard classification purposes (see section "Supplemental information - In depth analyses by RAC").

Acute Aquatic Toxicity

Relevant acute toxicity data of thiamethoxam is available for a wide range of invertebrate species, including *Daphnia magna*, *Daphnia pulex*, *Mysidopsis bahia*, *Crassostrea virginica*, etc. (25 invertebrate species in total). Therefore, only aquatic invertebrate species with EC_{50} <1 mg/L (most sensitive) have been summarized in following table.

Test organism	Guideline, test method	Short-term result (endpoint)	Reference
Asellus aquaticus	Not stated / GLP	48h EC_{50} = 0.084 mg/L (nom)	Ashwell and Dark, 2002
Crangonyx pseudogracilis	Not stated / GLP	48h EC_{50} = 0.42 mg/L (nom)	Ashwell and Dark, 2002[b]
Ostracoda	GLP / based on OECD, EEC and EPA guidelines with modifications.	48h EC_{50} = 0.18 mg/L (nom)	Knauer, 2000d[a]
Chironomus riparius	GLP / FIFRA Series 72-2 (OECD TG 235)	48h EC_{50} = 0.035mg/L (nom)	Mank and Krueger, 1998[a]
Chironomus riparius	Not stated / GLP	48h EC_{50} = 0.045 mg/L (nom)	Ashwell and Dark, 2002[b]
Chironomus riparius	Not stated / GLP	48h EC_{50} = 0.071 mg/L (nom)	Pickervance et al., 2003 [c, d]
Cloeon dipterum	Not stated / GLP	48hr EC_{50} = 0.021 mg/L (nom)	Ashwell and Dark, 2002[b]
Cloeon dipterum	Not stated / GLP	48h EC_{50} = 0.044 mg/L (nom)	Pickervance et al., 2003 [c, d]
Cloeon sp.	No guideline available, so based on: OECD TG 202 (1984) 92/69/EEC Part C.2 (1992)	48h EC_{50} = 0.014 mg/L (nom)	Knauer, 2000

	OPPTS 850.1010 (1996) EPA 540/9-86-141 FIFRA No.: 72-2		
Coenagrionidae	Not stated / GLP	48h EC_{50} = 0.98 mg/L (nom)	Ashwell and Dark, 2002[b]
Dytiscidae	Not stated / GLP	48h EC_{50} = 0.069 mg/L (nom)	Ashwell and Dark, 2002[b]
Dytiscidae	Not stated / GLP	48h EC_{50} = 0.047 mg/L (nom)	Pickervance et al., 2003 [c, d]

RAC acknowledges that some of the most sensitive species were not standard test species and there is no standardised testing guideline for these species. Nevertheless acute data are available for three different insect groups (mayfly, water beetle and midge) plus one crustacean species (water louse) and are in the same range for classification purposes. The substance is an insecticide, hence it is appropriate to consider the data even though not all of them are conducted to standard test guidelines. RAC recognises that most of studies comply with the current reliability and validity criteria for acute toxicity testing with *Daphnia magna* (equal to OECD TG 202) or with Sediment-Water Chironomid Toxicity Using Spiked Water test (OECD TG 219) and are relevant and reliable for classification.

Consequently, data are available for all three trophic levels, RAC agrees that the lowest acute endpoint for aquatic acute classification purpose is the 48h EC_{50} value for *Cloeon sp.* of 0.014 mg/L based on nominal concentrations.

Aquatic Chronic

RAC notes that the most sensitive invertebrate specie for aquatic **chronic** toxicity (*Chironomus riparius*) is not the most sensitive invertebrate species in invertebrate **acute** testing (*Cloeon sp.*). However, RAC also notes that in acute testing, toxicity to both species (*Chironomus riparius* and *Cloeon sp.*) were in same order of magnitude. Furthermore, RAC is of the opinion that the *Chironomus* tests are acceptable for classification purposes in this case because there is very little dissipation to sediment.

Hence, RAC gave preference to the available chronic toxicity data instead of using the surrogate approach. However, it should be noted that the surrogate approach would lead to the same aquatic chronic classification and M-factor.

Consequently, RAC agrees that lowest chronic endpoint for aquatic chronic classification purposes is the 30d NOEC value for *Chironomus riparius* of 0.0027 mg/L, based on geometric mean measured concentration. However, RAC would like to stress that if further aquatic chronic studies will became available with invertebrates (especially with *Cloeon*) the classification of thiamethoxam may require revision.

Conclusion on classification

Thiamethoxam is considered as not rapidly degradable and does not fulfil the criteria for bioaccumulation. Based on the available and reliable information, RAC is of the opinion that thiamethoxam warrants classification as:

Aquatic Acute 1 based on EC_{50} = 0.014 mg/L for *Cloeon sp.* As this acute toxicity value falls within the 0.01 < $L(E)C_{50}$ ≤ 0.1 mg/L range, the **acute M-factor is 10**.

Aquatic Chronic 1 based on NOEC = 0.0027 mg/L for *Chironomus riparius*. As this chronic toxicity value falls within the 0.001 < NOEC ≤ 0.01 mg/L range, the **chronic M-factor is 10.**

Supplemental information - In depth analyses by RAC

Relevance of major soil metabolite CGA322704 (clothianidin) for aquatic classification of thiamethoxam

The main metabolites which occur via hydrolysis at pH 9 (25°C) were CGA355190, NOA404617 and CGA309335. No CGA322704 (clothianidin) metabolite occurred.

Photolytic degradation led to formation of at least 25 degradants. Only one metabolite exceeds 10% of the total applied dose (CGA 353042, 65.8% at day 30). One component (CGA 355190) accumulated between 2% and 10% AR. The other minor components occurring at day 30 at levels below 2% were identified as **CGA 322704 (clothianidin)**, NOA 407475, and CGA 353968.

In the aerobic mineralisation in surface water study two major metabolites were identified as NOA404617 and CGA355190. No CGA322704 (clothianidin) was identified.

In all water/sediment studies, identified metabolites were NOA407475, NOA404617, and CGA355190. No CGA322704 (clothianidin) was identified.

CGA322704 (clothianidin) was a major metabolite in soils. However, in aquatic systems clothianidin did not occur. Only by photolytic degradation was clothianidin identified, below 2% of AR at day 30. Therefore, despite clothianidin appearing more toxic than the parent substance, RAC is of opinion that for aquatic classification of thiamethoxam the toxicity of major soil metabolite CGA322704 (clothianidin) should be not taken into account.

2.9.3 Summary of effects on arthropods

Table 2.9.3-1: Laboratory toxicity to bees of Thiamethoxam, metabolites and formulations

Thiamethoxam

Organism	Test type	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)	Key observation as reported in EFSA Conclusion 2015
Apis mellifera	Adult acute oral	LD_{50} = 0.005 µg a.s./bee	--	Agreed EU endpoint; No change	Kleiner, 1995 [a] CGA293343/0018	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006) and EFSA bee review 2015; No change
	Adult acute contact	LD_{50} = 0.024 µg a.s./bee	--	Agreed EU endpoint; No change		Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006) and EFSA bee review 2015; No change
		--	10 d LDD_{50} = 0.00433µg a.s./bee/day 10 d NOEDD = 0.00245 µg a.s./bee/day	New data available	Kling, 2016 [f] CGA293343_12093	New study not reviewed during EFSA 2015

Organism	Test type	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)	Key observation as reported in EFSA Conclusion 2015
	Adult Chronic	10 d LC_{50} > 32 µg a.s./L 10 d NOEC = 32 µg a.s./L (NOED = 8.978 ng a.s./bee) (highest dose tested)	10 d LDD_{50} > 0.0008978 µg a.s./bee/day 10 d NOED = 0.0008978 µg a.s./bee/day [e] (highest dose tested)	Converted to units appropriate for use in risk assessment	Kling, 2013 [c] CGA293343_11578	**EFSA 2015:** Two chronic oral toxicity studies with thiamethoxam were available in the dossiers, Belzunces (2002) (see study evaluation notes in EFSA, 2013a) and Kling (2012) (see study evaluation notes; EFSA, 2015a). Neither of the studies included an assessment of the HPG nor an assessment of accumulative effects. Both studies followed similar methodology whereby the honeybees were offered contaminated food for 10 hours per day for 10 days. During the remaining 14 hours the honeybees were offered uncontaminated food. In order to perform a risk assessment according to EFSA, 2013b, a chronic toxicity endpoint, where the honeybees were offered contaminated food continuously for 10 days, is needed. Consequently, the available chronic toxicity endpoints are not considered suitable for risk assessment in accordance with EFSA, 2013b.
	Larvae Chronic	--	7 d LOED = 0.48 µg a.s./larva/ development period = 0.12 µg a.s./larva/day [g] (No NOED was derived in this study)	New data requirement	Eckert, 2015 [d] CGA293343_11666	New study not reviewed during EFSA 2015, See RMS comment concerning the two available studies conducted by Eckert, 2015
		--	8 d NOED = 0.840 µg a.s./larva/ development period = 0.168 µg a.s./larva/day [h]	New data requirement	Eckert, 2015a [d] CGA293343_11766	New study not reviewed during EFSA 2015 See RMS comment concerning the two available studies conducted by Eckert, 2015

Organism	Test type	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)	Key observation as reported in EFSA Conclusion 2015
		--	8 d NOED = 0.251 µg a.s./larva/ development period = 0.0502 µg a.s./larva/day 22 d NOED = 0.0157 µg a.s./larva/ development period = 0.003925 µg a.s./larva/day [g]	New data available (including an assessment of mortality after pupation and Emergence)	Eckert, 2016 [f] CGA293343_12107	New study not reviewed during EFSA 2015

[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2

[c] Art. 21, Thiamethoxam EFSA bee review 2015 [11]; Study summary provided in volume 3 CA B.9

[d] Study has been performed since EU registration; Study summary provided in volume 3 CA B.9

[e] Adult bees were fed for 10 days, therefore the cumulative dose (ng/bee) was divided by 10 and converted from ng/bee/day to µg/bee/day.

[f] To convert the units from concentration (µg/g diet) to cumulative dose (µg/larva/development period), it was assumed that the larva consumed all food that they were fed (600 mg of food) during the test period. To convert to µg/larva/day, the cumulative dose (µg/larva/development period) was divided by 6 to account for the number of feedings during the test.

[g] To convert to µg/larva/day, the cumulative dose (µg/larva/development period) was divided by 4 to account for the number of days the larva were fed during the test period.

[h] To convert to µg/larva/day, the cumulative dose (µg/larva/development period) was divided by 5 to account for the length of the development period. This is worst case as the larva were fed for 4 days during the test period.

There are three studies examing the toxicity of thiamethoxam with honeybee larvae under laboratory conditions. In the study by ***Eckert (2015***), the test concentrations were 0.48, 1.48, 4.44, 13.32 and 40 µg a.s./larva/development period. A 7-d NOED could not be determined, as there was a significant effect on mortality (50% reduction) at the lowest concentration tested (0.48 µg a.s./larva/development period). In the study by ***Eckert (2015a)***, the test concentrations were 0.02171, 0.05390, 0.1344, 0.336 and 0.840 µg a.s./larva/development period. The 8-d NOED was determined to be 0.840 µg a.s./larva/development period, the highest concentration tested as there were no significant effects on mortality compared to control. In the study by ***Eckert (2016)***, the test concentrations were 0.0157, 0.0313, 0.0625, 0.125, 0.251 and 0.501 µg a.s./larva/development period. The 8-d NOED was determined to be 0.251 µg a.s./larva/development period.

There is some difference in toxicity between the three studies where the doses overlap, as demonstrated in the tables below. Biological endpoints can be variable and therefore the difference in toxicity here is difficult to fully explain. It should also be noted that the study duration differs between the three studies, however larvae were fed on days 3, 4, 5 and 6 in all studies. Consequently, the datasets have been combined to determine a conservative endpoint to use in the risk assessment.

Effect of thiamethoxam on bee larval mortality (Eckert, 2015)

Endpoint	Dose (µg a.s./larva/development period)					
	Control	0.48	1.48	4.44	13.32	40
Mortality at 7 days	0	50*	43.8*	75*	85.4*	100*

Treatment % mortality was corrected for control mortality

* Significantly different from control (Fisher's Exact Test ; $p < 0.05$)

[11] Peer Review Report to the conclusion regarding the peer review of the pesticide risk assessment for bees for the active substance thiamethoxam considering all uses other than seed treatments and granules, EFSA (European Food Safety Authority), 2015

Effect of thiamethoxam on bee larval mortality (Eckert, 2015a)

Endpoint	Dose (µg a.s./larva/development period)					
	Control	**0.02171**	**0.05390**	**0.1344**	**0.336**	**0.840**
Mortality at 8 days	0	8.0	13.1	15.8	8.0	15.8

Treatment % mortality was corrected for control mortality

Effect of thiamethoxam on bee larval mortality (Eckert, 2016)

Endpoint	Dose (µg a.s./larva/development period)						
	Control	**0.0157**	**0.0313**	**0.0625**	**0.125**	**0.251**	**0.501**
Mortality at 8 days	0	4.8	21.9**	9.7	14.7	17.0	19.5*

Treatment % mortality was corrected for control mortality

* Significantly different from control (Fisher's Exact Test ; $p < 0.05$)

** Significantly different from control (Fisher's Exact Test ; $p < 0.05$); however due to the lack of a clearly defined dose response the effect observed is not considered to be toxicant related.

RMS comment concerning the three available studies conducted by Eckert, 2015; 2016:

Based on the results from the three studies, the highest proposed NOED (no significant effect with 15.8% mortality) of 0.840 µg a.s./larva/development period from one study is above the lowest LOED (significant effect with 50 % mortality) of 0.48 µg a.s./larva/development period and LOED (significant effect with 19.5 % mortality) of 0.501 µg a.s./larva/development period from the other studies indicating variability and contradictory results. This is considered surprising as the studies followed similar methodology for the "larvae phase" (day 0 to 7 or 8) where the larvae were fed contaminated food for 4 days. The difference in toxicity here is therefore difficult to explain. It can also be noted that in Eckert, 2015a, three doses (including the proposed NOED of 0.840 µg a.s./larva/development) out of five resulted in a corrected mortality of more than 10% (13.1, 15.8 and 15.8 %), however there was no clear dose response. Moreover, in Eckert, 2016, there was a significant effect at 0.0313 µg a.s./larva/development (21.9%) but not observed at the next higher dose of 0.0625 µg a.s./larva/development (9.7%). Then in this study, the higher doses of 0.125 and 0.251 µg a.s./larva/development resulted in a corrected mortality of more than 10%, with a slight dose response tendancy. Based on these observations, a uncertainty remains concerning the NOED of 0.336 µg a.s./larva/development period selected by the notifier.

Moreover, it can be noted that one study (Eckert, 2016) out of three included also an assessment of mortality after pupation (Pupal Mortality from Day 8 through 22) and emergence of adults (day 22) whereas the two other studies stopped at day 7 or 8 (Larval Mortality on Day 7 or 8). The notifier did not take into account observed effect on emergence in the previous analysis whereas it was the most sensitive parameter in the study Eckert, 2016 (see below) with a 22 d NOED = 0.0157 µg a.s./larva/ development period (sum of applications on day 3, 4, 5, 6), corresponding to 0.003925 µg a.s./larva/day (0.0157 divided by 4 to account for the number of days the larva were fed during the test period).

Effect of thiamethoxam on emergence of adults (Eckert, 2016)

Endpoint	Dose (µg a.s./larva/development period)						
	Control	0.0157	0.0313	0.0625	0.125	0.251	0.501
Adult emergence on day 22 (%)	88.1	81	66.7*	61.9*	64.3*	47.6*	14.3*

* Significantly different from control (Fisher's Exact Test with Bonferroni correction, one-sided greater, $\alpha = 0.05$) evaluated for non-emergence on day 22

Based on previous remarks and taking into account effect on emergence from this study, RMS is of the opinion to consider the 22 d NOED = 0.0157 µg a.s./larva/ development period corresponding to 0.003925 µg a.s./larva/day (0.0157 divided by 4 to account for the number of days the larva were fed during the test period). This NOED would also cover larvae mortality, Pupal Mortality and emergence of adults.

Metabolite CGA322704 (Clothianidin)

Organism	Test type	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)	Key observation as reported in EFSA Conclusion 2015
Apis mellifera	Adult acute oral	LD_{50} = 0.0168 µg/bee	--	Agreed EU endpoint; No change	Nengel, 1997 [a] CGA322704/0011	LD_{50} = 0.00379 µg/bee An acute oral LD50 value of 0.0168 µg/bee for the metabolite clothianidin was indicated in the Review Report for thiamethoxam (European Commission, 2006). However, as this value was an order of magnitude higher than the acute oral LD50 reported in the Review Report (European Commission, 2005) for the active substance clothianidin, the latter value has been reported
	Adult acute contact	LD_{50} = 0.0275 µg/bee	--	Agreed EU endpoint; No change		Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006) and EFSA bee review 2015; No change
	Adult Chronic	--	10 d LDD_{50} = 0.00183 µg/bee/day [g] 10 d NOED = 0.00038 µg/bee/day [g]	New data requirement; Not previously included in thiamethoxam submissions	Kling, 2005 [c] CGA322704_10055, amended in 2015	**EFSA 2015 (clothianidin)** Regarding the adult chronic oral toxicity study, the study protocol followed was considered broadly in line with what is in the EFSA 2013a, but it was agreed to reanalyse the raw data and recalculate the endpoint in terms of 10-day LDD50 (µg a.s./bee per day). This reanalysis was performed by EFSA (01_THW-0174) and the recalculated 10-day LDD50 was 0.00138 µg a.s./bee per day. RMS comment: This reanalysis performed by EFSA is quite similar to the reanalysis performed by the notifier in th current dossier.
	Larvae Chronic	--	21 d NOEC = 0.68 µg/g diet 21 d NOED [j] = 0.748 µg/larva/ development period = 0.150 µg/larva/day	New data requirement; Not previously included in thiamethoxam submissions	Patnaude, 2011 [e] CGA322704_10053	New study not reviewed during EFSA 2015, see RMS comment thereafter concenring this study conducted by Patnaude, 2011 and the study conducted by Maus, 2011

Organism	Test type	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)	Key observation as reported in EFSA Conclusion 2015
			21 d EC_{10} = 0.36 µg/g diet 21 d NOED [j] = 0.396 µg/larva/ development period = 0.0792 µg/larva/day			
		--	7 d NOED = 0.00528 µg/larva/ development period [h] = 0.00176 µg/larva/day [i] (highest dose tested) 22 d NOED = 0.00132 µg/larva/ development period [h] = 0.00044 µg/larva/day [i]	New data requirement; Not previously included in thiamethoxam submissions	Maus, 2011 [d] CGA322704_10057	**EFSA 2015 (clothianidin)** 7-day NOEL mortality 0.00528 µg a.s./larva per development period (provisional endpoint because of 3 days exposure and nominal food consumption) Regarding the study on honeybee larvae (12_THW-0272), it was agreed to derive from this study a 7-day NOEC of 40 µg a.s./kg diet, which, expressed in terms of µg a.s./larvae, corresponds to a NOEL of 0.00528 µg a.s./larvae (nominal dose). It is acknowledged that the 7-day NOEC was selected by the experts instead of the 22-day NOEC of 10 µg a.s./kg diet (i.e. NOEL of 0.00132 µg a.s./larvae, nominal dose), to be in line with the endpoint used for risk assessment according to EFSA, 2013b. It was agreed that this endpoint should be used only as provisional endpoint for risk assessment because the study is not fully in line with the proposed protocol in EFSA, 2013b (i.e. exposure duration in the study was over 3 days rather than 5 days as recommended by EFSA, 2013b). In addition, the actual food consumption of larvae was not reported; therefore it was only possible to express the endpoint in terms of nominal dose. RMS comment: Effect on emergence (22 day) should be taken into account, 22-day NOEC of 10 µg a.s./kg

Organism	Test type	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)	Key observation as reported in EFSA Conclusion 2015
						diet (i.e. NOEL of 0.00132 µg a.s./larvae = 0.00044 µg/larva/day nominal dose) is considered more relevant by RMS.

[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2

[c] The following study has been amended since being reviewed (Art. 21, Clothianidin EFSA bee review 2013 [12]), a study summary is provided in volume 3 CA B.9

[d] The following study has been amended since being reviewed (Art. 21, Clothianidin EFSA bee review 2015[13]), a study summary is provided in volume 3 CA B.9

[e] Study has been performed since EU registration; Study summary provided in volume 3 CA B.9.

[g] The endpoint listed in the report was converted from ng/bee/day to µg/bee/day.

[h] The endpoint listed in the report was converted from ng/larva/development period to µg/larva/development period.

[i] To convert to µg/larva/day, the cumulative dose (µg/larva/development period) was divided by 3 to account for the number of days the larva were fed during the test period.

[j] To convert the units from concentration (µg/g diet) to cumulative dose (µg/larva/development period), the amount of food consumed during the test period was considered (1100 µL). To convert to µg/larva/day, the cumulative dose (µg/larva/development period) was divided by 5 to account for the length of the development period.

RMS comment concerning available Larvae Chronic studies (the study conducted by Patnaude, 2011 and the study conducted by Maus, 2011):

Study protocol

The study protocol (exposure of larvae via diet for few days and observation on mortality from larvae stage to adult stage) is quite similar to the one conducted in the study by Maus, 2011 dCGA322704_10057 (see summary in volume 3 CA), except exposure duration and tested concentrations. Indeed, exposure duration to contaminated diet in the study (Patnaude, 2011) was over 5 days, higher than 3 days in Maus, 2011; and tested concentrations (0.33 to 15 µg/g diet) in the study (Patnaude, 2011) were higher than those in Maus, 2011 (5 to 40 µg/kg diet, equivalent to 0.005 to 0.04 µg/g diet). The actual food consumption of larvae was not reported; therefore the endpoints are expressed in terms of nominal food consumption.

7-day NOEC (larvae mortality), see also table below

Regarding the study on honeybee larvae (Maus, 2011), the endpoint derived and reported in EFSA (2015, clothianidin) was a 7-day NOEC of 40 µg a.s./kg diet (0.04 µg/g diet), which, expressed in terms of µg a.s./larvae, corresponds to a NOEL of 0.00528 µg a.s./larvae (nominal dose). This 7-day NOEC was selected instead of the 22-day NOEC (larvae to adult mortality) of 10 µg a.s./kg diet (0.01 µg/g diet) (i.e. NOEL of 0.00132 µg a.s./larvae, nominal dose), to be in line with the endpoint used for risk assessment according to EFSA, 2013b (see summary of Maus, 2011). RMS considered for this AIR 3 dossier that effect on emergence (22 day) should be taken into account, 22-day NOEC of 10 µg a.s./kg diet (i.e. NOEL of 0.00132 µg a.s./larvae = 0.00044 µg/larva/day nominal dose) is considered more relevant by RMS. However, it should also be noted that there was variability in the results from the three runs in this test: Only one of the test runs, number 4, showed a consistent decline in larval survival as clothianidin concentration increased. Test run 1 showed no effect and test run 3 was inconsistent showing nearly equal survival at the lowest and highest concentrations.

[12] EFSA (European Food Safety Authority), 2013. Conclusion on the peer review of the pesticide risk assessment for bees for the active substance clothianidin. EFSA Journal 2013;11(1):3066, 58 pp. doi:10.2903/j.efsa.2013.3066

[13] EFSA (European Food Safety Authority), 2015. Conclusion on the peer review of the pesticide risk assessment for bees for the active substance clothianidin considering all uses other than seed treatments and granules . EFSA Journal 2015;13(8):4210, 77 pp. doi:10.2903/j.efsa.2015.4210

Regarding the study on honeybee larvae (Patnaude M.R., 2011), 21-day NOEC for clothianidin to honey bee was determined to be 0.68 µg/g (ppm) diet. This 21-day NOEC of 0.68 µg/g (ppm) diet covered the 7-day NOEC (larvae) not reported in the study report but that could be stated to 4.4 µg/g (ppm) diet and the NOEC (pupae) not reported in the study report but that could be stated to 0.68 µg/g (ppm) (see Table 8.3.1.3-9 in summary in volume 3 CA).

Based on the results from the two available studies, an overall 7-day NOEC (larvae) of 4.4 µg/g (ppm) = 4.84 µg/larva/development period = 0.968 µg/larva/day could be set. The 21-day NOEC of 0.68 µg/g (ppm) diet= 0.748 µg/larva/ development period = 0.150 µg/larva/day covered the overall 7-day NOEC (larvae) of 0.968 µg/larva/day. Based on the clear dose response of effect observed, RMS considered that the 21-day EC_{10} of 0.36 µg/g (ppm) diet for clothianidin to honey bee value is more relevant than the 21-day NOEC of 0.68 µg/g (ppm) diet.

21/22-day NOEC/EC_{10} (larvae to adult mortality), see also table below

Regarding the study (Maus, 2011), 22-day NOEC (larvae to adult mortality) of 10 µg a.s./kg diet (0.01 µg/g diet) (i.e. NOEL of 0.00132 µg a.s./larvae = 0.00044 µg/larva/day nominal dose) was determined in EFSA 2015 (clothianidin) even if not used in risk assessment as the 7 d NOEL of 0.00528 µg a.s./larvae (= 0.00176 µg/larva/day) was selected (see previous explanation).

Regarding the study (Patnaude M.R., 2011), based on the clear dose response of effect observed, RMS considered that the 21-day EC_{10} of 0.36 µg/g (ppm) diet for clothianidin to honey bee value is more relevant than the 21-day "NOEC" of 0.68 µg/g (ppm) diet.

It can be noted that the 22-day NOEC determined in the study (Maus 2011) was 10 µg a.s./kg diet (0.01 µg/g diet), and therefore 22-day LOEC was between 20 and 40 µg a.s./kg diet (between 0.02 and 0.04 µg/g diet). Therefore, based on the results from the two studies (Maus 2011 and Patnaude, 2011), the highest 21/22-day NOED of 0.68 µg/g (0.150 µg/larva/day) and 21-day EC_{10} of 0.36 µg/g (=0.0792 µg/larva/day) from one study (Patnaude, 2011) is above the lowest 21/22-day LOED of 0.02 µg/g diet (0.00264 µg/larva/day) from the other study (Maus 2011) indicating variability and contradictory results. This is considered surprising as the studies followed relatively similar methodology and the larvae were fed contaminated food for 3 days in Maus, 2011 and 5 days in Patnaude M.R., 2011. The difference in toxicity here is therefore difficult to explain. Due to the difference in toxicity observed it is considered that using either of the 21/22-day NOEC (or EC_{10}) endpoints could be potentially misleading. RMS considered that an uncertainty remains concerning the results from these two studies and considered the lowest endpoint in a conservative approach.

Maus, 2011

Endpoint	**Dose (µg/g diet)**				
	Control	0.005	0.01	0.02	0.04
Mortality at 7 days (larvae)	-	**NOEC**	**NOEC**	**NOEC**	**NOEC**
Mortality (pupae)	n.r	n.r	n.r	n.r	n.r
Mortality at 22 days (adult)	-	**NOEC**	**NOEC**	LOEC	ECx

n.r: not reported

Patnaude M.R., 2011

Endpoint		**Dose (µg/g diet)**					
	Control	0.33	(0.36)*	0.68	1.5	4.4	15
Mortality at 7 days (larvae)	-	**NOEC**	**(NOEC)**	**NOEC**	**NOEC**	**NOEC**	LOEC
Mortality (pupae)	-	**NOEC**	**(NOEC)**	**NOEC**	LOEC	ECx	ECx
Mortality at 21 days (adults)	-	**NOEC**	**EC_{10}**	LOEC	ECx	ECx	ECx

* Dose calculated (EC10 for mortality at 21 days)

Representative formulation A9584C

Organism	Test type	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)	Key observation as reported in EFSA Conclusion 2015
A9584C						
Apis mellifera	Acute oral	LD_{50} = 0.0178 µg formulation/bee	--	No change	Muniz, 2011 [d] A9584C_10190	LD50 = 0.0178 µg formulation/bee (= 0.00445 µg a.s./bee) Agreed endpoint in EFSA bee review 2015; **No change**
	Acute contact	LD_{50} = 0.093 µg formulation/bee	--	No change	Muniz, 2011 [d] A9584C_10189	LD50 = 0.093 µg formulation/bee (= 0.02325 µg a.s./bee) Agreed endpoint in EFSA bee review 2015; **No change**

[d] Art. 21, Thiamethoxam EFSA bee review 2015

Representative formulation A9765R

Organism	Test type	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)	Key observation as reported in EFSA Conclusion 2015
A9765R						
Apis mellifera	Acute oral	--	LD_{50} = 0.0179 µg formulation/bee	Data requirement	Schmitt, 2014 [e] A9765R _10083	New study not reviewed during EFSA 2015
	Acute contact	--	LD_{50} = 0.0514 µg formulation/bee			New study not reviewed during EFSA 2015

[e] Study has been performed since EU registration; Study summary provided in M-CP Section 10.3.1

Additionally, toxicity data on honeybees with another seed treatment formulation that was included in a DAR addendum is used to support the risk assessment for A9765R; therefore this study and a summary of the results are listed below.

Other formulations

Organism	Test type	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)	Key observation as reported in EFSA Conclusion 2015
A9700B treated maize seed dust *(and A9584C)*						
Honeybee	Acute oral toxicity to treated maize seed dust *and A9584C (spray)*	A9700B treated maize seed dust: 48 hr oral LD_{50} = 0.00936 µg a.s./bee *A9584C: 48 hr oral LD_{50} = 0.00631 µg a.s./bee*	--	No change	Kling, 2009 [a] A9700B_10904	Results from this study were not reported in EFSA 2015 conclusion. However study assessed and the assessments available in Addendum B9: Ecotoxicology, March 2012 48 hr LD50 = 0.00936 µg a.s./bee
	Acute contact toxicity to treated maize seed dust **(**Contact on cherry leaves sprinkled with dust) *and A9584C (spray)*	A9700B treated maize seed dust: 48 hr LD_{50} = 13.26 g a.s./ha *A9584C: 48 hr contact LD50 = 5.55 g a.s./ha*	--	No change		Results from this study were not reported in EFSA 2015 conclusion. However study assessed and the assessments available in Addendum B9: Ecotoxicology, March 2012 48 hr LD50 = 13.26 g a.s./ha

[a] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, March 2012

Higher tier: semi-field studies

Conducted with A9584C in *Phacelia*, *peach* and melons to further assess the risk to bees. The table in volume 3 CP B.9 present the results of all the semi-field bee studies.

RMS comment: RMS would like to note that these studies had already been reassessed and the assessments published in EFSA (2015)[14] for all studies reported below (except Bocksch, 2010 b, c A9700B_10908 that was reassessed and published in EFSA (2013)[15].

The conclusion concerning these higher tier studies, as reported in EFSA (2015), was the following:

"*The available higher tier effects studies from the dossiers and/or made available by Member States have been evaluated according to the criteria given in EFSA, 2013b. A full evaluation of each study was reported in the study evaluation notes; EFSA, 2015a. A brief summary of the observations is given in Appendix B (Tables 17 and 19). The fundamental basis for higher tier risk assessment according to EFSA, 2013b is to design higher tier effect studies which are able to address the specific protection goals (SPG) for worst case exposure (90th percentile worst case for the hives at the edge of the treated fields in the area of use) and to ensure that the studies are sufficiently sensitive in order to detect biological effects (i.e. cause effect relationship) to meet the*

[14] EFSA (European Food Safety Authority), 2015. Conclusion on the peer review of the pesticide risk assessment for bees for the active substance thiamethoxam considering all uses other than seed treatments and granules. EFSA Journal 2015;13(8):4212, 70 pp. doi:10.2903/j.efsa.2015.4212

[15] Conclusion on the peer review of the pesticide risk assessment for bees for the active substance thiamethoxam EFSA Journal 2013;11(1):3067

SPG for the level of effect (7% reduction in colony). In order to demonstrate that the studies have achieved the 90th percentile exposure, EFSA, 2013b suggests that an exposure assessment is undertaken by performing residue studies in areas representative of where the active substance will be applied. The level of exposure achieved in the effect field study can then be demonstrated to be representative across a wider area (i.e. if it equates to the 90th percentile exposure level). As discussed in Section 3.2, insufficient residue data were available to perform an exposure assessment (hence a tier 2 risk assessment) for any of the authorised uses of thiamethoxam. An alternative approach would be to have a sufficient number of suitable higher tier effects studies, which are also considered to be able to address the exposure SPG. The number of studies required would depend on numerous factors, such as the representative GAP, the area where the active substance will be applied, the quality of the exposure assessment within the studies and the consistency of results. However, the available higher tier effects studies for thiamethoxam were not suitable to be able to assess whether they met the exposure SPG. The second critical aspect of the usefulness of higher tier effects studies for a risk assessment in accordance with EFSA, 2013b is to ensure that the studies are sufficiently sensitive in order to detect biological effects to meet the SPG for the level of effect (7% reduction in colony strength). Several criteria are given in the guidance document, which are essential for such an assessment (e.g. an assessment of the power of detection). EFSA, 2013b also recommended several improvements to the methodology used for higher tier effects studies, e.g. to increase the size of field, to increase the distance between the test fields and the control, to include overwintering success or improvements to the measurements of mortality and colony strength. None of the available studies fulfilled the criteria of EFSA, 2013b. It is acknowledged that the studies were performed prior to the publication of EFSA, 2013b. In evaluating these studies, any deficiency in the study design, beyond those identified on the basis of the new elements introduced by EFSA, 2013b, was also highlighted. Several studies had severe limitations which question their reliability for any form of risk assessment (e.g. lack of untreated control). On the basis of the available data set, as general observation, differences between the treatment and the controls for foraging activity and forager mortality were noted at the tested application rates, crops and growth stages (including when applications were made a number of days before flowering). For higher tier risk assessment, a further consideration of the data included in the systematic literature review can be performed in the future."

RMS conclusion:

It should be noted that the question concerning the reliability of semi-field and field studies in risk assessment reported in EFSA 2015 conclusion was in relation with the requirement of EFSA, 2013b guidance document on bees while the studies were performed before the publication of the guidance document. Moreover, even if there are some limitations in the semi-field and field studies against the requirement of EFSA, 2013b, RMS considers that these studies (at least those studies without severe limitation) provided relevant information for intended uses, and they could be used in an overall risk assessment by considering them together.

The summary of observations as reported in EFSA (2015) or EFSA (2013) is reported in the last column of the table:

Table 2.9.3-2: Semi-field and field honeybee studies conducted with A9584C

Treated crop	Summary of design	Application rate (g a.s./ha)	Summary of Results	Reference (author, date, Syngenta File No.)	Key observation as reported in EFSA Conclusion 2015
Phacelia (semi-field)	Applications to *Phacelia* in full flower whilst bees were foraging	1	No effects on bee mortality were noted. No effects of A9584C were observed on the strength of the colonies, the egg laying rate of the queen and the bee brood development.	Nengel, 1998 [a] CGA293343/0597	At 1 g a.s/ha (during bee flight and after bee flight): Decrease in foraging activity. Remark as reported in EFSA (2015): Study does not meet the requirements of EFSA 2013b.
	Applications to *Phacelia* in full flower whilst bees were foraging	5	Led to a slight increase in mortality immediately after treatment. However, this was only a relatively small increase over a short period. Overall the mean post-application mortality was not increased compared to control or to the pre-application period. No effects of A9584C were observed on the strength of the colonies, the egg laying rate of the queen and the bee brood development.		At 5 g a.s/ha (during bee flight and after bee flight): Decrease in foraging activity. Increase in forager mortality (Note issued from study evaluation note: *The increase in mortality was only obvious on the day of application as indicated in previous study evaluation note*). Remark as reported in EFSA (2015): Study does not meet the requirements of EFSA 2013b.
Melon *(semi-field)*	Application to honey-dew melon before the beginning of flowering (BBCH 61-64), with exposure of the bees beginning either 5 or 10 days after treatment when the crop was in full flower (BBCH 66)	100	Applied 10 days before start of full flowering: Overall mortality was not increased when compared with the control. Flight intensity was statistically significantly lower on DAE+4 and DAE+6 only. Colonies recovered and two of the colonies regained all brood stages by the final assessment. Applied 5 days before start of full flowering: Effects on mortality over 7 days after start of exposure. No reduction of flight intensity was observed. Colony strength decreased only slightly. No abnormal bee behaviour was recorded in any of the treated replicates throughout the course of the trial.	Bocksch, 2011 [d] A9584C_10176	Bees introduced after 5 days of aging: Increased forager mortality (statistically significant), no statistically significant difference in flight intensity. Bees introduced after 10 days of aging: Increased forager mortality (statistically significant), Decrease in flight intensity (statistically significant). Remark as reported in EFSA (2015): Study does not meet the requirements of EFSA 2013b.

[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2
[d] Art. 21, Thiamethoxam EFSA bee review 2015

Higher tier field trials

Conducted in a variety of crops to assess the risk to bees. The table in volume 3 CP B.9 presents a summary of the results of all higher tier field bee studies.

RMS comment: RMS would like to note that these studies had already been reassessed and the assessments published in EFSA (2015)[16] for all studies reported below. It should be noted that the question concerning the reliability of semi-field and field studies in risk assessment reported in EFSA 2015 conclusion was in relation with the requirement of EFSA, 2013b guidance document on bees while the studies were performed before the publication of the guidance document. Moreover, even if there are some limitations in the semi-field and field studies against the requirement of EFSA, 2013b, RMS considers that these studies (at least those studies without severe limitation) provided relevant information for intended uses, and they could be used in an overall risk assessment by considering them together. The summary of observations as reported in EFSA (2015) or EFSA (2013) is reported in the last column of the table:

Table 2.9.3-3: Field honeybee studies conducted with A9584C

Treated crop	Summary of design	Application rate (g a.s./ha)	Summary of Results	Comment	Reference (author, date, Syngenta File No.)	Key observation as reported in EFSA Conclusion 2015
Honeybee (*Apis mellifera*)						
Pear *(field)*	Pre-flowering application; No flowering groundcover.	95	No effects on adult bee mortality from treatments 11, 8 and 5 days before flowering. Effects on adult bee mortality from treatments 3 and 1 days before flowering. Reduced colony strength from treatment 1 day before flowering.	No change	Britt, 2005 [b] CGA293343/2577	Study reassessed and the assessments available in Study evaluation notes prepared by EFSA in the context of the risk assessment for bees for thiamethoxam (see summary in volume 3 CA). However, results from this study were not reported in EFSA 2015 conclusion.
Peach (field)	Pre-flowering application; Exposure of bees beginning either 16 days (T1) or 7 days (T2) after treatment.	62.5	Applied 16 days before the start of flowering: No effects on mortality. Flight intensity was lower than control throughout the study, but was probably caused by environmental factors. Applied 7 days before the start of flowering: Slight increase in the bee mortality on DAE+2 and DAE+3 only. Flight intensity similar to control. No effects on colony strength and brood development were observed. No abnormal behaviour could be seen.	No change	Bocksch, 2011 [b] A9584C_10173	Peach (just before flowering) **Bees introduced 16 days after application: Slight increase in forager mortality. Decrease in foraging activity.** Peach (just before flowering) **Bees introduced 7 days after application: Increase in forager mortality. Decrease in foraging activity.** **Remark as reported in EFSA (2015): Study does not meet the requirements of EFSA 2013b.**

[16] EFSA (European Food Safety Authority), 2015. Conclusion on the peer review of the pesticide risk assessment for bees for the active substance thiamethoxam considering all uses other than seed treatments and granules. EFSA Journal 2015;13(8):4212, 70 pp. doi:10.2903/j.efsa.2015.4212

[b] Art. 21, Thiamethoxam EFSA bee review 2015

Table 2.9.3-4: Field honey bee guttation studies conducted with A9765R in sugar beet

Treated crop	Summary of design	Treatment rate (g a.s./ha)	Effects observed	Reference (author, date, Syngenta File No.)
Sugar beet	Guttation trial in South Germany	58.5	Limited levels of guttation occurred in the sugar beet treated and control fields and no honeybees were observed taking up guttation liquid during the entire observation period. Residues of thiamethoxam and CGA322704 were detected in plant (test item treatment group only) and guttation fluid samples taken on various sample dates during the study. No residues of thiamethoxam or CGA322704 were detected in pollen, nectar or wax samples taken during the study. No test item related effects occurred on mortality, foraging behaviour, colony strength and brood development thus far.	Dittbrenner, 2016 A9765R_10119
Sugar beet	Guttation trial in Celle, Germany	58.5		Gonsior, 2016 A9765R_10120
Sugar beet	Guttation trial in France	58.5		Gonsior, 2016a A9765R_10121

Table 2.9.3-5: Summary of colony feeding studies for bees for thiamethoxam

Organism	Test type	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Thiamethoxam					
Apis mellifera	Colony feeding	--	NOEC = 25 µg a.s./L (uncertainty remains concerning the overwintering success) [b]	New data available	Bocksch, 2015 [a] CGA293343_52922
		--	Endpoint not set yet [c]	New data available	Interim report: Bocksch, 2017 [a] CGA293343_53502

NOAEC = No Observed Adverse Effect Concentration

[a] Study has been performed since EU registration; Study summary provided in volume 3 CA B.9

[b] However, an uncertainty remains concerning the overwintering success (see study summary)

[c] It can be noted that at 25 µg a.s./L the treated hives (Bocksch, 2017) had stored slightly less and lost slightly more food stores compared to the control. A slight dose response trend was evident in hive weights whereas no dose response trend was evident in hive weights in previous study (Bocksch, S, 2015). A further colony condition assessment has been performed for (Bocksch, 2017) from 03 - 07Apr 2017 (CCA9), but results will be presented in the final report. These data would bring more information when final report will be available. Waiting for the submission of the final report, endpoint is not set yet (see study summary)

Table 2.9.3-6: Summary of toxicity data for to non-target arthropods other than bees

Formulation A9584C

Table 2.9.3-6-1: Summary of laboratory endpoints for non-target arthropods for A9584C

Organism	Test type	Current endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Tier I					
Typhlodromus pyri	Laboratory	200 g a.s./ha = 100% mortality	LR_{50} < 200 g a.s./ha	Agreed EU endpoint (SANCO/10390/2002 – rev. final 2006); Endpoint expressed in term of active substance to reflect how endpoints are used in risk assessment	Kleiner, 1998c [a] CGA293343/0840
Aphidius rhopalosiphi		200 g a.s./ha = 100% mortality	LR_{50} < 200 g a.s./ha		Kleiner, 1998b [a] CGA293343/0839
Orius laevigatus		200 g a.s./ha = 100% mortality	LR_{50} < 200 g a.s./ha		Kleiner, 1998d [a] CGA293343/0866
Poecilus cupreus		200 g a.s./ha = 100% mortality	LR_{50} < 200 g a.s./ha		Kleiner, 1998a [a] CGA293343/0841
Tier II					
Typhlodromus pyri	Extended laboratory, 2-D	LR_{50} = 162.8 g formulation/ha $NOEC_{reproduction}$ = 25 g formulation/ha (initial DAR, volume 3.B.9)	LR50 = 40.7 g a.s./ha ER50 reproduction > 6.25 g a.s./ha	Agreed EU endpoint (initial DAR, volume 3.B.9); Endpoint in term of active substance to reflect how endpoints used in risk assessment	Grimm, 2000b [a] CGA293343/1230
Aphidius rhopalosiphi	Extended laboratory, 2-D	LR_{50} = 0.52 g formulation/ha $NOEC_{reproduction}$ = 0.25 g formulation/ha (0.0625 g a.s./ha) (initial DAR,	LR_{50} = 0.13 g a.s./ha $ER_{50\ reproduction}$ > 0.0625 g a.s./ha		Grimm, 2000 [a] CGA293343/1244

Organism	Test type	Current endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
		volume 3.B.9)			
Orius laevigatus	Extended laboratory, 2-D	LR50 = 0.0141 g a.s./ha NOECreproduction = 0.05 g a.s./ha (initial DAR, volume 3.B.9)	LR50 = 0.0141 g a.s./ha ER50 reproduction > 0.05 g a.s./ha		Schuld, 2000 [a] CGA293343/1268
Pardosa spec.	Extended laboratory, 2-D [c] (soil)	200 g a.s./ha = 0% mortality (initial DAR, volume 3.B.9)	LR50 > 200 g a.s./ha ER50 (prey consumption) > 200 g a.s./ha		Brown, 2000 [a] CGA293343/1164
Coccinella septempunctata	Extended laboratory, 2-D	LR50 = 12.38 g a.s./ha NOECreproduction = 25 g a.s./ha (initial DAR, volume 3.B.9)	LR50 = 12.38 g a.s./ha ER50 reproduction > 25 g a.s./ha		Kemmeter, 2000 [a] CGA293343/1267
Leptomastix dactylopii	Extended laboratory, 2-D	200 g a.s./ha = 17% mortality 400 g a.s./ha = 36% mortality	LR50 = 0.47g a.s./ha (initial DAR, volume 3.B.9)	Existing EU endpoint is incorrect [d]	Eyre, 2000 [a] CGA293343/1227
Chrysoperla carnea	Extended laboratory, 3-D	--	LR50 = 20.6 g formulation/ha (5.139 g a.s./ha) ER50 reprodcution > 25 g formulation/ha (6.25 g a.s./ha)	New study, Supportive of the risk assessment	Vinall, 2007 [b] CGA293343/3388
Non-GLP					
Various parasitic wasps, predatory mites, soil-dwelling predators, leaf-dwelling predators	IPM test	Initial impacts but no long-term effects at up to 100 g a.s./ha	--	(initial DAR, volume 3.B.9) No change	Storck-Weyhermüller, 1999 [a] CGA293343/0946

[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2
[b] Study has been performed since EU registration; Study summary provided in volume 3 CP B.9.
[c] Study was incorrectly identified as Tier I in EU endpoint list
[d] The mortality results included in the endpoint list are only a portion of the mortality results presented in the study report. The reported mortalities are also incorrect. These % mortalities were recorded for 0.2 and 0.4 g a.s./ha, not 200 and 400 g a.s./ha, as indicated in the endpoint list. The report calculated the LR_{50} value, which should be used in the risk assessment.

Higher tier testing has been conducted to support the risk assessment for thiamethoxam. A summary of the available studies is included in the tables below.

Table 2.9.3-6-2: Summary of aged-residue studies for non-target arthropods for A9584C

Organism	Test type	Exposure	Summary of results	Comment	Reference (author, date, Syngenta File No.)
Aleochara bilineata	Semi-field	2 x 4 g a.s./ha (7 day interval)	<50% effects on reproduction at 0, 14, 28 and 42 DAT. **No statistically significant effects (13.3% effects on reproduction at 0 DAT, and <10% at 14, 28 and 42 DAT)**	EU endpoint (initial DAR, volume 3.B.9); No change	Kühner, 1999 [a] CGA293343/0895
		2 x 100 g a.s./ha (7 day interval)	>50% effects on reproduction at 0 and 14 DAT. <50% effects on reproduction at 28 and 42 DAT.		
Poecilus cupreus	Semi-field	2 x 4 g a.s./ha (7 day interval)	<50% effects on mortality and feeding rate at 0, 14, 31 and 45 DAT. **No statistically significant effects on mortality and feeding rate (<10% at 0, 14, 28 and 42 DAT.)**	EU endpoint (initial DAR, volume 3.B.9); No change	Kühner, 1998a [a] CGA293343/0879
		2 x 100 g a.s./ha (7 day interval)	>50% effect on mortality after exposure to 2 x 100 g a.s./ha <50% effect on mortality 14 to 45 DAT. <50% effects on feeding rate at 0, 14, 31 and 45 DAT.		
		2 x 2.38 g a.s./ha (7 day interval)	<50% effects on mortality and reproduction when exposed 3, 7, 14, 28, 49 and 92 DAT.	New study, Supportive of the risk assessment Only results for groups 14 and 28 days after	

Orius laevigatus	Glasshouse	2 x 100 g a.s./ha (7 day interval)	Mortality effects >50% at 3, 7, 14, 28, 49 and 92 DAT. Reproduction effects >50% at 14 and 92 DAT but greater than control at 49 DAT. Note: Treat results with caution due to low numbers of females and low egg hatch.	treatment are reliable (see study summary for more details) and reported below: Statistically significant effects on mortality compared to the control group were observed in the drift rate treatment group and in the field rate treatment group 28 days after the last treatment. Statistically significant differences between the number of hatched nymphs of the field rate treatment group compared to the control were observed 14 days after the last treatment (no assessment 28 days after treatment due to high mortality). No statistically significant differences between the	Schuld, 2002 [b] CGA293343/1559

				number of hatched nymphs of the drift rate treatment group compared to the control were observed 14 and 28 days after the last treatment. However, 22.8% effect 28 days after the last treatment is considered biologically relevant.	
Macrolophus caliginosus	Glasshouse	2 x 2.38 g a.s./ha (7 day interval)	Mortality effects <50% at 3, 8, 14 and 28 DAT. Reproduction effects >50% immediately after 2nd application but ≤50% from 8 days after 2nd application.	New study, Supportive of the risk assessment Only results on mortality for groups 3 and 8 days after treatment are reliable (see study summary for more details) and reported below: At 2.38 g a.s./ha, 20.5 and 18.8 % mortality was observed after 3 and 8 days of treatment, respectively. At 100.0 g a.s./ha, 100.0, 98.7% mortality was observed after 3, 8 days of treatment, respectively.	Schuld, 2002a [b] CGA293343/1566
		2 x 100 g a.s./ha (7 day interval)	Mortality effects >50% at 3, 8, 14 and 28 DAT. Effects <50% at 49 and 91 DAT. Reproduction effect >50% at 49 DAT but greater than control at 92 DAT.		

DAT = Days After Treatment
[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2
[b] Study not submitted during the original EU registration; Study summary provided in volume 3 CP B.9

Table 2.9.3-6-3: Summary of semi-field studies for non-target arthropods for A9584C

Organism	Exposure	Summary of results	Comment	Reference (author, date, Syngenta File No.)
Aphidius rhopalosiphi	1 x 12.5 g a.s./ha	Initally, >50% effect on reproduction. However, 8 DAT <50% effect on reproduction.	EU endpoint (initial DAR, volume 3.B.9); No change	Engelhard, 1997 [a] CGA293343/0385
	2 x 12.5 g a.s./ha (14 day interval)	<50% (42.1) effect on reproduction at 0 days after the 2nd application but >50% (57.1) effect on reproduction at 7 days after the 2nd application		
	1 x 100 g a.s./ha	>50% effect on reproduction at 0 and 8 DAT.		
	2 x 100 g a.s./ha (14 day interval)	>50% effect on reproduction at 0 and 7 days after the 2nd application.		
Orius laevigatus	2 x 200 g a.s./ha (14 day interval)	Trial I: 100% juvenile mortality immedietly after 2 applications. Trial II: 90% adult female mortality when introduced 2 days after 1st application; 100% mortality 13 days after exposure Trial III: 94% nymph mortality when introduced 3 days after 2nd application.	EU endpoint (initial DAR, volume 3.B.9); No change	Alferhof, 1997 [a] CGA293343/0331
Poecilus cupreus	2 x 12.5 g a.s./ha (13 day interval)	<50% effects on mortality and food consumption after 1st and 2nd applications.	EU endpoint (initial DAR, volume 3.B.9); No change	Moll, 1997 [a] CGA293343/0372
	2 x 100 g a.s./ha (13 day interval)	<50% effects on mortality and food consumption after 1st application. >50% effect on mortality and <50% effect on food consumption after 2nd application.		

	2 x 50 g a.s./ha (7 day interval)	<50% effect on mortality and food consumption.	EU endpoint (initial DAR, volume 3.B.9); No change	Balluf, 2000 [a] CGA293343/1295
Aleochara bilineata	2 x 50 g a.s./ha (7 day interval)	>50% effect on reproduction after 2nd application. <50% effect on reproduction 21 and 42 days after 2nd application.	EU endpoint (initial DAR, volume 3.B.9); No change	Balluf, 2000 [a] CGA293343/1295

DAT = Days After Treatment

[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2

Table 2.9.3-6-4: Summary of field studies for non-target arthropods for A9584C

Organism	Treated crop	Exposure	Summary of results	Comment	Reference (author, date, Syngenta File No.)
Typhlodromus pyri	Vineyard	2 x 100 g a.s./ha (28 d interval)	Results reported as additional information and could only be used for the risk assessment in combination with other studies to provide supporting evidence. Pronounced short term effect after 1st and 2nd application of 100 g a.s./ha with recovery within 2 months after the first application.	EU endpoint (initial DAR, volume 3.B.9); Support of the risk assessment	Reber, 1998 [a] CGA293343/0874
		2 x 4 g a.s./ha (7 d interval)	**Field study**: 4 g a.s/ha and 100 g a.s./ha		

Full fauna	Pear orchard	2 x 100 g a.s./ha (7 d interval)	Results reported as additional information and could only be used for the risk assessment in combination with other studies to provide supporting evidence. Data analyses and results were presented for 13 abundant taxa. For most of the taxa presented, i.e. pooled predatory Heteroptera, Pilophoris perplexus (Miridae, Heteroptera) pooled Araneae, Salticidae (Araneae), Chalcidoidea (Hymenoptera), Forficula auricularia (Dermaptera) it can be observed graphically that recovery occurred before the end of the 3-month sampling period. However, populations of predatory Episyrphus balteatus (Syrphidae, Diptera) and Heterotoma planicornis (Miridae, Heteroptera) and phytophagous Bryobia rubrioculus (Tetranychidae, Acari) disappeared from the field before numbers in test item treatments had reached levels similar to the control. No reliable NOAER population and NOAER community can be derived **Bioassay**: 4 g a.s/ha and 100 g a.s./ha Orius laevigatus: <50% effect on mortality within 6 weeks after 2nd application	EU endpoint (initial DAR, volume 3.B.9); Support of the risk assessment	Brown, 1999 [a] CGA293343/1160

			Aphidius colemani: <50% effect on mortality within 8 weeks after 2nd application.		
Full fauna	Citrus orchard	12.75 g a.s./ha (DV) 12.75 g a.s./ha (DC) 150 g a.s./ha (FR)	Results reported as additional information and could only be used for the risk assessment in combination with other studies to provide supporting evidence. A total of 74 taxa were sufficiently abundant for effect classification During the season, sixteen taxa (22%) were considered adversely affected by the FR treatment (144 g a.s/ha) and 7-8 (9-11%) by the DV (12.75 g a.s./ha) and DC treatment (12.75 g a.s./ha). The majority of arthropod populations recovered within the 5 month sampling period. The only taxa for which no full recovery was seen before the end of the 5-month period were hymenopteran Cales (Aphelinidae or Mymaridae) (FR and DV) and Apterencyrtus (Encyrtidae) (FR). By the end of the sampling period, those 2 taxa had not yet recovered to levels similar to the control but recovery was clearly in progress and it can reasonably be expected that recovery will occur. No NOER population nor NOER community can be set. NOAER population and NOAER community of 150 g a.s./ha can be set.	New study, Support of the risk assessment	Grimm, 2003 [b] CGA293343/1796
		Natural drift at 3 (equivalent to 0.69 g a.s./ha), 7 (equivalent to 0.12 g a.s./ha), 11 and 15m downwind of treated area 15.7 g a.s./ha	Results reported as additional information and could only be used for the risk assessment in combination with other studies to provide supporting evidence. No recovery samples. 18 of the 45 observed taxa showed a statistically significant treatment		

Full fauna	Apple orchard	100 g a.s./ha	effect in the maximum rate treatment (100 g a.s./ha) compared to the control and 11 taxa showed a statistically significant treatment effect in the artificial drift treatment (15.7 g a.s./ha), whereas 4 taxa were statistically significantly affected by the test item in the first natural drift row (3m). No statistically significant treatment effect in the natural drift rows beyond the first row were observed (7 m, equivalent to 0.12 g a.s./ha). The main insect groups affected by the test item were beetle larvae (Coleoptera larvae), adults and nymphs of plants bugs (Miridae), nymphs of other bugs (Heteroptera other nymphs), cicada	New study, Support of the risk assessment	Grimm, 2003a [b] CGA293343/1795

			(Auchenorrhyncha nymphs), aphids (Aphidina), flies of Nematocera and fly larvae (Diptera larvae). The treatment had no statistically significant direct effect on the non-insect community, consisting chiefly of mites, in any of the treatments.		
Full fauna	Apple orchard	Natural drift downwind of treated area (4 rows) 16.2 g a.s./ha (DC) 100 g a.s./ha (MR)	Results are reported as additional information and could only be used for the risk assessment in combination with other studies to provide supporting evidence. No recovery sample Because of the contamination of one sample of water control, results from this study, particularly on natural drift values around 0.63% (Natural Drift 2: 0.98%, Natural Drift 3: 0.56% and Natural Drift 4: 0.53%) are considered not reliable, and results from this study for other values relatively higher than 0.63% (Natural Drift 1: 2.4%; DC: 16.2% and MR: 100%) have to be taken with caution. 15 taxa showed a statistically significant treatment effect in the maximum rate treatment (100 g a.s.a/ha) compared to the control and 7 taxa showed a statistically significant treatment effect in the artificial drift treatment (16.2 g a.s./ha), whereas 3 taxa were statistically significantly affected by the test item in the natural drift rows (equivalent to 0.53 to 2.4 g a.s.s/ha). The main insect groups affected by the test item were plant bugs (Miridae), leaf hoppers (Cicadellidae), Neuroptera, bark lice (Psocoptera) and thrips (Thysanoptera). Although in most of these group treatment effect seen in maximum rate and drift concentration regime only, the bark lice (Psocoptera), the plant bugs (Miridae) and leaf hoppers (Cicadellidae) showed a continuing effect in the first natural drift row (2.4% of maximum application rate), and beyond the first row for bark lice (Psocoptera). The treatment had no statistically significant direct effect on the non-insect community, consisting chiefly of mites, in any of the treatments.	New study, Support of the risk assessment	Grimm, 2003b [b] CGA293343/1794

Full fauna	Grassland (off-crop surrogate)	0.057, 0.32, 0.57, 1.0 and 3.6 g a.s./ha	In community analyses a total of 282 taxa were included In total 66 taxa were sufficiently abundant for analyses at the population level.	New study, Support of the risk assessment	Bakker and Aldershof, 2014 [b] A9584C_10924

			NOER population = 0.057 g as/ha (covering NOER community)		

DAT = Days After Treatment
[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2
[b] Study was not included in the original EU registration; Study summary provided in volume 3 CP B.9

Formulation A9765R

Table 2.9.3-6-5: Summary of extended laboratory endpoints for non-target arthropods for A9765R

Organism	Test type	Current endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Tier II					
Typhlodromus pyri	Extended laboratory, 2-D	--	LR_{50} = 27.4 mL formulation/ha (equivalent to 16.9 g a.s./ha) ER_{50} > 27 mL formulation/ha (equivalent to 16.9 g a.s./ha)	New study, Data requirement	Fallowfield, 2014 [a, b] A9765R_10068
Aphidius rhopalosiphi	Extended laboratory, 2-D	--	LR_{50} = 0.028 mL formulation/ha (equivalent to 0.017 g a.s./ha) ER_{50} > 0.025 mL formulation/ha (equivalent to 0.015 g a.s./ha)	New study, Data requirement	Stevens, 2014 [a, c] A9765R_10061
Poecilus cupreus	Extended laboratory 3-D	--	LR_{50} > 1.03 mg formulation/kg* (equivalent to >0.62 mg a.s./kg) $ER_{50\ feeding\ activity}$ > 1.03 mg formulation/kg* (equivalent to >0.62 mg a.s./kg)	New study, Data requirement	Vaughan, 2014 [a, b] A9765R_10074
Aleochara bilineata	Extended laboratory 3-D	--	LR50 > 1 mg formulation/kg (equivalent to 0.60 mg a.s./kg); ER50 > 1 mg formulation/kg (equivalent to 0.60 mg a.s./kg)	New study, Data requirement	Tew, 2014 [a, b] A9765R_10075

[a] Study has been performed since EU registration
[b] Study summary provided in volume 3 CP B.9
[c] Study summary provided in volume 3 CP B.9
*highest tested concentration

New higher tier field studies have been conducted with other thiamethoxam solo formulations that are not the representative seed treatment formulation. However, as they are used to support the risk assessment, they are included here. The study summaries are provided in volume 3 CP B.9.

Table 2.9.3-6-5: Summary of new higher tier studies to support A9765R risk assessment

Test substance	Organism	Exposure	Summary of results	General Comment	RMS comment on results	Reference (author, date, Syngenta File No.)
Field						
A9700B	Surface and ground dwelling beetles	Treated pea seed at 30, 68 and 108 g a.s./ha	The majority of carabid populations and some staphylinid populations were unharmed by the treatments, or recovered within the next season. At the community level, moderate adverse responses observed in all three test item rates were statistically significant in spring and early summer. Recurrent adverse responses 1 year after treatment were statistically detectable in the highest test item rate only. No community effects were seen at rates 68 or 30 g a.s./ha, 1 year after treatment. $NOEAER_{Community}$ = 68 g a.s./ha	Lowest application rate (30 g a.s./ha) lower than intended uses (58.5 g a.s./ha) Two highest application rate (68 and 108 g a.s./ha) higher than intended uses (58.5 g a.s./ha) Support of the risk assessment in-field	Based on Effect classification according to De Jong et al, 2010 for the taxon "other staphilinidae" (class 8, at all application rates: No recovery more than 1 year (15 months) after sowing), recovery is not shown for "other Staphylinidae" indicating that no NOAER population can be derived. It is reported that effects at community level the next spring summer are only significant at 108 g a.s/ha. However, the difference in the sample the next spring and/or summer is marginal between all tested concentrations, and a clear tendancy and dose related recurrent effects next spring and/or summer are observed at all tested concentrations. (see study summary for more details)	Bakker and Aldershof, 2014 [a] A9700B_11439
A9700B / A9638A	Full fauna	Dust from treated maize seeds at 0.087, 0.435 and 0.870 g a.s./ha in alfalfa (off-crop surrogate)	There was no statistically significant impact of thiamethoxam on the overall ground and plant living arthropod communities at all treatment rates. There was a single transitory population reduction at the highest rate tested 7 days after treatment in one taxon only, which was considered dose-related; however populations recovered to control levels by the following sampling period (17 days after treatment). $NOEAER_{Community}$ =	Support of the risk assessment off field	No NOER population nor NOER community can be set from this study. The only endpoint that can be set from this study is a NOAER population and NOAER community of 0.87 g a.s./ha. (see study summary for more details)	Knäbe, 2012 [a] A9700B_10954

Test substance	Organism	Exposure	Summary of results	General Comment	RMS comment on results	Reference (author, date, Syngenta File No.)
			0.870 g a.s./ha			

[a] Study has been performed since EU registration, a study summary is provided in volume 3 CP B.9

The formulation A9567B (Cruiser 70 WS) is no longer supported as a representative formulation. However, the non-target arthropod studies included in the Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2 are referred to in the risk assessment for the new seed treatment representative formulation A9765R, therefore the studies are listed below. Additionally, higher tier toxicity data on non-target arthropods with other seed treatment formulations that were included in DAR addenda are also used to support the risk assessment for A9765R; therefore the studies are listed below.

Table 2.9.3-6-6: Summary of previously submitted studies with other seed treatment formulations

Test substance	Test type	Organism	Current endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Laboratory Tier II						
A9567B	Treated cotton seed in sand	*Poecilus cupreus*	210 g a.s./100 kg seeds = 66.7% mortality	LR_{50} < 210 g a.s./100 kg seeds	Endpoint transformed to reflect how endpoints used in risk assessment	Reber, 1997a [a] CGA293343/0181
		Aleochara bilineata	210 g a.s./100 kg seeds = 90% mortality	LR_{50} < 210 g a.s./100 kg seeds		Candolfi, 1997 [a] CGA293343/0164
Semi-field						
A9567B	Treated wheat seed	*Poecilus cupreus*	70 g a.s./100 kg seeds = 19% mortality = 0% feeding effect	70 g a.s./100 kg seeds: < 50% effect on mortality and feeding	Endpoint transformed to reflect how endpoints used in risk assessment	Candolfi, 1998 [a] CGA293343/0797
		Aleochara bilineata	70 g a.s./100 kg seeds = 66% reduction in reproduction[b]	70 g a.s./100 kg seeds: >50% effect on reproduction		Candolfi, 1998 [a] CGA293343/0842

[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2
[b] 27 days exposure under field conditions, followed by 35 day reproductive phase under laboratory conditions

The laboratory studies summarized above were conducted with treated seeds at a single rate (210 g a.s./100 kg seed). The application rate supported in this dossier is approximately 1500 g a.s./100 kg seed.
Semi-field studies have also been conducted and are summarized above; however these were conducted at a much higher rate (70 g a.s./kg seed; 140 g a.s./ha) than the proposed application rate (approximately 15 g a.s./kg seed; 58.5 g a.s./ha).

Table 2.9.3-6-6: Summary of previously submitted field studies with other seed treatment formulations

Test substance	Organism	Exposure	Summary of results	RMS general comment on status of the study	RMS comment on results	Reference (author, date, Syngenta File No.)
Field						
A9567B	Full fauna	Treated barley seed 105 g a.s./ha	Initial effect on a range of soil surface active and ground dwelling arthropod taxa, followed by recovery to control levels by the end of the sampling period, 102 days after sowing (with the exception of springtails, recovery of which was under way). No effects on the diversity from 89 days after sowing.	Study listed in the Referents relied on in Addendum B9: Ecotoxicology, January 2004 but no summary available in Addendum B9 (2004). Application rate (105 g a.s./ha) higher than intended uses (58.5 g a.s./ha) The study has a reliability index score of 3, calculated according to the guidance document of the Dutch Platform for the Assessment of Higher Tier Studies (De Jong et al., 2010). Results are reported as additional information and could only be used for the risk assessment in combination with other studies to provide supporting evidence.	By the end of the sampling period, recovery of collembolan taxa (Entomobryoidea and Sminthuridae) was in progress but had not recovered to levels similar to the control. Effect classification at Community level for Pitfall traps (for which collembolan (non target) taxa had the largest influences) was 8 (No recovery within study period (3.3 months)). Based on these considerations, no NOAER population and NOAER community can be derived from this study. However, it can be noted that all identified Sminthuridae belonged to two species: *Sminthurus viridis* and *Bourletiella hortensis* that are known to be herbivorous and can become potential pests in a wide variety of crops. (see study summary for more details)	Grimm, 2001 [a] CGA293343/1378

A9996C [c]	Full fauna	Treated wheat seed 92 g a.s./ha	Significant effects on arthropod population and community dynamics. However, the main groups influencing the community response were target or potential	Study from Addendum B9: Ecotoxicology, January 2005 Application rate (92 g a.s./ha) higher than intended uses (58.5 g a.s./ha)	Effect classification at Community level for Pitfall traps, Photoeclectors and Sweepnet (for which target and non target taxa had influences) was 8 (No recovery within study period (4 months)). Based on these considerations, no	Grimm, 2002a [b] CGA169374/2238

Test substance	Organism	Exposure	Summary of results	RMS general comment on status of the study	RMS comment on results	Reference (author, date, Syngenta File No.)
			secondary pest species. Therefore, it is likely that effects on the abundances of some predatory non-target arthropod species were indirect effects, caused by relocation of these predators to areas with a higher abundance of prey items. There were no effects of the test substance on the number of taxa caught (diversity) from 44 days after sowing.	The study has a reliability index score of 3, calculated according to the guidance document of the Dutch Platform for the Assessment of Higher Tier Studies (De Jong et al., 2010). Results are reported as additional information and could only be used for the risk assessment in combination with other studies to provide supporting evidence.	NOAER population and NOAER community can be derived from this study. (see study summary for more details)	

A10590C [d]	Full fauna	Treated maize seed 105 g a.s./ha	Effects on a range of foliar dwelling and soil surface active and phototactic ground dwelling arthropod taxa. This trend was followed by recovery to control levels in most cases by the end of the sampling period (112 days after sowing). Community effects were largely influenced by the population dynamics of the Sminthuridae (Collembola). The majority of all other arthropods sampled adequately during the study showed recovery of trapped	Study from Addendum B9: Ecotoxicology, January 2005 Application rate (105 g a.s./ha) higher than intended uses (58.5 g a.s./ha) RMS comment: The study has a reliability index score of 3, calculated according to the guidance document of the Dutch Platform for the Assessment of Higher Tier Studies (De Jong et al., 2010). Results are reported as additional information and could only be	Effect classification at Community level for Photoeclectors and Sweepnet (for which target and non target taxa had influences) was 8 (No recovery within study period (4 months)). Based on these considerations, no NOAER population and NOAER community can be derived from this study. (see study summary for more details)	Grimm, 2002c [b] CGA173506/5477

Test substance	Organism	Exposure	Summary of results	RMS general comment on status of the study	RMS comment on results	Reference (author, date, Syngenta File No.)
			numbers by the end of the sampling period. Exceptions were a few taxa that decreased in all treatments, due to normal seasonal decline, to such low numbers that it was impossible to demonstrate recovery. There were no effects of the test substance on the number of taxa caught (diversity) by the end of the test period.	used for the risk assessment in combination with other studies to provide supporting evidence.		

A9807C [d]	Full fauna	Treated oilseed rape seed 34 g a.s./ha	Significant effects on several ground-dwelling arthropod taxa in the early samples. This was followed in most cases by recovery to population densities similar to those observed in the control plots. It was clear that only a small number of the arthropod taxa sampled were affected by the test item. Almost all affected taxa either showed that recovery occurred by the end of the sampling period, or that apparent effects were due to chance probabilities. The exceptions were the Collembola family Sminthuridae, where recovery could not be fully proven. Sminthuridae	Addendum B9: Ecotoxicology, January 2005 Application rate (34 g a.s./ha) lower than intended uses (58.5 g a.s./ha) The study has a reliability index score of 3, calculated according to the guidance document of the Dutch Platform for the Assessment of Higher Tier Studies (De Jong et al., 2010). Results are reported as additional information and could only be used for the risk assessment in combination with other studies to provide supporting evidence.	Effect classification according to De Jong et al, 2010 for collembolan (non target) taxa was 4 (Recovery <4 months after sowing) with a note indicating that for one or few taxa recovery could not be confirmed due to low numbers at end sampling period and that no recovery was suspected for one or few taxa. This is the case for Sminthuridae (collembolan) populations that were considerably and persistently reduced throughout the sampling period. At the end of the period numbers were declining in all treatments, impeding confirmation of recovery. However, all identified Sminthuridae belonged to two species: *Sminthurus viridis* and *Bourletiella*	Grimm, 2002b [b] CGA173506/5478

Test substance	Organism	Exposure	Summary of results	RMS general comment on status of the study	RMS comment on results	Reference (author, date, Syngenta File No.)
			were also the most influential taxa in pitfall trapped community effects. However, the Sminthuridae were considered likely to be secondary pest species feeding on the crop. There were no effects of the test substance on the number of taxa caught (diversity).		*hortensis*. Both species are known to be herbivorous and can become potential pests in a wide variety of crops. Effect classification at Community level for Pitfall traps (for which collembolan taxa had the largest influences) was 4 (Recovery <4 months after sowing).	

[a] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, January 2004.
[b] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, January 2005
[c] Formulation containing thiamethoxam, difenoconazole, fludioxonil, tefluthrin
[d] Formulation containing thiamethoxam, fludioxonil, metalaxyl M

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

Table 2.9.4-1: Earthworm toxicity endpoints for Thiamethoxam, metabolites and formulations used in risk assessment

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Acute	Thiamethoxam	*Eisenia fetida*	LC_{50} > 1000 mg a.s./kg	--	An acute endpoint is no longer a data requirement. Endpoint not used in risk assessment	Candolfi, 1995 [a,d] CGA293343/0023
	CGA322704		LC_{50} = 5.93 mg/kg	--		Porch et al., 2000 [a,d] CGA322704/0026
	CGA322704		LC_{50} = 13.21 mg/kg	-		Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005)
	CGA355190		LC_{50} = 753 mg/kg	-		Bryan et al., 1999 [a,d] CGA355190/0006
	NOA407475		LC_{50} > 1000 mg/kg	-		Bryan et al., 1999 [a,d] NOA407475/0013
	NOA459602		LC_{50} > 1000 mg/kg	--		Gillham, 2002 [b] NOA459602/0004
	A9584C		LC_{50} > 1000 mg formulation/kg	--		Candolfi, 1998 [a] CGA293343/0688

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Chronic	Thiamethoxam	*Eisenia fetida*	NOEC = 5.34 mg a.s./kg	**NOEC = 1.54 mg a.s./kg** [c]	Derived from study with A9584C; The endpoint listed in the EC Review Report [d] was incorrectly calculated	Rufli, 1997d [a,d] CGA293343/0386
	CGA322704		NOEC = 2.5 mg/kg soil	NOEC = 0.06 mg/kg [g]	The endpoint listed in the EC Review Report [d] was derived from the 14 day acute toxicity study (Porch et al, 2000)	Bätscher, 2000 [b] CGA322704/0027
	CGA322704		-	**EC_{10} = 0.056 mg/kg** [g]	Endpoint derived from literature	Wang K, Pang S, Mu X, Qi S, Li D, Cui F and C Wang (2015). Biological response of earthworm, *Eisenia fetida*, to five neonicotinoid insecticides. *Chemosphere*, Vol. 132, pp. 120-6
	CGA355190		--	**NOEC = 125 mg/kg**	New data requirement	McCormac, 2014 [e] CGA355190_10002
	NOA407475		--	NOEC = 500 mg/kg	Conducted on a metabolite; included for completeness	McCormac, 2014b [e] NOA407475_10000
	NOA459602		--	NOEC = 62.5 mg/kg	Conducted on a metabolite; included for completeness	McCormac, 2014a [e] NOA459602_10002
	CGA282149		--	NOEC = 31.3 mg/kg **EC_{10} = 30.3 mg/kg**	Data requirement	Friedrich, 2015 [e] CA2343_10016
Chronic	NOA404617	*Eisenia fetida*	--	NOEC = 62.5 mg/kg **EC_{10} = 75.3 mg/kg soil d.w**	Conducted on a metabolite; included for completeness	Friedrich, 2015 [e] NOA404617_10007
	A9584C		NOEC = 4616 g formulation/ha	**NOEC = 6.15 mg formulation/kg**	Agreed EU endpoint; Converted to appropriate units for risk assessment [c]	Rufli, 1997d [a] CGA293343/0386
	A9765R		--	NOEC = 62.5 mg formulation/kg **EC_{10} = 65 mg formulation/kg**	New data requirement	Friedrich, 2014 [e] A9765R_10085

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Field	Thiamethoxam (tested as A9584C)	Earthworm population	No unacceptable adverse effects up to 200 g a.s./ha	--	Agreed EU endpoint (Addendum B9: Ecotoxicology, January 2004) Endpoint not used in current risk assessment (risk acceptable in Tier 1), study therefore not re-assessed in the current dossier	Forster and Salaun, 2003 [b] CGA293343/1642
	CGA322704		No unacceptable adverse effects up to 150 g/ha	--	No change	Pease and Webster, 2004 [f] CGA322704/0047
Field	CGA322704	Earthworm population	no effects up to 225 g a.s./ha	--	Study not submitted by the notifier in the current dossier. Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005) reported by RMS for completeness	Agreed EU endpoint (Clothianidin SANCO/10533/05 - Final 18 January 2005)

Endpoints in **bold** represent the lowest value for the respective substance and are used in the risk assessment.
[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2
[b] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, January 2004. However, concenrning the study Bätscher, 2000 CGA322704/0027, RMS did not find the summary in the monograph. A summary is available in volume 3 CA B.9.
[c] Considering a soil density of 1.5 g/mL and a soil depth of 5 cm
[d] EC Review Report of thiamethoxam (SANCO/10390/2002 – rev.final, 14 July 2006)
[e] Study has been performed since EU registration; Study summary provided in volume 3 CA B.9
[f] Thiamethoxam Monograph, Addendum B9: Ecotoxicology, November 2005
[g] Based on results from the publication and on results from from study conducted by the Notifier, RMS considered that an overall NOEC of 0.06 mg a.s./kg can be set for risk assessment for Tier 1 risk assessment on reproduction (see study summaries in volume 3 CA B.9 for more details)

Table 2.9.4-2: Chronic toxicity endpoints on *Folsomia candida* and *Hypoaspis aculeifer* for Thiamethoxam, metabolites and formulations used in risk assessment

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Chronic	Thiamethoxam	*Folsomia candida*	NOEC = 2.88 mg a.s./kg	EC_{10} = 1.384 mg a.s./kg	reliable EC_{10} re-calculated	Meister, 2001 CGA293343/1350
		Hypoaspis aculeifer	--	NOEC = 246 mg a.s./kg	New data requirement; Derived from study with A9584C (NOEC = 1000 mg A9584C/kg soil d.w)	Schultz, 2014 A9584C_10934

			--	NOEC = 153 mg a.s./kg EC_{10} = 280 mg	New data requirement; Derived from study with A9765R	Schultz, 2014a A9765R_10079

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
				a.s./kg	(NOEC = 309 mg A9765R /kg soil d.w EC_{10} = 565.1 mg A9765R /kg soil d.w)	
	CGA322704	*Folsomia candida*	NOEC < 0.15 mg/kg	--	Overall NOEC from these two studies = 0.1 mg/kg	Meister, 2001b CGA322704/0029
			--	NOEC = 0.32 mg/kg EC10 = 0.28 mg a.s./kg soil d.w	New data requirement; Not previously included in thiamethoxam submssions Overall NOEC from these two studies = 0.1 mg/kg	Dechert, 2000 CGA322704_10066
		Hypoaspis aculeifer	--	NOEC = 100 mg/kg EC10 = 98.95 mg/kg soil d.w	New data requirement	Moser, 2005 CGA322704/0052
Chronic	CGA355190	*Folsomia candida*	--	NOEC = 16.3 mg/kg	New data requirement	Geary, 2015 CGA355190_10006
		Hypoaspis aculeifer	--	NOEC = 1 000 mg/kg		Vinall, 2015 CGA355190_10005
	NOA407475	*Folsomia candida*	--	NOEC = 1 000 mg/kg	Conducted on a metabolite; included for completeness	Geary, 2015b NOA407475_10004
		Hypoaspis aculeifer	--	NOEC = 1 000 mg/kg		Vinall, 2015b NOA407475_10007
	NOA459602	*Folsomia candida*	--	NOEC = 1 000 mg/kg	Conducted on a metabolite; included for completeness	Geary, 2015a NOA459602_10009
		Hypoaspis aculeifer	--	NOEC = 1 000 mg/kg		Vinall, 2015a NOA459602_10010
	CGA282149	*Folsomia candida*	--	NOEC = 309 mg/kg EC_{10} = 377 mg/kg soil d.w	Data requirement	Friedrich, 2015 CA2343_10017
		Hypoaspis aculeifer	--	NOEC = 308.6 mg/kg		Schulz, 2015 CA2343_10020
	NOA404617	*Folsomia candida*	--	NOEC = 95 mg/kg	Conducted on a metabolite; included for completeness	Friedrich, 2015 NOA404617_10006
		Hypoaspis aculeifer	--	NOEC = 95.3 mg/kg		Schulz, 2015a NOA404617_10010
		Folsomia candida	--	NOEC = 10 mg formulation/kg		Friedrich, 2014 A9584C_10927

	A9584C	*Hypoaspis aculeifer*	--	NOEC = 1 000 mg formulation/kg	New data requirement	Schulz, 2014 A9584C_10934

Test type	Test item	Test species	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Chronic	A9765R	*Folsomia candida*	--	NOEC = 4.8 mg/kg EC_{10} = 4.72 mg/kg	New data requirement	Friedrich, 2014b A9765R_10072
		Hypoaspis aculeifer	--	(NOEC = 309 mg A9765R /kg soil d.w EC_{10} = 565.1 mg A9765R /kg soil d.w		Schultz, 2014a A9765R_10079
Field	Thiamethoxam	Organic matter decomposition	NOER = 200 g a.s./ha	--	Derived from study with A9584C; Studies on organic matter decomposition are no longer a data requirement Endpoint not used in risk assessment	Forster, 2001 CGA293343/1390
	CGA322704	Organic matter decomposition	70.7 g/ha (equivalent to 0.09 mg/kg soil)	--	Studies on organic matter decomposition are no longer a data requirement Endpoint not used in risk assessment	Bader, 2001 CGA322704/0030
	A9584C	Organic matter decomposition	NOER = 796.8 g formulation/ha	--	Studies on organic matter decomposition are no longer a data requirement Endpoint not used in risk assessment	Forster, 2001 CGA293343/1390

The metabolite CGA353042 is a major soil photolysis metabolite. Even if studies with the metabolite CGA353042 are not available for soil organisms, based on previous statement (see justification in B.9.8.1.1) and following a conservative approach, it can be assumed that CGA353042 has the same toxicity as the parent compound, thiamethoxam.

There are two studies examing the toxicity of CGA322704 with *Folsomia candida* under laboratory conditions. In the study by ***Meister (2001b)***, the test concentrations were 0.15, 0.30, 0.60, 1.2, 2.4, 4.8, 9.6 and 19.2 mg/kg. A NOEC could not be determined, as there was a significant effect on mortality (50% reduction) and reproduction (52.9% reduction) at the lowest concentration tested (0.15 mg/kg). In the study by ***Dechert (2000)***, the test concentrations were 0.01, 0.032, 0.1, 0.32 and 1.0 mg/kg. The NOEC was determined to be 0.32 mg/kg based on mortality (10% reduction) and reproduction (13% reduction). The EC_{10} was calculated to be 0.28 mg/kg; LC_{10} was not able to be calculated.

There is some difference in toxicity between the two studies where the doses overlap, as demonstrated in the tables below. Biological endpoints can be variable and therefore the difference in toxicity here is difficult to fully explain. Consequently, the datasets have been combined to determine a conservative endpoint to use in the risk assessment.

Effect of CGA322704 on mortality and reproduction in *Meister (2001b)*

Treatment	Control	0.15 mg/kg	0.30 mg/kg	0.60 mg/kg	1.2 mg/kg	2.4 mg/kg	4.8 mg/kg	9.6 mg/kg	19.2 mg/kg
Mortality	20%	31%*	82%*	79%*	82%*	82%*	82%*	82%*	82%*
Reproduction (% of control)	-	52.9%*	0%*	0%*	0%*	0%*	0%*	0%*	0%*

Treatment % mortality was corrected for control mortality; M = [(% treatment mortliaty - % control mortality) / (100 - % control mortality)] x 100. The study report only contains % mortality, not corrected for control mortality.
*Significantly different from control

Effect of CGA322704 on mortality and reproduction in *Dechert (2000)*

Treatment	Control	0.01 mg/kg	0.032 mg/kg	0.10 mg/kg	0.32 mg/kg	1.0 mg/kg
Mortality	2%	8.2%	6.1%	4.1%	8.2%	49%*
Reproduction (% of control)	-	101.1%	86.2%	107.7%	86.9%	36.2%*

Treatment % mortality was corrected for control mortality. The study report contains % mortality, as corrected for control mortality.
*Significantly different from control

RMS comment: There is some difference in toxicity between the two studies where the doses overlap. Indeed, there was 31% and 82% mortality at 0.15 mg/kg and 0.30 mg/kg respectively in Meister (2001b) whereas there was lower or equal to 10% mortality at around the same concentrations of 0.10 and 0.32 mg/kg in Dechert (2000). It can be noted that the level of mortality in the control was relatively lower in the study by Dechert (2000) (=2%) compared to the study by Meister (2001b) (=20%) that could explain in part the difference in toxicity between the two studies. Based on this lower level of mortality in the contrôle, results from Dechert (2000) are considered more reliable. However, as the validity criteria were met for the study Meister (2001b) (Mean adult mortality ≤20% at the end of the test), the effects on mortality and reproduction from both studies have been taken into account in risk assessment. RMS considered relevant the approach to use the highest NOEC below the lowest LOEC. Overall NOEC from these two studies is equal to 0.1 mg/kg. (see also volume 3 CA).
Additionally, the notifier indicated that he is currently in the process of obtaining the following field study on CGA322704 to further address the risk to collembola (*Folsomia candida*).

S. Schabio (2014) Field study to evaluate the effects of clothianidin on soil earthworms and collembolans under field conditions. Sumitomo Chemical Co., Ltd. Unpublished report No.: THW-0401

This field study would support the risk to the metabolite CGA322704 formed in soil, as it was conducted with an overspray application (representing the plateau concentration; equivalent to 0.246 mg a.s./kg soil) and a granular application representing the maximum annual application.

2.9.5 Summary of effects on soil nitrogen transformation

Table 2.9.5-1: Toxicity of thiamethoxam, metabolites, and formulations to soil micro-organisms

Test type	Test item	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Carbon and Nitrogen Transformation	Thiamethoxam	**NOAEC = 2.67 mg a.s./kg**	--	Agreed EU endpoint; Carbon transformation is no longer a data requirement	Bader, 1998 [a] CGA293343/0532
	CGA322704	**NOAEC = 0.5 mg/kg**	--		Bader, 1999 [a] CGA322704/0023
	CGA355190	**NOAEC = 0.5 mg/kg**	--		

	CGA459602	--	NOAEC = 0.78 mg/kg	Conducted on a metabolite; included for completeness	Hutcheson, 2014 [b] NOA459602_10005

Test type	Test item	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
	CGA407475	--	NOAEC = 0.78 mg/kg	Conducted on a metabolite; included for completeness	Hutcheson, 2014a [b] NOA407475_10002
	CGA282149	--	**NOAEC = 0.78 mg/kg**	Data requirement	Schulz, 2015b [b] CA2343_10012
	NOA404617	--	NOAEC = 0.78 mg/kg	Conducted on a metabolite; included for completeness	Schulz, 2015c [b] NOA404617_10004
	A9584C	--	**NOAEC = 2.7 mg formulation/kg soil**	Data requirement	Grade, 1998 [b] CGA293343/0689
	A9765R	--	**NOAEC = 0.65 mg formulation/kg soil**	Data requirement	Schulz, 2014b [b] A9765R_10070

Endpoints in **bold** represent the lowest value for the respective substance and are used in the risk assessment.
[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2
[b] Study was not included in or has been performed since EU registration; Study summary provided in 3 CA B.9

2.9.6 Summary of effects on terrestrial non-target higher plants

Table 2.9.6-1: Summary of effects on terrestrial non-target plants following exposure to A9584 C

Test type	Test item	Organism	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Screening study Seedling Emergence and Vegetative Vigour	A9584C	Non-Target Terrestrial Plants	--	NOER = 25 g a.s./ha	Data requirement	Buche, 2006 [a] CGA293343/2805
Tier I Vegetative Vigour	A9584C	Non-Target Terrestrial Plants	--	ER_{50} > 298 g a.s./ha	US data requirement; Included for completeness	Martin, 2013 [a] A9584C_10224
Tier I Seedling Emergence and Seedling Growth	A9584C	Non-Target Terrestrial Plants	--	ER_{50} > 298 g a.s./ha		Martin, 2013a [a] A9584C_10225

[a] Study has been performed since EU registration; Study summary provided in volume 3 CA B.9

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

No data available.

2.9.8 Summary of effects on biological methods for sewage treatment

Table 2.9.8-1: Summary of effects of Thiamethoxam on biological methods for sewage treatment

Organism	Test type	Current Endpoint	Endpoint proposed in this document	Comment	Reference (author, date, Syngenta File No.)
Activated sludge	Activated sludge respiration	EC_{50} > 100 mg/L	--	No change	Grade, 1996b [a] CGA293343/0034

[a] Thiamethoxam Monograph, B9: Ecotoxicology, March 2001_v.2

2.9.9 Summary of product exposure and risk assessment

Summary of products exposure and risk assessment for terrestrial vertebrates

The risk assessment for birds and mammals is carried out following the latest guidance document by EFSA (Anonymous 2009: Guidance Document on risk assessment for Birds & Mammals on request from EFSA. EFSA Journal 2009; 7(12):1438. European Food Safety Authority).

Risk assessment for birds

A9584 C

Greenhouse use:

A risk assessment is not necessary for uses restricted to permanent greenhouses.

Field uses (lettuce and potato)

Acute risk assessment

Based on lowest LD50 > 125 mg a.s./kg (14-d NOEL (mortality and regurgitation) = 125 mg a.s./kg, see explanation and study summary in volume 3 CA B.9)

Table 9.9.1: Screening step - Acute risk (TER_A) to birds from thiamethoxam

Test substance	Crop group	Indicator species	LD_{50} (mg a.s./kg bw)	DDD (mg a.s./kg bw/day)	TER_A
Thiamethoxam	Leafy vegetables	Small omnivorous bird	>125	7.94	>15.8
	Potato	Small omnivorous bird		3.18	>39

The TER_A values for thiamethoxam for all indicator species are greater than the Commission Regulation (EU) No. 546/2011 trigger of 10, indicating that acute risk to birds is acceptable following use of A9584C according to the proposed use pattern.

Acute risk assessment to birds through drinking water

Leaf scenario (lettuce)

The TER calculations are given in the tables below:

Table 9.9.2: Risk to birds from drinking water – leaf scenario

Test substance	PEC_{pool} (mg/kg)	DDD (mg a.s./kg bw/day)	LD_{50} (mg a.s./kg bw/day)	TER_A
Thiamethoxam	33.3	15.3	>125	>8.1

The TER value for thiamethoxam did not exceed the Commission Regulation (EU) No. 546/2011 trigger value of 10, indicating that the acute risk from thiamethoxam to birds drinking from leaf axils needs to be refined.

Puddle scenario

Due to the characteristics of the exposure scenario in connection with the standard assumptions for water uptake by animals, no specific calculations of exposure and TER are necessary since the ratio of effective application rate (in g/ha) to acute and long-term endpoints (in mg/kg bw/d) does not exceed 50 (Koc < 500 L/kg) as specified in EFSA Guidance Document (ref. 5.5, Step 2b).

Long-term toxicity exposure ratio (TERLT)

Table 9.9.3: Screening step – long-term (TER_{LT}) to birds from thiamethoxam

Test substance	Crop group	Indicator species	NOEC (mg a.s./kg bw/day)	DDD (mg a.s./kg bw/day)	TER_{LT}
Thiamethoxam	Leafy vegetables	Small omnivorous bird	24.1	1.72	14
	Potato	Small omnivorous bird		0.687	35

The TER_{LT} values for thiamethoxam for all indicator species are greater than the Commission Regulation (EU) No. 546/2011 trigger of 5, indicating that the long term risk to birds is acceptable following use of A9584C according to the proposed use pattern.

Long-term risk assessment to birds through drinking water

Long-term risk assessment is not relevant for leaf scenario. For the puddle scenario no long-term risk is expected. Please refer to previous explanation.

Effects of secondary poisoning

According to the **EFSA Guidance Document on Risk Assessment for Birds and Mammals (2009)**, substances with a log POW greater than 3 have potential for bioaccumulation. Since thiamethoxam has a log Pow of -0.13, a potential risk of secondary poisoning is not expected and therefore a risk assessment is not required.

A9765 R

Field uses (sugar beet)

Acute risk assessment

Consumption of treated seeds as grit

Based on lowest LD50 > 125 mg a.s./kg (14-d NOEL (mortality and regurgitation) = 125 mg a.s./kg, see explanation and study summary in volume 3 CA B.9)

Table 9.9.4: Acute risk to large omnivorous birds from thiamethoxam following the consumption of A9765R treated seeds as grit

Test substance	Crop grouping	Generic focal species	LD_{50} (mg a.s./kg bw)	$DGritD_{acute}$	TER_A
Thiamethoxam	Large granule	Large omnivorous bird	>125	2.54	>49

For birds consuming sugar beet seeds treated with thiamethoxam accidentally as grit the TER_A is greater than the Commission Regulation (EU) No. 546/2011 trigger of 10, indicating that acute risk to large omnivorous birds is acceptable following use of A9765R according to the proposed use pattern.

Consumption of newly emerged crop shoots

Based on lowest LD50 > 125 mg a.s./kg (14-d NOEL (mortality and regurgitation) = 125 mg a.s./kg

Table 9.9.5: Tier 1 – Acute TER value for small birds eating newly emerged crop shoots containing residues of thiamethoxam

Test substance	Crop grouping	Generic focal species	LD_{50} (mg a.s./kg bw)	DDD (mg a.s./kg bw/day)	TER_A
Thiamethoxam	Seedling	Small omnivorous bird	>125	1 556.5	**>0.08**

TERs shown in **bold** fall below the relevant trigger

For birds consuming newly emerged shoots from seeds treated with thiamethoxam the TER_A value is less than the Commission Regulation (EU) No. 546/2011 trigger of 10. This indicates a potential risk to small omnivorous birds and therefore a higher tier risk assessment is required.

Refinement based on geomean LD50 = 506 mg a.s./kg (see previous explanation and study summary), for completeness as TER was higher than the trigger value based on lowest endpoint (see previous table)

Table 9.9.6: Tier 1 – Acute TER value for small birds eating newly emerged crop shoots containing residues of thiamethoxam

Test substance	Crop grouping	Generic focal species	LD_{50} (mg a.s./kg bw)	DDD (mg a.s./kg bw/day)	TER_A
Thiamethoxam	Seedling	Small omnivorous bird	506	1 556.5	**0.32**

TERs shown in **bold** fall below the relevant trigger

For birds consuming newly emerged shoots from seeds treated with thiamethoxam the TER_A value is less than the Commission Regulation (EU) No. 546/2011 trigger of 10. This indicates a potential risk to small omnivorous birds and therefore a higher tier risk assessment is required.

Refined risk assessment for consumption of newly emerged crop shoots

In the Tier 1 risk assessment, the daily dietary dose is calculated assuming that the total amount of pesticide that was originally present on the treated seed is contained in a total mass of seedling that is 5 times the weight of the original seed. Field studies have been conducted to measure the amount of active substance that is contained within the newly emerged crop shoots.

Table 9.9.7: Maximum observed residues in seedling samples (*White, 2015*) and Sole 2004

Trial Number	Maximum observed total residue (mg/kg fresh weight) (Thiamethoxam + CGA322704)
White, 2015: S15-01163-01	40.77 (38.46 + 2.31)
White, 2015: S15-01163-04	3.67 (2.98 + 0.69)
White, 2015: S15-01163-05	16.38 (14.64+1.74)
White, 2015: S15-01163-06	61.69 (54.07 + 7.62)
Solé, 2004	42.5*

* Only residue of Thiamethoxam have been measured in Sole 2004 (no analyses of CGA322704). The maximum measured residue value was 32.8 mg a.s./kg fresh weight (fw), equivalent to 42.5 mg a.s./kg fw when normalised (see previous explanation)

As for generic RUD data, RMS used the 90th percentile (54 mg/kg fw) and arithmetic mean (33 mg/kg fw) which come from all trials, to refine the acute and long term risk assessment, respectively.

Table 9.9.8: Refined – Acute exposure estimate for birds eating newly emerged crop shoots containing residues of thiamethoxam

Test substance	Crop grouping	Generic focal species	90th percentile measured residue in shoots (mg/kg fw)	FIR/bw	DDD (mg a.s./kg bw/day)
Thiamethoxam	Seedling	Small omnivorous bird	54	0.5	27

Table 9.9.9: Refined – Acute TER value for small birds eating newly emerged crop shoots containing residues of thiamethoxam

Test substance	Crop grouping	Generic focal species	LD_{50} (mg a.s./kg bw)	DDD (mg a.s./kg bw/day)	TER_A
Thiamethoxam	Seedling	Small omnivorous bird	506	27	18.7

When consideration is given to measured residues from field trials, the TER_A value for birds consuming newly emerged shoots from treated seeds is greater than the Commission Regulation (EU) No. 546/2011 trigger of 10. This indicates an acceptable risk to small omnivorous birds.

Acute risk assessment to birds through drinking water

Leaf scenario

The leaf scenario is not relevant for seed treatments and the use of A9765R.

Puddle scenario

Due to the characteristics of the exposure scenario in connection with the standard assumptions for water uptake by animals, no specific calculations of exposure and TER are necessary since the ratio of effective application rate (in g/ha) to acute and long-term endpoints (in mg/kg bw/d) does not exceed 50 (Koc < 500 L/kg) as specified in EFSA Guidance Document (ref. 5.5, Step 2b).

Long-term toxicity exposure ratio (TERLT)

Consumption of treated seeds as grit

Table 9.9.10: Tier 1 – Long-term TER value for birds exposed to thiamethoxam following the consumption of A9765R treated seeds as grit

Test substance	Crop grouping	Generic focal species	NOEC (mg a.s./ kg bw)	$DGritD_{long\text{-}term}$	TER_{LT}
Thiamethoxam	Large granule	Large omnivorous bird	24.1	0.949	25

For birds consuming pelleted seeds treated with thiamethoxam as grit, the long-term TER value is greater than the Commission Regulation (EU) No. 546/2011 trigger of 5, indicating that the long-term risk to large omnivorous birds is acceptable following use of A9765R according to the proposed use pattern.

Consumption of newly emerged crop shoots

Table 9.9.11: Tier 1 – Long-term TER value for birds eating newly emerged crop shoots containing residues of thiamethoxam

Test substance	Crop grouping	Generic focal species	NOEC (mg a.s./kg bw/day)	DDD (mg a.s./kg bw/day)	TER_{LT}
Thiamethoxam	Seedling	Small omnivorous bird	24.1	825	**0.029**

TERs shown in **bold** fall below the relevant trigger

For birds consuming newly emerged shoots from seeds treated with thiamethoxam, the long-term TER value is less than the Commission Regulation (EU) No. 546/2011 trigger of 5. This indicates a potential risk to small

omnivorous birds and therefore a higher tier risk assessment is required.

Refined risk assessment for consumption of newly emerged crop shoots

In the Tier 1 risk assessment, the daily dietary dose is calculated assuming that the total amount of pesticide that was originally present on the treated seed is contained in a total mass of seedling that is 5 times the weight of the original seed. Additionally, the f_{twa} is based on the default assumption that the DT_{50} for thiamethoxam is 10 days. As discussed above in the refined acute risk assessment, field studies have been conducted to measure the amount of active substance that is contained within the newly emerged crop shoots and its disspation over time (***Solé, 2004***; ***White, 2015***).

Table 9.9.12: DT_{50} (days) from disspation of residues over time in seedling samples (*White, 2015*, and Sole 2004)

Study/Trial	Model	Visual	χ^2	Confidence (t-test)	DT_{50} (days)
White, 2015: S15-01163-01	SFO	Good	30.1*	0.02	3.35
White, 2015: S15-01163-04	SFO	Good	11.5	< 0.01	6.76
White, 2015: S15-01163-05	SFO	Acceptable	29*	0.03	4.61
White, 2015: S15-01163-06	SFO	Good	7.89	< 0.01	6.88
Solé, 2004	SFO	Acceptable	9.53	< 0.01	1.84
				Geometric mean	4.21

The geometric mean DT_{50} value was calculated to be 4.21 days.

The geometric mean f_{twa} (0.28) and the arithmetic mean residue value (33 mg/kg fw) will be used to refine the risk assessment.

Table 9.9.13: Refined – Long-term TER value for birds eating newly emerged crop shoots containing residues of thiamethoxam

Test substance	Crop grouping	Generic focal species	NOEC (mg a.s./kg bw/day)	DDD (mg a.s./kg bw/day)	TER_{LT}
Thiamethoxam	Seedling	Small omnivorous bird	24.1	4.62	5.2

When consideration is given to measured residues from field trials, the TER_{LT} value for birds consuming newly emerged shoots from treated seeds is higher than the Commission Regulation (EU) No. 546/2011 trigger of 5. This indicates an acceptable risk to small omnivorous birds.

Long-term risk assessment to birds through drinking water

Risk assessment is not relevant for leaf scenario. For the puddle scenario no long-term risk is expected. Please refer to previous explanation.

Effects of secondary poisoning

According to the **EFSA Guidance Document on Risk Assessment for Birds and Mammals (2009)**, substances with a log POW greater than 3 have potential for bioaccumulation. Since thiamethoxam has a log Pow of -0.13, a potential risk of secondary poisoning is not expected and therefore a risk assessment is not required.

Risk assessment for mammals

A9584 C

Greenhouse use:

A risk assessment is not necessary for uses restricted to permanent greenhouses.

Field uses (lettuce and potato)

Acute risk assessment

Table 9.9.14: Screening step - Acute risk (TER_A) to mammals from thiamethoxam

Test substance	Crop group	Indicator species	LD_{50} (mg a.s./kg bw)	DDD (mg a.s./kg bw/day)	TER_A
Thiamethoxam	Leafy vegetables	Small herbivorous mammal	783	6.82	110
	Potato			2.37	330

The TER_A values for thiamethoxam are greater than the Commission Regulation (EU) No. 546/2011 trigger value of 10, indicating that the acute risk to mammals is acceptable following use of A9584C according to the proposed use pattern.

Acute risk assessment to mammals through drinking water

Not necessary. Only the puddle scenario is relevant for risk assessment for mammals through drinking water. Due to the characteristics of the exposure scenario in connection with the standard assumptions for water uptake by animals, no specific calculations of exposure and TER are necessary since the ratio of effective application rate (in g/ha) to acute and long-term endpoints (in mg/kg bw/d) does not exceed 50 (Koc < 500 L/kg), as specified in EFSA Guidance Document (ref. 5.5, Step 2b).

Table 9.9.15: Screening step - long-term risk (TER_{LT}) to mammals

Test substance	Crop group	Indicator species	NOAEL (mg a.s./kg bw/day)	DDD (mg a.s./kg bw/day)	TER_{LT}
Thiamethoxam	Leafy vegetables	Small herbivorous mammal	1.2	1.92	0.625
	Potato			0.51	2.3

The TER_{LT} values for thiamethoxam are lower than the Commission Regulation (EU) No. 546/2011 trigger value of 5, indicating that the long-term risk to mammals is not acceptable following use of A9584C according to the proposed use pattern. Refinement needed (Tier 1)

RMS added TERlt calculation on Tier 1

Table 9.9.16: Tier 1 - long-term risk (TER_{LT}) to mammals

Test substance	Crop group	Generic focal species	NOAEL (mg a.s./kg bw/day)	TER_{LT}
Thiamethoxam	Leafy vegetables (BBCH 15-49)	Small herbivorous mammal	1.2	0.63
		Large herbivorous mammal		3.2
		Small insectivorous mammal		**10.7**
		Small omnivorous mammals		**5.8**
	Potato (BBCH 15-59)	Small herbivorous mammal		**5.2**
		Large herbivorous mammal		**7.8**
		Small insectivorous mammal		**26.7**

		Small omnivorous mammals		**14.4**

The TER_{LT} values for thiamethoxam are greater than the Commission Regulation (EU) No. 546/2011 trigger value of 5, indicating that the long-term risk to mammals is acceptable following use of A9584C on potatoes according to the proposed use pattern. However, for lettuce, the TER_{LT} values for thiamethoxam are lower than the Commission Regulation (EU) No. 546/2011 trigger value of 5 for small herbivorous mammal and large herbivorous mammal. Further refinements are needed for lettuce.

Long-term risk assessment to mammals through drinking water

Not necessary. (see previous explanation)

Effects of secondary poisoning

According to the **EFSA Guidance Document on Risk Assessment for Birds and Mammals (2009)**, substances with a log P_{OW} greater than 3 should be assessed for the risk of secondary poisoning. Thiamethoxam has a log P_{OW} value of -0.13. It was therefore not necessary to consider the risk from secondary poisoning further. Therefore, based on the log P_{OW} values the risk from bioaccumulation to fish-eating and worm-eating mammals is acceptable.

Field uses (sugar beet)

A9765R is a seed treatment of pelleted sugar beet seeds. According to the **EFSA Guidance Document on Risk Assessment for Birds and Mammals (2009)** "*for pelleted seeds an assessment of mammals is not required since mammals are not known to deliberately ingest grit. Nonetheless pelleted seeds may be consumed by wood mice (e.g.* ***Pelz, 1989*** [17]*,) but the Joint Working Group considered that the risk in these cases may be reduced due to animals cracking and discarding the pellet with most of the residue before ingesting the seed*."

However, thiamethoxam is systemic and can be taken up into the vegetative plant tissue (i.e. are xylem systemic). Mammals may therefore be exposed to thiamethoxam residues via the consumption of germinated sugar beet seedlings.

Acute risk assessment

Consumption of newly emerged crop shoots

Table 9.9.17: Tier 1 – Acute TER value for small mammals eating newly emerged crop shoots containing residues of thiamethoxam

Test substance	Crop grouping	Generic focal species	LD_{50} (mg a.s./kg bw)	DDD (mg a.s./kg bw/day)	TER_A
Thiamethoxam	Seedling	Small omnivorous mammal	783	747.12	**1.0**

TERs shown in **bold** fall below the relevant trigger

For mammals consuming newly emerged shoots from seeds treated with thiamethoxam the TER_A value is less than the Commission Regulation (EU) No. 546/2011 trigger of 10. This indicates a potential risk to small omnivorous mammals and therefore a higher tier risk assessment is required.

Refined risk assessment for consumption of newly emerged crop shoots

In the Tier 1 risk assessment, the daily dietary dose is calculated assuming that the total amount of pesticide that was originally present on the treated seed is contained in a total mass of seedling that is 5 times the weight of the original seed.
As discussed above in the refined bird acute risk assessment (Section "bird"), field studies have been conducted to measure the amount of active substance that is contained within the newly emerged crop shoots and its disspation over time (***Solé, 2004***; ***White, 2015***). The 90th percentile residue value is 54 mg/kg fw and will be used to refine the acute risk assessment.

[17] Pelz, HJ (1989). Ecological aspects of damage to sugar beet seeds by *Apodemus sylvaticus*. In: Mammals as pests (Ed. by Putman, R. J.), pp. 34-48. London: Chapman and Hall.

Table 9.9.18: Refined – Acute TER value for small mammals eating newly emerged crop shoots containing residues of thiamethoxam

Test substance	Crop grouping	Generic focal species	LD_{50} (mg a.s./kg bw)	DDD (mg a.s./kg bw/day)	TER_A
Thiamethoxam	Seedling	Small omnivorous mammal	783	12.96	60.4

When consideration is given to measured residues from field trials, the TER_A value for mammals consuming newly emerged shoots from treated seeds is greater than the Commission Regulation (EU) No. 546/2011 trigger of 10. This indicates an acceptable risk to small omnivorous mammals.

Long term risk assessment

Consumption of newly emerged crop shoots

Table 9.9.19: Tier 1 – Long-term TER value for mammals eating newly emerged crop shoots containing residues of thiamethoxam

Test substance	Crop grouping	Generic focal species	NOEC (mg a.s./kg bw/day)	DDD (mg a.s./kg bw/day)	TER_{LT}
Thiamethoxam	Seedling	Small omnivorous mammal	1.2	395.97	**0.003**

TERs shown in **bold** fall below the relevant trigger

For mammals consuming newly emerged shoots from seeds treated with thiamethoxam, the long-term TER value is less than the Commission Regulation (EU) No. 546/2011 trigger of 5. This indicates a potential risk to small omnivorous mammals and therefore higher tier risk assessment is required.

Refined risk assessment for consumption of newly emerged crop shoots

In the Tier 1 risk assessment, the daily dietary dose is calculated assuming that the total amount of pesticide that was originally present on the treated seed is contained in a total mass of seedling that is 5 times the weight of the original seed. Additionally, the f_{twa} is based on the default assumption that the DT_{50} for thiamethoxam is 10 days.
As discussed above in the refined acute risk assessment and the refined bird chronic risk assessment (Section "bird"), field studies have been conducted to measure the amount of active substance that is contained within the newly emerged crop shoots and its disspation over time (***Solé, 2004***; ***White, 2015***).

The geometric mean DT_{50} value was calculated to be 4.21 days.

The geometric mean f_{twa} (0.28) and the arithmetic mean measured residue value (33 mg/kg fw) will be used to refine the risk assessment.

Table 9.9.20: Refined – Long-term TER value for mammals eating newly emerged crop shoots containing residues of thiamethoxam

Test substance	Crop grouping	Generic focal species	NOEC (mg a.s./kg bw/day)	DDD (mg a.s./kg bw/day)	TER_{LT}
Thiamethoxam	Seedling	Small omnivorous mammal	1.2	2.22	0.6

When consideration is given to measured residues from field trials, the TER_{LT} value for mammals consuming newly emerged shoots from treated seeds is lower than the Commission Regulation (EU) No. 546/2011 trigger of 5. This indicates that further refinements are needed.

Effects of secondary poisoning

According to **EFSA Guidance Document on Risk Assessment for Birds and Mammals, 2009**, substances with a log P_{OW} greater than 3 have potential for bioaccumulation. Thiamethoxam has a log P_{OW} of - 0.13, indicating low potential risk of secondary poisoning. Therefore a risk assessment is not required.

Summary of products exposure and risk assessment for aquatic organisms

The risk assessments were carried out following application according to the proposed uses. The risk assessments followed the EFSA (2013) Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. The assessment is a tiered procedure which derives Regulatory Acceptable Concentrations (RACs) from the effects data by applying assessment factors appropriate to the taxon and tier assessed. The RAC is compared to the appropriate PEC_{SW} value. If the RAC is > PEC, then the risk is acceptable, otherwise the assessment should be refined with higher tiers.

A9584 C

Greenhouse use:

A risk assessment is not necessary for uses restricted to permanent greenhouses. EFSA guidance document on protected crops (EFSA, 2014) was not applicable at the time the dossier has been submitted (see volume 3 CP B8). PECsw through spray drift from the application site into adjacent water bodies were considered in E-Fate section (see volume 3 CP B8). Spray drift may occur if greenhouse vents are open during applications. As drift from application within a permanent greenhouse (0.1%, see E-Fate section) would be less than that of a field use, the PECsw values for field uses are worst-case and therefore protective of permanent greenhouse uses (PECsw for permanent greenhouse would be 0.067 µg formulation/L and 0.017 µg a.s/L considering 0.1% drift, see E-Fate section). PECs are lower than the lowest Tier 1 RACsw of 0.14 µg a.s/L, Tier 1 RACsw of 1.54 µg formulation/L and also lower than the Tier 3 RACsw of 0.15 µg a.s./L indicating an acceptable risk

Field uses (lettuce and potato)

Thiamethoxam

Table 9.9.21 Toxicity data and Tier 1 RACs for aquatic species and thiamethoxam

Organism group	Test organism	Endpoint		AF	Tier 1-RAC
		(type)	(µg/L)		(µg/L)
Acute effects					
Fish	Rainbow trout (*Oncorhynchus mykiss*)	96 hr LC_{50}	>125 000	100	>1 250
Aquatic invertebrates (Crustacea)	*Asellus aquaticus*	48 hr EC_{50}	84		0.84
Aquatic invertebrates (Insecta)	*Cloeon sp.*	48 hr EC_{50}	14		**0.14**
	Chironomus dilutus	10 d EC_{50}	> 2 600 µg a.s./kg		**> 26 µg a.s./kg**
Chronic effects					
Fish	Sheepshead minnow (*Cyprinodon variegatus*)	28 d NOEC	1 700	10	170
Aquatic invertebrates (Crustacea)	*Mysidopsis habia*	NOEC	560		56
Aquatic invertebrates (Insecta)	*Chironomus riparius*	30 d NOEC	10 (nom)		**1.0 (nom)**
			2.7 (mm)		**0.27 (mm)**
		30 d EC_{10}	85 µg a.s./kg (nom)		**8.5 µg a.s./kg** (nom)

Organism group	Test organism	Endpoint		AF	Tier 1-RAC
		(type)	(µg/L)		(µg/L)
			7.2 µg a.s./kg (mm)		**0.72 µg a.s./kg** (mm)
Green alga	*Selenastrum capricornutum*	72 hr $E_{r/b}C_{50}$	>81 800		>8 180
Aquatic macrophyte	*Lemna gibba*	7 d $E_{r/b}C_{50}$	>90 200		>9 020

Values in **bold** are the lowest Tier 1 RAC values

Acute effects: The lowest Tier 1 RACsw,ac is 0.14 µg a.s./L, based on the toxicity to the aquatic insect, *Cloeon* sp. The lowest tier 1 RACsed,ac is > 26 µg a.s./kg, based on the toxicity to the aquatic insect *Chironomus dilutus*.

Chronic effects: The lowest Tier 1 RACsw,ch is 1.0 µg a.s./L (nom) or 0.27 µg a.s./L (mm), based on the toxicity to the aquatic insect, *Chironomus riparius*. The lowest tier 1 RACsed,ch is 8.5 µg a.s./kg (nom) or 0.72 µg a.s./kg (mm), also based on the toxicity to *Chironomus riparius*

Following the EFSA Aquatic Guidance, these Tier 1 RACs are compared to the exposure values to determine if the risk is acceptable.

Tier 1 risk to aquatic invertebrates for thiamethoxam (covering other aquatic organisms)

Potato

Table 9.9.22: Thiamethoxam FOCUS Step 1 and 2 PEC and Tier 1 RAC for potato and aquatic species

Crop	FOCUS Step	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)		Maximum PECsed (µg/kg)	Tier 1 RACsed (µg/kg)	
			Acute	Chronic		Acute	Chronic
Potato	1	**6.30**	0.14	1.0 (nom) 0.27 (mm)	4.13	>26	8.5 (nom) 0.72 (mm)
	2	**2.19**			1.44		

Table 9.9.23: Thiamethoxam Tier 1 FOCUS Step 3 PEC_{SW} and Tier 1 RACsw for potato and aquatic species

Crop	FOCUS Step 3 Scenario	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)	
			Acute	Chronic
Potato BBCH 15	D3 (D)	**0.210**	0.14	1.0 (nom) 0.27 (mm)
	D4 (P)	**0.365**		
	D4 (S)	**0.221**		
	D6 (D)	0.133		
	R1 (P)	0.056		
	R1 (S)	**0.425**		
	R2 (S)	**0.306**		
	R3 (S)	**0.772**		
Potato BBCH 59	D3 (D)	**0.189**	0.14	1.0 (nom) 0.27 (mm)
	D4 (P)	**0.234**		
	D4 (S)	**0.172**		
	D6 (D)	0.136		
	R1 (P)	0.004		
	R1 (S)	0.086		
	R2 (S)	**0.366**		
	R3 (S)	**0.582**		

PECsw values in **bold** are greater than the RAC value

Table 9.9.24: Thiamethoxam Tier 1 FOCUS Step 3 PEC_{SED} and Tier 1 RACsed for potato and aquatic species

Crop	FOCUS Step 3 Scenario	Maximum PECsed (µg/kg)	Tier 1 RACsed (µg/kg)	
			Acute	Chronic
Potato BBCH 15	D3 (D)	0.594	>26	8.5 (nom) 0.72 (mm)
	D4 (P)	**1.18**		
	D4 (S)	0.647		
	D6 (D)	0.221		
	R1 (P)	0.065		
	R1 (S)	0.110		
	R2 (S)	0.057		
	R3 (S)	0.136		
Potato BBCH 59	D3 (D)	0.481	>26	8.5 (nom) 0.72 (mm)
	D4 (P)	**0.746**		
	D4 (S)	0.399		
	D6 (D)	0.244		
	R1 (P)	0.007		
	R1 (S)	0.015		
	R2 (S)	0.079		
	R3 (S)	0.139		

PECsed values in **bold** are greater than the RAC value

Lettuce

Table 9.9.24: Thiamethoxam FOCUS Step 1 and 2 PECand Tier 1 RAC for lettuce and aquatic species

Crop	FOCUS Step	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)		Maximum PECsed (µg/kg)	Tier 1 RACsed (µg/kg)	
			Acute	Chronic		Acute	Chronic
Lettuce	1	**15.8**	0.14	1.0 (nom) 0.27 (mm)	**10.3**	>26	8.5 (nom) 0.72 (mm)
	2	**4.88**			3.20		

Table 9.9.25: Thiamethoxam Tier 1 FOCUS Step 3 PEC_{SW} and Tier 1 RACsw for lettuce and aquatic species

Crop	FOCUS Step 3 Scenario	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)	
			Acute	Chronic
Lettuce BBCH 15	D3 (D)	**0.684**	0.14	1.0 (nom) 0.27 (mm)
	D4 (P)	**1.04**		
	D4 (S)	**0.620**		
	D6 (D)	**0.653**		
	R1 (P)	0.017		
	R1 (S)	**0.224**		
	R2 (S)	**0.718**		
	R3 (S)	**0.695**		
	R4 (S)	**0.209**		
Lettuce BBCH 49	D3 (D)	**0.529**	0.14	1.0 (nom) 0.27 (mm)
	D4 (P)	**0.561**		
	D4 (S)	**0.423**		
	D6 (D)	**6.59**		
	R1 (P)	0.109		
	R1 (S)	**1.48**		
	R2 (S)	**0.521**		
	R3 (S)	**0.603**		
	R4 (S)	**1.83**		

PECsw values in **bold** are greater than the RAC value

Table 9.9.26: Thiamethoxam Tier 1 FOCUS Step 3 PEC_{SED} and Tier 1 RACsed for lettuce and aquatic species

Crop	FOCUS Step 3 Scenario	Maximum PECsed (µg/kg)	Tier 1 RACsed (µg/L)	
			Acute	Chronic
Lettuce BBCH 15	D3 (D)	**1.86**	>26	8.5 (nom) 0.72 (mm)
	D4 (P)	**3.17**		
	D4 (S)	**1.81**		
	D6 (D)	**1.18**		
	R1 (P)	0.028		
	R1 (S)	0.046		
	R2 (S)	0.149		
	R3 (S)	0.123		
	R4 (S)	0.018		
Lettuce BBCH 49	D3 (D)	**1.16**	>26	8.5 (nom) 0.72 (mm)
	D4 (P)	**1.7**		
	D4 (S)	**0.933**		
	D6 (D)	**2.093**		
	R1 (P)	0.132		
	R1 (S)	0.248		
	R2 (S)	0.171		
	R3 (S)	0.103		
	R4 (S)	0.385		

PECsed values in **bold** are greater than the RAC value

Refined risk to aquatic invertebrates for thiamethoxam

Potato

Table 9.9.27: Thiamethoxam Tier 1 FOCUS Step 3 and 4 PEC_{SW} values and worst-case ETO-RACsw for potato

Crop	FOCUS Scenario	Step 3 PECsw (µg/L)	Step 4 PECsw (µg/L)	Tier 3 ETO-RACsw (µg/L)
			Run-off mitigation 18-20m	
			Spray-drift buffer 20m	
Potato BBCH 15	D3 (D)	**0.210**	0.116	0.15
	D4 (P)	**0.365**	**0.365**	
	D4 (S)	**0.221**	**0.221**	
	D6 (D)	0.133	0.080	
	R1 (P)	0.056	0.012	
	R1 (S)	**0.425**	0.105	
	R2 (S)	**0.306**	0.071	
	R3 (S)	**0.772**	**0.772**	
Potato BBCH 59	D3 (D)	**0.189**	0.093	0.15
	D4 (P)	**0.234**	**0.234**	
	D4 (S)	**0.172**	**0.172**	
	D6 (D)	0.136	0.107	
	R1 (P)	0.004	0.002	
	R1 (S)	0.086	0.020	
	R2 (S)	**0.366**	0.084	
	R3 (S)	**0.582**	0.139	

PECsw values in **bold** are greater than the RAC value

Lettuce

Table 9.9.28: Thiamethoxam Tier 1 FOCUS Step 3 and 4 PEC_{SW} values and worst-case ETO-RACsw for lettuce

Crop	FOCUS Scenario	Step 3 PECsw (µg/L)	Step 4 PECsw (µg/L)	Tier 3 ETO-RACsw (µg/L)
			Run-off mitigation 18-20m	
			Spray-drift buffer 20m	
Lettuce BBCH 15	D3 (D)	**0.684**	**0.399**	0.15
	D4 (P)	**1.04**	**1.04**	
	D4 (S)	**0.620**	**0.620**	
	D6 (D)	**0.653**	**0.653**	
	R1 (P)	0.017	0.005	
	R1 (S)	**0.224**	0.053	
	R2 (S)	**0.718**	**0.169**	
	R3 (S)	**0.695**	**0.163**	
	R4 (S)	**0.209**	0.021	
Lettuce BBCH 49	D3 (D)	**0.529**	**0.240**	0.15

Crop	FOCUS Scenario	Step 3 PECsw (µg/L)	Step 4 PECsw (µg/L)	Tier 3 ETO-RACsw (µg/L)
			Run-off mitigation 18-20m	
			Spray-drift buffer 20m	
	D4 (P)	**0.561**	**0.560**	
	D4 (S)	**0.423**	**0.399**	
	D6 (D)	**6.59**	**6.59**	
	R1 (P)	0.109	0.024	
	R1 (S)	**1.48**	**0.346**	
	R2 (S)	**0.521**	0.124	
	R3 (S)	**0.603**	0.136	
	R4 (S)	**1.83**	**0.435**	

PECsw values in **bold** are greater than the RAC value

Risk to other groups for thiamethoxam

Table 9.9.29: Thiamethoxam Tier 1 FOCUS Step 3 PEC_{SW} and Tier 1 RACsw for aquatic species other than aquatic invertebrates

Crop	FOCUS Step	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)			
			Fish acute	Fish chronic	Algae	Aquatic plants
Potato	3	0.773	>1 250	170	>8 180	>9 020
Lettuce	3	1.83				

Conclusion for thiamethoxam for field uses (potatoes and lettuce)

The risk to aquatic organisms from exposure to thiamethoxam via early application to potatoes is acceptable for for 5 out of 8 scenarios, but still not acceptable for 3 out of 8 scenarios even when consideration is given to standard mitigation measures: 20 m drift + run-off buffer.

The risk to aquatic organisms from exposure to thiamethoxam via late application to potatoes is acceptable for for 6 out of 8 scenarios, but still not acceptable for 2 out of 8 scenarios even when consideration is given to standard mitigation measures: 20 m drift + run-off buffer.

The risk to aquatic organisms from exposure to thiamethoxam via an early application to lettuce is acceptable for for 3 out of 9 scenarios, but still not acceptable for 6 out of 9 scenarios even when consideration is given to standard mitigation measures: 20 m drift + run-off buffer.

The risk to aquatic organisms from exposure to thiamethoxam via a late application to lettuce is acceptable for for 3 out of 9 scenarios, but still not acceptable for 6 out of 9 scenarios even when consideration is given to standard mitigation measures: 20 m drift + run-off buffer.

Thiamethoxam metabolites other than CGA322704

Table 9.9.30: Toxicity data and Tier 1 RACs for aquatic species and thiamethoxam metabolites

Organism group	Test organism	Endpoint		AF	Tier 1-RAC
		(type)	(µg/L)		(µg/L)
CGA355190					
Fish	Rainbow trout (*Oncorhynchus mykiss*)	96 hr LC_{50}	>100 000	100	>1 000
Aquatic invertebrates (Crustacea)	*Daphnia magna*	48 hr EC_{50}	>100 000		>1 000
Aquatic invertebrates (Insecta)	*Chironomus riparius*	48 hr EC_{50}	4 100		41
Green algae	*Selenastrum capricornutum*	72 hr $E_{r/b}C_{50}$	>100 000	10	>1 000
NOA407475					
Fish	Rainbow trout (*Oncorhynchus mykiss*)	96 hr LC_{50}	>100 000	100	>1 000
Aquatic invertebrates (Crustacea)	*Daphnia magna*	48 hr EC_{50}	82 900		829
Aquatic invertebrates (Insecta)	*Chironomus riparius*	28 d NOEC	1000 µg/kg sed.	10	100 µg/kg sed.
Green algae	*Selenastrum capricornutum*	72 hr E_rC_{50}	33 800		3 380
NOA404617					
Aquatic invertebrates (Insecta)	*Chironomus riparius*	48 hr EC_{50}	>110 000	100	>1 100
CGA353042					
Aquatic invertebrates (Insecta)	*Chironomus riparius*	26 d NOEC	100 000	10	10 000
CGA282149					
Fish	Rainbow trout *(Oncorhynchus mykiss)*	96 hr LC_{50}	>100 000	100	>1 000
	Fathead Minnow *Pimephales promelas*	32 d NOEC	115 000	10	11 500
Aquatic invertebrates (Crustacea)	*Daphnia magna*	48 hr EC_{50}	>100 000	100	>1 000
		21 d NOEC	56 000	10	5 600
Aquatic invertebrates (Insecta)	*Chironomus riparius*	48 hr EC_{50}	>100 000	100	>1 000
Green algae	*Selenastrum capricornutum*	72 hr E_rC_{50}	16 400	10	1 640

Potato

Table 9.9.31: Metabolite FOCUS Step 2 PEC_{sw} and Tier 1 RAC_{sw} for potato and aquatic species

Metabolite	FOCUS Step	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)						
			Fish acute	Aquatic crustaceans acute	Aquatic insects acute	Fish chronic	Aquatic crustaceans chronic	Aquatic insects chronic	Algae
CGA355190	2	0.536	>1 000	>1 000	41	-	-	-	>1 000
NOA407475	2	0.451	>1 000	829	-	-	-	-	3 380
NOA404617	2	0.148	-	-	>1 100	-	-	-	-
CGA353042	2	0.698	-	-	-	-	-	10 000	-
CGA282149	2	0.074	>1 000	>1 000	>1 000	11 500	5 600	-	1 640

Table 9.9.32: Metabolite FOCUS Step 2 PEC_{sed} and Tier 1 RAC_{sed} for potato and aquatic species

Metabolite	FOCUS Step	Maximum PECsed (µg/kg)	Tier 1 RACsed (µg/kg)						
			Fish acute	Aquatic crustaceans acute	Aquatic insects acute	Fish chronic	Aquatic crustaceans chronic	Aquatic insects chronic	Algae
NOA407475	2	3.86	-	-	-	-	100	-	-

Lettuce

Table 9.9.33: Metabolite FOCUS Step 2 PEC_{sw} and Tier 1 RAC_{sw} for lettuce and aquatic species

Metabolite	FOCUS Step	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)						
			Fish acute	Aquatic crustaceans acute	Aquatic insects acute	Fish chronic	Aquatic crustaceans chronic	Aquatic insects chronic	Algae
CGA355190	2	1.19	>1 000	>1 000	41	-	-	-	>1000
NOA407475	2	1.01	>1 000	829	-	-	-	-	3380
NOA404617	2	0.331	-	-	>1100	-	-	-	-
CGA353042	2	1.55	-	-	-	-	-	10 000	-
CGA282149	2	0.164	>1 000	>1 000	>1 000	11 500	5 600	-	1 640

Table 9.9.34: Metabolite FOCUS Step 2 PEC_{sed} and Tier 1 RAC_{sed} for lettuce and aquatic species

Metabolite	FOCUS Step	Maximum PECsed (µg/kg)	Tier 1 RACsed (µg/kg)						
			Fish acute	Aquatic crustaceans acute	Aquatic insects acute	Fish chronic	Aquatic crustaceans chronic	Aquatic insects chronic	Algae
NOA407475	2	8.61	-	-	-	-	100	-	-

Conclusion for Thiamethoxam metabolites other than CGA322704 for field uses

When applied in accordance with the intended uses, thiamethoxam metabolites, other than CGA322704, poses an acceptable risk to aquatic organisms.

Metabolite CGA322704 (clothianidin)

Table 9.9.35: Toxicity data and Tier 1 RACs for aquatic species and CGA322704

Organism group	Test organism	Endpoint		AF	Tier 1-RAC
		(type)	(µg/L)		(µg/L)
Acute effects					
Fish	Rainbow trout (*Oncorhynchus mykiss*)	96 hr LC_{50}	>100 000	100	>1000
Aquatic invertebrates (Crustacea)	*Crangonyx pseudogracilis*	48 hr EC_{50}	14		0.14
Aquatic invertebrates (Insecta)	*Dytiscidae*	48 hr EC_{50}	7		**0.07**
Chronic effects					
Fish	*Pimephales promelas*	28 d NOEC	20 000	10	**2000**
Aquatic invertebrates (Insecta)	*Chironomus riparius*	28 d NOEC	0.67 (nom)	10	**0.067 (nom)**
			0.18 (mm)		**0.018 (mm)**
		28 d NOEC	15 µg/kg sed. (nom)		**1.5 µg/kg sed.** (nom)
			5.5 µg/kg sed. (mm)		**0.55 µg/kg sed.** (mm)
Green algae	*Selenastrum capricornutum*	72 h $E_{r/b}C_{50}$	>100 000		>10 000

Acute effects: The lowest Tier 1 RACsw,ac is 0.07 µg/L, based on the toxicity to the aquatic insect, Dytiscidae.

Chronic effects: The lowest Tier 1 RACsw,ch is 0.067 µg/L (nom) or 0.018 µg/L (mm), based on the toxicity to the aquatic insect, *Chironomus riparius*. The lowest tier 1 RACsed,ch is 1.5 µg/kg (nom) or 0.55 µg/kg (mm), also based on the toxicity to *Chironomus riparius*.

Following the EFSA Aquatic Guidance, these Tier 1 RACs are compared to the exposure values to determine if the risk is acceptable.

Tier 1 risk to aquatic invertebrates for CGA322704 (clothianidin) (covering other aquatic organisms)

Potato

Table 9.9.36: CGA322704 FOCUS Step 1 and 2 PEC and Tier 1 RAC for potato and aquatic species

Crop	FOCUS Step	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)		Maximum PECsed (µg/kg)	Tier 1 RACsed (µg/kg)
			Acute	Chronic		Chronic
Potato	1	**1.70**	0.07	0.067 (nom) 0.018 (mm)	**2.51**	1.5 (nom) 0.55 (mm)
	2	**0.558**			0.826	

PECsw values in bold are greater than the RAC value

Table 9.9.37: CGA322704 Tier 1 FOCUS Step 3 PEC_{sw} and Tier 1 RAC_{sw} for potato and aquatic species

Crop	FOCUS Step 3 Scenario	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)	
			Acute	Chronic
Potato BBCH 15	D3 (D)	0.005	0.07	0.067 (nom) 0.018 (mm)
	D4 (P)	**0.026***		
	D4 (S)	0.018		
	D6 (D)	0.011		

	R1 (P)	<0.001		
	R1 (S)	0.001		
	R2 (S)	0.001		
	R3 (S)	0.002		
Potato BBCH 59	D3 (D)	0.003	0.07	0.067 (nom) 0.018 (mm)
	D4 (P)	0.012		
	D4 (S)	0.009		
	D6 (D)	0.013		
	R1 (P)	<0.001		
	R1 (S)	0.002		
	R2 (S)	0.001		
	R3 (S)	0.004		

*FOCUS Step 4 PECsw with consideration of 20 m drift + run-off buffer would result in the same PECsw value of 0.026 µg/L

Table 9.9.38: CGA322704 Tier 1 FOCUS Step 3 PEC_{sed} and Tier 1 RAC_{sw} for potato and aquatic species

Crop	FOCUS Step 3 Scenario	Maximum PECsed (µg/kg)	Tier 1 RACsed (µg/L)
			Chronic
Potato BBCH 15	D3 (D)	0.035	1.5 (nom) 0.55 (mm)
	D4 (P)	0.144	
	D4 (S)	0.055	
	D6 (D)	0.017	
	R1 (P)	0.001	
	R1 (S)	0.001	
	R2 (S)	0.002	
	R3 (S)	0.001	
Potato BBCH 59	D3 (D)	0.023	1.5 (nom) 0.55 (mm)
	D4 (P)	0.074	
	D4 (S)	0.029	
	D6 (D)	0.018	
	R1 (P)	0.002	
	R1 (S)	0.001	
	R2 (S)	0.001	
	R3 (S)	0.003	

Lettuce

Table 9.9.39: CGA322704 FOCUS Step 1 and 2 PEC and Tier 1 RAC for lettuce and aquatic species

Crop	FOCUS Step	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)		Maximum PECsed (µg/kg)	Tier 1 RACsed (µg/kg)
			Acute	Chronic		Chronic
Lettuce	1	**4.24**	0.07	0.067 (nom) 0.018 (mm)	**6.28**	1.5 (nom) 0.55 (mm)
	2	**1.23**			**1.82**	

PECsw values in **bold** are greater than the RAC value

Table 9.9.40: CGA322704 Tier 1 FOCUS Step 3 PEC_{sw} and Tier 1 RAC_{sw} for lettuce and aquatic species

Crop	FOCUS Step 3 Scenario	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)		Maximum PECsed (µg/kg)	Tier 1 RACsed (µg/kg)
			Acute	Chronic		Chronic
Lettuce BBCH 15	D3 (D)	**0.024***	0.07	0.067 (nom) 0.018 (mm)	0.162	1.5 (nom) 0.55 (mm)
	D4 (P)	**0.084***			0.440	
	D4 (S)	**0.053***			0.172	
	D6 (D)	**0.067***			0.094	
	R1 (P)	<0.001			0.002	
	R1 (S)	0.005			0.002	
	R2 (S)	0.002			0.003	
	R3 (S)	0.003			0.001	
	R4 (S)	0.002			0.001	
Lettuce BBCH 49	D3 (D)	0.013	0.07	0.067 (nom) 0.018 (mm)	0.094	1.5 (nom) 0.55 (mm)
	D4 (P)	**0.033***			0.185	
	D4 (S)	**0.022***			0.073	
	D6 (D)	**0.028***			0.067	
	R1 (P)	<0.001			0.002	
	R1 (S)	0.002			0.002	
	R2 (S)	0.004			0.004	
	R3 (S)	0.007			0.003	
	R4 (S)	0.003			0.002	

*FOCUS Step 4 PECsw with consideration of 20 m drift + run-off buffer would result in the same PECsw values

For CGA322704, the risk to aquatic invertebrates was acceptable based on Tier 1 RACsw, except for some scenarios (D3, D4, D6).

Refined risk to aquatic invertebrates for CGA322704 (clothianidin)

Two mesocosm studies are available for CGA322704 (See summaries in volume 3 CA). An overall ETO-RAC of 0.25 µg a.s./L. was derived by applying an assessment factor (AF) of 2 on the NOEC (0.5 µg/L) based on effect class 1. However, an uncertainty remains concerning effects and recovery (abundance and emergence) of the known sensitive Ephemeroptera, particularly species *Cloeon dipterum* and *Caenis sp* in this cosm. As it was the case for Thiamethoxam, a mesocosm study could be peformed focusing on abundance and emergence of Ephemeroptera (i.e. Cloeon dipterum.)

Risk to other groups for CGA322704

Table 9.9.41: CGA322704 Tier I FOCUS Step 3 PEC_{SW} and refined Tier 1 RACsw for aquatic species

Crop	FOCUS Step	Maximum PECsw (µg/L)		Tier 1 RACsw (µg/L)	
			Fish acute	Fish chronic	Algae
Potato	3	0.026	>1000	2000	>10 000
Lettuce	3	0.067			

A9765R

RACs for aquatic organisms are the same as the one presented in previous part for A9584 C

Field uses (sugar beet)

Thiamethoxam

Tier 1 risk to aquatic insects for thiamethoxam (covering other aquatic organsims)

Table 9.9.42: Thiamethoxam FOCUS Step 1 and 2 PEC and Tier 1 RAC_{sw} for aquatic species

Crop	FOCUS Step	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)		Maximum PECsed (µg/kg)	Tier 1 RACsed (µg/kg)	
			Acute	Chronic		Acute	Chronic
Sugar beet	1	**17.9**	0.14	1.0 (nom) 0.27 (mm)	**12.0**	>26	8.5 (nom) 0.72 (mm)
	2	**7.00**			4.70		

PECsw values in **bold** are greater than the RAC value

Table 9.9.43: Thiamethoxam Tier 1 FOCUS Step 3 and Tier 1 RAC_{sw} for aquatic species

Crop	Scenario	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)	
			Acute	Chronic
Sugar beet	D3 (D)	**0.570**	0.14	1.0 (nom) 0.27 (mm)
	D4 (P)	**0.927**		
	D4 (S)	**0.620**		
	R1 (P)	0.006		
	R1 (S)	0.069		
	R3 (S)	**0.498**		

PECsw values in **bold** are greater than the RAC value

Table 9.9.44: Thiamethoxam Tier 1 FOCUS Step 3 and Tier 1 RAC_{sw} for aquatic species

Crop	Scenario	Maximum PECsed (µg/L)	Tier 1 RACsed (µg/kg)	
			Acute	Chronic
Sugar beet	D3 (D)	**2.60**	>26	8.5 (nom) 0.72 (mm)
	D4 (P)	**2.70**		
	D4 (S)	**1.59**		
	R1 (P)	0.010		
	R1 (S)	0.013		
	R3 (S)	0.076		

PECsw values in **bold** are greater than the RAC value

Refined risk to aquatic insects for thiamethoxam

Table 9.9.45: Thiamethoxam Tier 1 FOCUS Step 3 PEC_{SW} and worst-case ETO-RACsw

Crop	FOCUS Scenario	Step 3 PECsw (µg a.s./L)	Tier 3 ETO-RACsw (µg a.s./L)
Sugar beet	D3 (D)	**0.570**	0.15
	D4 (P)	**0.927**	
	D4 (S)	**0.620**	
	R1 (P)	0.006	
	R1 (S)	0.069	
	R3 (S)	**0.498**	

PECsw values in **bold** are greater than the RAC value

The risk could be refined using standard mitigation measures. However, FOCUS Step 4 PECsw (Tier 1) were not available in E-Fate section and FOCUS Step 4 PECsw (Tier 2) were not accepted by RMS in E-Fate section (see volume 3 CP B.8). Therefore, TER with FOCUS Step 4 PECsw are not provided.

Risk to other groups for thiamethoxam

Table 9.9.46: Thiamethoxam Tier 1 FOCUS Step 3 PECsw and Tier 1 RAC_{sw} for aquatic species

Crop	FOCUS Step	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)			
			Fish acute	Fish chronic	Algae	Aquatic plants
Sugar beet	3	0.927	>1 250	170	>8 180	>9 020

Conclusion for Thiamethoxam

The risk to aquatic organisms from exposure to thiamethoxam to sugar beet is acceptable for 2 out 6 scenarios with FOCUS Step 3 PECsw (no mitigation measure). However, risk to aquatic organisms is not acceptable for 4 out 6 scenarios. FOCUS Step 4 PECsw considering mitigation measures are not available. Further refinement (i.e. mitigation measure) is required.

Thiamethoxam metabolites except CGA322704

Table 9.9.47: Metabolite FOCUS Step 2 PEC and Tier 1 RAC_{sw} for aquatic species

Metabolite	FOCUS Step	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)						
			Fish acute	Aquatic crustaceans acute	Aquatic insects acute	Fish chronic	Aquatic crustaceans chronic	Aquatic insects chronic	Algae
CGA355190	2	1.80	>1 000	>1 000	41	-	-	-	>1 000
NOA407475	2	1.41	>1 000	829	-	-	-	-	3 380
NOA404617	2	0.475	-	-	>1 100	-	-	-	-
CGA282149	2	0.256	>1 000	>1 000	>1 000	11 500	5 600	-	1 640

Table 9.9.48: Metabolite FOCUS Step 2 and Tier 1 RAC_{sed} for aquatic species

Metabolite	FOCUS Step	Maximum PECsed (µg/kg)	Tier 1 RACsed (µg/kg)						
			Fish acute	Aquatic crustaceans acute	Aquatic insects acute	Fish chronic	Aquatic crustaceans chronic	Aquatic insects chronic	Algae
NOA407475	2	12.3	-	-	-	-	100	-	-

Conclusion for metabolites except CGA322704

When applied in accordance with the intended uses, thiamethoxam metabolites, other than CGA322704, poses an acceptable risk to aquatic organisms.

Metabolite CGA322704 (Clothianidin)

Tier 1 risk to aquatic insects for CGA322704 (covering other aquatic organsims)

Table 9.9.49: CGA322704 Tier 1 FOCUS Step 3 PEC values and Tier 1 RAC for aquatic species

Crop	FOCUS Step 3 Scenario	Maximum PECsw (µg/L)	Tier 1 RACsw (µg/L)		Maximum PECsed (µg/kg)	Tier 1 RACsed (µg/kg)
			Acute	Chronic		Chronic
Sugar beet	D3 (D)	**0.032**	0.07	0.067 (nom) 0.018 (mm)	0.212	1.5 (nom) 0.55 (mm)
	D4 (P)	**0.056**			0.299	
	D4 (S)	**0.034**			0.132	
	R1 (P)	<0.001			<0.001	
	R1 (S)	0.001			<0.001	
	R3 (S)	0.002			0.001	

For CGA322704, the risk to aquatic invertebrates was acceptable based on Tier 1 RACsw, except for 3 scenarios: D3 (D), D4 (P), D4 (S).

Refined risk to aquatic insects for CGA322704

Two mesocosm studies are available for CGA322704 (See summaries in volume 3 CA). An overall ETO-RAC of 0.25 µg a.s./L was derived by applying an assessment factor (AF) of 2 on the NOEC (0.5 µg/L) based on effect class 1. However, an uncertainty remains concerning effects and recovery (abundance and emergence) of the known sensitive Ephemeroptera, particularly species *Cloeon dipterum* and *Caenis sp* in this cosm. As it was the case for Thiamethoxam, a mesocosm study could be peformed focusing on abundance and emergence of Ephemeroptera (i.e. Cloeon dipterum.)

Risk to other groups for CGA322704

The Tier 1 RACsw for fish and algae exceed the maximum FOCUS Step 3 PECsw values of 0.056 µg/L

Table 9.9.50: CGA322704 Tier 1 FOCUS Step 3 PEC_{SW} and refined Tier 1 RACsw for aquatic species

Crop	FOCUS Step	Maximum PECsw (µg/L)		Tier 1 RACsw (µg/L)	
			Fish acute	Fish chronic	Algae
Sugar beet	3	0.056	>1000	2000	>10 000

Thus for fish and algae, the risk is acceptable.

Conclusion for CGA322704

When applied in accordance with the intended uses, thiamethoxam metabolite CGA322704 poses an acceptable risk to aquatic organisms, except for 3 scenarios: D3 (D), D4 (P), D4 (S). Moreover, an uncertainty remains concerning effects and recovery (abundance and emergence) of the known sensitive Ephemeroptera, particularly species Cloeon dipterum and Caenis sp in this cosm. As it was the case for Thiamethoxam, a mesocosm study could be peformed focusing on abundance and emergence of Ephemeroptera (i.e. Cloeon dipterum.)

Summary of products exposure and risk assessment for bees

The risk to bees has been assessed following the EPPO 2010 scheme[18] as proposed in the list of guidance documents relevant to the implementation of Regulation 1107/2009, published in the official EU Journal 2013/C 95/01 and 95/02.

A9584 C

Greenhouse use:

A risk assessment is not necessary for uses restricted to permanent greenhouses.

Field uses (lettuce and potato)

Risk assessment from exposure via the crop

Acute risk assessment

The potential acute risk from use of A9584C was assessed using the maximum single application rates in potatoes and lettuce and the LD_{50} values to calculate hazard quotients in accordance with the current Terrestrial Guidance Document[19] and EPPO 2010.

Table 9.9.51: Risk to bees from oral exposure to A9584C

Test substance	GAP Crop	Application rate (g/ha)	Oral LD_{50} (µg/bee)	Hazard quotient
Thiamethoxam	Potato	20	0.005	**4 000**
A9584C		80	0.0178	**4 500**
Thiamethoxam	Lettuce	50	0.005	**10 000**
A9584C		200	0.0178	**11 000**

Table 9.9.52: Risk to bees from contact exposure to A9584C

Test substance	GAP Crop	Application rate (g/ha)	Contact LD_{50} (µg/bee)	Hazard quotient
Thiamethoxam	Potato	20	0.024	**830**
A9584C		80	0.093	**860**
Thiamethoxam	Lettuce	50	0.024	**2 100**
A9584C		200	0.093	**2 200**

Values in **bold** exceed the trigger and indicate potential risk.

All the hazard quotients for thiamethoxam, and the formulated product A9584C are above the trigger of 50, indicating further refinement of the risk to bees is required following the use of A9584C according to the proposed use pattern. The notifier considered that as potato and lettuce crops are not attractive to honey bees and applications will be made before flowering, bees are unlikely to be exposed following direct over spray or by contact with residues on the crop.

RMS comment: As reported in Thiamethoxam EFSA bee review 2015 "*If the crop is harvested before flowering there is a low risk to bees from contact exposure and foraging for pollen and nectar directly from the treated*

[18] EPPO/OEPP (2010) Environmental risk assessment scheme for plant protection products, Chapter 10: Honeybees (PP 3/10(3)). Bulletin OEPP/EPPO Bulletin 40: 323-331.

[19] Anonymous (2002b). Guidance Document on terrestrial ecotoxicology under Council Directive 91/414/EEC. SANCO/10329/2002. 17 October 2002.

crop", therefore this statement is in accordance with Thiamethoxam EFSA bee review 2015 for lettuce. However, during Pesticides Peer Review Meeting 145 (7 - 9 June 2016), it was still reported that for potato, based on EFSA (2015)[20], data were available showing pollen collection by honeybees. Therefore, exposure via potato crop should not be excluded. Higher tier refinement is necessary. (see after)

Chronic risk assessment

Chronic adult and larval bee studies have been conducted according to the data requirements under 1007/2009. The endpoints from these studies have been assessed by adapting the EPPO 2010 scheme.

Larval assessment

A worst-case risk assessment to honey bee larvae can be conducted through the calculation of a TER value as set out in the EPPO 2010 scheme (point 5 on the scheme).

A worst-case of potential exposure via residues in pollen / nectar can be estimated based on the default worst-case residue of 1 mg a.s./kg proposed in the EPPO 2010 scheme (see Note 6).

The default residues can then be combined with a measure of consumption in order to estimate the exposure. Worst case data from **Rortais *et al.*, 2005**[21] as proposed in the EPPO scheme have been used to estimate the consumption by bee larvae:

Worst case: drone larvae consuming 98.2 mg sugar in 6.5 days (= 15.1 mg sugar /day).

Assuming 40% sugar content of nectar: (98.2 * 2.5)/6.5 = 37.8 mg nectar/day

Thus considering residues of 1 mg a.s./kg x consumption of 37.8 mg nectar/larva/day

Total exposure ETE = 0.0378 µg a.s./larva/day

This can be compared to the thiamethoxam larval NOED of 0.003925µg a.s./larva/day (based on a 4 day exposure during development period).

TER = NOED (µg a.s./larva/day)/ ETE (µg a.s./larva/day)
= 0.003925/0.0378 = 0.1 (EPPO 2010 trigger = 1)

A comparison can also be made to the CGA322704 larval NOED of 0.00044 µg a.s./larva/day (based on a 3 day exposure during development period).

TER = NOEL (µg a.s./larva/day)/ ETE (µg a.s./larva/day)
= 0.00044 /0.0378 = 0.012 (EPPO 2010 trigger = 1)

The EPPO 2010 scheme proposes a trigger of 1 for assessment of the risk to honey bees. With TER values of 0.1, 0.012 for thiamethoxam, CGA322704, the proposed uses pose an unacceptable risk to bee larval development for Thiamethoxam and CGA322704. Higher tier refinement is necessary. (see after)

It can also be noted that previous TER calculations are based on nectar consumption, whereas potato doesn't produce nectar and exposure from such crop would result in consumption of pollen only. RMS added calculation on pollen consumption:

Worst case data from **Rortais *et al.*, 2005**:

workers larvae consuming 5.4 mg pollen in 5 days (= 1.08 mg pollen /day).

[20] EFSA (European Food Safety Authority), 2015. Conclusion on the peer review of the pesticide risk assessment for bees for the active substance imidacloprid considering all uses other than seed treatments and granules. EFSA Journal 2015;13(8):4211, 82 pp, doi:10.2903/j.efsa.2015.4211

[21] Agnès RORTAIS, Gérard ARNOLD, Marie-Pierre HALM, Frédérique TOUFFET-BRIENS (2005) Modes of honeybees exposure to systemic insecticides: estimated amounts of contaminated pollen and nectar consumed by different categories of bees. Apidologie 36 (2005) 71–83

Thus considering residues of 1 mg a.s./kg x consumption of 1.08 mg nectar/larva/day

Total exposure ETE = 0.00108 µg a.s./larva/day

This can be compared to the thiamethoxam larval NOED of 0.003925µg a.s./larva/day (based on a 4 day exposure during development period).

TER = NOED (µg a.s./larva/day)/ ETE (µg a.s./larva/day)
= 0.003925/0.00108 = 3.6 (EPPO 2010 trigger = 1)

A comparison can also be made to the CGA322704 larval NOED of 0.00044 µg a.s./larva/day (based on a 3 day exposure during development period).

TER = NOEL (µg a.s./larva/day)/ ETE (µg a.s./larva/day)
= 0.00044 /0.00108 = 0.4 (EPPO 2010 trigger = 1)

Higher tier refinement is necessary. (see after)

Adult chronic assessment

The EPPO 2010 scheme does not recommend a chronic assessment for adults for foliar spray applications. However, as an approach is proposed as an assessment refinement for seed coatings/soil treatments (point 7 on the scheme), this approach can be adapted to provide a worst-case assessment for foliar sprays.

A worst-case of potential exposure via residues in pollen / nectar can be estimated as before based on the default worst-case value of 1 mg a.s./kg proposed in the EPPO 2010 scheme (see Note 6).

The default residues can then be combined with a measure of consumption in order to estimate the exposure. Worst case data from ***Rortais et al., 2005*** as proposed in the EPPO 2010 scheme have been used to estimate the consumption by bee foragers:

Worst case: forager consuming 128 mg sugar/day.

Assuming 40% sugar content of nectar: (128 * 2.5) = 320 mg nectar/day

Thus considering residues of 1 mg a.s./kg sugar x consumption of 320 mg nectar/bee/day

Total exposure ETE = 0.32 µg a.s./bee/day

This can be compared to the thiamethoxam adult NOED of 0.00245 µg a.s./bee/day.

TER = NOED (µg a.s./bee/day)/ ETE (µg a.s./bee/day)

= (0.00245 /0.32) = 0.0076 (EPPO 2010 trigger = 1)

A comparison can also be made to CGA322704 adult NOED of 0.00038 µg/bee/day.

TER = NOEL (µg a.s./bee/day)/ ETE (µg a.s./bee/day)

= (0.00038/0.32) = 0.0012 (EPPO 2010 trigger = 1)

The EPPO 2010 scheme proposes a trigger of 1 for assessment of the risk to honey bees when a NOED is used in this assessment. The TER values for thiamethoxam and CGA322704 are less than this trigger, indicating that further assessment of the risk is required. Higher tier refinement is necessary. (see after)

The notifier considered that as potato and lettuce crops are not attractive to honey bees and applications will be made before flowering, adults are unlikely to be chronically exposed to residues of thiamethoxam or CGA322704 on the crop.

RMS comment: As already commented previously, as lettuce is harvested before flowering, risk is considered to be acceptable. However, a refinement is required for potatoes.

It can also be noted that preivous TER calculations are based on nectar consumption, whereas potato doesn't produce nectar and exposure from such crop would result in consumption of pollen only. Forager did not consume pollen, therefore TER calculation based on pollen consumption are not relevant for foragers. However, regarding the attractiveness of potatoes to honeybees, data were provided by Denmark during the experts' meeting (EFSA, 2015a) indicating that honeybees collect pollen from potatoes. Exposure of larve from pollen collected may not be excluded (see previous calculations). Higher tier studies (tunnel and field studies) are considered more relevant.

Higher tier risk assessment arising from spray application on potatoes

The semi-field studies conducted with A9584C show the NOEL was determined to be 1 g a.s./ha following application directly onto foraging bees in *Phacelia*. At 1 g a.s./ha no effects were found on mortality, foraging behaviour, strength of the colony and brood development. Direct application of A9584C onto foraging bees at 5 g a.s./ha resulted in a slight increase in mortality immediately after application. However, mean post-application mortality was not increased compared to control or to the pre-application period. Additionally, no effects were observed on the strength of the colonies and brood development. A similar study where thiamethoxam was sprayed directly onto foraging bees at 5 g a.s./ha showed effects on mortality and foraging activity compared to the control on the day of application. There were however no lasting effects on mortality or foraging activity and no effects on the condition of the colony. Semi-field trials conducted at 50 g a.s./ha and above where A9584C was applied directly onto foraging bees showed high levels of mortality and reductions in colony strength.

RMS comment: The notifier referred to the semi-field conducted by Nengel, 1998a (ref. CGA293343/0597). A summary is provided above. RMS would like to note that this study had been reassessed and the assessments published in 2015. Summary of observations as reported in EFSA (2015): At 1 g a.s/ha (during bee flight and after bee flight): Decrease in foraging activity. At 5 g a.s/ha (during bee flight and after bee flight): Decrease in foraging activity. Increase in forager mortality (The increase in mortality was only obvious on the day of application as indicated in previous study evaluation note). The application rate in this tunnel study (1 to 5 g a.s./ha) does not cover the intended application rate of 20 g a.s./ha for potatoes.

Applications made 5 and 10 days before flowering in melons at 100 g a.s./ha were investigated for effects on mortality, foraging activity and colony strength. When thiamethoxam was applied 10 days before flowering at 100 g a.s./ha, there were no overall statistically significant effect on mortality, however foraging activity was significantly reduced on day 4 and 6 after application. When applied 5 days before flowering at 100 g a.s./ha mortality was significantly increased compared to the control on all days after the start of exposure except on day 2 and 8. Foraging activity was however not statistically different to the control during the exposure period. Colony strength decreased in all treatment groups including the control due to enclosure in the tunnel. In colonies exposed to thiamethoxam applied 10 days before flowering brood development increased when colonies were removed from the tunnels and reached the starting levels at the same time as the control colonies. In colonies from tunnels where thiamethoxam was applied 5 days before flowering, brood development was slightly reduced compared to the control mainly due to one colony which lost its queen.

RMS comment: The notifier referred to the semi-field conducted by Bocksch, 2011a (ref. A9584C_10176). A summary is provided above. RMS would like to note that this study had been reassessed and the assessments published in 2015. Summary of observations as reported in EFSA (2015): Bees introduced after 5 days of aging: Increased forager mortality (statistically significant), no statistically significant difference in flight intensity. Bees introduced after 10 days of aging: Increased forager mortality (statistically significant), Decrease in flight intensity (statistically significant).

Fields trials have been conducted with A9584C in a variety of bee attractive crops with flowering ground cover or where ground cover has been mulched to remove flowers. The trials also investigated the effects of applications pre- and post-flowering or in the evening to identify possible risk mitigation options. The results show that, provided applications are made at least 5 days before flowering begins and any flowering ground cover is mulched, there are no effects on adult bee mortality, foraging activity, brood development or colony strength.

RMS comment: The notifier referred to the field conducted by Rin Britt, 2005 (ref. CGA293343/2577), Bocksch, 2011b (ref A9584C_10173), and Schur (2002). A summary is provided above. RMS would like to

note that this study had been reassessed and the assessments published in 2015. Summary of observations as reported in EFSA (2015):

Rin Britt, 2005: Study not reported in EFSA (2015)

Bocksch, 2011b/ Peach (just before flowering), 62.5 g a.s./ha/ Bees introduced 16 days after application: Slight increase in forager mortality. Decrease in foraging activity. Bees introduced 7 days after application: Increase in forager mortality. Decrease in foraging activity.

Schur (2002)/ Apple (flowering), 100 g a.s/ha Bees introduced 8 days after application: No clear differences in foraging activity between the control and treatment hives. Possible increase in forager mortality.

RMS comment:

RMS would like to note that all these semi field and field studies had already been reassessed and the assessments published in EFSA (2015)[22]. The conclusion concernning these higher tier studies, as reported in EFSA (2015), was the following:

"*The available higher tier effects studies from the dossiers and/or made available by Member States have been evaluated according to the criteria given in EFSA, 2013b. A full evaluation of each study was reported in the study evaluation notes; EFSA, 2015a. A brief summary of the observations is given in Appendix B (Tables 17 and 19). The fundamental basis for higher tier risk assessment according to EFSA, 2013b is to design higher tier effect studies which are able to address the specific protection goals (SPG) for worst case exposure (90th percentile worst case for the hives at the edge of the treated fields in the area of use) and to ensure that the studies are sufficiently sensitive in order to detect biological effects (i.e. cause effect relationship) to meet the SPG for the level of effect (7% reduction in colony). In order to demonstrate that the studies have achieved the 90th percentile exposure, EFSA, 2013b suggests that an exposure assessment is undertaken by performing residue studies in areas representative of where the active substance will be applied. The level of exposure achieved in the effect field study can then be demonstrated to be representative across a wider area (i.e. if it equates to the 90th percentile exposure level). As discussed in Section 3.2, insufficient residue data were available to perform an exposure assessment (hence a tier 2 risk assessment) for any of the authorised uses of thiamethoxam. An alternative approach would be to have a sufficient number of suitable higher tier effects studies, which are also considered to be able to address the exposure SPG. The number of studies required would depend on numerous factors, such as the representative GAP, the area where the active substance will be applied, the quality of the exposure assessment within the studies and the consistency of results. However, the available higher tier effects studies for thiamethoxam were not suitable to be able to assess whether they met the exposure SPG. The second critical aspect of the usefulness of higher tier effects studies for a risk assessment in accordance with EFSA, 2013b is to ensure that the studies are sufficiently sensitive in order to detect biological effects to meet the SPG for the level of effect (7% reduction in colony strength). Several criteria are given in the guidance document, which are essential for such an assessment (e.g. an assessment of the power of detection). EFSA, 2013b also recommended several improvements to the methodology used for higher tier effects studies, e.g. to increase the size of field, to increase the distance between the test fields and the control, to include overwintering success or improvements to the measurements of mortality and colony strength. None of the available studies fulfilled the criteria of EFSA, 2013b. It is acknowledged that the studies were performed prior to the publication of EFSA, 2013b. In evaluating these studies, any deficiency in the study design, beyond those identified on the basis of the new elements introduced by EFSA, 2013b, was also highlighted. Several studies had severe limitations which question their reliability for any form of risk assessment (e.g. lack of untreated control). On the basis of the available data set, as general observation, differences between the treatment and the controls for foraging activity and forager mortality were noted at the tested application rates, crops and growth stages (including when applications were made a number of days before flowering). For higher tier risk assessment, a further consideration of the data included in the systematic literature review can be performed in the future.*"

RMS conclusion:

[22] EFSA (European Food Safety Authority), 2015. Conclusion on the peer review of the pesticide risk assessment for bees for the active substance thiamethoxam considering all uses other than seed treatments and granules. EFSA Journal 2015;13(8):4212, 70 pp. doi:10.2903/j.efsa.2015.4212

It should be noted that the question concerning the reliability of semi-field and field studies in risk assessment reported in EFSA 2015 conclusion was in relation with the requirement of EFSA, 2013b guidance document on bees while the studies were performed before the publication of the guidance document. Moreover, even if there are some limitations in the semi-field and field studies against the requirement of EFSA, 2013b, RMS considers that these studies (at least those studies without severe limitation) provided relevant information and they could be used in an overall risk assessment by considering them together.

Based on results from all semi-field and fields studies (only studies without severe limitations) considered together in an overall risk assessment, risk for bee can be considered acceptable for intended uses with appropriate mitigation measure as follow:

Dangerous to bees/To protect bees and pollinating insects do not apply to crop plants when in flower or during the honeydew production period /Do not use where bees are actively foraging/ Respect a delay of 16 days between application and flowering period (potatoes).

Risk from in-field deposition onto flowering weeds

A new study report (Maynard et al. 2017) investigating Syngenta herbicide efficacy trial data for potatoes has been submitted. In general, such study is relatively similar than those herbicide efficacy trials investigating the occurrence of flowering weeds in cereals, potato and sugar beet fields of other neonicotinoides (clothianidin, imidacloprid), recently peer reviewed during Pesticides Peer Review Meeting 145 (7 - 9 June 2016).

The location of the different trial sites was well spread over Europe. An analysis based on the total weed ground cover was performed. There are no recordings of flowering weeds which cover >10% and only two instances where weeds are present at >10% ground cover (1.4% of weeds recorded). These results suggest that exposure to honeybees and non-Apis bees through nectar and pollen of flowering weeds in the treated fields will be negligibly low, even in non-herbicide treated fields. It can be noted that the trials were conducted at all principle crop BBCH stages to a larger or lesser extent. The majority of data is from early or late BBCH stages, expectedly representing the main uses of herbicides in potatoes (pre- and early post- emergence and desiccation uses). This study on potatoes therefore bring more information than thoses of other neonicotinoides (clothianidin, imidacloprid) wich focused on only relatively early growth stages of the considered crop as it was reflected in Pesticides Peer Review Meeting 145 (7 - 9 June 2016) and reported in EFSA conclusion 2016: "It has to be noted that this analysis focused on only relatively early growth stages of the considered crop (i.e. up to BBCH 40 for cereals, BBCH 20 for beets and BBCH 30 for potatoes). From the data available for clothianidin (EFSA, 2016c) for the granular uses, it was noted that the presence of weeds increases throughout the crop growing season. Overall, on the basis of the available data, it was concluded that the total ground cover of flowering weeds in potato, winter cereals and sugar beet could be considered generally unlikely to exceed the trigger of 10% suggested in EFSA, 2013. Therefore, the exposure to bees via this scenario could be considered of low relevance for these uses, particularly when weed control is applied."The same conclusion should be considered for Thiamethoxam for uses under evaluation (potatoes) based on results of this new study. As indicated by the notifier, no specific trials were examined from lettuce or other similar crops. According to the notifier, the exposure to bees via weeds in lettuce crop could be considered of low relevance as weed control is applied. No such data and assessments were available for the uses in leafy vegetables, therefore a data gap was identified for this potential route of exposure for these uses during Pesticides Peer Review Meeting 145 (7 - 9 June 2016). As no specific trials were examined for lettuce, RMS considered that risk for bees via weeds can be considered acceptable with appropriate mitigation measure for lettuce as follows:

"Do not apply when flowering weeds are present" (lettuce)

Risk from spray drift onto surrounding bee attractive crops and weeds

Bees may be exposed to thiamethoxam residues whilst foraging on surrounding bee attractive crops and weeds due to spray drift following the application of A9584C on potatoes and lettuce. The thiamethoxam drift values onto surrounding crops can be calculated according to **Rautmann et al. (2001)[23]** and are presented in the table below.

[23] Rautmann, D., M. Streloke, R. Winkler (2001). New basic drift values in the authorization procedure for plant protection products. Mitt. Biol. Bundesanst. Land- Forstwirtsch. No. 383. Berlin.

Table 9.9.53: Drift rates of thiamethoxam following application of A9584C in potatoes and lettuce

Potato (1 x 20 g a.s./ha)		
Distance (m)	1	5
Drift value (%)	2.77	0.57
Drift rate (g a.s./ha)	0.55	0.11
Lettuce (1 x 50 g a.s./ha)		
Distance (m)	1	5
Drift value (%)	2.77	0.57
Drift rate (g a.s./ha)	1.38	0.28

The drift rates for thiamethoxam onto surrounding bee attractive crops and weeds at 1m are 0.55 g a.s./ha for potatoes and 1.38 g a.s./ha for lettuce. In the semi-field trial conducted by Nengel (1998), applications of thiamethoxam during *Phacelia* flowering directly onto foraging bees at 1 g a.s./ha showed no effects on mortality compared to control or to the pre-application period. No effects of A9584C were observed on the strength of the colonies, the egg laying rate of the queen and the bee brood development. This rate is higher than the drift rate of thiamethoxam at 1m in potatoes indicating the risk to bees from spray drift onto surrounding bee attractive crops and weeds is considered acceptable. In lettuce, the drift rate is below 1 g a.s./ha when a 5m buffer is included.

RMS comment: see previous comments concerning the semi-field conducted by Nengel, 1998a (ref. CGA293343/0597). RMS considered that risk from spray drift onto bees foraging flowering field margin is acceptable with appropriate mitigation measure:

Respect an unsprayed buffer zone of 1 m to flowering field margin for potatoes.

Respect an unsprayed buffer zone of 5 m to flowering field margin for lettuce.

Risk through foraging on guttation fluid

RMS comment: According to the recent discussions during Pesticides Peer Review Meeting 145 (7 - 9 June 2016), as a general line of evidence, the experts noted the guttation fluids may not be the primary route of exposure for bees. Generally bees using guttation are only rarely observed. The experts agreed that the risk from exposure to residues in guttation fluids, for uses under evaluation, including potatoes and lettuce, can be considered of low relevance.

Risk from exposure to residues in pollen and nectar in succeeding crops

The likely period for a bee to be potentially exposed to attractive crops (as succeeding crop) is one to two years following application to potatoes and lettuce.

Then, regarding degradation of thiamethoxam and Clothianidin, PEC soil calculation in E-Fate section have been calculated considering accumulation over 10 to 13 years, and majority of degradation field studies has not been validated by RMS in E-Fate section (for more details, see E-Fate section). Therefore, previous statement of the notifier considering that the likelihood that residues in the pollen and nectar of succeeding crops will reach concentrations that would result in a risk to foraging bees is negligible cannot be accepted by RMS.

Therefore, RMS considered that risk via succeeding crop is acceptable with appropriate mitigation measure:
Bee-attractive crops should not be sown as a succeeding crop.

RMS overall conclusion for A9584 C

Based on results from all semi-field and fields studies (only studies without severe limitations) considered together in an overall risk assessment, risk for bee can be considered acceptable with appropriate mitigation measure as follows:

Dangerous to bees/To protect bees and pollinating insects do not apply to crop plants when in flower or during the honeydew production period /Do not use where bees are actively foraging/ Respect a delay of 16 days between application and flowering period (potatoes) / Respect an unsprayed buffer zone of 1 m to flowering field margin for potatoes and of 5 m for lettuce. Do not apply when flowering weeds are present (lettuce)/ Bee-attractive crops should not be sown as a succeeding crop.

A9765R

Field uses (sugar beet)

Risk through foraging on the crop

The EPPO 2010 risk assessment scheme[24] for bees as proposed in the list of guidance documents for the implementation of Regulation 1107/2009 is only relevant and validated for plant protection products directly applied as a foliar spray. As A9765R is applied as a sugar beet seed treatment, calculation of hazard quotients is not considered a relevant approach for assessment of risk to bees. Furthermore, as sugar beet is harvested before flowering, exposure to residues of thiamethoxam via pollen and nectar is not considered a relevant route in the risk assessment.

RMS comment: As reported in Thiamethoxam EFSA bee review 2015 "If the crop is harvested before flowering there is a low risk to bees from contact exposure and foraging for pollen and nectar directly from the treated crop", therefore this statement is in accordance with Thiamethoxam EFSA bee review 2015. Moreover, during Pesticides Peer Review Meeting 145 (7 - 9 June 2016), it was confirmed that there is a low risk to bees for uses as seed treatment of beets when the crop is harvested before flowering.

Risk from exposure to residues in dust

Table 9.9.54: HQ values calculated using a measured dust deposition value for sugar beet treated with A9765R

Treated crop	Parameter	Risk assessment for A9765R	
		Mechanical driller	Deflected pneumatic driller
Sugar beet	Application rate (g a.s./ha)	58.5	58.5
	% deposition (adjacent vegetation)	0.0036 [a]	0.1244 [a]
	Predicted off-field deposition rate (g a.s./ha)	0.0021	0.073
	Acute oral HQ [b]	0.42	15
	Acute contact HQ [c]	0.088	3.0

[a] Based on the highest mean 2 D vertical value for 0.5 mg a.s./ha quality seeds from Naeb (2015)
[b] Calculated using the acute oral LD_{50} value for thiamethoxam of 0.005 µg a.s./bee
[c] Calculated using the contact oral LD_{50} value for thiamethoxam of 0.024 µg a.s./bee

The resulting HQ values for sugar beet for both oral and contact exposure are low and less than the proposed trigger value of 50. Therefore, the risk to honey bees foraging in adjacent vegetation following dust emission during the drilling of A9765R treated sugar beet is considered acceptable.

The risk assessment for honey bees exposed to dust drift was discussed at the Pesticides Peer Review Experts" Meeting 97 and the outcome of this discussion was included in the EFSA Conclusion on the risk assessment for bees for the active substance thiamethoxam (Journal 2013;. 11(1):3067). The expert agreed to use the default deposition values for dust drift in the draft "Guidance document on the authorization of plant protection products for seed treatment" (SANCO/10553/201213). Based on this draft guidance, EFSA concluded that there was no risk to honey bee from exposure to dust after drilling of sugar beet seeds treated with thiamethoxam considering the HQ approach and a trigger of 50.

[24] EPPO/OEPP (2010) Environmental risk assessment scheme for plant protection products, Chapter 10: Honeybees (PP 3/10(3)). Bulletin OEPP/EPPO Bulletin 40: 323-331.

In accordance with the interim report of the same studies submitted by Syngenta and assessed by ES as RMS in Addendum (February 2016) to Draft Assessment Report prepared in the context of the assessment of the Confirmatory Information requested by Reg. (EU) No 485/2013, ES concluded that the exposure to bees through dust produced during the drilling of treated sugar beet seeds could be considered almost negligible and the risk to honey bees from exposure to dust produced during drilling of treated sugar beet was considered acceptable.

In accordance to the final report submitted by Syngenta in this AIR 3 dossier, the low exposure to bees through dust produced during the drilling of treated sugar beet seeds is confirmed. The risk to honey bees from exposure to dust produced during drilling of treated sugar beet can be considered acceptable.

Risk from exposure to residues in guttation fluid

A statement has been submitted and is in line with the recently discussed similar statement for potatoes, winter cereals and beets during Pesticides Peer Review Meeting 145 (7 - 9 June 2016). In general, the available new studies followed relatively similar protocol than those field studies investigating the effects of Residues of other neonicotinoides (clothianidin, imidacloprid) in Guttation Fluid on Honeybees in sugar beet fields, recently peer reviewed during Pesticides Peer Review Meeting 145 (7 - 9 June 2016). Same concern than those already done during this meeting could be repeated here (i.e statistical power of the studies not reported, ect…). However, in the end the results of these new studies confirmed results from those similar studies previously reviewed during Praper 145: There is evidence that bees are not primary collecting water from guttation fluids, as a general line of evidence bees using guttation are only rarely observed, guttation occurred rarely for beet and no clear effect was observed. Therefore, although robustness of such studies to assess the effects was questioned during the meeting and there was uncertainty around the exposure assessment, the experts agreed that the risk from exposure to residues of neonicotinoides (clothianidin, imidacloprid) in guttation fluids, for uses under evaluation (on potatoes, winter cereals and beets) can be considered of low relevance. The same conclusion should be considered for Thiamethoxam for uses under evaluation (sugar beet) based on results of these new studies.

Risk from exposure to residues in pollen and nectar in flowering weeds

A new study report (Maynard et al. 2017) investigating Syngenta herbicide efficacy trial data for sugar beet has been submitted. In general, such study is relatively similar than those herbicide efficacy trials investigating the occurrence of flowering weeds in cereals, potato and sugar beet fields of other neonicotinoides (clothianidin, imidacloprid), recently peer reviewed during Pesticides Peer Review Meeting 145 (7 - 9 June 2016). The location of the different trial sites was well spread over Europe. An analysis based on the total weed ground cover was performed. There are no recordings of flowering weeds which cover ≥10% and only one instances where post-flowering weeds are present at >10% ground cover (around 1.2% of weeds recorded). These results suggest that exposure to honeybees and non-Apis bees through nectar and pollen of flowering weeds in the treated fields will be negligibly low, even in non-herbicide treated fields. It can be noted that the trials were all conducted relatively early in the crop growing season with observations mainly made at a crop BBCH stage below 20. It would be interesting to investigate the presence of weeds also later in the season in order to fully assess the relevance of the weed scenario at later crop growth stages. However, the presence of weeds was not investigated later in the season (up to crop flowering) as these trials are herbicide efficacy trials and therefore reflect the use patterns of herbicides in sugar beet; generally pre-emergence and early post-emergence. This was also reflected in Pesticides Peer Review Meeting 145 (7 - 9 June 2016) and reported in EFSA conclusion 2016: "*It has to be noted that this analysis focused on only relatively early growth stages of the considered crop (i.e. up to BBCH 40 for cereals, BBCH 20 for beets and BBCH 30 for potatoes). From the data available for clothianidin (EFSA, 2016c) for the granular uses, it was noted that the presence of weeds increases throughout the crop growing season. Overall, on the basis of the available data, it was concluded that the total ground cover of flowering weeds in potato, winter cereals and sugar beet could be considered generally unlikely to exceed the trigger of 10% suggested in EFSA, 2013. Therefore, the exposure to bees via this scenario could be considered of low relevance for these uses, particularly when weed control is applied.*"The same conclusion should be considered for Thiamethoxam for uses under evaluation (sugar beet) based on results of this new study.

Risk from exposure to residues in pollen and nectar in succeeding crops

RMS comment

Regarding degradation of thiamethoxam and Clothianidin, PEC soil calculation in E-Fate section have been calculated considering accumulation over 10 to 13 years, and majority of degradation field studies has not been validated by RMS in E-Fate section (for more details, see E-Fate section). Therefore,

previous statement of the notifier considering that the likelihood that residues in the pollen and nectar of succeeding crops will reach concentrations that would result in a risk to foraging bees is negligible cannot be accepted by RMS.

The NOEL of 25 ppb from Bocksch (2015) was used by the notifier, however an uncertainty remains concerning the overwintering success in this study. No firm conclusion can be drawned from the interim report Bocksch (2017). Waiting for the submission of the final report, endpoint cannot be set yet.

When consideration is given to measured residue levels in succeeding crops and proportion of pollen and nectar within honey bee diets, if 100% of bee diet is obtained within the treated area the worst-case exposure of adult and larval bees to thiamethoxam + CGA322704 residues ranges from 7.5 to 10 µg/kg.

RMS comment: Waiting for the submission of the final report, endpoint cannot be set and risk for bee can be considered acceptable with appropriate mitigation measure as follows:

Bee-attractive crops should not be sown as a succeeding crop.

RMS overall conclusion for A9765R

Based on results from all available studies, risk for bee can be considered acceptable with appropriate mitigation measure as follows:

Dangerous to bees / Bee-attractive crops should not be sown as a succeeding crop.

Summary of product exposure and risk assessment for non-target arthropods other than bees

The testing and risk assessment strategy used here follow the approach recommended in the ESCORT 2 guidance document and the EC Guidance Document on Terrestrial Ecotoxicology (SANCO/10329, 17 October 2002).

A9584 C

Greenhouse use:

A risk assessment is not necessary for uses restricted to permanent greenhouses.

Field uses (lettuce and potato)

In-field

Table 9.9.55: In-field risk assessment for foliar applications of A9584C based on results from extended laboratory studies

Test type	Species	Endpoints	Maximum In-field PER (g a.s./ha)		Acceptable in-field risk
			Foliar	Soil	
Potato					
Extended laboratory, 2-D	*Typhlodromus pyri*	LR_{50} = 40.7 g a.s./ha $ER_{50\ fecundity}$ > 12.5 g a.s./ha	20	17	No
	Orius laevigatus	LR_{50} = 0.014 g a.s./ha $ER_{50\ fecundity}$ > 0.05 g a.s./ha			No
	Coccinella septempunctata	LR_{50} = 12.33 g a.s./ha $ER_{50\ fecundity}$ > 25 g a.s./ha			No
	Leptomastix dactylopii	LR_{50} = 0.47 g a.s./ha No sublethal assessments			No
	Pardosa spec.	LR_{50} >200 g a.s./ha $ER_{50\ feeding\ rate}$ > 200 g a.s./ha			Yes
	Aphidius rhopalosiphi	LR_{50} = 0.13 g a.s./ha $ER_{50\ reproduction}$ > 0.0625 g a.s./ha			No
Extended laboratory, 3-D	*Chrysoperla carnea*	LR_{50} = 5.14 g a.s./ha $ER_{50\ reproduction}$ > 6.25 g a.s./ha			No
Lettuce					
Extended laboratory, 2-D	*Typhlodromus pyri*	LR_{50} = 40.7 g a.s./ha $ER_{50\ fecundity}$ > 12.5 g a.s./ha	50	37.5	No
	Orius laevigatus	LR_{50} = 0.014 g a.s./ha $ER_{50\ fecundity}$ > 0.05 g a.s./ha			No
	Coccinella septempunctata	LR_{50} = 12.33 g a.s./ha $ER_{50\ fecundity}$ > 25 g a.s./ha			No
	Leptomastix dactylopii	LR_{50} = 0.47 g a.s./ha No sublethal assessments			No
	Pardosa spec.	LR_{50} >200 g a.s./ha $ER_{50\ feeding\ rate}$ > 200 g a.s./ha			Yes
	Aphidius rhopalosiphi	LR_{50} = 0.13 g a.s./ha $ER_{50\ reproduction}$ > 0.0625 g a.s./ha			No
Extended laboratory, 3-D	*Chrysoperla carnea*	LR_{50} = 5.14 g a.s./ha $ER_{50\ reproduction}$ > 6.25 g a.s./ha			No

The extended laboratory studies showed the following acceptable effects in-field:

- Potato and Lettuce: *Pardosa spp.* (wolf spider)

Effects on the remaining species were unacceptable or inconclusive, indicating a potential risk. Further consideration is required which is outlined below.

Off-field

Table 9.9.56: Off-field risk assessment for foliar applications of A9584C based on results from extended laboratory studies

Test type	Test species	Endpoints	Maximum Off-field PER (g a.s./ha)	Acceptable off-field risk
Potato				
Extended laboratory, 2-D	*Typhlodromus pyri*	LR_{50} = 40.7 g a.s./ha $ER_{50\ fecundity}$ > 12.5 g a.s./ha	0.277	Yes
	Orius laevigatus	LR_{50} = 0.014 g a.s./ha $ER_{50\ fecundity}$ > 0.05 g a.s./ha		No
	Coccinella septempunctata	LR_{50} = 12.33 g a.s./ha $ER_{50\ fecundity}$ > 25 g a.s./ha		Yes
	Leptomastix dactylopii	LR_{50} = 0.47 g a.s./ha No sublethal assessments		Yes
	Pardosa spec.	LR_{50} >200 g a.s./ha $ER_{50\ feeding\ rate}$ > 200 g a.s./ha		Yes
	Aphidius rhopalosiphi	LR_{50} = 0.13 g a.s./ha $ER_{50\ reproduction}$ > 0.0625 g a.s./ha		No
Extended laboratory, 3-D	*Chrysoperla carnea*	LR_{50} = 5.14 g a.s./ha $ER_{50\ reproduction}$ > 6.25 g a.s./ha	2.77	Yes
Lettuce				
Extended laboratory, 2-D	*Typhlodromus pyri*	LR_{50} = 40.7 g a.s./ha $ER_{50\ fecundity}$ > 12.5 g a.s./ha	0.6925	Yes
	Orius laevigatus	LR_{50} = 0.014 g a.s./ha $ER_{50\ fecundity}$ > 0.05 g a.s./ha		No
	Coccinella septempunctata	LR_{50} = 12.33 g a.s./ha $ER_{50\ fecundity}$ > 25 g a.s./ha		Yes
	Leptomastix dactylopii	LR_{50} = 0.47 g a.s./ha No sublethal assessments		No
	Pardosa spec.	LR_{50} >200 g a.s./ha $ER_{50\ feeding\ rate}$ > 200 g a.s./ha		Yes
	Aphidius rhopalosiphi	LR_{50} = 0.13 g a.s./ha $ER_{50\ reproduction}$ > 0.0625 g a.s./ha		No
Extended laboratory, 3-D	*Chrysoperla carnea*	LR_{50} = 5.14 g a.s./ha $ER_{50\ reproduction}$ > 6.25 g a.s./ha	6.925	No

The extended laboratory studies showed the following acceptable effects off-field:

- Potato: *Typhlodromus pyri* (predatory mite), *Coccinella septempunctata* (ladybird), *Leptomastix dactylopii* (parasitic wasp) and *Pardosa spp.* (wolf spider).
- Lettuce: *Typhlodromus pyri* (predatory mite), *Coccinella septempunctata* (ladybird)) and *Pardosa spp.* (wolf spider).

Effects on the remaining species (leaf dwellers: *Orius laevigatus*, *Aphidius rhopalosiphi* and *Leptomastix dactylopii*) were unacceptable or inconclusive, indicating a potential risk for leaf dwelling organisms. Further consideration is required which is outlined below.

Higher Tier Risk Assessment (based on semi-field and field studies)

Semi-field studies

RMS comment: Based on the results from the semi-field studies, the recovery was not clearly demonstrated for *A. rhopalosiphi* (Engelhard, 1997), and *O. laevigatus* (Schuld, 2002). Indeed, for *A. rhopalosiphi* even if at 1 x 12.5 g a.s./ha (below the intended application rate of 20 g a.s./ha and 50 g a.s./ha), there was lower than 50% effect on reproduction after the application, at 2 x 12.5 g a.s./ha (below the intended application rate of 20 g a.s./ha and 50 g a.s./ha), there was lower than 50% (42.1) effect on reproduction at 0 days after the 2nd application but there was higher than 50% (57.1) effect on reproduction at 7 days after the 2nd application for *A. rhopalosiphi.* For *O. laevigatus,* even if the results should be treated with caution (due to low numbers of females and low egg hatch), mortality effects were higher than 50% at 3, 7, 14, 28, 49 and 92 DAT and reproduction effects were higher than 50% at 14 and 92 DAT.

Field studies

RMS comment concerning the results from this field study (*Reber 1998*): It would be helpful to have an analysis of the study according to the guidance document of the Dutch Platform for the Assessment of Higher Tier Studies (even without classification of the effects as those effect were indeed only evaluated on one species: *T. pyri*) to calculate the reliability index score of the study. Results are therefore reported as additional information and could only be used for the risk assessment in combination with other studies to provide supporting evidence.

Pronounced short term effect after 1st and 2nd application of 100 g a.s./ha with recovery within 2 months after the first application.

RMS comment concerning the results from this field study (Brown and Phil, 1999):

The study has a reliability index score of 3, calculated according to the guidance document of the Dutch Platform for the Assessment of Higher Tier Studies (De Jong et al., 2010), indicating that the study should be considered unreliable. Results are reported as additional information and could only be used for the risk assessment in combination with other studies to provide supporting evidence.

Data analyses and results were presented for 13 abundant taxa. Data analyses and results are presented in the study report for selected taxa for which adverse effects were noted. It could not be deduced from the presented analyses whether these taxa comprised a small or a large part of the entire arthropod community. While analyses and presentation of results are insufficient, for most of the taxa presented, i.e. pooled predatory Heteroptera, Pilophoris perplexus (Miridae, Heteroptera) pooled Araneae, Salticidae (Araneae), Chalcidoidea (Hymenoptera), Forficula auricularia (Dermaptera) it can be observed graphically (original study reports) that recovery occurred before the end of the 3-month sampling period. However, populations of predatory *Episyrphus balteatus* (Syrphidae, Diptera) and *Heterotoma planicornis* (Miridae, Heteroptera) and phytophagous *Bryobia rubrioculus* (Tetranychidae, Acari) disappeared from the field before numbers in test item treatments had reached levels similar to the control. The notifier considered that population decline in all treatments including the control is due to natural behavior and hence unrelated to treatment. RMS considered that this may not be the case with a population decline that seems related to treatment (see graphes below for *Episyrphus balteatus* and *Heterotoma planicornis,* and table below for *Bryobia rubrioculus*). As indicated previously, it could not be deduced from the presented analyses whether these taxa comprised a small or a large part of the entire arthropod community, and therefore the weight of these effects on these taxa on the community (No community analysis performed).

Fig. 6: Mean no. (n+1) Episyrphus balteatus (Diptera: Syrphidae) per inventory sample

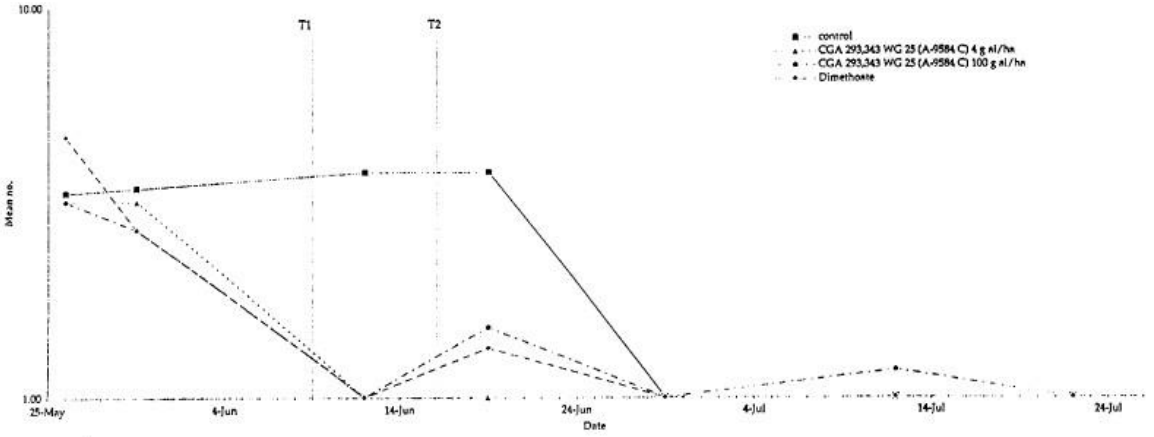


Fig. 4: Mean no. (n+1) Heterotoma planicornis (Hemiptera: Miridae) per inventory sample

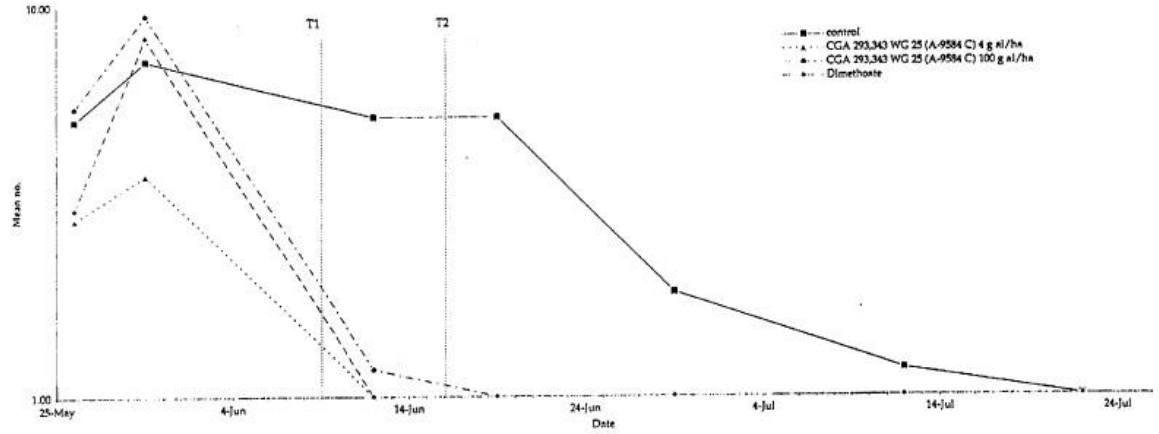


Table 9 : Mean No. of Bryobia rubrioculus (Acari: Tetranychidae) observed per 50 leaves

Date	25-May-98	31-May-98	13-Jun-98	20-Jun-98	1-Jul-98
	16 days before T1	*10 days before T1*	*4 days after T1*	*4 days after T2*	*14 days after T2*
Control	10.50	11.75	7.75	5.75	10.50
CGA 293,343 WG 25 (A-9584 C) at 4 g ai/ha	9.00	6.50	0.50	1.00	0*
CGA 293,343 WG 25 (A-9584 C) at 100 g ai /ha	9.00	8.00	0	0	0*
dimethoate at 680 g ai /ha	11.00	10.00	0	0	0

T1 and T2 refer to the first and second applications of test substances

* = significant difference between treatment and control at P=<0.05 in Anova and Tukey test

Effect classification at population level was 0 to 2 (Reduction once or twice immediately after first application). However, analyses and presentation of results are insufficient, and conclusions are uncertain. Based on these considerations, no reliable NOAER population and NOAER community can be derived from this study.

Concerning bioassay on *Orius laevigatus* and *Aphidius colemani* at 4 g a.s/ha and 100 g a.s./ha, for *Orius laevigatus* there was <50% effect on mortality within 6 weeks after 2nd application and for *Aphidius colemani* there was <50% effect on mortality within 8 weeks after 2nd application.

RMS comment concerning the results from this field study *Grimm 2003a*: The study has a reliability index score of 3, calculated according to the guidance document of the Dutch Platform for the Assessment of Higher Tier Studies (De Jong et al., 2010), indicating that the study should be considered unreliable. Results are reported as additional information and could only be used for the risk assessment in combination with other studies to provide supporting evidence. Results are based on inventory data examinations, which included all abundant taxa encountered in leaf samples (but present in much higher numbers). A total of 74 taxa were sufficiently abundant for effect classification from inventory samples. During the season, sixteen taxa (22%) were considered adversely affected by the FR treatment and 7-8 (9-11%) by the DV and DC treatment. The majority of arthropod populations recovered within the five-month sampling period of this study. The only taxa for which no full recovery was seen before the end of the 5-month sampling period were hymenopteran *Cales* (Aphelinidae) (FR and DV) and *Apterencyrtus* (Encyrtidae) (FR). More details of abundance (graphes) are reported below for these species:

Figure 45 Abundance of *Cales* spp. (Aphelinidae; Hymenoptera), inventory samples

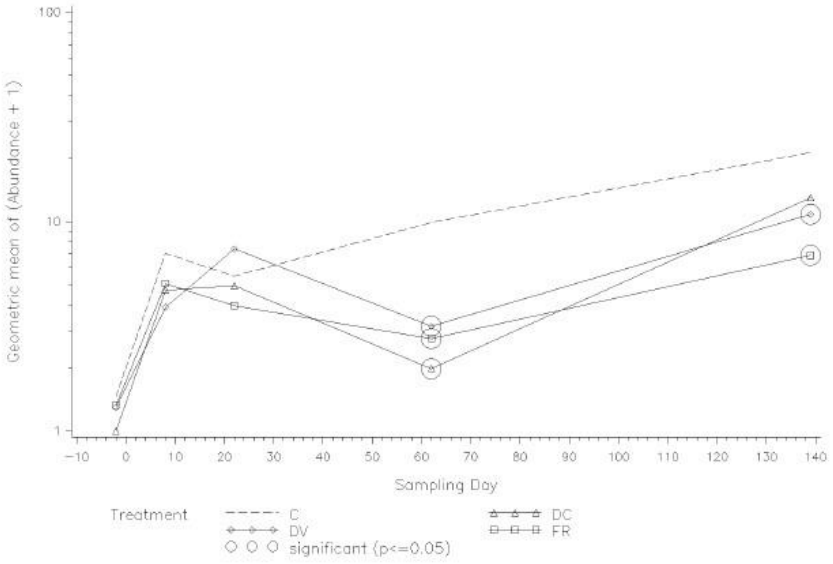
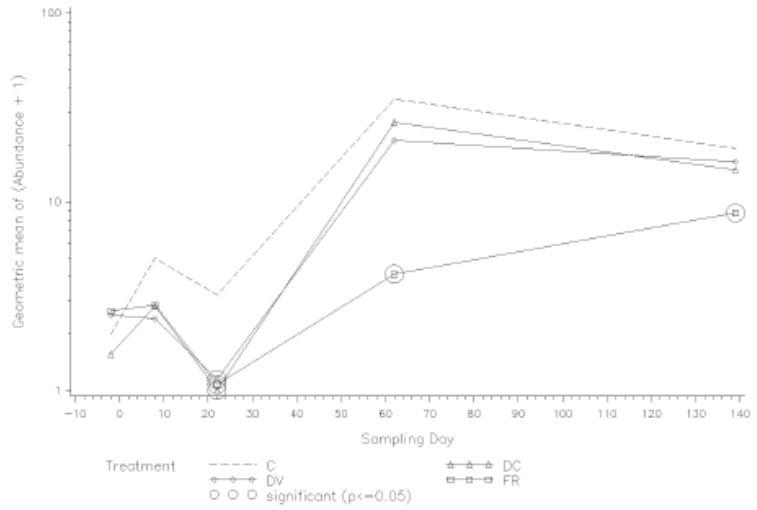


Figure 48 Abundance of *Apterencyrtus* spp. (Encyrtidae; Hymenoptera), inventory samples



By the end of the sampling period, those 2 taxa had not yet recovered to levels similar to the control but recovery was clearly in progress and it can reasonably be expected that recovery will occur. *Apterencyrtus* (Encyrtidae) have a weight in the PRC Curve for the community of tree-dwelling arthropods, inventory samples (see previous

Figure 10.3.2.4-5 in summary) and recovery was seen at the community level on the last sampling date (Effect classification at Community level for inventory sample was 4 for the FR treatment (recovery within 4 months after application).

Based on those considerations, RMS considered that no NOER population nor NOER community can be set from this study. The only endpoint that can be set from this study is a NOAER population and NOAER community of 150 g a.s./ha. The arthropod population and communities in the various treatments followed similar patterns but differed in magnitude depending on the amount of test item applied; treatment effects lasted longer for higher treatment concentrations (150 g a.s/ha) compared to DC treatment (12.75 g a.s./ha).

However, among those 74 taxa in this study, *Episyrphus balteatus* (or other taxa of the family of Syrphoidea) and *Heterotoma planicornis* (or other taxa of the family of Miridae) have not been sampled. The uncertainty concerning potential of recovery for these species remains (see previous comment). It is nor reported if *Bryobia rubrioculus* was sampled in this study, however the family of Tetranychidae (Acari) was sampled and no effect related to the test item was observed in this study based on classification of Jong.

RMS position concerning the results from these field studies *Grimm 2003b, c*:

Grimm 2003b: It would be helpful to have an analysis of the study according to the guidance document of the Dutch Platform for the Assessment of Higher Tier Studies (even without classification of the effects as those effect were indeed only evaluated immediately after application and no recovery samples in field were collected) to calculate the reliability index score of the study. Results are therefore reported as additional information and could only be used for the risk assessment in combination with other studies to provide supporting evidence. Many arthropods were found to have been knocked down by the application volume itself and not (or not only) by the toxic effect of the test item. 18 of the 45 observed taxa showed a statistically significant treatment effect in the maximum rate treatment compared to the control and 11 taxa showed a statistically significant treatment effect in the artificial drift treatment, whereas 4 taxa were statistically significantly affected by the test item in the first natural drift row. No recovery sample in field. No statistically significant treatment effect in the natural drift rows beyond the first row were observed (equivalent to 0.12 g a.s./ha). The main insect groups affected by the test item were beetle larvae (Coleoptera larvae), adults and nymphs of plants bugs (Miridae), nymphs of other bugs (Heteroptera other nymphs), cicada and leaf hopper nymphs (Auchenorrhhyncha nymphs), aphids (Aphidina), flies of Nematocera and fly larvae (Diptera larvae). The treatment had no statistically significant direct effect on the non-insect community, consisting chiefly of mites, in any of the treatments.

Note: Among those taxa in this study, *Episyrphus balteatus* (or other taxa of the family of Syrphoidea) have not been sampled. The family of Miridae has been sampled and confirms that this family is affected by treatment (affected at full rate of 100 g a.s./ha and also drift rate of 17.57 g a.s./ha, no effect at 0.69 g a.s/ha)

Grimm 2003c: It would be helpful to have an analysis of the study according to the guidance document of the Dutch Platform for the Assessment of Higher Tier Studies (even without classification of the effects as those effect were indeed only evaluated immediately after application and no recovery samples were collected) to calculate the reliability index score of the study. It can be noted that the residue concentration from water control application was 0.63 % (equivalent to 0.63 g a.s./ha) of the maximum rate (100 g a.s./ha). It is reported in the study report that this comparable high value of the test item in the water control is due to one sample where 2% (2 g a.s/ha) of maximum rate was retriewed, that very likely resulted from contamination by spray drift due to change in wind direction during application of maximum application rate. Based on those consideration (contamination of one sample of water control), results from this study, particularly on natural drift values around 0.63% (Natural Drift 2: 0.98%, Natural Drift 3: 0.56% and Natural Drift 4: 0.53%) are considered not reliable, and results from this study for other values relatively higher than 0.63% (Natural Drift 1: 2.4%; DC: 16.2% and MR: 100%) have to be taken with caution. Results are reported as additional information and could only be used for the risk assessment in combination with other studies to provide supporting evidence. 15 taxa showed a statistically significant treatment effect in the maximum rate treatment compared to the control and 7 taxa showed a statistically significant treatment effect in the artificial drift treatment, whereas 3 taxa were statistically significantly affected by the test item in the natural drift rows. No recovery sample in field. The main insect groups affected by the test item were plant bugs (Miridae), leaf hoppers (Cicadellidae), Neuroptera, bark lice (Psocoptera) and thrips (Thysanoptera). Although in most of these group treatment effect seen in maximum rate and drift concentration regime only, the bark lice (Psocoptera), the plant bugs (Miridae) and leaf hoppers (Cicadellidae) showed a continuing effect in the first natural drift row (2.4% of maximum application rate), and beyond the first row for bark lice (Psocoptera).

Note: Among those taxa in this study, *Episyrphus balteatus* (or other taxa of the family of Syrphoidea) have not been sampled. The family of Miridae has been sampled and confirms that this family is affected by treatment (affected at full rate of 100 g a.s./ha and also drift rate of 16.2 g a.s./ha and 2.4 g a.s./ha, no effect at 0.98 g a.s/ha).

RMS overall conclusion concerning all those field studies

These studies of up to 2 x 100 g a.s./ha or 1 x 150 g a.s./ha cover the use maximum proposed rates of A9584C of 1 x 50 g a.s./ha in lettuce and 1 x 20 g a.s./hain potatoes. Those studies are not fully reliable based on the re-assessment according to the guidance document of the Dutch Platform for the Assessment of Higher Tier Studies. However, it should be kept in mind that those studies have been conducted before the guidance document of the Dutch Platform. Results are reported as additional information and RMS considers that these studies provided relevant information and they could be used in an overall risk assessment by considering them together and in combination with other studies to provide supporting evidence. Based on uncertainties concerning effect and potential of recovery for some taxa, particularly Syrphoidea and Miridae, no NOER population nor NOER community can be set from these studies. In-field risk cannot be finalised based on available field studies.

Off-field

RMS comment: Based on the results from the semi-field studies, the recovery was not clearly demonstrated for *A. rhopalosiphi* (Engelhard, 1997), and *O. laevigatus* (Schuld, 2002). (see previous comment). However bioassay from field study on *Orius laevigatus* and *Aphidius colemani* at 4 g a.s/ha and 100 g a.s./ha indicated that there was <50% effect on mortality within 6 weeks after 2nd application for *O. laevigatus* and there was <50% effect on mortality within 8 weeks after 2nd application for *Aphidius colemani*. However, the endpoints from to be used in risk assessment for off-field areas should be a NOER population and community (no effect), and not NOEAER.

RMS comment: The aim of the field study carried out by Bakker and Aldershof, 2014 is to assess the potential effects on non-target arthropods fauna in off-crop habitats that might occur at various distances from a treated area. The notifier considered NOEAER Population and Community (endpoint based on recovery) to be used in risk assessment off-field. The endpoints from this study to be used in risk assessment for off-field areas should be a NOER population and community (no effect), and not NOEAER. RMS considered that a NOER population of 0.057 g as/ha (covering the NOER community) should be retained from this study and used in risk assessment for off-field. (See summary of the field study). Based on this endpoint, the off field risk assessment has been conducted by RMS in the table below.

Table 9.9.57: Off-field risk assessment for foliar applications of A9584C based on results from Higher Tier Field study

Exposure scenario	Maximum in-field PER (g a.s./ha)	Distance	drift factor (% drift/100)	Off-field PER (g a.s./ha)	Acceptable off-field risk (Off-field PER < NOER population)
Higher Tier, Field	20 (potatoes)	1 m	0.0277	0.554	N
		5 m	0.0057	0.114	N
		10 m	0.0029	0.058	N
		15 m	**0.0020**	**0.040**	**Y**
Higher Tier, Field	50 (lettuce)	1 m	0.0277	1.385	N
		5 m	0.0057	0.285	N
		10 m	0.0029	0.145	N
		15 m	0.0020	0.100	N
		20 m	0.0015	0.075	N
		30 m	**0.0010**	**0.050**	**Y**

Therefore, RMS considered that risk for non target arthropods is acceptable with appropriate mitigation measure:

Respect an unsprayed buffer zone of 15 m to non-agricultural land for potatoes.

Respect an unsprayed buffer zone of 30 m to non-agricultural land for lettuce.

A9765 R

Field uses (sugar beet)

In-field

Table 9.9.58: In-field risk to soil-dwelling non-target arthropods

Test species	LR50/ER50 (mg A9765R/kg)	PEC_S (mg A9765R/kg)	Acceptable in-field risk based on laboratory studies
Poecilus cupreus	>1.03	0.162	Yes
Aleochara bilineata	>1		Yes

While an acceptable risk is expected for ground dwelling arthropods for this use pattern based on the risk assessment presented above, laboratory studies conducted on the previous representative seed treatment formulation indicated a potential risk. Therefore semi-field and field studies have been conducted to examine the effects of thiamethoxam treated seeds on in-field non-target arthropod populations.

ZRMS position concerning the results from these field studies

Concerning the studies conducted on wheat seeds at 92 g a.s./ha, barley seeds at 105 g a.s./ha, maize seeds at 105 g a.s./ha, and oilseed rape at 34 g a.s./ha, they are not fully reliable based on the re-assessment according to the guidance document of the Dutch Platform for the Assessment of Higher Tier Studies. However, it should be kept in mind that those studies have been conducted before the guidance document of the Dutch Platform. Results are reported as additional information and RMS considers that these studies provided relevant information and they could be used in an overall risk assessment by considering them together and in combination with other studies to provide supporting evidence. Based on results reported the studies conducted on wheat seeds at 92 g a.s./ha, barley seeds at 105 g a.s./ha, maize seeds at 105 g a.s./ha (see study summaries), some Effect classification at Community level for which target and non target taxa had influences (directly or indirectly) was 8 (No recovery

within study period (4 months)). Based on these considerations, no NOAER population and NOAER community can be derived from these study. Based on results reported the study conducted oilseed rape at 34 g a.s./ha (see study summaries), some Effect classification at Community level for which target and non target taxa had influences (directly or indirectly) was 4 (recovery within study period (4 months)). However, for one or few taxa recovery could not be confirmed due to low numbers at end sampling period and no recovery was suspected for one or few taxa. Moreover, the application rate in this study do not cover intended application rate (58.5 g a.s./ha) and as indicated previously, results from this study cannot be used without combination with other studies to provide supporting evidence. Based on these considerations, no NOAER population and NOAER community can be derived from all those studies.

Concerning the study conducted on peas (Bakker and Aldersof, 2014), it has a reliability index score of 2, calculated according to the guidance document of the Dutch Platform for the Assessment of Higher Tier Studies (De Jong et al., 2010). Results are less reliable than an index score of 1 but can be used for the risk assessment according to the guidance document.

Two staphylinid taxa were adversely affected in spring and/or summer 2012 and effects reappeared in the summer of the next season. These were Oxytelinae (mainly *Oxytelus rugosus*), and a rest group of other Staphylinidae (mainly Omaliinae).

Based on Effect classification according to De Jong et al, 2010 the only taxa for which no recovery was seen more than 1 year (15 months) after sowing (class 8) was “other staphilinidae”. More details of abundance are reported in previous summary for “other staphilinidae” (see Figure 10.3.2.4-8: Summary of “other staphylinidae” density). One year after treatment (spring 2013) control populations had a constant density-activity, but numbers collected in all thiamethoxam test item treatments declined, leading to a statistically significant difference compared to the control in all test item rates on the last sampling moment in summer 2013, fifteen months after treatment. Detailed data examination indicated that reductions were not due to single deviating replicates indicating that observed reduction on the last sampling (next summer) were related to the test item treatment rather than to inconsistencies in control numbers. The faster or stronger population decline was best explained in relation to the test item treatment. The significant response curve (percentage of taxa that occurred at statistically significantly lower numbers than the control on each sampling moment) shows a dose related increase in significant occurences on the last sampling moment for the test item treatments (see Figure 10.3.2.4-9). No such increase was observed in the reference treatment, which is supportive of the hypothesis that observed reductions on the last sampling moment were indedd related to the test item treatment rather than to inconsistencies in control numbers (alone).

Those effects (class 8) on “other staphilinidae” are also observed when data on all staphilinidae are pooled (see previous table “effect classifications single taxa” and also previous Figure 10.3.2.4-6: Summary of staphylinidae pooled density, and Figure 10.3.2.4-3: Summary of staphylinidae community level effects (Principle Response Curve) indicating that “other staphilinidae” have a relatively hight weight in the PRC Curve for the community of staphilinidae.

Based on Effect classification according to De Jong et al, 2010, for Oxytelinae no recovery was seen more than 1 year (15 months) after sowing (class 8) only at the highest tested concentration (see previous table “effect classifications single taxa”). However, based on abundances observed for this species (see previous Figure 10.3.2.4-7: Summary of Oxytelinae density (Principle Response Curve), the difference of abundance in the sample the next spring and summer is marginal between all tested concentrations, and a clear tendancy of dose related recurrent effects next spring and/or summer are observed for this taxon. Oxytelinae (mainly *Oxytelus rugosus*) have a relatively high weight in the PRC Curve for the community staphilinidae, and also in the PRC Curve for the total community (see previous Figure 10.3.2.4-1: Summary of total community level effects (Principle Response Curve).

Based on Effect classification according to De Jong et al, 2010, for Total community no recovery was seen more than 1 year (15 months) after sowing (class 8) only at the highest tested concentration (see previous table “effect classifications single taxa”). However, based on principal response curve for total community (see Figure 10.3.2.4-1), the difference in magnitude of community effect in the sample the next spring and summer is marginal between all tested concentrations, and a tendancy of dose related recurrent effects next spring and/or summer are observed. This dose related trend was also observed both in the proportion of taxa affected in a statistically significant manner, and in the observed duration of effects (see Figure 10.3.2.4-9)). Those effects on staphilinidae have a relatively high weight in the PRC Curve for the total community (see previous Figure 10.3.2.4-1).

Based on those considerations, RMS considers that no NOAER population can be derived from these studies and an uncertainty remains concenring the acceptability of risk in-field.

The notifier informed RMS that an additional field study is on-going to determine the effects of sugar beet seeds treated with A9765R on natural non-target arthropod (NTA) communities under field conditions. The study will monitor the full fauna of naturally occurring NTAs for a period that covers at least two generations. The evaluation will be based on (1) time to recovery and (2) persistence of effect. Interim reports will be available February 2018 and 2019, while the final report will be available March 2020.

RMS considers that this on-going study could be usefull to address the uncertainty concerning the acceptability of risk in-field.

Off-field

Table 9.9.59: Off-field risk to foliar non-target arthropods for Deflected pneumatic driller

Test species	Endpoint (mL/ha)	Off-field foliar PER (mL/ha)	HQ	Trigger
Typhlodromus pyri Tier II, 2D exposure scenario	LR_{50} = 27.4	0.607	0.022	1
	ER_{50} > 27		< 0.023	
Aphidius rhopalosiphi Tier II, 2D exposure scenario	LR_{50} = 0.028	0.607	21	
	ER_{50} > 0.025		< 24	

The HQ values for *Typhlodromus pyri* are below the trigger value of 1, indicating acceptable risk from off-field dust drift following use of A9765R according to the proposed use pattern with Deflected pneumatic driller. However, the HQ values for *Aphidius rhopalosiphi* are above the trigger value of 1, indicating a need of refinement risk from off-field dust drift following use of A9765R according to the proposed use pattern with Deflected pneumatic driller.

Table 9.9.60: Off-field risk to foliar non-target arthropods for Mechanical driller

Test species	Endpoint (mL/ha)	Off-field foliar PER (mL/ha)	HQ	Trigger
Typhlodromus pyri Tier II, 2D exposure scenario	LR_{50} = 27.4	0.0176	0.0006	1
	ER_{50} > 27		< 0.0007	
Aphidius rhopalosiphi Tier II, 2D exposure scenario	LR_{50} = 0.028	0.0176	0.62	
	ER_{50} > 0.025		< 0.704	

A field study has been conducted to examine the effects of dust drift from thiamethoxam treated seeds on off-field non-target arthropod populations.

RMS comment: The aim of this study (Knäbe, 2012 aA9700B_10954) was to assess the potential effects on non-target arthropods fauna in off-crop habitats that might occur. The endpoints to be derived from this study and to be used in risk assessment for off field areas should be a NOER population and community. RMS considered that no NOER population nor NOER community can be set from this study. The only endpoint that can be set from this study is a NOAER population and NOAER community of 0.87 g a.s./ha.

Considering that observed effects for the three tested concentrations in the field study (0.087 g a.s./ha, 0.435 and 0.870 g a.s./ha.) were around the same (see graph of PRC in summary) and classified of class 2 (Slight and transient effects) in only one sampling (7 days after application), RMS considered that this NOAER population/community of 0.87 g a.s./ha can be considered reliable and sufficiently protective to be used in off-field risk assessment. RMS conducted an off-field risk assessement based on this NOAER population/community of 0.87 g a.s./ha. It can be noted that risk would also be acceptable based on the if the lowest tested concentration of 0.087 g a.s/ha as a NOAER population/community (see below)

Table 9.9.61: Off-field risk to foliar non-target arthropods for Deflected pneumatic driller based on results from Higher Tier Field study

Exposure scenario	Distance	Off-field foliar PER at 3 m Deflected pneumatic driller	Acceptable off-field risk (Off-field PER < NOAER population)
Higher Tier, Field	3 m	0.073 g a.s./ha	Y

Therefore, RMS considered that off-field risk for non target arthropods is acceptable.

Conclusion for A9765R

It is concluded that A9765R is not expected to have any unacceptable long-term effects on non-target arthropods off-field when applied according to the uses supported in this submission. However, an uncertainty remains concerning the acceptability of risk in field. The new on-going field study could be usefull to address this uncertainty.

Summary of product exposure and risk assessment for non-target soil meso- and macrofauna

The risk assessment procedure follows the requirements as given in the EU Regulation 1107/2009 and the Guidance Document on Terrestrial Ecotoxicology.

Risk assessment for earthworms

A9584 C

Greenhouse use:

A risk assessment is not necessary for uses restricted to permanent greenhouses.

Field uses (lettuce and potato)

Table 9.9.62: Long-term TER values for earthworms

Test substance	NOEC / EC_{10} (mg/kg soil)	PEC_S (Maximum or Accumulation) (mg/kg soil)	TER_{LT}	Trigger value
A9584C	6.15	0.200	31	5
Thiamethoxam	1.54	0.079 (accu)	19.5	
CGA322704	0.06	0.025 (accu)	**2.4**	
		0.018 (accu) [b]	**3.3**	
CGA355190	125	0.011	11 000	
CGA353042	1.54 [a]	0.003	510	
CGA282149	30.3	0.002	15150	

Values in **bold** are less than the trigger value

[a] Studies have not been conducted on this metabolite. As a conservative approach, it is assumed to have the same toxicity as the parent compound, thiamethoxam, in the risk assessment. (see justification in B.9.8.1.1)

[b] depth 20 cm, including till (see E-Fate section)

With the exception of CGA322704, the long-term TER values all exceed the Commission Regulation (EU) No. 546/2011 long-term trigger value of 5, indicating that the risk to earthworms is acceptable.

A field study has been conducted investigating the effects of a single application of the metabolite CGA322704 at rates of 37.5, 75 and 150 g/ha upon natural earthworm populations (***Pease and Webster, 2004***). Exposure to CGA322704 at 150 g/ha did not have any adverse effects on earthworm numbers or total biomass. This application rate would be equivalent to 0.2 mg/kg soil (assuming 5 cm incorporation depth). As the PEC_S accu. values for application to lettuce is 0.025 mg/kg soil (5 cm incorporation depth) and 0.018 mg/kg soil (20 cm

incorporation depth (approximately 8 to 10x less than the NOEC from the field study), this confirms an acceptable long-term risk to earthworms from CGA322704 following the proposed uses of A9584C.

A9765 R

Field uses (sugar beet)

Table 9.9.63: Long-term TER values for earthworms

Test substance	NOEC/ EC_{10} (mg/kg soil)	PEC_S (Maximum/Accu.) (mg/kg soil)	TER_{LT}	Trigger value
A9765R	65	0.162	401	5
Thiamethoxam	1.54	0.093 (accu.)	17	
CGA322704	0.06	0.029 (accu.)	**2.1**	
		0.025 (accu.) [b]	**2.4**	
CGA355190	125	0.016	7 800	
CGA282149	30.3	0.003	10 100	

Values in **bold** are less than the trigger value
[b] depth 20 cm, including till

With the exception of CGA322704, the long-term TER values all exceed the Commission Regulation (EU) No. 546/2011 long-term trigger value of 5, indicating that the long-term risk to earthworms is acceptable.

A field study has been conducted investigating the effects of a single application of the metabolite CGA322704 at rates of 37.5, 75 and 150 g/ha upon natural earthworm populations (***Pease and Webster, 2004***). Exposure to CGA322704 at 150 g/ha did not have any adverse effects on earthworm numbers or total biomass. This application rate would be equivalent to 0.2 mg/kg soil (assuming 5cm incorporation depth). As the PEC_S accu. values for application to sugar beet is 0.029 mg/kg soil (5cm incorporation depth) and 0.025 mg/kg soil (20cm incorporation depth) (7 to 8 x less than the NOEC from the field study), this confirms an acceptable long-term risk to earthworms from CGA322704 following the proposed uses of A9765R.

Risk assessment for non-target soil meso- and macrofauna other than earthworms

A9584 C

Greenhouse use:

A risk assessment is not necessary for uses restricted to permanent greenhouses.

Field uses (lettuce and potato)

Table 9.9.64: Long-term TER values for other soil meso- and macro-fauna

Organism	Test substance	NOEC / EC_{10} (mg/kg soil)	PEC_S (Maximum or Accumulation) (mg/kg soil)	TER_{LT}	Trigger value
Folsomia candida	A9584C	10	0.200	50	5
	Thiamethoxam	1.384	0.079 (accu.)	17.5	
	CGA322704	0.10 [a]	0.025(accu.)	**4**	
			0.018 (accu.) [d]	5.6	
	CGA355190	16.3	0.011	1 500	
	CGA353042	1.384 [c]	0.003	461	
	CGA282149	377	0.002	188500	
Hypoaspis aculeifer	A9584C	1 000	0.200	5 000	5
	Thiamethoxam	246 [b]	0.079 (accu.)	3114	
	CGA322704	98.95	0.025 (accu.)	3958	
			0.018 (accu.) [d]	5458	
	CGA355190	1 000	0.011	91 000	
	CGA353042	246 [c]	0.003	82 000	
	CGA282149	308.6	0.002	150 000	

[a] When considering the effects on mortality and reproduction from both studies presented, the highest NOEC below the lowest LOEC is determined to be 0.1 mg/kg.
[b] The EC_{10} derived from the study conducted with the other representative formulation A9765R is not used in the risk assessment for the active substance, as the EC_{10} derived from this study (280 mg a.s./kg) is greater than the NOEC from the A9584C study (246 mg a.s./kg; highest concentration tested), conservative approach.
[c] Studies have not been conducted on this metabolite. As a conservative approach, it is assumed to have the same toxicity as the parent compound, thiamethoxam, in the risk assessment. (see justification in B.9.8.1.1)
[d] depth 20 cm, including till

The long-term TER values all exceed the Commission Regulation (EU) No. 546/2011 long-term trigger value of 5, indicating that the long-term risk to soil macro-organisms is acceptable following use of A9584C according to the proposed use pattern.

A9765 R

Field uses (sugar beet)

Table 9.9.65: Long-term TER values for other soil meso- and macro-fauna

Organism	Test substance	NOEC/ EC10 (mg/kg soil)	PEC_S (Maximum/Accumulation) (mg/kg soil)	TER_{LT}	Trigger value
Folsomia candida	A9765R	4.72	0.162	29	5
	Thiamethoxam	1.384	0.093 (accu.)	15.04	
	CGA322704	0.10 [a]	0.029 (accu.)	**3.45**	
			0.025 (accu.) [c]	**4**	
	CGA355190	16.3	0.016	1 000	
	CGA282149	377	0.003	125666	
Hypoaspis aculeifer	A9765R	565.1	0.162	3488	5
	Thiamethoxam	246 [b]	0.093 (accu.)	2673	
	CGA322704	98.95	0.029 (accu.)	3412	
			0.025 (accu.) [c]	3958	
	CGA355190	1 000	0.016	63 000	
	CGA282149	308.6	0.003	100 000	

Values in **bold** are less than the trigger value
[a] When considering the effects on mortality and reproduction from both studies presented, the highest NOEC below the lowest LOECD is determined to be 0.1 mg/kg.
[b] The EC_{10} derived from the study conducted with the other representative formulation A9765R is not used in the risk assessment for the active substance, as the EC_{10} derived from this study (280 mg a.s./kg) is greater than the NOEC from the A9584C study (246 mg a.s./kg; highest concentration tested), conservative approach.
[c] depth 20 cm, including till

With the exception of CGA322704 and *Folsomia candida*, the long-term TER values all exceed the Commission Regulation (EU) No. 546/2011 long-term trigger value of 5, indicating that there are no unacceptable long-term risk to other soil meso/macrofauna.

The maximum PEC_S value for CGA322704 has been refined taking into consideration 20 cm soil tillage between applications.

The refined long-term TER value is still lower than the Commission Regulation (EU) No. 546/2011 long-term trigger value of 5, indicating that the long-term risk to *Folsomia candida* is not acceptable.

The notifier indicated that he is currently in the process of obtaining the following field study on CGA322704 to further address the risk to collembola (*Folsomia candida*).

S. Schabio (2014) Field study to evaluate the effects of clothianidin on soil earthworms and collembolans under field conditions. Sumitomo Chemical Co., Ltd. Unpublished report No.: THW-0401

This field study would support the risk to the metabolite CGA322704 formed in soil, as it was conducted with an overspray application (representing the plateau concentration; equivalent to 0.246 mg a.s./kg soil) and a granular application representing the maximum annual application.

Summary of product exposure and risk assessment for soil micro-organisms

According to current regulatory requirements the risk is considered acceptable if the effect on nitrogen mineralisation at the recommended application rate of a compound/product is ≤ 25% after 100 days.

A9584 C

Greenhouse use:

A risk assessment is not necessary for uses restricted to permanent greenhouses.

Field uses (lettuce and potato)

Table 9.9.66: Risk assessment for effects on soil micro-organisms

Test substance	NOEC (mg/kg)	PEC_S (mg/kg) (Maximum/Accumulation)
A9584C	2.7	0.200
Thiamethoxam	2.67	0.079 (accu.)
CGA322704	0.5	0.025 (accu.)
CGA355190	0.5	0.011
CGA353042	2.67 [a]	0.003
CGA282149	0.78	0.002

[a] Studies have not been conducted on this metabolite. As a conservative approach, it is assumed to have the same toxicity as the parent compound, thiamethoxam, in the risk assessment. (see justification in B.9.8.1.1)

This indicates that the risk to non-target soil micro-organisms is acceptable following use of A9584C according to the proposed use pattern.

A9765 R

Field uses (sugar beet)

Table 9.9.67: Risk assessment for effects on soil micro-organisms

Test substance	NOEC (mg/kg)	PEC_S (mg/kg) (Maximum/Accumulation)
A9765R	0.65	0.162
Thiamethoxam	2.67	0.093 (accu.)
CGA322704	0.5	0.029 (accu.)
CGA355190	0.5	0.016
CGA282149	0.78	0.003

This indicates that the risk to non-target soil micro-organisms is acceptable following use of A9584C according to the proposed use pattern.

Summary of product exposure and risk assessment for non-target terrestrial plants

The risk assessment is based on the "Guidance Document on Terrestrial Ecotoxicology", (SANCO/10329/2002 rev2 final, 2002). It is restricted to off-field situations, as non-target plants are non-crop plants located outside the treated area.

A9584 C

Greenhouse use:

A risk assessment is not necessary for uses restricted to permanent greenhouses.

Field uses (lettuce and potato)

A9584C is an insecticide and is therefore not expected to have any significant herbicidal activity. A screening study of the effects on pre- and post-emergence non-target higher plants was conducted and showed no effects on any of the six species tested at rates up to and including 25 g a.s./ha, the highest rate tested. In a study on effects on pre- and post-emergence on ten species, higher rates were tested and the ER_{50} was determined to be > 298 g a.s./ha, the highest rate tested. The calculated maximum $PER_{off\text{-}field}$ values of 0.554 g a.s./ha and 1.385 g a.s./ha are below the level found to have no effects on the non-target plants (factor of 215 and 538).

It can therefore be concluded that the risk to non-target plants is acceptable following use of A9584C according to the proposed use pattern.

A9765 R

Field uses (sugar beet)

The formulation A9765R is a seed treatment and as such, a risk assessment for non-target terrestrial plants is not required.

2.10 PROPOSED HARMONISED CLASSIFICATION AND LABELLING ACCORDING TO THE CLP CRITERIA *[SECTIONS 1-6 OF THE CLH REPORT]*

2.10.1 Identity of the substance [section 1 of the CLH report]

2.10.1.1 Name and other identifiers of the substance

All of the information in this section is also available under section 1.3.

2.10.1.2 Composition of the substance

Table 54: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
thiamethoxam (ISO); 3-(2-chloro-thiazol-5-ylmethyl)-5-methyl[1,3,5]oxadiazinan-4-ylidene-*N*-nitroamine	≥ 98% (w/w)	/	H228 Flammable solid category 1

Table 55: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
Details on impurities are confidential and can be found in the IUCLID dossier				

Table 56: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**
No relevant additive					

Table 57: Test substances (non-confidential information)

Identification of test substance	**Purity**	**Impurities and additives (identity, %, classification if**	**Other information**	**The study(ies) in which the test substance is used**
Thiamethoxam pure substance 99.7%	99.7% w/w	/	/	See table 1 of physico-chemical properties
Thiamethoxam technical substance 99.0%	99.0% w/w	/	/	See table 1 of physico-chemical properties
Thiamethoxam technical substance 98.2%	98.2% w/w	/	/	See table 1 of physico-chemical properties
Thiamethoxam technical substance 98.3%	98.3% w/w	/	/	See table 1 of physico-chemical properties
Thiamethoxam technical substance 97.3%	98.3% w/w	/	/	See table 1 of physico-chemical properties
Thiamethoxam technical substance 98.5%	98.3% w/w	/	/	See table 1 of physico-chemical properties
Thiamethoxam technical substance 99.3%	98.3% w/w	/	/	See table 1 of physico-chemical properties

2.10.2 Proposed harmonized classification and labelling

2.10.2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 58: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	613-267-00-9	thiamethoxam (ISO); 3-(2-chloro-thiazol-5-ylmethyl)-5-methyl[1,3,5]oxadiazi nan-4-ylidene-N- nitroamine	428-650-4	153719-23-4	Acute Tox. 4* Aquatic Acute 1 Aquatic Chronic 1	H302 H400 H410	GHS07 GHS09 Wng	H302 H410		M=10	
Dossier submitters proposal	613-267-00-9	thiamethoxam (ISO); 3-(2-chloro-thiazol-5-ylmethyl)-5-methyl[1,3,5]oxadiazi nan-4-ylidene-N- nitroamine	428-650-4	153719-23-4	**Retain** Acute Tox. 4 Aquatic Acute 1 Aquatic Chronic 1 **Add** Flam. Sol. 1 Repr. 2	**Retain** H302 H400 H410 **Add** H228 H361	**Retain** GHS07 GHS09 **Add** GHS02 GHS08 **Modify** Dgr	**Retain** H302 H410 **Add** H228 H361		**Add** oral: ATE = 800 mg/kg bw **Retain** M=10 **Add** M=10	
Resulting Annex VI entry if agreed by RAC and	613-267-00-9	thiamethoxam (ISO); 3-(2-chloro-thiazol-5-ylmethyl)-5-methyl[1,3,5]oxad	428-650-4	153719-23-4	Flam. Sol. 1 Repr. 2 Acute Tox. 4 Aquatic Acute 1 Aquatic	H228 H361 H302 H400 H410	GHS02 GHS08 GHS07 GHS09 Dgr	H228 H361 H302 H410		oral: ATE = 800 mg/kg bw M=10	

COM		iazi nan-4-ylidene-N- nitroamine			Chronic 1					M=10	

2.10.2.2 Additional hazard statements / labelling

Table 59: Reason for not proposing harmonised classification and status under CLH public consultation

Hazard class	Reason for no classification	Within the scope of CLH public consultation
Explosives	Hazard class not applicable Classification already harmonized and not considered for this proposal.	No
Flammable gases (including chemically unstable gases)	Hazard class not applicable Classification already harmonized and not considered for this proposal.	No
Oxidising gases	Hazard class not applicable Classification already harmonized and not considered for this proposal.	No
Gases under pressure	Hazard class not applicable Classification already harmonized and not considered for this proposal.	No
Flammable liquids	Hazard class not applicable Classification already harmonized and not considered for this proposal.	No
Flammable solids	**H228 Flammable solid category 1** **New proposal**	**Yes**
Self-reactive substances	Hazard class not assessed in the dossier Classification already harmonized and not considered for this proposal.	No
Pyrophoric liquids	Hazard class not applicable Classification already harmonized and not considered for this proposal.	No
Pyrophoric solids	Hazard class not assessed in the dossier Classification already harmonized and not considered for this proposal.	No
Self-heating substances	Hazard class not applicable Classification already harmonized and not considered for this proposal.	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in the dossier Classification already harmonized and not considered for this proposal.	No
Oxidising liquids	Hazard class not applicable Classification already harmonized and not considered for this proposal.	No
Oxidising solids	Hazard class not applicable Classification already harmonized and not considered for this proposal.	No
Organic peroxides	Hazard class not applicable Classification already harmonized and not considered for this proposal.	No
Corrosive to metals	Hazard class not assessed in the dossier Classification already harmonized and not considered for this proposal.	No
Acute toxicity via oral route	**H302 Harmull if swallowed** Data is presented and compared with the CLP criteria to remove the minimum classification and confirm Acute tox 4 (H302), removing the asterix in the current	**Yes**

Hazard class	Reason for no classification	Within the scope of CLH public consultation
	entry.	
Acute toxicity via dermal route	Conclusive but no sufficient for classification Classification already harmonized and not considered for this proposal	No
Acute toxicity via inhalation route	Conclusive but no sufficient for classification Classification already harmonized and not considered for this proposal	No
Skin corrosion/irritation	Conclusive but no sufficient for classification Classification already harmonized and not considered for this proposal	No
Serious eye damage/eye irritation	Conclusive but no sufficient for classification Classification already harmonized and not considered for this proposal	No
Respiratory sensitisation	Conclusive but no sufficient for classification Classification already harmonized and not considered for this proposal	No
Skin sensitisation	Conclusive but no sufficient for classification Classification already harmonized and not considered for this proposal	No
Germ cell mutagenicity	Conclusive but no sufficient for classification Classification already harmonized and not considered for this proposal	No
Carcinogenicity	Conclusive but no sufficient for classification Classification already harmonized and not considered for this proposal	No
Reproductive toxicity	**H361: Suspected of damaging fertility or the unborn child**	**Yes**
Specific target organ toxicity-single exposure	Conclusive but no sufficient for classification Classification already harmonized and not considered for this proposal	No
Specific target organ toxicity-repeated exposure	Conclusive but no sufficient for classification Classification already harmonized and not considered for this proposal	No
Aspiration hazard	Hazard class not applicable Classification already harmonized and not considered for this proposal.	No
Hazardous to the aquatic environment	H400, Acute M-factor = 10 H410, **Chronic M-factor = 10 (New proposal)**	**Yes**
Hazardous to the ozone layer	Hazard class not applicable Classification already harmonized and not considered for this proposal.	No

2.10.3 History of the previous classification and labelling

The harmonised classification and labelling of Thiamethoxam has been considered previously in the EU (ATP01). The existing entry in Annex VI of CLP Regulation (EU) 1272/2008 is:
Acute Tox. 4*, H302: Harmful if swallowed
Aquatic Acute 1, H400 (M = 10): Very toxic to aquatic life
Aquatic Chronic 1, H410: Very toxic to aquatic life with long lasting effects

During the renewal assessment of Thiamethoxam under Regulation (EU) 1107/2009, RMS proposed to reconsidered the current and harmonised classification of the active substance for the **Flammable Solids (H228)** and the **Reproductive Toxicity Category 2 (H361)** and to retain the current classification for environment but to add a **chronic M-factor of 10**. Therefore, in this context, a **targeted CLH proposal** is presented in this

document for these 3 endpoints. Furthermore, for "acute toxicity via oral route", data is presented and compared with the CLP criteria to remove the minimum classification and confirm **Acute tox 4 (H302)**.
Co-RMS agreed with RMS proposal for classification Repr. Cat2 H361.

2.10.4 Identified uses

Thiamethoxam is an insecticide active substance used for many years in Europe on various crop.
For more details, please refer above on chapter, 1.5 Detailed Uses of the plant protection products.

2.10.5 Data sources

The data source is the dossier submitted by the applicant and supporting the Annex I Renewal of the active substance Thiamethoxam under Regulation EC 1107/2009.

RAC general comment
Thiamethoxam is a neonicotinoid insecticide used in plant protection products. The substance has a current Annex VI entry. During the renewal assessment of thiamethoxam under Reg. (EU) 1107/2009, the Rapporteur Member State proposed to reconsider harmonized classification for selected hazard classes.

2.11 RELEVANCE OF METABOLITES IN GROUNDWATER

2.11.1 STEP 1: Exclusion of degradation products of no concern

The guidance document allows for a degradation product to be classified as a product of no concern if one of the following conditions apply:

- It is CO2 or an inorganic compound, not containing a heavy metal; or,
- It is an organic compound of aliphatic structure, with a chain length of 4 or less, which consists only of C, H, N or O atoms and which has no alerting structures such as epoxide, nitrosamine, nitrile or other functional groups of known toxicological concern.
- It is a substance known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment.

These conditions do not apply to any of the metabolites; therefore additional considerations are required as described in the following sections.

2.11.2 STEP 2: Quantification of potential groundwater contamination

Quantification of predicted environmental concentrations in groundwater for the active substance and its metabolites is described in detail in Vol.3-CP-ACTARA and Vol.3-CP-CRUISER– Sections 8.

As PECgw provided by the applicant in Tier II (using field soil DT_{50} for thiamethoxam and metabolite CGA322704-clothianidin) were not considered acceptable by RMS, the PECgw values provided correspond to Tier I calculations.

- PECgw for CGA353042 and CGA355190 are below 0.1 µg/L in all scenarios and crops assessed (maximal respective values of < 0.001 µg/L and 0.078 µg/L);
- PECgw for CGA282149 and SYN501406 remain below 0.75 µg/L (maximal respective values of 0.237 µg/L and 0.284 µg/L);
- PECgw for NOA459602 is in the range of 0.1-10 µg/L (maximal value of 2.1 µg/L).

Further consideration of the relevance of CGA282149, SYN501406 and NOA459602 is therefore required.

2.11.3 STEP 3: Hazard assessment – identification of relevant metabolites

2.11.3.1 STEP 3, Stage 1: screening for biological activity

Studies have been conducted to examine the biological activity of thiamethoxam metabolites on multiple target insect species.

Table 2.11.3.1: Summary of insecticidal activity of metabolites

Metabolite	Species tested	Activity relative to thiamethoxam (%)	Test result / Conclusion	Reference (author, date, Syngenta File No.)
NOA459602	*Aphis craccivora* *Myzus persicae* *Spodoptera littoralis* *Diabrotica balteata* *Nilaparvata lugens*	0 0 0 0 0	Not biologically active	Rindlisbacher, 2001 NOA459602/0010
SYN501406	*Aphis craccivora* *Myzus persicae* *Spodoptera littoralis* *Diabrotica balteata* *Nilaparvata lugens*	0 0 0 0 0	Not biologically active	Rindlisbacher, 2001 SYN501406/0001
CGA282149	*Aphis craccivora* (systemic) *Aphis craccivora* (contact) *Myzus persicae* *Nilaparvata lugens* *Frankliniella occidentalis* *Bemisia tabaci* *Spodoptera littoralis*	0 0 0 0 0 0 15	Not biologically active	Rindlisbacher, 2016 CA2343_10024

The comparative ecotoxicity of thiamethoxam and metabolites to a sensitive non-target aquatic organism (*Chironomus riparius*) has also been conducted.

Table 2.11.3.2: Ecotoxicity of thiamethoxam and metabolites CGA282149, SYN501406 and NOA459602 to a sensitive non-target aquatic organism

Test substance	Test species: *Chironomus riparius*
Thiamethoxam	48 hr EC_{50} = 0.035 mg a.s./L
	30 d NOEC = 0.0027 mg a.s./L
CGA282149	48 hr EC_{50} > 100 mg/L
NOA459602	24 d NOEC = 50 mg/L
SYN501406	28 d NOEC = 1.1 mg/L

For metabolites CGA282149, NOA459602 and SYN501406, these findings reflect a general reduction in biological activity and are consistent with the fact that the metabolites do not retain any insecticidal activity.

2.11.3.2 STEP 3, Stage 2: screening for genotoxicity

PECgw > 0.1 µg/L:

CGA282149 is negative in an Ames test and is clastogenic with metabolic activation in an *in vitro* chromosome aberrations test (CHO cells). It is negative in an *in vitro* micronucleus test in mouse and a specific studt in mouse

confirms the presence of the test item in circulating blood and plasma. It is also negative in an UDS test in rat.

SYN501406 is negative in an Ames test, in an *in vitro* gene mutation assay in mammalian cells and in an *in vitro* chromosome aberrations test (human lymphocytes).

NOA459602 is negative in an Ames test, in an *in vitro* gene mutation assay in mammalian cells and in an *in vitro* chromosome aberrations test (human lymphocytes).

None of the three metabolites showed genotoxic potential.

2.11.3.3 STEP 3, Stage 3: screening for toxicity

PECgw: 0.1 µg/L > < 0.75 µg/L:
CGA282149: An acute orale toxicity is available
LD_{50}: 1000 mg/kg bw > < 2000 mg/kg bw
No other toxicological data is available. Based on the current harmonized classification of thiamethoxam and according to Sanco/221/2000, CGA282149 is not relevant.

SYN501406: An acute orale toxicity is available
LD_{50} = 2000 mg/kg bw
No other toxicological data is available. Based on the current harmonized classification of thiamethoxam and according to Sanco/221/2000, SYN501406 is not relevant.

PECgw > 0.75 µg/L
NOA459602: An actute oral toxicity, a 28-d study and 90-d study have been submitted.
DL_{50} = 2000 mg/kg bw
28-d study- NOAEL = 15.7 mg/kg bw/day (males) based on increased motor activity at 161.2 mg/kg bw/day
90-d study- NOAEL = 140 mg/kg bw/day (females) based on increased motor activity at 1450 mg/kg bw/day
Based on the current harmonized classification of thiamethoxam and according to Sanco/221/2000, NOA459602 is not relevant.

It should be noted that if the classification proposal for reproductive toxicity is agreed, the reprotoxic profile of groundwater metabolites should be addressed in order to assess their relevance according to Sanco/221/2000 –rev.10- final 25 February 2003.

2.11.4 STEP 4: Exposure assessment – threshold of concern approach

For NOA459602 (PECgw > 0.75 µg/L < 10 µg/L), refine risk assessment is necessary.

2.11.5 STEP 5: Refined risk assessment

Proposed reference values for NOA459602:
Applying a safety factor of 1000 to the 28-d study NOAEL of 15.7 mg/kg bw/day, an ADI of 0.016 mg/kg bw/day could be proposed. However, in view of the limited data package, it is proposed to use the reference doses set for the parent:
ADI = 0.006 mg/kg bw/day
ARfD = 0.35 mg/kg bw

2.11.6 Overall conclusion

PECgw for metabolites CGA355190 and CGA353042 are < 0.1 µg/L for all scenarios of the simulated representative uses. There is no need to further assess their relevance.

PECgw for metabolites CGA282149, NOA459602 and SYN501406 exceed 0.1µg/L but stay below 10 µg/L for all scenarios of the simulated representative uses. These metabolites are not relevant according to SANCO 221/2000 based on the current harmoniszed classification.
Consequently, no unacceptable risk of groundwater contamination is expected for the representative uses of thiamethoxam.

2.12 CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

2.12.1 Identity and physical chemical properties

See section 2.2.1.

2.12.2 Methods of analysis

Analytical method SA-1/2 (Duell B., 2014 and Ebi E, 2014) for the determination of thiamethoxam in technical active substance has been provided and validated according to guidance SANCO3030/99/rev.4.

2.12.3 Mammalian toxicity

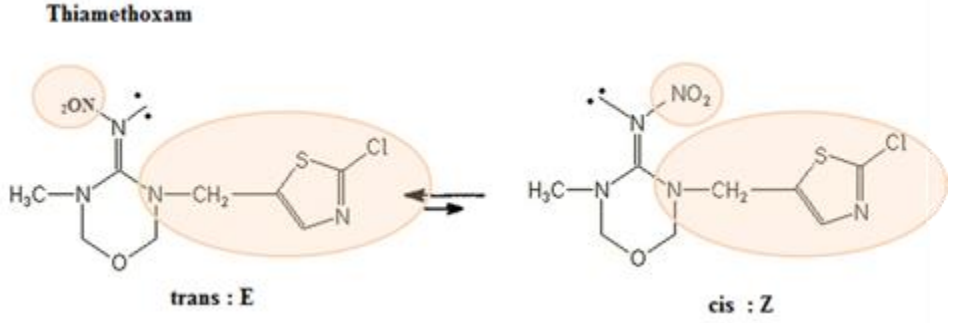
Thiamethoxam is described as an EZ mixture. It is generally believed that the activation energy for the E-Z interconversion for the C = N bond is low and that an equilibrium mixture is rapidly established at ambient temperature.
Toxicological studies have been perforemed with an unspecified E/Z isomer mixture of thiamethoxam.

2.12.4 Operator, Worker, Bystander and Resident exposure

Operator and bystander are directly exposed to the formulated product containing thiamethoxam with the same ratio as tested in toxicological studies.
As mentioned in JMPR evaluation (FAO/JMPR, 2010) and in Article 12 of Regulation (EC) N°396/2005, EFSA (2014), it is is expected that the ratio will be subject to a rapid thermodynamic equilibrium at ambient temperature. Consequently, the ratio of isomers to which worker and resident are exposed is expected to be the same as the ratio used in the toxicological studies.

2.12.5 Residues and Consumer risk assessment

Thiamethoxam contains an imine moiety which can induce E/Z isomers for thiamethoxam as described below:



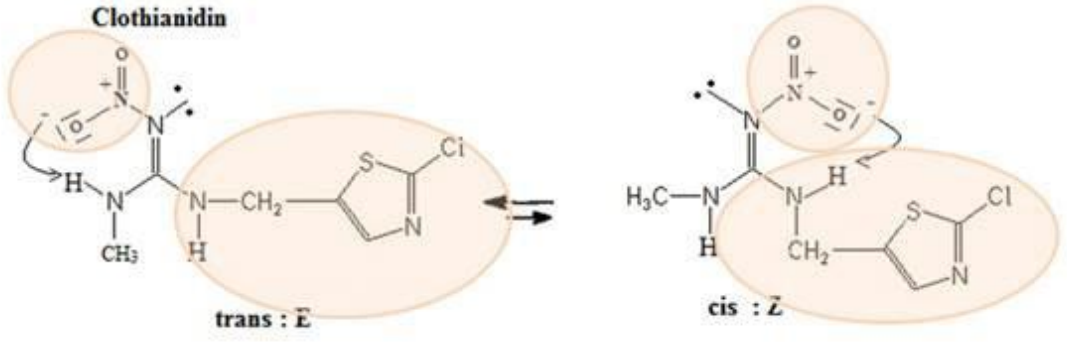
During the review of the existing maximum residue levels (MRLs) for clothianidin and thiamethoxam according to Article 12 of Regulation (EC) N°396/2005, EFSA (2014)
”emphasizes that the above studies do not investigate the possible impact of plant metabolism on the isomer ratio of thiamethoxam and clothianidin. Nevertheless, data were evaluated by JMPR indicating that the Z isomer of clothianidin is rather unstable and that the thermodynamic equilibrium of clothianidin results in the occurrence of the E isomer only, regardless whether clothianidin was applied as such or whether it results from metabolism of thiamethoxam (FAO/JMPR, 2010). Therefore, occurrence of the Z isomer is not expected. For thiamethoxam, the ratio of isomers is unspecified, but it is expected that the ratio will be subject to a rapid thermodynamic equilibrium at ambient temperature. Consequently, the ratio of isomers occurring in plants is expected to be the

same as the ratio used in the toxicological studies. Therefore, further investigation on this matter is not deemed necessary."

Metabolite CGA 322704 (a.k.a clothianidin),

- without the oxirane moiety,
- pseudo cycle formed by hydrogen bond
- steric hindrance

would also act in favor of the E form of the clothianidin.



Nevertheless, this point should also be reviewed in accordance with the concomitant assessment for the renewal of the active substance clothianidin.

2.12.6 Environmental fate

Not required since thiamethoxam is not a mixture of isomers.

2.12.7 Ecotoxicology

The active substance thiamethoxam is not a mixture of isomers.

2.13 RESIDUE DEFINITIONS

2.13.1 Definition of residues for exposure/risk assessment

Food of plant origin:

Plant residue definition for risk assessment (RD-RA)
Respectively (pending toxicological consideration):

Lettuce (foliar application)	CGA204261 CGA265307 CGA322704 (a.k.a clothianidin or TI-435) and its conjugates CGA349208 and its conjugates CGA353042 CGA353968 and its conjugates CGA355190 and its conjugates CGA382191 NOA405217 (a.k.a MNG) NOA407475 NOA421275 (a.k.a TMG) NOA424255 (a.k.a NTG) Thiamethoxam (CGA293343)
Cucumber (soil and foliar application)	NOA407475 Thiamethoxam (CGA293343)
Pear (foliar application)	CGA322704 (a.k.a clothianidin or TI-435) and its conjugates Thiamethoxam (CGA293343)
Tobacco (soil and foliar application)	CGA322704 (a.k.a clothianidin or TI-435) and its conjugates CGA353968 and its conjugates Thiamethoxam (CGA293343)
Potato (seed treatment)	CGA282149 CGA322704 (a.k.a clothianidin or TI-435) CGA353968 and its conjugates Thiamethoxam (CGA293343)
Rice (soil and foliar treatment)	CGA322704 (a.k.a clothianidin or TI-435) and its conjugates Thiamethoxam (CGA293343)
Maize (soil and foliar treatment)	CGA322704 (a.k.a clothianidin or TI-435) and its conjugates Thiamethoxam (CGA293343)

Food of animal origin:

Animal residue definition for risk assessment (RD-RA)	
Respectively (pending toxicological data on most of metabolites):	
Poultry	
Lean meat	CGA265307 MU3 NOA421275 (a.k.a TMG) Thiamethoxam (CGA293343)
Fat + skin	CGA265307 CGA322704 (a.k.a clothianidin or TI-435) MU3 Thiamethoxam (CGA293343)
Liver	CGA265307 CGA322704 (a.k.a clothianidin or TI-435) NOA421275 (a.k.a TMG) MU3

Egg	CGA265307 CGA322704 (a.k.a clothianidin or TI-435) NOA404617 Thiamethoxam (CGA293343)
Ruminant	
Muscle	CGA322704 (a.k.a clothianidin or TI-435) MU12 NOA421276 Thiamethoxam (CGA293343)
Fat	CGA322704 (a.k.a clothianidin or TI-435) NOA421275 (a.k.a TMG) NOA421276 Thiamethoxam (CGA293343)
Liver	L14 NOA 407475 NOA 421275 (a.k.a TMG) NOA421276
Kidney	L14 MU12 N5 NOA 421275 (a.k.a TMG) NOA 421276 Thiamethoxam (CGA293343)
Milk	CGA265307 CGA322704 (a.k.a clothianidin or TI-435) Thiamethoxam (CGA293343)

In terms of chemical structures, several of these metabolites could perhaps be grouped and considered as "thiamethoxam-like" or "clothianidin-like" but at this time considerations based on structural/activity remain unstated.

In addition and to avoid discrepancies, this assessment should be also confronted with corresponding conclusions from the concomitant assessment for the renewal of the active substance clothianidin.

Soil: Thiamethoxam, CGA322704 (clothianidin), CGA355190, CGA282149, CGA353042.

Groundwater: Thiamethoxam, CGA322704 (clothianidin), CGA355190, CGA282149, NOA459602, SYN501406, CGA353042

Surface water: Thiamethoxam, CGA322704 (clothianidin), CGA355190, CGA282149, CGA353042, NOA407475, NOA404617.

Sediment: Thiamethoxam, CGA322704 (clothianidin), CGA355190, CGA282149, CGA353042, NOA407475, NOA404617.

Air: Thiamethoxam

2.13.2 Definition of residues for monitoring

Food of plant origin:

Plant residue definition for monitoring (RD-Mo)
Respectively (pending toxicological consideration):
thiamethoxam, clothiandin, respectively

Food of animal origin:

Animal residue definition for monitoring (RD-Mo)	
Respectively (pending toxicological data on most of metabolites):	
Poultry	Thiamethoxam, clothianidin, CGA265307, MU03, NOA421275
Ruminant	Thiamethoxam, clothianidin, CGA265307, NOA421276, NOA421275

In terms of chemical structures several of these metabolites could perhaps be grouped and considered as "thiamethoxam-like" or "clothianidin-like" but at this time considerations based on structural/activity remain unstated.

In addition and to avoid discrepancies, this assessment should be also confronted with corresponding conclusions from the concomitant assessment for the renewal of the active substance clothianidin.

Soil: Thiamethoxam, CGA322704 (clothianidin)

Groundwater: Thiamethoxam, CGA322704 (clothianidin)

Surface water: Thiamethoxam, CGA322704 (clothianidin)

Sediment: Thiamethoxam, CGA322704 (clothianidin)

Air: Thiamethoxam, CGA322704 (clothianidin)

Body fluids and tissues: Thiamethoxam, CGA322704 (clothianidin)

Level 3

THIAMETHOXAM

3 PROPOSED DECISION WITH RESPECT TO THE APPLICATION

3.1 BACKGROUND TO THE PROPOSED DECISION

3.1.1 Proposal on acceptability against the decision making criteria – Article 4 and annex II of regulation (EC) No 1107/2009

3.1.1.1 Article 4				
		Yes	No	
i)	It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with. Specifically the RMS considers that authorisation in at least one Member State is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.			**It is still inconclusive whether Thiamethoxam can be renewed under Regulation (EC) No 1107/2009.** -Additional information is needed to finalise the consumer and environmental risk assessment on Clothianidin, the major metabolite of Thiamethoxam. Indeed, Clothianidin is an active substance also under renewal according to Regulation (EC) No 1107/2009 and for which the availability of Renewal Assessment Report is pending, -If the RMS proposal to add the classification Repr. Cat.2 H361 to the current harmonised classification is confirmed at European level, given that thiamethoxam also induces adverse endocrine-mediated effects (e.g. testicular effects, decreased sperm cells, delayed male puberty observed in offspring), the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties will be fulfilled.
3.1.1.2 Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted	X		However, additional information is necessary. Please refer to 3.1.4
ii)	It is considered that in the absence of a full dossier the active substance may be approved even though certain information is still to be submitted because: (a) the data requirements have been amended or refined after the submission of the dossier; or (b) the information is considered to be confirmatory in nature, as			

	required to increase confidence in the decision.			
3.1.1.3 Restrictions on approval				
		Yes	No	
	It is considered that in line with Article 6 of Regulation (EC) No 1107/2009 approval should be subject to conditions and restrictions.			Please refer to 3.1.1.1
3.1.1.4 Criteria for the approval of an active substance				
Dossier				
		Yes	No	
	It is considered the dossier contains the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).	X		Please refer to Level 2.6
	It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes (relevant for substances for which one or more representative uses includes use on feed or food crops or leads indirectly to residues in food or feed). In particular it is considered that the dossier: (a) permits any residue of concern to be defined; (b) reliably predicts the residues in food and feed, including succeeding crops (c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing; (d) permits a maximum residue level to be defined and to be determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.	X		**This is acceptable for the use on sugar beet but not for the use on lettuce and disputable for the use potatoes for the following reasons**: (a) The residue definition can not be finalized : Use on lettuce Pending information about the toxicity of several metabolites in lettuce, the level of the residues in lettuce according to the GAP and corresponding risk assessment for the consumer is considered as not finalized. Use on potatoes The representative use on potatoes in the frame of the renewal concerns a foliar application of 20 g a.s/ha whereas the metabolism study was performed with a seed treatment. Comparability between these 2 different modes of applications could be discussed. However this question could be toned down since residue levels show a non-residue situation (<LOQ of 0.02 mg/kg) for both thiamethoxam and metabolite CGA 322704 (a.k.a clothianidin) in tubers following a foliar treatment. Additional contribution to the consumer intakes through drinking water resulting from groundwater metabolite(s) Pending information about the toxicity of relevant identified metabolites in groundwater, contribution to the consumer intakes through drinking water resulting from groundwater metabolites is considered as not finalized.

				Renewal assessment of clothianidin Pending the concomitant assessment for the renewal of the active substance clothianidin a metabolite of thiamethoxam, the residue definitions proposed in plants and animals, dietary burden, toxicological reference values for metabolite CGA 322704 (a.k.a clothianidin) and risk assessment for the consumer are considered as not finalized. To avoid discrepancy, a global overview, discussions and harmonization are considered necessary. (b) In consequence level of residues depends on the outcome of the residue definition (c)(e) No major deficiencies have been identified in processed products (d) MRLs were proposed on the basis of residues of thiamethoxam and clothianidin respectively.
	It is considered that the dossier submitted is sufficient to permit, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.		X	Impact of the active substance on non-target species. Further data are necessary to address the uncertainty remaining in the non target arthropods field studies conducted with the formulations concerning effect and potential of recovery for some taxa (Syrphoidea, Miridae) for uses on lettuce (field), potato (field), Staphilinidae). Further data are necessary to address the uncertainty remaining in the non target arthropods field studies conducted with the formulations concerning effect and potential of recovery for some taxa (Staphilinidae) for use on sugar beet (field).
Efficacy				
		Yes	No	
	It is considered that it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use is sufficiently effective.	X		The efficacy was not assessed for the renewal process of thiamethoxam. Thiamethoxam based products are currently registered on the representative uses in some MS. Thiamethoxam based products will be re-assessed following the renewal of thiamethoxam.
Relevance of metabolites				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.		X	Toxicological relevance of groundwater metabolites: Not relevant according to SANCO 221/2000 based on the current harmoniszed classification of thiamethoxam. If the classification proposal Repr; Cat.2 H361 is approved, the reprotoxic profile of groundwater metabolites should be addressed in

				order to assess their relevance according to Sanco/221/2000 –rev.10-final 25 February 2003. Residues Relevance of metabolites is considered as not finalized pending: - information on the toxicity of metabolites listed in proposed residue definitions - RAR of clothianidin to complete risk assessment for thiamethoxam and for harmonization. Ecotoxicological relevance of metabolites Further data are necessary to address the uncertainty remaining in the aquatic mesocosms study conducting with the metabolite CGA322704 (Clothianidin) concerning effects and recovery (abundance and emergence) of the known sensitive Ephemeroptera, particularly species *Cloeon dipterum* and *Caenis sp*. Relevant for uses on lettuce (field), potato (field) and sugar beet (field).
Composition				
		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.	X		Thiamethoxam is manufactured with a minimum purity of 980 g/kg
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	X		FAO Specification 637 / TC (April 2014*)
	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	NA	NA	/
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently	X		Analytical methods for the determination of Thiamethoxam and its manufacturing impurities, in technical material, were evaluated and considered acceptable and relevant in terms of current standards and test guidelines. For the significant impurities see Volume 4 of the RAR. See level 2, part 2.5.2.

	specific, correctly calibrated, accurate and precise.			
	It is considered that the methods of residue analysis for the active substance and relevant metabolites in plant, animal and environmental matrices and drinking water, as appropriate, shall have been validated and shown to be sufficiently sensitive with respect to the levels of concern.	X		See level 2, part 2.5.2.
	It is confirmed that the evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		/
Impact on human health				
Impact on human health - ADI, AOEL, ARfD				
		Yes	No	
	It is confirmed that (where relevant) an ADI, AOEL and ARfD can be established with an appropriate safety margin of at least 100 taking into account the type and severity of effects and the vulnerability of specific groups of the population.	X		The ADI is set at 0.006 mg/kg bw/d, based on the 2-generation study and by using a safety factor of 100 *(see level 2.6.11).* The ARfD is set at 0.35 mg/kg bw based on the developmental neurotoxicity study and using a safety factor of 100 *(see level 2.6.12).* The AOEL is set at 0.006 mg/kg bw/d, based on the 2-generation study and by using a safety factor of 100 *(see level 2.6.13).* The AAOEL is set at 0.35 mg/kg bw based on the developmental neurotoxicity study and using a safety factor of 100 *(see level 2.6.13).*
Impact on human health – proposed genotoxicity classification				
		Yes	No	
	It is considered that, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as mutagen category 1A or 1B.**		X	According to its current harmonized classification, thiamethoxam is not classified for genotoxicity. Based on the results of *in vitro* and *in vivo* genotoxicity studies, thiamethoxam is not considered genotoxic *(see level 2.6.4).*
Impact on human health – proposed carcinogenicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and		X	According to its current harmonized classification, thiamethoxam is not classified for carcinogenicity. Thiamethoxam induced hepatocellular tumors in mice. The submitted mechanistic data as well as published

	other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as carcinogen category 1A or 1B.**			data demonstrated that the liver tumours observed in mice are induced through sustained cytotoxicity and subsequent regenerative hyperplasia induced by hepatocyte cytotoxicant metabolite. Human relevance of the mode of action can reasonably be excluded on the basis of marked quantitative differences in metabolism between mice and humans Therefore, no classification for carcinogenicity is warranted according to CLP criteria *(Refer to Level 2.6.5).*
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as toxic for reproduction category 1A or 1B.**		X	According to its current harmonized classification, thiamethoxam is not classified for reproductive toxicity. Thiamethoxam neither affected reproductive parameters in the two 2-generation studies nor induce severe developmental effects in the developmental toxicity studies. However, effects were observed on reproductive postnatal development in F1 males in the absence of general toxicity consisting of testicular atrophy in the first study and decreased sperm cells in the second one. In the developmental neurotoxicity study, reduced brain weight and significant changes in brain morphometric measurements were observed in offspring. There is evidence of increased quantitative and qualitative susceptibility of developing organisms in the multigeneration studies and in the developmental neurotoxicity study. As it is unclear whether the effects observed on reproductive postnatal development trigger classification for fertility or developmental toxicity, no specification (f or d) is proposed**.** **A classification Repr. Cat.2 H361 is therefore proposed** *(Refer to Level 2.6.6).*

ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties**		X	*[If yes cross refer to classification section and go to ii) and iii) immediately below.]*
ii)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **toxic for reproduction category 2 and** in addition the RMS considers the substance **has toxic effects on the endocrine organs and on that basis shall be considered to have endocrine disrupting properties**	X		If RMS proposal for reproductive classification Repr. Cat.2 H361 is confirmed at European level, given that thiamethoxam also induces adverse endocrine-mediated effects (e.g. testicular effects, decreased sperm cells, delayed male puberty observed in offspring), the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties will be fulfilled. Definive regulatory criteria are not published and dedicated guidance document is not available. No hormonal measurement has been performed and no investigating studies on the putative modes of action involved in testicular effects have been generated. In the absence of specific data, demonstrating alternative non-endocrine MoA(s) or showing that the adversity of the effects is not human relevant, it cannot be excluded that the testicular effects and the delayed male puberty could be plausibly linked to endocrine activity *(refer to Level 2.6.8.3).*
iii)	Linked to either i) or ii) immediately above. It is considered that exposure of humans to the active substance,		X	No information regarding negligible exposure has been submitted through the initial renewal dossier.

	safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Fate and behaviour in the environment				
Persistent organic pollutant (POP)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1.		X	The criterion for persistence is fulfilled based on OECD 309 (aerobic mineralization in dark) DT_{50} of 96 days. No validated DT_{50} in water-sediment system is available yet. The criterion for bioaccumulation is not fulfilled. The criterion for long range transport is not fulfilled.
Persistent, bioaccumulative and toxic substance (PBT)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2.		X	The criterion for persistence is fulfilled based on : - OECD 309 (aerobic mineralization in dark) DT_{50} of 96 days, - Maximal non-normalized field DT_{50} in soil of 192 days. The criterion for bioaccumulation is not fulfilled. The criterion for toxicity (T) is fulfilled (NOEC < 0.01 mg/L)
Very persistent and very bioaccumulative substance (vPvB).				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		X	The criterion for persistence is fulfilled based on the maximal non-normalized field DT_{50} in soil of 192 days. The criterion for bioaccumulation is not fulfilled.
Ecotoxicology				
		Yes	No	
	It is considered that the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or synergist. The RMS is content that the assessment takes into account the severity of		X	The long-term risk assessment for small herbivorous and large herbivorous mammals could not be finalized for the active substance for uses on lettuce (field). The long-term risk assessment for small omnivorous mammals could not be finalized for the active substance for uses on sugar beet (field). TER_{LT} values for thiamethoxam are lower than the Commission Regulation (EU) No. 546/2011 trigger value of 5. Further refinements are needed.

	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.			The long term risk assessment for aquatic organisms could not be finalized for the metabolite CGA322704 (clothianidin) for uses on lettuce (field), potato (field) and sugar beet (field). Two mesocosm studies are available for CGA322704 (clothianidin), however, an uncertainty remains in these mesocosms concerning effects and recovery (abundance and emergence) of the known sensitive Ephemeroptera, particularly species *Cloeon dipterum* and *Caenis sp*. Further refinements are needed. The in-field risk assessment for non-target arthropods could not be finalized for the uses on lettuce (field), potato (field) and sugar beet (field). Field studies are available, however based on uncertainties concerning effect and potential of recovery for some taxa (*Syrphoidea*, *Miridae*, *Staphilinidae*), no NOAER population nor NOAER community can be set from these studies. Further refinements are needed. The risk assessment for collembola could not be finalized for the metabolite CGA322704 (clothianidin) for the uses on sugar beet (field). TER_{LT} value for CGA322704 (clothianidin) is lower than the Commission Regulation (EU) No. 546/2011 trigger value of 5. Further refinements are needed.
	It is considered that, on the basis of the assessment of Community or internationally agreed test guidelines, the substance **HAS** endocrine disrupting properties that may cause adverse effects on non-target organisms.	X		For mammals: please refer to toxicological section. For non target organisms other than mammals, considered in Ecotoxicological risk assessment: No indications for potential for endocrine disrupting properties were found. However, RMS considered that literature search should be re-checked by the notifier to take into account publication giving information for evaluating potential endocrine activity of thiamethoxam or clothianidin on non target organisms other than mammals (see volume 3 CA B.9 for more details).
	Linked to the consideration of the endocrine properties immediately above. It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic	X		Exposure of non-target organisms for the uses on lettuce (permanent greenhouses) is negligible.

	proposed conditions of use is negligible.			
	It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist: — will result in a negligible exposure of honeybees, or — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.	X		For lettuce (permanent greenhouses), a risk assessment is not required. For sugar beet (field), lettuce (field) and potato (field), risk for honeybees can be considered acceptable with appropriate mitigation measure as follows: For sugar beet (field): Dangerous to bees / Bee-attractive crops should not be sown as a succeeding crop. (sugar beet seed treatment) For lettuce (field) and potato (field): Dangerous to bees/To protect bees and pollinating insects do not apply to crop plants when in flower or during the honeydew production period /Do not use where bees are actively foraging/ Respect a delay of 16 days between application and flowering period (potato) / Respect an unsprayed buffer zone of 1 m to flowering field margin (potato) and of 5 m (lettuce). Do not apply when flowering weeds are present (lettuce)/ Bee-attractive crops should not be sown as a succeeding crop.
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.		X	Residues Proposed residue definitions are considered as not finalized pending: - information on the toxicity of metabolites listed in proposed residue definitions - RAR of clothianidin to complete risk assessment for thiamethoxam and for harmonization.
Fate and behaviour concerning groundwater				
		Yes	No	
	It is considered that it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites, degradation or reaction products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article	X		Please refer to 2.8.6.

	29(6) of Regulation 1107/2009.			

3.1.2 Proposal – Candidate for substitution

Candidate for substitution				
		Yes	No	
	It is considered that the active substance shall be approved as a candidate for substitution	X		**Toxicology:** - It is to be noted that proposed reference values for Thiamethoxam are not significantly lower than those of the majority of active substances taking into account the thresholds mentioned in the Commission document *Questions and Answers on Candidates for Substitution* Rev. 1, January 2015 in which threshold for ADI is 0.001 mg/kg bw/d, threshold for ARfD is 0.004 mg/kg bw and threshold for AOEL is 0.001 mg/kg bw/d →No - While developmental neurotoxic and immunotoxic effects were observed, they did not trigger classification→No - If RMS proposal for reproductive classification Repr. Cat.2 H361 is confirmed at European level, given that thiamethoxam also induces adverse endocrine-mediated effects (e.g. testicular effects, decreased sperm cells, delayed male puberty observed in offspring), the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) →Yes **Fate and behaviour in the environnement and Ecotoxicology**: Yes - Toxicity criterion is fulfilled, NOEC < 0.01 mg/L - Persistence: persistence criterion is fulfilled, the highest non-normalized DT_{50} in soil is 508 days under laboratory conditions and 192 days under field conditions; the DT_{50} in aerobic natural water mineralization study is 96 days

3.1.3 Proposal – Low risk active substance

Low-risk active substances				
		Yes	No	
	It is considered that the active substance **shall be considered of low risk.** In particular it is considered that the substance **should NOT be classified or proposed for classification** in accordance with Regulation (EC) No 1272/2008 as at least one of the following: — carcinogenic, — mutagenic, — toxic to reproduction, — sensitising chemicals, — very toxic or toxic, — explosive, — corrosive. In addition it is considered that **the substance is NOT**: — persistent (half-life in soil more than 60 days), — has a bioconcentration factor higher than 100, — is deemed to be an endocrine disrupter, or — has neurotoxic or immunotoxic effects.		X	Proposed classification for reproductive toxicity Repr. Cat2 H361 in accordance with Regulation (EC) No 1272/2008 If RMS proposal for reproductive classification Repr. Cat.2 H361 is confirmed at European level, given that thiamethoxam also induces adverse endocrine-mediated effects (e.g. testicular effects, decreased sperm cells, delayed male puberty observed in offspring), the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC). The active substance is considered very toxic to aquatic life with long lasting effects: Aquatic acute 1; H400 Aquatic chronic 1; H410

3.1.4 List of studies to be generated, still ongoing or available but not peer reviewed

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	Study on-going and anticipated date of completion	Study available but not peer-reviewed
3.1.4.1 Identity of the active substance or formulation				
Not necessary				
3.1.4.2 Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
ACTARA 25WG The attrition test is outside the acceptable limit (<98%), consequently the size of particles of the formulation formed after the attrition test is required and the potential risk of operator must be evaluated	Relevant for all representative uses.	X		
3.1.4.3 Data on uses and efficacy				
No further data/studies required				
3.1.4.4 Data on handling, storage, transport, packaging and labelling				
No further data/studies required				
3.1.4.5 Methods of analysis				
Validation of the methods used in the toxicological, ecotoxicological studies and in the	Relevant for all representative uses.	X		

environmental studies are not provided and are required (see Volume 3 CA B.5)				
3.1.4.6 Toxicology and metabolism				
Several metabolites were identified in foodstuff (see level 2.6.8.1 and residue section 2.7). Depending on the level they are retrieved in foodstuff, their genotoxic potential and their toxicological profiles have to be addressed.	Relevant for lettuce use.	X		
Further data are necessary to further address the underlying mode of action of the testicular effects and the delayed male puberty observed in offspring in order to conclude on endocrine disruption properties.	Relevant for all representative uses.	X		
3.1.4.7 Residue data				
Information on the toxicity of metabolites listed in residue definitions		X		
Information on the toxicity of significant metabolites in ground water		X		
Studies to assess storage stability and level of the residues of relevant metabolites identified in the residue definition and considered relevant in term of their respective toxicity.		X		
RAR of clothianidin to complete risk assessment for thiamethoxam and for harmonization.		X		
3.1.4.8 Environmental fate and behaviour				
Information on the effect of water treatment processes on the nature of thiamethoxam residues	Relevant for all representative uses.	X		

when surface water or ground water are abstracted for drinking water should be provided. It is however noticeable that no guidance to address this issue is available				
Determination of the persistence and modeling triggers for the thiamethoxam degradation in water-sediment systems	Relevant for all representative uses.	X		
3.1.4.9 Ecotoxicology				
Further data are necessary to address the concerns on the potential long-term risk assessment for the active substance for small herbivorous and large herbivorous mammals for uses on lettuce (field) and for small omnivorous mammals for uses on sugar beet (field).	Relevant for uses on lettuce (field) and sugar beet (field).	X		
Further data are necessary to address the uncertainty remaining in the aquatic mesocosms study conducting with the metabolite CGA322704 (clothianidin) concerning effects and recovery (abundance and emergence) of the known sensitive Ephemeroptera, particularly species *Cloeon dipterum* and *Caenis sp*.	Relevant for uses on lettuce (field), potato (field) and sugar beet (field).	X		
Further data are necessary to address the uncertainty remaining in the non target arthropods field studies conducted with the formulations concerning effect and potential of recovery for some taxa (*Syrphoidea*, *Miridae*). No NOAER population or NOAER community can be set from these studies.	Relevant for uses on lettuce (field), potato (field).	X		
Further data are necessary to address the uncertainty remaining in the non target arthropods field studies conducted with the formulations concerning effect and potential of recovery for one taxon (*Staphilinidae*). No NOAER population or NOAER community can be set from these studies.	Relevant for uses on sugar beet (field).		The applicant informed the RMS that an additional field study is on-going to determine the effects of sugar beet seeds	

			treated with A9765R on natural non-target arthropod (NTA) communities under field conditions. The study will monitor the full fauna of naturally occurring NTAs for a period that covers at least two generations. The evaluation will be based on (1) time to recovery and (2) persistence of effect. Interim reports will be available February 2018 and 2019, while the final report will be available March 2020.	
Further data are necessary to address the concerns on the potential long-term risk assessment for collembolan for the metabolite CGA322704 (clothianidin).	Relevant for uses on sugar beet (field).			The notifier indicated that he is currently in the process of obtaining the following field study on CGA322704 to further address the risk to collembola (*Folsomia candida*). *S. Schabio (2014) Field study to evaluate the effects of clothianidin on soil earthworms and collembolans under field conditions. Sumitomo Chemical*

				Co., Ltd. Unpublished report No.: THW-0401
The following Interim Report has been submitted. K-CA 8.3.1.4/02, Bocksch, S, (2017), Thiamethoxam Technical – Honey Bee Brood and Colony Level Effects Following Thiamethoxam Intake via Treated Sucrose Solution in a Field Study in North Carolina – USA 2106. Interim Report Number S16-02808. Eurofins Agroscience Services EcoChem GmbH, Eutinger Str. 2475223 Niefern-Öschelbronn, Germany. (Syngenta file No. CGA293343_53502). Final report (Bocksch, 2017) not yet available.	Relevant for uses on lettuce (field), potato (field) and sugar beet (field).		X	

3.1.5 Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) No 546/2011, and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

Area of the risk assessment that could not be finalised on the basis of the available data	**Relevance in relation to representative use(s)**
Tox: If classification proposal for reproductive toxicity is agreed for thiamethoxam, the reprotoxic profile of groundwater metabolites should be addressed in order to assess their relevance.	Representative uses on lettuce (field), potato (field).
Ecotox Long-term risk for the active substance for small herbivorous and large herbivorous mammals for uses on lettuce (field). Long-term risk for the active substance for small omnivorous mammals for uses on sugar beet (field).	Representative uses on lettuce (field) and sugar beet (field).
Ecotox Long term risk to aquatic organisms for the metabolite CGA322704 (clothianidin) for uses on lettuce (field), potato (field) and sugar beet (field).	Representative uses on lettuce (field), potato (field) and sugar beet (field).
Ecotox Long term risk for collembola for the metabolite CGA322704 (clothianidin) for the uses on sugar beet (field).	Representative uses on sugar beet (field).
Ecotox The in-field risk for non-target arthropods for the uses on lettuce (field), potato (field) and sugar beet (field).	Representative uses on lettuce (field), potato (field) and sugar beet (field).
Residues Pending information about the toxicity of several metabolites in lettuce, the level of the residues in lettuce according to the GAP and corresponding risk assessment for the consumer is considered as not finalized.	Use on lettuce
Residues The representative use on potatoes in the frame of the renewal concerns a foliar application of 20 g a.s/ha whereas the metabolism study was performed with a seed treatment. Comparability between these 2 different modes of applications could be discussed. However this question could be toned down since residue levels show a non-residue situation (<LOQ of 0.02 mg/kg) for both thiamethoxam and metabolite CGA 322704 (a.k.a clothianidin) in tubers following a foliar treatment.	Use on potatoes
Residues Pending information about the toxicity of relevant identified metabolites in groundwater, contribution to the consumer intakes through drinking water resulting from groundwater metabolites is considered as not finalized.	Additional contribution to the consumer intakes through drinking water resulting from groundwater metabolite(s)

Residues Pending the concomitant assessment for the renewal of the active substance clothianidin a metabolite of thiamethoxam, the residue definitions proposed in plants and animals, dietary burden, toxicological reference values for metabolite CGA 322704 (a.k.a clothianidin) and risk assessment for the consumer are considered as not finalized. To avoid discrepancy, a global overview, discussions and harmonization are considered necessary.	Renewal assessment of clothianidin

3.1.6 Critical areas of concern

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

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

Critical area of concern identified	**Relevance in relation to representative use(s)**
If the RMS proposal to add the classification Repr. Cat.2 H361 to the current harmonised classification is confirmed at European level, given that thiamethoxam also induces adverse endocrine-mediated effects (e.g. testicular effects, decreased sperm cells, delayed male puberty observed in offspring), the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties will be fulfiled.	All uses / products
PECgw values for thiamethoxam > 0.1 µg/L for all 9 EU scenarios. Unacceptable risk of groundwater contamination identified.	Representative use on sugar beet (field).

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

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

Representative use		Use sugar beet (field) (X[1])	Use potato (field) (X[1])	Use lettuce (field) (X[1])	Use lettuce (greenhouse) (X[1])
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		X	X	X
Risk to wild non target terrestrial vertebrates	Risk identified				
	Assessment not finalised	X		X	
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified				
	Assessment not finalised	X	X	X	
Risk to aquatic organisms	Risk identified				
	Assessment not finalised	X	X	X	
Groundwater exposure active substance	Legal parametric value breached	X	X**	X***	
	Assessment not finalised				
Groundwater exposure metabolites	Legal parametric value breached				
	Parametric value of 10µg/L[(a)] breached				
	Assessment not finalised	X	X	X	X
Comments/Remarks					

The superscript numbers in this table relate to the numbered points indicated within chapter 3.1.5 and 3.1.6. Where there is no superscript number, see level 2 for more explanation.
(a): Value for non relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003
* Operator: the risk is not acceptable according to EFSA model for lettuce use (greenhouse).
Worker: is not acceptable according to EFSA model for lettuce uses field and greenhouse. If the default value of 50% for dermal absorption is used then worker exposure would be lower than the AOEL.
Bystander: for resident (children), the risk is not acceptable according to EFSA model for lettuce use. If the default value of

50% for dermal absorption is used then resident (children) exposure would be lower than the AOEL.
**: Unacceptable risk considering 1 application every year: No unacceptable risk if applied every other year.
***: Unacceptable risk considering 1 application every year: No unacceptable risk if applied every third year.

3.1.8 Area(s) where expert consultation is considered necessary

It is recommended to organise a consultation of experts on the following parts of the assessment report:

Area(s) where expert consultation is considered necessary	**Justification**
Toxicology	Endocrine disruption properties of Thiamethoxam. New reference values.
Residues Use on lettuce	Pending information about the toxicity of several metabolites in lettuce, the level of the residues in lettuce according to the GAP and corresponding risk assessment for the consumer is considered as not finalized.
Residues Use on potatoes	The representative use on potatoes in frame of the renewal concerns a foliar application of 20 g a.s/ha whereas the metabolism study was performed with a seed treatment. Comparability between these 2 different modes of applications could be discussed. However this question could be toned down since residue levels show a non-residue situation (<LOQ of 0.02 mg/kg) for both thiamethoxam and metabolite CGA 322704 (a.k.a clothianidin) in tubers following a foliar treatment.
Residues Additional contribution to the consumer intakes through drinking water resulting from groundwater metabolite(s)	Pending information about the toxicity of relevant identified metabolites in groundwater, contribution to the consumer intakes through drinking water resulting from groundwater metabolites is considered as not finalized.
Residues Renewal assessment of clothianidin	Pending the concomitant assessment for the renewal of the active substance clothianidin a metabolite of thiamethoxam, the residue definitions proposed in plants, animals, dietary burden, toxicological reference value for the metabolite CGA 322704 (a.k.a clothianidin) and risk assessment for the consumer are considered as not finalized. To avoid discrepancy, a global overview, discussions and harmonization are considered necessary.

3.1.9 Critical issues on which the Co RMS did not agree with the assessment by the RMS

Points on which the co-rapporteur Member State did not agree with the assessment by the rapporteur member state. Only the points relevant for the decision making process should be listed.

Issue on which Co-RMS disagrees with RMS	**Opinion of Co-RMS**	**Opinion of RMS**
Ecotoxicology, Aquatic organsims, Thiamethoxam.	Co-RMS (ES) agrees with RMS for considering the mesocosm study conducted by Hommen et al. (2016) useful for deriving a RAC. However, Co-RMS if of the opinion that higher AF would be applied to the NOEC = 0.3 µg as/L taking into account the uncertainties detected in this study	RMS: Two cosms studies were available for thiamethoxam. In the first study (Ashwell et al., 2003), the test system was representative of a realistic freshwater community and the diversity of the insect populations in the cosm was sufficiently high.

	(please see comments below). Co-RMS (ES): This study was conducted for assessing the effects on thiamethoxam on myfly Cloeon dipterum under natural conditions. The test systems contained indigenous flora and fauna (i.e., algae, macrophytes, zooplankton and macroinvertebrates) which originated from the sediments, water and aerial colonisation by flying insects. In this study, the effects on abundance were assessed only on the species Cloeon dipterum. Abundance and effects on the rest of species were not considered or evaluated. Consequently, the representation of the different populations of aquatic species and the aquatic community in the enclosure cannot be evaluated and it is not possible to know if the test system represent a realistic freshwater community. In the opinion of Co-RMS this limitation impedes the assessment of adverse effects at community or population level. The experimental period lasted for 5 weeks of continues exposure. Originally, the aim of the study was to investigate effects of a chronic exposure over at least eight weeks. However, 35 days after the first application, the study was terminated by author's decision due to the declining trend on the abundance of Cloeon larvae in control enclosures for five consecutive week. Consequently, authors considered the continuation of the study was not likely to yield further statistically robust endpoints. Co-RMS considers the study is not long enough to allow the observation of delayed effects. RMS uses the results of this study on Cloeon dipterum combined with the results of other mesocosm study (Ashwell et al., 2003 study, analyzed by Hommen 2015) for deriving an overall Tier 3 RAC. Co-RMS concerns about this approach since the study of Hommen et al., (2016) could be considered useful for	Following the recommendations of the aquatic guidance document (EFSA 2013) and recommendations of Brock et al. (2015), 11 crustacean and insect taxa met the MDD criteria taxa (category 1) of Brock et al. (2015) for a reliable analysis. However, only 7 of those 11 taxa represent potentially sensitive populations. These include: Crustaceans Asellus aquaticus and Crangonyx pseudogracilis; Insects Chironomidae, Zygoptera, Cecidomyiidae, Notonecta sp. and Ephydridae. The NOEC for the crustacean and insect community in this study (7 sensitive populations with reliable MDD criteria) has been set to 3.7 µg a.s./L (mean measured), based on class 1 and class 2 effects at this concentration. However, the mayfly species Cloeon dipterum, (known to be very sensitive population to neonicotinoids) were not sampled sufficiently to allow for robust analysis in Ashwell et al., 2003. Therefore, the effects of thiamethoxam on mayflies, specifically Cloeon dipterum, have been examined further in another cosm study (K-CA 8.2.8/03, Hommen, U. (2016). The aim of this second study (Hommen, U. (2016) was therefore to investigate effects only on mayfly (larvae abundance and emergence). However, characterisation of the test systems was investigated twice before the exposure period to characterize the community (results reported in Appendix 1 of the study report). The test system contained a diverse assemblage of invertebrates (zooplankton, macroinvertebrates) and plants (phytoplankton, periphyton and macrophytes) indicating a full fauna assemblage. Therefore the community can be considered to be representative of a realistic freshwater community. Further results from this appendix 1 could be added for completeness. The NOEC for Cloeon dipterum was determined to be 0.3 µg a.s./L (Effect Class 1). Then, as the new aquatic guidance document recommends that at least 8

	assessing effects on only one species and consequently it could be located closer to Tier 2 than a Tier 3 which have a clear repercussion on the AF to be applied. RMS considers adequate an AF = 2 to extrapolate the results observed in this experiment to the edge-of –field water conditions. Co-RMS considers the size of the AF would be higher than the one proposed by RMS and than the range proposed in the EFSA Aquatic GD (EFSA, 2013) The study was conducted for covering the worst-case exposure (35 days of almost constant exposure of thiamethoxam). However, it is important to consider the potential entry to water bodies of the metabolite CGA322704 (clothianidin) through drainage and runoff in order to characterize a realistic exposure regimen.	potentially sensitive populations should present a reliable MDD analysis, results from these two cosms have been combined (7 potentially sensitive populations in Ashwell et al., 2003 study) and 1 very sensitive population in cosm study in Hommen, U. (2016) to derive an overall endpoint to be used in refined risk assessment. It can be noted that exposure was worst-case in the cosm study (Hommen et al, 2016) compared to exposure in cosm (Ashwell et al., 2003. Since the Hommen, U. (2016) study provides a lower endpoint than the Ashwell et al., 2003 study (NOEC of 0.3 µg/L vs. NOEC of 3.7 from Ashwell et al. 2003), the Hommen (2016) study consequently provided the worst-case endpoint of the combined data set. Overall NOEC for the crustacean and insect community (8 sensitive populations) based on results from the two cosm studies can be set to 0.30 µg/L (nom), based on class 1 effects. The Aquatic Guidance document recommends an AF of 2 to derive an ETO-RACsw based on an effect class 1 NOEC concentration. Originally, the aim of the study was to investigate effects of a chronic exposure over eight weeks on mayflies in the test systems. On July 14, 2015, 35 days after the first application, the study was terminated for the following reasons: 1. Abundance of Cloeon larvae in control had been on a declining trend for five consecutive weeks, since initiation of exposure. Numbers of Cloeon larvae in control enclosures on day 34 were very low, with the consequent inflation of the MDD value to 87 %. 2. The abundance data up to and including the Day 27 indicated that the population of Cloeon larvae in the test system had declined naturally, and continuation of the study was not likely to yield further statistically

		robust endpoints. 3. Up to and including sampling 27 days after first application (four samplings post-first application), MDD values for Cloeon had been consistently below 50 %, enabling detection of "small effects". 4. Dosing of mesocosms with test substance to achieve maintained exposure had been successful and adequately mimicked a worst-case exposure (e.g. FOCUS scenarios driven by drainage). In order to achieve constant exposure levels as close to the nominal concentrations as practical, the test item was applied 9 times over the course of the study. It can be noted that DT50 Water/Sediment from E-Fate section was determined to be 32.5 days. Then, endpoint derived from this study is a NOEC of 0.3 µg/L, indicating no effect over 35 days of constant exposure that is a worst case regime. (see previous remark on 9 applications in the cosm study to maintain the concentration and DT50 Water/Sediment of 32.5 days). At higher tested concentrations (1, 3, 10 µg/L), effects were observed from around day 21, 14 and 7, respectively. Based on all these considerations (worst case exposure regime over 35 days, natural declining trend of population over the duration of the study but with reliable MDD statistical analysis up to the end of the study, continuation of the study would not likely to yield further statistically robust data), 35 days was considered to be long enough to allow the observation of potential delayed effects. Concerning the metabolite CGA322704 (soil metabolite), two cosm studies are available. An overall ETO-RAC of 0.25 µg a.s./L. was derived. However, an uncertainty remains concerning effects and recovery (abundance and emergence) of the known sensitive Ephemeroptera, particularly species Cloeon dipterum and Caenis sp in

		this cosm. As it was the case for Thiamethoxam, a mesocosm study could be peformed focusing on abundance and emergence of Ephemeroptera (i.e. Cloeon dipterum.). Moreover, it should be noted that co-exposure of active substance and soil metabolites is not an approach required in current regulation.

3.2 PROPOSED DECISION

[redacted]

None

3.3 RATIONAL 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)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

3.4 APPENDICES

GUIDANCE DOCUMENTS USED IN THIS ASSESSEMENT

General

Guidance Document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) 844/2012 (the Renewal Regulation), SANCO/2012/11251 rev. 4

Section identity, physical chemical and analytical methods

Section physico chemical properties

Manual on development and use of FAO and WHO specifications for pesticides, November 2010 - second revision of the First Edition, WHO, Rome 2010

Chemicals Regulation Directorate, DATA REQUIREMENTS HANDBOOK, (Version 2.2, June 2012)
Technical monograph N°17, 2nd edition, Guidelines for Specifying the Shelf Life of Plant Protection Products, June 2009

Evaluation Manual for the Authorisation of plant protection products and biocides according to Regulation (EC) No 1107/2009, EU part, Plant Protection Products, Chapter 2 Physical and chemical properties, version 2.0; January 2014, Board
Guidance ST/SG/AC 10/11/Rev.5 for the safety properties
CLP regulation 1272/2008

Regulation (UE) N°283/2013 (1st March 2013) setting out 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

Regulation (UE) N°284/2013 (1st March 2013) setting out data requirements for plant protection products, in accordance with regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market

Section analytical methods

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

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

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

Section Toxicology

SANCO 7531 - rev.10 Draft GUIDANCE FOR THE SETTING AND APPLICATION OF ACCEPTABLE OPERATOR EXPOSURE LEVELS (AOELs) 7 July 2006

SANCO 7199/VI/99 rev. 5 Draft Guidance Document GUIDANCE FOR THE SETTING OF AN ACUTE REFERENCE DOSE (ARfD) 05/07/2001

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

EFSA Guidance on dermal absorption. EFSA Journal 2017;15(6):4873

Guidance on the Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated Under Council Directive 91/414/EEC, SANCO/221/2000-Rev 10 (2003)

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 (2012)

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, 1-1355.

ECHA Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, version 4.1 June 2015.

WHO/IPCS Harmonization Project Document No. 4 PART 1: IPCS FRAMEWORK FOR ANALYSING THE RELEVANCE OF A CANCER MODE OF ACTION FOR HUMANS AND CASE-STUDIES, 2009.

Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874

EFSA Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology. EFSA Supporting publication 2016:EN-1074

Section Residue and consumer risk assessment

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, 2013, Introduction to OECD Test Guidelines on Pesticide Residues Chemistry - Section 5 Part A, Paris 2013

Section fate and behavior in environment

FOCUS (1997) Soil persistence models and EU registration, Doc. 7617/VI/96, 29.2.97

EC (2000) Guidance Document on Persistence in Soil, Doc 9188/VI/97 rev. 8, 12.07.2000

FOCUS (2006) “Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration” Report of the FOCUS Work Group on Degradation Kinetics, EC Document Reference Sanco/10058/2005 version 2.0, 434 pp

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