

Thiamethoxam

NOTIFICATION OF AN ACTIVE SUBSTANCE UNDER COMMISSION REGULATION (EU) 844/2012

DOCUMENT M-CA, Section 9

Metabolism and Residues Data

LITERATURE DATA

Version history¹

Date	Data points containing amendments or additions and brief description	Document identifier and version number

¹ It is suggested that applicants adopt a similar approach to showing revisions and version history as outlined in SANCO/10180/2013 Chapter 4 How to revise an Assessment Report

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CA 9 LITERATURE DATA

CA 9.1 Title

This document is a Literature Review Report for thiamethoxam, relevant metabolites and EU representative formulations A9584C (ACTARA® 25WG) and A9765R (CRUISER® 600FS) relevant to Metabolism and Residue Data.

CA 9.2 Author(s) of the review

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CA 9.3 Summary: A brief summary indicating the purpose of the report, the methodology employed and the results obtained

This report summarises the search for “scientific peer-reviewed open literature on thiamethoxam and its relevant metabolites dealing with metabolism and residues data which may impact health, the environment and non-target species and published within the last ten years before the date of submission of the dossier” in accordance with Article 8(5) of Regulation (EC) No. 1107/2009.

The exact search strategy is detailed in the Tables 9.5-1 to -5 but a summary of the methodology employed is given below.

1. A very broad search was conducted in 16 scientific source databases (detailed in Table 9.5-2) for thiamethoxam and its metabolite using the search terms listed in CA 9.5.1.
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 (see Table 9.4.2-1).
6. Any relevant papers were highlighted and assessed for reliability.

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 is summarised in the table below and full details are provided in Section 9.5.

Data requirement(s) captured in the search	Number			
	Initial Search	Top-Up Search	Clothianidin Search ^(a)	Total
Total number of <i>summary records</i> retrieved after <i>all</i> ^(b) searches of peer-reviewed literature (excluding duplicates)	1244	83	651	1978
Number of <i>summary records</i> excluded from the search results after rapid assessment for relevance ^(c)	1231	83	649	1963
Total number of <i>full-text</i> documents assessed in detail ^(b)	13	0	2	15
Number of <i>studies</i> excluded from further consideration after detailed assessment for relevance	13	0	2	15
Number of <i>studies</i> 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

CA 9.4 Protocol

CA 9.4.1 Statement of the objective of the review

The review has the objective of identifying “scientific peer-reviewed open literature on thiamethoxam and its potentially relevant metabolites dealing with metabolism and residue studies which may impact health, the environment and non-target species and published within the last ten years before the date of submission of the dossier” in accordance with Article 8(5) of Regulation (EC) No. 1107/2009.

CA 9.4.2 Criteria for relevance with which decisions to select studies in the dossier were made

Table 9.4.2-1: List of Criteria for relevance for each data requirement

Data requirements(s) (indicated by the correspondent CA data point(s))	Criteria for relevance
Metabolism and residues data (CA 6.1 to 6.9)	
Summary	<p>The relevance criteria applied to determine whether a literature reference was relevant for the residues and metabolism sections of the active substance renewal process are given below.</p> <ol style="list-style-type: none"> Well defined test material. e.g. are purity and batch data provided? Applicable test species. e.g. is the crop a representative use; were relevant animal commodities used? Study conditions should not differ significantly from guidelines and recommended protocols. e.g. did the study meet the relevant guidelines? Trial site/test system not previously exposed to the test material or other contaminants e.g. was the compound used previously at the trial site; was the animal feed free from the compound? Sufficient experimental information is provided to substantiate and evaluate whether the study conclusions and endpoints are robust. e.g. were storage intervals recorded; are weather conditions and plot histories available?

Data requirements(s) (indicated by the correspondent CA data point(s))	Criteria for relevance
	<ol style="list-style-type: none"> Validated Analytical methodology employed. e.g. were control samples used, acceptable recoveries obtained, clear example chromatograms given? Study conditions do not interfere with the interpretation of the study results. e.g. starting processing material residue is robust and there is measurable residue in processed products?
CA 6.1 Storage Stability of Residues (plant and animal)	<u>Storage Stability Studies</u> <ol style="list-style-type: none"> Well defined test material. e.g. are purity and batch data provided? Applicable test species. e.g. is the crop a representative use; were relevant animal commodities used? Study conditions should not differ significantly from guidelines and recommended protocols, and must be relevant to those in the submission. e.g. did the study meet the relevant guidelines and GAP? Sufficient experimental information is provided to substantiate and evaluate whether the study conclusions and endpoints are robust. e.g. were storage intervals recorded; are weather conditions and plot histories available? Validated analytical methodology employed e.g. were control samples used, acceptable recoveries obtained, clear example chromatograms given? Study conditions do not interfere with the interpretation of the study results. e.g. starting processing material residue is robust and there is measurable residue in processed products?
CA 6.2 Metabolism, distribution and Expression of Residues (plant and animal) CA 6.6.2 Metabolism and Distribution in Succeeding Crops	<ol style="list-style-type: none"> Well defined test material. e.g. if radiolabelled material was used, was an appropriate isotope used? Applicable test species. e.g. ruminant, poultry, etc.? Study conditions should not differ significantly from guidelines and recommended protocols, and must be relevant to those in the submission. e.g. is the application rate relevant and equivalent to maximum seasonal rate on rotated crops? Trial site/test system not previously exposed to the test material or other contaminants e.g. is plot history supplied? Sufficient experimental information is provided to substantiate and evaluate whether the study conclusions and endpoints are robust. e.g. Were metabolites identified by appropriate techniques? Validated analytical methodology employed. e.g. were representative clear chromatograms provided to support metabolite identification? Study conditions do not interfere with the interpretation of the study results. e.g. if the test item is photolabile was the study conducted outdoors?
CA 6.3 Magnitude of Residues Trials in Plants	<p>Published monitoring reports were not considered relevant due to the fact that it would not be possible to determine whether or not a misuse scenario had resulted in the residue levels reported.</p> <p><u>Crop Studies</u></p> <ol style="list-style-type: none"> Well defined test material (including purity/content) Applicable test species Study conditions should not differ significantly from guidelines and recommended protocols. Trial site/test system not previously exposed to the test material or other contaminants. Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust. Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc. Study conditions should not interfere with the interpretation of the study results. <p><u>Notes for above criteria</u></p> <ol style="list-style-type: none"> Well defined test material (including purity/content)

Data requirements(s) (indicated by the correspondent CA data point(s))	Criteria for relevance
	<p>e.g. was the formulation comparable to the proposed representative formulation?</p> <ol style="list-style-type: none"> Applicable test species e.g. is it a representative use crop? Study conditions should not differ significantly from guidelines and recommended protocols. e.g. Is the GAP relevant? Correct rate, application method, interval, PHI, spray volume, BBCH (if applicable), region, indoor/outdoor, control samples taken? e.g. were weather details available? e.g. were the control plots well separated from treated plots? e.g. was the field phase conducted according to GLP? e.g. were samples stored deep frozen? Were appropriate numbers of samples taken, e.g. 2kg of apples? e.g. was appropriate sampling methodology employed? Was the sample handling traceable? Trial site/test system not previously exposed to the test material or other contaminants. e.g. Plot history supplied, e.g. evidence that compound not used that year or previous year, and information on other plant protection products (e.g. to check for common metabolites). Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust. Examples as in 3 above and also, have they proposed an endpoint, e.g. MRL, what statistical methods have they used for this? Study conditions should not interfere with the interpretation of the study results. Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc. e.g. Was a validated method used, were acceptable recoveries obtained, were control samples analysed, were control samples 'clean', were representative clear chromatograms provided, Was the analytical phase conducted according to GLP? Were all components of the residue definition analysed for? Were samples analysed within a time period covered by storage stability data?
CA 6.4 Livestock Feeding Studies	<p>Same criteria as for crop studies, examples could be as above with the following additions.</p> <p><u>Livestock Feeding Studies Notes</u></p> <ol style="list-style-type: none"> Well defined test material (including purity/content) Applicable test species e.g. Ruminant, poultry, pig, fish, any edible animal. Study conditions should not differ significantly from recommended protocols. e.g. is the dosing level extreme? e.g. was the application form appropriate, e.g. capsule? e.g. was the number of test species correct, e.g. three cows, nine hens? e.g. was the dosing period appropriate, e.g. minimum 28 days? e.g. were control animals included? e.g. were the animals healthy? e.g. were the animals acclimatized? Trial site/test system not previously exposed to the test material or other contaminants. e.g. is it clear that additional animal feed did not contain treated substance? Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust. Study conditions should not interfere with the interpretation of the study

Data requirements(s) (indicated by the correspondent CA data point(s))	Criteria for relevance
	<p>results.</p> <p>7. Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc.</p>
CA 6.5 Effects of Processing	<p><u>High Temperature Hydrolysis</u></p> <ol style="list-style-type: none"> Well defined test material (including purity/content) e.g. if radiolabelled test item was used, was an appropriate isotope used (e.g. ^{14}C and <u>not</u> ^3H)? e.g. if radiolabelled test item was used, was the labelling position(s) appropriate to capture potential metabolites? e.g. if radiolabelled test item was used, was the specific activity adequate to meet an LOQ of 0.01 mg/kg? N.B. If water solubility of test item is < 0.01 mg/L then no study is required and can be deemed non-relevant Applicable test system e.g. Was the test undertaken in a <u>sterilised</u> buffer medium? Study conditions should not differ significantly from guidelines and recommended protocols. e.g. Were the temperature and pH conditions applied typical of processing operations carried out on commodities relevant to the test item? e.g. were samples stored deep frozen? Trial site/test system not previously exposed to the test material or other contaminants. Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust. Examples as in 3 above e.g. Were metabolites identified by appropriate techniques (e.g. co-chromatography with known standards using two dissimilar chromatographic systems or by techniques capable of positive structural identification e.g. MS, NMR)? Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc. e.g. Were relevant control experiments carried out when harsher techniques (e.g. acid/base hydrolysis) were used to identify metabolites (i.e. to ensure metabolites identified are not merely artefacts)? e.g. were representative clear chromatograms provided to support metabolite identification? e.g. where sample analysis exceeded 6 months from sample collection was storage stability of samples demonstrated? Study conditions should not interfere with the interpretation of the study results. <p><u>Field Studies</u></p> <ol style="list-style-type: none"> Well defined test material (including purity/content) Applicable test species Study conditions should not differ significantly from guidelines and recommended protocols. Trial site not previously exposed to the test material or other contaminants. Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust. Study conditions should not interfere with the interpretation of the study results. Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc.
CA 6.6 Residues in Rotational crops	<p>Same criteria as for crop residue studies, examples could be subtly different, e.g. acceptable PBIs, crop types, again monitoring information should not be considered relevant.</p>

Data requirements(s) (indicated by the correspondent CA data point(s))	Criteria for relevance
CA 6.7 Proposed residue definition and MRLs	Residue definition would only be affected if data generated in another section, e.g. metabolism/tox. MRLs would only be affected if residues generated and this is covered under 6.3.
CA 6.8 Proposed Safety Intervals	Not required. Any animal safety reports that might affect withholding periods would be covered in the review of literature in the Toxicology Section.
CA 6.9 Risk Assessment	Not required – any adverse findings for the risk assessment will have to be due to a data point from one of the other sections, and are therefore covered in other sections of this document.
CA 6.10 Other Studies	Not required.

* Recommended protocols under each data point include but are not limited to those listed in the Commission Communications 2013/C 95/01 and 2013/C 95/02

CA 9.5 Search methods

Date of initial search	19 January 2015
Date of most recent update to search	27 April 2015
Date of additional search ^(a)	27 April 2015
Date span of the search	10 years

(a) Additional search for clothianidin as a relevant metabolite

For the initial rapid assessment the study titles and abstracts were scanned to identify whether studies were of potential relevance to crop and livestock metabolism and/or residue studies in the context of human exposure through the diet. Studies clearly not within the remit of Regulation (EU) No. 283/2013 and regulation (EU) No. 284/2013 (such as metabolism studies in environmental compartments or microorganisms, other environmental fate studies, toxicological studies, efficacy studies, studies on plants other than crops, and mode of action studies) were eliminated during rapid assessment. Studies on the development of analytical methods relevant to routine (multi-residue) monitoring of active substance(s) residues in plant and animal commodities for compliance with MRLs, and reports summarising country monitoring data were also excluded from further consideration at rapid assessment.

Assessment of the full text of the remaining titles which were identified as potentially relevant or unclear on the basis of their titles and/or abstracts was conducted.

Table 9.5-1: Detailed Search Parameters for Metabolism and Residues data (CA 6.1 to 6.10) – Search Terms

Search Strategy	
L1	QUE (153719-23-4 OR (A(W)97565N) OR A97565N OR A9765N)
L2	QUE (ACTARA(W)(25WG OR (25(W)WG) OR 2GR OR (2(W)GR)))
L3	QUE ((A(W)9765N) OR (ADAGE(W)(5FS OR (5(W)FS))) OR TIAMETHOXAM?)
L4	QUE (THIAMETHOXAM? OR CGA293343 OR (CGA(W)293343) OR DIACLODEN?)
L5	QUE ((CRUISER(W)(350FS OR (350(W)FS) OR 5FS OR (5(W)FS))))
L6	QUE ((CRUISER(W)(A9765 OR (A(W)9765))) OR THIAMETOXAM?)
L7	QUE ((ACTARA OR CRUISER OR FLAGSHIP OR ADAGE)(10A)INSECTICID?)
L8	QUE L1-7 THIAMETHOXAM
L9	QUE (135018-15-4 OR 153719-38-1 OR 120740-08-1 OR 131748-59-9)

Search Strategy

L10 QUE (915125-06-3 OR 634192-72-6 OR 902493-06-5 OR 902493-08-7)
 L11 QUE (4245-76-5 OR 868542-26-1 OR 635283-91-9 OR 939773-18-9)
 L12 QUE (CGA265307 OR CGA282149 OR CGA309335 OR CGA322704)
 L13 QUE (CGA(W)(265307 OR 282149 OR 309335 OR 322704))
 L14 QUE (CGA353042 OR CGA353968 OR CGA355190 OR NOA404617)
 L15 QUE ((CGA(W)(353042 OR 353968 OR 355190)) OR (NOA(W)404617))
 L16 QUE (NOA405217 OR NOA407475 OR NOA421275 OR NOA459602)
 L17 QUE (NOA(W)(405217 OR 407475 OR 421275 OR 459602))
 L18 QUE (SYN501406 OR (SYN(W)501406))
 L19 QUE (N(2W)2(W)CHLOROTHIAZOL(W)5(W)YL(W)METHYL(2W)N(2W) METHYLGUANIDINE?)
 L20 QUE (3(W)METHYL(W)4(W)NITROIMINO(W)TETRAHYDRO(W)1(W)3(W)5(W) OXADIAZINE)
 L21 QUE (2(W)CHLORO(W)5(W)THIAZOLYL(2W)METHYLAMINE)
 L22 QUE (2(W)CHLORO(W)5(2W)AMINOMETHYL(W)THIAZOLE)
 L23 QUE (2(W)CHLORO(W)5(W)THIAZOLEMETHANAMINE)
 L24 QUE (2(W)CHLORO(W)5(W)THIAZOLEMETHYLAMINE)
 L25 QUE (5(2W)AMINOMETHYL(2W)2(W)CHLOROTHIAZOLE)
 L26 QUE (150221-74-2 OR (1(W)METHYL(W)3(W)NITROGUANIDINE))
 L27 QUE (N(W)METHYL(W)N(2W)NITROGUANIDINE)
 L28 QUE ((N(W)METHYL(W)N(2W)NITRO)(2A)GUANIDINE)
 L29 QUE (5(2W)5(W)METHYL(W)4(W)NITROIMINO(2W)1(W)3(W)5(W)OXADIAZINAN)
 L30 QUE (L29(W)3(W)YLMETHYL(W)THIAZOLE(W)2(W)SULFONATE)
 L31 QUE (5(2W)N(2W)METHYL(W)N(3W)NITRO(W)GUANIDINOMETHYL)
 L32 QUE (L31(2W)THIAZOLE(W)2(W)SULFONATE)
 L33 QUE (L9-L29 OR L30 OR L32) THIAMETHOXAM METABOLITES

Or (for additional search)

L1 QUE (210880-92-5 OR CLOTHIANIDIN? OR 205510-53-8 OR (TITAN(W)ST))
 L2 QUE (CLUTCH OR DANTOP OR DANTOTSU OR PONCHO OR ARENA)
 L3 QUE (L2(10A)(INSECTICID? OR NEONICOTIN?))
 L4 QUE (PONCHO(W)(250 OR 600)) OR (TAKELOC(W)(CLMN OR MC OR MC50#))
 L5 QUE (DANTOTSU(W)(16WSG OR (16(W)WSG)))
 L6 QUE (L1 OR L3-5)

Plus:

L1 QUE (METABOL? OR RESIDUE# OR TRANSFORM? OR BIOTRANSFORM?)
 L2 QUE (DEGRAD? OR BIODEGRAD? OR FATE# OR MRL OR MRLS)
 L3 QUE (CONJUGAT? OR EXCRET? OR ELIMINAT?)
 L4 QUE (FOOD# OR FEED# OR DIET# OR DIETARY OR CONSUMER? OR HUMAN#)
 L5 QUE (CONTAMINAT? OR SAFE? OR EXPOS? OR ANALY? OR ASSES?)
 L6 QUE (INTAKE? OR (IN(W)TAKE?) OR SURVEY? OR RISK?)
 L7 QUE (TOXIC? OR STUDY? OR STUDIES?)
 L8 QUE (L4(10A)(L5 OR L6 OR L7))
 L9 QUE (LIVESTOCK# OR COW# OR GOAT# OR CATTLE# OR BULLOCK#)
 L10 QUE (BOVINE? OR BOVIDAE? OR BOS OR BULL# OR HEIFER? OR CAPRA#)
 L11 QUE (SHEEP# OR EWE OR EWES OR RAM# OR SWINE# OR PIGLET#)
 L12 QUE (PIG# OR SUIDAE? OR SUS OR OVIS OR OX OR OXEN)
 L13 QUE (RUMINANT? OR HEN# OR CHICKEN# OR FOWL# OR TURKEY?)
 L14 QUE (DUCK# OR GOOSE OR GEESE OR CAPON# OR POULTRY?)
 L15 QUE (MEAT OR MILK OR EGG# OR TISSUE#)
 L16 QUE (((BROKEN? OR BREAK?)(W)(DOWN OR UP)) OR BREAKDOWN?)
 L17 QUE (BREAKSDOWN? OR UPTAKE? OR PROCESSING? OR BOUND?)

Search Strategy

L18 QUE ((NON(W)EXTRACTAB?) OR (ROTATIONAL(3A)CROP#))
L19 QUE ((L1 OR L2 OR L3) OR L8 OR (L9 OR L10 OR L11 OR L12 OR L13
 OR L14) OR (L15 OR L16 OR L17 OR L18))

Table 9.5-2: Detailed Search Parameters for Metabolism and Residues data (CA 6.1 to 6.9)

Provider	Database	Justification	Limits applied	Number of results*			
				Initial Search	Top-Up Search	Clothianidin Search ^(a)	Total
Host STN	MEDLINE	Contains information on every area of medicine providing comprehensive coverage from 1948 to present. Sources include journals and chapters in books or symposia. The database is updated 5 times each week with an annual reload and therefore stays very current in its cover.	10 years	203	11	116	330
	EMBASE	The database, covers worldwide literature in the biomedical and pharmaceutical fields, including biological science, biochemistry, human medicine, forensic science, pediatrics, pharmacy, pharmacology and drug therapy, pharmacoeconomics, psychiatry, public health, biomedical engineering and instrumentation, and environmental science. Sources include more than 4,000 journals from approximately 70 countries, monographs, conference proceedings, dissertations, and reports. The databases covers data from 1974-present and is updated daily.		49	4	20	73
	EMBAL	The database provides early access to bibliographic data and the abstracts for references that will appear in EMBASE. Bibliographic information for references is available in EMBAL for the latest 8 weeks of EMBASE data. The database covers the worldwide literature on the biomedical and pharmaceutical fields. Bibliographic information, abstracts, and author keywords are searchable. Sources include over 4,000 journals. The database covers current data and is updated daily.		2	0	1	3
	ESBIOBASE	A database providing comprehensive coverage of the entire spectrum of biological research worldwide. Coverage includes the following areas: applied microbiology, biotechnology, cancer research, cell & developmental biology, clinical chemistry, ecological & environmental sciences, endocrinology, genetics, immunology, infectious diseases, metabolism, molecular biology, neuroscience, plant and crop science, protein biochemistry, and toxicology. Records are selected from over 1,700 international scientific journals, books, and conference proceedings. The database covers the period 1994 - present and is updated weekly.		6	2	3	11
	AGRICOLA	A bibliographic database containing selected worldwide literature of agriculture and related fields. Coverage of the database includes agricultural economics and rural sociology, agricultural production, animal sciences, chemistry, entomology, food and human nutrition, forestry, natural resources, pesticides, plant science, soils and fertilizers, and water resources. Also covered are related areas such as biology and biotechnology, botany, ecology, and natural history. The database draws on bibliographies, serial articles, book chapters, monographs, computer files, serials, maps, audiovisuals, and reports. It covers the period 1970-present and is updated monthly.		13	2	4	19

Provider	Database	Justification	Limits applied	Number of results*			
				Initial Search	Top-Up Search	Clothianidin Search ^(a)	Total
Host STN	BIOSIS	A large and comprehensive worldwide life science database covers original research reports, reviews, and selected U.S. patents in biological and biomedical areas, with subject coverage ranging from aerospace biology to zoology. Sources include periodicals, journals, conference proceedings, reviews, reports, patents, and short communications. Nearly 6,000 life source journals, 1,500 international meetings as well as review articles, books, and monographs are reviewed for inclusion. It covers the period 1926 – present and is updated weekly.	10 years	46	10	36	92
	CABA	Covers worldwide literature from all areas of agriculture and related sciences including biotechnology, forestry, and veterinary medicine. Sources include journals, books, reports, published theses, conference proceedings, and patents. It covers the period 1973-present and is updated weekly.		330	21	139	490
	CAPLUS	Covers worldwide literature from all areas of chemistry, biochemistry, chemical engineering, and related sciences including applied, macromolecular, organic, physical, inorganic, and analytical chemistry. Current sources include over 8,000 journals, patents, technical reports, books, conference proceedings, dissertations, product reviews, bibliographic items, book reviews, and meeting abstracts. Electronic-only journals and Web preprints are also covered. Cited references are included for journals, conference proceedings and basic patents from the U.S., EPO, WIPO, and German patent offices added to the CAS databases from 1999 to the present. Also provides early access to the bibliographic information, abstracts and CAS Registry Numbers for documents in the process of being indexed by CAS. Covers the period 1907 – present and is updated daily		496	25	278	799
	FSTA	The database provides worldwide coverage of all scientific and technological aspects of the processing and manufacture of human food products including basic food sciences, biotechnology, hygiene and toxicology, engineering, packaging, and all individual foods and food products. Sources include more than 2,200 journals, books, reviews, conference proceedings, patents, standards, and legislation. It covers the period 1969 – present and is updated weekly.		15	0	9	24
	FROSTI	The database contains citations to the worldwide literature on food science and technology including food and beverages, analytical methods, quality control, manufacturing, microbiology, food processing, health and nutrition, recipes, and additives. Sources include approximately 800 scientific and technical journals, bulletins, technical reports, conference proceedings, grey literature, and British, European (EP), U.S., Japanese, and international (PCT) patent applications. Covers the period 1972 – present and is updated twice weekly.		2	0	0	2

Provider	Database	Justification	Limits applied	Number of results*			
				Initial Search	Top-Up Search	Clothianidin Search ^(a)	Total
Host STN	GEOREF	Covers international literature on geology and geosciences. Sources include the Bibliography of North American Geology, Bibliography and Index of Geology Exclusive of North America, Geophysical Abstracts, Bibliography of Fossil Vertebrates, selected records from Geoline and from geology sections of PASCAL and state and national geological surveys. Covers the period 1669 – present and is updated twice a month.	10 years	0	1	0	1
	TOXCENTER	Covers the pharmacological, biochemical, physiological, and toxicological effects of drugs and other chemicals. It is composed of the following subfiles: BIOSIS, CAPLUS, IPA and MEDLINE and sources include abstracts, books and book chapters, bulletins, conference proceedings, journal articles, letters, meetings, monographs, notes, papers, patents, presentations, research and project summaries, reviews, technical reports, theses, translations, unpublished material, web reprints. Covers the period 1907 – present and is updated weekly		0	0	0	0
	PQSCITECH	Is a huge resource in all areas of science and technology from engineering to lifescience. The file is a merge of 25 STN databases formerly known as CSA databases (Cambridge Scientific Abstracts): AEROSPACE, ALUMINIUM, ANTE, AQUALINE, AQUASCI, BIOENG, CERAB, CIVILENG, COMPUAB, CONFSCI, COPPERLIT, CORROSION, ELCOM, EMA, ENVIROENG, HEALSAFE, LIFESCI, LISA, MATBUS, MECHENG, METADEX, OCEAN, POLLUAB, SOLIDSTATE, and WATER. Sources are journals, patents, books, reports, and conference proceedings spanning the period 1962 – present and it is updated monthly.		32	2	14	48
	PASCAL	The database provides access to the world's scientific and technical literature including physics and chemistry, life sciences (biology, medicine, and psychology), applied sciences and technology, earth sciences, and information sciences. French and European literature is particularly well represented. Approximately 5,000 journal titles are indexed. References to theses and to conference proceedings are also included. Spans the period 1977 to present and is updated weekly		6	0	4	10
	SCISEARCH	Is an international index to the literature covering virtually every subject area within the broad fields of science, technology, and biomedicine. SciSearch contains all the records published in Science Citation Index Expanded™ and additional records from the Current Contents series of publications. Bibliographic information and cited references from over 5,600 scientific, technical, and medical journals are contained in the database. Spans the period 1974 to present and is updated weekly.		43	5	26	74

Provider	Database	Justification	Limits applied	Number of results*			
				Initial Search	Top-Up Search	Clothianidin Search ^(a)	Total
Host STN	ANABST	Covers worldwide literature on analytical chemistry. The ANABSTR file contains bibliographic records with abstracts (since 1984) for documents reported in printed Analytical Abstracts. Sources for ANABSTR include journals, books, conference proceedings, reports, and standards. Spans the period 1980 to present and is updated weekly.	10 years	1	0	1	2

(a) Additional search for clothianidin as a relevant metabolite

* Total number of summary records retrieved after removing duplicates

Table 9.5-3: Detailed Search Parameters for Web searches

Website name and service publisher	URL	Justification	Search terms	Limits applied	Number*
A web search has not been conducted as the database search reported above is considered to provide an adequately comprehensive search of the quality peer reviewed literature.					

* Total number of summary records or full-text documents retrieved after removing duplicates

Table 9.5-4: Detailed Search Parameters for Journal Table of Contents

Journal name	Journal URL or publisher	Dates, volumes and issues searched	Method of searching	Search terms	Number*
A search for journal table of contents has not been conducted as the database search reported above is considered to provide an adequately comprehensive search of the quality peer reviewed literature.					

* Total number of summary records or full-text documents retrieved after removing duplicates

Table 9.5-5: Detailed Search Parameters for Reference Lists

Bibliographic details of documents whose reference lists were scanned	Number*
A search for reference lists has not been conducted as the database search reported above is considered to provide an adequately comprehensive search of the quality peer reviewed literature.	

* Total number of summary records or full-text documents retrieved after removing duplicates

CA 9.6 Results

Table 9.6-1: Results of study selection process

Data requirement(s) captured in the search	Number			
	Initial Search	Top-Up Search	Additional Search ^(a)	Total
Total number of <i>summary records</i> retrieved after <i>all</i> ^(b) searches of peer-reviewed literature (excluding duplicates)	1244	83	651	1978
Number of <i>summary records</i> excluded from the search results after rapid assessment for relevance ^(c)	1231	83	649	1963
Total number of <i>full-text</i> documents assessed in detail ^(b)	13	0	2	15
Number of <i>studies</i> excluded from further consideration after detailed assessment for relevance	13	0	2	15
Number of <i>studies</i> 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

The references that were assessed in detail are summarised below:

Table 9.6-2: List of references for all relevant and unclear studies listed by data point number

CA data point number	Author(s)	Year	Title	Source
Initial search				
CA 6.10.1	Bernal, J., L.; Nozal, M., J.; Martin, M., T.;	2013	Determination of seven neonicotinoid insecticides in beeswax by liquid chromatography coupled to electrospray-mass spectrometry using a fused-core column.	Journal of chromatography. A, (2013 Apr 12) Vol. 1285, 110-117
CA 6.5.3	Colazzo, M.; Perez-Parada, A.; Besil N.; Heinzen, H.; Bocking, B.; Cesio, V.; Fernandez-Alba, A., R.	2012	Occurrence and distribution study of residues from pesticides applied under controlled conditions in the field during rice processing.	Journal of agricultural and food chemistry, (2012 May 9) Vol. 60, No. 18, 4440-4448
CA 6.10.1	Czerwenka, C.	2011	LC-MS/MS analysis of neonicotinoid insecticides in honey: methodology and residue findings in Austrian honeys.	Journal of agricultural and food chemistry, (2011 Dec 14) Vol. 59, No. 23, 12271-12277
CA 6.2.1	Casida, J., E.	2011	Neonicotinoid Metabolism: Compounds, Substituents, Pathways, Enzymes, Organisms, and Relevance.	Journal of Agricultural and Food Chemistry, (APR 13 2011) Vol. 59, No. 7, 2923-2931
CA 6.10.1	Barganska, Z.; Slebioda, M.; Namiesnik, J.	2013	Pesticide residues levels in honey from apiaries located of Northern Poland.	Food Control (2013), Volume 31, Number 1, 196-201
CA 6.10.1	Tomasini, D.; Sampaio, M. R. F.; Caldas, S. S.; Buffon, J. G.; Duarte, F. A.; Primel, E. G.	2012	Simultaneous determination of pesticides and 5-hydroxymethylfurfural in honey by the modified QuEChERS method and liquid chromatography coupled to tandem mass spectrometry.	Talanta (2012), Volume 99, 380-386

CA data point number	Author(s)	Year	Title	Source
CA 6.2.1	Ford, K. A.; Casida, J., E.	2008	Comparative metabolism and pharmacokinetics of seven neonicotinoid insecticides in spinach.	Journal of Agricultural and Food Chemistry (2008), Volume 56, Number 21, 10168-10175
CA 6.9	Chen, M.; Tao, L.; McLean, J.; Lu, C.	2014	Quantitative Analysis of Neonicotinoid Insecticide Residues in Foods: Implication for Dietary Exposures	Journal of Agricultural and Food Chemistry (2014), 62 (26), 6082-6090
CA 6.10.1	Kasiotis, K., M.; Anagnostopoulos, C.; Anastasiadou, P.; Machera, K.	2014	Pesticide residues in honeybees, honey and bee pollen by LC-MS/MS screening: Reported death incidents in honeybees	Science of the Total Environment (2014), 485-486, 633-64
CA 6.10.1	Paradis, D.; Berail, G.; Bonmatin, JM.; Belzunces, L., P.	2014	Sensitive analytical methods for 22 relevant insecticides of 3 chemical families in honey by GC-MS/MS and LC-MS/MS	Analytical and Bioanalytical Chemistry (2014), 406 (2), 621-633
CA 6.10.1	Wiest, L.; Bulete, A.; Giroud, B.; Fratta, C.; Amic, S.; Lambert, O.; Pouliquen, H.; Arnaudguilhem, C.	2011	Multi-residue analysis of 80 environmental contaminants in honeys, honeybees and pollens by one extraction procedure followed by liquid and gas chromatography coupled with mass spectrometric detection	Journal of Chromatography A (2011), 1218 (34), 5743-5756
CA 6.5.3	Inoue, T.; Nagatomi, Y.; Suga, K.; Uyama, A.; Mochizuki, N.	2011	Fate of Pesticides during Beer Brewing	Journal of Agricultural and Food Chemistry (2011), 59 (8), 3857-3868
CA 6.9	Nougadere, A.; Reninger, JC.; Volatier, JL.; Leblanc, JC.	2011	Chronic dietary risk characterization for pesticide residues: A ranking and scoring method integrating agricultural uses and food contamination data	Food and Chemical Toxicology (2011), 49 (7), 1484-1510
Top-Up search				
	No relevant results			
Additional Search ^(a)				
CA 6.10.1	Kujawski, M.,W.; Namiesnik, J.	2011	Levels of 13 multi-class pesticide residues in Polish honeys determined by LC-ESI-MS/MS	Food Control (2011), Volume 22, Number 6, 914-919
CA 6.10.1	Gbylik-Sikorska, M.; Sniegocki, T.; Posyniak, A.	2015	Determination of neonicotinoid insecticides and their metabolites in honey bee and honey by liquid chromatography tandem mass spectrometry	Journal of Chromatography B, 990 (2015), 132–140

(a) Additional search for clothianidin as a relevant metabolite

Table 9.6-3: List of references for all relevant and unclear studies listed by Author

Author(s)	Year	OECD data point number	Title	Source
Initial Search				
Barganska, Z.; Slebiada, M.; Namiesnik, J.	2013	CA 6.10.1	Pesticide residues levels in honey from apiaries located of Northern Poland.	Food Control (2013), Volume 31, Number 1, 196-201

Author(s)	Year	OECD data point number	Title	Source
Bernal, J., L.; Nozal, M., J.; Martin, M., T.;	2013	CA 6.10.1	Determination of seven neonicotinoid insecticides in beeswax by liquid chromatography coupled to electrospray-mass spectrometry using a fused-core column.	Journal of chromatography. A, (2013 Apr 12) Vol. 1285, 110-117
Casida, J., E.	2011	CA 6.2.1	Neonicotinoid Metabolism: Compounds, Substituents, Pathways, Enzymes, Organisms, and Relevance.	Journal of Agricultural and Food Chemistry, (APR 13 2011) Vol. 59, No. 7, 2923-2931
Chen, M.; Tao, L.; McLean, J.; Lu, C.	2014	CA 6.9	Quantitative Analysis of Neonicotinoid Insecticide Residues in Foods: Implication for Dietary Exposures	Journal of Agricultural and Food Chemistry (2014), 62 (26), 6082-6090
Colazzo, M.; Perez-Parada, A.; Besil N.; Heinzen, H.; Bocking, B.; Cesio, V.; Fernandez-Alba, A., R.	2012	CA 6.5.3	Occurrence and distribution study of residues from pesticides applied under controlled conditions in the field during rice processing.	Journal of agricultural and food chemistry, (2012 May 9) Vol. 60, No. 18, 4440-4448
Czerwenka, C.	2011	CA 6.10.1	LC-MS/MS analysis of neonicotinoid insecticides in honey: methodology and residue findings in Austrian honeys.	Journal of agricultural and food chemistry, (2011 Dec 14) Vol. 59, No. 23, 12271-12277
Ford, K. A.; Casida, J., E.	2008	CA 6.2.1	Comparative metabolism and pharmacokinetics of seven neonicotinoid insecticides in spinach.	Journal of Agricultural and Food Chemistry (2008), Volume 56, Number 21, 10168-10175
Inoue, T.; Nagatomi, Y.; Suga, K.; Uyama, A.; Mochizuki, N.	2011	CA 6.5.3	Fate of Pesticides during Beer Brewing	Journal of Agricultural and Food Chemistry (2011), 59 (8), 3857-3868
Kasiotis, K., M.; Anagnostopoulos, C.; Anastasiadou, P.; Machera, K.	2014	CA 6.10.1	Pesticide residues in honeybees, honey and bee pollen by LC-MS/MS screening: Reported death incidents in honeybees	Science of the Total Environment (2014), 485-486, 633-664
Nougadere, A.; Reninger, JC.; Volatier, JL.; Leblanc, JC.	2011	CA 6.9	Chronic dietary risk characterization for pesticide residues: A ranking and scoring method integrating agricultural uses and food contamination data	Food and Chemical Toxicology (2011), 49 (7), 1484-1510
Paradis, D.; Berail, G.; Bonmatin, JM.; Belzunces, L., P.	2014	CA 6.10.1	Sensitive analytical methods for 22 relevant insecticides of 3 chemical families in honey by GC-MS/MS and LC-MS/MS	Analytical and Bioanalytical Chemistry (2014), 406 (2), 621-633
Tomasini, D.; Sampaio, M. R. F.; Caldas, S. S.; Buffon, J. G.; Duarte, F. A.; Primel, E. G.	2012	CA 6.10.1	Simultaneous determination of pesticides and 5-hydroxymethylfurfural in honey by the modified QuEChERS method and liquid chromatography coupled to tandem mass spectrometry.	Talanta (2012), Volume 99, 380-386
Wiest, L.; Bulete, A.; Giroud, B.; Fratta, C.; Amic, S.; Lambert, O.; Pouliquen, H.; Arnaudguilhem, C.	2011	CA 6.10.1	Multi-residue analysis of 80 environmental contaminants in honeys, honeybees and pollens by one extraction procedure followed by liquid and gas chromatography coupled with mass spectrometric detection	Journal of Chromatography A (2011), 1218 (34), 5743-5756
Top-Up search				
No relevant results				
Additional Search^(a)				

Author(s)	Year	OECD data point number	Title	Source
Gbylik-Sikorska, M.; Sniegocki, T.; Posyniak, A.	2015	CA 6.10.1	Determination of neonicotinoid insecticides and their metabolites in honey bee and honey by liquid chromatography tandem mass spectrometry	Journal of Chromatography B, 990 (2015), 132–140
Kujawski, M.,W.; Namiesnik, J.	2011	CA 6.10.1	Levels of 13 multi-class pesticide residues in Polish honeys determined by LC-ESI-MS/MS	Food Control (2011), Volume 22, Number 6, 914-919

(a) Additional search for clothianidin as a relevant metabolite

A detailed review of the full-text documents identified in Table 9.6-2 resulted in the additional exclusion of the following studies from the dossier.

Table 9.6-4: List of references excluded following detailed review listed by data point number

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
Initial search					
CA 6.2.1	Casida, J., E.	2011	Neonicotinoid Metabolism: Compounds, Substituents, Pathways, Enzymes, Organisms, and Relevance.	Journal of Agricultural and Food Chemistry, (APR 13 2011) Vol. 59, No. 7, 2923-2931	Relevance criteria not met. Investigation into the metabolic pathways in spinach. No significant difference from the accepted pathways.
CA 6.2.1	Ford, K. A.; Casida, J., E.	2008	Comparative metabolism and pharmacokinetics of seven neonicotinoid insecticides in spinach.	Journal of Agricultural and Food Chemistry (2008), Volume 56, Number 21, 10168-10175	Relevance criteria not met. Investigation into the metabolic pathways in spinach. No significant difference from the accepted pathways.
CA 6.5.3	Colazzo, M.; Perez-Parada, A.; Besil N.; Heinzen, H.; Bocking, B.; Cesio, V.; Fernandez-Alba, A., R.	2012	Occurrence and distribution study of residues from pesticides applied under controlled conditions in the field during rice processing.	Journal of agricultural and food chemistry, (2012 May 9) Vol. 60, No. 18, 4440-4448	Relevance criteria not met. Residues detected in rice were below EU MRL. No impact on risk assessment.
CA 6.5.3	Inoue, T.; Nagatomi, Y.; Suga, K.; Uyama, A.; Mochizuki, N.	2011	Fate of Pesticides during Beer Brewing	Journal of Agricultural and Food Chemistry (2011), 59 (8), 3857-3868	Relevance criteria not met. Analytical study to investigate processing factors from ground malt to beer in Japan. For thiamethoxam processing factor found to be 0.6.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 6.9	Chen, M.; Tao, L.; McLean, J.; Lu, C.	2014	Quantitative Analysis of Neonicotinoid Insecticide Residues in Foods: Implication for Dietary Exposures	Journal of Agricultural and Food Chemistry (2014), 62 (26), 6082-6090	Relevance criteria not met. Analytical study in cucumber and honey. Residues detected below EU MRLs. Only detection in honey was in organically produced, residue level 0.0004 mg/kg.
CA 6.9	Nougadere, A.; Reninger, JC.; Volatier, JL.; Leblanc, JC.	2011	Chronic dietary risk characterization for pesticide residues: A ranking and scoring method integrating agricultural uses and food contamination data	Food and Chemical Toxicology (2011), 49 (7), 1484-1510	Review of risk assessment position in France using national techniques. No reported issues for thiamethoxam.
CA 6.10.1	Barganska, Z.; Slebioda, M.; Namiesnik, J.	2013	Pesticide residues levels in honey from apiaries located of Northern Poland.	Food Control (2013), Volume 31, Number 1, 196-201	Relevance criteria not met. Residues above EU MRL reported but reliability too low to consider. Five samples all contained residues of every tested active substance at approximately the same level; all above the MRL. No confirmatory analysis to eliminate the possibility of contamination.
CA 6.10.1	Bernal, J., L.; Nozal, M., J.; Martin, M., T.;	2013	Determination of seven neonicotinoid insecticides in beeswax by liquid chromatography coupled to electrospray-mass spectrometry using a fused-core column.	Journal of chromatography. A, (2013 Apr 12) Vol. 1285, 110-117	Relevance criteria not met. Residues detected in beeswax at 0.15 mg/kg. Authors conclude more development work is required.
CA 6.10.1	Czerwenka, C.	2011	LC-MS/MS analysis of neonicotinoid insecticides in honey: methodology and residue findings in Austrian honeys.	Journal of agricultural and food chemistry, (2011 Dec 14) Vol. 59, No. 23, 12271-12277	Relevance criteria not met. No quantifiable residues detected in honey.
CA 6.10.1	Kasiotis, K., M.; Anagnostopoulos, C.; Anastasiadou, P.; Machera, K.	2014	Pesticide residues in honeybees, honey and bee pollen by LC-MS/MS screening: Reported death incidents in honeybees	Science of the Total Environment (2014), 485-486, 633-664	Relevance criteria not met. Thiamethoxam residues detected in "complaint" samples in range 0.0005 – 0.05 mg/kg.
CA 6.10.1	Paradis, D.; Berail, G.; Bonmatin, JM.; Belzunces, L., P.	2014	Sensitive analytical methods for 22 relevant insecticides of 3 chemical families in honey by GC-MS/MS and LC-MS/MS	Analytical and Bioanalytical Chemistry (2014), 406 (2), 621-633	Relevance criteria not met. Thiamethoxam residue detected in honey in range 0 – 0.002 mg/kg

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 6.10.1	Tomasini, D.; Sampaio, M. R. F.; Caldas, S. S.; Buffon, J. G.; Duarte, F. A.; Primel, E. G.	2012	Simultaneous determination of pesticides and 5-hydroxymethylfurfural in honey by the modified QuEChERS method and liquid chromatography coupled to tandem mass spectrometry.	Talanta (2012), Volume 99, 380-386	Relevance criteria not met. LOQ of methodology used too high for relevance (0.5 mg/kg)
CA 6.10.1	Wiest, L.; Bulete, A.; Giroud, B.; Fratta, C.; Amic, S.; Lambert, O.; Pouliquen, H.; Arnaudguilhem, C.	2011	Multi-residue analysis of 80 environmental contaminants in honeys, honeybees and pollens by one extraction procedure followed by liquid and gas chromatography coupled with mass spectrometric detection	Journal of Chromatography A (2011), 1218 (34), 5743-5756	Relevance criteria not met. No residues of thiamethoxam detected in bees, pollen or honey.
Top-Up search					
	No relevant results				
Additional Search ^(a)					
CA 6.10.1	Gbylik-Sikorska, M.; Sniegocki, T.; Posyniak, A.	2015	Determination of neonicotinoid insecticides and their metabolites in honey bee and honey by liquid chromatography tandem mass spectrometry	Journal of Chromatography B, 990 (2015), 132–140	Relevance criteria not met. No residues of thiamethoxam detected. Residue of clothianidin detected at low levels in bees and honey (0.013 mg/kg)
CA 6.10.1	Kujawski, M.,W.; Namiesnik, J.	2011	Levels of 13 multi-class pesticide residues in Polish honeys determined by LC-ESI-MS/MS	Food Control (2011), Volume 22, Number 6, 914-919	Relevance criteria not met. Thiamethoxam not included in study. Clothianidin detected in honey at very low levels (0.0025 mg/kg)

(a) Additional search for clothianidin as a relevant metabolite

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 Document MCA Section 6 Supplement.