Thiamethoxam

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

DOCUMENT M-CA, Section 9

Toxicological and Toxicokinetic Studies

LITERATURE DATA

Version history[1]

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, it's potentially relevant metabolites and EU representative formulations A9584C (Actara 25WG®) and A9567R (Cruiser 600FS®).

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 potentially relevant metabolites(s) dealing with side effects on health 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 metabolites using the search terms listed in CA 9.5.1. For MCA Section 6 of this submission 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.
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 Tables 9.4.2-1 and -2).
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)**	**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.

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 side effects on health 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 toxicological and toxicokinetic studies

Data requirements(s) (indicated by the correspondent CA data point (s))	Criteria for relevance
*CA 5.1 ADME studies	1. Well identified test material including purity and impurity profile 2. Relevant test species e.g. rodent – rat/mouse – non-rodent – dog 3. Relevant endpoint e.g. ADME measurement or metabolite identification 4. Well described condition of the test and quantitative assessment of results to substantiate and evaluate whether the study conclusions and endpoints are robust
*CA 5.2 Acute toxicity	1. Well identified test material including purity and impurity profile 2. Test species likely to be relevant to mammalian toxicology assessment – rats and mice, rabbit, guinea pig 3. Relevant route of administration for risk assessment 4. Describe observations, examinations, analyses performed or necropsy 5. Different outcome to those studies currently reported
*CA 5.4 Genotoxicity	1. Well identified test material including purity and impurity profile 2. Relevant cell line or species used 3. "validated" or widely used test method 4. *In vitro* observation not addressed by *in vivo* data (including tissue specific effects) 5. *In vivo* effect in somatic or germs cells in relevant species 6. Relevant route of exposure to test substance 7. Contradicts submitted studies, impacts WoE. 8. Recognised methods for scoring studies outcomes used where applicable
*CA 5.3, 5.5, 5.6, 5.7, 5.8.1 Short term, chronic, reproductive and neurotoxicity, studies on metabolites	1. Well identified test material including purity and impurity profile 2. Test species likely to be relevant to mammalian toxicology assessment – rodents rats and mice, non- rodent dog is preferred 3. Sufficient number of animals per group to establish statistical significance 4. Test several dose levels (minimum 3) 5. Relevant route of administration for risk assessment 6. Include negative control (preferable) 7. Establish dose response 8. Describe observations, examinations, analyses performed or necropsy 9. Contradicts submitted studies and/or changes key endpoints
CA 5.8.2 Supplementary studies on the active substance	1. Identified test material 2. Unusual routes of exposure acceptable as they may introduce important information on other possible toxicological effects 3. Regulatory use usually limited to addressing species sensitivity /safety factors etc. 4. Examples of studies a. Effects of combined exposures b. Hormonal effects (if not guideline studies or included in 5.8.3) c. Hypersensitivity of specific sub-populations d. Gender and age variation in susceptibility (if not included in 5.6 Reproductive studies) e. Mode of action investigations
CA 5.8.3 Endocrine disrupting properties	1. Identified test material 2. All studies considered relevant at this stage – need to be checked for reliability

Data requirements(s) (indicated by the correspondent CA data point (s))	Criteria for relevance
CA 5.9 Medical data (including epidemiology) CP 7.2 to 7.4	1. Identified test material 2. All records considered relevant at this stage - need to be checked for reliability

* 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

Any documents deemed relevant will be checked for reliability according to the criteria described by Klimisch *et al* (1997)[1] using the ToxRTool (http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/archive-publications/toxrtool). Other criteria may also be used to complete the evaluation. Details of reliability evaluations will be included in the relevant part of the MCA Section 5.

Table 9.4.2-2: List of Criteria for relevance for operator exposure information/studies

Data requirements(s) (indicated by the correspondent CP data point (s))	Criteria for relevance
General criteria CP 7.2 all sections	5. Sufficient replicates must be included in the study to demonstrate statistical robustness 6. Agronomic practices must be relevant to scenario in submission, including: crop type ,application method and parameters (e.g. boom height), application rate 7. Leaf type and plant growth stage must be relevant to scenario in submission 8. Climactic/meteorological conditions of study must be relevant to scenario in submission, including rainfall, wind speed and temperature 9. Raw data must be available for analysis 10. Statistical analysis must be robust and relevant 11. Assessment of outliers/extreme values must be robust and relevant
Operator/worker exposure studies CP 7.2.1.2 and CP 7.2.3.2	1. Studies should follow accepted OECD protocol 2. Studies performed to GLP are preferred 3. Replicates should be minimum of 10
Biomonitoring studies CP 7.2.1.2, CP 7.2.2.2 and CP 7.2.3.2	1. Internal exposures must be clearly related to specific external doses 2. Replicates should be minimum of 10
Air monitoring studies CP 7.2.2.2	10. Monitoring parameters must be relevant to bystander/resident exposures, including monitoring distance, height and duration: 11. Accurate logs of relevant local activity must be available (e.g. crop spraying) 12. Accurate logs of local climactic/meteorological conditions must be available for the duration of the monitoring period, including rainfall, wind speed, wind direction, temperature and humidity
Dislodgeable foliar residue studies CP 7.2.3.2	1. Study must have been conducted on a similar formulation 2. Application number and interval must be relevant 3. Replicates must be minimum of 40
Foliar decline studies CP 7.2.3.2	3. Data must demonstrate minimum of two clear half lives 4. Sufficient data points must be provided to demonstrate decline curves between repeat applications 5. Studies with significant rainfall in first 48 hours should be discounted 6. Replicates must be minimum of 10

* 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

[1] Klimisch H-J, Andreae M and Tillmann U (1997) A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Reg Tox Pharmacol 25, 1-5

CA 9.5 Search methods

Date of initial search	19 January 2015
Date of most recent update to search	27 April 2015
Date of 'clothianidin' term search	27 April 2015
Date span of the search	10 years

Table 9.5-1: Detailed Search Parameters for Toxicological and Toxicokinetic studies (CA 5.1 to 5.9)

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)
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

Plus
L1 QUE (MUTAG? OR CANCER? OR TERATO? OR GENETOX? OR CARCIN?)
L2 QUE (TUMOUR? OR TUMOR? OR CYTOTOX? OR GENOTOX? OR MELANOM?)
L3 QUE (NEUROTOXI? OR LD50 OR IC50 OR ((LD OR IC)(W)50))
L4 QUE (((LONG OR SHORT)(W)TERM?)(L)(EFFECT? OR STUD? OR TOXIC?))
L5 QUE (ENDOCRIN? OR INHALAT? OR IRRITAT? OR REPROTOX?)
L6 QUE (PERCUTANEOU? OR DERMAL? OR ORAL? OR INTOXICAT? OR INGEST?)
L7 QUE (((REPRODUCT? OR EMBRYO? OR FOET? OR DEVELOP?)(5A)TOXI?))
L8 QUE ((ACUTE? OR CHRONIC?)(5A)(EFFECT? OR TOXIC? OR TOXIN#))
L9 QUE (GIRL# OR CHILD OR CHILDREN OR PATIENT# OR HUMAN# OR MAN)
L10 QUE (MEN OR WOM!N OR BOY# OR WORKER# OR OPERATOR# OR FARMER#)
L11 QUE (APPLICATOR# OR PERSONNEL? OR WORKFORCE OR EMPLOYEE#)
L12 QUE (MAMMAL? OR RODENT# OR RAT OR RATS OR MOUSE OR MICE)
L13 QUE (ACCIDENT? OR POISON? OR ALLERG? OR EXPOSURE? OR EXPOSE#)
L14 QUE (OCCUPAT? OR EPIDEMIOL? OR SENSITIZ? OR SENSITIS?)
L15 QUE ((HEALTH OR ADVERSE)(5A)(EFFECT# OR RISK#))
L16 QUE (MEDICAL OR (FIRST(W)AID) OR (TOXIC?(3A)STUD?) OR THERAPE?)
L17 QUE (TOXICOKINETIC# OR EXTRACTAB? OR (RADIO(W)LABEL?))
L18 QUE (DOG# OR (GUINEA(W)PIG#) OR RABBIT# OR SKIN? OR EYE#)
L19 QUE (HAND# OR DERMAL? OR BYSTANDER# OR RESIDENT#)
L20 QUE ((ROTAT? OR SUCCEDING OR FOLLOWING)(3A)CROP#)
L21 QUE ((DIETARY OR CONSUM? OR CUMULAT? OR AGGREGAT?)(5A)RISK?)
L22 QUE (L1 OR L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10
OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19
OR L20 OR L21)

Table 9.5-1: Details of databases searched and justification for selection as well as number of hits per database

Provider	Database	Justification	Limits applied	Number* (Initial Search)	Number* (Top-Up Search)	Number* (Clothianidin search)
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	179	5	95
	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.		40	2	22
	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.		1	0	1
	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.		9	3	4
	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.		10	1	3

Provider	Database	Justification	Limits applied	Number* (Initial Search)	Number* (Top-Up Search)	Number* (Clothianidin search)
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	47	7	32
	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.		287	12	91
	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		215	12	121
	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.		5	0	4
	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.		4	0	0

Provider	Database	Justification	Limits applied	Number* (Initial Search)	Number* (Top-Up Search)	Number* (Clothianidin search)
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
	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
	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.		21	3	13
	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		5	0	2
	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.		38	3	25

Provider	Database	Justification	Limits applied	Number* (Initial Search)	Number* (Top-Up Search)	Number* (Clothianidin search)
	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.		1	0	0

* 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)	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.

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 5.1	Bednarska, AJ	2013	A toxicokinetic model for thiamethoxam in rats: implications for higher-tier risk assessment.	Ecotoxicology (London, England), Vol. 22, No. 3, pp. 548-57.
CA 5.1	Lin, L; Yu, W; Pang, Y; Meng, Q; Sun, C; Li, X; Duan, M	2014	LC-MS/MS method for quantification of thiamethoxam in rat plasma and its toxicokinetics study.	Nongyao, 53 (6), 418-420, 465.
CA 5.3	Ivanova, R	2013	Study on the effect of Actara and Confidor on rabbits submited to chronic intoxication.	Agrarni Nauki, Volume 5, Number 14, pp. 253-257, 15 refs.
CA 5.4	Noaishi, MA; Eweis, EA; Kandil, MA	2006	Evaluation of the chromosomal aberrations induction in rat lymphocyte cultures after subchronic treatment with different pesticides.	Bulletin of Faculty of Agriculture, Cairo University, Volume 57, Number 2, pp. 295-305, 16 refs.
CA 5.4	Knight, AW; Little, S; Houck, K; Dix, D; Judson, R; Richard, A; McCarroll, N; Akerman, G; Yang, C; Birrell, L; Walmsley, RW	2009	Evaluation of high-throughput genotoxicity assays used in profiling the US EPA ToxCast chemicals.	Regulatory Toxicology and Pharmacology, 55 (2), 188-199.

CA data point number	Author(s)	Year	Title	Source
CA 5.4	Karamova, NS; Denisova, AP; Stashevski, Z	2008	Evaluation of mutagenic activities of pesticides: actara, sencor, mospilan, pencozeb and fastac, in the Ames test.	Ekologicheskaya Genetika, 6 (4), 29-33.
CA 5.5	Martin, MT; Judson, RS; Reif, DM; Kavlock, RJ; Dix, DJ	2009	Profiling chemical based on chronic toxicity results from the U.S. EPA ToxRef Database.	Environmental Health Perspectives, 117 (3), 392-399.
CA 5.6	Padilla, S; Corum, D; Padnos, B; Hunter, DL; Beam, A; Houck, KA; Sipes, N; Kleinstreuer, N; Knudsen, T; Dix, DJ; Reif, DM	2012	Zebrafish developmental screening of the ToxCast Phase I chemical library.	Reproductive Toxicology, 33 (2), 174-187.
CA 5.6	Martin, MT; Mendez, E; Corum, DG; Judson, RS; Kavlock, RJ; Rotroff, DM; Dix, DJ	2009	Profiling the Reproductive Toxicity of Chemicals from Multigeneration Studies in the Toxicity Reference Database.	Toxicological Sciences, Vol. 110, No. 1, pp. 181-190.
CA 5.6	Martin, MT; Knudsen, TB; Reif, DM; Houck, KA; Judson, RS; Kavlock, RJ; Dix, DJ	2011	Predictive model of rat reproductive toxicity from ToxCast high throughput screening.	Biology of Reproduction, 85 (2), 327-339.
CA 5.6	Sipes, NS.; Martin, Matthew T.; Reif, David M.; Kleinstreuer, Nicole C.; Judson, Richard S.; Singh, Amar V.; Chandler, Kelly J.; Dix, David J.; Kavlock, Robert J.; Knudsen, Thomas B.	2011	Predictive Models of Prenatal Developmental Toxicity from ToxCast High- Throughput Screening Data.	Toxicological Sciences, 124 (1), 109-127.
CA 5.7	Rodrigues, KJA; Santana, MB; Do Nascimento, JLM; Picanco-Diniz, DLW; Maues, LAL; Santos, SN; Ferreira, VMM; Alfonso, M; Duran, R; Faro, LRF	2010	Behavioral and biochemical effects of neonicotinoid thiamethoxam on the cholinergic system in rats.	Ecotoxicology and environmental safety, Vol. 73, No. 1, pp. 101-7.
CA 5.8.2	Swenson, TL; Casida JE	2013	Neonicotinoid formaldehyde generators: possible mechanism of mouse-specific hepatotoxicity/hepatocarcinogenicity of thiamethoxam.	Toxicology letters, Vol. 216, No. 2-3, pp. 139-45.
CA 5.8.2	Pastoor T; Rose P; Lloyd S; Peffer R; Green T	2005	Case study: weight of evidence evaluation of the human health relevance of thiamethoxam-related mouse liver tumors.	Toxicological sciences : an official journal of the Society of Toxicology, Vol. 86, No. 1, pp. 56-60.
CA 5.8.2	Green T; Toghill A; Lee R; Waechter F; Weber E; Peffer R; Noakes J; Robinson M	2005	Thiamethoxam induced mouse liver tumors and their relevance to humans. Part 2: species differences in response.	Toxicological sciences : an official journal of the Society of Toxicology, Vol. 86, No. 1, pp. 48-55.

CA data point number	Author(s)	Year	Title	Source
CA 5.8.2	Green T; Toghill A; Lee R; Waechter F; Weber E; Noakes J	2005	Thiamethoxam induced mouse liver tumors and their relevance to humans. Part 1: mode of action studies in the mouse.	Toxicological sciences : an official journal of the Society of Toxicology, Vol. 86, No. 1, pp. 36-47.
CA 5.8.2	Yeboue-Kouame, BY; Vagamon, B; Tchicaya, AF; Wognin, SB; Kouassi, YM; Aka, I; Bonny, JS	2010	A case of Stevens Johnson's syndrome in an Ivorian farmer: what imputability to pesticides? Syndrome de Stevens Johnson chez un agriculteur ivoirien: quelle relation avec l'exposition aux insecticides?	Archives des Maladies Professionnelles et de l'Environnement, Volume 71, Number 2, pp. 117-121, 17 refs.
CA 5.8.2	Rotroff, DM; Martin, MT; Dix, DJ; Filer, DL; Houck, KA; Knudsen, TB; Sipes, NS; Reif, DM; Xia, M; Huang, R; Judson, RS	2014	Predictive Endocrine Testing in the 21st Century Using *in vitro* Assays of Estrogen Receptor Signaling Responses.	Environmental Science & Technology (2014), 48 (15), 8706-8716.
CA 5.8.2	Shah, I; Houck, K; Judson, RS; Kavlock, RJ; Martin, MT; Reif, DM; Wambaugh, J; Dix, DJ	2011	Using nuclear receptor activity to stratify hepatocarcinogens.	PLoS One, 6 (2), e14584.
CA 5.8.2	Judson, RS; Houck, KA; Kavlock, RJ; Knudsen, TB; Martin, MT; Mortensen, HM; Reif, DM; Rotroff, DM; Shah, I; Richard, AM; Dix, DJ	2010	*In vitro* Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project.	Environmental Health Perspectives, 118 (4), 485-492.
CA 5.8.2	Rotroff, DM; Beam, AL; Dix, DJ; Farmer, A; Freeman, KM; Houck, KA; Judson, RS; LeCluyse, EL; Martin, MT; Reif, DM; Ferguson, SS	2010	Xenobiotic-Metabolizing Enzyme and Transporter Gene Expression in Primary Cultures of Human Hepatocytes Modulated by Toxcast Chemicals.	Journal of Toxicology and Environmental Health, Part B: Critical Reviews, 13 (2-4), 329-346.
CA 5.8.2	Lloyd, S; Green, T; Toghill, A; Lee, R; Waechter, F; Noakes, J; Pastoor, TP	2005	Thiamethoxam induced mouse liver tumors and their relevance to humans 1. Mode of action studies in the mouse.	Conference: 44th Annual Meeting of the Society of Toxicology, New Orleans, LA (USA)
CA 5.8.2	Pastoor, TP; Rose, P; Lloyd, S; Peffer, R; Green, T	2005	Thiamethoxam induced mouse liver tumors and their relevance to humans 3. Weight of evidence evaluation.	Conference: 44th Annual Meeting of the Society of Toxicology, New Orleans, LA (USA)
CA 5.8.2	Waterfield, C; Green, T; Lee, R; Toghill, A; Waechter, F; Peffer, R; Noakes, J; Robinson, M; Pastoor, TP	2005	Thiamethoxam induced mouse liver tumors and their relevance to humans 2. Species differences in response.	Conference: 44th Annual Meeting of the Society of Toxicology, New Orleans, LA (USA)
CA 5.8.2	Pastoor, T; Rose, P; Lloyd, S; Peffer, R; Green, T	2005	Weight of Evidence Evaluation of the Human Health Relevance of Thiamethoxam-Related Mouse Liver Tumors.	Toxicological Sciences, Vol. 86, no. 1, pp. 56-60.

CA data point number	Author(s)	Year	Title	Source
CA 5.8.3	Wambaugh, JF; Setzer, RW; Reif, DM; Gangwal, S; Mitchell-Blackwood, J; Arnot, JA; Joliet, O; Frame, A; Rabinowitz, J; Knudsen, TB; Judson, RS; Egeghy, P; Vallero, D; Cohen Hubal, EA	2013	High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project.	Environmental Science & Technology, 47 (15), 8479-8488.
CA 5.8.3	Reif, David M; Martin, Matthew T; Tan, Shirlee W; Houck, Keith A; Judson, Richard S; Richard, Ann M; Knudsen, Thomas B; Dix, David J; Kavlock, Robert J	2010	Endocrine profiling and prioritization of environmental chemicals using ToxCast data.	Environmental Health Perspectives, 118 (12), 1714-1720.
CA 5.9	Vale, JA	2008	Poisoning Due to Neonicotinoid Insecticides.	Clinical Toxicology, Vol. 46, no. 5, p. 404.
CA 5.9	Zeljezic, D; Mladinic, M	2015	Evaluation of the mechanism of nucleoplasmic bridge formation due to premature telomere shortening in agricultural workers exposed to mixed pesticides: Indication for further studies.	Chemosphere, Vol. 120, pp. 45-51. Refs: 40.
CA 5.9	Manfo, FPT; Moundipa, PF; Dechaud, H; Tchana, AN; Nantia, EA; Zabot, MT; Pugeat, M	2012	Effect of agropesticides use on male reproductive function: A study on farmers in Djutitsa (Cameroon).	Environmental Toxicology, 27 (7), 423-432.
CA 5.9	Costa, C; Silva, S; Neves, J; Coelho, P; Costa, S; Laffon, B; Snawder, J; Teixeira, JP	2011	Micronucleus Frequencies in Lymphocytes and Reticulocytes in a Pesticide-Exposed Population in Portugal.	Journal of Toxicology and Environmental Health, Part A: Current Issues, 74 (15-16), 960-970.
CA 5.9	Jensen, HK; Konradsen, F	2011	Pesticide use and self-reported symptoms of acute pesticide poisoning among aquatic farmers in phnom penh, cambodia.	Journal of Toxicology, Vol. 2011. arn. 639814. Refs: 31.
CA 5.9	Dasgupta, S; Meisner, C; Wheeler, D; Xuyen, K; Lam, NT	2007	Pesticide poisoning of farm workers-implications of blood test results from Vietnam.	International Journal of Hygiene and Environmental Health, 210 (2), 121-132.
CP 7.2.3	Mota-Sanchez D	2012	Penetrative and dislodgeable residue characteristics of 14C-insecticides in apple fruit.	Journal of Agricultural and Food Chemistry, Vol. 60, No. 12, pp. 2958-66.
Top-Up search				
5.8.2	Sinha, S; Thaker, AM	2014	Study on the impact of lead acetate pollutant on immunotoxicity produced by thiamethoxam pesticide	Indian Journal of Pharmacology, Vol. 46, No. 6, pp. 596-600

Clothianidin search				
CA 5.1	Ford, KA	2006	Unique and common metabolites of thiamethoxam, clothianidin, and dinotefuran in mice	Chemical research in toxicology, Vol. 19, No. 11, pp. 1549-56
CA 5.1	Dick, RA	2006	Substrate specificity of rabbit aldehyde oxidase for nitroguanidine and nitromethylene neonicotinoid insecticides	Chemical research in toxicology, Vol. 19, No. 1, pp. 38-43
CA 5.3	Ozsahin, AD; Bal, R; Yilmaz, O	2014	Biochemical alterations in kidneys of infant and adult male rats due to exposure to the neonicotinoid insecticides imidacloprid and clothianidin	Toxicology Research, Vol. 3, No. 5, pp. 324-330
CA 5.4	Calderon-Segura ME	2012	Evaluation of genotoxic and cytotoxic effects in human peripheral blood lymphocytes exposed in vitro to neonicotinoid insecticides news	Journal of toxicology, Vol. 2012, pp. 612647
CA 5.4	Knight, AW; Little, S; Houck, K; Dix, D; Judson, R; Richard, A; McCarroll, N; Akerman, G; Yang, C; Birrell, L; Walmsley, RM	2009	Evaluation of high-throughput genotoxicity assays used in profiling the US EPA ToxCast chemicals	Regulatory Toxicology and Pharmacology, 55 (2), 188-199
CA 5.6	Bal R	2013	Effects of the neonicotinoid insecticide, clothianidin, on the reproductive organ system in adult male rats	Drug and chemical toxicology, Vol. 36, No. 4, pp. 421-9.
CA 5.6	Bal R	2012	Effects of clothianidin exposure on sperm quality, testicular apoptosis and fatty acid composition in developing male rats	Cell biology and toxicology, Vol. 28, No. 3, pp. 187-200
CA 5.6	Li P	2011	Activation and modulation of human α4β2 nicotinic acetylcholine receptors by the neonicotinoids clothianidin and imidacloprid	Journal of neuroscience research, Vol. 89, No. 8, pp. 1295-301
CA 5.6	Martin, MT; Knudsen, TB; Reif, DM; Houck, KA;Judson, RS; Kavlock, RJ; Dix, DJ	2011	Predictive model of rat reproductive toxicity from ToxCast high throughput screening	Biology of Reproduction, 85 (2), 327-339
CA 5.6	Sipes, NS; Martin, MT; Reif, DM; Kleinstreuer, NC; Judson, RS; Singh, AV; Chandler, KJ; Dix, DJ; Kavlock, RJ; Knudsen, TB	2011	Predictive Models of Prenatal Developmental Toxicity from ToxCast High- Throughput Screening Data	Toxicological Sciences, 124 (1), 109-127
CA 5.7	Tanaka T	2012	Reproductive and neurobehavioral effects of clothianidin administered to mice in the diet	Birth defects research. Part B, Developmental and reproductive toxicology, Vol. 95, No. 2, pp. 151-9
CA 5.7	Tanaka T	2012	Effects of maternal clothianidin exposure on behavioral development in F1 generation mice	Toxicology and industrial health, Vol. 28, No. 8, pp. 697-707

CA 5.7	Ozdemir HH	2014	Determination of the effects on learning and memory performance and related gene expressions of clothianidin in rat models	Cognitive neurodynamics, Vol. 8, No. 5, pp. 411-6
CA 5.7	Faro LRF	2012	In vivo neurochemical characterization of clothianidin induced striatal dopamine release	Toxicology, Vol. 302, No. 2-3, pp. 197-202
CA 5.8.2	Sipes, NS; Martin, MT; Kothiya, P; Reif, DM; Judson, RS; Richard, AM; Houck, KA; Dix, DJ; Kavlock, RJ; Knudsen, TB	2013	Profiling 976 ToxCast Chemicals across 331 Enzymatic and Receptor Signaling Assays	Chemical Research in Toxicology, 26 (6), 878-895
CA 5.8.2	Judson, RS; Houck, KA; Kavlock, RJ; Knudsen, TB; Martin, MT; Mortensen, HM; Reif, DM; Rotroff, DM; Shah, I; Richard, AM; Dix, DJ	2010	In Vitro Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project	Environmental Health Perspectives, 118 (4), 485-492
CA 5.8.2	Rotroff, DM; Wetmore, BA; Dix, DJ; Ferguson, AS; Clewell, HJ; Houck, KA; Le Cluyse, EL; Andersen, ME; Judson, RS; Smith, CM; Sochaski, MA; Kavlock, RJ; Boellmann, F; Martin, MT; Reif, DM; Wambaugh, JF; Thomas, RS	2010	Incorporating Human Dosimetry and Exposure into High-Throughput In Vitro Toxicity Screening	Toxicological Sciences, 117 (2), 348-358
CA 5.8.2	Rotroff, DM; Beam, AL; Dix, DJ; Farmer, A; Freeman, KM; Houck, KA; Judson, RS; LeCluyse, EL; Martin, MT; Reif, DM; Ferguson, SS	2010	Xenobiotic-Metabolizing Enzyme and Transporter Gene Expression in Primary Cultures of Human Hepatocytes Modulated by Toxcast Chemicals	Journal of Toxicology and Environmental Health, Part B: Critical Reviews, 13 (2-4), 329-346
CA 5.8.3	Rotroff, DM; Martin, MT; Dix, DJ; Filer, DL; Houck, KA; Knudsen, TB; Sipes, NS; Reif, DM; Xia, M; Huang, R; Judson, RS	2014	Predictive Endocrine Testing in the 21st Century Using in Vitro Assays of Estrogen Receptor Signaling Responses	Environmental Science & Technology, 48 (15), 8706-8716
CA 5.8.3	Reif, DM; Martin, MT; Tan, SW; Houck, KA; Judson, RS; Richard, AM; Knudsen, TB; Dix, DJ; Kavlock, RJ	2010	Endocrine profiling and prioritization of environmental chemicals using ToxCast data	Environmental Health Perspectives , 118 (12), 1714-1720
CA 5.9	So, BH; Kim, HM	2010	Two Cases of Severe Neonicotinoid Intoxication	Clinical Toxicology, Vol. 48, No. 6, pp. 611
CA 5.9	Phua, DH; Lin, CC; Wu, M; Deng, J; Yang, C	2009	Neonicotinoid insecticides: an emerging cause of acute pesticide poisoning	Clinical Toxicology, 47 (4), 336-341
CA 5.9	Vale, JA	2008	Poisoning Due to Neonicotinoid Insecticides	Clinical Toxicology, Vol. 46, no. 5, p. 404.

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

Author(s)	Year	CA data point number	Title	Source
Initial Search				
Bednarska, AJ	2013	CA 5.1	A toxicokinetic model for thiamethoxam in rats: implications for higher-tier risk assessment.	Ecotoxicology (London, England), Vol. 22, No. 3, pp. 548-57.
Costa, C; Silva, S; Neves, J; Coelho, P; Costa, S; Laffon, B; Snawder, J; Teixeira, JP	2011	CA 5.9	Micronucleus Frequencies in Lymphocytes and Reticulocytes in a Pesticide-Exposed Population in Portugal.	Journal of Toxicology and Environmental Health, Part A: Current Issues, 74 (15-16), 960-970.
Dasgupta, S; Meisner, C; Wheeler, D; Xuyen, K; Lam, NT	2007	CA 5.9	Pesticide poisoning of farm workers-implications of blood test results from Vietnam.	International Journal of Hygiene and Environmental Health, 210 (2), 121-132.
Green T; Toghill A; Lee R; Waechter F; Weber E; Noakes J	2005	CA 5.8.2	Thiamethoxam induced mouse liver tumors and their relevance to humans. Part 1: mode of action studies in the mouse.	Toxicological sciences : an official journal of the Society of Toxicology, Vol. 86, No. 1, pp. 36-47.
Green T; Toghill A; Lee R; Waechter F; Weber E; Peffer R; Noakes J; Robinson M	2005	CA 5.8.2	Thiamethoxam induced mouse liver tumors and their relevance to humans. Part 2: species differences in response.	Toxicological sciences : an official journal of the Society of Toxicology, Vol. 86, No. 1, pp. 48-55.
Ivanova, R	2013	CA 5.3	Study on the effect of Actara and Confidor on rabbits submited to chronic intoxication.	Agrarni Nauki, Volume 5, Number 14, pp. 253-257, 15 refs.
Jensen, HK; Konradsen, F	2011	CA 5.9	Pesticide use and self-reported symptoms of acute pesticide poisoning among aquatic farmers in phnom penh, cambodia.	Journal of Toxicology, Vol. 2011. arn. 639814. Refs: 31.
Judson, RS; Houck, KA; Kavlock, RJ; Knudsen, TB; Martin, MT; Mortensen, HM; Reif, DM; Rotroff, DM; Shah, I; Richard, AM; Dix, DJ	2010	CA 5.8.2	*In vitro* Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project.	Environmental Health Perspectives, 118 (4), 485-492.
Karamova, NS; Denisova, AP; Stashevski, Z	2008	CA 5.4	Evaluation of mutagenic activities of pesticides: actara, sencor, mospilan, pencozeb and fastac, in the Ames test.	Ekologicheskaya Genetika, 6 (4), 29-33.
Knight, AW; Little, S; Houck, K; Dix, D; Judson, R; Richard, A; McCarroll, N; Akerman, G; Yang, C; Birrell, L; Walmsley, RW	2009	CA 5.4	Evaluation of high-throughput genotoxicity assays used in profiling the US EPA ToxCast chemicals.	Regulatory Toxicology and Pharmacology, 55 (2), 188-199.
Lin, L; Yu, W; Pang, Y; Meng, Q; Sun, C; Li, X; Duan, M	2014	CA 5.1	LC-MS/MS method for quantification of thiamethoxam in rat plasma and its toxicokinetics study.	Nongyao, 53 (6), 418-420, 465.

Author(s)	Year	CA data point number	Title	Source
Lloyd, S; Green, T; Toghill, A; Lee, R; Waechter, F; Noakes, J; Pastoor, TP	2005	CA 5.8.2	Thiamethoxam induced mouse liver tumors and their relevance to humans 1. Mode of action studies in the mouse.	Conference: 44th Annual Meeting of the Society of Toxicology, New Orleans, LA (USA)
Manfo, FPT; Moundipa, PF; Dechaud, H; Tchana, AN; Nantia, EA; Zabot, MT; Pugeat, M	2012	CA 5.9	Effect of agropesticides use on male reproductive function: A study on farmers in Djutitsa (Cameroon).	Environmental Toxicology, 27 (7), 423-432.
Martin, MT; Judson, RS; Reif, DM; Kavlock, RJ; Dix, DJ	2009	CA 5.5	Profiling chemical based on chronic toxicity results from the U.S. EPA ToxRef Database.	Environmental Health Perspectives, 117 (3), 392-399.
Martin, MT; Knudsen, TB; Reif, DM; Houck, KA; Judson, RS; Kavlock, RJ; Dix, DJ	2011	CA 5.6	Predictive model of rat reproductive toxicity from ToxCast high throughput screening.	Biology of Reproduction, 85 (2), 327-339.
Martin, MT; Mendez, E; Corum, DG; Judson, RS; Kavlock, RJ; Rotroff, DM; Dix, DJ	2009	CA 5.6	Profiling the Reproductive Toxicity of Chemicals from Multigeneration Studies in the Toxicity Reference Database.	Toxicological Sciences, Vol. 110, No. 1, pp. 181-190.
Mota-Sanchez D	2012	CP 7.2.3	Penetrative and dislodgeable residue characteristics of 14C-insecticides in apple fruit.	Journal of Agricultural and Food Chemistry, Vol. 60, No. 12, pp. 2958-66.
Noaishi, MA; Eweis, EA; Kandil, MA	2006	CA 5.4	Evaluation of the chromosomal aberrations induction in rat lymphocyte cultures after subchronic treatment with different pesticides.	Bulletin of Faculty of Agriculture, Cairo University, Volume 57, Number 2, pp. 295-305, 16 refs.
Padilla, S; Corum, D; Padnos, B; Hunter, DL; Beam, A; Houck, KA; Sipes, N; Kleinstreuer, N; Knudsen, T; Dix, DJ; Reif, DM	2012	CA 5.6	Zebrafish developmental screening of the ToxCast Phase I chemical library.	Reproductive Toxicology, 33 (2), 174-187.
Pastoor T; Rose P; Lloyd S; Peffer R; Green T	2005	CA 5.8.2	Case study: weight of evidence evaluation of the human health relevance of thiamethoxam-related mouse liver tumors.	Toxicological sciences : an official journal of the Society of Toxicology, Vol. 86, No. 1, pp. 56-60.
Pastoor, T; Rose, P; Lloyd, S; Peffer, R; Green, T	2005	CA 5.8.2	Weight of Evidence Evaluation of the Human Health Relevance of Thiamethoxam-Related Mouse Liver Tumors.	Toxicological Sciences, Vol. 86, no. 1, pp. 56-60.
Pastoor, TP; Rose, P; Lloyd, S; Peffer, R; Green, T	2005	CA 5.8.2	Thiamethoxam induced mouse liver tumors and their relevance to humans 3. Weight of evidence evaluation.	Conference: 44th Annual Meeting of the Society of Toxicology, New Orleans, LA (USA)

Author(s)	Year	CA data point number	Title	Source
Reif, David M; Martin, Matthew T; Tan, Shirlee W; Houck, Keith A; Judson, Richard S; Richard, Ann M; Knudsen, Thomas B; Dix, David J; Kavlock, Robert J	2010	CA 5.8.3	Endocrine profiling and prioritization of environmental chemicals using ToxCast data.	Environmental Health Perspectives, 118 (12), 1714-1720.
Rodrigues, KJA; Santana, MB; Do Nascimento, JLM; Picanco-Diniz, DLW; Maues, LAL; Santos, SN; Ferreira, VMM; Alfonso, M; Duran, R; Faro, LRF	2010	CA 5.7	Behavioral and biochemical effects of neonicotinoid thiamethoxam on the cholinergic system in rats.	Ecotoxicology and environmental safety, Vol. 73, No. 1, pp. 101-7.
Rotroff, DM; Beam, AL; Dix, DJ; Farmer, A; Freeman, KM; Houck, KA; Judson, RS; LeCluyse, EL; Martin, MT; Reif, DM; Ferguson, SS	2010	CA 5.8.2	Xenobiotic-Metabolizing Enzyme and Transporter Gene Expression in Primary Cultures of Human Hepatocytes Modulated by Toxcast Chemicals.	Journal of Toxicology and Environmental Health, Part B: Critical Reviews, 13 (2-4), 329-346.
Rotroff, DM; Martin, MT; Dix, DJ; Filer, DL; Houck, KA; Knudsen, TB; Sipes, NS; Reif, DM; Xia, M; Huang, R; Judson, RS	2014	CA 5.8.2	Predictive Endocrine Testing in the 21st Century Using *in vitro* Assays of Estrogen Receptor Signaling Responses.	Environmental Science & Technology (2014), 48 (15), 8706-8716.
Shah, I; Houck, K; Judson, RS; Kavlock, RJ; Martin, MT; Reif, DM; Wambaugh, J; Dix, DJ	2011	CA 5.8.2	Using nuclear receptor activity to stratify hepatocarcinogens.	PLoS One, 6 (2), e14584.
Sipes, NS.; Martin, Matthew T.; Reif, David M.; Kleinstreuer, Nicole C.; Judson, Richard S.; Singh, Amar V.; Chandler, Kelly J.; Dix, David J.; Kavlock, Robert J.; Knudsen, Thomas B.	2011	CA 5.6	Predictive Models of Prenatal Developmental Toxicity from ToxCast High- Throughput Screening Data.	Toxicological Sciences, 124 (1), 109-127.
Swenson, TL; Casida JE	2013	CA 5.8.2	Neonicotinoid formaldehyde generators: possible mechanism of mouse-specific hepatotoxicity/hepatocarcinogenicity of thiamethoxam.	Toxicology letters, Vol. 216, No. 2-3, pp. 139-45.
Vale, JA	2008	CA 5.9	Poisoning Due to Neonicotinoid Insecticides.	Clinical Toxicology, Vol. 46, no. 5, p. 404.

Author(s)	Year	CA data point number	Title	Source
Wambaugh, JF; Setzer, RW; Reif, DM; Gangwal, S; Mitchell-Blackwood, J; Arnot, JA; Joliet, O; Frame, A; Rabinowitz, J; Knudsen, TB; Judson, RS; Egeghy, P; Vallero, D; Cohen Hubal, EA	2013	CA 5.8.3	High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project.	Environmental Science & Technology, 47 (15), 8479-8488.
Waterfield, C; Green, T; Lee, R; Toghill, A; Waechter, F; Peffer, R; Noakes, J; Robinson, M; Pastoor, TP	2005	CA 5.8.2	Thiamethoxam induced mouse liver tumors and their relevance to humans 2. Species differences in response.	Conference: 44th Annual Meeting of the Society of Toxicology, New Orleans, LA (USA)
Yeboue-Kouame, BY; Vagamon, B; Tchicaya, AF; Wognin, SB; Kouassi, YM; Aka, I; Bonny, JS	2010	CA 5.8.2	A case of Stevens Johnson's syndrome in an Ivorian farmer: what imputability to pesticides? Syndrome de Stevens Johnson chez un agriculteur ivoirien: quelle relation avec l'exposition aux insecticides?	Archives des Maladies Professionnelles et de l'Environnement, Volume 71, Number 2, pp. 117-121, 17 refs.
Zeljezic, D; Mladinic, M	2015	CA 5.9	Evaluation of the mechanism of nucleoplasmic bridge formation due to premature telomere shortening in agricultural workers exposed to mixed pesticides: Indication for further studies.	Chemosphere, Vol. 120, pp. 45-51. Refs: 40.
Top-Up search				
Sinha, S; Thaker, AM	2014	5.8.2	Study on the impact of lead acetate pollutant on immunotoxicity produced by thiamethoxam pesticide	Indian Journal of Pharmacology, Vol. 46, No. 6, pp. 596-600
Clothianidin search				
Bal R	2013	CA 5.6	Effects of the neonicotinoid insecticide, clothianidin, on the reproductive organ system in adult male rats	Drug and chemical toxicology, Vol. 36, No. 4, pp. 421-9.
Bal R	2012	CA 5.6	Effects of clothianidin exposure on sperm quality, testicular apoptosis and fatty acid composition in developing male rats	Cell biology and toxicology, Vol. 28, No. 3, pp. 187-200
Calderon-Segura ME	2012	CA 5.4	Evaluation of genotoxic and cytotoxic effects in human peripheral blood lymphocytes exposed in vitro to neonicotinoid insecticides news	Journal of toxicology, Vol. 2012, pp. 612647
Dick, RA	2006	CA 5.1	Substrate specificity of rabbit aldehyde oxidase for nitroguanidine and nitromethylene neonicotinoid insecticides	Chemical research in toxicology, Vol. 19, No. 1, pp. 38-43
Faro LRF	2012	CA 5.7	In vivo neurochemical characterization of clothianidin induced striatal dopamine release	Toxicology, Vol. 302, No. 2-3, pp. 197-202

Author(s)	Year	CA data point number	Title	Source
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Judson, RS; Houck, KA; Kavlock, RJ; Knudsen, TB; Martin, MT; Mortensen, HM; Reif, DM; Rotroff, DM; Shah, I; Richard, AM; Dix, DJ	2010	CA 5.8.2	In Vitro Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project	Environmental Health Perspectives, 118 (4), 485-492
Knight, AW; Little, S; Houck, K; Dix, D; Judson, R; Richard, A; McCarroll, N; Akerman, G; Yang, C; Birrell, L; Walmsley, RM	2009	CA 5.4	Evaluation of high-throughput genotoxicity assays used in profiling the US EPA ToxCast chemicals	Regulatory Toxicology and Pharmacology, 55 (2), 188-199
Li P	2011	CA 5.6	Activation and modulation of human α4β2 nicotinic acetylcholine receptors by the neonicotinoids clothianidin and imidacloprid	Journal of neuroscience research, Vol. 89, No. 8, pp. 1295-301
Martin, MT; Knudsen, TB; Reif, DM; Houck, KA;Judson, RS; Kavlock, RJ; Dix, DJ	2011	CA 5.6	Predictive model of rat reproductive toxicity from ToxCast high throughput screening	Biology of Reproduction, 85 (2), 327-339
Ozdemir HH	2014	CA 5.7	Determination of the effects on learning and memory performance and related gene expressions of clothianidin in rat models	Cognitive neurodynamics, Vol. 8, No. 5, pp. 411-6
Ozsahin, AD; Bal, R; Yilmaz, O	2014	CA 5.3	Biochemical alterations in kidneys of infant and adult male rats due to exposure to the neonicotinoid insecticides imidacloprid and clothianidin	Toxicology Research, Vol. 3, No. 5, pp. 324-330
Phua, DH; Lin, CC; Wu, M; Deng, J; Yang, C	2009	CA 5.9	Neonicotinoid insecticides: an emerging cause of acute pesticide poisoning	Clinical Toxicology, 47 (4), 336-341
Reif, DM; Martin, MT; Tan, SW; Houck, KA; Judson, RS; Richard, AM; Knudsen, TB; Dix, DJ; Kavlock, RJ	2010	CA 5.8.3	Endocrine profiling and prioritization of environmental chemicals using ToxCast data	Environmental Health Perspectives , 118 (12), 1714-1720
Rotroff, DM; Beam, AL; Dix, DJ; Farmer, A; Freeman, KM; Houck, KA; Judson, RS; LeCluyse, EL; Martin, MT; Reif, DM; Ferguson, SS	2010	CA 5.8.2	Xenobiotic-Metabolizing Enzyme and Transporter Gene Expression in Primary Cultures of Human Hepatocytes Modulated by Toxcast Chemicals	Journal of Toxicology and Environmental Health, Part B: Critical Reviews, 13 (2-4), 329-346
Rotroff, DM; Martin, MT; Dix, DJ; Filer, DL; Houck, KA; Knudsen, TB; Sipes, NS; Reif, DM; Xia, M; Huang, R; Judson, RS	2014	CA 5.8.3	Predictive Endocrine Testing in the 21st Century Using in Vitro Assays of Estrogen Receptor Signaling Responses	Environmental Science & Technology, 48 (15), 8706-8716

Author(s)	Year	CA data point number	Title	Source
Rotroff, DM; Wetmore, BA; Dix, DJ; Ferguson, AS; Clewell, HJ; Houck, KA; Le Cluyse, EL; Andersen, ME; Judson, RS; Smith, CM; Sochaski, MA; Kavlock, RJ; Boellmann, F; Martin, MT; Reif, DM; Wambaugh, JF; Thomas, RS	2010	CA 5.8.2	Incorporating Human Dosimetry and Exposure into High-Throughput In Vitro Toxicity Screening	Toxicological Sciences, 117 (2), 348-358
Sipes, NS; Martin, MT; Kothiya, P; Reif, DM; Judson, RS; Richard, AM; Houck, KA; Dix, DJ; Kavlock, RJ; Knudsen, TB	2013	CA 5.8.2	Profiling 976 ToxCast Chemicals across 331 Enzymatic and Receptor Signaling Assays	Chemical Research in Toxicology, 26 (6), 878-895
Sipes, NS; Martin, MT; Reif, DM; Kleinstreuer, NC; Judson, RS; Singh, AV; Chandler, KJ; Dix, DJ; Kavlock, RJ; Knudsen, TB	2011	CA 5.6	Predictive Models of Prenatal Developmental Toxicity from ToxCast High- Throughput Screening Data	Toxicological Sciences, 124 (1), 109-127
So, BH; Kim, HM	2010	CA 5.9	Two Cases of Severe Neonicotinoid Intoxication	Clinical Toxicology, Vol. 48, No. 6, pp. 611
Tanaka T	2012	CA 5.7	Reproductive and neurobehavioral effects of clothianidin administered to mice in the diet	Birth defects research. Part B, Developmental and reproductive toxicology, Vol. 95, No. 2, pp. 151-9
Tanaka T	2012	CA 5.7	Effects of maternal clothianidin exposure on behavioral development in F1 generation mice	Toxicology and industrial health, Vol. 28, No. 8, pp. 697-707
Vale, JA	2008	CA 5.9	Poisoning Due to Neonicotinoid Insecticides	Clinical Toxicology, Vol. 46, no. 5, p. 404.

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 5.1	Bednarska, AJ	2013	A toxicokinetic model for thiamethoxam in rats: implications for higher-tier risk assessment.	Ecotoxicology (London, England), Vol. 22, No. 3, pp. 548-57.	This paper presents an analysis of toxicokinetics data for thiamethoxam which demonstrates that the acute oral lethality risk to rats is likely to be reduced if the same external dose is administered normally in the diet rather than as a bolus gavage. No data is presented which could be considered to change any endpoint for thiamethoxam.
CA 5.1	Lin, L; Yu, W; Pang, Y; Meng, Q; Sun, C; Li, X; Duan, M	2014	LC-MS/MS method for quantification of thiamethoxam in rat plasma and its toxicokinetics study.	Nongyao, 53 (6), 418-420, 465.	Paper presents the development of a LC-MS/MS method for the detection of thiamethoxam in rat plasma. A toxicokinetic assessment of single administrations of thiamethoxam indicated Tmax and Cmax/2 values consistent with those previously proposed for thiamethoxam. No data is presented which could be considered to change any endpoint for thiamethoxam.
CA 5.3	Ivanova, R	2013	Study on the effect of Actara and Confidor on rabbits submited to chronic intoxication.	Agrarni Nauki, Volume 5, Number 14, pp. 253-257, 15 refs.	This paper was determined to be non-relevant as it does not comply with the following relevance criteria for studies of this type: 1. Well identified test material including purity and impurity profile *Whilst it may be determined that the Actara variant used in this study was Actara 25 WG no indication of the purity of the test material was provided.* 3. Sufficient number of animals per group to establish statistical significance *Group sizes of 1 male and 4 females per dose group are lower than the 4 males and 4 females per dose group required for sub-chronic toxicity assessments in non-rodents in OECD test guideline 409. In addition, whilst the paper claims to have established statistically significant differences in some measured parameters, no indication of statistical methodology is presented.* 4. Test several dose levels (minimum 3) *Actara was tested only at a single dose level (diets were supplemented with 50 mg per kg live weight). As no food consumption data is presented it is not possible to determine the administered*

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
					dose in mg/kg bw/day. 7. Establish dose response *As only a single dose level was investigated it is not possible to establish a dose response for any parameter measured in this study.* For these reasons this study cannot be considered relevant for assessment of the toxicity of thiamethoxam.
CA 5.4	Noaishi, MA; Eweis, EA; Kandil, MA	2006	Evaluation of the chromosomal aberrations induction in rat lymphocyte cultures after subchronic treatment with different pesticides.	Bulletin of Faculty of Agriculture, Cairo University, Volume 57, Number 2, pp. 295-305, 16 refs.	*It has not been possible to locate the full paper, but based on analysis of the abstract:* Rats were exposed to thiamethoxam at 10% and 0.3% of the oral LD_{50} value (exact doses not stated) per day for 5 days. After treatment rats were allowed to recover for 14 days, at which point blood samples were obtained and analysed for chromosome aberrations. Thiamethoxam induced a statistically significant increase in chromosome aberrations at the 10% LD_{50} level only. In the absence of a number of key criteria for evaluating the studies of this type (including number of cells scored / sample, number of animals / dose level, tests used to determine statistical significance, variability of response in exposed and control animals, and the positive and negative control chromosome aberration levels) it is not possible to determine the relevance of this paper to human risk and hazard assessment. No evidence of clastogenicity was observed in any of the GLP and OECD test guideline compliant *in vitro* or *in vivo* studies conducted with thiamethoxam presented in **M-CA section 5.4** and as such this study cannot be considered to change any genotoxicity endpoint for thiamethoxam.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.4	Knight, AW; Little, S; Houck, K; Dix, D; Judson, R; Richard, A; McCarroll, N; Akerman, G; Yang, C; Birrell, L; Walmsley, RW	2009	Evaluation of high-throughput genotoxicity assays used in profiling the US EPA ToxCast chemicals.	Regulatory Toxicology and Pharmacology, 55 (2), 188-199.	Paper presents data from in greenScreen HC, CellCiphr p53 and CellSensor p53RE-bla high-throughput genotoxicity screens to evaluate the use of such screens as an aid to prioritization of carcinogenicity assessment. Thiamethoxam gave a negative response in all screens. This paper does not add any data to that available from OECD guideline studies on thiamethoxam presented in **M-CA section 5.4** and as such this study cannot be considered to change any genotoxicity endpoint for thiamethoxam.
CA 5.4	Karamova, NS; Denisova, AP; Stashevski, Z	2008	Evaluation of mutagenic activities of pesticides: actara, sencor, mospilan, pencozeb and fastac, in the Ames test.	Ekologicheskaya Genetika, 6 (4), 29-33.	Paper presents bacterial mutagenicity data for an Actara thiamethoxam formulation. Actara was shown to be non-mutagenic both in the presence and absence of S9 metabolic activation. This data is consistent with the mutation assays conducted with thiamethoxam presented in **M-CA section 5.4** and as such this study cannot be considered to change any genototxicity endpoint for thiamethoxam.
CA 5.5	Martin, MT; Judson, RS; Reif, DM; Kavlock, RJ; Dix, DJ	2009	Profiling chemical based on chronic toxicity results from the U.S. EPA ToxRef Database.	Environmental Health Perspectives, 117 (3), 392-399.	Paper data mined the ToxRfDB which contains guideline studies on thiamethoxam. No new data are presented and as such this study cannot be considered to change any endpoint for thiamethoxam.
CA 5.6	Padilla, S; Corum, D; Padnos, B; Hunter, DL; Beam, A; Houck, KA; Sipes, N; Kleinstreuer, N; Knudsen, T; Dix, DJ; Reif, DM	2012	Zebrafish developmental screening of the ToxCast Phase I chemical library.	Reproductive Toxicology, 33 (2), 174-187.	Paper described screening studies on zebrafish. As part of an evaluation of the model as a screening tool for developmental toxicity. No new mammalian data is presented and as such this study cannot be considered to change any toxicity endpoint for thiamethoxam.
CA 5.6	Martin, MT; Mendez, E; Corum, DG; Judson, RS; Kavlock, RJ; Rotroff, DM; Dix, DJ	2009	Profiling the Reproductive Toxicity of Chemicals from Multigeneration Studies in the Toxicity Reference Database.	Toxicological Sciences, Vol. 110, No. 1, pp. 181-190.	Paper describes the assessment of existing *in vivo* data on thiamethoxam to help build a predictive model for reproductive toxicity. No new data is presented and as such this study cannot be considered to change any endpoint for thiamethoxam.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.6	Martin, MT; Knudsen, TB; Reif, DM; Houck, KA; Judson, RS; Kavlock, RJ; Dix, DJ	2011	Predictive model of rat reproductive toxicity from ToxCast high throughput screening.	Biology of Reproduction, 85 (2), 327-339.	Paper describes use of existing *in vivo* data on thiamethoxam to help build a predictive model for reproductive toxicity. No new data is presented and as such this study cannot be considered to change any endpoint for thiamethoxam.
CA 5.6	Sipes, NS.; Martin, Matthew T.; Reif, David M.; Kleinstreuer, Nicole C.; Judson, Richard S.; Singh, Amar V.; Chandler, Kelly J.; Dix, David J.; Kavlock, Robert J.; Knudsen, Thomas B.	2011	Predictive Models of Prenatal Developmental Toxicity from ToxCast High-Throughput Screening Data.	Toxicological Sciences, 124 (1), 109-127.	Paper describes use of existing *in vivo* data on thiamethoxam to help build a predictive model for developmental toxicity. No new data is presented and as such this study cannot be considered to change any endpoint for thiamethoxam.
CA 5.7	Rodrigues, KJA; Santana, MB; Do Nascimento, JLM; Picanco-Diniz, DLW; Maues, LAL; Santos, SN; Ferreira, VMM; Alfonso, M; Duran, R; Faro, LRF	2010	Behavioral and biochemical effects of neonicotinoid thiamethoxam on the cholinergic system in rats.	Ecotoxicology and environmental safety, Vol. 73, No. 1, pp. 101-7.	Paper examines the effect of thiamethoxam on the acetylcholinestrerase activity and high-affinity choline uptake in the brains of rats dosed at 25, 50 and 100 mg/kg bw/day for 7 days. In the two highest dose groups an increase in anxiety behaviour was observed in conjunction with reduced alcholinestrerase activity and high-affinity choline uptake. These findings are not consistent with the GLP and OECD test guideline compliant neurotoxicity studies presented in **M-CA section 5.7.** These studies include a sub-chronic neurotoxicity study which showed no neurobehavioral or neuromorphological effects at doses equivalent to, or exceeding, those used in this study over a considerably longer exposure period. As such the 90 day rat neurotoxicity study presented in **M-CA section 5.7** should be considered the definite study for this endpoint and this paper cannot be considered to change the current position on the neurotoxicity of thiamethoxam.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.8.2	Swenson, TL; Casida JE	2013	Neonicotinoid formaldehyde generators: possible mechanism of mouse-specific hepatotoxicity/hepatocarcinogenicity of thiamethoxam.	Toxicology letters, Vol. 216, No. 2-3, pp. 139-45.	This paper examines the mouse-specific metabolic formation of formaldehyde as a causative factor in the hepatoxicity observed in repeat dose toxicity studies with thiamethoxam in the mouse presented in **M-CA section 5.8.2.** Whist the formation of formaldehyde has not been specifically examined in the presented mechanistic studies with thiamethoxam, the results of this paper are not inconsistent with the position that the observed hepatic effects in the mouse are the result of differences in the metabolism of thiamethoxam between mice, rats and humans and are not relevant to human risk assessment. This study cannot be considered to change any endpoint for thiamethoxam.
CA 5.8.2	Pastoor T; Rose P; Lloyd S; Peffer R; Green T	2005	Case study: weight of evidence evaluation of the human health relevance of thiamethoxam-related mouse liver tumors.	Toxicological sciences : an official journal of the Society of Toxicology, Vol. 86, No. 1, pp. 56-60.	Paper reviews the mouse liver tumorigenesis mode of action case presented in **M-CA section 5.8.2**. The authors demonstrate that the mechanism of tumorigenesis is specific to the mouse and that thiamethoxam does not pose a carcinogenic risk in humans.
CA 5.8.2	Green T; Toghill A; Lee R; Waechter F; Weber E; Peffer R; Noakes J; Robinson M	2005	Thiamethoxam induced mouse liver tumors and their relevance to humans. Part 2: species differences in response.	Toxicological sciences : an official journal of the Society of Toxicology, Vol. 86, No. 1, pp. 48-55.	This paper reviews the comparative mouse and rat metabolism studies presented in **M-CA section 5.8.2** alongside clinical chemistry and histopathology data from the rat and mouse carcinogenesis studies in **M-CA section 5.5**. The differential response to thiamethoxam in rats and mice is a result of greatly increased formation of the tumorigenic metabolites CGA330050 and CGA265307 in the mouse when compared to rats and humans. This explains the absence of tumours in the rat carcinogenesis study with thiamethoxam and demonstrates that the liver tumours observed in the mouse carcinogenesis study are not relevant to human risk assessment.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.8.2	Green T; Toghill A; Lee R; Waechter F; Weber E; Noakes J	2005	Thiamethoxam induced mouse liver tumors and their relevance to humans. Part 1: mode of action studies in the mouse.	Toxicological sciences: an official journal of the Society of Toxicology, Vol. 86, No. 1, pp. 36-47.	This paper reviews the mouse carcinogenesis study presented in **M-CA section 5.5** and the mode of action studies presented in **M-CA section 5.8.2**. The paper identifies the principle tumorigenic events as increased single cell necrosis and apoptosis followed by regenerative hyperplasia. When three mouse metabolites of thiamethoxam were tested in 20 week mouse dietary studies only one metabolite (CGA330050) induced hepatic changes similar to those seen for thiamethoxam. In addition, metabolite CGA265307 was shown to inhibit nitric oxide synthase and to exacerbate the hepatotoxoic effects of carbon tetrachloride. It was proposed that the tumorigenic effects of thiamethoxam in the mouse are the result of CGA330050 induced hepatic toxicity exacerbated by CGA265307 mediated inhibition of nitric oxide synthase.
CA 5.8.2	Pastoor, T; Rose, P; Lloyd, S; Peffer, R; Green, T	2005	Weight of Evidence Evaluation of the Human Health Relevance of Thiamethoxam-Related Mouse Liver Tumors.	Toxicological Sciences, Vol. 86, no. 1, pp. 56-60.	This paper presents a weight of evidence evaluation of the mouse carcinogenesis study presented in **M-CA section 5.5** and the mode of action studies presented in **M-CA section 5.8.2** alongside the comparative metabolism studies presented in **M-CA section 5.8.2**. The paper examines the presented evidence against the Hill criteria for causality and concludes that the coherence and extent of the database clearly demonstrates the mode of action for mouse liver tumorigenesis and also allows for the conclusion that thiamethoxam does not pose a carcinogenic risk to humans.
CA 5.8.2	Shah, I; Houck, K; Judson, RS; Kavlock, RJ; Martin, MT; Reif, DM; Wambaugh, J; Dix, DJ	2011	Using nuclear receptor activity to stratify hepatocarcinogens.	PLoS One, 6 (2), e14584.	Paper reviews *in vitro* screening ToxCast™ data. No data on thiamethoxam is presented which would change the current position on toxicity or mode of action.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.8.2	Judson, RS; Houck, KA; Kavlock, RJ; Knudsen, TB; Martin, MT; Mortensen, HM; Reif, DM; Rotroff, DM; Shah, I; Richard, AM; Dix, DJ	2010	*In vitro* Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project.	Environmental Health Perspectives, 118 (4), 485-492.	Paper reviews *in vitro* screening ToxCast™ data. No data on thiamethoxam is presented which would change the current position on toxicity or mode of action.
CA 5.8.2	Rotroff, DM; Beam, AL; Dix, DJ; Farmer, A; Freeman, KM; Houck, KA; Judson, RS; LeCluyse, EL; Martin, MT; Reif, DM; Ferguson, SS	2010	Xenobiotic-Metabolizing Enzyme and Transporter Gene Expression in Primary Cultures of Human Hepatocytes Modulated by Toxcast Chemicals.	Journal of Toxicology and Environmental Health, Part B: Critical Reviews, 13 (2-4), 329-346.	Tests 320 ToxCast™ chemicals in human hepatocyte culture. No data on thiamethoxam is presented which would change the current position on toxicity or mode of action.
CA 5.8.2	Lloyd, S; Green, T; Toghill, A; Lee, R; Waechter, F; Noakes, J; Pastoor, TP	2005	Thiamethoxam induced mouse liver tumors and their relevance to humans 1. Mode of action studies in the mouse.	Conference: 44th Annual Meeting of the Society of Toxicology, New Orleans, LA (USA)	*Conference proceeding, abstract only.* This entry represents the presentation of the mouse liver mode of action studies presented in **M-CA section 5.8.2** to the 44th Annual Meeting of the Society of Toxicology.
CA 5.8.2	Waterfield, C; Green, T; Lee, R; Toghill, A; Waechter, F; Peffer, R; Noakes, J; Robinson, M; Pastoor, TP	2005	Thiamethoxam induced mouse liver tumors and their relevance to humans 2. Species differences in response.	Conference: 44th Annual Meeting of the Society of Toxicology, New Orleans, LA (USA)	*Conference proceeding, abstract only.* This entry represents the presentation of the comparative metabolism studies presented in **M-CA section 5.8.2** to the 44th Annual Meeting of the Society of Toxicology.
CA 5.8.2	Pastoor, TP; Rose, P; Lloyd, S; Peffer, R; Green, T	2005	Thiamethoxam induced mouse liver tumors and their relevance to humans 3. Weight of evidence evaluation.	Conference: 44th Annual Meeting of the Society of Toxicology, New Orleans, LA (USA)	*Conference proceeding, abstract only.* This entry represents the presentation of the weight of evidence evaluation of mouse liver mode of action studies and comparative metabolism studies presented in **M-CA section 5.8.2** to the 44th Annual Meeting of the Society of Toxicology.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.8.2	Wambaugh, JF; Setzer, RW; Reif, DM; Gangwal, S; Mitchell-Blackwood, J; Arnot, JA; Joliet, O; Frame, A; Rabinowitz, J; Knudsen, TB; Judson, RS; Egeghy, P; Vallero, D; Cohen Hubal, EA	2013	High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project.	Environmental Science & Technology, 47 (15), 8479-8488.	No specific reference to thiamethoxam, paper is a general ExpoCast analysis.
CA 5.8.3	Reif, David M; Martin, Matthew T; Tan, Shirlee W; Houck, Keith A; Judson, Richard S; Richard, Ann M; Knudsen, Thomas B; Dix, David J; Kavlock, Robert J	2010	Endocrine profiling and prioritization of environmental chemicals using ToxCast data.	Environmental Health Perspectives, 118 (12), 1714-1720.	Paper considered relevant but has been reviewed as part of thiamethoxam - Review for Potential for Endocrine Disruption in Mammalian Species in **M-CA Section 5.8.3**.
CA 5.8.3	Rotroff, DM; Martin, MT; Dix, DJ; Filer, DL; Houck, KA; Knudsen, TB; Sipes, NS; Reif, DM; Xia, M; Huang, R; Judson, RS	2014	Predictive Endocrine Testing in the 21st Century Using *in vitro* Assays of Estrogen Receptor Signaling Responses.	Environmental Science & Technology (2014), 48 (15), 8706-8716.	Paper considered relevant but has been reviewed as part of Thiamethoxam - Review for Potential for Endocrine Disruption in Mammalian Species presented in **M-CA Section 5.8.3**.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.9	Yeboue-Kouame, BY; Vagamon, B; Tchicaya, AF; Wognin, SB; Kouassi, YM; Aka, I; Bonny, JS	2010	A case of Stevens Johnson's syndrome in an Ivorian farmer: what imputability to pesticides? Syndrome de Stevens Johnson chez un agriculteur ivoirien: quelle relation avec l'exposition aux insecticides?	Archives des Maladies Professionnelles et de l'Environnement, Volume 71, Number 2, pp. 117-121, 17 refs.	This paper presents a case study in which a farmer exhibited symptomology consistent with Stevens Johnson syndrome after use of a crop protection product containing lambda-cyhalothrin (106 g/L) and thiamethoxam (141 g/L). The authors do not present any conclusive evidence of a causative link between exposure to this crop protection product and the onset of Stevens Johnson syndrome, and the picture is complicated by the administration of an unspecified herbal drug treatment. Neither lambda-cyhalothrin nor thiamethoxam exhibits evidence of immunotoxicity in comprehensive databases of *in vivo* studies and no plausible mechanism by which a synergistic immunotoxic effect may manifest is presented. In addition, occupational health monitoring of personnel involved in the manufacturing and use of thiamethoxam and lambda-cyhalothrin conducted by Syngenta indicates no evidence of immunotoxic effects in general, or Stevens Johnson syndrome in particular and as such this study cannot be considered to change any endpoint for thiamethoxam.
CA 5.9	Vale, JA	2008	Poisoning Due to Neonicotinoid Insecticides.	Clinical Toxicology, Vol. 46, no. 5, p. 404.	*Conference proceeding, abstract only. Based upon analysis of the abstract:* Paper reviews the data on neonicotinoid insecticide (including thiamethoxam and clothianidin) health effects in humans after chronic and acute exposures. The paper notes the paucity of published information and makes recommendations for medical intervention in cases of overexposure. No data is presented linking thiamethoxam to any health effects. The data published in this study does not add to the health monitoring information for thiamethoxam presented in **M-CA section 5.9 and** as such this study cannot be considered to change any endpoint for thiamethoxam.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.9	Zeljezic, D; Mladinic, M	2015	Evaluation of the mechanism of nucleoplasmic bridge formation due to premature telomere shortening in agricultural workers exposed to mixed pesticides: Indication for further studies.	Chemosphere, Vol. 120, pp. 45-51. Refs: 40.	Paper examines a group of agricultural workers (27 males; 3 females) and studied each reported occupational use of 17 different pesticides including thiamethoxam. The authors concluded that agricultural workers seasonally exposed to multiple pesticides, in addition to higher levels of chromatin instabilities (i.e. nucleoplasmic bridges), exhibited slightly longer relative telomere length in peripheral blood lymphocytes, thus indicating that nucleoplasmic bridges arise from dicentric chromosomes, and also suggesting that these workers do not have higher cancer risk due to occupational exposure. No specific information was given about exposure and consequently health effects cannot be attributed to any specific pesticide and as such this study cannot be considered to change any endpoint for thiamethoxam.
CA 5.9	Manfo, FPT; Moundipa, PF; Dechaud, H; Tchana, AN; Nantia, EA; Zabot, MT; Pugeat, M	2012	Effect of agropesticides use on male reproductive function: A study on farmers in Djutitsa (Cameroon).	Environmental Toxicology, 27 (7), 423-432.	This paper presents a cross-sectional investigation of male reproductive health and pesticide exposure in Cameroon. Self-reported health status, serum reproductive hormone levels and thyroid hormone levels were compared between 47 rural, uneducated users of pesticides and 37 educated, urban residents of another region (39 pesticide users and 33 controls provided blood samples). Thiamethoxam was one of 25 active ingredients reported by the farmers, but was used by only 1 farmer (2.1%) and was one of 8 active ingredients that were stated to be the least used. Its frequency of use relative to all active ingredients was stated to be 0.3% (not clear whether this was based on quantity used or time sprayed). The main finding was a small but significant reduction in total testosterone levels among pesticide users ($p < 0.05$), and a significantly higher androstenedione level ($p<0.001$). However, no adjustment for age was made and pesticide users were almost 4 years older on average. More importantly, no effects can be related to thiamethoxam exposure because analyses were not performed for individual pesticides and only one farmer reported using it. This study cannot be considered to change any endpoint for thiamethoxam.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.9	Costa, C; Silva, S; Neves, J; Coelho, P; Costa, S; Laffon, B; Snawder, J; Teixeira, JP	2011	Micronucleus Frequencies in Lymphocytes and Reticulocytes in a Pesticide-Exposed Population in Portugal.	Journal of Toxicology and Environmental Health, Part A: Current Issues, 74 (15-16), 960-970.	This paper examines the frequency of micronucleated lymphocytes and reticulocytes in 84 pesticide exposed famers and 93 unexposed office workers. Thiamethoxam was one of 26 active ingredients used by the farmers. No attempt to quantitatively assess exposure to any compound was made and no indication of the number of workers exposed to thiamethoxam was given. The main finding of the study was a statistically significant increase in lymphocye and reticulocyte micronuclei frequency in pesticide exposed farmers when compared to office workers. As no data were presented for exposure to individual pesticides no effects can be related to thiamethoxam exposure. This study cannot be considered to change any endpoint for thiamethoxam.
CA 5.9	Jensen, HK; Konradsen, F	2011	Pesticide use and self-reported symptoms of acute pesticide poisoning among aquatic farmers in phnom penh, cambodia.	Journal of Toxicology, Vol. 2011. arn. 639814. Refs: 31.	The study, a questionnaire-based survey with personal interviews, was conducted to assess pesticide handling practices and knowledge, attitudes, and self-perceived health effects of acute pesticide poisoning. Farmers were recruited from 93 households with a total of 113 farmers of which 89 were pesticide sprayers. Thiamethoxam was one of the 16 pesticides that households reported using (8 of the other pesticides belonged to WHO class I + II). However, only 1 household reported using thiamethoxam, and the study provides no information about health effects related to thiamethoxam exposure. This study cannot be considered to change any endpoint for thiamethoxam.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.9	Dasgupta, S; Meisner, C; Wheeler, D; Xuyen, K; Lam, NT	2007	Pesticide poisoning of farm workers-implications of blood test results from Vietnam.	International Journal of Hygiene and Environmental Health, 210 (2), 121-132.	The study is largely targeted at the effect of exposure to cholinesterase-inhibiting insecticides i.e. organophosphates and carbamates. However, some information on the prevalence of self-reported symptoms is given for certain classes of pesticides including neonicotionoids. A total number of 1252 applications of pesticides (a total of 338 kg of a.i.) were made by 190 farmers during the study period. The number of applications of thiamethoxam is not stated, but it is stated that 0.3kg of a.i. were applied. A total of 29 applications (2.47kg) of neonicotinoids, including thiamethoxam, were made. The probit analysis provided no information relating to thiamethoxam. No health effects can be related to thiamethoxam exposure and as such this study cannot be considered to change any endpoint for thiamethoxam.
Top-Up search					
5.8.2	Sinha, S; Thaker, AM	2014	Study on the impact of lead acetate pollutant on immunotoxicity produced by thiamethoxam pesticide	Indian Journal of Pharmacology, Vol. 46, No. 6, pp. 596-600	Paper considered relevant but has been reviewed as part of Thiamethoxam - Position Statement Concerning Immunotoxicity Potential in **M-CA Section 5.8.2**.
Clothianidin search					
CA 5.1	Dick, RA	2006	Substrate specificity of rabbit aldehyde oxidase for nitroguanidine and nitromethylene neonicotinoid insecticides	Chemical research in toxicology, Vol. 19, No. 1, pp. 38-43	This paper investigates the importance of the nitroguanidine moieties in the *in vitro* metabolism of thiamethoxam and clothianidin. Differences in aldehyde oxidase substrate specificity were observed between compounds, with clothianidin undergoing a more rapid transformation than thiamethoxam. This paper cannot be considered to alter any endpoint for thiamethoxam or clothianidin.
CA 5.1	Ford, KA	2006	Unique and common metabolites of thiamethoxam, clothianidin, and dinotefuran in mice	Chemical research in toxicology, Vol. 19, No. 11, pp. 1549-56	Paper investigates the metabolic products of thiamethoxam and clothianidin in mice. Whilst some common metabolites of thiamethoxam and clothianidin were identified, significant differences were observed between metabolic pathways of the two compounds. This paper cannot be considered to alter any endpoint for thiamethoxam or clothianidin.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.3	Ozsahin, AD; Bal, R; Yilmaz, O	2014	Biochemical alterations in kidneys of infant and adult male rats due to exposure to the neonicotinoid insecticides imidacloprid and clothianidin	Toxicology Research, Vol. 3, No. 5, pp. 324-330	This paper was determined to be non-relevant as it does not comply with the following relevance criteria for studies of this type: 3. Sufficient number of animals per group to establish statistical significance: *Group sizes of 7 males per dose group were lower than the 5 males and 5 females per dose group required for sub-chronic toxicity assessments in rodents in OECD test guideline 408.* 4. Test several dose levels (minimum 3): *Clothianidin was tested only at a single dose level (diets were supplemented with 12 mg/kg bw/day).* 7. Establish dose response: *As only a single dose level was investigated it is not possible to establish a dose response for any parameter measured in this study.* For these reasons this study cannot be considered relevant for assessment of the toxicity of clothianidin.
CA 5.4	Calderon-Segura ME	2012	Evaluation of genotoxic and cytotoxic effects in human peripheral blood lymphocytes exposed in vitro to neonicotinoid insecticides news	Journal of toxicology, Vol. 2012, pp. 612647	This paper examines the geneotoxic effects of a clothianidin containing formulation using the comet assay with human peripheral blood lymphocytes. As this study is conducted with a clothianidin containing formulation and not with clothianidin itself this paper is not relevant to human risk or hazard assessment of clothianidin as a metabolite of thiamethoxam.
CA 5.4	Knight, AW; Little, S; Houck, K; Dix, D; Judson, R; Richard, A; McCarroll, N; Akerman, G; Yang, C; Birrell, L; Walmsley, RM	2009	Evaluation of high-throughput genotoxicity assays used in profiling the US EPA ToxCast chemicals	Regulatory Toxicology and Pharmacology, 55 (2), 188-199	Paper presents data from in greenScreen HC, CellCiphr p53 and CellSensor p53RE-bla high-throughput genotoxicity screens to evaluate the use of such screens as an aid to prioritization of carcinogenicity assessment. Clothianidin gave a negative response in all screens. This paper does not alter any endpoint for thiamethoxam or clothianidin.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.6	Bal R	2013	Effects of the neonicotinoid insecticide, clothianidin, on the reproductive organ system in adult male rats	Drug and chemical toxicology, Vol. 36, No. 4, pp. 421-9.	This paper examined the effects of Dantotsu, a clothianidin containing formulation, on reproductive parameters in adult male rats when delivered by gavage over 90 days. As this study is conducted with a clothianidin containing formulation and not with clothianidin itself this paper is not relevant to human risk or hazard assessment of clothianidin as a metabolite of thiamethoxam.
CA 5.6	Bal R	2012	Effects of clothianidin exposure on sperm quality, testicular apoptosis and fatty acid composition in developing male rats	Cell biology and toxicology, Vol. 28, No. 3, pp. 187-200	This paper examined the effects of Dantotsu, a clothianidin containing formulation, on reproductive parameters in suckling male rats when delivered by gavage over 90 days. As this study is conducted with a clothianidin containing formulation and not with clothianidin itself this paper is not relevant to human risk or hazard assessment of clothianidin as a metabolite of thiamethoxam.
CA 5.6	Li P	2011	Activation and modulation of human α4β2 nicotinic acetylcholine receptors by the neonicotinoids clothianidin and imidacloprid	Journal of neuroscience research, Vol. 89, No. 8, pp. 1295-301	This paper examines the effects of clothianidin on the activation and modulation of human α4β2 nicotinic receptors. Clothianidin potentiated α4β2 nicotinic receptor responses to low concentrations of acetylcholine but this was not associated with effects on currents elicited by saturating concentrations of the transmitter, indicating no functional effect. This paper does not alter any endpoint for thiamethoxam or clothianidin.
CA 5.6	Martin, MT; Knudsen, TB; Reif, DM; Houck, KA;Judson, RS; Kavlock, RJ; Dix, DJ	2011	Predictive model of rat reproductive toxicity from ToxCast high throughput screening	Biology of Reproduction, 85 (2), 327-339	Paper describes use of existing *in vivo* data on clothianidin to help build a predictive model for reproductive toxicity. No data on clothianidin is presented which would change the current position on toxicity or mode of action.
CA 5.6	Sipes, NS; Martin, MT; Reif, DM; Kleinstreuer, NC; Judson, RS; Singh, AV; Chandler, KJ; Dix, DJ; Kavlock, RJ; Knudsen, TB	2011	Predictive Models of Prenatal Developmental Toxicity from ToxCast High-Throughput Screening Data	Toxicological Sciences, 124 (1), 109-127	Paper describes use of existing *in vivo* data on clothianidin to help build a predictive model for developmental toxicity. No data on clothianidin is presented which would change the current position on toxicity or mode of action.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.7	Faro LRF	2012	In vivo neurochemical characterization of clothianidin induced striatal dopamine release	Toxicology, Vol. 302, No. 2-3, pp. 197-202	This paper was considered non-relevant as it does not comply with relevance criteria 5 as the intrastriatal route of administration used in this study is not considered a relevant route of administration for human risk assessment.
CA 5.7	Ozdemir HH	2014	Determination of the effects on learning and memory performance and related gene expressions of clothianidin in rat models	Cognitive neurodynamics, Vol. 8, No. 5, pp. 411-6	This paper examines the effects of clothianidin on learning and memory parameters of infant and adult rats. Clothianidin was not shown to alter learning or expression of genes involved in cognitive development. A small, but statistically significant, reduction in memory performance was observed in high dose (24 mg/kg) juveniles only. Clothianidin is a major mammalian metabolite of thiamethoxam, with 10% of an administered dose of thiamethoxam being rapidly converted to clothianidin. As described in M-CA section 5.7 of this dossier a full set of neurotoxicity studies have been conducted with thiamethoxam. This package includes a developmental neurotoxicity study in which no evidence of neurotoxic effects were observed in adults or juveniles up to a top dose of 298.7 mg/kg bw/day. Correction for formation of clothianidin from thiamethoxam in this developmental neurotoxicity study indicates that in the thiamethoxam developmental neurotoxicity study animals were exposed to clothianidin at a dose level equivalent to 29.9 mg/kg bw/day. As this paper describes a finding not present in a GLP and OECD test guideline compliant studies conducted at higher dose levels it cannot be considered to alter any neurotoxicity endpoint for clothianidin.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.7	Tanaka T	2012	Reproductive and neurobehavioral effects of clothianidin administered to mice in the diet	Birth defects research. Part B, Developmental and reproductive toxicology, Vol. 95, No. 2, pp. 151-9	This paper was determined to be non-relevant as it does not comply with the following relevance criteria for studies of this type: 7. Establish dose response: *This study showed no convincing pattern of treatment related effects across dose levels, sex or time. As a result it is not possible to determine any clear evidence of developmental effects or indications of neurotoxicity from the data presented in this paper.* For this reason this study cannot be considered relevant for assessment of the toxicity of clothianidin.
CA 5.7	Tanaka T	2012	Effects of maternal clothianidin exposure on behavioral development in F1 generation mice	Toxicology and industrial health, Vol. 28, No. 8, pp. 697-707	This paper was determined to be non-relevant as it does not comply with the following relevance criteria for studies of this type: 7. Establish dose response: *This study showed no convincing pattern of treatment related effects across dose levels, sex or time. As a result it is not possible to determine any clear evidence of developmental effects or indications of neurotoxicity from the data presented in this paper.* For this reason this study cannot be considered relevant for assessment of the toxicity of clothianidin.
CA 5.8.2	Judson, RS; Houck, KA; Kavlock, RJ; Knudsen, TB; Martin, MT; Mortensen, HM; Reif, DM; Rotroff, DM; Shah, I; Richard, AM; Dix, DJ	2010	In Vitro Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project	Environmental Health Perspectives, 118 (4), 485-492	Paper reviews *in vitro* screening ToxCast™ data. No data presented on clothianidin which would change the position on toxicity or mode of action.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.8.2	Rotroff, DM; Beam, AL; Dix, DJ; Farmer, A; Freeman, KM; Houck, KA; Judson, RS; LeCluyse, EL; Martin, MT; Reif, DM; Ferguson, SS	2010	Xenobiotic-Metabolizing Enzyme and Transporter Gene Expression in Primary Cultures of Human Hepatocytes Modulated by Toxcast Chemicals	Journal of Toxicology and Environmental Health, Part B: Critical Reviews, 13 (2-4), 329-346	Tests 320 ToxCast™ chemicals in human hepatocyte culture. No data presented on clothianidin which would change the position on toxicity or mode of action.
CA 5.8.2	Rotroff, DM; Wetmore, BA; Dix, DJ; Ferguson, AS; Clewell, HJ; Houck, KA; Le Cluyse, EL; Andersen, ME; Judson, RS; Smith, CM; Sochaski, MA; Kavlock, RJ; Boellmann, F; Martin, MT; Reif, DM; Wambaugh, JF; Thomas, RS	2010	Incorporating Human Dosimetry and Exposure into High-Throughput In Vitro Toxicity Screening	Toxicological Sciences, 117 (2), 348-358	Paper reports results from *in vitro* experiments. No data presented on clothianidin which would change the position on toxicity or mode of action.
CA 5.8.2	Sipes, NS; Martin, MT; Kothiya, P; Reif, DM; Judson, RS; Richard, AM; Houck, KA; Dix, DJ; Kavlock, RJ; Knudsen, TB	2013	Profiling 976 ToxCast Chemicals across 331 Enzymatic and Receptor Signaling Assays	Chemical Research in Toxicology, 26 (6), 878-895	Paper reports results from *in vitro* experiments. No data presented on clothianidin which would change the position on toxicity or mode of action.
CA 5.8.3	Reif, DM; Martin, MT; Tan, SW; Houck, KA; Judson, RS; Richard, AM; Knudsen, TB; Dix, DJ; Kavlock, RJ	2010	Endocrine profiling and prioritization of environmental chemicals using ToxCast data	Environmental Health Perspectives, 118 (12), 1714-1720	This paper tests chemicals in a battery of hormone receptor binding assays. Clothianidin excreted no response in any assay, indicating no evidence for an effect on the endocrine system.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.8.3	Rotroff, DM; Martin, MT; Dix, DJ; Filer, DL; Houck, KA; Knudsen, TB; Sipes, NS; Reif, DM; Xia, M; Huang, R; Judson, RS	2014	Predictive Endocrine Testing in the 21st Century Using in Vitro Assays of Estrogen Receptor Signaling Responses	Environmental Science & Technology, 48 (15), 8706-8716	Paper tests chemicals in a battery of hormone receptor binding assays and used the results of the assays to create composite scores assessing the overall potential of a compound to have an effect. For clothianidin, the composite scores for ER agonist activity, ER antagonist activity, ER binding activity and ER-dependent cell growth were all zero, indicating no evidence for an effect on the endocrine system.
CA 5.9	Phua, DH; Lin, CC; Wu, M; Deng, J; Yang, C	2009	Neonicotinoid insecticides: an emerging cause of acute pesticide poisoning	Clinical Toxicology, 47 (4), 336-341	Paper examines 70 reported incidences of poisoning following exposure to neonicatinoid insecticides. No incidences of poisoning following exposure to thiamethoxam were presented. Whilst two incidences of exposure to clothianidin were presented, no information regarding symptomology or severity of effect following these exposures was given. No data was presented which would change the position on the toxicity or mode of action of clothianidin or thiamethoxam.
CA 5.9	So, BH; Kim, HM	2010	Two Cases of Severe Neonicotinoid Intoxication	Clinical Toxicology, Vol. 48, No. 6, pp. 611	*Conference proceeding, abstract only. Based upon analysis of the abstract:* This paper presents a case report of an intentional ingestion of an unnamed formulation containing 8% clothianidin. As this report examines the effects of a clothianidin containing formulation and not with clothianidin itself this paper is not relevant to human risk or hazard assessment of clothianidin as a metabolite of thiamethoxam.
CA 5.9	Vale, JA	2008	Poisoning Due to Neonicotinoid Insecticides	Clinical Toxicology, Vol. 46, no. 5, p. 404.	*Conference proceeding, abstract only. Based upon analysis of the abstract:* Paper reviews the data on neonicotinoid insecticide (including thiamethoxam and clothianidin) health effects in humans after chronic and acute exposures. The paper notes the paucity of published information and makes recommendations for medical intervention in cases of overexposure. No data is presented linking thiamethoxam or clothianidin to health effects.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CP 7.2.3	Mota-Sanchez, David	2012	Penetrative and dislodgeable residue characteristics of 14C-insecticides in apple fruit.	Journal of Agricultural and Food Chemistry, Vol. 60, No. 12, pp. 2958-66.	The rate and extent of penetration of three insecticides in fruit were investigated and the extraction characteristics of the remaining dislodgeable residues on the fruit were measured. The residues measured were on the apple fruits and are therefore not relevant when determining a dislodgeable foliar residue. Exposures to thiamethoxam to workers carrying out harvesting/maintenance activities (worker exposure assessment) have been provided as part of the MCP Section 7 and are considered protective and precautionary.

All documents listed in Table 9.6-2 were excluded in Table 9.6-4 and therefore none of these literature references have been discussed further within the supplementary dossier for thiamethoxam.