S-Metolachlor

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

Table of Contents

CA 9 LITERATURE DATA

CA 9.1 Title

This document is a Literature Review Report for S-metolachlor, relevant metabolite(s) and EU representative formulation A9396G (Dual Gold®).

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 S-metolachlor 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 search strategy is detailed in the tables below. In summary, initially a very broad search was done to look for any references which included the active substance S-metolachlor, or its major metabolites, in conjunction with any of the key words set out in Table 9.5-1. The names searched for were:

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L1      QUE  (693288-41-4 OR 131068-72-9 OR 1217465-10-5 OR 244270-80-2)
L2      QUE  (244270-82-4 OR 887649-86-7 OR 244270-79-9 OR 244270-81-3)
L3      QUE  (887649-85-6 OR 947601-85-6 OR 446027-17-4 OR 1173021-76-5)
L4      QUE  (1418095-19-8 OR 126605-22-9 OR 153516-68-8 OR 61520-53-4)
L5      QUE  (82508-08-5 OR 82508-09-6 OR 61520-54-5 OR 97055-05-5)
L6      QUE  (32428-71-0 OR 97055-06-6 OR 52559-52-1 OR 51219-00-2)
L7      QUE  (96394-97-7 OR 121073-75-4 OR 170379-74-5 OR 152019-73-3)
L8      QUE  (120375-14-6 OR 65513-61-3 OR 159956-64-6 OR 171118-09-5)
L9      QUE  (CGA098847 OR CGA98847 OR CGA46129 OR CGA138868)
L10     QUE  (CGA354743 OR CGA41507 OR CGA51202 OR CGA40172)
L11     QUE  (CGA40919 OR CGA37735 OR CGA49751 OR CGA37913)
L12     QUE  (CGA351915 OR CGA133275 OR CGA046129 OR CGA13656)
L13     QUE  (CGA(2W)(098847 OR 98847 OR 46129 OR 138868))
L14     QUE  (CGA(2W)(354743 OR 41507 OR 51202 OR 40172))
L15     QUE  (CGA(2W)(40919 OR 37735 OR 49751 OR 37913))
L16     QUE  (CGA(2W)(351915 OR 133275 OR 046129 OR 13656))
L17     QUE  (SYN542491 OR SYN542489 OR SYN542492 OR SYN547969)
L18     QUE  (SYN542488 OR SYN542490 OR SYN542607 OR NOA436611)
L19     QUE  (SYN(2W)(542491 OR 542489 OR 542492 OR 547969))
L20     QUE  ((SYN(2W)(542488 OR 542490 OR 542607)) OR (NOA(2W)436611))
L21     QUE  (55762-76-0 OR 63150-68-5 OR 94449-58-8 OR (CGA(W)77102))
L22     QUE  (METETILACHLOR OR METOLACHLOR OR (CGA(W)24705) OR CGA24705)
L23     QUE  ((S OR ALPHA)(2W)(METOLACHLOR OR METHOLACHLOR))
L24     QUE  (CGA77102 OR 51218-45-2 OR 87392-12-9 OR METHOLACHLOR)
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L25      QUE  (L1-L20)   METABOLITES
L26      QUE  (L21 OR L22 OR L23 OR L24)   METOLACHLOR
L27      QUE  (L25 OR L26)   METOLACHLOR & METABOLITES
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An overview of the results is summarised in the table below and further details are provided in Section 9.5.

Data requirement(s) captured in the search	**Number (Initial Search)**
Total number of *summary records* retrieved after *all** searches of peer-reviewed literature (excluding duplicates)	1059
Number of *summary records* excluded from the search results after rapid assessment for relevance	940
Total number of *full-text* documents assessed in detail	119
Number of *studies* excluded from further consideration after detailed assessment for relevance	86
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	33

*both from bibliographic databases and other sources of peer-reviewed literature

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 S-metolachlor 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.

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

Data requirements(s) (indicated by the correspondent CA data point (s))	Criteria for relevance
*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 3. Relevant to ED assessment
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 3. Deemed relevant following review from epidemiologist

* 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

In addition to the above, the criteria for relevance were expanded to consider whether the publication described any effect that was adverse, novel, or likely to affect the risk assessment, or impact on classification or labelling. Where this judgement has been used it is clearly explained in Table 9.6-4.

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.

[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

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	4. Data must demonstrate minimum of two clear half lives 5. Sufficient data points must be provided to demonstrate decline curves between repeat applications 6. Studies with significant rainfall in first 48 hours should be discounted 7. 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

CA 9.5 Search methods

Date of initial search	22.08.2014
Date of most recent update to search	-
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 (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: Detailed Search Parameters for Toxicological and Toxicokinetic studies (CA 5.1 to 5.9)

Provider	Database	Justification	Limits applied
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.	None
	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.	
	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.	
	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.	
	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.	
	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.	
	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.	

Provider	Database	Justification	Limits applied
	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	
	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.	
	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.	
	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.	
	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	
	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.	

Provider	Database	Justification	Limits applied
	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	
	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.	
	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.	

* 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)
Total number of *summary records* retrieved after *all** searches of peer-reviewed literature (excluding duplicates)	1059
Number of *summary records* excluded from the search results after rapid assessment for relevance	940
Total number of *full-text* documents assessed in detail	119
Number of *studies* excluded from further consideration after detailed assessment for relevance	86
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	33

*both from bibliographic databases and other sources of peer-reviewed literature

For the initial rapid assessment, study titles were scanned to identify the relevance of studies for mammalian toxicology. Studies dismissed immediately included those clearly not related to toxicology and those unambiguously belonging to other section (ecotoxicology, residue data). In some cases the title did not provide sufficient information to dismiss the reference and in these cases the abstract was checked to confirm whether the full paper should be reviewed.

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				
Not applicabl e	Gordon A	2012	Review of toxicological effects caused by episodic stressor exposure.	Environmental Toxicology and Chemistry, (May 2012) Vol. 31, No. 5, pp. 1169-1174.
Not applicabl e	Pressman J	2010	Concentration, Chlorination, and Chemical Analysis of Drinking Water for Disinfection Byproduct Mixtures Health Effects Research: U.S. EPA's Four Lab Study	Environmental Science & Technology (2010), 44 (19), 7184-7192.
CA 5.1	Endo S	2011	Serum Albumin Binding of Structurally Diverse Neutral Organic Compounds: Data and Models	Chemical Research in Toxicology (2011), 24(12), 2293-2301.
CA 5.2.6	Gorski J	2012	An in vitro method for detecting chemical sensitization using human reconstructed skin models and its applicability to cosmetic, pharmaceutical, and medical device safety testing.	Cutaneous and Ocular Toxicology, (December 2012) Vol. 31, No. 4, pp. 292-305.
CA 5.3.2	Zhou M	2009	Observation on toxicity experiment of S-metolachlor	Zhiye Yu Jiankang (2009), 25(24), 2657-2661
CA 5.3.3	Val S *et al.*	2011	Role of size and composition of traffic and agricultural aerosols in the molecular responses triggered in airway epithelial cells.	Inhalation Toxicology (2011), 23 (11), 627-640.
CA 5.3.3	Val S *et al.*	2011	Role of size and composition of traffic and agricultural aerosols in the molecular responses triggered in airway epithelial cells [Erratum to document cited in CA156:382398]	Inhalation Toxicology (2011), 23 (14), 957.

CA data point number	Author(s)	Year	Title	Source
CA 5.4.1	Nikoloff N *et al.*	2013	Comparative study of cytotoxic and genotoxic effects induced by herbicide S-metolachlor and its commercial formulation Twin Pack Gold® in human hepatoma (HepG2) cells.	Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association, (2013 Dec) Vol. 62, pp. 777-81.
CA 5.4.2	Bokan K *et al.*	2010	Application of the SMART mutagenicity test and an aquatic toxicity biotest on pesticides as environmental stressors.	Noevenytermeles (2010), Volume 59, Number Supplement, pp. 187-190.
CA 5.5	Kleinstreuer N, *et al.*	2013	In Vitro Perturbations of Targets in Cancer Hallmark Processes Predict Rodent Chemical Carcinogenesis	Toxicological Sciences (2013), 131(1), 40-55
CA 5.6.2	Kleinstreuer N, *et al.*	2011	Environmental impact on vascular development predicted by high-throughput screening.	Environmental Health Perspectives, (November 2011) Vol. 119, No. 11, pp. 1596-1603.
CA 5.6.2	Padilla S *et al.*	2012	Zebrafish developmental screening of the ToxCast Phase I chemical library	Reproductive Toxicology (2012), 33 (2), 174-187.
CA 5.6.2	Zhou B *et al.*	2008	Study on zebrafish embryo-toxicity of four pesticides	Zhejiang Gongye Daxue Xuebao (2008), 36 (2), 136-140.
CA 5.8.1	Kubatova A *et al*.	2006	Genotoxicity of polar fractions from a herbicide-contaminated soil does not correspond to parent contaminants.	Environmental Toxicology and Chemistry, (JUL 2006) Vol. 25, No. 7, pp. 1742-1745.
CA 5.8.1	Rodriguez C *et al.*	2012	Assessing health risks from pesticides in recycled water: a case study of augmentation of drinking water supplies in Perth, Western Australia.	Human and Ecological Risk Assessment (2012), Volume 18, Number 6, pp. 1216-1236
CA 5.8.2	Ait-Aissa S *et al.*	2010	Anti-androgenic activities of environmental pesticides in the MDA-kb2 reporter cell line	Toxicology in Vitro (2010), 24(7), 1979-1985.
CA 5.8.2	Baldwin W *et al.*	2009	A Concentration Addition Model for the Activation of the Constitutive Androstane Receptor by Xenobiotic Mixtures	Toxicological Sciences (2009), 107 (1), 93-105.
CA 5.8.2	Cho H-Y	2008	Study on the biochemical characterization of herbicide detoxification enzyme, glutathione S-transferase	BioFactors, (2007) Vol. 30, No. 4, pp. 281-7.
CA 5.8.2	Crettaz P	2004	In silico methods used in a weight of evidence approach for assessing the human health effects of plant protection products.	Toxicology and Applied Pharmacology, (JUN 15 2004) Vol. 197, No. 3, pp. 284.
CA 5.8.2	Cunningham A *et al*.	2009	A structure-activity relationship (SAR) analysis for the identification of environmental estrogens: the categorical-SAR (cat-SAR) approach	Endocrine Disruption Modeling (2009), 173-198.

CA data point number	Author(s)	Year	Title	Source
CA 5.8.2	Genter M *et al*.	2009	Comparison of rat olfactory mucosal responses to carcinogenic and non-carcinogenic chloracetanilides.	Food and chemical toxicology: an international journal published for the British Industrial Biological Research Association, (2009 Jun) Vol. 47, No. 6, pp. 1051-7.
CA 5.8.2	Genter M *et al.*	2010	Chloroacetanilide-induced nasal carcinogenesis in rats	Nose and Viral Cancer (2010), 427-434.
CA 5.8.2	Gohill V *et al.*	2010	Nutrient-sensitized screening for drugs that shift energy metabolism from mitochondrial respiration to glycolysis	Nature Biotechnology (2010), 28 (3), 249-255.
CA 5.8.2	Greenlee E *et al.*	2004	Low-dose agrochemicals and lawn-care pesticides induce developmental toxicity in murine preimplantation embryos.	Environmental health perspectives, (2004 May) Vol. 112, No. 6, pp. 703-9.
CA 5.8.2	Hartnett S *et al.*	2013	Cellular effects of metolachlor exposure on human liver (HepG2) cells.	Chemosphere, (2013 Jan) Vol. 90, No. 3, pp. 1258-66
CA 5.8.2	Hu J	2009	Immunotoxicity effect of metolachlor on mice	Harbin Yike Daxue Xuebao (2009), 43(1), 53-55
CA 5.8.2	Hu L-L *et al.*	2011	Predicting biological functions of compounds based on chemical-chemical interactions	PLoS One (2011), 6 (12), e29491.
CA 5.8.2	Judson R *et al*.	2010	In Vitro Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project	Environmental Health Perspectives (2010), 118 (4), 485-492.
CA 5.8.2	Kale V	2007	Mechanistic studies on hepatotoxicity of chloroacetanilide herbicides and hematotoxicity of munitions compound RDX and environmental degradation product MNX.	Dissertation Abstracts International. Vol. 68, no. 12. 2007
CA 5.8.2	Kale V *et al.*	2008	Comparative cytotoxicity of alachlor, acetochlor, and metolachlor herbicides in isolated rat and cryopreserved human hepatocytes.	Journal of biochemical and molecular toxicology, (2008 Feb) Vol. 22, No. 1, pp. 41-50.
CA 5.8.2	Kojima H *et al.*	2011	Comparative study of human and mouse pregnane X receptor agonistic activity in 200 pesticides using in vitro reporter gene assays	Toxicology (2011), 280(3), 77-87
CA 5.8.2	Kueblbeck J *et al.*	2011	Use of comprehensive screening methods to detect selective human CAR activators	Biochemical Pharmacology (2011), 82(12), 1994-2007
CA 5.8.2	Lemaire G *et al*.	2006	Activation of α- and β-estrogen receptors by persistent pesticides in reporter cell lines	Life Sciences (2006), 79(12), 1160-1169.
CA 5.8.2	Lemaire G *et al.*	2006	Identification of new human pregnane X receptor ligands among pesticides using a stable reporter cell system.	Toxicological sciences : an official journal of the Society of Toxicology, (2006 Jun) Vol. 91, No. 2, pp. 501-9.
CA 5.8.2	Leslie E	2005	Multidrug resistance proteins: Role of P-glycoprotein, MRP1, MRP2, and BCRP (ABCG2) in tissue defense.	Toxicology and Applied Pharmacology, (2005) Vol. 204, No. 3, pp. 216-237.

CA data point number	Author(s)	Year	Title	Source
CA 5.8.2	Lowry D *et al.*	2013	Mechanism of metolachlor action due to alterations in cell cycle progression	Cell biology and toxicology, (2013 Aug) Vol. 29, No. 4, pp. 283-91.
CA 5.8.2	Miranda S *et al.*	2007	Cytotoxicity of chloroacetanilide herbicide alachlor in HepG2 cells independent of CYP3A4 and CYP3A7	Food and Chemical Toxicology (2007), 45 (5), 871-877.
CA 5.8.2	Oosterhuis B *at al.*	2008	Specific interactions of chloroacetanilide herbicides with human ABC transporter proteins.	Toxicology, (2008 Jun 3) Vol. 248, No. 1, pp. 45-51.
CA 5.8.2	Pereira S et al.	2009	Toxicity assessment of the herbicide metolachlor comparative effects on bacterial and mitochondrial model systems.	Toxicology in vitro : an international journal published in association with BIBRA, (2009 Dec) Vol. 23, No. 8, pp. 1585-90.
CA 5.8.2	Rotroff D *et al.*	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 (2010), 13(2-4), 329-346
CA 5.8.2	Sinclair C *et al.*	2006	Prioritization of pesticide environmental transformation products in drinking water supplies	ENVIRONMENTAL SCIENCE & TECHNOLOGY, (1 DEC 2006) Vol. 40, No. 23, pp. 7283-7289.
CA 5.8.2	Sipes N *et al.*	2013	Profiling 976 ToxCast Chemicals across 331 Enzymatic and Receptor Signaling Assays	Chemical Research in Toxicology (2013), 26 (6), 878-895.
CA 5.8.2	Smital T	2011	Assessment of toxicological profiles of the municipal wastewater effluents using chemical analyses and bioassays	Ecotoxicology and Environmental Safety (2011), 74 (4), 844-851.
CA 5.8.2	Takeuchi S *et al.*	2006	In vitro screening of 200 pesticides for agonistic activity via mouse peroxisome proliferator-activated receptor (PPAR)α and PPARγ and quantitative analysis of in vivo induction pathway	Toxicology and Applied Pharmacology (2006), 217 (3), 235-244
CA 5.8.2	Takeuchi S *et al.*	2008	In vitro screening for aryl hydrocarbon receptor agonistic activity in 200 pesticides using a highly sensitive reporter cell line, DR-EcoScreen cells, and in vivo mouse liver cytochrome P450-1A induction by propanil, diuron and linuron	Chemosphere (2008), 74(1), 155-165
CA 5.8.2	Toccalino P *et al.*	2012	Chemical mixtures in untreated water from public-supply wells in the U.S. - Occurrence, composition, and potential toxicity	Science of the Total Environment (2012), 431, 262-270.
CA 5.8.2	Yoshida M *et al.*	2013	Simulation of acute reference dose (ARfD) settings for pesticides in Japan	Journal of Toxicological Sciences (2013), 38 (2), 205-214.
CA 5.8.3	Bishop P *et al.*	2014	The Use and Acceptance of Other Scientifically Relevant Information (OSRI) in the U.S. Environmental Protection Agency (EPA) Endocrine Disruptor Screening Program	Birth Defects Research, Part B: Developmental and Reproductive Toxicology (2014), 101 (1), 3-22.

CA data point number	Author(s)	Year	Title	Source
CA 5.8.3	Hayes T	2006	Chemical mixtures: Hayes responds [4].	Environmental Health Perspectives, (Sep 2006) Vol. 114, No. 9, pp. A518-A519.
CA 5.8.3	Jarosova B *et al.*	2012	Changes in concentrations of hydrophilic organic contaminants and of endocrine-disrupting potential downstream of small communities located adjacent to headwaters	Environment International (2012), 45, 22-31.
CA 5.8.2	Kojima H *et al.*	2004	Screening for estrogen and androgen receptor activities in 200 pesticides by in vitro reporter gene assays using chinese hamster ovary cells	Environmental Health Perspectives (2004), 112 (5), 524-531.
CA 5.8.2	Laville N *et al*.	2006	Modulation of aromatase activity and mRNA by various selected pesticides in the human choriocarcinoma JEG-3 cell line.	Toxicology, (2006 Nov 10) Vol. 228, No. 1, pp. 98-108.
CA 5.8.3	Mathias *F et al.*	2012	Herbicide Metolachlor Causes Changes in Reproductive Endocrinology of Male Wistar Rats	ISRN Toxicology (2012) 130846.
CA 5.8.3	Mnif W	2011	Effect of endocrine disruptor pesticides: A review.	International Journal of Environmental Research and Public Health, (June 2011) Vol. 8, No. 6, pp. 2265-2303.
CA 5.8.3	Reif D *et al*.	2010	Endocrine profiling and prioritization of environmental chemicals using ToxCast data.	Environmental Health Perspectives (2010), 118(12), 1714-1720.
CA 5.8.3	Rotroff D *et al.*	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 5.8.3	Wambaugh J *et al*.	2013	High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project.	Environmental Science & Technology (2013), 47 (15), 8479-8488.
CA 5.9.2	Beard J *et al.*	2011	Suicide and pesticide use among pesticide applicators and their spouses in the Agricultural Health Study.	Environmental Health Perspectives, (November 2011) Vol. 119, No. 11, pp. 1610-1615.
CA 5.9.2	Hsu B-G	2009	Late-onset Methemoglobinemia Induced by Metobromuron/metolachlor.	Tzu Chi Medical Journal, (December 2009) Vol. 21, No. 4, pp. 334-338
CA 5.9.4	Alavanja M *et al.*	2004	Pesticides and lung cancer risk in the agricultural health study cohort.	American journal of epidemiology, (2004 Nov 1) Vol. 160, No. 9, pp. 876-85.
CA 5.9.4	Andreotti G *et al.*	2009	Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort	International Journal of Cancer (2009), 124(10), 2495-2500
CA 5.9.4	Andreotti G *et al.*	2010	Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Study cohort.	Cancer causes & control: CCC, (2010 Nov) Vol. 21, No. 11, pp. 1759-75.
CA 5.9.4	Barr D	2010	Pesticide concentrations in maternal and umbilical cord sera and their relation to birth outcomes in a population of pregnant women and newborns in New Jersey.	The Science of the total environment, (2010 Jan 15) Vol. 408, No. 4, pp. 790-5.

CA data point number	Author(s)	Year	Title	Source
CA 5.9.4	Barry K *et al.*	2011	Genetic variation in base excision repair pathway genes, pesticide exposure, and prostate cancer risk	Environmental Health Perspectives (2011), 119(12), 1726-1732
CA 5.9.4	Bonner M *et al.*	2005	The Agricultural Health Study biomarker workshop on cancer etiology.	Journal of Biochemical and Molecular Toxicology, (2005) Vol. 19, No. 3, pp. 169-171.
CA 5.9.4	Dayton S *et al.*	2010	Pesticide use and myocardial infarction incidence among farm women in the agricultural health study.	Journal of Occupational and Environmental Medicine, (July 2010) Vol. 52, No. 7, pp. 693-697.
CA 5.9.4	Dennis L *et al.*	2010	Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural heath study	Environmental Health Perspectives (2010), 118(6), 812-817
CA 5.9.4	Fantke P *et al.*	2012	Health impact and damage cost assessment of pesticides in Europe	Environment International (2012), 49, 9-17.
CA 5.9.4	Flower K *et al*.	2004	Cancer risk and parental pesticide application in children of agricultural health study participants	Environmental Health Perspectives (2004), 112(5), 631-635.
CA 5.9.4	Freeman L *et al*.	2011	Atrazine and cancer incidence among pesticide applicators in the agricultural health study (1994-2007)	Environmental Health Perspectives (2011), 119 (9), 1253-1259.
CA 5.9.4	Gallois J	2011	DNA adduct variations in non-smoking crop farmers: Potential relationship with occupational exposure to pesticides?	Environmental Toxicology and Pharmacology, (July 2011) Vol. 32, No. 1, pp. 1-9.
CA 5.9.4	Hoppin J *et al.*	2006	Pesticides and adult respiratory outcomes in the agricultural health study.	Annals of the New York Academy of Sciences, (Sep 2006) Vol. 1076, pp. 343-354.
CA 5.9.4	Hou L	2013	Lifetime pesticide use and telomere shortening among male pesticide applicators in the Agricultural Health Study.	Environmental health perspectives, (2013 Aug) Vol. 121, No. 8, pp. 919-24.
CA 5.9.4	Huijbregts M *et al.*	2005	Human toxicological effect and damage factors of carcinogenic and noncarcinogenic chemicals for life cycle impact assessment	Integrated Environmental Assessment and Management (2005), 1(3), 181-244.
CA 5.9.4	Kamel F *et al.*	2012	Pesticide exposure and amyotrophic lateral sclerosis	NeuroToxicology (2012), 33(3), 457-462
CA 5.9.4	Koutros S *et al.*	2010	Pesticide Use Modifies the Association Between Genetic Variants on Chromosome 8q24 and Prostate Cancer	Cancer Research (2010), 70(22), 9224-9233
CA 5.9.4	Koutros S *et al.*	2011	Xenobiotic-metabolizing gene variants, pesticide use, and the risk of prostate cancer	Pharmacogenetics and Genomics (2011), 21(10), 615-623
CA 5.9.4	Koutros S	2013	Genetic susceptibility loci, pesticide exposure and prostate cancer risk	PLoS One (2013), 8 (4), e58195.
CA 5.9.4	Landgren O *et al.*	2009	Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study	Blood (2009), 113(25), 6386-6391

CA data point number	Author(s)	Year	Title	Source
CA 5.9.4	Lee W *et al.*	2004	Agricultural pesticide use and adenocarcinomas of the stomach and oesophagus	Occupational and Environmental Medicine (2004), 61(9), 743-749
CA 5.9.4	Lee W *et al.*	2005	Agricultural pesticide use and risk of glioma in Nebraska, United States	Occupational and Environmental Medicine (2005), 62(11), 786-792
CA 5.9.4	Lee W *et al.*	2007	Pesticide use and colorectal cancer risk in the Agricultural Health Study	International Journal of Cancer (2007), 121(2), 339-346
CA 5.9.4	Metayer C	2013	Exposure to herbicides in house dust and risk of childhood acute lymphoblastic leukemia	Journal of exposure science & environmental epidemiology, (2013 Jul) Vol. 23, No. 4, pp. 363-70
CA 5.9.4	Migeot V	2013	Drinking-water exposure to a mixture of nitrate and low-dose atrazine metabolites and small-for-gestational age (SGA) babies: A historic cohort study.	Environmental Research (2013), 122, 58-64.
CA 5.9.4	Pellizzari E	2004	Assessment of data quality for the NHEXAS - Part II: Minnesota children's pesticide exposure study (MNCPES). [Erratum to document cited in CA140:308309]	Journal of Exposure Analysis and Environmental Epidemiology (2004), 14(1), 108
CA 5.9.4	Perry M	2008	Effects of environmental and occupational pesticide exposure on human sperm: A systematic review.	Human Reproduction Update, (2008) Vol. 14, No. 3, pp. 233-242.
CA 5.9.4	Phillips K	2008	Human exposure to endocrine disrupters and semen quality.	Journal of Toxicology and Environmental Health - Part B: Critical Reviews, (Mar 2008) Vol. 11, No. 3-4, pp. 188-220.
CA 5.9.4	Red R	2011	Environmental toxicant exposure during pregnancy.	Obstetrical and Gynecological Survey, (March 2011) Vol. 66, No. 3, pp. 159-169.
CA 5.9.4	Rosenfeld P *et al.*	2011	Pesticides.	Rosenfeld, PE; Feng, LGH. (2011) pp. 127-154. Risks of Hazardous Wastes.
CA 5.9.4	Ruder A *et al.*	2004	Gliomas and farm pesticide exposure in men: The upper midwest health study.	Archives of Environmental Health, (Dec 2004) Vol. 59, No. 12, pp. 650-657.
CA 5.9.4	Rusiecki J *et al.*	2005	Cancer incidence among pesticide applicators exposed to metolachlor in the agricultural health study	EPIDEMIOLOGY, (SEP 2005) Vol. 16, No. 5, pp. S98-S98.
CA 5.9.4	Rusiecki J	2006	Cancer incidence among pesticide applicators exposed to metolachlor in the Agricultural Health Study.	International journal of cancer. Journal international du cancer, (2006 Jun 15) Vol. 118, No. 12, pp. 3118-23.
CA 5.9.4	Sathiakumar N *et al.*	2011	A review of epidemiologic studies of triazine herbicides and cancer.	Critical Reviews in Toxicology, (April 2011) Vol. 41, No. SUPPL. 1, pp. 1-34.

CA data point number	Author(s)	Year	Title	Source
CA 5.9.4	Slager R	2010	Rhinitis associated with pesticide use among private pesticide applicators in the agricultural health study.	Journal of toxicology and environmental health. Part A, (2010) Vol. 73, No. 20, pp. 1382-93.
CA 5.9.4	Thorpe N	2005	Herbicides and nitrates in groundwater of Maryland and childhood cancers: a geographic information systems approach.	Journal of environmental science and health. Part C, Environmental carcinogenesis & ecotoxicology reviews, (2005) Vol. 23, No. 2, pp. 261-78.
CA 5.9.4	Wang N *et al.*	2012	Pollution level and human health risk assessment of some pesticides and polychlorinated biphenyls in Nantong of Southeast China.	Journal of Environmental Sciences (2012), Volume 24, Number 10, pp.1854-1860.
CA 5.9.4	Weichenthal *et al.*	2010	A review of pesticide exposure and cancer incidence in the Agricultural Health Study cohort.	Environmental health perspectives, (2010 Aug) Vol. 118, No. 8, pp. 1117-25.
CA 5.9.4	Wells K et al.	2010	Development of a gis-based model for estimating residential agricultural pesticide exposure and its application to a study of prostate cancer incidence and pesticide exposure.	American Journal of Epidemiology, (JUN 1 2010) Vol. 171, No. Suppl. 11, pp. S84.
CA 5.9.4	Wickerham E et al.	2012	Reduced birth weight in relation to pesticide mixtures detected in cord blood of full-term infants.	Environment International, (OCT 15 2012) Vol. 47, pp. 80-85.
CA 5.9.4	Wofford P et al.	2014	Community air monitoring for pesticides. Part 3: using health-based screening levels to evaluate results collected for a year.	Environmental monitoring and assessment, (2014 Mar) Vol. 186, No. 3, pp. 1355-70.
CA 5.9.4	Yan X *et al.*	2009	Pesticide concentrations in matrices collected in the perinatal period in a population of pregnant women and newborns in New Jersey, USA	Human and Ecological Risk Assessment (2009), 15(5), 948-967
CA 5.9.7	Seok S-J *et al.*	2012	Acute oral poisoning due to chloracetanilide herbicides.	Journal of Korean medical science, (2012 Feb) Vol. 27, No. 2, pp. 111-4.
CP 7.2.1.2,	Hayat K. *et al.*	2010	Determination of pesticide residues in blood samples of villagers involved in pesticide application at District Vehari (Punjab), Pakistan	African Journal of Environmental Science and Technology Vol. 4(10), pp. 666-684, October 2010
CP 7.2.1.2, CP 7.2.3.2	Panuwet P. *et al.*	2008	Concentrations of urinary pesticide metabolites in small-scale farmers in Chiang Mai Province, Thailand.	Sci. Total Environ. (2008 Dec) 15;407(1):655-68
CP 7.2.1.2, CP 7.2.2.2, CP 7.2.3.2	Curwin B. et al.	2005	Urinary and hand wipe pesticide levels among farmers and nonfarmers in Iowa	Journal of Exposure Analysis and Environmental Epidemiology (2005) 15, 500–508

CA data point number	Author(s)	Year	Title	Source
CP 7.2.1.2, CP 7.2.2.2, CP 7.2.3.2	Curwin B. et al.	2007	Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in iowa.	Ann. Occup. Hyg. (2007 Jan);51(1):53-65
CP 7.2.1.2, CP 7.2.3.2	Schummer C. et al.	2012	Determination of farm workers' exposure to pesticides by hair analysis.	Toxicol. Lett. (2012 Apr) 25;210(2):203-10
CP 7.2.1.2, CP 7.2.3.2	Arcury T. et al.	2010	Repeated pesticide exposure among North Carolina migrant and seasonal farmworkers	Am. J. Ind. Med. (2010 Aug);53(8):802-13
CP 7.2.1.2, CP 7.2.3.2	Arcury T. et al.	2009	Seasonal Variation in the Measurement of Urinary Pesticide Metabolites among Latino Farmworkers in Eastern North Carolina	Int. J. Occup. Environ. Health. (2009 Oct–Dec); 15(4): 339–350
CP 7.2.2.2	Curwin B. et al.	2005	Pesticide contamination inside farm and nonfarm homes.	J. Occup. Environ. Hyg. (2005 Jul);2(7):357-67
CP 7.2.2.2	Ward M. et al.	2006	Proximity to crops and residential exposure to agricultural herbicides in iowa.	Environ. Health Perspect. 2006 Jun;114(6):893-7
CP 7.2.2.2	Curwin B. et al.	2007	Pesticide dose estimates for children of Iowa farmers and non-farmers	Environmental Research, Volume 105, Issue 3, (November 2007), Pages 307–315
CP 7.2.2.2	Arcury T. et al.	2007	Pesticide urinary metabolite levels of children in eastern North Carolina farmworker households.	Environ. Health Perspect. (2007 Aug);115(8):1254-60
CP 7.2.2.2	Aulagnier F et al.	2008	Pesticides measured in air and precipitation in the Yamaska Basin (Québec): occurrence and concentrations in 2004.	Sci. Total Environ. (2008 May) 15;394 (2-3) 338-48
CP 7.2.2.2	Peck A. et al.	2005	Gas-Phase Concentrations of Current-Use Pesticides in Iowa	Environ. Sci. Technol. (**2005**), 39, 2952-2959
CA 5.9.4	Swan	2003	Semen Quality in Relation to Biomarkers of Pesticide Exposure	Environmental Health Perspectives, vol 111, 12 September 2003.
CA 5.9.4	Munger	2007	Intrauterine Growth Retardation in Iowa Communities with Herbicide-contaminated Drinking Water Supplies	Environmental Health Perspectives, Volume 105, Number 3, March 1997
CA 5.9.4	Chevrier Gwendolina	2011	Urinary biomarkers of prenatal atrazine exposure and adverse birth outcomes in the PELAGIE birth cohort.	Environmental health perspectives, (2011 Jul) Vol. 119, No. 7, pp. 1034-41.
CA 5.9.4	Alavanja M *et al.*	2003	Use of Agricultural Pesticides and Prostate Cancer Risk in the Agricultural Health Study Cohort	Am J Epidemiol 2003;157:800–814

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				
Ait-Aissa S *et al.*	2010	CA 5.8.2	Anti-androgenic activities of environmental pesticides in the MDA-kb2 reporter cell line	Toxicology in Vitro (2010), 24(7), 1979-1985.
Alavanja M *et al.*	2003	CA 5.9.4	Use of Agricultural Pesticides and Prostate Cancer Risk in the Agricultural Health Study Cohort	Am J Epidemiol 2003;157:800–814
Alavanja M *et al.*	2004	CA 5.9.4	Pesticides and lung cancer risk in the agricultural health study cohort.	American journal of epidemiology, (2004 Nov 1) Vol. 160, No. 9, pp. 876-85.
Andreotti G *et al.*	2009	CA 5.9.4	Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort	International Journal of Cancer (2009), 124(10), 2495-2500
Andreotti G *et al.*	2010	CA 5.9.4	Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Study cohort.	Cancer causes & control: CCC, (2010 Nov) Vol. 21, No. 11, pp. 1759-75.
Arcury T. et al.	2007	CP 7.2.2.2	Pesticide urinary metabolite levels of children in eastern North Carolina farmworker households.	Environ. Health Perspect. (2007 Aug);115(8):1254-60
Arcury T. et al.	2010	CP 7.2.1.2, CP 7.2.3.2	Repeated pesticide exposure among North Carolina migrant and seasonal farmworkers	Am. J. Ind. Med. (2010 Aug);53(8):802-13
Arcury T. et al.	2009	CP 7.2.1.2, CP 7.2.3.2	Seasonal Variation in the Measurement of Urinary Pesticide Metabolites among Latino Farmworkers in Eastern North Carolina	Int. J. Occup. Environ. Health. (2009 Oct–Dec); 15(4): 339–350
Aulagnier F et al.	2008	CP 7.2.2.2	Pesticides measured in air and precipitation in the Yamaska Basin (Québec): occurrence and concentrations in 2004.	Sci. Total Environ. (2008 May) 15;394 (2-3) 338-48
Baldwin W *et al.*	2009	CA 5.8.2	A Concentration Addition Model for the Activation of the Constitutive Androstane Receptor by Xenobiotic Mixtures	Toxicological Sciences (2009), 107 (1), 93-105.
Barr D	2010	CA 5.9.4	Pesticide concentrations in maternal and umbilical cord sera and their relation to birth outcomes in a population of pregnant women and newborns in New Jersey.	The Science of the total environment, (2010 Jan 15) Vol. 408, No. 4, pp. 790-5.
Barry K *et al.*	2011	CA 5.9.4	Genetic variation in base excision repair pathway genes, pesticide exposure, and prostate cancer risk	Environmental Health Perspectives (2011), 119(12), 1726-1732
Beard J *et al.*	2011	CA 5.9.2	Suicide and pesticide use among pesticide applicators and their spouses in the Agricultural Health Study.	Environmental Health Perspectives, (November 2011) Vol. 119, No. 11, pp. 1610-1615.
Bishop P *et al.*	2014	CA 5.8.3	The Use and Acceptance of Other Scientifically Relevant Information (OSRI) in the U.S. Environmental Protection Agency (EPA) Endocrine Disruptor Screening Program	Birth Defects Research, Part B: Developmental and Reproductive Toxicology (2014), 101 (1), 3-22.

Author(s)	Year	CA data point number	Title	Source
Bokan K *et al.*	2010	CA 5.4.2	Application of the SMART mutagenicity test and an aquatic toxicity biotest on pesticides as environmental stressors.	Noevenytermeles (2010), Volume 59, Number Supplement, pp. 187-190.
Bonner M *et al.*	2005	CA 5.9.4	The Agricultural Health Study biomarker workshop on cancer etiology.	Journal of Biochemical and Molecular Toxicology, (2005) Vol. 19, No. 3, pp. 169-171.
Chevrier Gwendolina	2011	CA 5.9.4	Urinary biomarkers of prenatal atrazine exposure and adverse birth outcomes in the PELAGIE birth cohort.	Environmental health perspectives, (2011 Jul) Vol. 119, No. 7, pp. 1034-41.
Cho H-Y	2008	CA 5.8.2	Study on the biochemical characterization of herbicide detoxification enzyme, glutathione S-transferase	BioFactors, (2007) Vol. 30, No. 4, pp. 281-7.
Crettaz P	2004	CA 5.8.2	In silico methods used in a weight of evidence approach for assessing the human health effects of plant protection products.	Toxicology and Applied Pharmacology, (JUN 15 2004) Vol. 197, No. 3, pp. 284.
Cunningham A *et al.*	2009	CA 5.8.2	A structure-activity relationship (SAR) analysis for the identification of environmental estrogens: the categorical-SAR (cat-SAR) approach	Endocrine Disruption Modeling (2009), 173-198.
Curwin B. et al.	2005	CP 7.2.2.2	Pesticide contamination inside farm and nonfarm homes.	J. Occup. Environ. Hyg. (2005 Jul);2(7):357-67
Curwin B. et al.	2005	CP 7.2.1.2, CP 7.2.2.2, CP 7.2.3.2	Urinary and hand wipe pesticide levels among farmers and nonfarmers in Iowa	Journal of Exposure Analysis and Environmental Epidemiology (2005) 15, 500–508
Curwin B. et al.	2007	CP 7.2.2.2	Pesticide dose estimates for children of Iowa farmers and non-farmers	Environmental Research, Volume 105, Issue 3, (November 2007), Pages 307–315
Curwin B. et al.	2007	CP 7.2.1.2, CP 7.2.2.2, CP 7.2.3.2	Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in iowa.	Ann. Occup. Hyg. (2007 Jan);51(1):53-65
Dayton S *et al.*	2010	CA 5.9.4	Pesticide use and myocardial infarction incidence among farm women in the agricultural health study.	Journal of Occupational and Environmental Medicine, (July 2010) Vol. 52, No. 7, pp. 693-697.
Dennis L *et al.*	2010	CA 5.9.4	Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural heath study	Environmental Health Perspectives (2010), 118(6), 812-817
Endo S	2011	CA 5.1	Serum Albumin Binding of Structurally Diverse Neutral Organic Compounds: Data and Models	Chemical Research in Toxicology (2011), 24(12), 2293-2301.
Fantke P *et al.*	2012	CA 5.9.4	Health impact and damage cost assessment of pesticides in Europe	Environment International (2012), 49, 9-17.
Flower K *et al.*	2004	CA 5.9.4	Cancer risk and parental pesticide application in children of agricultural health study participants	Environmental Health Perspectives (2004), 112(5), 631-635.

Author(s)	Year	CA data point number	Title	Source
Freeman L *et al*.	2011	CA 5.9.4	Atrazine and cancer incidence among pesticide applicators in the agricultural health study (1994-2007)	Environmental Health Perspectives (2011), 119 (9), 1253-1259.
Gallois J	2011	CA 5.9.4	DNA adduct variations in non-smoking crop farmers: Potential relationship with occupational exposure to pesticides?	Environmental Toxicology and Pharmacology, (July 2011) Vol. 32, No. 1, pp. 1-9.
Genter M *et al*.	2009	CA 5.8.2	Comparison of rat olfactory mucosal responses to carcinogenic and non-carcinogenic chloracetanilides.	Food and chemical toxicology: an international journal published for the British Industrial Biological Research Association, (2009 Jun) Vol. 47, No. 6, pp. 1051-7.
Genter M *et al.*	2010	CA 5.8.2	Chloroacetanilide-induced nasal carcinogenesis in rats	Nose and Viral Cancer (2010), 427-434.
Gohill V *et al.*	2010	CA 5.8.2	Nutrient-sensitized screening for drugs that shift energy metabolism from mitochondrial respiration to glycolysis	Nature Biotechnology (2010), 28 (3), 249-255.
Gordon A	2012	Not applicable	Review of toxicological effects caused by episodic stressor exposure.	Environmental Toxicology and Chemistry, (May 2012) Vol. 31, No. 5, pp. 1169-1174.
Gorski J	2012	CA 5.2.6	An in vitro method for detecting chemical sensitization using human reconstructed skin models and its applicability to cosmetic, pharmaceutical, and medical device safety testing.	Cutaneous and Ocular Toxicology, (December 2012) Vol. 31, No. 4, pp. 292-305.
Greenlee E *et al.*	2004	CA 5.8.2	Low-dose agrochemicals and lawn-care pesticides induce developmental toxicity in murine preimplantation embryos.	Environmental health perspectives, (2004 May) Vol. 112, No. 6, pp. 703-9.
Hartnett S *et al.*	2013	CA 5.8.2	Cellular effects of metolachlor exposure on human liver (HepG2) cells.	Chemosphere, (2013 Jan) Vol. 90, No. 3, pp. 1258-66
Hayat K. *et al.*	2010	CP 7.2.1.2,	Determination of pesticide residues in blood samples of villagers involved in pesticide application at District Vehari (Punjab), Pakistan	African Journal of Environmental Science and Technology Vol. 4(10), pp. 666-684, October 2010
Hayes T	2006	CA 5.8.3	Chemical mixtures: Hayes responds [4].	Environmental Health Perspectives, (Sep 2006) Vol. 114, No. 9, pp. A518-A519.
Hoppin J *et al.*	2006	CA 5.9.4	Pesticides and adult respiratory outcomes in the agricultural health study.	Annals of the New York Academy of Sciences, (Sep 2006) Vol. 1076, pp. 343-354.
Hou L	2013	CA 5.9.4	Lifetime pesticide use and telomere shortening among male pesticide applicators in the Agricultural Health Study.	Environmental health perspectives, (2013 Aug) Vol. 121, No. 8, pp. 919-24.
Hsu B-G	2009	CA 5.9.2	Late-onset Methemoglobinemia Induced by Metobromuron/metolachlor.	Tzu Chi Medical Journal, (December 2009) Vol. 21, No. 4, pp. 334-338
Hu J	2009	CA 5.8.2	Immunotoxicity effect of metolachlor on mice	Harbin Yike Daxue Xuebao (2009), 43(1), 53-55

Author(s)	Year	CA data point number	Title	Source
Hu L-L *et al.*	2011	CA 5.8.2	Predicting biological functions of compounds based on chemical-chemical interactions	PLoS One (2011), 6 (12), e29491.
Huijbregts M *et al.*	2005	CA 5.9.4	Human toxicological effect and damage factors of carcinogenic and noncarcinogenic chemicals for life cycle impact assessment	Integrated Environmental Assessment and Management (2005), 1(3), 181-244.
Kleinstreuer N, *et al.*	2011	CA 5.6.2	Environmental impact on vascular development predicted by high-throughput screening.	Environmental Health Perspectives, (November 2011) Vol. 119, No. 11, pp. 1596-1603.
Kleinstreuer N, *et al.*	2013	CA 5.5	In Vitro Perturbations of Targets in Cancer Hallmark Processes Predict Rodent Chemical Carcinogenesis	Toxicological Sciences (2013), 131(1), 40-55
Kubatova A *et al.*	2006	CA 5.8.1	Genotoxicity of polar fractions from a herbicide-contaminated soil does not correspond to parent contaminants.	Environmental Toxicology and Chemistry, (JUL 2006) Vol. 25, No. 7, pp. 1742-1745.
Jarosova B *et al.*	2012	CA 5.8.3	Changes in concentrations of hydrophilic organic contaminants and of endocrine-disrupting potential downstream of small communities located adjacent to headwaters	Environment International (2012), 45, 22-31.
Judson R *et al.*	2010	CA 5.8.2	In Vitro Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project	Environmental Health Perspectives (2010), 118 (4), 485-492.
Kale V	2007	CA 5.8.2	Mechanistic studies on hepatotoxicity of chloroacetanilide herbicides and hematotoxicity of munitions compound RDX and environmental degradation product MNX.	Dissertation Abstracts International. Vol. 68, no. 12. 2007
Kale V *et al.*	2008	CA 5.8.2	Comparative cytotoxicity of alachlor, acetochlor, and metolachlor herbicides in isolated rat and cryopreserved human hepatocytes.	Journal of biochemical and molecular toxicology, (2008 Feb) Vol. 22, No. 1, pp. 41-50.
Kamel F *et al.*	2012	CA 5.9.4	Pesticide exposure and amyotrophic lateral sclerosis	NeuroToxicology (2012), 33(3), 457-462
Kojima H *et al.*	2004	CA 5.8.2	Screening for estrogen and androgen receptor activities in 200 pesticides by in vitro reporter gene assays using chinese hamster ovary cells	Environmental Health Perspectives (2004), 112 (5), 524-531.
Kojima H *et al.*	2011	CA 5.8.2	Comparative study of human and mouse pregnane X receptor agonistic activity in 200 pesticides using in vitro reporter gene assays	Toxicology (2011), 280(3), 77-87
Koutros S *et al.*	2010	CA 5.9.4	Pesticide Use Modifies the Association Between Genetic Variants on Chromosome 8q24 and Prostate Cancer	Cancer Research (2010), 70(22), 9224-9233
Koutros S *et al.*	2011	CA 5.9.4	Xenobiotic-metabolizing gene variants, pesticide use, and the risk of prostate cancer	Pharmacogenetics and Genomics (2011), 21(10), 615-623
Koutros S	2013	CA 5.9.4	Genetic susceptibility loci, pesticide exposure and prostate cancer risk	PLoS One (2013), 8 (4), e58195.

Author(s)	Year	CA data point number	Title	Source
Kueblbeck J *et al.*	2011	CA 5.8.2	Use of comprehensive screening methods to detect selective human CAR activators	Biochemical Pharmacology (2011), 82(12), 1994-2007
Landgren O *et al.*	2009	CA 5.9.4	Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study	Blood (2009), 113(25), 6386-6391
Laville N *et al.*	2006	CA 5.8.2	Modulation of aromatase activity and mRNA by various selected pesticides in the human choriocarcinoma JEG-3 cell line.	Toxicology, (2006 Nov 10) Vol. 228, No. 1, pp. 98-108.
Lee W *et al.*	2004	CA 5.9.4	Agricultural pesticide use and adenocarcinomas of the stomach and oesophagus	Occupational and Environmental Medicine (2004), 61(9), 743-749
Lee W *et al.*	2005	CA 5.9.4	Agricultural pesticide use and risk of glioma in Nebraska, United States	Occupational and Environmental Medicine (2005), 62(11), 786-792
Lee W *et al.*	2007	CA 5.9.4	Pesticide use and colorectal cancer risk in the Agricultural Health Study	International Journal of Cancer (2007), 121(2), 339-346
Lemaire G *et al*.	2006	CA 5.8.2	Activation of α- and β-estrogen receptors by persistent pesticides in reporter cell lines	Life Sciences (2006), 79(12), 1160-1169.
Lemaire G *et al.*	2006	CA 5.8.2	Identification of new human pregnane X receptor ligands among pesticides using a stable reporter cell system.	Toxicological sciences : an official journal of the Society of Toxicology, (2006 Jun) Vol. 91, No. 2, pp. 501-9.
Leslie E	2005	CA 5.8.2	Multidrug resistance proteins: Role of P-glycoprotein, MRP1, MRP2, and BCRP (ABCG2) in tissue defense.	Toxicology and Applied Pharmacology, (2005) Vol. 204, No. 3, pp. 216-237.
Lowry D *et al.*	2013	CA 5.8.2	Mechanism of metolachlor action due to alterations in cell cycle progression	Cell biology and toxicology, (2013 Aug) Vol. 29, No. 4, pp. 283-91.
Mathias *F et al.*	2012	CA 5.8.3	Herbicide Metolachlor Causes Changes in Reproductive Endocrinology of Male Wistar Rats	ISRN Toxicology (2012) 130846.
Metayer C	2013	CA 5.9.4	Exposure to herbicides in house dust and risk of childhood acute lymphoblastic leukemia	Journal of exposure science & environmental epidemiology, (2013 Jul) Vol. 23, No. 4, pp. 363-70
Migeot V	2013	CA 5.9.4	Drinking-water exposure to a mixture of nitrate and low-dose atrazine metabolites and small-for-gestational age (SGA) babies: A historic cohort study.	Environmental Research (2013), 122, 58-64.
Miranda S *et al.*	2007	CA 5.8.2	Cytotoxicity of chloroacetanilide herbicide alachlor in HepG2 cells independent of CYP3A4 and CYP3A7	Food and Chemical Toxicology (2007), 45 (5), 871-877.
Mnif W	2011	CA 5.8.3	Effect of endocrine disruptor pesticides: A review.	International Journal of Environmental Research and Public Health, (June 2011) Vol. 8, No. 6, pp. 2265-2303.

Author(s)	Year	CA data point number	Title	Source
Munger	2007	CA 5.9.4	Intrauterine Growth Retardation in Iowa Communities with Herbicide-contaminated Drinking Water Supplies	Environmental Health Perspectives, Volume 105, Number 3, March 1997
Nikoloff N *et al.*	2013	CA 5.4.1	Comparative study of cytotoxic and genotoxic effects induced by herbicide S-metolachlor and its commercial formulation Twin Pack Gold® in human hepatoma (HepG2) cells.	Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association, (2013 Dec) Vol. 62, pp. 777-81.
Oosterhuis B *at al.*	2008	CA 5.8.2	Specific interactions of chloroacetanilide herbicides with human ABC transporter proteins.	Toxicology, (2008 Jun 3) Vol. 248, No. 1, pp. 45-51.
Padilla S *et al.*	2012	CA 5.6.2	Zebrafish developmental screening of the ToxCast Phase I chemical library	Reproductive Toxicology (2012), 33 (2), 174-187.
Panuwet P. *et al.*	2008	CP 7.2.1.2, CP 7.2.3.2	Concentrations of urinary pesticide metabolites in small-scale farmers in Chiang Mai Province, Thailand.	Sci. Total Environ. (2008 Dec) 15;407(1):655-68
Peck A. et al.	2005	CP 7.2.2.2	Gas-Phase Concentrations of Current-Use Pesticides in Iowa	Environ. Sci. Technol. (**2005**), 39, 2952-2959
Pellizzari E	2004	CA 5.9.4	Assessment of data quality for the NHEXAS - Part II: Minnesota children's pesticide exposure study (MNCPES). [Erratum to document cited in CA140:308309]	Journal of Exposure Analysis and Environmental Epidemiology (2004), 14(1), 108
Pereira S et al.	2009	CA 5.8.2	Toxicity assessment of the herbicide metolachlor comparative effects on bacterial and mitochondrial model systems.	Toxicology in vitro : an international journal published in association with BIBRA, (2009 Dec) Vol. 23, No. 8, pp. 1585-90.
Perry M	2008	CA 5.9.4	Effects of environmental and occupational pesticide exposure on human sperm: A systematic review.	Human Reproduction Update, (2008) Vol. 14, No. 3, pp. 233-242.
Phillips K	2008	CA 5.9.4	Human exposure to endocrine disrupters and semen quality.	Journal of Toxicology and Environmental Health - Part B: Critical Reviews, (Mar 2008) Vol. 11, No. 3-4, pp. 188-220.
Pressman J	2010	Not applicable	Concentration, Chlorination, and Chemical Analysis of Drinking Water for Disinfection Byproduct Mixtures Health Effects Research: U.S. EPA's Four Lab Study	Environmental Science & Technology (2010), 44 (19), 7184-7192.
Red R	2011	CA 5.9.4	Environmental toxicant exposure during pregnancy.	Obstetrical and Gynecological Survey, (March 2011) Vol. 66, No. 3, pp. 159-169.
Reif D *et al.*	2010	CA 5.8.3	Endocrine profiling and prioritization of environmental chemicals using ToxCast data.	Environmental Health Perspectives (2010), 118(12), 1714-1720.
Rodriguez C *et al.*	2012	CA 5.8.1	Assessing health risks from pesticides in recycled water: a case study of augmentation of drinking water supplies in Perth, Western Australia.	Human and Ecological Risk Assessment (2012), Volume 18, Number 6, pp. 1216-1236

Author(s)	Year	CA data point number	Title	Source
Rosenfeld P *et al.*	2011	CA 5.9.4	Pesticides.	Rosenfeld, PE; Feng, LGH. (2011) pp. 127-154. Risks of Hazardous Wastes.
Rotroff D *et al.*	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 (2010), 13(2-4), 329-346
Rotroff D *et al.*	2014	CA 5.8.3	Predictive Endocrine Testing in the 21st Century Using in Vitro Assays of Estrogen Receptor Signaling Responses.	Environmental Science & Technology (2014), 48 (15), 8706-8716.
Ruder A *et al.*	2004	CA 5.9.4	Gliomas and farm pesticide exposure in men: The upper midwest health study.	Archives of Environmental Health, (Dec 2004) Vol. 59, No. 12, pp. 650-657.
Rusiecki J *et al.*	2005	CA 5.9.4	Cancer incidence among pesticide applicators exposed to metolachlor in the agricultural health study	EPIDEMIOLOGY, (SEP 2005) Vol. 16, No. 5, pp. S98-S98.
Rusiecki J	2006	CA 5.9.4	Cancer incidence among pesticide applicators exposed to metolachlor in the Agricultural Health Study.	International journal of cancer. Journal international du cancer, (2006 Jun 15) Vol. 118, No. 12, pp. 3118-23.
Sathiakumar N *et al.*	2011	CA 5.9.4	A review of epidemiologic studies of triazine herbicides and cancer.	Critical Reviews in Toxicology, (April 2011) Vol. 41, No. SUPPL. 1, pp. 1-34.
Schummer C. et al.	2012	CP 7.2.1.2, CP 7.2.3.2	Determination of farm workers' exposure to pesticides by hair analysis.	Toxicol. Lett. (2012 Apr) 25;210(2):203-10
Seok S-J *et al.*	2012	CA 5.9.7	Acute oral poisoning due to chloracetanilide herbicides.	Journal of Korean medical science, (2012 Feb) Vol. 27, No. 2, pp. 111-4.
Sinclair C *et al.*	2006	CA 5.8.2	Prioritization of pesticide environmental transformation products in drinking water supplies	ENVIRONMENTAL SCIENCE & TECHNOLOGY, (1 DEC 2006) Vol. 40, No. 23, pp. 7283-7289.
Sipes N *et al.*	2013	CA 5.8.2	Profiling 976 ToxCast Chemicals across 331 Enzymatic and Receptor Signaling Assays	Chemical Research in Toxicology (2013), 26 (6), 878-895.
Slager R	2010	CA 5.9.4	Rhinitis associated with pesticide use among private pesticide applicators in the agricultural health study.	Journal of toxicology and environmental health. Part A, (2010) Vol. 73, No. 20, pp. 1382-93.
Smital T	2011	CA 5.8.2	Assessment of toxicological profiles of the municipal wastewater effluents using chemical analyses and bioassays	Ecotoxicology and Environmental Safety (2011), 74 (4), 844-851.
Swan	2003	CA 5.9.4	Semen Quality in Relation to Biomarkers of Pesticide Exposure	Environmental Health Perspectives, vol 111, 12 September 2003.
Takeuchi S *et al.*	2006	CA 5.8.2	In vitro screening of 200 pesticides for agonistic activity via mouse peroxisome proliferator-activated receptor (PPAR)α and PPARγ and quantitative analysis of in vivo induction pathway	Toxicology and Applied Pharmacology (2006), 217 (3), 235-244

Author(s)	Year	CA data point number	Title	Source
Takeuchi S *et al.*	2008	CA 5.8.2	In vitro screening for aryl hydrocarbon receptor agonistic activity in 200 pesticides using a highly sensitive reporter cell line, DR-EcoScreen cells, and in vivo mouse liver cytochrome P450-1A induction by propanil, diuron and linuron	Chemosphere (2008), 74(1), 155-165
Thorpe N	2005	CA 5.9.4	Herbicides and nitrates in groundwater of Maryland and childhood cancers: a geographic information systems approach.	Journal of environmental science and health. Part C, Environmental carcinogenesis & ecotoxicology reviews, (2005) Vol. 23, No. 2, pp. 261-78.
Toccalino P *et al.*	2012	CA 5.8.2	Chemical mixtures in untreated water from public-supply wells in the U.S. - Occurrence, composition, and potential toxicity	Science of the Total Environment (2012), 431, 262-270.
Val S *et al.*	2011	CA 5.3.3	Role of size and composition of traffic and agricultural aerosols in the molecular responses triggered in airway epithelial cells.	Inhalation Toxicology (2011), 23 (11), 627-640.
Val S *et al.*	2011	CA 5.3.3	Role of size and composition of traffic and agricultural aerosols in the molecular responses triggered in airway epithelial cells [Erratum to document cited in CA156:382398]	Inhalation Toxicology (2011), 23 (14), 957.
Wambaugh J *et al.*	2013	CA 5.8.3	High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project.	Environmental Science & Technology (2013), 47 (15), 8479-8488.
Wang N *et al.*	2012	CA 5.9.4	Pollution level and human health risk assessment of some pesticides and polychlorinated biphenyls in Nantong of Southeast China.	Journal of Environmental Sciences (2012), Volume 24, Number 10, pp.1854-1860.
Ward M. et al.	2006	CP 7.2.2.2	Proximity to crops and residential exposure to agricultural herbicides in iowa.	Environ. Health Perspect. 2006 Jun;114(6):893-7
Weichenthal *et al.*	2010	CA 5.9.4	A review of pesticide exposure and cancer incidence in the Agricultural Health Study cohort.	Environmental health perspectives, (2010 Aug) Vol. 118, No. 8, pp. 1117-25.
Wells K et al.	2010	CA 5.9.4	Development of a gis-based model for estimating residential agricultural pesticide exposure and its application to a study of prostate cancer incidence and pesticide exposure.	American Journal of Epidemiology, (JUN 1 2010) Vol. 171, No. Suppl. 11, pp. S84.
Wickerham E et al.	2012	CA 5.9.4	Reduced birth weight in relation to pesticide mixtures detected in cord blood of full-term infants.	Environment International, (OCT 15 2012) Vol. 47, pp. 80-85.
Wofford P et al.	2014	CA 5.9.4	Community air monitoring for pesticides. Part 3: using health-based screening levels to evaluate results collected for a year.	Environmental monitoring and assessment, (2014 Mar) Vol. 186, No. 3, pp. 1355-70.
Yan X *et al.*	2009	CA 5.9.4	Pesticide concentrations in matrices collected in the perinatal period in a population of pregnant women and newborns in New Jersey, USA	Human and Ecological Risk Assessment (2009), 15(5), 948-967

Author(s)	Year	CA data point number	Title	Source
Yoshida M *et al.*	2013	CA 5.8.2	Simulation of acute reference dose (ARfD) settings for pesticides in Japan	Journal of Toxicological Sciences (2013), 38 (2), 205-214.
Zhou B *et al.*	2008	CA 5.6.2	Study on zebrafish embryo-toxicity of four pesticides	Zhejiang Gongye Daxue Xuebao (2008), 36 (2), 136-140.
Zhou M	2009	CA 5.3.2	Observation on toxicity experiment of S-metolachlor	Zhiye Yu Jiankang (2009), 25(24), 2657-2661

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					
Not applicable	Gordon A	2012	Review of toxicological effects caused by episodic stressor exposure.	Environmental Toxicology and Chemistry, (May 2012) Vol. 31, No. 5, pp. 1169-1174.	On review this is a purely environmental toxicity paper, and not relevant to MCA section 5.
Not applicable	Pressman J	2010	Concentration, Chlorination, and Chemical Analysis of Drinking Water for Disinfection Byproduct Mixtures Health Effects Research: U.S. EPA's Four Lab Study	Environmental Science & Technology (2010), 44 (19), 7184-7192.	This paper looks at water disinfection processes and does not feature any toxicity data.
CA 5.1	Endo S	2011	Serum Albumin Binding of Structurally Diverse Neutral Organic Compounds: Data and Models	Chemical Research in Toxicology (2011), 24(12), 2293-2301.	This paper looks at serum albumin binding potential of a number of chemicals, and a log KBSA/w (BSA-water partition coefficient) of 1.74 is reported for metolachlor. This data does not alter any endpoints.
CA 5.2.6	Gorski J	2012	An in vitro method for detecting chemical sensitization using human reconstructed skin models and its applicability to cosmetic, pharmaceutical, and medical device safety testing.	Cutaneous and Ocular Toxicology, (December 2012) Vol. 31, No. 4, pp. 292-305.	Appears this was flagged in the search as metol, but has erroneously been indexed as metolachlor. There is no metolachlor data in this paper.
CA 5.3.3	Val S *et al.*	2011	Role of size and composition of traffic and agricultural aerosols in the molecular responses triggered in airway epithelial cells.	Inhalation Toxicology (2011), 23 (11), 627-640.	Neither this article, nor the erratum contain data on metolachlor/S-metolachlor. Metolachlor is simply mentioned in the title of one of the references.
CA 5.3.3	Val S *et al.*	2011	Role of size and composition of traffic and agricultural aerosols in the	Inhalation Toxicology (2011), 23 (14), 957.	Neither this erratum, nor the original journal article contain data on

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
			molecular responses triggered in airway epithelial cells [Erratum to document cited in CA156:382398]		metolachlor/S-metolachlor. Metolachlor is simply mentioned in the title of one of the references.
CA 5.4.2	Bokan K *et al.*	2010	Application of the SMART mutagenicity test and an aquatic toxicity biotest on pesticides as environmental stressors.	Noevenytermeles (2010), Volume 59, Number Supplement, pp. 187-190.	This publication looks at ecotoxicity and mutagenicity of specific samples of groundwater that are from a former industrial site and contain a number of pesticides, including very low levels of metolachlor. Given that this is a complex mixture with very little metolachlor content this data is not considered relevant for MCA section 5.
CA 5.5	Kleinstreuer N, *et al.*	2013	In Vitro Perturbations of Targets in Cancer Hallmark Processes Predict Rodent Chemical Carcinogenesis	Toxicological Sciences (2013), 131(1), 40-55	This paper compares Toxcast high-throughput screening output to in vivo rodent carcinogenicity data in the Toxicity Reference Database (ToxRefDB. No new *in vivo* data are presented.
CA 5.6.2	Kleinstreuer N, *et al.*	2011	Environmental impact on vascular development predicted by high-throughput screening.	Environmental Health Perspectives, (November 2011) Vol. 119, No. 11, pp. 1596-1603.	This paper attempts to link profiles from high throughput *in vitro* Toxcast data to developmental toxicity outcomes from the ToxRefDB dataset (i.e. the exiting metolachlor/S-metolachlor studies, which are included in the original EU review). As these *in vivo* data are already available the *in vitro* data reviewed is not considered relevant.
CA 5.6.2	Padilla S *et al.*	2012	Zebrafish developmental screening of the ToxCast Phase I chemical library	Reproductive Toxicology (2012), 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 *in vivo* mammalian data is presented.
CA 5.6.2	Zhou B *et al.*	2008	Study on zebrafish embryo-toxicity of four pesticides	Zhejiang Gongye Daxue Xuebao (2008), 36 (2), 136-140.	Paper described screening studies on zebrafish. No new *in vivo* mammalian data is presented.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.8.1	Kubatova A *et al*.	2006	Genotoxicity of polar fractions from a herbicide-contaminated soil does not correspond to parent contaminants.	Environmental Toxicology and Chemistry, (JUL 2006) Vol. 25, No. 7, pp. 1742-1745.	This study looked at the genotoxicity (by SOS chromotest) of herbicide contaminated soil rinsed with hot pressurised water. Several tested fractions of the contaminant soil extract were considered to be genotoxic in this assay. As the soil samples contained a mixture of herbicide residues any response cannot reliability by attributed to metolachlor.
CA 5.8.1	Rodriguez C *et al.*	2012	Assessing health risks from pesticides in recycled water: a case study of augmentation of drinking water supplies in Perth, Western Australia.	Human and Ecological Risk Assessment (2012), Volume 18, Number 6, pp. 1216-1236	No toxicology information is presented, not relevant for MCA section 5.
CA 5.8.2	Baldwin W *et al.*	2009	A Concentration Addition Model for the Activation of the Constitutive Androstane Receptor by Xenobiotic Mixtures	Toxicological Sciences (2009), 107 (1), 93-105.	This gene reporter assay paper demonstrated that metolachlor is able to active murine CAR, which is consistent with Omiecinski 2014 (MCA Section 5).
CA 5.8.2	Cho H-Y	2008	Study on the biochemical characterization of herbicide detoxification enzyme, glutathione S-transferase	BioFactors, (2007) Vol. 30, No. 4, pp. 281-7.	This paper looks at metolachlor activity towards glutathione-S-transferase (GST) in *E. coli* constructs containing the human pi class GST enzyme. As metolachlor is already known to be metabolised by GST *in vivo* this is not new information.
CA 5.8.2	Crettaz P	2004	In silico methods used in a weight of evidence approach for assessing the human health effects of plant protection products.	Toxicology and Applied Pharmacology, (JUN 15 2004) Vol. 197, No. 3, pp. 284.	This poster analyses DEREK for Windows output on dimethachlor and does not present any new data on metolachlor.
CA 5.8.2	Genter M *et al.*	2009	Comparison of rat olfactory mucosal responses to carcinogenic and non-carcinogenic chloracetanilides.	Food and chemical toxicology: an international journal published for the British Industrial Biological Research Association, (2009 Jun) Vol. 47, No. 6, pp. 1051-7.	This paper looks primarily at alachlor, butachlor and propachlor and does not present new data on metolachlor, which is mentioned as a comparator chloroacetanilide.
CA 5.8.2	Genter M *et al.*	2010	Chloroacetanilide-induced nasal carcinogenesis in rats	Nose and Viral Cancer (2010), 427-434.	This is review and as such does not present any new data.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.8.2	Gohill V *et al.*	2010	Nutrient-sensitized screening for drugs that shift energy metabolism from mitochondrial respiration to glycolysis	Nature Biotechnology (2010), 28 (3), 249-255.	Does not present metolachlor/S-metolachlor data in the paper, although it appears to be one of 3500 chemicals tested. The relevance of energy metabolism shift in cultured fibroblasts is considered of low relevance compared to the *in vivo* testing database.
CA 5.8.2	Hu L-L *et al.*	2011	Predicting biological functions of compounds based on chemical-chemical interactions	PLoS One (2011), 6 (12), e29491.	This is a very general paper looking at several thousand chemicals but has no specific information on metolachlor/S-metolachlor.
CA 5.8.2	Judson R *et al.*	2010	In Vitro Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project	Environmental Health Perspectives (2010), 118 (4), 485-492.	This is a general EPA approach for prioritisation of testing based on use of ToxCast data. Metolachlor/S-metolachlor are part of the underlying data set but are not discussed in this paper specifically.
CA 5.8.2	Kale V	2007	Mechanistic studies on hepatotoxicity of chloroacetanilide herbicides and hematotoxicity of munitions compound RDX and environmental degradation product MNX.	Dissertation Abstracts International. Vol. 68, no. 12. 2007	This dissertation investigated cytotoxicity of alachlor, acetochlor and metolachlor to rat and human isolated hepatocytes. Metolachlor was less cytotoxic that alachlor and acetochlor to rat hepatocytes, but similarly toxic to human cryopreserved hepatocytes. This is not considered relevant new data as Syngenta have conducted studies on rat and human hepatocytes (Elcombe 2014), and in fact it highlights cytotoxicity at lower concentrations that in Kale's analysis. As the female rat liver tumours have been demonstrated to be due to a CAR activating mode of action rather than resulting

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
					from regeneration of frank liver damage these *in vitro* findings are considered incidental.
CA 5.8.2	Kale V *et al.*	2008	Comparative cytotoxicity of alachlor, acetochlor, and metolachlor herbicides in isolated rat and cryopreserved human hepatocytes.	Journal of biochemical and molecular toxicology, (2008 Feb) Vol. 22, No. 1, pp. 41-50.	This investigation is similar to Kale 2007, and looks are alachlor, acetochlor and metolachlor cytotoxicity in rat and human hepatocytes. Metolachlor was less cytotoxic that alachlor and acetochlor to rat hepatocytes, but similarly toxic to human cryopreserved hepatocytes. This is not considered relevant new data as Syngenta have conducted studies on rat and human hepatocytes (Elcombe 2014), and in fact it highlights cytotoxicity at lower concentrations that in Kale's analysis. As the female rat liver tumours have been demonstrated to be due to a CAR activating mode of action rather than resulting from regeneration of frank liver damage these *in vitro* findings are considered incidental.
CA 5.8.2	Leslie E	2005	Multidrug resistance proteins: Role of P-glycoprotein, MRP1, MRP2, and BCRP (ABCG2) in tissue defense.	Toxicology and Applied Pharmacology, (2005) Vol. 204, No. 3, pp. 216-237.	This is a review article that mentions transport by MRP1 of metolachlor conjugates, but does not present new data.
CA 5.8.2	Miranda S *et al.*	2007	Cytotoxicity of chloroacetanilide herbicide alachlor in HepG2 cells independent of CYP3A4 and CYP3A7	Food and Chemical Toxicology (2007), 45 (5), 871-877.	This paper investigated the effects of CYP3A4 and CYP3A7 on alachlor toxicity in HepG2 cells. Metolachlor is used as a comparator and is less cytotoxic (the EC50 for cytotoxicity was approximately 800 µM). This paper does not add meaningful data to the existing metolachlor/S-metolachlor database.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.8.2	Sinclair C *et al.*	2006	Prioritization of pesticide environmental transformation products in drinking water supplies	ENVIRONMENTAL SCIENCE & TECHNOLOGY, (1 DEC 2006) Vol. 40, No. 23, pp. 7283-7289.	This paper outlines a general approach for prioritising assessment of transformation products of pesticides – metolachlor is only mentioned in the references – and even then not in a toxicological context.
CA 5.8.2	Smital T	2011	Assessment of toxicological profiles of the municipal wastewater effluents using chemical analyses and bioassays	Ecotoxicology and Environmental Safety (2011), 74 (4), 844-851.	This paper looks at *in vitro* activity (cytotoxicity, Ames mutagenicity, oestrogenicity and CYP induction) of untreated wastewater and secondary effluent from a wastewater treatment plant. Metolachlor was detected in samples of both, however due to the complex nature of the tested mixtures no reliable conclusions can be drawn with regard to metolachlor/S-metolachlor.
CA 5.8.2	Takeuchi S *et al.*	2006	In vitro screening of 200 pesticides for agonistic activity via mouse peroxisome proliferator-activated receptor (PPAR)α and PPARγ and quantitative analysis of in vivo induction pathway	Toxicology and Applied Pharmacology (2006), 217 (3), 235-244	This reporter gene assay paper looks at activation of PPAR by a number of pesticides. Specific data is not shown for metolachlor, but by inference it is negative for PPAR activity
CA 5.8.2	Toccalino P *et al.*	2012	Chemical mixtures in untreated water from public-supply wells in the U.S. - Occurrence, composition, and potential toxicity	Science of the Total Environment (2012), 431, 262-270.	This paper looks at monitoring data, including analysis for metolachlor. No toxicity data are presented.
CA 5.8.2	Yoshida M *et al.*	2013	Simulation of acute reference dose (ARfD) settings for pesticides in Japan	Journal of Toxicological Sciences (2013), 38 (2), 205-214.	This publication outlines the approach taken by Japan's Food Safety Commission to derive acute reference doses from existing data to suit their national requirements. Metolachlor is mentioned as being included in this exercise but no substance specific data are presented – therefore it is not considered of relevance.
CA 5.8.3	Bishop P *et al.*	2014	The Use and Acceptance of Other Scientifically Relevant Information (OSRI) in the U.S. Environmental Protection	Birth Defects Research, Part B: Developmental and Reproductive Toxicology (2014), 101 (1), 3-22.	Generalised EDSP review – doesn't contain data on metolachlor/S-metolachlor.

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			Agency (EPA) Endocrine Disruptor Screening Program		
CA 5.8.3	Hayes T	2006	Chemical mixtures: Hayes responds [4].	Environmental Health Perspectives, (Sep 2006) Vol. 114, No. 9, pp. A518-A519.	On review this is ecotoxicology based so not relevant for MCA Section 5.
CA 5.8.3	Jarosova B *et al.*	2012	Changes in concentrations of hydrophilic organic contaminants and of endocrine-disrupting potential downstream of small communities located adjacent to headwaters	Environment International (2012), 45, 22-31.	This paper primarily focuses on water monitoring. It also features some cell based anti/oestrogenicity and androgenicity assays, however as water samples of varying composition were tested no meaningful conclusions can be made with regard to metolachlor/S-metolachlor.
CA 5.8.3	Mnif W	2011	Effect of endocrine disruptor pesticides: A review.	International Journal of Environmental Research and Public Health, (June 2011) Vol. 8, No. 6, pp. 2265-2303.	Review article – does not present new data. Refers to Lemaire 2006 (discussed above).
CA 5.8.3	Wambaugh J *et al*.	2013	High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project.	Environmental Science & Technology (2013), 47 (15), 8479-8488.	No specific reference to metolachlor/S-metoachlor, it is a general ExpoCast analysis.
CA 5.9.2	Beard J *et al.*	2011	Suicide and pesticide use among pesticide applicators and their spouses in the Agricultural Health Study.	Environmental Health Perspectives, (November 2011) Vol. 119, No. 11, pp. 1610-1615.	This paper examines relationships between pesticide use and suicide. Metolachlor appeared to be inversely correlated with suicide. These data do no impact on the endpoints, references values or classifications so are not considered relevant.
CA 5.9.2	Hsu B-G	2009	Late-onset Methemoglobinemia Induced by Metobromuron/metolachlor.	Tzu Chi Medical Journal, (December 2009) Vol. 21, No. 4, pp. 334-338	This paper describes a suicide attempt case report where the patient ingested a litre of Galex (25% metolachlor/2% metobromuron) and was treated for methaemoglobinaemia. It appears highly likely that the methaemoglobinaemia observed was due to metobromuron which is known to cause this effect in animal studies (Conclusion on the peer

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					review of the pesticide risk assessment of the active substance metobromuron, EFSA Journal 2014;12(2):3541)
CA 5.9.4	Alavanja M *et al.*	2004	Pesticides and lung cancer risk in the agricultural health study cohort.	American journal of epidemiology, (2004 Nov 1) Vol. 160, No. 9, pp. 876-85.	On advice on epidemiology review, this paper can be excluded. This study is referenced in Rusiecki et al 2006 and provides no additional findings.
CA 5.9.4	Andreotti G *et al.*	2009	Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort	International Journal of Cancer (2009), 124(10), 2495-2500	On advice on epidemiology review, this paper can be excluded. Well conducted prospective study of pancreatic cancer incidence among pesticide applicators and their spouses. Recall bias is a potential limitation of the exposure data, but the reliability was evaluated. There was no evidence of an increased risk of pancreatic cancer among applicators and spouses exposed to metolachlor, and no evidence of a trend with lifetime days of exposure among applicators.
CA 5.9.4	Barry K *et al.*	2011	Genetic variation in base excision repair pathway genes, pesticide exposure, and prostate cancer risk	Environmental Health Perspectives (2011), 119(12), 1726-1732	On advice on epidemiology review, this paper can be excluded. There were no significant interactions between metolachlor and any of the haplotypes investigated in this study.
CA 5.9.4	Bonner M *et al.*	2005	The Agricultural Health Study biomarker workshop on cancer etiology.	Journal of Biochemical and Molecular Toxicology, (2005) Vol. 19, No. 3, pp. 169-171.	A review paper – does not contain new data. Refers to Alavanja 2004, which was also picked up in this search.
CA 5.9.4	Dayton S *et al.*	2010	Pesticide use and myocardial infarction incidence among farm women in the agricultural health study.	Journal of Occupational and Environmental Medicine, (July 2010) Vol. 52, No. 7, pp. 693-697.	On advice on epidemiology review, this paper can be excluded. Well conducted prospective study of myocardial infarction incidence among women.

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					Limitations include self-reported outcome and date of event, and subjects were only asked to report whether they had ever used metolachlor. No evidence of an association between ever use of metolachlor and myocardial infarction incidence.
CA 5.9.4	Dennis L *et al.*	2010	Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural heath study	Environmental Health Perspectives (2010), 118(6), 812-817	On advice on epidemiology review, this paper can be excluded. Not included in dossier as metolachlor was not associated with increased melanoma incidence.
CA 5.9.4	Fantke P *et al.*	2012	Health impact and damage cost assessment of pesticides in Europe	Environment International (2012), 49, 9-17.	This is a very general paper, and the only reference to metolachlor relates to its use pattern – no toxicity data.
CA 5.9.4	Flower K *et al.*	2004	Cancer risk and parental pesticide application in children of agricultural health study participants	Environmental Health Perspectives (2004), 112(5), 631-635.	Looks at the incidence of tumours amongst children of pesticide applicators. Metolachlor is not correlated to an increase in childhood cancer risk. On advice on epidemiology review, this paper can be excluded. Hybrid study design in which incidence of childhood cancer was identified retrospectively before parent enrolled in study and prospectively. Limitations include inability to determine whether prenatal exposure occurred for mothers and prenatal exposure for father could only be determined using information on decade of first use and duration of use. Timing of exposure in relation to pregnancy not known. No evidence of an association between maternal or paternal exposure to metalochlor and childhood cancer.

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CA 5.9.4	Freeman L *et al*.	2011	Atrazine and cancer incidence among pesticide applicators in the agricultural health study (1994-2007)	Environmental Health Perspectives (2011), 119 (9), 1253-1259.	This paper focuses on atrazine-related cancer incidence. Metolachlor is mentioned as a potential confounder (often used alongside atrazine), but is not assessed itself.
CA 5.9.4	Gallois J	2011	DNA adduct variations in non-smoking crop farmers: Potential relationship with occupational exposure to pesticides?	Environmental Toxicology and Pharmacology, (July 2011) Vol. 32, No. 1, pp. 1-9.	This paper looks at seasonal differences in DNA adduct levels in farmers. Metolachlor is one of a number of pesticides for which exposure is reported in the study, however analysis was conducted based on groupings rather than individual pesticides, so no conclusions can be made on the effect of metolachlor.
CA 5.9.4	Huijbregts M *et al.*	2005	Human toxicological effect and damage factors of carcinogenic and noncarcinogenic chemicals for life cycle impact assessment	Integrated Environmental Assessment and Management (2005), 1(3), 181-244.	This paper describes a methodology for deriving human damage and effect factors for over 1100 chemicals including metolachlor. No experimental data is described therefore it is not considered relevant.
CA 5.9.4	Kamel F *et al.*	2012	Pesticide exposure and amyotrophic lateral sclerosis	NeuroToxicology (2012), 33(3), 457-462	On advice on epidemiology review, this paper can be excluded. Well conducted case-control of ALS among pesticide applicators and their spouses. Recall bias is a potential limitation of the exposure data, but the reliability was evaluated. Another limitation is the small number (41) of cases. There was no evidence of an increased risk of ALS among applicators and spouses exposed to metolachlor, and no evidence of a trend with lifetime days of exposure among applicators.
CA 5.9.4	Koutros S *et al.*	2010	Pesticide Use Modifies the Association Between Genetic Variants on Chromosome 8q24 and Prostate Cancer	Cancer Research (2010), 70(22), 9224-9233	On advice on epidemiology review, this paper can be excluded. An interaction between metolachlor and

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
					rs12547643, which is telomeric to regions 3 and 1, was not statistically significant after correction for multiple testing. There was no a priori reason to expect an association as prostate cancer risk decreased with increasing metolachlor exposure, and a previous AHS report provided no evidence that a family history of prostate cancer modified prostate cancer risk among those exposed to metolachlor (Alavanja et al, (2003).
CA 5.9.4	Koutros S *et al.*	2011	Xenobiotic-metabolizing gene variants, pesticide use, and the risk of prostate cancer	Pharmacogenetics and Genomics (2011), 21(10), 615-623	On advice on epidemiology review, this paper can be excluded. There were no significant interactions between metolachlor and any of the haplotypes investigated in this study.
CA 5.9.4	Koutros S	2013	Genetic susceptibility loci, pesticide exposure and prostate cancer risk	PLoS One (2013), 8 (4), e58195.	Metolachlor is mentioned briefly in the supplementary table but is not specifically linked with human disease.
CA 5.9.4	Landgren O *et al.*	2009	Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study	Blood (2009), 113(25), 6386-6391	On advice on epidemiology review, this paper can be excluded. Well conducted study of MGUS prevalence in a neurobehavioral study nested within the AHS (a stratified random sample based on lifetime organophosphate use of male pesticide applicators). Comparison between applicators and general population were limited by the lack of a control group from the same states where applicators resided, but comparisons between ever and never users of individual pesticides are more robust. There was no evidence of increased MGUS prevalence among ever users of metolachlor.
CA 5.9.4	Lee W *et al.*	2004	Agricultural pesticide use and adenocarcinomas of the stomach and oesophagus	Occupational and Environmental Medicine (2004), 61(9),	On advice on epidemiology review, this paper can be excluded.

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				743-749	Well conducted case-control study of adenocarcinomas of the stomach and oesophagus and exposure to pesticides including nitrosatiable pesticides. There was no evidence of increased risk for exposure to acetanilide herbicides (alachor, metolachlor, propachlor), but no results were presented for metolachlor because fewer than 5 stomach and 5 oesophageal cancer cases were ever exposed to metolachlor.
CA 5.9.4	Lee W *et al.*	2005	Agricultural pesticide use and risk of glioma in Nebraska, United States	Occupational and Environmental Medicine (2005), 62(11), 786-792	Due to the large number of epidemiology studies that have included metolachlor and apparent complexity of the dataset, Syngenta have commissioned an expert to conduct a review of all of the studies to enable of weight of evidence analysis. This will be submitted at the earliest opportunity. On advice on epidemiology review, this paper can be excluded. Well conducted case-control study of glioma and exposure to pesticides including nitrosatiable pesticides. Among proxy respondents brain cancer risk was significantly increased for male farmers, but the association with farming was inverse among self-respondents. There was no overall association with metolachlor exposure, but the OR was non significantly increased among proxy respondents, and the association with metalochor was inverse among self-respondents. The pattern was unsurprising as non-farmers were the reference group for both analyses of

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					farming and individual pesticides.
CA 5.9.4	Metayer C	2013	Exposure to herbicides in house dust and risk of childhood acute lymphoblastic leukemia	Journal of exposure science & environmental epidemiology, (2013 Jul) Vol. 23, No. 4, pp. 363-70	On advice on epidemiology review, this paper can be excluded. Case-control study examining the association between exposure to herbicides in house dust and childhood acute lymphoblastic leukemia. The quantification of past exposure had numerous major limitations, not least the fact that samples were collected on average 1-2 years after diagnosis. Metolachlor was not detected in the house dust of any cases and only 2 controls (< 1%), and the study had little power to detect an effect of exposure to metolachlor.
CA 5.9.4	Migeot V	2013	Drinking-water exposure to a mixture of nitrate and low-dose atrazine metabolites and small-for-gestational age (SGA) babies: A historic cohort study.	Environmental Research (2013), 122, 58-64.	This paper primarily looks at atrazine. There are mentions of metolachlor as part of the French drinking water monitoring program but there is no toxicity data in this paper.
CA 5.9.4	Pellizzari E	2004	Assessment of data quality for the NHEXAS - Part II: Minnesota children's pesticide exposure study (MNCPES). [Erratum to document cited in CA140:308309]	Journal of Exposure Analysis and Environmental Epidemiology (2004), 14(1), 108	The erratum, and the original paper it belongs to analyse for presence of metolachlor in air, drinking water and beverages, and no toxicity data is presented. Consequently it is not considered relevant for inclusion in MCA Section 5.
CA 5.9.4	Perry M	2008	Effects of environmental and occupational pesticide exposure on human sperm: A systematic review.	Human Reproduction Update, (2008) Vol. 14, No. 3, pp. 233-242.	This is a review article and does not feature new data. It refers to Swan 2003 (Environmental Health Perspectives, Vol 111, 4, April 2003) with reference to metolachlor, but on review of that paper there is no reference to metolachlor.
CA 5.9.4	Phillips K	2008	Human exposure to endocrine disrupters and semen quality.	Journal of Toxicology and Environmental Health - Part B: Critical Reviews, (Mar 2008)	It refers to Swan 2003 (Environmental Health Perspectives, Vol 111, 4, April 2003) with reference

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				Vol. 11, No. 3-4, pp. 188-220.	to metolachlor, but on review of that paper there is no reference to metolachlor
CA 5.9.4	Red R	2011	Environmental toxicant exposure during pregnancy.	Obstetrical and Gynecological Survey, (March 2011) Vol. 66, No. 3, pp. 159-169.	A review article that does not present new data. .
CA 5.9.4	Rosenfeld P *et al.*	2011	Pesticides.	Rosenfeld, PE; Feng, LGH. (2011) pp. 127-154. Risks of Hazardous Wastes.	This is a book chapter summarising findings on a number of pesticides. Metolachlor is covered but as this a review no novel data is reported.
CA 5.9.4	Ruder A *et al.*	2004	Gliomas and farm pesticide exposure in men: The upper midwest health study.	Archives of Environmental Health, (Dec 2004) Vol. 59, No. 12, pp. 650-657.	On advice on epidemiology review, this paper can be excluded. Well conducted case-control study of glioma and pesticide exposure. There was no association between glioma and exposure to chloroactanilides (including metolachlor and alachlor). Results are not shown for metolachlor but the authors state that there was not a statistically significant association between glioma and metolachlor exposure (either including or excluding proxy respondents).
CA 5.9.4	Rusiecki J *et al.*	2005	Cancer incidence among pesticide applicators exposed to metolachlor in the agricultural health study	EPIDEMIOLOGY, (SEP 2005) Vol. 16, No. 5, pp. S98-S98.	On advice on epidemiology review, this paper can be excluded. This abstract has been superseded by Rusiecki et al 2006) which has an additional year of follow-up and reports more refined and better documented analyses. The conclusion of the abstract is also similar to that of Rusiecki et al (2006).
CA 5.9.4	Sathiakumar N *et al.*	2011	A review of epidemiologic studies of triazine herbicides and cancer.	Critical Reviews in Toxicology, (April 2011) Vol. 41, No. SUPPL. 1, pp. 1-34.	This is review article that does not present new data, but refers to Thorpe 2005, which is reviewed separately.
CA 5.9.4	Slager R	2010	Rhinitis associated with pesticide use among private pesticide applicators in the agricultural health study.	Journal of toxicology and environmental health. Part A, (2010) Vol. 73, No. 20, pp. 1382-93.	On advice on epidemiology review, this paper can be excluded.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
					Well conducted cross-sectional study of the prevalence of rhinitis among farmers and commercial pesticide applicators. Limitations include self-reported outcome, and the cross-sectional design resulting in an inability to determine when rhinitis episodes occurred in relation to exposure There was no evidence that current users (used in year before enrolment) of metolachlor were more likely to develop rhinitis or any pattern of association with number of rhinitis episodes. It is stated that metolachlor, was significant in an exposure-response model, but no other information is provided,1 and the analysis is described as an exploratory subgroup analysis. No persuasive evidence is presented that there is an association between rhinitis and metolachlor exposure.
CA 5.9.4	Wang N *et al.*	2012	Pollution level and human health risk assessment of some pesticides and polychlorinated biphenyls in Nantong of Southeast China.	Journal of Environmental Sciences (2012), Volume 24, Number 10, pp.1854-1860.	On review there is no toxicological data in this paper.
CA 5.9.4	Weichenthal *et al.*	2010	A review of pesticide exposure and cancer incidence in the Agricultural Health Study cohort.	Environmental health perspectives, (2010 Aug) Vol. 118, No. 8, pp. 1117-25.	This is a review paper that cites papers by Rusiecki and Alavanja, which are already covered in this literature review. No new primary data is provided therefore this review is not considered of relevance.
CA 5.9.4	Wells K et al.	2010	Development of a gis-based model for estimating residential agricultural pesticide exposure and its application to a study of prostate cancer incidence and pesticide exposure.	American Journal of Epidemiology, (JUN 1 2010) Vol. 171, No. Suppl. 11, pp. S84.	No metolachlor data is presented in this abstract – therefore it is not relevant for this assessment.

[1] The p value is stated to be 0.03 in the NIH Public Access manuscript.

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CA 5.9.4	Wickerham E et al.	2012	Reduced birth weight in relation to pesticide mixtures detected in cord blood of full-term infants.	Environment International, (OCT 15 2012) Vol. 47, pp. 80-85.	This study analyses for a relationship between umbilical cord detects of pesticides and birth weights. Only two subjects had metolachlor detects amongst those measured for in this study, therefore there is insufficient data to make and conclusions.
CA 5.9.4	Yan X *et al.*	2009	Pesticide concentrations in matrices collected in the perinatal period in a population of pregnant women and newborns in New Jersey, USA	Human and Ecological Risk Assessment (2009), 15(5), 948-967	This paper reports potential gestational exposure to pesticides, including metolachlor – showing that metolachlor is detectable in cord serum. No clinical abnormities or aberrant birth outcomes in the newborns were associated with the pesticide exposures.
CA 5.9.7	Seok S-J *et al.*	2012	Acute oral poisoning due to chloracetanilide herbicides.	Journal of Korean medical science, (2012 Feb) Vol. 27, No. 2, pp. 111-4.	This paper summaries the cases of patients admitted to two university hospitals apparently suffering from acute chloroacetanilide poisoning. 5 Of the cases were related to metolachlor. These findings do not alter the AOEL, ADI or classification and labelling as the actual levels of exposure are not defined.
CP 7.2.1.2,	Hayat K. *et al.*	2010	Determination of pesticide residues in blood samples of villagers involved in pesticide application at District Vehari (Punjab), Pakistan	African Journal of Environmental Science and Technology Vol. 4(10), pp. 666-684, October 2010	No residues of metolachlor or s-metolachlor were detected in any of the samples. In addition, there is insufficient detail concerning GAP parameters (e.g. application rates, formulation type, dermal absorption, whether the use was from metolachlor or S-metolachlor) to enable further comparison to the proposed use in the EU. Therefore, the operator assessment provided as part of the re-registration submission dossier (MCP section 7) is

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					considered to be precautionary and appropriate.
CP 7.2.1.2, CP 7.2.3.2	Panuwet P. *et al.*	2008	Concentrations of urinary pesticide metabolites in small-scale farmers in Chiang Mai Province, Thailand.	Sci. Total Environ. (2008 Dec) 15;407(1):655-68	The paper states that metolachlor metabolite was measured in the range from <0.2 to 0.71 µg/L with the 95th percentile being less than the LOD (limit of detection). There are no details given to be able to compare this to an external exposure value. There is insufficient detail concerning GAP parameters (e.g. application rates, formulation type, dermal absorption, whether the use was from metolachlor or S-metolachlor) to enable further comparison to the proposed use in the EU. Therefore, the operator and worker exposure assessments provided as part of the re-registration submission dossier (MCP section 7) are considered to be precautionary and appropriate.
CP 7.2.1.2, CP 7.2.2.2, CP 7.2.3.2	Curwin B. et al.	2005	Urinary and hand wipe pesticide levels among farmers and nonfarmers in Iowa	Journal of Exposure Analysis and Environmental Epidemiology (2005) 15, 500–508	With all bio-monitoring studies where urine is sampled, an indication of complete collection is required (including the measurement of creatinine levels), in conjunction with robust pharmacokinetic data to be able to predict either systemic dose, or to back calculate to external exposure. This study only involved spot sampling of urine which is an indicator of exposure, but not of use for quantitative assessment. Additionally, only a relatively small number of hand wipe samples were obtained for operators applying metolachlor and the determinants of exposure (application parameters, timing etc.) were self-reported; again this was

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					essentially an indicator of exposure but not a quantitative measure. However, whilst this study reported that farmers had detectable levels of metolachlor in hand wipe samples, the levels were not significantly higher than for non-farmers. There is nothing in this study, which was intended as a comparison between operators and non-operators, rather than a full exposure study, that suggests that the first tier assessments of exposure for the proposed EU use of S-metolachlor are not sufficiently protective. In addition, there is insufficient detail concerning GAP parameters (e.g. application rates, formulation type, dermal absorption, whether the use was from metolachlor or S-metolachlor) to enable further comparison to the proposed use in the EU. Therefore, the operator and worker exposure assessments provided as part of the re-registration submission dossier (MCP section 7) are considered to be precautionary and appropriate.
CP 7.2.1.2, CP 7.2.2.2, CP 7.2.3.2	Curwin B. et al.	2007	Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in iowa.	Ann. Occup. Hyg. (2007 Jan);51(1):53-65	Geometric mean concentrations of metolachlor mercapturate in urine for fathers, mothers and children were typically in the range 0.3 to 0.8 µg/L with the exception of the subgroup ‘fathers who had made an application with metolachlor’ where the geometric mean concentration was 4.5 µg/L. Although this does demonstrate that application of metolachlor results in a systemic dose, it is not possible to compare it to the

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					assessments provided in the current re-registration submission dossier (MCP section 7) as the corresponding external exposure cannot be calculated with the available information and no details of use patterns (GAPs, whether the use was from metolachlor or S-metolachlor, formulation, dermal absorption, use of PPE etc.) are given. The operator and resident exposure assessments provided as part of the re-registration submission dossier (MCP section 7) are considered to be precautionary and appropriate.
CP 7.2.1.2, CP 7.2.3.2	Schummer C. et al.	2012	Determination of farm workers' exposure to pesticides by hair analysis.	Toxicol. Lett. (2012 Apr) 25;210(2):203-10	S-metolachlor was determined in hair from farm workers taking part in the study. Positive detections of S-metolachlor were seen in 4 out of 18 workers. The median residue in hair was 14.5 pg/mg, but this cannot be related to external exposure or systemic dose. Exposures to S-metolachlor to farm workers carrying out spraying (operator risk assessment) and other farm activities (worker exposure assessment) have been provided as part of the MCP Section 7 and are considered protective and precautionary. Residues in hair are not required to further refine any exposure assessment already provided.
CP 7.2.1.2, CP 7.2.3.2	Arcury T. et al.	2010	Repeated pesticide exposure among North Carolina migrant and seasonal farmworkers	Am. J. Ind. Med. (2010 Aug);53(8):802-13	Report gives number of detections of urinary metabolite (metolachlor mercapturate) above the LOD (limit of detection) for the farmworkers, but no quantitative residue levels nor an indication of how the measured internal exposures relate to a

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					specific external dose are given. No details of GAPs (e.g. application rates, formulation types) are provided. The operator and worker exposure assessments provided as part of the re-registration submission dossier (MCP section 7) are considered to be sufficiently precautionary and appropriate.
CP 7.2.1.2, CP 7.2.3.2	Arcury T. et al.	2009	Seasonal Variation in the Measurement of Urinary Pesticide Metabolites among Latino Farmworkers in Eastern North Carolina	Int. J. Occup. Environ. Health. (2009 Oct–Dec); 15(4): 339–350	The report gives information on the frequency (e.g. number of workers with a detectable level) but does not give the actual level measured and no comparison of internal metabolite dose is made to a potential external dose. Therefore, it is not possible to compare it to the assessments provided in the current re-registration submission dossier (MCP section 7). No details of use patterns (GAPs) are given, or whether the local use was with metolachlor or S-metolachlor. Cultural practices concerning PPE may also lead to differences between levels found in this study from the United States and any expected levels present in the European Union. The operator and worker exposure assessments provided as part of the re-registration submission dossier (MCP section 7) are considered to be precautionary and appropriate.
CP 7.2.2.2	Curwin B. et al.	2005	Pesticide contamination inside farm and nonfarm homes.	J. Occup. Environ. Hyg. (2005 Jul);2(7):357-67	The report claims that pesticides, including metolachlor are found in dust from farm and non-farm households implicating contamination from farmer's shoes and clothing. Although this does represent a potential route of exposure for the resident it is not possible

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					to compare it to the assessments provided in the current submission. No details of use patterns (e.g. application rates, formulation types) are given, or whether the local use was with metolachlor or S-metolachlor. Cultural practices concerning PPE and footwear may also lead to differences between levels found in this study from the United States and any expected levels present in the European Union. The resident exposure assessments provided as part of the re-registration submission dossier (MCP section 7) are considered to be sufficiently precautionary and appropriate to account for any additional exposure via this route.
CP 7.2.2.2	Ward M. et al.	2006	Proximity to crops and residential exposure to agricultural herbicides in iowa.	Environ. Health Perspect. 2006 Jun;114(6):893-7	The report claims that metolachlor was found in carpet dust at a median concentration of 129.5 ng/g. Although this does represent a potential, albeit minor route of exposure for the resident it is not possible to compare it to the assessments provided in the current submission. No details of local use patterns (GAPs) are given, or whether the local use was with metolachlor or S-metolachlor. Cultural practices concerning PPE and footwear may also lead to differences between levels found in this study from the United States and any expected levels present in the European Union. The resident exposure assessments provided as part of the re-registration submission dossier (MCP section 7) are considered to be sufficiently precautionary and appropriate to account for

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
					any additional exposure via this route.
CP 7.2.2.2	Curwin B. et al.	2007	Pesticide dose estimates for children of Iowa farmers and non-farmers	Environmental Research, Volume 105, Issue 3, (November 2007), Pages 307–315	An estimation of metolachlor exposure has been made for children on the basis of their metolachlor mercapturate urine levels and modelling. The modelling requires a value for the amount of metolachlor mercapturate excreted in urine, which was not known, so an estimated conservative figure of 60% was used (based on the fact that the percentage of alachlor mercapturate in human urine has been shown to range from 25% to 62% and they are considered to be structurally similar). Therefore, the modelling itself is not validated to predict exposures of metolachlor. No details of use patterns (GAPs) are given, formulation type including dermal absorption values or whether the local use was with metolachlor or S-metolachlor. The report claims that the highest estimated dose for metolachlor was 3.16 µg/kg/day, equating to 0.0032 mg/kg bw/day, or 2.1% of the AOEL. The resident exposure assessments provided as part of the re-registration submission dossier (MCP section 7) are considered to be precautionary and appropriate.
CP 7.2.2.2	Arcury T. et al.	2007	Pesticide urinary metabolite levels of children in eastern North Carolina farmworker households.	Environ. Health Perspect. (2007 Aug);115(8):1254-60	No details of use patterns (e.g. application rates or other GAP parameters) are given, or whether the local use was with metolachlor or S-metolachlor. The report claims that out of the 14 pesticides that were monitored in urine samples, metolachlor was the only one that had no detects from any of the 60

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
					Latino farmworker children. The resident exposure assessments provided as part of the re-registration submission dossier (MCP section 7) are therefore considered to be precautionary and appropriate.
CP 7.2.2.2	Aulagnier F et al.	2008	Pesticides measured in air and precipitation in the Yamaska Basin (Québec): occurrence and concentrations in 2004.	Sci. Total Environ. (2008 May) 15;394 (2-3) 338-48	The report gives an average metolachlor concentration in air of 7713 pg/m^3. No details are provided for the exact distance from an application, or to know the exact use patterns (e.g application rates) that were used in local applications of metolachlor, nor whether metolachlor or S-metolachlor were used and if the same results would be expected from both of these active ingredients. However, the resident exposure assessment submitted in the re-registration submission (MCP section 7) which used a default value of 1 µg/m^3, based on the vapour pressure of S-metolachlor being considered semi-volatile, is considered protective.
CP 7.2.2.2	Peck A. et al.	2005	Gas-Phase Concentrations of Current-Use Pesticides in Iowa	Environ. Sci. Technol. (**2005**), 39, 2952-2959	The report gives an average metolachlor concentration in air of 2.3 ng/m^3. No details are provided for the exact distance from an application, or to know the exact use patterns (e.g application rates, formulation types) that were used in local applications of metolachlor, nor whether metolachlor or S-metolachlor were used and if the same results would be expected from both of these active ingredients. Consequently, the resident exposure assessment submitted in the re-registration submission

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
					(MCP section 7) used a much larger default value of 1 µg/m^3 based on the vapour pressure of S-metolachlor being considered semi-volatile is considered protective in comparison.
CP 7.2.2.2	Wofford P et al.	2014	Community air monitoring for pesticides. Part 3: using health-based screening levels to evaluate results collected for a year.	Environmental monitoring and assessment, (2014 Mar) Vol. 186, No. 3, pp. 1355-70.	The report states that metolachlor was one of seventeen out of forty pesticides and pesticide degradation products monitored but not detected at concentrations above the detection limit. Irrespective of this, no details are provided for the exact distance from an application, or for the exact use patterns (e.g application rates) that were used in local applications of metolachlor, nor whether metolachlor or S-metolachlor were used and if the same results would be expected from both of these active ingredients. Consequently, the resident exposure assessment submitted in the re-registration submission (MCP section 7) which used a default value of 1 µg/m^3, based on the vapour pressure of S-metolachlor being considered semi-volatile, is considered protective.

All documents listed in Table 9.6-2 and not excluded (i.e. not listed in Table 9.6-4) are given below.

Table 9.6-5: List of references which are discussed further (listed by data point number)

CA data point number	Author(s)	Year	Title	Source	Ref. ID
CA 5.3.2	Zhou M	2009	Observation on toxicity experiment of S-metolachlor	Zhiye Yu Jiankang (2009), 25(24), 2657-2661	EU001
CA 5.4.1	Nikoloff N *et al.*	2013	Comparative study of cytotoxic and genotoxic effects induced by herbicide	Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association, (2013 Dec) Vol. 62, pp. 777-81.	EU002

CA data point number	Author(s)	Year	Title	Source	Ref. ID
CA 5.8.2	Ait-Aissa S *et al.*	2010	Anti-androgenic activities of environmental pesticides in the MDA-kb2	Toxicology in Vitro (2010), 24(7), 1979-1985.	EU003
CA 5.8.2	Greenlee E *et al.*	2004	Low-dose agrochemicals and lawn-care pesticides induce developmental	Environmental health perspectives, (2004 May) Vol. 112, No. 6, pp. 703-9.	EU004
CA 5.8.2	Hartnett S *et al.*	2013	Cellular effects of metolachlor exposure on human liver (HepG2) cells.	Chemosphere, (2013 Jan) Vol. 90, No. 3, pp. 1258-66	EU005
CA 5.8.2	Hu J	2009	Immunotoxicity effect of metolachlor on mice	Harbin Yike Daxue Xuebao (2009), 43(1), 53-55	EU006
CA 5.8.2	Takeuchi S *et al.*	2008	In vitro screening for aryl hydrocarbon receptor agonistic activity in 200	Chemosphere (2008), 74(1), 155-165.	EU007
CA 5.8.2	Kojima H *et al.*	2011	Comparative study of human and mouse pregnane X receptor agonistic activity in 200 pesticides using in vitro reporter gene assays	Toxicology (2011), 280(3), 77-87	EU008
CA 5.8.2	Kueblbeck J *et al.*	2011	Use of comprehensive screening methods to detect selective human CAR	Biochemical Pharmacology (2011), 82(12), 1994-2007	EU009
CA 5.8.2	Lemaire G *et al.*	2006	Activation of α- and β-estrogen receptors by persistent pesticides in reporter cell lines	Life Sciences (2006), 79(12), 1160-1169.	EU010
CA 5.8.2	Lemaire G et al.	2006	Identification of new human pregnane X receptor ligands among pesticides using a stable reporter cell system.	Toxicological sciences : an official journal of the Society of Toxicology,	EU011
CA 5.8.2	Lowry D *et al.*	2013	Mechanism of metolachlor action due to alterations in cell cycle progression	Cell biology and toxicology, (2013 Aug) Vol. 29, No. 4, pp. 283-91.	EU012
CA 5.8.2	Oosterhuis B *at al.*	2008	Specific interactions of chloroacetanilide herbicides with human ABC	Toxicology, (2008 Jun 3) Vol. 248, No. 1, pp. 45-51.	EU013
CA 5.8.2	Pereira S et al.	2009	Toxicity assessment of the herbicide metolachlor comparative effects on	Toxicology in vitro : an international journal published in association	EU014
CA 5.8.2	Rotroff D *et al.*	2010	Xenobiotic-Metabolizing Enzyme and Transporter Gene Expression in Primary	Journal of Toxicology and Environmental Health, Part B: Critical Reviews (2010), 13(2-4), 329-346	EU015
CA 5.8.2	Laville N *et al.*	2006	Modulation of aromatase activity and mRNA by various selected pesticides	Toxicology, (2006 Nov 10) Vol. 228, No. 1, pp. 98-108.	EU016
CA 5.8.2	Cunningham A *et al.*	2009	A structure-activity relationship (SAR) analysis for the identification of	Endocrine Disruption Modeling (2009), 173-198.	EU017
CA 5.8.2	Sipes N *et al.*	2013	Profiling 976 ToxCast Chemicals across 331 Enzymatic and Receptor Signaling Assays	Chemical Research in Toxicology (2013), 26 (6), 878-895.	EU018
CA 5.8.2	Kojima H *et al.*	2004	Screening for estrogen and androgen receptor activities in 200 pesticides by in vitro reporter gene assays using chinese hamster ovary cells	Environmental Health Perspectives (2004), 112 (5), 524-531.	EU019

CA data point number	Author(s)	Year	Title	Source	Ref. ID
CA 5.8.3	Mathias *F et al.*	2012	Herbicide Metolachlor Causes Changes in Reproductive Endocrinology of Male Wistar Rats	ISRN Toxicology (2012) 130846.	EU020
CA 5.8.3	Reif D *et al.*	2010	Endocrine profiling and prioritization of environmental chemicals using ToxCast data.	Environmental Health Perspectives (2010), 118(12), 1714-1720.	EU021
CA 5.8.3	Rotroff D *et al.*	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.	EU022
CA 5.9.4	Alavanja M *et al.*	2003	Use of Agricultural Pesticides and Prostate Cancer Risk in the Agricultural Health Study Cohort	Am J Epidemiol 2003;157:800–814	EU023
CA 5.9.4	Andreotti G *et al.*	2010	Body mass index, agricultural pesticide use, and cancer incidence in the	Cancer causes & control: CCC, (2010 Nov) Vol. 21, No. 11, pp. 1759-75.	EU024
CA 5.9.4	Barr D	2010	Pesticide concentrations in maternal and umbilical cord sera and their relation to birth outcomes in a population of pregnant women and newborns in New Jersey.	The Science of the total environment, (2010 Jan 15) Vol. 408, No. 4, pp. 790-5.	EU025
CA 5.9.4	Chevrier Gwendolina	2011	Urinary biomarkers of prenatal atrazine exposure and adverse birth outcomes in the PELAGIE birth cohort.	Environmental health perspectives, (2011 Jul) Vol. 119, No. 7, pp. 1034-41.	EU026
CA 5.9.4	Hoppin J *et al.*	2006	Pesticides and adult respiratory outcomes in the agricultural health study.	Annals of the New York Academy of Sciences, (Sep 2006) Vol. 1076, pp. 343-354.	EU027
CA 5.9.4	Hou L	2013	Lifetime pesticide use and telomere shortening among male pesticide applicators in the Agricultural Health Study.	Environmental health perspectives, (2013 Aug) Vol. 121, No. 8, pp. 919-24.	EU028
CA 5.9.4	Lee W *et al.*	2007	Pesticide use and colorectal cancer risk in the Agricultural Health Study	International Journal of Cancer (2007), 121(2), 339-346	EU029
CA 5.9.4	Munger	2007	Intrauterine Growth Retardation in Iowa Communities with Herbicide-contaminated Drinking Water Supplies	Environmental Health Perspectives, Volume 105, Number 3, March 1997	EU030
CA 5.9.4	Rusiecki J	2006	Cancer incidence among pesticide applicators exposed to metolachlor in the Agricultural Health Study.	International journal of cancer. Journal international du cancer, (2006 Jun 15) Vol. 118, No. 12, pp. 3118-23.	EU031
CA 5.9.4	Swan	2003	Semen Quality in Relation to Biomarkers of Pesticide Exposure	Environmental Health Perspectives, vol 111, 12 September 2003.	EU032
CA 5.9.4	Thorpe N	2005	Herbicides and nitrates in groundwater of Maryland and childhood cancers: a	Journal of environmental science and health. Part C, Environmental	EU033

S-Metolachlor

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

DOCUMENT M-CA, Section 9

Metabolism and Residues Data

LITERATURE DATA

Version history[1]

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

Table of Contents

CA 9 LITERATURE DATA

CA 9.1 Title

This document is a Literature Review Report for S-metolachlor, relevant metabolite(s) and EU representative formulation A9396G (Dual Gold®).

CA 9.2 Author(s) of the review

Syngenta
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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 S-metolachlor and its relevant metabolites dealing with metabolism and residues data which may impact health, the environment and non-target species and published within the last ten years before the date of submission of the dossier" in accordance with Article 8(5) of Regulation (EC) No. 1107/2009.

The search strategy is detailed in the tables below. A search was conducted to identify references that included the active substance S-metolachlor, or its major metabolites, or representative formulations, in conjunction with any of the key words set out in Table 9.5-1. The names searched for were:

```
L1      QUE  (693288-41-4 OR 131068-72-9 OR 1217465-10-5 OR 244270-80-2)
L2      QUE  (244270-82-4 OR 887649-86-7 OR 244270-79-9 OR 244270-81-3)
L3      QUE  (887649-85-6 OR 947601-85-6 OR 446027-17-4 OR 1173021-76-5)
L4      QUE  (1418095-19-8 OR 126605-22-9 OR 153516-68-8 OR 61520-53-4)
L5      QUE  (82508-08-5 OR 82508-09-6 OR 61520-54-5 OR 97055-05-5)
L6      QUE  (32428-71-0 OR 97055-06-6 OR 52559-52-1 OR 51219-00-2)
L7      QUE  (96394-97-7 OR 121073-75-4 OR 170379-74-5 OR 152019-73-3)
L8      QUE  (120375-14-6 OR 65513-61-3 OR 159956-64-6 OR 171118-09-5)
L9      QUE  (CGA098847 OR CGA98847 OR CGA46129 OR CGA138868)
L10     QUE  (CGA354743 OR CGA41507 OR CGA51202 OR CGA40172)
L11     QUE  (CGA40919 OR CGA37735 OR CGA49751 OR CGA37913)
L12     QUE  (CGA351915 OR CGA133275 OR CGA046129 OR CGA13656)
L13     QUE  (CGA(2W)(098847 OR 98847 OR 46129 OR 138868))
L14     QUE  (CGA(2W)(354743 OR 41507 OR 51202 OR 40172))
L15     QUE  (CGA(2W)(40919 OR 37735 OR 49751 OR 37913))
L16     QUE  (CGA(2W)(351915 OR 133275 OR 046129 OR 13656))
L17     QUE  (SYN542491 OR SYN542489 OR SYN542492 OR SYN547969)
L18     QUE  (SYN542488 OR SYN542490 OR SYN542607 OR NOA436611)
L19     QUE  (SYN(2W)(542491 OR 542489 OR 542492 OR 547969))
L20     QUE  ((SYN(2W)(542488 OR 542490 OR 542607)) OR (NOA(2W)436611))
L21     QUE  (55762-76-0 OR 63150-68-5 OR 94449-58-8 OR (CGA(W)77102))
L22     QUE  (METETILACHLOR OR METOLACHLOR OR (CGA(W)24705) OR CGA24705)
L23     QUE  ((S OR ALPHA)(2W)(METOLACHLOR OR METHOLACHLOR))
L24     QUE  (CGA77102 OR 51218-45-2 OR 87392-12-9 OR METHOLACHLOR)
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L25      QUE  (L1-L20)   METABOLITES
L26      QUE  (L21 OR L22 OR L23 OR L24)   METOLACHLOR
L27      QUE  (L25 OR L26)   METOLACHLOR & METABOLITES
```

An overview of the results is summarised in the table below and further details are provided in Section 9.5.

Data requirement(s) captured in the search	**Number (Initial Search)**
Total number of *summary records* retrieved after *all** searches of peer-reviewed literature (excluding duplicates)	1629
Number of *summary records* excluded from the search results after rapid assessment for relevance	1620
Total number of *full-text* documents assessed in detail*	9
Number of *studies* excluded from further consideration after detailed assessment for relevance	9
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	0

*both from bibliographic databases and other sources of peer-reviewed literature

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 S-metolachlor and its potentially relevant metabolites dealing with metabolism and residue studies which may impact health, the environment and non-target species and published within the last ten years before the date of submission of the dossier” in accordance with Article 8(5) of Regulation (EC) No. 1107/2009.

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

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

Data requirements(s) (indicated by the correspondent CA data point(s))	**Criteria for relevance**
Metabolism and residues data (CA 6.1 to 6.10)	
Summary	The relevance criteria applied to determine whether a literature reference was relevant for the residues and metabolism sections of the active substance renewal process are given below. 1. Well defined test material. e.g. are purity and batch data provided? 2. Applicable test species. e.g. is the crop a representative use; were relevant animal commodities used? 3. Study conditions should not differ significantly from guidelines and recommended protocols. e.g. did the study meet the relevant guidelines? 4. Trial site/test system not previously exposed to the test material or other contaminants e.g. was the compound used previously at the trial site; was the animal feed free from the compound? 5. Sufficient experimental information is provided to substantiate and evaluate whether the study conclusions and endpoints are robust.

Data requirements(s) (indicated by the correspondent CA data point(s))	Criteria for relevance
	e.g. were storage intervals recorded; are weather conditions and plot histories available? 6. Validated Analytical methodology employed. e.g. were control samples used, acceptable recoveries obtained, clear example chromatograms given? 7. Study conditions do not interfere with the interpretation of the study results. e.g. starting processing material residue is robust and there is measurable residue in processed products?
6.1 Storage stability **Storage stability studies, plant and animal**	Storage Stability Studies 1. Well defined test material (including purity/content) 2. Applicable test species 3. Study conditions should not differ significantly from guidelines and recommended protocols. 5. Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust. 6. Study conditions should not interfere with the interpretation of the study results. 7. Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc.
6.2 Metabolism	Primary Crop Studies Notes for criteria 1. Well defined test material (including purity/content) 2. Applicable test species • N.B. any crop used for food and/or feed could be relevant from a metabolism perspective as results can be extrapolated to other crops 3. Study conditions should not differ significantly from guidelines and recommended protocols. 4. Trial site/test system not previously exposed to the test material or other contaminants. 5. Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust. 6. Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc. 7. Study conditions should not interfere with the interpretation of the study results. Metabolism in Rotational Crops Notes for criteria 1. Well defined test material (including purity/content) 2. Applicable test species • N.B. relevant crop groupings are small grain, root and tuber, leafy vegetable (soybean and rice if relevant to product). Bulb vegetable (e.g. onions and garlic) should not be used. 3. Study conditions should not differ significantly from guidelines and recommended protocols. 4. Trial site/test system not previously exposed to the test material or other contaminants. 5. Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust. 6. Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc. 7. Study conditions should not interfere with the interpretation of the study results. Livestock Metabolism Studies

<table>
<tr><th>Data requirements(s) (indicated by the correspondent CA data point(s))</th><th>Criteria for relevance</th></tr>
<tr><td></td><td>Notes for criteria
1. Well defined test material (including purity/content)
2. Applicable test species
• Ruminant, poultry, pig, fish, any edible animal
3. Study conditions should not differ significantly from guidelines and recommended protocols.
4. Trial site/test system not previously exposed to the test material or other contaminants.
5. Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust.
6. Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc.
7. Study conditions should not interfere with the interpretation of the study results.</td></tr>
<tr><td>6.3 Residue studies</td><td>Published monitoring reports were not considered relevant due to the fact that it would not be possible to determine whether or not a misuse scenario had resulted in the residue levels reported.

<u>Crop Studies</u>
1. Well defined test material (including purity/content)
2. Applicable test species
3. Study conditions should not differ significantly from guidelines and recommended protocols.
4. Trial site/test system not previously exposed to the test material or other contaminants.
5. Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust.
6. Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc.
7. Study conditions should not interfere with the interpretation of the study results.</td></tr>
<tr><td>6.4 Livestock Feeding studies</td><td>Same criteria as for crop studies, examples could be as above with the following additions.

<u>Livestock Feeding Studies Notes</u>
1. Well defined test material (including purity/content)
2. Applicable test species
• e.g. Ruminant, poultry, pig, fish, any edible animal.
3. Study conditions should not differ significantly from recommended protocols.
4. Trial site/test system not previously exposed to the test material or other contaminants.
5. Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust.
6. Study conditions should not interfere with the interpretation of the study results.
7. Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc.</td></tr>
<tr><td>6.5 Processing</td><td><u>High Temperature Hydrolysis</u>

Notes for criteria
1. Well defined test material (including purity/content)
2. Applicable test system
3. Study conditions should not differ significantly from guidelines and recommended protocols.
4. Trial site/test system not previously exposed to the test material or other contaminants.</td></tr>
</table>

Data requirements(s) (indicated by the correspondent CA data point(s))	Criteria for relevance
	5. Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust. 6. Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc. 7. Study conditions should not interfere with the interpretation of the study results. <u>Field Studies</u> 1. Well defined test material (including purity/content) 2. Applicable test species 3. Study conditions should not differ significantly from guidelines and recommended protocols. 4. Trial site not previously exposed to the test material or other contaminants. 5. Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust. 6. Study conditions should not interfere with the interpretation of the study results. 7. Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc. <u>Notes for above criteria</u> 1. Well defined test material (including purity/content) 2. Applicable test species 3. Study conditions should not differ significantly from guidelines and recommended protocols. • NB. Processing studies can be conducted at elevated rates and shorter PHI and grown under different conditions to maximize residues. 4. Trial site not previously exposed to the test material or other contaminants. 5. Sufficient experimental information provided to substantiate and evaluate whether the study conclusions and endpoints are robust. 6. Study conditions should not interfere with the interpretation of the study results. 6. Validated Analytical methodology employed, e.g. control samples used, acceptable recoveries obtained, clear example chromatograms etc.
6.6 Residues in succeeding crops	Same criteria as for crop residue studies, examples could be subtly different, e.g. acceptable PBIs, crop types, again monitoring information should not be considered relevant.
6.7 Proposed residue definition and MRLs	<u>Residue definition</u> Notes for criteria 1. Developed following appropriate EU guidance 2. Any toxicological data relevant to the residue definition are generated following relevant acceptability criteria 3. Metabolism data relevant to the residue definition are generated following relevant acceptability criteria covered in 6.2 <u>Maximum Residue Levels</u> Notes for criteria 1. MRLs are calculated via residues generated following criteria covered in 6.3 2. Correct monitoring residue definition has been used 3. Appropriate MRL calculator utilised
6.8 Proposed PHI, re-entry and withholding periods	Same criteria as for residues generated following criteria covered in 6.3
6.9 Other/special studies	Generic criteria are appropriate as laid out in the summary box above

Data requirements(s) (indicated by the correspondent CA data point(s))	Criteria for relevance
6.10 Risk assessment	Dietary risk assessment conducted using appropriate EU methodology

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

CA 9.5 Search methods

Date of initial search	20 August 2014
Date of most recent update to search	-
Date span of the search	10 years

For the initial rapid assessment the study titles and abstracts were scanned to identify studies of potential relevance to crop and livestock metabolism and/or residue studies in the context of human exposure through the diet. Studies clearly not within the remit of Regulation (EU) No. 283/2013 and regulation (EU) No. 284/2013 (such as metabolism studies in environmental compartments or microorganisms, other environmental fate studies, toxicological studies, efficacy studies, studies on plants other than crops, and mode of action studies) were eliminated. A second scan checked the full text of 9 records identified as potentially relevant or unclear on the basis of their titles. In-depth review of these papers identified no literature references that were considered to be potentially relevant.

Table 9.5-1: Detailed Search Parameters for Metabolism and Residues data (CA 6.1 to 6.9)

Search Strategy	
L1	QUE (693288-41-4 OR 131068-72-9 OR 1217465-10-5 OR 244270-80-2)
L2	QUE (244270-82-4 OR 887649-86-7 OR 244270-79-9 OR 244270-81-3)
L3	QUE (887649-85-6 OR 947601-85-6 OR 446027-17-4 OR 1173021-76-5)
L4	QUE (1418095-19-8 OR 126605-22-9 OR 153516-68-8 OR 61520-53-4)
L5	QUE (82508-08-5 OR 82508-09-6 OR 61520-54-5 OR 97055-05-5)
L6	QUE (32428-71-0 OR 97055-06-6 OR 52559-52-1 OR 51219-00-2)
L7	QUE (96394-97-7 OR 121073-75-4 OR 170379-74-5 OR 152019-73-3)
L8	QUE (120375-14-6 OR 65513-61-3 OR 159956-64-6 OR 171118-09-5)
L9	QUE (CGA098847 OR CGA98847 OR CGA46129 OR CGA138868)
L10	QUE (CGA354743 OR CGA41507 OR CGA51202 OR CGA40172)
L11	QUE (CGA40919 OR CGA37735 OR CGA49751 OR CGA37913)
L12	QUE (CGA351915 OR CGA133275 OR CGA046129 OR CGA13656)
L13	QUE (CGA(2W)(098847 OR 98847 OR 46129 OR 138868))
L14	QUE (CGA(2W)(354743 OR 41507 OR 51202 OR 40172))
L15	QUE (CGA(2W)(40919 OR 37735 OR 49751 OR 37913))
L16	QUE (CGA(2W)(351915 OR 133275 OR 046129 OR 13656))
L17	QUE (SYN542491 OR SYN542489 OR SYN542492 OR SYN547969)
L18	QUE (SYN542488 OR SYN542490 OR SYN542607 OR NOA436611)
L19	QUE (SYN(2W)(542491 OR 542489 OR 542492 OR 547969))
L20	QUE ((SYN(2W)(542488 OR 542490 OR 542607)) OR (NOA(2W)436611))
L21	QUE (55762-76-0 OR 63150-68-5 OR 94449-58-8 OR (CGA(W)77102))
L22	QUE (METETILACHLOR OR METOLACHLOR OR (CGA(W)24705) OR CGA24705)
L23	QUE ((S OR ALPHA)(2W)(METOLACHLOR OR METHOLACHLOR))
L24	QUE (CGA77102 OR 51218-45-2 OR 87392-12-9 OR METHOLACHLOR)
L25	QUE (L1-L20) METABOLITES
L26	QUE (L21 OR L22 OR L23 OR L24) METOLACHLOR
L27	QUE (L25 OR L26) METOLACHLOR & METABOLITES
Plus	
L1	QUE (METABOL? OR RESIDUE# OR TRANSFORM? OR BIOTRANSFORM?)
L2	QUE (DEGRAD? OR BIODEGRAD? OR FATE# OR MRL OR MRLS)
L3	QUE (CONJUGAT? OR EXCRET? OR ELIMINAT?)
L4	QUE (FOOD# OR FEED# OR DIET# OR DIETARY OR CONSUMER? OR HUMAN#)
L5	QUE (CONTAMINAT? OR SAFE? OR EXPOS? OR ANALY? OR ASSES?)
L6	QUE (INTAKE? OR (IN(W)TAKE?) OR SURVEY? OR RISK?)
L7	QUE (TOXIC? OR STUDY? OR STUDIES?)
L8	QUE (L4(10A)(L5 OR L6 OR L7))
L9	QUE (LIVESTOCK# OR COW# OR GOAT# OR CATTLE# OR BULLOCK#)
L10	QUE (BOVINE? OR BOVIDAE? OR BOS OR BULL# OR HEIFER? OR CAPRA#)
L11	QUE (SHEEP# OR EWE OR EWES OR RAM# OR SWINE# OR PIGLET#)
L12	QUE (PIG# OR SUIDAE? OR SUS OR OVIS OR OX OR OXEN)
L13	QUE (RUMINANT? OR HEN# OR CHICKEN# OR FOWL# OR TURKEY?)
L14	QUE (DUCK# OR GOOSE OR GEESE OR CAPON# OR POULTRY?)
L15	QUE (MEAT OR MILK OR EGG# OR TISSUE#)
L16	QUE (((BROKEN? OR BREAK?)(W)(DOWN OR UP)) OR BREAKDOWN?)
L17	QUE (BREAKSDOWN? OR UPTAKE? OR PROCESSING? OR BOUND?)
L18	QUE ((NON(W)EXTRACTAB?) OR (ROTATIONAL(3A)CROP#))
L19	QUE ((L1 OR L2 OR L3) OR L8 OR (L9 OR L10 OR L11 OR L12 OR L13 OR L14) OR (L15 OR L16 OR L17 OR L18))

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

Provider	Database	Justification	Limits applied	Number*
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.	None	247
	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.		64
	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.		0
	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.		5
	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.		28
	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.		74
	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

Provider	Database	Justification	Limits applied	Number*
	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		685
	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.		3
	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.		0
	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.		43
	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
	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.		48
	PASCAL	The database provides access to the world’s scientific and technical literature including physics and chemistry, life sciences (biology, medicine, and psychology), applied sciences and technology, earth sciences, and information sciences. French and European literature is particularly well represented. Approximately 5,000 journal titles are indexed. References to theses and to conference proceedings are also included. Spans the period 1977 to present and is updated weekly		5

Provider	Database	Justification	Limits applied	Number*
	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.		135
	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.		5

* 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)
Total number of *summary records* retrieved after *all** searches of peer-reviewed literature (excluding duplicates)	1629
Number of *summary records* excluded from the search results after rapid assessment for relevance	1620
Total number of *full-text* documents assessed in detail*	9
Number of *studies* excluded from further consideration after detailed assessment for relevance	9
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	0

*both from bibliographic databases and other sources of peer-reviewed literature

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
CA 6.2.1	Pang Sen; Ran Zhaojin; Liu Zhiqian; Song Xiaoyu; Duan Liusheng; Li Xuefeng; Wang Chengju	2012	Enantioselective induction of a glutathione-S-transferase, a glutathione transporter and an ABC transporter in maize by Metolachlor and its (S)-isomer.	PloS one, (2012) Vol. 7, No. 10, pp. e48085
CA 6.2.1	Perez Sandra; Farkas Michael; Barcelo Damia; Aga Diana S	2007	Characterization of glutathione conjugates of chloroacetanilide pesticides using ultra-performance liquid chromatography /quadrupole time-of-flight mass spectrometry and liquid chromatography/ion trap mass spectrometry	Rapid communications in mass spectrometry : RCM, (2007) Vol. 21, No. 24, pp. 4017-22
CA 6.2.1	Berry James O; Aga Diana S	2007	Determination of enzyme kinetics and glutathione conjugates of chlortetracycline and chloroacetanilides using liquid chromatography-mass spectrometry	The Analyst, (2007 Jul) Vol. 132, No. 7, pp. 664-71
CA 6.3	Muhammad Amjad; Tanveer Ahmad; Qumer Iqbal; Aamir Nawaz; Jahangir, M. M.	2013	Herbicide contamination in carrot grown in Punjab, Pakistan	Pakistan Journal of Agricultural Sciences (2013), Volume 50, Number 1, pp. 7-10
CA 6.7	US Environmental Protection Agency	2012	S-Metolachlor; Pesticide Tolerances	[USA] Federal Register (2012), 77 (158), 48902-48907, 15 Aug 2012
CA 6.7	US Environmental Protection Agency	2014	S-Metolachlor; Pesticide Tolerances	Federal Register (2014), 79 (100), 29729-29732, 23 May 2014
CA 6.9	Fantke, Peter; Juraske, Ronnie; Anton, Assumpcio; Friedrich, Rainer; Jolliet, Olivier	2011	Dynamic Multicrop Model to Characterize Impacts of Pesticides in Food	Environmental Science & Technology (2011), 45 (20), 8842-8849
CA 6.9	Nougadere, Alexandre; Reninger, Jean-Cedric; Volatier, Jean-Luc; Leblanc, Jean-Charles	2011	Chronic dietary risk characterization for pesticide residues: A ranking and scoring method integrating agricultural uses and food contamination data	Food and Chemical Toxicology (2011), 49 (7), 1484-1510

CA data point number	Author(s)	Year	Title	Source
CA 6.9	Juraske, Ronnie; Mutel, Christopher L.; Stoessel, Franziska; Hellweg, Stefanie	2009	Life cycle human toxicity assessment of pesticides: Comparing fruit and vegetable diets in Switzerland and the United States	Chemosphere (2009), 77 (7), 939-945

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
Berry James O; Aga Diana S	2007	CA 6.2.1	Determination of enzyme kinetics and glutathione conjugates of chlortetracycline and chloroacetanilides using liquid chromatography-mass spectrometry	The Analyst, (2007 Jul) Vol. 132, No. 7, pp. 664-71
Fantke, Peter; Juraske, Ronnie; Anton, Assumpcio; Friedrich, Rainer; Jolliet, Olivier	2011	CA 6.9	Dynamic Multicrop Model to Characterize Impacts of Pesticides in Food	Environmental Science & Technology (2011), 45 (20), 8842-8849
Juraske, Ronnie; Mutel, Christopher L.; Stoessel, Franziska; Hellweg, Stefanie	2009	CA 6.9	Life cycle human toxicity assessment of pesticides: Comparing fruit and vegetable diets in Switzerland and the United States	Chemosphere (2009), 77 (7), 939-945
Muhammad Amjad; Tanveer Ahmad; Qumer Iqbal; Aamir Nawaz; Jahangir, M. M.	2013	CA 6.3	Herbicide contamination in carrot grown in Punjab, Pakistan	Pakistan Journal of Agricultural Sciences (2013), Volume 50, Number 1, pp. 7-10
Nougadere, Alexandre; Reninger, Jean-Cedric; Volatier, Jean-Luc; Leblanc, Jean-Charles	2011	CA 6.9	Chronic dietary risk characterization for pesticide residues: A ranking and scoring method integrating agricultural uses and food contamination data	Food and Chemical Toxicology (2011), 49 (7), 1484-1510
Pang Sen; Ran Zhaojin; Liu Zhiqian; Song Xiaoyu; Duan Liusheng; Li Xuefeng; Wang Chengju	2012	CA 6.2.1	Enantioselective induction of a glutathione-S-transferase, a glutathione transporter and an ABC transporter in maize by Metolachlor and its (S)-isomer.	PloS one, (2012) Vol. 7, No. 10, pp. e48085
Perez Sandra; Farkas Michael; Barcelo Damia; Aga Diana S	2007	CA 6.2.1	Characterization of glutathione conjugates of chloroacetanilide pesticides using ultra-performance liquid chromatography /quadrupole time-of-flight mass spectrometry and liquid chromatography/ion trap mass spectrometry	Rapid communications in mass spectrometry : RCM, (2007) Vol. 21, No. 24, pp. 4017-22
US Environmental Protection Agency	2012	CA 6.7	S-Metolachlor; Pesticide Tolerances	[USA] Federal Register (2012), 77 (158), 48902-48907, 15 Aug 2012
US Environmental Protection Agency	2014	CA 6.7	S-Metolachlor; Pesticide Tolerances	Federal Register (2014), 79 (100), 29729-29732, 23 May 2014

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

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

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
Initial search					
CA 6.2.1	Pang Sen; Ran Zhaojin; Liu Zhiqian; Song Xiaoyu; Duan Liusheng; Li Xuefeng; Wang Chengju	2012	Enantioselective induction of a glutathione-S-transferase, a glutathione transporter and an ABC transporter in maize by Metolachlor and its (S)-isomer.	PloS one, (2012) Vol. 7, No. 10, pp. e48085	Discusses differences in metabolism of racemic and S-metolachlor; these differences are well known. No impact on S-metolachlor endpoints
CA 6.2.1	Perez Sandra; Farkas Michael; Barcelo Damia; Aga Diana S	2007	Characterization of glutathione conjugates of chloroacetanilide pesticides using ultra-performance liquid chromatography /quadrupole time-of-flight mass spectrometry and liquid chromatography/ion trap mass spectrometry	Rapid communications in mass spectrometry : RCM, (2007) Vol. 21, No. 24, pp. 4017-22	Study conducted in plant extracts in-vitro; similar conditions will never be encountered in whole plant hence results not relevant to plant metabolism.
CA 6.2.1	Berry James O; Aga Diana S	2007	Determination of enzyme kinetics and glutathione conjugates of chlortetracycline and chloroacetanilides using liquid chromatography-mass spectrometry	The Analyst, (2007 Jul) Vol. 132, No. 7, pp. 664-71	Study conducted in plant extracts in-vitro; similar conditions will never be encountered in whole plant hence results not relevant to plant metabolism.
CA 6.3	Muhammad Amjad; Tanveer Ahmad; Qumer Iqbal; Aamir Nawaz; Jahangir, M. M.	2013	Herbicide contamination in carrot grown in Punjab, Pakistan	Pakistan Journal of Agricultural Sciences (2013), Volume 50, Number 1, pp. 7-10	Relevant only to non-controlled uses of pesticide products in Pakistan.
CA 6.7	US Environmental Protection Agency	2012	S-Metolachlor; Pesticide Tolerances	[USA] Federal Register (2012), 77 (158), 48902-48907, 15 Aug 2012	MRL setting in the US. Not relevant to EU scenario
CA 6.7	US Environmental Protection Agency	2014	S-Metolachlor; Pesticide Tolerances	Federal Register (2014), 79 (100), 29729-29732, 23 May 2014	MRL setting in the US. Not relevant to EU scenario
CA 6.9	Fantke, Peter; Juraske, Ronnie; Anton, Assumpcio; Friedrich, Rainer; Jolliet, Olivier	2011	Dynamic Multicrop Model to Characterize Impacts of Pesticides in Food	Environmental Science & Technology (2011), 45 (20), 8842-8849	Development of generic exposure assessment model. Metolachlor not specifically mentioned in paper.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 6.9	Nougadere, Alexandre; Reninger, Jean-Cedric; Volatier, Jean-Luc; Leblanc, Jean-Charles	2011	Chronic dietary risk characterization for pesticide residues: A ranking and scoring method integrating agricultural uses and food contamination data	Food and Chemical Toxicology (2011), 49 (7), 1484-1510	Describes method to rank pesticides based on levels of concern to stimulate targeted national monitoring programmes. S-metolachlor identified as an active substance that presents no risk for consumers
CA 6.9	Juraske, Ronnie; Mutel, Christopher L.; Stoessel, Franziska; Hellweg, Stefanie	2009	Life cycle human toxicity assessment of pesticides: Comparing fruit and vegetable diets in Switzerland and the United States	Chemosphere (2009), 77 (7), 939-945	Generic exposure assessment of Swiss and US diets. Metolachlor not specifically mentioned in paper.

No literature references were deemed to be relevant to the residue or metabolism endpoints for S-metolachlor.