Fludioxonil

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
12/1/17	In response to questions from the RMS: CA 9.6 Additional details on the rapid assessment are provided in the results summary. All amendments are highlighted in yellow.	CGA173506_11860 11 April 2016 updated 12/1/17

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

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CA 9 LITERATURE DATA

CA 9.1 Title

This document is a Literature Review Report for fludioxonil, metabolites and EU representative formulations A8702M (CELEST®) and A8240D (GEOXE®).

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 fludioxonil and its potentially relevant metabolites(s) dealing with side effects on health and published within the last ten years before the date of submission of the dossier" in accordance with Article 8(5) of Regulation (EC) No. 1107/2009.

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

1. A very broad search was conducted in 18 scientific source databases (detailed in Table 9.5-2) for fludioxonil and its metabolites (CGA192155, CGA265378, CGA339833 & CGA344623) using the search terms listed in CA 9.5.1.
2. Duplicates titles from between the data bases were automatically removed from the output.
3. A rapid assessment of the titles was conducted to remove any additional duplicates and any obviously irrelevant titles (where enough information was available from the title alone).
4. A further rapid assessment was conducted using summary abstracts and any clearly irrelevant titles were removed.
5. A detailed assessment of the full-text documents for the remaining titles was conducted using the criteria developed for study relevance (see Table 9.4.2-1)
6. Any relevant papers were highlighted and assessed for reliability.

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)	Number (Top-Up Search)
Total number of *summary records* retrieved after *all** searches of peer-reviewed literature (excluding duplicates)	343	83
Number of *summary records* excluded from the search results after rapid assessment for relevance**	326	78
Total number of *full-text* documents assessed in detail*	17	5
Number of *studies* excluded from further consideration after detailed assessment for relevance	12	4
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	5	1

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

CA 9.4 Protocol

CA 9.4.1 Statement of the objective of the review

The review has the objective of identifying "scientific peer-reviewed open literature on fludioxonil and its potentially relevant metabolites dealing with side effects on health and published within the last ten years before the date of submission of the dossier" in accordance with Article 8(5) of Regulation (EC) No. 1107/2009.

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

Table 9.4.2-1: List of Criteria for relevance for toxicological and toxicokinetic studies

Data requirements(s) (indicated by the correspondent CA data point (s))	Criteria for relevance
*CA 5.1 ADME studies	1. Well identified test material including purity and impurity profile 2. Relevant test species e.g. rodent – rat/mouse – non-rodent – dog 3. Relevant endpoint e.g. ADME measurement or metabolite identification 4. Well described condition of the test and quantitative assessment of results to substantiate and evaluate whether the study conclusions and endpoints are robust
*CA 5.2 Acute toxicity	1. Well identified test material including purity and impurity profile 2. Test species likely to be relevant to mammalian toxicology assessment – rats and mice, rabbit, guinea pig 3. Relevant route of administration for risk assessment 4. Describe observations, examinations, analyses performed or necropsy 5. Different outcome to those studies currently reported
*CA 5.4 Genotoxicity	1. Well identified test material including purity and impurity profile 2. Relevant cell line or species used 3. "validated" or widely used test method 4. In vitro observation not addressed by in vivo data (including tissue specific effects) 5. In vivo effect in somatic or germs cells in relevant species 6. Relevant route of exposure to test substance 7. Contradicts submitted studies, impacts WoE. 8. Recognised methods for scoring studies outcomes used where applicable

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

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

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

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

[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

Data requirements(s) (indicated by the correspondent CP data point (s))	Criteria for relevance
Biomonitoring studies CP 7.2.1.2, CP 7.2.2.2 and CP 7.2.3.2	1. Internal exposures must be clearly related to specific external doses 2. Replicates should be minimum of 10
Air monitoring studies CP 7.2.2.2	10. Monitoring parameters must be relevant to bystander/resident exposures, including monitoring distance, height and duration: 11. Accurate logs of relevant local activity must be available (e.g. crop spraying) 12. Accurate logs of local climactic/meteorological conditions must be available for the duration of the monitoring period, including rainfall, wind speed, wind direction, temperature and humidity
Dislodgeable foliar residue studies CP 7.2.3.2	1. Study must have been conducted on a similar formulation 2. Application number and interval must be relevant 3. Replicates must be minimum of 40
Foliar decline studies CP 7.2.3.2	3. Data must demonstrate minimum of two clear half lives 4. Sufficient data points must be provided to demonstrate decline curves between repeat applications 5. Studies with significant rainfall in first 48 hours should be discounted 6. Replicates must be minimum of 10

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

CA 9.5 Search methods

Date of initial search	27 May 2014
Date of most recent update to search	28 October 2015
Date span of the search	10 years

An additional search was also conducted on the new metabolite SYN454245. Details are given in the table below. The search returned no results.

Date of initial search (SYN545245)	03 February 2016
Date of most recent update to search	Not applicable
Date span of the search	Unlimited

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

Search Strategy	
L1	QUE (131341-86-1 OR CGA173506 OR (CGA(W)173506) OR CELESTE)
L2	QUE (FLUDIOXONIL OR (MAXIM(W)(4FS OR PSP)) OR (BERET(W)GOLD))
L3	QUE (GEOXE OR MAXIM OR SAPHIRE OR SAVIOR OR SCHOLAR OR SEIBIA)
L4	QUE ((L3(10A)(PESTICID? OR FUNGICID?)) OR 1135442-63-5)
L5	QUE (L1 OR L2 OR L4) FLUDIOXONIL
L6	QUE (1418095-12-1 OR 126120-85-2 OR 1418095-13-2 OR 166982-10-1)
L7	QUE (CGA339833 OR (CGA(W)(339833 OR 192155)) OR CGA192155)
L8	QUE (CGA344623 OR (CGA(W)(344623 OR 265378)) OR CGA265378)
L9	QUE (L6 OR L7 OR L8) METABOLITES
L10	QUE L5 OR L9
	Plus

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)
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Additional SYN545245 search

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L1              QUE SPE=ON  ABB=ON  PLU=ON  (SYN545245 OR SYN(W)545245)
L2              QUE SPE=ON  ABB=ON  PLU=ON  (3(W)CYANO(W)2(W) 2(W)2(W)DIFLUORO(
                W)BENZO(W)1(W)3(W)DIOXOL(W)4(W)YL(W)(PROPIONIC OR PROPANOIC)(W)
                ACID OR 3(W)CYANO(W)2(W)2(W)2(W)DIFLUORO(W)1(W)3(W)BENZODIOXOL(
                W)4(W)YL(W)(PROPIONIC OR PROPANOIC)(W)ACID)
L3              QUE SPE=ON  ABB=ON  PLU=ON  (3(W)CYANO(W)2(W) 2(W)2(W)DIFLUORO(
                W)BENZO(W)1(W)3(W)DIOXOLYL(W)(PROPIONIC OR PROPANOIC)(W)ACID
                OR 3(W)CYANO(W)2(W)2(W)2(W)DIFLUORO(W)1(W)3(W)BENZODIOXOLYL(W)(
                PROPIONIC OR PROPANOIC)(W)ACID)
L4              QUE SPE=ON  ABB=ON  PLU=ON  (2(W)2(W)DIFLUORO(W)1(W)3(W)BENZODI
                OXOL(W)YL(W)3(W)CYANO(W)(PROPIONIC OR PROPANOIC)(W)ACID OR
                2(W)2(W)DIFLUORO(W)1(W)3(W)BENZODIOXOLYL(W)3(W)CYANO(W)(PROPION
                IC OR PROPANOIC)(W)ACID)
L5              QUE SPE=ON  ABB=ON  PLU=ON  (2(W)2(W)DIFLUORO(W)1(W)3(W)BENZODI
                OXOLYL(W)1(W)CARBOXY(W)3(W)PROPAN(1W)NITRIL OR 2(W)2(W)DIFLUORO
                (W)1(W)3(W)BENZODIOXOL(W)YL(W)1(W)CARBOXY(W)3(W)PROPAN(1W)NITRI
                L)
L6              QUE SPE=ON  ABB=ON  PLU=ON  (DIFLUORO(2W) BENZODIOXOLYL(1W)
                CARBOXY(1W) PROPAN(1W)NITRIL OR DIFLUORO(2W)BENZODIOXOL(W)YL(1W
                )CARBOXY(1W) PROPAN(1W)NITRIL)
L7              QUE SPE=ON  ABB=ON  PLU=ON  (CYANO(3W)DIFLUORO(W)BENZO(2W)DIOXO
                L(1W)YL(W)(PROPIONIC OR PROPANOIC)(W)ACID OR CYANO(3W)DIFLUORO(
                2W)BENZODIOXOL(1W)YL(W)(PROPIONIC OR PROPANOIC)(W)ACID)
L8              QUE SPE=ON  ABB=ON  PLU=ON  (DIFLUORO(2W)BENZODIOXOL(W)YL(1W)CY
                ANO(W)(PROPIONIC OR PROPANOIC)(W)ACID OR DIFLUORO(2W)BENZODIOXO
                LYL(1W)CYANO(W)(PROPIONIC OR PROPANOIC)(W)ACID)
L9              QUE SPE=ON  ABB=ON  PLU=ON  (DIFLUORO(2W)BENZODIOXOL(W)YL(1W)CY
                ANO(W)(PROPIONIC OR PROPANOIC)(W)ACID OR DIFLUORO(2W)BENZODIOXO
                LYL(1W)CYANO(W)(PROPIONIC OR PROPANOIC)(W)ACID)
L10             QUE SPE=ON  ABB=ON  PLU=ON  (DIFLUOROBENZODIOXOLYL(5A)(CYANO(W)
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Search Strategy	
	(PROPIONIC OR PROPANOIC)(W)ACID OR CARBOXY(1W) PROPAN(1W)NITRIL))
L11	QUE SPE=ON ABB=ON PLU=ON (3(W)CYANO(W)2(W) 2(W)2(W)DIFLUOROB ENZO(W)1(W)3(W)DIOXOL(W)4(W)YL(W)(PROPIONIC OR PROPANOIC)(W)ACI D OR ACIDE(W)3(W)CYANO(W)2(W)2(W)2(W)DIFLUOROBENZO(W)3(W)DIOXOL (W)4(W)YL(W)PROPIONIQUE)
L12	**QUE SPE=ON ABB=ON PLU=ON (L1 OR L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11)**
Please note: CAS registry number and record are not available	

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

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.	10 years	**62**
	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.		**26**
	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.		**3**
	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.		**11**
	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.		**44**
	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.		**92**
	HCAPLUS	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		**108**

Provider	Database	Justification	Limits applied	Number*
	FSTA	The database provides worldwide coverage of all scientific and technological aspects of the processing and manufacture of human food products including basic food sciences, biotechnology, hygiene and toxicology, engineering, packaging, and all individual foods and food products. Sources include more than 2,200 journals, books, reviews, conference proceedings, patents, standards, and legislation. It covers the period 1969 – present and is updated weekly.		**5**
	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.		**5**
	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.		**0**
	TOXCENTER	Covers the pharmacological, biochemical, physiological, and toxicological effects of drugs and other chemicals. It is composed of the following subfiles: BIOSIS, CAplus, IPA and MEDLINE and sources include abstracts, books and book chapters, bulletins, conference proceedings, journal articles, letters, meetings, monographs, notes, papers, patents, presentations, research and project summaries, reviews, technical reports, theses, translations, unpublished material, web reprints. Covers the period 1907 – present and is updated weekly		**31**
	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.		**25**
	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**
	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.		**9**

Provider	Database	Justification	Limits applied	Number*
	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.		**0**
	HCHEMLIST	The database identifies the regulatory requirements for a specific substance from many of the world's most significant regulated substances lists. It records substance identity information, inventory status, source of information, and summaries of regulatory activity, reports, and other compliance information.		**0**
	CROPU	The database covers all aspects of pesticides, including their use in crop protection and pest control. Information on plant and insect growth regulators, attractants, repellents and biological control is also included. The database draws on 1,100 scientific journals, conference proceedings, and patents beginning in 1996. Records contain bibliographic information, titles, abstracts, in-depth indexing, and Enzyme Commission Numbers. Spans the period 1985 to 2003.		**0**
	CROPB	The Crop Protection Backfile is the companion backfile to the current Crop Protection File, CROPU, covering all aspects of pesticides, including their use in crop protection and pest control. Information on plant and insect growth regulators, attractants, repellents and biological control is also included. Bibliographic information and indexing terms are searchable. Spans the period 1968 to 1984.		**0**

* Total number of summary records retrieved after removing duplicates

Table 9.5-3: Detailed Search Parameters for Web searches

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

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

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

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

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

Table 9.5-5: Detailed Search Parameters for Reference Lists

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

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

CA 9.6 Results

Table 9.6-1: Results of study selection process

Data requirement(s) captured in the search	Number (Initial Search)	Number (Top-Up Search)
Total number of *summary records* retrieved after *all** searches of peer-reviewed literature (excluding duplicates)	343	83
Number of *summary records* excluded from the search results after rapid assessment for relevance**	326	78
Total number of *full-text* documents assessed in detail	17	5
Number of *studies* excluded from further consideration after detailed assessment for relevance	12	4
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	5	1

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

Following exclusion of references from the rapid assessment, the full text was assessed from the remaining 22 titles which were identified as potentially relevant or unclear on the basis of their titles. Full details of these papers are given in the tables below.

For the initial rapid assessment, the titles were scanned to identify whether the studies were indeed relevant to toxicology and operator exposure or not. For the initial rapid assessment the study titles and/or abstracts were assessed to identify studies of potential relevance to crop and livestock metabolism, and/or residue studies in the context of human exposure through the diet. Any studies clearly not in the remit of the European review or unambiguously belonging to other sections were excluded.

Here is a summary of the 404 titles removed during rapid assessment -

- 37 titles were discounted from further assessment as they were obviously irrelevant e.g. refer to commodities with similar names, or do not concern toxicology and crop protection products.
- 96 titles were papers concerned with exposures and residues
- 32 titles were removed as they related to describing the analytical methods.
- 206 titles were removed as they were relevant to the control of disease i.e. they were related to biological activity, so not relevant to the metabolism and residues section.
- 23 titles were discounted as although they were not clearly related to toxicology.

Assessment of the full text from the remaining 22 titles which were identified as potentially relevant or unclear on the basis of their titles and/or abstracts identified none of the studies as potentially relevant for this submission of fludioxonil. Full details of these papers are given in the tables below.

Details of why each paper has been excluded for relevance or reliability are given in Table 9.6.4.

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

CA data point number	Author(s)	Year	Title	Source
Initial search				

CA data point number	Author(s)	Year	Title	Source
CA 5.4.1	Graillot V.; Takakura N; Hegarat L.L.; Fessard V.; Audebert M.; Cravedi J.P.	2012	Genotoxicity of pesticide mixtures present in the diet of the French population	Environ Mol Mutagen 53 (3) 173-84
CA 5.4.1	Kligerman A D; Young R R; Stankowski L F; Pant K; Lwlor T; Aardema M J; Houck K A.	2015	An evaluation of 25 selected ToxCast chemicals in medium-throughput assays to detect genotoxicity	Environmental and Molecular Mutagenesis 56 (5) 468–476
CA 5.4.1	Knight A W; Little S; Houck K; Dix D; Judson R; Richard A; McCarroll N; Akerman G; Yang C; Birrell L; Walmsley R M.	2009	Evaluation of high-throughput genotoxicity assays used in profiling the US EPA ToxCast™ chemicals.	Regulatory Toxicology and Pharmacology 55 188–199.
CA 5.5.1	Martin M.T.; Judson R.S.; Reif D.M.; Kavlock R.J.; Dix D.J..	2009	Profiling Chemicals based on Chronic Toxicity Results from the US EPA ToxRef database	Environmental Health Perspectives 117 (3) 392-399
CA 5.6.2	Sipes N S; Martin M T; Reif D M; Kleinstreuer N C; Judson, R S; Singh, A V.; Chandler K J; Dix D J.; Kavlock R J.; Knudsen T B.	2011	Predictive Models of Prenatal Developmental Toxicity from ToxCast™ High-Throughput Screening Data.	Toxicological Sciences 124 (1) 109-127.
CA 5.6.2	Padilla S; Corum D; Padnos B; Hunter D L; Beam A; Houck K A; Sipes N; Kleistreuer N; Knudsen T; Dix D J; Reif D M.	2012	Zebrafish developmental screening of the ToxCast™ Phase I chemical library.	Reproductive Toxicology 33 174-187.
CA 5.7	Chandler K.J.; Barrier M.; Jeffay S.; Nichols H.; Kleinstreuer N.N.; Singh A.V.; Reif D.M.; Sipes N.S.; Judson R.S.; Dix D.J.; Kavlock R.; Hunter E.S.; Knudsen T.B..	2011	Evaluation of 309 environmental chemicals using a mouse embryonic stem cell adherent cell differentiation and cytotoxicity assay	PLoS ONE 6(6) e18540 1-11
CA 5.7	Knudsen T.B.; Martin M.T.; Kavlock R.J.; Judson R.S.; Dix D.J.; Singh A.V..	2009	Profiling the activity of environmental chemicals in prenatal development toxicity studies using the US EPA's ToxRefDB	Reproductive Toxicology 28 (2009) 209-219
CA 5.8.2	Judson R S; Houck K A; Kavlock R J; Knudsen T B; Martin M T; Mortensen H M; Reif D M; Rotroff D M; Shah I; Richard A M; Dix D J.	2010	*In Vitro* Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast™ Project	Environmental Health Perspectives 118 (4), 485-492.
CA 5.8.2	Sipes N; Martin M; Kothiya P; Reif D; Judson R; Richard A; Houck K; Dix D; Kavlock R; Knudsen T	2013	Profiling 976 ToxCast chemicals across 331 enzymatic and receptor signalling assays	Chemical Research in Toxicology 2013, 26 878-895
CA 5.8.2	Wetmore B A; Wambaugh J F; Ferguson S S; Sochaski M A; Rotroff D M; Freeman K; Clewell H J; Dix D J; Andersen M E; Houck K A; Allen B; Judson R S; Singh R; Kavlock R J; Richard A M; Thomas R S.	2012	Integration of Dosimetry, Exposure, and High-Throughput Screening Data in Chemical Toxicity Assessment	Toxicological Sciences 125(1), 157–174 (2012)
CA 5.8.3	Medjakovic S, Zoechling A, Gerster P, Ivanova MM, Teng Y, Klinge CM, Schildberger B, Gartner M, Jungbauer A.	2013	Effect of nonpersistent pesticides on estrogen receptor, androgen receptor, and aryl hydrocarbon receptor.	Environmental Toxicology 10, 1201-1216

CA data point number	Author(s)	Year	Title	Source
CA 5.8.3	Orton F, Rosivatz E, Scholze M, Kortenkamp A.	2011	Widely used pesticides with previously unknown endocrine activity revealed as *in vitro* anti-androgens.	Environmental Health Perspectives 119 (6):794-800.
CA 5.8.3	Orton F, Rosivatz E, Scholze M, Kortenkamp A	2012	Competitive androgen receptor antagonism as a factor determining the predictability of cumulative anti-androgenic effects of widely used pesticides.	Environmental Health Perspectives 120 (11):1578-1584.
CA 5.8.3	Reif DM, Martin MT, Tan SW, Houck KA, Judson RS, Richard AM, Knudsen TB, Dix DJ, Kavlock RJ.	2010	Endocrine profiling and prioritization of environmental chemicals using ToxCast™ data.	Environmental Health Perspectives 118 (2) 1714-1720.
CA 5.8.3	Wambaugh, JF; Woodrow Setzer R; Reif, DM.; Gangwal S; Mitchell-Blackwood J; Arnot JA; Joliet O; Frame A; Rabinowitz J; Knudsen, TB; Judson,RS; Egeghy P; Vallero D; Cohen Hubal EA.	2013	High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project.	Environmental Science & Technology, 47 (15), 8479-8488.
CA 5.8.3	Teng Y, Manavalan TT, Hu C, Medjakovic S, Jungbauer A, Klinge CM.	2013	Endocrine disruptors fludioxonil and fenhexamid stimulate miR-21 expression in breast cancer cells.	Toxicol Sci. 131:71-83.
Top-Up search				
CA 5.1	Wambaugh J F; Wetmore B A; Pearce R; Strope C; Goldsmith R; Sluka J P; Sedykh A; Tropsha A; Bosgra S; Shah I; Judson R; Thomas R S; Setzer R W.	2015	Toxicokentic Triage for Environmental Chemicals	Toxicological Sciences, 147 (1) 55-67
CA 5.4	Kligerman A D; Young R R; Stankowski L F; Pant K; Lwlor T; Aardema M J; Houck K A.	2015	An evaluation of 25 selected ToxCast chemicals in medium-throughput assays to detect genotoxicity	Environmental and Molecular Mutagenesis 56 (5) 468–476
CA 5.8.3	Rotroff D M; Martin M T; Dix D J; Filer D L; Houck K A; Knudsen T B; Sipes N S; Reif D M; Xia M; Huang R; Judson R S.	2014	Predictive Endocrine Testing in the 21st Century Using in Vitro Assays of Estrogen Receptor Signaling Responses.	Environmental Science & Technology, 48 (15), 8706-8716.
CA 5.8.3	Kugathas S.; Audouze K.; Ermler S.; Orton F.; Rosivatz E.; Scholze M.; Kortenkamp A..	2015	Effects of Common Pesticides on Prostaglandin D2 (PGD2) Inhibition in SC5 Mouse Sertoli Cells, Evidence of Binding at the COX2 Active Site, and Implications for Endocrine Disruption	Environ Health Perspect – not published (online article)
CA 5.8.3	Go R-E; Choi K-C	2015	Antifungal agents as agricultural products, fenhexamid, fludioxonil, and cyprodinil, induced the expression of cytochrome p450 family and cell cyclerelated genes in estrogen receptor expressing BG-1 ovarian cancer cells.	Reproduction Fertility and Development, 27 (1), 201.

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

Author(s)	Year	CA data point number	Title	Source
Initial Search				
Chandler K.J.; Barrier M.; Jeffay S.; Nichols H.; Kleinstreuer N.N.; Singh A.V.; Reif D.M.; Sipes N.S.; Judson R.S.; Dix D.J.; Kavlock R.; Hunter E.S.; Knudsen T.B..	2011	CA 5.7	Evaluation of 309 environmental chemicals using a mouse embryonic stem cell adherent cell differentiation and cytotoxicity assay	PLoS ONE 6(6) e18540 1-11
Graillot V.; Takakura N; Hegarat L.L.; Fessard V.; Audebert M.; Cravedi J.P.	2012	CA 5.4.1	Genotoxicity of pesticide mixtures present in the diet of the French population	Environ Mol Mutagen 53 (3) 173-84
Kligerman A D; Young R R; Stankowski L F; Pant K; Lwlor T; Aardema M J; Houck K A.	2015	CA 5.4.1	An evaluation of 25 selected ToxCast chemicals in medium-throughput assays to detect genotoxicity	Environmental and Molecular Mutagenesis 56 (5) 468–476
Knight A W; Little S; Houck K; Dix D; Judson R; Richard A; McCarroll N; Akerman G; Yang C; Birrell L; Walmsley R M.	2009	CA 5.4.1	Evaluation of high-throughput genotoxicity assays used in profiling the US EPA ToxCast™ chemicals.	Regulatory Toxicology and Pharmacology 55 188–199.
Knudsen T.B.; Martin M.T.; Kavlock R.J.; Judson R.S.; Dix D.J.; Singh A.V..	2009	CA 5.7	Profiling the activity of environmental chemicals in prenatal development toxicity studies using the US EPA's ToxRefDB	Reproductive Toxicology 28 (2009) 209-219
Judson R S; Houck K A; Kavlock R J; Knudsen T B; Martin M T; Mortensen H M; Reif D M; Rotroff D M; Shah I; Richard A M; Dix D J.	2010	CA 5.8.2	*In Vitro* Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast™ Project	Environmental Health Perspectives 118 (4), 485-492.
Martin M.T.; Judson R.S.; Reif D.M.; Kavlock R.J.; Dix D.J..	2009	CA 5.5.1	Profiling Chemicals based on Chronic Toxicity Results from the US EPA ToxRef database	Environmental Health Perspectives 117 (3) 392-399
Medjakovic S, Zoechling A, Gerster P, Ivanova MM, Teng Y, Klinge CM, Schildberger B, Gartner M, Jungbauer A.	2013	CA 5.8.3	Effect of nonpersistent pesticides on estrogen receptor, androgen receptor, and aryl hydrocarbon receptor.	Environmental Toxicology 10, 1201-1216.
Padilla S; Corum D; Padnos B; Hunter D L; Beam A; Houck K A; Sipes N; Kleistreuer N; Knudsen T; Dix D J; Reif D M.	2012	CA 5.6.2	Zebrafish developmental screening of the ToxCast™ Phase I chemical library.	Reproductive Toxicology 33 174-187.
Orton F, Rosivatz E, Scholze M, Kortenkamp A.	2011	CA 5.8.3	Widely used pesticides with previously unknown endocrine activity revealed as *in vitro* anti-androgens.	Environmental Health Perspectives 119 (6):794-800.
Orton F, Rosivatz E, Scholze M, Kortenkamp A	2012	CA 5.8.3	Competitive androgen receptor antagonism as a factor determining the predictability of cumulative anti-androgenic effects of widely used pesticides.	Environmental Health Perspectives 120 (11):1578-1584.
Reif D; Martin M; Tan S; Houck K; Judson R; Richard A; Knudsen T; Dix D; Kavlock R	2010	CA 5.8.3	Endocrine profiling and prioritisation of environmental chemicals using ToxCast data	Environmental Health perspectives Volume 118 (12) 1714-1720

Author(s)	Year	CA data point number	Title	Source
Sipes N; Martin M; Kothiya P; Reif D; Judson R; Richard A; Houck K; Dix D; Kavlock R; Knudsen T	2013	CA 5.8.2	Profiling 976 ToxCast chemicals across 331 enzymatic and receptor signalling assays	Chemical Research in Toxicology 2013, 26 878-895
Sipes N S; Martin M T; Reif D M; Kleinstreuer N C; Judson R S; Singh A V; Chandler K J; Dix D J; Kavlock R J; Knudsen T B	2011	CA 5.6	Predictive models of prenatal developmental toxicity from ToxCast high-throughput screening data	Toxicological Sciences 124(1) 109-127
Wambaugh, JF; Woodrow Setzer R; Reif, DM.; Gangwal S; Mitchell-Blackwood J; Arnot JA; Joliet O; Frame A; Rabinowitz J; Knudsen, TB; Judson,RS; Egeghy P; Vallero D; Cohen Hubal EA.	2013	CA 5.8.3	High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project.	Environmental Science & Technology, 47 (15), 8479-8488.
Wetmore B A; Wambaugh J F; Ferguson S S; Sochaski M A; Rotroff D M; Freeman K; Clewell H J; Dix D J; Andersen M E; Houck K A; Allen B; Judson R S; Singh R; Kavlock R J; Richard A M; Thomas R S.	2012	CA 5.8.2	Integration of Dosimetry, Exposure, and High-Throughput Screening Data in Chemical Toxicity Assessment	Toxicological Sciences 125(1), 157–174 (2012)
Teng Y, Manavalan TT, Hu C, Medjakovic S, Jungbauer A, Klinge CM.	2013	CA 5.8.3	Endocrine disruptors fludioxonil and fenhexamid stimulate miR-21 expression in breast cancer cells.	Toxicol Sci. 131:71-83.
Top-Up search				
Go R-E; Choi K-C	2015	CA 5.8.3	Antifungal agents as agricultural products, fenhexamid, fludioxonil, and cyprodinil, induced the expression of cytochrome p450 family and cell cyclerelated genes in estrogen receptor expressing BG-1 ovarian cancer cells.	Reproduction Fertility and Development, 27 (1), 201.
Kligerman A D; Young R R; Stankowski L F; Pant K; Lwlor T; Aardema M J; Houck K A.	2015	CA 5.4	An evaluation of 25 selected ToxCast chemicals in medium-throughput assays to detect genotoxicity	Environmental and Molecular Mutagenesis 56 (5) 468–476
Kugathas S.; Audouze K.; Ermler S.; Orton F.; Rosivatz E.; Scholze M.; Kortenkamp A..	2015	CA 5.8.3	Effects of Common Pesticides on Prostaglandin D2 (PGD2) Inhibition in SC5 Mouse Sertoli Cells, Evidence of Binding at the COX2 Active Site, and Implications for Endocrine Disruption	Environ Health Perspect – not published (online article)
Rotroff D; Martin M; Dix D; Filer D; Houck K; Knudsen T; Sipes N; Reif D; Xia M; Huang R; Judson R	2014	CA 5.8.3	Predictive endocrine testing in the 21st Century using *in vitro* assays of estrogen receptor signaling responses	Environmental Science and Technology 2014, 48, 8706-8716

Author(s)	Year	CA data point number	Title	Source
Wambaugh J F; Wetmore B A; Pearce R; Strope C; Goldsmith R; Sluka J P; Sedykh A; Tropsha A; Bosgra S; Shah I; Judson R; Thomas R S; Setzer R W.	2015	CA 5.1	Toxicokentic Triage for Environmental Chemicals	Toxicological Sciences, 147 (1) 55-67

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

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

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
Initial search					
CA 5.4.1	Graillot V.; Takakura N; Hegarat L.L.; Fessard V.; Audebert M.; Cravedi J.P.	2012	Genotoxicity of pesticide mixtures present in the diet of the French population	Environ Mol Mutagen 53 (3) 173-84	Paper presents data concerning potential mixture effects and does not test fludixonil individually therefore no new data that would change the current position on toxicity.
CA 5.4.1	Knight A W; Little S; Houck K; Dix D; Judson R; Richard A; McCarroll N; Akerman G; Yang C; Birrell L; Walmsley R M.	2009	Evaluation of high-throughput genotoxicity assays used in profiling the US EPA ToxCast™ chemicals.	Regulatory Toxicology and Pharmacology 55 188–199.	Pesticides of known genotoxic potential were screened in high through-put screens to evaluate the use of such screens as an aid to prioritization of carcinogenicity assessment. This paper does not add any data to that available from OECD guideline studies on fludioxonil.
CA 5.5.1	Martin M.T.; Judson R.S.; Reif D.M.; Kavlock R.J.; Dix D.J..	2009	Profiling Chemicals based on Chronic Toxicity Results from the US EPA ToxRef database	Environmental Health Perspectives 117 (3) 392-399	Paper describes use of existing *in vivo* data on fludioxonil to help build a predictive model for chronic toxicity – no new data is presented.
CA 5.6.2	Sipes N S; Martin M T; Reif D M; Kleinstreuer N C; Judson, R S; Singh, A V.; Chandler K J; Dix D J.; Kavlock R J.; Knudsen T B.	2011	Predictive Models of Prenatal Developmental Toxicity from ToxCast™ High-Throughput Screening Data.	Toxicological Sciences 124 (1) 109-127.	Paper describes use of existing *in vivo* data on fludioxonil to help build a predictive model for developmental toxicity – no new data is presented.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.6.2	Padilla S; Corum D; Padnos B; Hunter D L; Beam A; Houck K A; Sipes N; Kleistreuer N; Knudsen T; Dix D J; Reif D M.	2012	Zebrafish developmental screening of the ToxCast™ Phase I chemical library.	Reproductive Toxicology 33 174-187.	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 5.7	Chandler K.J.; Barrier M.; Jeffay S.; Nichols H.; Kleinstreuer N.N.; Singh A.V.; Reif D.M.; Sipes N.S.; Judson R.S.; Dix D.J.; Kavlock R.; Hunter E.S.; Knudsen T.B..	2011	Evaluation of 309 environmental chemicals using a mouse embryonic stem cell adherent cell differentiation and cytotoxicity assay	PLoS ONE 6(6) e18540 1-11	Paper described screening studies using an in vitro cell line. As part of an evaluation of the model as a screening tool for developmental toxicity. No new *in vivo* mammalian data is presented.
CA 5.7	Knudsen T.B.; Martin M.T.; Kavlock R.J.; Judson R.S.; Dix D.J.; Singh A.V..	2009	Profiling the activity of environmental chemicals in prenatal development toxicity studies using the US EPA's ToxRefDB	Reproductive Toxicology 28 (2009) 209-219	Paper reviews screening ToxCast™ data. No data on fludioxonil which would change the current position on toxicity or mode of action.
CA 5.8.2	Judson R S; Houck K A; Kavlock R J; Knudsen T B; Martin M T; Mortensen H M; Reif D M; Rotroff D M; Shah I; Richard A M; Dix D J.	2010	*In Vitro* Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast™ Project.	Environmental Health Perspectives 118 (4), 485-492.	Paper reviews *in vitro* screening ToxCast™ data. No data on fludioxonil which would change the current position on toxicity or mode of action.
CA 5.8.3	Sipes N; Martin M; Kothiya P; Reif D; Judson R; Richard A; Houck K; Dix D; Kavlock R; Knudsen T	2013	Profiling 976 ToxCast chemicals across 331 enzymatic and receptor signalling assays	Chemical Research in Toxicology 2013, 26 878-895	No specific reference to Fludioxonil in this reference. No data which would change the current position on toxicity or mode of action.

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.8.2	Wetmore B A; Wambaugh J F; Ferguson S S; Sochaski M A; Rotroff D M; Freeman K; Clewell H J; Dix D J; Andersen M E; Houck K A; Allen B; Judson R S; Singh R; Kavlock R J; Richard A M; Thomas R S.	2012	Integration of Dosimetry, Exposure, and High-Throughput Screening Data in Chemical Toxicity Assessment	Toxicological Sciences 125(1), 157–174 (2012)	Paper reviews *in vitro* screening ToxCast™ data. No data on fludioxonil which would change the current position on toxicity or mode of action.
~~CA 5.8.3~~	~~Orton F, Rosivatz E, Scholze M, Kortenkamp A~~	~~2012~~	~~Competitive androgen receptor antagonism as a factor determining the predictability of cumulative anti-androgenic effects of widely used pesticides.~~	~~Environmental Health Perspectives 120 (11):1578-1584.~~	~~Paper presents data concerning potential mixture effects and does not test Fludioxonil individually therefore no new data that would change the current position on toxicity.~~
CA 5.8.3	Wambaugh, JF; Woodrow Setzer R; Reif, DM.; Gangwal S; Mitchell-Blackwood J; Arnot JA; Joliet O; Frame A; Rabinowitz J; Knudsen, TB; Judson,RS; Egeghy P; Vallero D; Cohen Hubal EA.	2013	High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project.	Environmental Science & Technology, 47 (15), 8479-8488.	No specific reference to Fludioxonil, it is a general ExpoCast analysis.
Top-Up search					
CA 5.1	Wambaugh J F; Wetmore B A; Pearce R; Strope C; Goldsmith R; Sluka J P; Sedykh A; Tropsha A; Bosgra S; Shah I; Judson R; Thomas R S; Setzer R W.	2015	Toxicokentic Triage for Environmental Chemicals	Toxicological Sciences, 147 (1) 55-67	No specific reference to Fludioxonil, although the paper makes numerous references to other literature citations (e.g. ToxCast) where Fludioxonil is mentioned. There is no toxicokinetic data for Fludioxonil and it is assumed that it is one of the thousands of man-made chemicals for which the authors propose a 4-element framework for chemical triage

CA data point number	Author(s)	Year	Title	Source	Reason(s) for not including the study in the dossier
CA 5.4	Kligerman A D; Young R R; Stankowski L F; Pant K; Lwlor T; Aardema M J; Houck K A.	2015	An evaluation of 25 selected ToxCast chemicals in medium-throughput assays to detect genotoxicity	Environmental and Molecular Mutagenesis 56 (5) 468–476	Paper reviews genotoxic screening ToxCast™ data. No data on fludioxonil which would change the current position on toxicity or mode of action.
CA 5.8.3	Go R-E; Choi K-C	2015	Antifungal agents as agricultural products, fenhexamid, fludioxonil, and cyprodinil, induced the expression of cytochrome p450 family and cell cyclerelated genes in estrogen receptor expressing BG-1 ovarian cancer cells.	Reproduction Fertility and Development, 27 (1), 201.	*Only the abstract was available and based on analysis of the abstract:* This *in vitro* investigation indicated some potential for endocrine activity in the ovarian cancer cell line. However, the effects observed are not consistent with the findings of Reif *et al*. (2010) which showed no evidence of endocrine activity and has been reviewed as part of Fludioxonil - Review for Potential for Endocrine Disruption in Mammalian Species in **MCA Section 5**. In addition, there is no data on fludioxonil which would change the current position on toxicity or mode of action.
~~CA 5.8.3~~	~~Kugathas S.; Audouze K.; Ermler S.; Orton F.; Rosivatz E.; Scholze M.; Kortenkamp A..~~	~~2015~~	~~Effects of Common Pesticides on Prostaglandin D2 (PGD2) Inhibition in SC5 Mouse Sertoli Cells, Evidence of Binding at the COX2 Active Site, and Implications for Endocrine Disruption~~	~~Environ Health Perspect – not published (online article)~~	~~Paper discussed the potential of Fludioxonil in an in vitro assay but admits the human relevance is difficult to anticipate, recommending supporting in vivo data.~~

Six studies listed in Table 9.6-2 are not excluded (i.e. not listed in Table 9.6-4) and have been discussed further in MCA Section 5 (CA 5.8.3) where an assessment of reliability has been conducted and the conclusions documented.

Details of the summaries for the selected literature references that have been included in an amended **M-CA Section 5** as requested by the RMS are presented in Table 9.6-5.

Table 9.6-5: List of references presented as summaries in the M-CA Section 5 listed by data point number

CA data point number	Author(s)	Year	Title	Source
Initial search				
CA 5.8.3	Orton F, Rosivatz E, Scholze M, Kortenkamp A.	2011	Widely used pesticides with previously unknown endocrine activity revealed as *in vitro* anti-androgens.	Environmental Health Perspectives 119 (6):794-800.
CA 5.8.3	Medjakovic S, Zoechling A, Gerster P, Ivanova MM, Teng Y, Klinge CM, Schildberger B, Gartner M, Jungbauer A.	2013	Effect of nonpersistent pesticides on estrogen receptor, androgen receptor, and aryl hydrocarbon receptor.	Environmental Toxicology 10, 1201-1216
CA 5.8.3	Orton F, Rosivatz E, Scholze M, Kortenkamp A.	2012	Competitive androgen receptor antagonism as a factor determining the predictability of cumulative antiandrogenic effects of widely used pesticides.	Environmental Health Perspectives 120 (11):1578-1584.
CA 5.8.3	Teng Y, Manavalan TT, Hu C, Medjakovic S, Jungbauer A, Klinge CM.	2013	Endocrine disruptors fludioxonil and fenhexamid stimulate miR-21 expression in breast cancer cells.	Toxicol Sci. 131:71-83.
Top-Up search				
CA 5.8.3	Kugathas S.; Audouze K.; Ermler S.; Orton F.; Rosivatz E.; Scholze M.; Kortenkamp A..	2015	Effects of Common Pesticides on Prostaglandin D2 (PGD2) Inhibition in SC5 Mouse Sertoli Cells, Evidence of Binding at the COX2 Active Site, and Implications for Endocrine Disruption	Environ Health Perspect – not published (online article)