

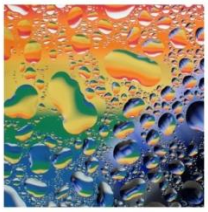

Extended impact assessment study of the human health and environmental criteria for endocrine disrupting substances proposed by HSE, CRD

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Extended impact assessment study of the human health and environmental criteria for endocrine disrupting substances proposed by HSE, CRD

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Contents

Appendices

List of Tables

1. Introduction

1.1 Regulatory background to the project

The prompt for this project was the introduction into the new European Union Plant Protection Products (PPP) Regulation (1107/2009) of an exclusion criterion for approval which explicitly indicates that any active substance, safener and synergist with endocrine disrupting properties that may cause adverse effects in humans cannot be approved for marketing and use unless the exposure of humans under realistic proposed conditions of use is negligible. A similar approval exclusion criterion has been introduced in the new EU Biocidal Products Regulation (Reg EU 528/2012).

Substances with endocrine disrupting properties are also targeted within the REACH Regulation (1907/2006). Identification of substances as endocrine disrupters (EDs) in accordance with the criteria in Article 57(f) may lead to their inclusion in the list of substances of very high concern (SVHCs) as possible candidates for Authorisation. In addition, in accordance with Article 138(7), by 1 June 2013 the Commission shall carry out a review to assess whether or not, taking into account the latest developments in scientific knowledge, to extend the scope of Article 60(3) (Authorisation of SVHCs through the socio-economic route) to substances identified under Article 57(f) as having endocrine disrupting properties.

Despite these stipulations, at the present time there is no set of criteria within these pieces of legislation, by which to identify endocrine disrupters which are considered to be more likely to pose a risk. However, work has been on-going to develop appropriate criteria for human health and environmental assessments and these are described in:

- "*Regulatory Definition of an Endocrine Disrupter in Relation to Potential Threat to Human Health*" prepared as a joint German-UK Position in May 2011 (The document is available at: http://www.pesticides.gov.uk/guidance/industries/pesticides/topics/pesticide-approvals/pesticides-registration/applicant-guide/updates/joint-de-uk-proposal-for-a-regulatory-definition-of-an-endocrine-disruptor-in-relation-to-human-heal)

- "*Definition of an Ecotoxicological Endocrine Disrupter for Regulatory Purposes*" - an EU discussion document prepared by the UK Chemicals Regulation Directorate which was provided as part of the tender specification.

Under Regulation (1107/2009), by 14 December 2013, the Commission has to present to the Standing Committee on the Food Chain and Animal Health a draft of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties to be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 79(4). However, pending the adoption of these criteria, substances that are or have to be classified, as carcinogenic category 2 and toxic for reproduction category 2 (in accordance

with the provisions of Regulation (EC) No 1272/2008) will be considered to have endocrine disrupting properties. In addition, substances such as those that are or have to be classified as toxic for reproduction category 2 and which have toxic effects on the endocrine organs (in accordance with the provisions of Regulation (EC) No 1272/2008) may be considered to have such endocrine disrupting properties.

1.2 Background information on endocrine disruption

The last two decades have witnessed growing scientific concerns and public debate over the potential adverse effects that may result from exposure to a group of chemicals termed "*endocrine disrupters*" that have the potential to alter the normal functioning of the endocrine system in humans and wildlife. Concerns regarding exposure to these endocrine disrupting chemicals are due primarily to:

1. the increased incidence of certain endocrine-related human diseases;

2. adverse effects observed in certain wildlife species; and

3. endocrine disruption observed in laboratory experimental animals exposed to certain environmental chemicals.

These concerns have stimulated many national governments, international organisations, scientific societies, the chemical industry, and public interest groups to establish research programmes, organise conferences and workshops, and form expert groups and committees to address and evaluate endocrine disrupting chemical-related issues. In the light of continuing uncertainties and highly publicized concerns, the International Programme on Chemical Safety (WHO, 2002) provided an objective, global assessment of the current state-of-the-science relative to environmental endocrine disruption in humans, experimental studies, and wildlife species.

In Table 1.1 examples of observed effects in target groups of humans and wildlife which could be endocrine-mediated are given (WHO, 2002). In humans, potential exposure to endocrine disrupters have been associated with increased incidences of cancers in males and females, alterations in the normal patterns of development and reproduction, changes in behaviour during development and adulthood and modifications of the function of the immune system. In the environment, exposure to perceived endocrine disrupting chemicals has been associated with adverse effects on the development and/or reproduction of a wide range of wildlife groups, including molluscs, crustaceans, fish, amphibians, reptiles, birds and mammals. Clearly, changes in individuals of wildlife species have the greatest significance where they are translated into population level effects which may affect ecosystem structure and/or function (for example the worldwide effects of tributyltin on molluscs – see Matthiessen, 2003).

In the context of the work described in this report the following points are of importance:

- The definition of an endocrine disrupter developed by WHO/IPCS (2002) is applied as the starting point for characterising an ED for regulatory purposes, namely: *An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes* ***adverse*** *effects in an* ***intact organism****, or its progeny, or (sub)populations*."

- With regard to adversity the following definition is applied: "*A change in morphology, physiology, growth, reproduction, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences (WHO/IPCS 2004)*."

- Endocrine perturbation is considered as a mode of action, potentially on a pathway to other outcomes, rather than a toxicological or ecotoxicological endpoint in itself. Crucially, to designate a substance as a toxicological or ecotoxicological endocrine disrupter, any endocrine perturbation must result in, or be plausibly connected with, observed adverse toxicological or ecotoxicological effects in intact organisms that can impact detrimentally on humans or the population of one or more environmental (wildlife) species.

For this project a substance is regarded as a human health and/or an ecotoxicological endocrine disrupter for regulatory purposes when it satisfies the definition and associated criteria given in Table 1.2, which are described in the discussion documents listed in Section 1.1.

Table 1.1 Examples of observed effects in target groups of humans and wildlife which could be endocrine mediated (adapted from WHO, 2002)

Humans

Reproduction

- Increased evidence of precocious puberty in females
- Increased rates of endometriosis in females
- Increased evidence of polycystic ovarian syndrome (PCOS) in females
- Reduced fecundity and fertility in females
- Increased rates of spontaneous abortions in females
- Reduced sex ratios (as evidenced by reductions in the number of male births)
- Shortened lactation periods in females
- Decreased sperm count/quality and testis function in males
- Increased incidences of male reproductive tract malformations (such as hypospadias) and testicular maldescent (cryptorchidism)

Cancer

- Increased rates of breast and endometrial cancer in females
- Increased rates of prostate and testicular cancer in males
- Increased rates of thyroid cancer

Neurobehaviour

- Impairment of neurobehavioural development
- Impairment of adult neurobehaviour

Immune system

- Immunosuppression and potential disease susceptibility

Wildlife

Invertebrates

- Increased incidences of imposex in molluscs
- Increased incidences of disruption of ecdysteroid-regulated and juvenoid-regulated processes in crustaceans

Fish

- Increased incidences of intersexuality in freshwater species
- Induction of vitellogenesis in juvenile or male fish
- Altered adrenal physiology
- Increased incidences of thyroid dysfunction

Amphibians

- Changes in amphibian populations

Reptiles

- Increased incidences of developmental abnormalities in alligators and snapping turtles

Birds

- Increased incidences of abnormal reproductive physiology
- Skewed sex ratio's and female-female pairings
- Increased incidences of egg thinning
- Alterations of behaviour

Mammals

- Increased incidences of reproductive dysfunction in feral rodents, mustelids, and marine mammals

Table 1.2 Definition and associated criteria to be used in the project to identify endocrine disrupters with potential human health and/or ecotoxicological concerns taken from discussion documents given in Section 1.1

	Potential toxicological concerns	Potential ecotoxicological concerns
Definition	An exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations	
Associated criteria	a) adverse effects to have been seen in one or more toxicity studies of acceptable quality, in which the substance was administered by a route relevant for human exposure. b) a plausible mode-of-action/ mechanistic link between the toxic effects of concern and endocrine disruption to have been inferred. c) the effects seen in experimental animals to be judged to be of potential relevance to human health. d) serious adverse effect(s) related to endocrine disruption to have been produced at a dose at or below the relevant guidance value for the application of Category 1 "Specific Target Organ Toxicity-Repeated Exposure, STOT-RE" classification and labelling.	a) the nature of the effect must pose a threat to population recruitment or stability: and b) there should be a reasonable and coherent line of evidence from within the same taxonomic group that the mode-of-action underlying the effect observed is endocrine disruption. c) there should be a consideration of the concentration/dose causing adverse endocrine effects.

1.3 Objectives of the work programme

The general objective of the study is: "*to determine which active substances from the PPP Approved List can be regarded as EDs more likely to pose a risk, which substances require further information, which substances are considered EDs less likely to pose a risk and which substances are not EDs*".

Since the PPP Approved List contains over 400 active substances it was agreed that the project would be achieved most effectively by adopting a staged approach, namely:

1) Stage 1 – Conduct of a feasibility study to:

- Initially evaluate the effectiveness of the assessment approach with 20 substances, from different regulatory sources, that have been identified in consultation with HSE.

- Identify any issues that need to be addressed before the evaluation of a wider group of substances is conducted. The knowledge gained from the feasibility study was used to modify the approach adopted in Stage 2 whilst maintaining its scientific rigour.

2) Stage 2 – Application of the finalised and modified methodology to address a larger group of substances in a cost-effective manner. This involved:

   a) Carrying out human health assessments of a further group of approximately 80 substances that were selected by HSE.

   b) Carrying out detailed ecotoxicological assessments of 20 substances selected by HSE and WRc.

1.4 Scope of the report

This report describes the outcome of Stages 1 and 2. It provides:

1. A description of the approach that was adopted in assessing the endocrine disrupting properties of a series of 20 substances in Stage 1 of the project and the revised approach that was implemented in Stage 2. This includes a review of the issues that became apparent during the feasibility study and which were considered before Stage 2 of the project was initiated.

2. The results of the assessments of the substances which are given in a separate datasheet for each chemical (see Appendices A, B and C).

2. Approach Adopted in the Feasibility Study

2.1 Substances addressed in the feasibility study

For the feasibility study it was agreed with HSE that the range of substances considered should include fungicides herbicides, insecticides (including acaracides and molluscicides) and insect and plant growth regulators. The substances selected are summarised in Table 2.1.

Table 2.1 Twenty substances evaluated in the feasibility study

Substance type	Substances evaluated in the feasibility study
Fungicide (5)	Carbendazim, Chlorothalonil, Cyflamid, Dimoxystrobin and Mancozeb
Herbicide (6)	2,4-D, Dicamba, Glufosinate-ammonium, Glyphosate, Linuron and Mecoprop
Insecticide (including acaracides and molluscicides) (7)	Chlorpyrifos, Cyflumetofen, Cypermethrin, Dimethoate, Malathion, Methiocarb and Pirimicarb
Plant growth regulators (1)	Chlormequat
Insect growth regulators (1)	Methoprene

2.2 Approach adopted in the evaluation

The approach adopted in the evaluation of each of the 20 substances identified in Table 2.1 involved five tasks, namely:

1. Collating all the readily available mammalian toxicology and ecotoxicology data and identifying that which is relevant to the human health and ecotoxicological assessments of the endocrine disrupting properties of each of the substances (Task 1). The key source of data was primarily the European Union Draft Assessment Reports (EU DARs) and European Food Safety Authority (EFSA) conclusions. However, as described later in this report, it was necessary to supplement this data with information from the published literature particular for the purpose of the ecotoxicological assessment undertaken in Stage 2.

2. Reviewing the data using the Klimisch Criteria approach to define the quality of the information used in the human health and ecotoxicological assessments (Task 2).

3. Summarising the data that was used for the human health assessments (and where relevant ecotoxicological assessments) on a template prepared in consultation with HSE (Task 3).

4. Assessing the data for evidence of endocrine disruption in humans and wildlife against the specific criteria given in Table 1.2 (Task 4).

5. Assigning the substances into the relevant group for human health and the environment (Task 5), recognising that none of the groups established for the different substances represent regulatory decisions.

In the feasibility study an ecotoxicological assessment was only conducted where no potential effects on human health were identified.

2.2.1 Collation of available mammalian toxicology and ecotoxicology data (Task 1)

The information used in the assessments in Stage 1 has largely been obtained from the Draft Assessment Reports (DARs) and European Food Safety Authority (EFSA) conclusions. In the case of older DARs (i.e. those prepared before 2000) a limited literature search to identify new relevant information has been carried out where deemed appropriate. The search terms used in the literature search included the following:

Endocrine disruption, oestrogenic effects, anti-oestrogenic effects, androgenic effects, anti-androgenic effects, adrenal effects, thyroid effects, reproduction, growth, development, carcinogenicity, fish, amphibians, birds, mammals.

2.2.2 Assessment of the quality of the available mammalian toxicology and ecotoxicology data (Task 2)

In Task 2, a systematic and critical assessment of the mammalian toxicity and ecotoxicology data collated in Task 1 was conducted using the Klimisch Criteria system (Klimisch *et al.* 1997) to quality assess the data. The Klimisch Criteria has four quality categories for data:

1. **Reliable without restrictions**: Refers to studies/data carried out or generated according to internationally accepted testing-guidelines (preferably GLP) or in which the test parameters documented are based on a specific (national) testing guideline (preferably GLP), or in which all parameters described are closely related/comparable to a guideline method.

2. **Reliable with restrictions**: Studies or data (mostly not performed according to GLP) in which the test parameters documented do not comply totally with the specific testing guideline, but are sufficient to accept the data or in which investigations are described

that cannot be subsumed under a testing guideline, but which are nevertheless well-documented and scientifically acceptable.

3. **Not reliable**: Studies/data in which there are interferences between the measuring system and the test substance, or in which organisms/test systems were used that are not relevant in relation to exposure, or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for an assessment and which is not convincing for an expert assessment.

4. **Not assignable**: Studies or data which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature.

Information on the validity of the whole organism studies is typically given in the DARs and EFSA conclusions.

2.2.3 Summarising the reliable mammalian toxicology and ecotoxicology data (Task 3)

At the start of the project a template was prepared in consultation with HSE that summarises all the mammalian toxicology and ecotoxicology data used in the human health (and possibly ecotoxicological) assessments of endocrine disruption and the relevant quality ratings. This includes data from both studies on intact (whole) organisms and *in-vitro* and *in-vivo* studies that provide mechanistic information.

In the template, for each whole organism study of acceptable quality, information is given on:

- the tests employed and the species used;
- the experimental design (including the exposure regime and the test durations);
- the endpoints of relevance and the reported effects levels for both endocrine mediated and systemic (non-endocrine mediated) toxicity responses, in particular the NOAEL/LOAEL values from the mammalian toxicology studies and the NOEC/LOEC values from the ecotoxicological studies;
- the quality assessment for the study;
- the reference for the study, when the study was not included in the Draft Assessment Reports (DARs) and/or European Food Safety Authority (EFSA) conclusions.

For *in-vitro* or *in-vivo* studies assessing the mechanistic action of the substance, information is given on:

- the test system used;
- the endpoints of relevance;
- the reported results;
- the quality assessment for the study;
- the reference for the study, when the study was not included in the Draft Assessment Reports (DARs) and/or European Food Safety Authority (EFSA) conclusions.

2.2.4 Assessing the data for evidence of endocrine disruption in relation to human health and the environment (Task 4)

The approach that has been taken to assess the data for endocrine disruption for human health and the environment against the specific criteria given in Table 1.2 has been developed from those described in:

- "*Regulatory Definition of an Endocrine Disrupter in Relation to Potential Threat to Human Health*" prepared as a joint German-UK Position in May 2011.
- "*Definition of an Ecotoxicological Endocrine Disrupter for Regulatory Purposes prepared by the UK Chemicals Regulation Directorate*".

The key points in the assessment are:

1. Initially assess whether the substance is already classified as a CMR Category 1A or 1B under the CLP Regulation. If this is the case an assessment of endocrine disrupting properties is not required as the same regulatory consequences that would result from categorisation as an endocrine disrupter, would already apply.

2. If the substance is not classified as CMR Category 1A or 1B under the CLP Regulation then it is necessary to collate all the relevant toxicological, and if appropriate ecotoxicological, data for the substance and determine their quality.

3. Where there is robust and reliable data for the human health and/or ecotoxicological assessments determine whether:

    - There are adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.

- The available evidence demonstrates that an endocrine disruption mode of action in animals is plausible.

- The effects are judged to be relevant to humans or wildlife populations.

For the human health assessment a crucial issue is whether or not serious endocrine disrupting effects are observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation.

The European Classification, Labelling and Packaging (CLP) Regulations, which implement the Globally Harmonised System for classification and labelling of chemicals (GHS), contains discriminatory dose thresholds for use in determining whether or not a wide range of expressions of toxicity seen in single and repeated exposure studies, collectively termed "Specific Target Organ Toxicity (STOT)", should be identified by hazard classification and be assigned appropriate labelling (this concept was also used in the predecessor to CLP, the Dangerous Substances Directive). In accordance with the German-UK position paper of May 2011 the dose thresholds for STOT Repeated Exposure-RE were used to determine whether or not the hazardous property of "endocrine disruption" should be identified for regulatory purposes.

There are two categories (Categories 1 and 2) of classification for STOT-RE, covering substances of relatively higher and lower potency. The guidance values ("cut-offs") for both categories are defined in CLP and GHS.

Table 2.2 shows the guidance values for sub-acute and other short-term studies (e.g. developmental toxicity studies).

Table 2.2 Guidance values for sub-acute and other short-term studies

	STOT-RE Category 1	STOT-RE Category 2
Oral	30 mg/kg bw/day	300 mg/kg bw/day
Dermal	60 mg/kg bw/day	600 mg/kg bw/day
Inhalation (vapour)	0.6 mg/l/6h/day	3.0 mg/l/6h/day
Inhalation (dust/mist/fume)	0.06 mg/l/6h/day	0.6 mg/l/6h/day

Table 2.3 shows the guidance values for subchronic and other medium-term studies (e.g. two generation reproduction studies).

Table 2.3 Guidance values for subchronic and other medium-term studies

	STOT-RE Category 1	STOT-RE Category 2
Oral	10 mg/kg bw/day	100 mg/kg bw/day
Dermal	20 mg/kg bw/day	200 mg/kg bw/day
Inhalation (vapour)	0.2 mg/l/6h/day	1.0 mg/l/6h/day
Inhalation (dust/mist/fume)	0.02 mg/l/6h/day	0.2 mg/l/6h/day

There are no guidance values in the CLP Regulations for chronic studies, but it is proposed here that they should be half the subchronic study values (by applying the subchronic to chronic extrapolation assessment factor of 2 recommended in the REACH guidance on Information Requirements and Chemical Safety Assessment, Chapter R8 (see Table 2.4).

Table 2.4 Proposed guidance values for chronic studies

	STOT-RE Category 1	STOT-RE Category 2
Oral	5.0 mg/kg bw/day	50 mg/kg bw/day
Dermal	10 mg/kg bw/day	100 mg/kg bw/day
Inhalation (vapour)	0.1 mg/l/6h/day	0.5 mg/l/6h/day
Inhalation (dust/mist/fume)	0.01 mg/l/6h/day	0.1 mg/l/6h/day

These potency-based guidance values are pragmatic, but have been in place within the framework of the regulatory hazard classification system in Europe since 1967 and are well established and accepted. They are also widely accepted at a global level through GHS. Therefore, these guidance values are considered to be appropriate discriminatory values to identify those hazards for which a regulatory warning should be given. They are not strict demarcation values; they should always be taken into account along with severity of effects, dose spacing and other issues in a weight of evidence approach.

The Regulatory Definition of an Endocrine Disrupter in Relation to Potential Threat to Human Health" prepared as a joint German-UK Position in May 2011 states that: "*In line with the CLP Regulation STOT RE criteria (Annex I, 3.9), it is proposed that the dose level at which serious adverse effects related to endocrine disruption are seen is compared with the guidance values presented above. Serious adverse effects are defined in the CLP Regulation as significant and/or severe toxic effects such as morbidity, death, significant functional changes, marked organ dysfunction/damage, etc*.

It is suggested that only where a substance produces endocrine disruption at a dose level at or below the discriminatory guidance dose levels for the application of Category 1 STOT-RE hazard classification, the substance should be considered an ED more likely to pose a risk requiring severe action (e.g. consideration for non-approval in the context of the PPP or BP

regulations and consideration for inclusion in the list of SVHCs as possible candidates for Authorisation in the context of REACH").

At the time of commissioning the project the possible approaches to establishing ecotoxicological criteria for regulatory purposes were not sufficiently developed to conduct an analysis equivalent to that carried out for human health. For the purpose of the ecotoxicological assessment the crucial issue for 'classification' purposes was taken to be whether there are other systemic effects seen at concentration levels orders of magnitude below those at which endocrine effects are observed. If this were to be the case, then the endocrine disrupter would be regarded as being less likely to pose a risk. However, if the ED-mediated adverse effects were to be the most sensitive effects, then the substance would be considered more likely to pose a risk.

2.2.5 Assigning the substances to the relevant group for human health and the environment (Task 5)

In this task the assessment carried out in Task 4 was used to assign the substance to one of four groups based on the mammalian toxicology and/or ecotoxicology data:

A. Substances requiring further information;

B. Endocrine disrupters more likely to pose a risk;

C. Endocrine disrupters less likely to pose a risk;

D. Substances not considered to be endocrine disrupters on the basis of the available evidence.

In the feasibility study a consideration was made of whether it was appropriate to carry out an assessment of the potential for endocrine disruption in wildlife species if the substance was not considered to be an endocrine disrupter based on the mammalian toxicology data (Group D).

It should be recognised that none of the groups established for the different substances are regulatory decisions.

2.3 Results of the ED assessments of the initial 20 substances in the feasibility study

The results of the human health and ecotoxicological ED assessments of the initial 20 substances are shown in Tables A.1 to A.20 in Appendix A.

2.3.1 Human health ED assessments

In the feasibility study, three substances (carbenazim, glufosinate-ammonium and linuron) were identified as CMR 1B substances but the human health assessment was carried out anyway to provide further information on the effectiveness of the assessment process.

In the assessments, short-term studies have not been included when no adverse effects were seen or when effects similar to those observed in the long-term studies were noted. Studies where no endocrine disruption effects occur have also been included.

Table 2.5 summarises the outcomes of the human health ED assessments, based on the review of available mammalian toxicological data, which indicate that:

- Two substances (mancozeb[1] and linuron) were identified as endocrine disrupting substances more likely to pose a risk. Linuron was also classified as CMR Category 1B.
- No substances were identified as being endocrine disrupters less likely to pose a risk.
- Four substances (carbendazim, chlorpyrifos, 2,4-D and glufosinate-ammonium) were identified as requiring further information. However, for carbendazim and glufosinate-ammonium, any further testing would not be worth pursuing because these two substances are already classified as CMR 1B.
- Fourteen substances were not considered to be endocrine disrupters for human health and an assessment of the available ecotoxicological data was proposed following discussions with HSE (see Section 2.3.2).

[1] Assessment relates to the primary metabolite, ethylenethiourea (ETU)

Table 2.5 Summary of the human health ED assessments of the initial 20 plant protection substances in the feasibility study

Substance type	Substance	Substance grouping based on the assessment of mammalian toxicology data				Comments	Ecotoxicological assessment required?
		Further information required	More likely to pose a risk	Less likely to pose a risk	Not considered to be endocrine disrupters		
Fungicide	Carbendazim	**Yes**	No	No	No	Classified as CMR Category 1A or 1B	No
	Chlorothalonil	No	No	No	**Yes**	-	**Yes**
	Cyflamid	No	No	No	**Yes**	-	**Yes**
	Dimoxystrobin	No	No	No	**Yes**	-	**Yes**
	Mancozeb	No	**Yes**	No	No	-	No
Herbicide	2,4-D	**Yes**	No	No	No	-	No
	Dicamba	No	No	No	**Yes**	-	**Yes**
	Glufosinate-ammonium	**Yes**	No	No	No	Classified as CMR Category 1A or 1B	No
	Glyphosate	No	No	No	**Yes**	-	**Yes**
	Linuron	No	**Yes**	No	No	Classified as CMR Category 1A or 1B	No
	Mecoprop	No	No	No	**Yes**	-	**Yes**
Insecticides	Chlorpyrifos	**Yes**	No	No	No	-	No
	Cyflumetofen	No	No	No	**Yes**	-	**Yes**
	Cypermethrin	No	No	No	**Yes**	-	**Yes**
	Dimethoate,	No	No	No	**Yes**	-	**Yes**
	Malathion	No	No	No	**Yes**	-	**Yes**
	Methiocarb	No	No	No	**Yes**	-	**Yes**
	Pirimicarb	No	No	No	**Yes**	-	**Yes**
Plant growth regulators	Chlormequat	No	No	No	**Yes**	-	**Yes**
Insect growth regulators	Methoprene	No	No	No	**Yes**	-	**Yes**

Table 2.6 consolidates the information on the twenty plant protection substances for which detailed human health ED assessments were conducted in Stage 1 in terms of the number of fungicides, herbicides, insecticides, plant growth regulators and insect growth regulators and the numbers and percentages of these that were identified as falling into each group.

Table 2.6 Summary information on the outcome of the human health ED assessments of the twenty substances in Stage 1

Parameter	Outcome of the human health ED assessments in Stage 1				
	Fungicides	Herbicides	Insecticides	Plant growth regulators	Insect growth regulators
Number of substances assessed	**5**	**6**	**7**	**1**	**1**
Number (and percentages of substances) in each group					
Substances requiring further information (Group A)	1 (20%)	2 (33%)	1 (14%)	0 (0%)	0 (0%)
Endocrine disrupters more likely to pose a risk (Group B)	1 (20%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)
Endocrine disrupters less likely to pose a risk (Group C)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Substances not considered to be endocrine disrupters (Group D)	3 (60%)	3 (50%)	6 (86%)	1 (100%)	1 (100%)
Total	**5**	**6**	**7**	**1**	**1**

A similar pattern of grouping was found for fungicides, herbicides and insecticides in terms of the ranking of the percentages of substances in different groups, namely: Group D (67%) > Group A (22%) > Group B (11%) > Group C (0%).

2.3.2 Ecotoxicological ED assessments

Ecotoxicological assessments were carried out on substances identified in the human health assessments as being Group D - Substances not considered to be endocrine disrupters in the human health assessments (see Table 2.2).

Table 2.3 summarises the outcomes of the ecotoxicological assessments, based on the review of the ecotoxicological data available in EU DARs and EFSA conclusions. The evaluation indicates that:

- Information in the European Union Draft Assessment Reports on the potential of the substances to elicit endocrine mediated effects in wildlife species is limited by the

availability of guideline *in vivo* and *in vitro* test methods. A fundamental difficulty is that none of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances' potential endocrine disrupting effects.

- For the fourteen substances evaluated in the feasibility study further information from tests such as the Fish Short Term Reproduction Assay (OECD 229, adopted September 2009), the Fish Sexual Development Test (OECD 234, adopted July 2011), the Fish Full Life-Cycle Test (EPA OPPTS 850.1500); and the Amphibian Metamorphosis Assay (OECD 231, adopted September 2009)[2] is needed to be able to carry out effective assessments of the endocrine properties of substances in wildlife species. This conclusion prompted the conduct of more extensive (by including information from the published literature) ecotoxicological assessments for a series of twenty substances (including a number of those already considered in Stage 1) in Stage 2 (see Section 4).

[2] Under the latest Regulation 1107/2009 data requirements adopted in 2012 these tests together with OECD 230 (21 day fish assay) are all now required

Table 2.7 Summary of the ecotoxicological ED assessments for the relevant plant protection substances in the feasibility study

Substance type	Substance	Substance grouping based on the assessment of the ecotoxicology data				Human health assessment group
		An ED assessment cannot be performed	More likely to pose a risk	Less likely to pose a risk	Not considered to be endocrine disrupters	
Fungicide	Chlorothalonil	**Yes**	No	No	No	Not considered to be an endocrine disrupter
	Cyflamid	**Yes**	No	No	No	Not considered to be an endocrine disrupter
	Dimoxystrobin	**Yes**	No	No	No	Not considered to be an endocrine disrupters
Herbicide	Dicamba	**Yes**	No	No	No	Not considered to be endocrine disrupter
	Glyphosate	**Yes**	No	No	No	Not considered to be an endocrine disrupter
	Mecoprop	**Yes**	No	No	No	Not considered to be an endocrine disrupter
Insecticides	Cyflumetofen	**Yes**	No	No	No	Not considered to be an endocrine disrupter
	Cypermethrin	**Yes**	No	No	No	Not considered to be an endocrine disrupter
	Dimethoate,	**Yes**	No	No	No	Not considered to be an endocrine disrupter
	Malathion	**Yes**	No	No	No	Not considered to be an endocrine disrupter
	Methiocarb	**Yes**	No	No	No	Not considered to be an endocrine disrupter
	Pirimicarb	**Yes**	No	No	No	Not considered to be an endocrine disrupter
Plant growth regulators	Chlormequat	**Yes**	No	No	No	Not considered to be an endocrine disrupter
Insect growth regulators	Methoprene	**Yes**	No	No	No	Not considered to be an endocrine disrupter

2.4 Issues to be addressed in the assessment of the larger set of substances in Stage 2

The following issues were identified that required discussion with HSE prior to the assessment of the larger set of substances in Stage 2:

- Obtaining the correct version of the Draft Assessment Report was not always straightforward due to the multiple documents and revisions that are available at on-line regulatory sites.

- Determining whether to conduct an ecotoxicological assessment of a substance was problematic given that the relevant ecotoxicological data set available in EU DARs and EFSA conclusions was far more limited than that which was available for the human health assessment.

- There was some difficulty in determining whether effects on the reproductive and thyroid system observed in toxicological studies originated through an endocrine disruptive mode-of-action or were the consequence of generalised toxicity.

These issues were discussed and resolved with HSE prior to the conduct of Stage 2 of the project.

3. Stage 2 – Human Health ED Assessments of a Larger Set of Substances

3.1 Substances for which human health ED assessments have been carried out in Stage 2

In this element of Stage 2, eighty one additional substances proposed by HSE were evaluated in relation to human health. Table 3.1 lists the thirty two fungicides, thirty two herbicides, fourteen insecticides and three plant growth regulators that were selected for review by HSE from the PPP Approved List.

Table 3.1 Eighty one substances for which it was proposed that human health ED assessments were carried out in Stage 2

Substance type	Substances for which human health ED assessments were carried out in Stage 2
Fungicides (32)	Azoxystrobin Boscalid Bupirimate Captan Cyazofamid Cymoxanil Cyprodinil Dimethomorph Fenhexamid Fenpropimorph Fluazinam Fludioxonil Fluoxastrobin Fosetyl aluminium Hymexazol Imazaquin Iprodione Kresoxim-methyl Mandipropamid Metalaxyl-M Metrafenone Myclobutanil Prochloraz Propamocarb hydrochloride Prothioconazole Pyraclostrobin Silthiofam Tebuconazole Thiophanate-methyl Thiram Toclofos-methyl Triazoxide
Herbicides (32)	Bentazone Bromoxynil Chloridazon Chlorpropham Clomazone Clopyralid

Substance type	Substances for which human health ED assessments were carried out in Stage 2
	Dimethenamid-P Diquat Ethofumesate Fluazifop-P-butyl Flufenacet Fluroxypyr Ioxynil Isoxaben Lenacil Mesosulfuron-methyl Metamitron Metazachlor S-metolachlor Metribuzin Metsulfuron-methyl Napropamide Oxadiazon Phenmedipham Pinoxaden Propyzamide Prosulfocarb Pyridate Tepraloxydim Terbuthylazine Triallate Triclopyr
Insecticide (including acaracides and molluscicides)(14)	Abamectin Clothianidin Beta-cyfluthrin Lambda-cyhalothrin Diflubenzuron Fenoxycarb Imidacloprid Indoxacarb Pymetrozine Spinosad Spiromesifen Spirotetremat Tebufenpyrad Thiacloprid
Plant growth regulators (3)	Maleic hydrazide Paclobutrazol Prohexadione-calcium

As a result of the absence of suitable regulatory dossiers for the herbicides flufenacet, and pyridate and the insecticide indoxacarb, no human health assessments were conducted for these substances. Therefore, human health assessments were carried out on a total of seventy eight substances in Stage 2.

3.2 Approach adopted in the assessments

The approach adopted for the human health assessments of the additional seventy eight substances was essentially the same as that used in the feasibility study (see Section 2.2). However, for these substances, additional data was sought from a literature search:

- In the case of older DARs (i.e. those prepared before 2000);

- In the case of DARs where there was limited data on key regulatory studies that are considered most relevant for evaluating endocrine disrupting effects.

3.3 Results of the human health ED assessments of substances in Stage 2

The results of the human health assessments for the seventy eight substances in Stage 2 are shown in Tables B.1 to B.81 in Appendix B.

Table 3.2 indicates the outcomes of the human health assessments, based on the review of available mammalian toxicological data. It also indicates whether there is a requirement to carry out an ecotoxicological assessment, which relates to those substances identified as Group D – Substances not considered to be endocrine disrupters for human health.

Table 3.3 consolidates this information in terms of the number of fungicides, herbicides, insecticides and plant growth regulators for which human health assessments were carried out and the numbers and percentages of these that were identified as falling into each group. From the collation of the data it is evident that:

- The criteria adopted for the human health assessments were able to discriminate the substances into the different groups.

- There were representatives of all groups. Group B (Endocrine disrupters more likely to pose a risk) and Group C (Endocrine disrupters less likely to pose a risk) represented 3.8% (3 of 78) and 11.5% (9 of 78) of all the substances evaluated.

- Group D substances (Substances not considered to be endocrine disrupters) were found to be the major group, being 56.4% (44 of 78) of all the substances evaluated.

- Group A substances (Substances requiring further information) represented 28.2% (22 of 78) of all the substances evaluated.

- A similar pattern of grouping was found for fungicides, herbicides and insecticides in terms of the ranking of the percentages of substances in different groups, namely: Group D (56%) > Group A (28%) > Group C (12%) > Group B (4%).

Table 3.2 Summary of the human health ED assessments for the 78 plant protection substances identified for evaluation in Stage 2

Substance type	Substance	Substance ED grouping based on the assessment of mammalian toxicology data				Comments	Ecotoxicological assessment required?
		Further information required	More likely to pose a risk	Less likely to pose a risk	Not considered to be endocrine disrupters		
Fungicides (32)	Azoxystrobin	No	No	No	**Yes**	-	**Yes**
	Boscalid	No	No	No	**Yes**	-	**Yes**
	Bupirimate	No	No	**Yes**	N**o**	-	No
	Captan	No	No	No	**Yes**	-	**Yes**
	Cyazofamid	No	No	No	**Yes**	-	**Yes**
	Cymoxanil	**Yes**	No	No	No	-	No
	Cyprodinil	No	No	No	**Yes**	-	**Yes**
	Dimethomorph	No	No	No	**Yes**	-	**Yes**
	Fenhexamid	No	No	No	**Yes**	-	**Yes**
	Fenpropimorph	No	No	No	**Yes**	-	**Yes**
	Fluazinam	**Yes**	No	No	No	-	No
	Fludioxonil	No	No	No	**Yes**	-	**Yes**
	Fluoxastrobin	No	No	No	**Yes**	-	**Yes**
	Fosetyl aluminium	**Yes**	No	No	No	-	No
	Hymexazol	**Yes**	No	No	No	-	No
	Imazaquin	No	No	No	**Yes**	-	**Yes**
	Iprodione	No	No	**Yes**	No	-	No
	Kresoxim-methyl	No	No	No	**Yes**	-	**Yes**
	Mandipropamid	**Yes**	No	No	No	-	No
	Metalaxyl-M	No	No	No	**Yes**	-	**Yes**
	Metrafenone	No	No	No	**Yes**	-	**Yes**
	Myclobutanil	No	No	**Yes**	No	-	No
	Prochloraz	No	No	**Yes**	No	-	No
	Propamocarb hydrochloride	No	No	No	**Yes**	-	**Yes**
	Prothioconazole	**Yes**	No	No	No		No
	Pyraclostrobin	No	No	No	**Yes**	-	**Yes**

Substance type	Substance	Substance ED grouping based on the assessment of mammalian toxicology data				Comments	Ecotoxicological assessment required?
		Further information required	More likely to pose a risk	Less likely to pose a risk	Not considered to be endocrine disrupters		
	Silthiofam	**Yes**	No	No	No	-	No
	Tebuconazole	No	No	**Yes**	No	-	No
	Thiophanate-methyl	No	No	**Yes**	No	-	No
	Thiram	**Yes**	No	No	No	-	No
	Toclofos-methyl	No	No	No	**Yes**	-	**Yes**
	Triazoxide	No	No	No	**Yes**	-	**Yes**
Herbicides (32)	Bentazone	No	No	No	**Yes**	-	**Yes**
	Bromoxynil	No	No	No	**Yes**	-	**Yes**
	Chloridazon	No	No	No	**Yes**	-	**Yes**
	Chlorpropham	**Yes**	No	No	No	-	No
	Clomazone	No	No	No	**Yes**	-	**Yes**
	Clorpyralid	No	No	No	**Yes**	-	**Yes**
	Dimethenamid-P	**Yes**	No	No	No	-	No
	Diquat	No	No	No	**Yes**	-	**Yes**
	Ethofumesate	**Yes**	No	No	No	-	**No**
	Fluazifop-p-butyl	**Yes**	No	No	No	-	No
	Flufenacet	**Assessment not carried out due to the absence of a suitable regulatory dossier**					
	Fluroxypyr	No	No	No	**Yes**	-	**Yes**
	Ioxynil	No	**Yes**	No	No	-	No
	Isoxaben	No	No	No	**Yes**	-	**Yes**
	Lenacil	**Yes**	No	No	No	-	No
	Mesosulfuron-methyl	No	No	No	**Yes**	-	**Yes**
	S-metolachlor	**Yes**	No	No	No	-	No
	Metamitron	No	No	No	**Yes**	-	**Yes**
	Metazochlor	No	No	No	**Yes**	-	**Yes**
	Metribuzin	No	No	**Yes**	No	-	No
	Metsulfuron-methyl	No	No	No	**Yes**	-	**Yes**
	Napropamide	No	No	No	**Yes**	-	**Yes**
	Oxadiazon	No	No	No	**Yes**	-	**Yes**

Substance type	Substance	Substance ED grouping based on the assessment of mammalian toxicology data				Comments	Ecotoxicological assessment required?
		Further information required	More likely to pose a risk	Less likely to pose a risk	Not considered to be endocrine disrupters		
	Phenmedipham	No	No	No	**Yes**	-	**Yes**
	Pinoxaden	**Yes**	No	N**o**	No	-	No
	Propyzamide	No	No	**Yes**	No	-	No
	Prosulfocarb	No	No	No	**Yes**	-	**Yes**
	Pyridate	**Assessment not carried out due to the absence of a suitable regulatory dossier**					
	Tepraloxydim	**Yes**	No	No	No	-	No
	Terbuthylazine	**Yes**	No	No	No	-	No
	Triallate	No	No	No	**Yes**	-	**Yes**
	Triclopyr	No	No	No	**Yes**	-	**Yes**
Insecticides (14)	Abamectin	N**o**	**Yes**	No	No	-	No
	Clothianidin	**Yes**	No	No	No	-	No
	Beta-cyfluthrin	**Yes**	No	No	No	-	No
	Lamda-cyhalothrin	**Yes**	No	No	No	-	No
	Diflubenzuron	No	No	No	**Yes**	-	**Yes**
	Fenoxycarb	No	No	No	**Yes**	-	**Yes**
	Imidacloprid	No	No	No	**Yes**	-	**Yes**
	Indoxacarb	**Assessment not carried out due to the absence of a suitable regulatory dossier**					
	Pymetrozine	No	No	No	**Yes**	-	**Yes**
	Spinosad	**Yes**	No	No	No	-	No
	Spiromesifen	No	No	**Yes**	No	-	No
	Spirotetremat	**Yes**	No	No	No	-	No
	Tebufenpyrad	No	No	No	**Yes**	-	**Yes**
	Thiacloprid	No	**Yes**	No	No	-	No
Plant growth regulators (3)	Maleic hydrazide	No	No	No	**Yes**	-	**Yes**
	Paclobutrazol	No	No	No	**Yes**	-	**Yes**
	Prohexadione-calcium	No	No	No	**Yes**	-	**Yes**

Table 3.3 Summary information on the outcome of the human health ED assessments of the seven eight substances in Stage 2

Parameter	Outcome of the human health ED assessments in Stage 2				
	Fungicides	**Herbicides**	**Insecticides**	**Plant growth regulators**	**Insect growth regulators**
Number of substances identified by HSE	32	32	14	3	0
Number of substances assessed (excluding those for which suitable regulatory dossiers were not available)	**32**	**30**	**13**	**3**	**0**
Number (and percentage of substances) in each group					
Substances requiring further information (Group A)	8 (25%)	9 (30%)	5 (38%)	0 (0%)	0 (0%)
Endocrine disrupters more likely to pose a risk (Group B)	0 (0%)	1 (3%)	2 (25%)	0 (0%)	0 (0%)
Endocrine disrupters less likely to pose a risk (Group C)	6 (19%)	2 (7%)	1 (8%)	0 (0%)	0 (0%)
Substances not considered to be endocrine disrupters (Group D)	18 (56%)	18 (60%)	5 (38%)	3 (100%)	0 (0%)
Total	**32**	**30**	**13**	**3**	**0**

From these human health ED assessments the following issues were identified:

- Guideline apical studies although present in the majority of the plant protection substances evaluated, may not (depending on the test date) have included more recently validated endocrine-sensitive endpoints (e.g. thyroid hormones, anogenital distance, nipple retention, etc.). However, it is noted that general histopathology on all the relevant organs was available.
- Some of the recently validated *in vitro* and *in vivo* assays for endocrine activity (particularly those determining androgen, oestrogen activity or steroidogenesis interference) may not have been routinely part of the DAR, including even the latest ones, as they are not included in the standard data requirements for pesticides.
- More specific data for the assessment of endocrine disruption were sometimes available in recent reviews or in published papers. However, it was difficult to assess the relevance and quality of some of these more recent but non-regulatory data because the sources did not always provide sufficient information on the test procedure.

3.4 Additional assessment of the 26 pesticide active substances identified as requiring further information

3.4.1 Introduction

It is evident from Section 3.3 that a large group of 26 (out of 98) pesticide active substances were identified as requiring further information (Group A) in the human health assessment of 98 substances for possible endocrine disruptive properties, using the human health UK-DE criteria. This was mainly due to a lack of mechanistic data. It is possible that some of these pesticides may be endocrine disrupters (EDs) but without mechanistic data this cannot be assumed. If such mechanistic data were to be available and were to be positive (i.e. showing that an endocrine mode-of-action underlies the observed adverse effects), it would be of value to ascertain whether these 26 substances would be EDs more or less likely to pose a risk.

3.4.2 Approach

In order to conduct the additional assessment of the 26 pesticide active substances identified as requiring further information the following exercise was conducted:

- The 26 pesticides were assumed to have mechanistic data showing them to be EDs.
- The toxicity apical data were re-assessed and a LOAEL relevant to endocrine-related adverse effects determined – more than one LOAEL may be derived based on different regulatory tests (e.g. 90-days, 2-years and reproduction).
- Where there was no relevant LOAEL based on endocrine-related adverse effects in standard toxicity tests, a LOAEL (or LOEL) from an endocrine activity/disruption *in vivo* screening assay was used in the assessment.
- The LOAEL values and the severity of the effects at the LOAELs were compared to the STOT-RE Cat 1 guidance values and the substances ranked as EDs more or less likely to pose a risk. For the overall conclusion for each substance, the lowest LOAEL identifying the highest level of concern was used.

3.4.3 Results

Using the assessment of the apical data for the 26 pesticides for which further information was required as outlined in the introduction above, the following results (see Appendix D) were obtained with the assumption that endocrine mechanistic data were available showing them to be endocrine disrupters:

- 4 pesticides would be considered EDs more likely to pose a risk: fluazinam, S-metolachlor, terbuthylazine, chlorpyrifos
- 22 pesticides would be considered EDs less likely to pose a risk; carbendazim, cymoxanil, fosetyl-aluminum, hymexazol, mandipropamid, prothioconazole, silthiofam, thiram, 2,4-D, cloropropham, dimethenamid-P, ethofumesate, fluazifop-p-butyl, glufosinate-ammonium, lenacil, pinoxaden, tepraloxydim, clothianidin, beta-cyfluthrin, lambda-cyhalothrin, spinosad and spirotetremat.

4. Stage 2 – Extended Ecotoxicological ED Assessments of Selected Substances

4.1 Substances for which more extensive ecotoxicological assessments have been carried out in Stage 2

As previously indicated, given the more limited relevant ecotoxicology data available in EU DARs a different approach was necessary for this stage. For Stage 2, a group of substances was identified for a more extensive ecotoxicological ED assessment based on a discussion between WRc and HSE. For the identification of appropriate plant protection substances three independent regulatory and non-governmental lists of potential endocrine disruptors have been reviewed to identify those which occur most frequently and, therefore, can be considered to be of greater value to this evaluation. These lists were:

1. European Union List of Potential Endocrine Disrupters as indicated in the EDS_2003_DHI2006 database (see http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm).

2. The TEDX List of Endocrine Disruptors which is maintained by The Endocrine Disruption Exchange (see http://www.endocrinedisruption.org).

3. United States Environmental Protection Agency Endocrine Disruption Screening Program List (see http://www.epa.gov/endo).

Table 4.1 shows which substances from the 100 selected for the human health ED assessments were present in all the lists (highlighted in red) or two of the lists (highlighted in orange). From the review it is evident that there are **five** substances identified in all the lists, namely:

Fungicides	**None**
Herbicides	**Linuron and Metribuzin**
Insecticides	**Cypermethrin, Dimethoate and Malathion**

It is also evident that there are **seventeen** substances identified in two of the lists, namely:

Fungicides	**Carbenzadim, Chlorothalonil, Iprodione, Mancozeb, Myclobutanil, Prochloraz, Tebuconazole and Thiram**
Herbicides	**2,4-D, Glyphosate, Ioxynil and S-metolachlor**
Insecticides	**Abamectin, Chlorpyrifos, Beta-cyfluthrin, Lambda-cyhalothrin and Fenoxycarb**

These substances (with the exception of linuron and mancozeb, which are already EDs more likely to pose a risk for human health) have been evaluated in the more extensive ecotoxicological ED assessments.

Table 4.1 Distribution of the selected 100 substances (feasibility study substances are highlighted in grey) against 3 lists of potential endocrine disrupters

Substances	European Union List of Potential Endocrine Disrupters (Category 1 and 2)	TEDX List of Endocrine Disruptors	United States Environmental Protection Agency Endocrine Disruption Screening Program List
Fungicides			
Azoxystrobin			
Boscalid			
Bupirimate		**Yes**	
Captan			**Yes**
Carbendazim	**Yes**	**Yes**	
Chlorothalonil		**Yes**	**Yes**
Cyazofamid			
Cyflamid			
Cymoxanil			
Cyprodinil		**Yes**	
Dimethomorph			
Dimoxystrobin			
Fenhexamid		**Yes**	
Fenpropimorph			
Fluazinam			
Fludioxonil		**Yes**	
Fluoxastrobin			
Fosetyl aluminium			**Yes**
Hymexazol			
Imazaquin			
Iprodione		**Yes**	**Yes**
Kresoxim-methyl			
Mancozeb	**Yes**	**Yes**	
Mandipropamid			
Metalaxyl-M			
Metrafenone			
Myclobutanil		**Yes**	**Yes**
Prochloraz	**Yes**	**Yes**	
Propamocarb hydrochloride			
Prothioconazole			
Pyraclostrobin			
Silthiofam			
Tebuconazole		**Yes**	**Yes**
Thiophanate-methyl			
Thiram	**Yes**	**Yes**	
Toclofos-methyl		**Yes**	
Triazoxide			
Herbicides			
2,4-D		**Yes**	**Yes**
Bentazone		**Yes**	
Bromoxynil		**Yes**	
Chloridazon			
Chlorpropham			
Clomazone			**Yes**
Clopyralid			
Dicamba			
Dichloroprop		**Yes**	
Dimethenamid-P			
Diquat		**Yes**	
Ethofumesate			

Substances	European Union List of Potential Endocrine Disrupters (Category 1 and 2)	TEDX List of Endocrine Disruptors	United States Environmental Protection Agency Endocrine Disruption Screening Program List
Fluazifop-P-butyl		Yes	
Flufenacet		Yes	
Fluroxypyr			
Glyphosate		Yes	Yes
Ioxynil	Yes	Yes	
Isoxaben			Yes
Lenacil			
Linuron	Yes	Yes	Yes
Mecoprop		Yes	
Mesosulfuron-methyl			
Metamitron			
Metazachlor			
S-metolachlor		Yes	Yes
Metribuzin	Yes	Yes	Yes
Metsulfuron-methyl			
Napropamide			
Oxadiazon			
Phenmedipham			
Pinoxaden			
Propyzamide			Yes
Prosulfocarb			
Pyridate			
Tepraloxydim			
Terbuthylazine			
Triallate			
Triclopyr			
Insecticides			
Abamectin		Yes	Yes
Chlorpyrifos		Yes	Yes
Clothianidin			
Cyflumetofen			
Beta-cyfluthrin		Yes	Yes
Lambda-cyhalothrin	Yes	Yes	
Cypermethrin	Yes	Yes	Yes
Diflubenzuron			
Dimethoate	Yes	Yes	Yes
Fenoxycarb		Yes	Yes
Imidacloprid			Yes
Indoxacarb			
Malathion	Yes	Yes	Yes
Methiocarb		Yes	
Pirimicarb			
Pymetrozine			
Spinosad			
Spiromesifen			
Spirotetremat			
Tebufenpyrad			
Thiacloprid			
Plant Growth Regulators			
Chlormequat			
Maleic hydrazide			
Paclobutrazol			Yes
Prohexadione-calcium			
Insect growth regulators			
Methoprene		Yes	

4.2 Approach adopted in the more extensive ecotoxicological ED assessments

The approach adopted for the more extensive ecotoxicological ED assessments of the identified twenty substances was based on that used in the feasibility study (see Section 2.2). However, in the feasibility study it was recognised that the European Union Draft Assessment Reports and other regulatory dossiers may not contain sufficient information for an adequate ecotoxicological ED assessment. Therefore, for each of these 20 substances a literature search was carried out to identify whether additional relevant information was available. In particular, if it was not available in the regulatory dossiers, information was sought on the following tests:

- Fish Short Term Reproduction Assay (OECD 229, adopted September 2009);
- Fish Sexual Development Test (OECD 234, adopted July 2011);
- Fish Full Life-Cycle Test (EPA OPPTS 850.1500);
- Amphibian Metamorphosis Assay (OECD 231, adopted September 2009).

The search string used comprised the following terms:

Fish life cycle test, fish sexual development test , fish reproduction test, amphibian growth and development test, avian reproduction test, mammalian reproduction test, mammalian life cycle test, hatching success, growth, development, reproduction, sex ratio, oestrogen binding, oestrogen receptor, androgen binding, androgen receptor, steroidogenesis, thyroid hormone binding, vitellogenin, thyroxine.

In the evaluation, substances could be categorised as endocrine disrupters if they showed endocrine-mediated adverse effects relevant to populations in fish, birds or mammals. The assessment of potential endocrine disruption in mammals was based on the data collated for the human health assessment.

The Document “Definition of an Ecotoxicological Endocrine Disrupter for Regulatory Purposes” indicated that:

“Currently several aquatic and terrestrial invertebrates are considered as part of the regulatory process. However, the current absence of relevant international test guidelines means that in most cases it is not possible to pursue the question of endocrine disruption capability in relation to invertebrates. There is a research requirement to develop appropriate screening tools as well as higher tier studies.

However, it should be noted that some pesticidal or biocidal substances (e.g. insect growth regulators) are designed to interfere directly with the hormonal system of some invertebrates. It is proposed that for such compounds, investigations should be undertaken to explore whether or not there is an adverse effect at the population level and at the field scale. Where

such findings arise, then it might be appropriate to conclude that a substance is an ED in relation to non-target invertebrates in the environment."

The available chronic invertebrate toxicity data were considered in the light of this statement.

4.3 Results of the ecotoxicological ED assessments of substances in Stage 2

The results of the ecotoxicological ED assessments of substances in Stage 2 are shown in Tables C.1 to C.20 in Appendix C.

Table 4.2 summarises the outcomes of the more extensive ecotoxicological ED assessments. Table 4.3 consolidates this information in terms of the number of fungicides, herbicides and insecticides for which ecotoxicological ED assessments were carried out and the numbers and percentages of these that were identified as falling into each group. From the collation of the data it is evident that:

- Eleven substances (the fungicides carbendazim, chlorothalonil, and thiram, the herbicides 2,4-D, s-metalochlor and metribuzin and the insecticides , chlorpyrifos, beta-cyfluthrin, lambda-cyhalothrin, dimethoate and malathion) were categorised as substances for which further information was required (Group A).

- Seven substances (the fungicides iprodione, myclobutanil, prochloraz and tebuconazole, the herbicide ioxynil and the insecticides cypermethrin and fenoxycarb) were categorised as endocrine disrupters more likely to pose a risk (Group B). All of these group B substances (except fenoxycarb) were considered to be endocrine disrupters based on data from fish and mammals. Fenoxycarb was identified as a group B endocrine disrupter based on its ability to act as an insect juvenile hormone analogue and affect moulting in invertebrates.

- One substance (the insecticide abamectin) were categorised as endocrine disrupters of less likely to pose a risk (Group C).

- One substance (the herbicide glyphosate) was categorised as not being considered to be an endocrine disrupter (Group D).

- The ranking of the percentages of substances in different groups was Group A (60%) > Group B (35%) > Group D (5%) > Group C (0%).

The inclusion of additional relevant data from the open literature alongside that from the European Union Draft Assessment Reports or EFSA Conclusions enhanced the effective application of the grouping process as evidenced by the different conclusions reached for the substances considered in both Stage 1 and Stage 2.

Table 4.2 Summary of the more extensive ecotoxicological ED assessments of the twenty identified substances in Stage 2

Substance type	Substance	Substance ED grouping based on the assessment of ecotoxicological data				Human health assessment
		Further information required	More likely to pose a risk	Less likely to pose a risk	Not considered to be endocrine disrupters	
Fungicides	Carbendazim	**Yes**	No	No	No	Substances requiring further information
	Chlorothalonil	**Yes**	No	No	No	Substances not considered to be endocrine disrupters
	Iprodione	**No**	**Yes**	No	No	Endocrine disrupters less likely to pose a risk
	Myclobutanil	**No**	**Yes**	No	No	Endocrine disrupters less likely to pose a risk
	Prochloraz	No	**Yes**	No	No	Endocrine disrupters less likely to pose a risk
	Tebuconazole	No	**Yes**	No	No	Endocrine disrupters less likely to pose a risk
	Thiram	**Yes**	No	No	No	Substances requiring further information
Herbicides	2,4-D	**Yes**	No	No	No	Substances requiring further information
	Glyphosate	No	No	No	**Yes**	Substances not considered to be endocrine disrupters
	Ioxynil	No	**Yes**	No	No	Endocrine disrupters more likely to pose a risk
	S-metolachlor	**Yes**	No	No	No	Substances requiring further information
	Metribuzin	**Yes**	No	No	No	Endocrine disrupters less likely to pose a risk
Insecticides	Abamectin	No	No	**Yes**	No	Endocrine disrupters more likely to pose a risk
	Chlorpyrifos	**Yes**	No	No	No	Substances requiring further information

Substance type	Substance	Substance ED grouping based on the assessment of ecotoxicological data				Human health assessment
		Further information required	More likely to pose a risk	Less likely to pose a risk	Not considered to be endocrine disrupters	
	Beta-cyfluthrin	**Yes**	No	No	No	Substances requiring further information
	Lambda-cyhalothrin	**Yes**	No	No	No	Substances requiring further information
	Cypermethrin	No	**Yes**	No	No	Substances not considered to be endocrine disrupters
	Dimethoate	**Yes**	No	No	No	Substances not considered to be endocrine disrupters
	Fenoxycarb	No	**Yes**	No	No	Substances not considered to be endocrine disrupters
	Malathion	**Yes**	No	No	No	Substances not considered to be endocrine disrupters

Table 4.3 Summary information on the outcome of the ecotoxicological ED assessments of the twenty substances in Stage 2

Parameter	Outcome of the ecotoxicological ED assessments in Stage 2				
	Fungicides	**Herbicides**	**Insecticides**	**Plant growth regulators**	**Insect growth regulators**
Number of substances assessed	**7**	**5**	**8**	**0**	**0**
Number (and percentages of substances) in each group					
Substances requiring further information (Group A)	3 (43%)	3 (60%)	5 (63%)	0 (0%)	0 (0%)
Endocrine disrupters more likely to pose a risk (Group B)	4 (57%)	1 (20%)	2 (25%)	0 (0%)	0 (0%)
Endocrine disrupters less likely to pose a risk (Group C)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	0 (0%)
Substances not considered to be endocrine disrupters (Group D)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)
Total	**7**	**5**	**8**	**0**	**0**

5. Overall Results

An assessment process has been developed to allow active substances from the PPP Approved List to be assigned to one of four groupings, in respect of their potential to disrupt endocrine systems. The approach taken for human health involves the use of the criteria given in the discussion document "*Regulatory Definition of an Endocrine Disrupter in Relation to Potential Threat to Human Health*" prepared as a joint German-UK Position in May 2011. For the purpose of the ecotoxicological assessment the approach described in Section 2.2.4 was followed.

The four groupings are:

A. Substances requiring further information;

B. Endocrine disrupters more likely to pose a risk;

C. Endocrine disrupters less likely to pose a risk; and

D. Substances which are not considered to be endocrine disrupters.

In the process the potential of approximately 100 substances to exert endocrine-mediated adverse effects on human health has been assessed. In addition, assessments of 32 substances for their potential to exert ecotoxicological endocrine disrupting effects have been conducted. The principal data sources used were the European Union Draft Assessment Reports (EU DARs) and European Food Safety Authority (EFSA) conclusions. However, where necessary to supplement this data, appropriate information identified via literature searches was also used. This was particularly the case for the ecotoxicological assessment.

The approach proposed in the joint German-UK approach for the human health assessments was found to be generally straightforward to apply.

It should be recognised that none of the assignments of substances to the four groups are regulatory decisions.

5.1 Human health ED assessments

Table 5.1 consolidates the information on the ninety eight plant protection substances for which detailed human health assessments were conducted in Stages 1 and 2 in terms of the number of fungicides, herbicides, insecticides, plant growth regulators and insect growth regulators and the numbers and percentages of these that were identified as falling into each grouping.

Table 5.1 Summary information on the outcome of the human health ED assessments of the ninety eight substances in Stages 1 and 2

Parameter	Outcome of the human health ED assessments in Stages 1 and 2				
	Fungicides	Herbicides	Insecticides	Plant growth regulators	Plant growth regulators
Number of substances identified by HSE	37	38	21	4	1
Number of substances assessed (excluding those for which suitable regulatory dossiers were not available)	**37**	**36**	**20**	**4**	**1**
Number (and percentage of substances) in each grouping					
Substances requiring further information (Group A)	9 (24%)	11 (31%)	6 30%)	0 (0%)	0 (0%)
Endocrine disrupters more likely to pose a risk (Group B)	1 (3%)	2 (6%)	2 (10%)	0 (0%)	0 (0%)
Endocrine disrupters less likely to pose a risk (Group C)	6 (16%)	2 (6%)	1 (5%)	0 (0%)	0 (0%)
Substances not considered to be endocrine disrupters (Group D)	21 (57%)	21 (58%)	11 (55%)	4 (100%)	1 (100%)
Total	**37**	**36**	**20**	**4**	**1**

The key results from the analysis were that:

1. Where sufficient relevant data was available the criteria given in the joint UK-German discussion document permitted substances to be discriminated into the different groupings. For these human health assessments:

    - There were representatives of all groupings. Group B (Endocrine disrupters more likely to pose a risk) and Group C (Endocrine disrupters less likely to pose a risk) represented 5% (5 of 98) and 9% (9 of 98) of all the substances evaluated.
    - Group D substances (Substances not considered to be endocrine disrupters) were found to be the major group, being 59% (58 of 98) of all the substances evaluated.
    - Group A substances (Substances requiring further information) represented 27% (26 of 98) of all the substances evaluated.

- A similar pattern was found for fungicides, herbicides and insecticides in terms of the ranking of the percentages of substances in different groups, namely: Group D (59%) > Group A (27%) > Group C (9%) > Group B (5%).

2. The inclusion of additional literature data alongside that from the European Union Draft Assessment Reports and/or EFSA Conclusions enhanced the process for both the human health and, especially, the ecotoxicological assessments.

3. Using the assessment of the apical data for the 26 pesticides for which further information was required the following results were obtained with the assumption that endocrine mechanistic data were available showing them to be endocrine disrupters; 4 pesticides would be considered EDs more likely to pose a risk and 22 pesticides would be considered EDs less likely to pose a risk.

5.2 Ecotoxicological ED assessments

Table 5.2 consolidates the information on the twenty substances for which detailed ecotoxicological assessments were conducted in stage 2

Table 5.2 Summary information on the outcome of the ecotoxicological assessment of twenty substances (Stage 2)

Parameter	Outcome of the ecotoxicological ED assessments in Stage 2				
	Fungicides	Herbicides	Insecticides	Plant growth regulators	Plant growth regulators
Number of substances identified by HSE	7	5	8	0	0
Number of substances assessed (excluding those for which suitable regulatory dossiers were not available)	**7**	**5**	**8**	**0**	**0**
Number (and percentage of substances) in each grouping					
Substances requiring further information (Group A)	3 (43%)	3 (60%)	5 (62%)	0 (0%)	0 (0%)
Endocrine disrupters more likely to pose a risk (Group B)	4 (57%)	1 (20%)	2 (25%)	0 (0%)	0 (0%)
Endocrine disrupters less likely to pose a risk (Group C)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	0 (0%)
Substances not considered to be endocrine disrupters (Group D)	0 (0%)	1 (20%)	0(0%)	0 (0%)	0 (0%)
Total	**7**	**5**	**8**	**0**	**0**

At the time of project commissioning the possible approaches to establishing ecotoxicological criteria for EDs were not sufficiently developed to carry out an assessment equivalent to that undertaken for human health. However, using the approach described in Section 2.2.4 the results from the more extensive ecotoxicological ED assessments that were carried out in Stage 2 were that:

- Eleven substances (three fungicides three herbicides and five insecticides) were categorised as substances for which further information was required (Group A).

- Seven substances (four fungicides, one herbicide and two insecticides) were categorised as endocrine disrupters more likely to pose a risk (Group B). All of these group B substances (except fenoxycarb) were considered to be endocrine disrupters based on data from fish and mammals. Fenoxycarb was identified as a group B substance based on its ability to act as an insect juvenile hormone analogue and affect moulting in invertebrates.

- One substance (the insecticide abamectin) was categorised as endocrine disrupters less likely to pose a risk (Group C).

- One substance (the herbicide glyphosate) was categorised as not being considered to be an endocrine disrupter (Group D).

- The ranking of the percentages of substances in different groupings was Group A (55%) > Group B (35%) > Group D (5%) > Group C (5%).

5.3 Summary

Overall, the study considered 98 active substances for toxicological assessment and 20 for ecotoxicological assessment. The findings for each group are summarised in Table 5.3 below. These assessments indicate that a number of agronomically important active substances would be eliminated as being more likely to pose a risk, whilst others might also be eliminated despite being less likely to pose a risk, depending upon the final criteria adopted. Additional data (predominantly mechanistic data) would have to be generated and evaluated before the status of a significant number of “potential” endocrine disrupters (those requiring further information – group A) could be determined.

Table 5.3 Summary of the overall findings

A) Toxicological assessments for 98 substances

ED more likely to pose a risk	ED less likely to pose a risk	Potential ED - Further information needed	Not considered ED
Fungicides (37)			
Mancozeb	Bupirimate Iprodione Myclobutanil Prochloraz Tebuconazole Thiophanate-methyl	Carbendazim Cymoxanil Fluazinam Fosetyl aluminium Hymexazol Mandipropamid Prothioconazole Silthiofam Thiram	Azoxystrobin Boscalid Captan Chlorothalonil Cyazofamid Cyflufenamid Cyprodinil Dimethomorph Dimoxystrobin Fenhexamid Fenpropimorph Fludioxonil Fluoxastrobin Imazaquin Kresoxim-methyl Metalaxyl-M Metrafenone Propamocarb Pyraclostrobin Tolclofos-methyl Triazoxide
Herbicides (36)			
Ioxynil Linuron	Metribuzin Propyzamide	2,4-D Chlorpropham Dimethenamid-P Ethofumesate Fluazifop-p-butyl Glufosinate-ammonium Lenacil S-metalochlor Pinoxaden Tepraloxydim Terbuthylazine	Bentazone Bromoxynil Chloridazon Clomazone Clopyralid Dicamba Diquat Fluroxypyr Glyphosate Isoxaben Mecoprop Mesosulfuron-methyl Metamitron Metazachlor Metsulfuron-methyl Napropamide Oxadiazon Phenmedipham Prosulfocarb Tri-allate Triclopyr

ED more likely to pose a risk	ED less likely to pose a risk	Potential ED - Further information needed	Not considered ED
Insecticides (20)			
Abamectin Thiacloprid	Spiromesifen	Chlorpyrifos Clothianidin Beta-cyfluthrin Lambda-cyhalothrin Spinosad Spirotetramat	Cyflumetofen Cypermethrin Diflubenzuron Dimethoate Fenoxycarb Imidacloprid Malathion Methiocarb Pirimicarb Pymetrozine Tebufenpyrad
Plant growth regulators (4)			
			Chlormequat Maleic hydrazide Paclobutrazol Prohexadione
Insect growth regulators (1)			
			Methoprene

B) Ecotoxicological assessments (20 substances)

ED more likely to pose a risk	ED less likely to pose a risk	Potential ED - Further information needed	Not considered ED
Fungicides (7)			
Iprodione Myclobutanil Prochloraz Tebuconazole		Carbendazim Chlorothalonil Thiram	
Herbicides (5)			
Ioxynil		2,4-D S-metolachlor Metribuzin	Glyphosate
Insecticides (8)			
Cypermethrin Fenoxycarb	Abamectin	Chlorpyrifos Beta-cyfluthrin Lambda-cyhalothrin Dimethoate Malathion	
Plant growth regulators (0)			
-	-	-	-
Insect growth regulators (0)			
-	-	-	-

References

Klimisch, H.-J., Andreae, M. and Tillmann, U. (1997) A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology,* **25**, 1–5.

Matthiessen, P. (2003) An historical perspective on endocrine disruption in wildlife. In: Implication of Endocrine Active Substances for Human and Wildlife (Eds: J. Miyamoto and J. Burger) Pure and Applied Chemistry, 75 (11-12), pp2197-2206.

WHO/IPCS (2002). Global assessment of the state-of-the-science of endocrine disruptors. Geneva, World Health Organisation.

WHO/IPCS (2004). IPCS Risk Assessment Terminology, IPCS/OECD Key Generic Terms used in Chemical Hazard/Risk Assessment. Geneva, World Health Organisation. http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf.

Appendix A Datasheets for the Assessments of the Initial Twenty Substances

Fungicides

Table A.1 Endocrine Disruption Evaluation for Carbendazim

Substance details		
Substance Name	**Carbendazim**	
Substance Synonyms	-	
Substance CAS Number	10605-21-7	
Substance EC Number	234-232-0	
Data Source(s)	European Union Draft Assessment Report (2009) Lu, S.Y., Liao, J.W., Kuo, M.L., Wang, S.C., Hwang, J.S., Ueng, T.H., (2004) Endocrine disrupting activity in carbendazim-induced reproductive and developmental toxicity in rats. Journal of Toxicology and Environmental Health Part A: Current Issues, 67, 1501–1515. Yu G, Guo Q, Xie L, Liu and Wang X (2009) Effects of subchronic exposure to carbendazim on spermatogenesis and fertility in male rats, Toxicology and Industrial Health, 25, 41–47.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Muta. Cat. 2; R46 Repr. Cat. 2; R60-61 N; R50-53 Muta. 1B Repr. 1B Aquatic Acute 1 Aquatic Chronic 1	 May cause heritable genetic damage. May impair fertility. May cause harm to the unborn child. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. May cause genetic defects May damage fertility. May damage the unborn child. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**Yes (For the feasibility study the assessment has been completed)**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day Rat study	1/2	Liver ↑wt., clinical chemistry, histological findings, Testes ↓wt., azoospermia at high doses ↓bw gain, feed intake	No information reported	163	780	Effect on testes but no information to suggest ED. Other 90 day studies on rats and dogs with similar effects on liver and mild effect on testes
2-year Rat study	1/2	Liver ↑wt., clinical chemistry, histological findings, ↓wt higher doses RBC slight anaemia, equivocal evidence No evidence of carcinogenicity	No information reported	22	318	No evidence of an endocrine effect.
18-month Mouse; CD-1, Swiss and NMRKf mice study	1/2	Liver ↑wt., clinical chemistry, histological findings, ↓wt higher doses RBC slight anaemia, equivocal evidence ↑Mortality Liver tumours CD-1, Swiss but not NMRKf mice	Tumours not considered relevant for humans.	22.5	45	No evidence of an endocrine effect.
2-year Dog study	1/2	Liver ↑wt., clinical chemistry, histological findings, ↓wt higher doses RBC slight anaemia, equivocal evidence ↑Mortality No evidence of carcinogenicity	No information reported	2.6	12.4	No evidence of an endocrine effect.
Rat reproduction study	1/2	<u>Adult</u> ↑bw gain <u>Reproduction and Fertility</u> Infertility males ↓Sperm numbers Testicular atrophy and absence of spermatogenesis <u>Offspring</u> ↓bw gain	No information reported	100 (Parental) 100 (Reproductive) 100 (Offspring) Highest dose tested	-	Effects indicate disruption of male reproductive system

Rat developmental study	1/2	Maternal ↓bw gain, clinical signs of toxicity, abortions Developmental high resorption rate, ↓foetal wt, skeletal variation, malformations	No information reported	30 (Maternal) 10 (Developmental)	60 (Maternal) 30 (Developmental)	-
Rabbit reproduction study	1/2	Maternal ↓bw gain, abortions Developmental ↓implantations, ↑resorptions, ↓live litter size, skeletal malformations	No information reported	20 (Maternal) 10 (Developmental)	125 (Maternal) 20 (Developmental)	-
In vitro rat testis extract - Lu *et al*. (2004)	2	Inhibition of [3 H]-5-dihydro-testosterone to androgen receptor	-	956 µg/l (5 µM)	9560 µg/l (50 µM)	The results suggest that androgen- and androgen receptor-dependent mechanisms are possibly involved in carbendazim-induced toxicity in mammals.
In vivo rat fertility study (80 days exposure to carbendazim) – Yu *et al.* (2009)	2	Decreasing luteinizing hormone (LH) levels Follicle stimulating hormone (FSH) and testosterone (T) levels	-	100 mg/kg 200 mg/kg	200 mg/kg >200 mg/kg	The results suggest that carbendazim has adverse effects on meiotic transformation and spermatogenesis, resulting in reduced fertility in male rats.
In vivo rat fertility study (60 days exposure to carbendazim) – Yu *et al*. (2009)	2	Decreased stem cell factors (SCF)s levels Increased amyloid beta protein (ABP) levels	-	20 mg/kg 20 mg/kg	100 mg/kg 100 mg/kg	The results suggest that alterations of Sertoli cell morphology and function were involved in spermato-genic failure

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There are a number of adverse effects on the male reproductive system (relating to testes and sperm production) that may indicate endocrine disruption but no mechanism has been identified to suggest that carbendazim disrupts endocrine systems.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is some data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies, but these are not conclusive.

Are the effects judged to be relevant to humans?	Yes	There is nothing to suggest that the reproductive toxicity of carbendazim is not relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Effects resulting from endocrine disruption are not present in the available studies.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**No** (if yes complete the sections below)	**-**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Not required						

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Not required	-
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Not required	-
Are the effects judged to be relevant to fish, birds and/or mammalian populations?	Not required	-
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Not required	-
Grouping of the substance regarding its endocrine disrupting properties	***Not required here – However a detailed ecotoxicological assessment was carried out in Stage 2 (see Appendix C) to assess the potential implications for grouping of having additional relevant endocrine disruption data from the open literature (where available).***	

Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**There is some evidence of endocrine disrupting effects in reproductive studies, but there is insufficient data on potential mechanisms.**
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.2 Endocrine Disruption Evaluation for Chlorothalonil

Substance details		
Substance Name	**Chlorothalonil**	
Substance Synonyms	Tetrachloroisophthalonitrile	
Substance CAS Number	1897-45-6	
Substance EC Number	217-588-1	
Data Source(s)	Andersen HR, Vinggaard AM, Rasmussen TH, Gjermandsen IM, and Bonefeld-Jorgensen EC (2002) Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro. Toxicology and Applied Pharmacology, 179, 1-12. European Union Draft Assessment Report (2003)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	 Carc. Cat. 3; R40 T+; R26 Xi; R37-41 R43 N; R50-53	 Limited evidence of a carcinogenic effect Very toxic by inhalation Irritating to respiratory system Risk of serious damage to eyes May cause sensitization by skin contact Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Carc. 2 Acute Tox. 2 * STOT SE 3 Eye Dam. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	Suspected of causing cancer Fatal if inhaled May cause respiratory irritation Causes serious eye damage May cause an allergic skin reaction Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day Rat study	2	Stomach and kidneys (histopathological changes and increased organ weights in kidneys)	Mechanistic studies suggest inhibition of mitochondrial respiration.	1.5	3.0	Kidney is the main target organ for toxicity.
2-year Rat/Mouse chronic/ carcinogenicity studies	1/2	Fore-stomach (pre-neoplastic and neoplastic) tumours in rats and mice, kidney tumours in rats	No information reported	1.8 (rat)	3.8 (rat)	Due to anatomical difference, forestomach tumours are not considered relevant to human risk assessment
Rat reproductive two-generation study	1	Decreased pup weight and histopathological changes in stomach at parental toxic doses.	No information reported	<22.6 (Parental) 22.6 (Developmental) 145.1 (Reproductive)	-	Effects only at doses maternally toxic.
Rabbit developmental study	1	Decreased number of live foetuses (rat), increased number of rudimentary ribs (rabbit).	No information reported	10 (Maternal and developmental)	-	No indications of teratogenicity
Cell proliferation assay using human breast cancer MCF-7 cells – Andersen *et al*. (2002)	2	Marked effects were evident at low exposure concentrations due to cytotoxicity	Assay not suitable for evaluating potential hormone disrupting effects of the substance	No data reported	>1329.5 µg/l (>5 µM) (cytotoxicity)	The presence of four electrophilic groups means the substance is extremely reactive towards intra-cellular thiol groups causing high cytotoxicity
Estrogen receptor transactivation assay using human breast cancer MCF-7 cells – Andersen *et al*. (2002)	2	Marked effects were evident at low exposure concentrations due to cytotoxicity	Assay not suitable for evaluating potential hormone disrupting effects of the substance	No data reported	>1329.5 µg/l (>5 µM) (cytotoxicity)	
Androgen receptor transactivation assay using Chinese hamster ovary cells (CHO K1) – Andersen *et al*. (2002)	2	Marked effects were evident at low exposure concentrations due to cytotoxicity	Assay not suitable for evaluating potential hormone disrupting effects of the substance	No data reported	>265.9 µg/l (>1 µM) (cytotoxicity)	
Aromatase assay based on placental microsomes – Andersen *et al*. (2002)	2	Marked effects were evident at low exposure concentrations due to cytotoxicity	Assay not suitable for evaluating potential hormone disrupting effects of the substance	No data reported	13295 µg/l 50 µM (cytotoxicity)	

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects in the full set of toxicological data required for a human health assessment do not indicate an endocrine mode of action.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence in the full set of toxicological data is available to suggest an endocrine mode of action. Cellular assays are not suitable for evaluating the potential hormone-disrupting effects of chlorothalonil owing to four electrophilic chlorine atoms that are very reactive toward intracellular thiol groups and result in cytotoxicity even at low exposure concentrations.
Are the effects judged to be relevant to humans?	Yes	There is nothing to suggest that the reproductive toxicity of chlorothalonil is not relevant to humans
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	Yes – but no ED effects	Effects resulting from endocrine disruption are not present in the available studies.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (if yes complete the sections below)	**-**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Algal *Navicula pelliculosa* growth inhibition test (120 hour exposure to chlorothalonil, 98.1%)	1	Inhibition of cell growth	No information reported	0.0035	0.007	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to Chlorothalonil 75WG, 500 g/l)	1	Reduction in juvenile production Reduced adult survival	No information reported No information reported	0.019 0.0006	0.075 0.018	Effects are evidently not endocrine-mediated
Fish early life stage test	No data reported	-	-	-	-	-
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish fathead minnow *Pimephales promelas* one generational test (297 day exposure to chlorothalonil, 96.0%)	1	Reduced hatchability and fry survival of the F0 eggs Reduced reproduction success of F0 fish	No information reported No information reported	0.0065 0.0065	0.016 0.016	Effects could be endocrine- mediated

		Reduced hatchability of second generation F1 eggs	No information reported	0.003	0.0065	
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard *Anas platyrhynchos* reproduction test (18 week exposure to technical grade chlorothalonil)	1	Reproductive and adult health effects	No information reported	10000 mg a.s./kg diet	>10000 mg a.s./kg diet	No reproductive or adult health effects were measured at any test concentration
Bobwhite quail *Coilinus virginianus* reproduction test (22 week exposure to Chlorothalonil 75WG, 500 g/l)	1	Reduction in number of eggs laid and number of 14 day survivors per female	No information reported	160 mg a.s./kg diet (reproduction) 640 mg a.s./kg diet (adult health)	640 mg a.s./kg diet (reproduction)	No treatment related effects at necropsy Effects could be endocrine-mediated

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for chlorothalonil, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the one generation study in fathead minnow reported effects on reproduction and development which could be endocrine-mediated and could affect populations. For birds the one generation study in bobwhite quail reported reproductive effects that could be endocrine-mediated.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies. Cellular assays are not suitable for evaluating the potential hormone-disrupting effects of chlorothalonil owing to four electrophilic chlorine atoms that are very reactive toward intracellular thiol groups and result in cytotoxicity even at low exposure concentrations.
Are the effects judged to be relevant to fish, bird and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	The most sensitive endpoint for aquatic species is the reduction in juvenile production in the invertebrate *Daphnia magna* which is not evidently endocrine-mediated, though algal growth inhibition effects and fish growth effects are evident at similar concentrations.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information*** ***A detailed ecotoxicological assessment was carried out in Stage 2 (see Appendix C) to assess the potential implications for grouping of having additional relevant endocrine disruption data from the open literature (where available).***	

Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, chlorothalonil is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.3 Endocrine Disruption Evaluation for Cyflamid (containing the active ingredient cyflufenamid)

Substance details						
Substance Name	**Cyflamid** is a product containing the active constituent, cyflufenamid					
Substance Synonyms	*(Z)-N*-[α-(cyclopropylmethoxyimino)-2,3-difluoro-6-(trifluoromethyl)benzyl]-2-phenylacetamide (IUPAC).					
Substance CAS Number	180409-60-3					
Substance EC Number	Not assigned					
Data Source(s)	European Union Draft Assessment Report (2006) EFSA Scientific Report (2009) 258, 1-99 Conclusion on the peer review of the pesticide risk assessment of the active substance cyflufenamid					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/2008	 Not available Not available	 Not available Not available				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day Rat dietary study	1/2	Histopathological changes in the liver and kidney. Histopathological findings were also noted in the thyroid, heart and testis at 670 mg/kg bw/day	No information reported	20	117	Findings in organs associated with the endocrine system.
90-day Dog dietary study with 13 and 26 week recovery periods	1/2	↓body wt. gain, histopathology in the liver and thymus. Brain vacuolation	No information reported	6.5	23	Brain vacuolation was not completely reversed at 13 weeks

				23	76	but the lesions had reversed at 26 weeks
1-year Dog study	1/2	Alteration in liver function as indicated by ↑serum alkaline phosphatase activity (liver derived). There were no brain lesions.	No information reported	4	17	No evidence of endocrine disruption.
2-year Rat combined long-term toxicity and carcinogenicity study	1/2	Histopathological changes in the kidneys of males, and in the livers of females. Thyroid adenomas and carcinomas at highest dose	Thyroid tumours were a secondary consequence of increased metabolism of the thyroid hormones due to the enhanced metabolic activity in the liver. Confirmation from supplementary study in male rats where there was disturbance of the negative feedback to the pituitary caused by reductions in plasma T3 and T4 hormone levels increased TSH release which stimulated thyroid activity. This continuous stimulation resulted in thyroid follicular cell tumours. However, the thyroid of rats is known to be more sensitive to hormonal disturbance than its human counterpart, and so these thyroid tumours are not relevant to the human risk assessment	4.4 (non neoplastic changes) >115 (neoplasia)	22	Thyroid adenomas and carcinomas are not relevant for human risk assessment as their mechanism of formation in rats does not occur in man.
18 month Mouse carcinogenicity study	1/2	↓body wt. gain,↑ minor liver wt, and histopathology in the liver, heart and lungs, including hepatocellular adenomas.	No information reported	63 (non neoplastic and neoplastic changes)	174	The increase in liver tumours was considered to be a secondary response to continuous stimulation of hepatocytes by high concs and deemed to have a threshold.

Rat two-generation (dietary)	-	↑liver and thyroid wt in F0 adults and F1 and F2 offspring. ↓body wt gain in F1 and F2 offspring during late lactation	No information reported	18.0-23.0 (General) 57-75 (Reproductive) (top dose	57	Thyroid effects evident
Rat developmental toxicity (gavage)	-	↑ post-dosing salivation at 1000 mg/kg/day, of brown staining; ↑dose-related in absolute and relative liver wt.	No information reported	100 (Maternal) 1000(Developmental, top dose)	300	No evidence of an effect on the endocrine system.
Rabbit developmental toxicity	-	↓Dose related in body wt gain (including terminal weight adjusted for gravid uterine weight) and food consumption. Abortions at 300 mg/kg/day; total litter resorption at 60 mg/kg/day; loose/few faeces and ventral hairloss; ↓embryofetal weight; ↑incomplete ossification of epiphyses and metacarpals/phalanges. Pale placentae; ↑incidence of enlarged anterior fontanel and incompletely ossified cervical vertebrae at 300 mg/kg alone.	No information reported	<10 (Maternal) 10 (Developmental)	60	

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response(Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There was disturbance of the negative feedback to the pituitary caused by reductions in plasma T3 and T4 hormone levels and increased TSH release which stimulated thyroid activity. This continuous stimulation resulted in thyroid follicular cell tumours. This appears to be due to increased metabolism in the liver and the increased sensitivity of the thyroid in rats. Therefore this mechanism is not considered relevant to humans.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	The supplementary studies on rats suggest that the effects on thyroid hormones and the subsequent formation of tumours is due to effects on the liver and increased metabolism rather than endocrine disruption.

Are the effects judged to be relevant to humans?	No	The effects on the thyroid leading to adenomas and carcinomas are not considered relevant to humans (see above)
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	NA	ED effects are not relevant to humans.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (If yes complete the sections below)	**-**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Algal *Pseudokichneriella subcapitata* growth inhibition test (72 hours exposed to cyflufenamid, 95.2% purity)	1	Inhibition of growth	No information provided	0.828	Not appropriate, only one concentration tested	Effects were evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to cyflufenamid, purity not stated)	1	Reduction in juvenile production and parental survival	No information provided	0.0406 (Adult survival) 0.246 (Reproduction)	0.10 (Adult survival) 0.575 (Reproduction)	Effects were evidently not endocrine-mediated
Fish fathead minnow *Pimephales promelas* early-life stage test (28 day exposure to cyflufenamid, 95.2% purity)	1	Fish growth (as weight and length)	No information provided	0.024	0.045	Effects could have been endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data available	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard *Anas platyrhynchos* reproduction test	No data available	-	-	-	-	-
Bobwhite quail *Coilinus virginianus* reproduction test (22 week exposure to cyflufenamid, purity not stated)	1	Reproductive and adult health endpoints	No information provided	>1000 mg a.s/kg diet (98 mg/kg bw/day)	Not applicable	No dose related effects were observed in the reproductive endpoints even at the highest dose tested

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for cyflamid, which is relevant to mammalian wildlife species, indicated that "*There was disturbance of the negative feedback to the pituitary caused by reductions in plasma T3 and T4 hormone levels and increased TSH release which stimulated thyroid activity. This continuous stimulation resulted in thyroid follicular cell tumours. This appears to be due to increased metabolism in the liver and the increased sensitivity of the thyroid in rats. Therefore this mechanism is not considered relevant to humans*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test in fathead minnow reported effects on growth which could be endocrine-mediated and could affect populations. For birds the one generation study in bobwhite quail reported no reproductive effects that could be endocrine-mediated at the highest test dose.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.
Are the effects judged to be relevant to fish, bird and/or mammalian populations?	No	The thyroid effects measured in the chronic studies are probably not relevant to mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	The most sensitive endpoint for aquatic species is the reduction in growth in fathead minnow which could be endocrine-mediated.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information***	

Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response(Yes/No)**	**Comments**
(A)Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were observed in standard toxicity tests but these were not relevant to humans. Therefore, cyflamid is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.4 Endocrine Disruption Evaluation for Dimoxystrobin

Substance details		
Substance Name	**Dimoxystrobin** (ISO common name)	
Substance Synonyms	(E)-*o*-(methoxyimino)-*N*-methyl-2-[α-(2,5-xylyloxy)-*o*-tolyl]acetamide (IUPAC) (E)-o-(2,5-dimethylphenoxymethyl)-2-methoxyimino-N-methylphenylacetamide (IUPAC)	
Substance CAS Number	149961-52-4	
Substance EC Number	Not assigned	
Data Source(s)	European Union Draft Assessment Report (2003) EFSA Scientific Report (2005) 46, 1-82 Conclusion on the peer review of dimoxystrobin	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	 Carc. Cat. 3; R40 Repr. Cat. 3; R63 Xn; R20 N; R50-53	 Limited evidence of a carcinogenic effect Possible risk of harm to the unborn child Harmful by inhalation Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	 Carc. 2 Repr. 2 Acute Tox. 4* Aquatic Acute 1 Aquatic Chronic 1	 Suspected of causing cancer Suspected of damaging the unborn child Harmful if inhaled Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
Short-term toxicity 90-day rat oral/dermal	1	Duodenal (mucosal) thickening	Duodenum is main site for iron absorption. Duodenal thickening linked to decreased levels of iron in serum.	3 (oral) >1000 (dermal)	21 (oral)	No evidence of an endocrine effect.
Long-term toxicity and carcinogenicity (2-year) rat study	1	↓body wt gain and/or duodenal thickening, thyroid adenomas (no dose response)	No information reported	7	23	No evidence of an endocrine effect.
Long-term toxicity and carcinogenicity (18-month) mouse study	1	↓body wt gain and/or duodenal thickening, duodenal tumours (adenoma and adenocarcinoma)	Duodenal tumours caused by persistent cell proliferation (BrdU labelling studies) related to ↑functional demand on duodenum to compensate for ↓serum iron levels.	4	20	No evidence of an endocrine effect.
Reproductive toxicity	1	No effects on reproductive performance or fertility	No information reported	136 (reproductive performance) 17 (parental based on slight anaemia)	NOAEL was highest dose tested	No evidence of an endocrine effect.
Developmental toxicity	1	↓gravid uterus wt., ↑resorption rate, post-implantation loss, no. of foetuses with variations (fused sternebrae)	No information reported	20 (developmental effects) 5 (maternal toxicity based on ↓food consumption and body wt loss	75 20	Evidence of endocrine effect?
Mechanistic studies - 7-day studies in young and adult rats	4	↓serum iron	Up to 5x greater depression in serum iron in young rats compared to adults at effect level of 33 mg/kg bw/day	4 (based on serum depression of iron)	20	Evidence of endocrine effect?

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	No evidence of adverse effects on endocrine organs. Toxicity is based on depression of iron levels leading to a thickening of duodenal mucosa, the main route of iron absorption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	-
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	-
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (if yes complete the sections below)	**-**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Algal *Pseudokirchneriella subcapitata* growth inhibition test (96 hour exposure to dimoxystrobin, 97.4% purity)	No data available	Inhibition of growth	No information reported	<0.004	0.004	Effects were evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to dimoxystrobin, 99.7% purity)	1	Reduction in juvenile production	No information reported	0.0125 (Reproduction)	0.025 (Reproduction)	Effects were evidently not endocrine-mediated
Fish rainbow trout *Oncorhynchus mykiss* early-life stage test (97 day exposure to dimoxystrobin, 98.4% purity)	1	Fish growth (as weight)	No information reported	0.001	0.0032	Effects could have been endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data available	-	-	-	-	-

Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard *Anas platyrhynchos* reproduction test (22 week exposure to dimoxystrobin, 98.4% purity)	1	Reduction in number of eggs laid	No information reported	300 mg a.s./kg diet (Reproduction) 1000 mg a.s/kg diet (Adult health)	1000 mg a.s./kg diet (Reproduction) (Adult health)	Effects could have been endocrine-mediated
Bobwhite quail *Coilinus virginianus* reproduction test (22 week exposure to dimoxystrobin, 98.4% purity)	1	Reproductive and adult health endpoints	No information reported	>1000 mg a.s/kg diet	Not applicable	No dose related effects were observed in the reproductive endpoints even at the highest dose tested

Evaluation of the available ecotoxicological toxicity data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for dimoxystrobin, which is relevant to mammalian wildlife species, indicated that "*No evidence of adverse effects on endocrine organs. Toxicity is based on depression of iron levels leading to a thickening of duodenal mucosa, the main route of iron absorption*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test in rainbow trout reported effects on growth which could be endocrine-mediated and could affect populations. For birds the one generation study in mallard reported reproductive effects that could be endocrine-mediated at the highest test dose.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.
Are the effects judged to be relevant to fish, bird and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	The most sensitive endpoint for aquatic species is the reduction in growth in rainbow trout which could be endocrine-mediated. However, effects on algal growth are evident at similar concentrations.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information***	

Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, dimoxystrobin is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.5 Endocrine Disruption Evaluation for Mancozeb

Substance details		
Substance Name	**Mancozeb**	
Substance Synonyms	IUPAC Name Manganese ethylene (dithiocarbamate) ((polymeric) complex with zinc salt)	
Substance CAS Number	8018-01-7	
Substance EC Number	Not assigned	
Data Source(s)	European Union Draft Assessment Report (2001)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Repr.Cat. 3: R63 R43 N; R50 Repro. 2 Skin sens. 1 Aquatic Acute 1	 Possible risk of harm to unborn child May cause sensitisation by skin contact Very toxic to aquatic organisms Suspected of damaging the unborn child May cause allergic skin reaction Very toxic to aquatic life
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
Mouse 28-day (subacute) and 90-day (subchronic) study	1	↑Thyroid wt,, follicular cell hyperplasia	Similar results with ETU so likely to be the effect of the metabolite.	18	180	Effects on organs in endocrine system.

Rat 90-day (subchronic) study	1	↑Thyroid wt,, Slight ↓T4, ↑TSH, Hypertrophy of pituitary cells.	Similar results with ETU so likely to be the effect of the metabolite.	7.4 based on ↓T4, ↑TSH	14.8	2 studies, NOAEL in other study 1.7 mg/kg bw/day based on non-significant ↓T4
Dog 90-day (subchronic) study	1	Thyroid follicular cell hyperplasia	Similar results with ETU so likely to be the effect of the metabolite.	3.0	28	Second study effects at all treatment groups, LOAEL 5.7 mg/kg bw/day and effects reversible
Dog 1-year (chronic) study	1	↓T4, ↑thyroid wt and follicular distension	Similar results with ETU so likely to be the effect of the metabolite.	2.3 based on ↓T4	22	Two studies, NOAEL in one, 7 mg/kg bw/day based on non-thyroid endpoints
Rat 2-year (chronic) study	1	↓T4, ↑TSH, thyroid follicular hyperplasia/hypertrophy, carcinomas, adenomas	Attributable to ETU. Inhibition of T4 leads to ↑TSH release by pituitary. Tumours occur in rats when threshold for pituitary-thyroid feedback is exceeded on achronic basis resulting in over-stimulation of thyroid and subsequent development of proliferative lesions.	5	30	A further 2-year study gave no increased incidence of tumours and a NOAEL of 4 mg/kg bw/day based on ↓T4
Mouse 18-months (chronic) study	1	↓T4, no tumours	No information reported	13	130	No evidence of endocrine effects.
Rat 2-generation (subchronic) study	1	Microscopic changes in thyroid in both generations, thyroid follicular hyperplasia and adenomas	No information reported	1.7 in adults based on thyroid histopathology	6.8	Effects in organs in endocrine system.
Monkey 5-5.5 months (subchronic) study	-	↓T4, ↑TSH, ↑Iodine uptake, ↑Thyroid wt. hyperplasia and hypertrophy	No information reported	0.1 to 0.5	2.5	Effects in organs in endocrine system.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?	Yes	There are a wide range of studies performed to OECD and equivalent guidelines and GLP in mice, rats, dogs and monkeys for the relevant target organs and toxicological endpoints. These show effects on the pathology of the thyroid and on levels of thyroid hormones.

Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	The metabolite of mancozeb, ETU has been shown to inhibit thyroid peroxidase and produce antithyroid effects in a range of species including monkeys. Thyroid peroxidase is responsible for the iodination and coupling of tyrosine residues into thyroglobulin which is the precursor of thyroid hormones.
Are the effects judged to be relevant to humans?	Yes	Humans are expected to be less sensitive to chemically-induced thyroid disruption for two reasons. In thyroid-binding globulin, humans have a reserve source of thyroid hormone, not present in rodents. Therefore in rodents there is a comparatively rapid turnover of T4 and normally higher levels of TSH. Secondly prolonged thyroid insufficiency in humans (e.g. iodine deficiency in human populations) is normally expressed as goitre rather than tumours. Therefore the thyroid tumours in the rodents may be of limited relevance. However, the ED effects of mancozeb appear to be due to the inhibition of thyroid peroxidase by its metabolite, ETU. Thyrotoxicosis in humans can be treated by thioamide drugs, (e.g. propylthiouracil) which also work by a similar inhibition. Therefore, humans are sensitive to effects on the thyroid by inhibition of thyroid peroxidase. Human thyroid function is normally controlled by sensitive feedback loops. However, there are substantial vulnerable human sub-groups where thyroid function may be impaired, e.g. post-menopausal women who might be sensitive to the effects of mancozeb on the thyroid.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	Yes	There are subacute, subchronic and chronic studies where the LOAELs are lower than the STOT-RE Cat 1 cut-offs with the toxic effects being effects on the pathology of the thyroid or thyroid hormones.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**No** (If yes complete the sections below)	-

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Not required						

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Not required	-
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Not required	-

Are the effects judged to be relevant to fish, bird and/or mammalian populations?	Not required	-
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Not required	-
Grouping of the substance regarding its endocrine disrupting properties	***Not required***	
Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There are full set of regulatory toxicological studies on experimental animals.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	**Yes**	**There are sub-acute, sub-chronic and chronic studies where the NOAELs are lower than the STOT-RE Cat 1 cut-offs with the toxic effects being effects on the pathology of the thyroid or thyroid hormones. Therefore, mancozeb is considered to be a substance more likely to pose a risk**
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	-
(C) Substances not considered to be endocrine disrupters based on currently available data	No	-

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Herbicides

Table A.6 Endocrine Disruption Evaluation for 2,4-D

Substance details		
Substance Name	**2,4-D** (ISO)	
Substance Synonyms	2,4-dichlorophenoxyacetic acid	
Substance CAS Number	94-75-7	
Substance EC Number	202-361-1	
Data Source(s)	No European Union Draft Assessment Report located, WHO (2003) 2,4-D in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*; IPCS (1984) 2,4-D Environmental Health Criteria Monograph 29; IUCLID (2000) 2,4-D European Chemicals Bureau, European Commission Liu R C (1996) The direct effects of hepatic peroxisome proliferators on rat Leydig cell function in vitro. Fundamental Applied Toxicology, 30, 102–108.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	 Xn; R22 Xi; R37-41 R43 R52-53	 Harmful if swallowed Irritating to respiratory system, Risk of serious damage to eyes May cause sensitization by skin contact Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/2008	Acute Tox. 4 * STOT SE 3 Eye Dam. 1 Skin Sens. 1 Aquatic Chronic 3 H412	Harmful if swallowed May cause respiratory irritation Causes serious eye damage May cause an allergic skin reaction Harmful to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day Mouse Study	1/2	↓glucose level in females, ↓thyroxine activity in males and ↑absolute and/or relative kidney wts in males.	No information reported	15	100	-
90-day Rat study	1/2	Renal lesions	No information reported	1	5	
2-year long-term toxicity and carcinogenicity Mouse study	1/2	↑absolute and/or relative kidney wts and renal lesions. There was no evidence of carcinogenicity	No information reported	1	15	No evidence of an endocrine effect.
2-year long-term toxicity and carcinogenicity Rat study	1/2	Renal lesions were seen in animals of both sexes. There was no evidence of carcinogenicity.	No information reported	1	5	No evidence of an endocrine effect.
2-year long-term toxicity and carcinogenicity Rat study	1/2	↓body wt gains and food consumption, ↑serum alanine and aspartate aminotransferase activities, ↓thyroxine concentrations, ↑absolute and relative thyroid wts and histopathological lesions in the eyes, kidneys, liver, lungs and mesenteric fat. There was no evidence of carcinogenicity.	No information reported	5	75	-
2-generation Rat reproductive toxicity study	1/2	↓body wts of F1 dams and renal lesions in F0 and F1 adults.	No information reported	5 (parental and reproductive toxicity)	20	-
Rat developmental toxicity study	1/2	↓foetal body wts.	No information reported	88 (maternal toxicity, top dose) 25 (developmental toxicity)	 50	There was no maternal toxicity.
In vitro leydig cell function test – Liu (1996)	2	Effect of peroxisome proliferators on the hCG stimulated release of testosterone from 24-hr cultures of Leydig cells Effect of peroxisome proliferators on the non-stimulated release of		No data No data	No data No data	No minimum effective concentration established No minimum effective concentration

		testosterone from 24-hr cultures of Leydig cells Effect of peroxisome proliferator on the baseline release of estradiol from 2l-hr cultures of Leydig cells		22.1 (100 µM)	110.5 (500 µM)	established

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response(Yes/ No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There is some evidence of effects on thyroid weight and thyroxine levels in long-term toxicity studies that constitute part of the full range of toxicological tests. However, no modern studies to indicate whether this is due to any direct disrupting effects on the thyroid system.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence of a mechanism to suggest that 2,4-D has a disrupting effect on the thyroid system.
Are the effects judged to be relevant to humans?	Yes	There is no reason to suggest that effects on the thyroid would not be seen in humans although the rat thyroid is generally more sensitive than the human to metabolic effects. Further studies would inform this effect.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	-
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**No** (If yes complete the sections below)	

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Not required						

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Not required	-
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Not required	-
Are the effects judged to be relevant to fish, bird and/or mammalian populations?	Not required	-
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Not required	-
Grouping of the substance regarding its endocrine disrupting properties	***Not required here – However, a detailed ecotoxicological assessment was carried out in Stage 2 (see Appendix C) to assess the potential implications for grouping of having additional relevant endocrine disruption data from the open literature (where available).***	
Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A)Substances requiring further information	**Yes**	**There is some evidence of effects on the thyroid but there is insufficient data on potential mechanisms.**
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.7 Endocrine Disruption Evaluation for Dicamba

Substance details		
Substance Name	**Dicamba**	
Substance Synonyms	2,5-dichloro-6-methoxybenzoic acid 2,5-dichloro-6-methoxybenzoic acid	
Substance CAS Number	1918-00-9	
Substance EC Number	217-635-6	
Data Source(s)	European Union Draft Assessment Report (2007)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xn; R22 Xi; R41 R52-53 Acute Tox. 4 * H302 Eye Dam. 1 H318 Aquatic Chronic 3 H412	 Harmful if swallowed Risk of serious damage to eyes Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment Harmful if swallowed Causes serious eye damage Harmful to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
28-day Rat study	1	↓body wt. gain and food consumption, impaired mobility of hind limbs	No information reported	1000	1400	No evidence of an endocrine effect.

90-day Rat study	1	↓body wt. gain, liver effects, altered relative wt., clinical chemistry and histopathology	No information reported	479	1000	No evidence of an endocrine effect.
90-day Dog study	1	↓body wt. gain, clinical symptoms, haematology	No information reported	50	300	No evidence of an endocrine effect.
1-year Dog study	1	No systemic toxicity, initial palatability problems	No information reported	52	>52	No evidence of an endocrine effect.
Long-term and carcinogenicity 2-year Rat study	1/2	No systemic toxicity or carcinogenicity	No information reported	99	-	No evidence of an endocrine effect.
Mouse carcinogenicity study	1/2	↓body wt. gain in females, no carcinogenicity	No information reported	121	364	No evidence of an endocrine effect.
Multigeneration Rat study	1	Parental ↓body wt. gain, clinical signs and ↑liver wt in F_0, F_1 females	No effects on oestrus cycle or in sperm analysis	105 (parental) 35 (developmental (offspring)) >350 (reproduction)	-	No evidence of an endocrine effect.
Rat teratology study	1	Maternal toxicity, ↓body wt. gain and food consumption, clinical signs, mortality	No information reported	160 (maternal) 400 (foetal)	-	No evidence of an endocrine effect.
Rabbit teratology study	1	Maternal toxicity, ↓body wt. gain and food consumption, clinical signs, mortality, ↑ abortions and clinical signs No developmental or teratological effects	No information reported	30 (maternal) 150 (foetal)	-	No evidence of an endocrine effect.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects in the full set of toxicological data required for a human health assessment do not indicate an endocrine mode of action.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence is available to suggest an endocrine mode of action.

Are the effects judged to be relevant to humans?	Yes – but no ED effects	Effects resulting from endocrine disruption are not present in the available studies. The effects observed are relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Effects resulting from endocrine disruption are not present in the available studies.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (If yes complete the sections below)	**-**

Ecotoxicogical data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Algal *Skeletonema costatum* growth inhibition test (72 hour exposure to dicamba, 89.5% purity)	1	Inhibition of growth	No information reported	0.011	0.032	Effects were evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to dicamba, 88.6% purity)	1	Reduction in juvenile production	No information reported	97	Not applicable	Effects were evidently not endocrine-mediated
Fish rainbow trout *Oncorhynchus mykiss* sub-lethal test (21 day exposure to dicamba, 86.6% purity)	1	Fish growth (as weight and length)	No information reported	180 (Behaviour) 1000 (Survival)	320 (Behaviour)	Effects were evidently not endocrine-mediated
Fish early-life stage test	No data reported	-	-	-	-	-
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard *Anas platyrhynchos* reproduction test (21 week exposure to dicamba, 89.6% purity))	1	Reproductive and adult health endpoints	No information reported	>1600 mg a.s./kg diet (170 mg a.s./kg bw/day)	Not applicable	No dose related effects were observed in the reproductive endpoints even at the highest dose tested

Bobwhite quail *Coilinus virginianus* reproduction test (21 week exposure to dicamba, 89.6% purity))	1	Reproductive and adult health endpoints	No information reported	>1600 mg a.s./kg diet (186 mg a.s./kg bw/day)	Not applicable	No dose related effects were observed in the reproductive endpoints even at the highest dose tested

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for dicamba, which is relevant to mammalian wildlife species, indicated that "*Adverse effects in the full set of toxicological data required for a human health assessment do not indicate an endocrine mode of action.*" None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the observed effects in the chronic study were evidently not endocrine mediated. For birds the one generation studies in bobwhite quail and mallard reported no reproductive effects that could be endocrine-mediated at the highest test dose.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.
Are the effects judged to be relevant to fish, bird and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint for aquatic species is the inhibition of algal growth. This occurs at markedly lower exposure concentrations that those causing effects in fish.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information***	

Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.

(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, dicamba is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.8 Endocrine Disruption Evaluation for Glufosinate-ammonium

Substance details		
Substance Name	**Glufosinate-ammonium**	
Substance Synonyms	IUPAC: Ammonium(DL)-homoalanin-4-yl(methyl)phosphinate CA: 2-amino-4-(hydroxymethylphosphinyl)butanoic acid, monoammonium salt	
Substance CAS Number	77182-82-2	
Substance EC Number	278-636-6	
Data Source(s)	European Union Draft Assessment Report (2005)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Repr. Cat. 2; R60 Repr. Cat. 3; R63 Xn; R20/21/22-48/20/22	May impair fertility. Possible risk of harm to the unborn child. Harmful by inhalation, in contact with skin and if swallowed. Harmful: danger of serious damage to health by prolonged exposure through inhalation and if swallowed.H360Fd May damage fertility. Suspected of damaging the unborn child.
Regulation (EC) No 1272/ 2008	Repr. 1B Acute Tox. 4 * Acute Tox. 4 * Acute Tox. 4 * STOT RE 2 *	Harmful if inhaled Harmful in contact with skin. Harmful if swallowed. May cause damage to organs through prolonged or repeated exposure.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**Yes (For the feasibility study the assessment has been completed)**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
Rat 28-day study	1-2	↑kidney wt., ↓food consumption	No treatment related changes or systemic toxicity	53	276	No endocrine effects observed

Dog 28-day study	2	No change in standard biochemical parameters ↓ brain glutamine synthetase (GS) and brain amino acids, ↓heart taurine and glutamine	Inhibition of glutamine synthetase (GS).	1	-	No endocrine effects observed
Rat 90-day study	2	↓ body wt. gain, food consumption, ↓LDH, ↑ kidney wt.	Inhibition of GS	4.1	39	No endocrine effects observed
Rat 90-day study	2	↓ liver GS which was reversible	Inhibition of GS	3.2	-	A further 90-day study gave haematological effects at all doses (521, 686, 1351 mg/kg bw/day)
Mouse 90-day study	2	Changes in haematological parameters, ↑ alkaline phosphatase. No histological changes	Inhibition of GS. The mechanism behind the changes in haematological parameters is unclear	278	Highest dose	The changes were considered not to be toxicologically significant as there are not accompanied by histological changes.
Dog 90-day study	2	↓ bw, food consumption ↓ phosphate, plasma bilirubin	Inhibition of GS. The mechanism behind the changes in haematological parameters is unclear.	7.63 (Highest dose tested)	-	Uterus and epididymus not weighed
Rat 2.5-year study	2	↓bw, food consumption ↑kidney wt. Haematological changes Biochemical changes No carcinogenic potential	Inhibition of GS. The mechanism behind the changes in haematological parameters is unclear	24.4 (Highest dose tested)	-	Low dose used
Rat 2-year study	2	↓bw, food consumption ↑kidney wt. ↑ retinal atrophy	No information reported	57.1	228.9	No endocrine effects observed
Mouse 2-year	2	↓bw gain Biochemical changes ↑ Mortality No carcinogenic potential	No information reported	11	-	No endocrine effects observed
Rat Preliminary to 2-generation	2	Female ↑post-implantation loss, ↓liver weight Male ↓kidney weight,	The underlying mechanism for the reproductive effects are unclear.	4.4 (Female parent) 44 (Male parent)	-	-

		food consumption				
Rat 2-generation study	2	↑kidney wt. ↓litter size	The underlying mechanism for the reproductive effects are unclear.	2.4 (Parental) 7.5 (Reproductive)	-	There was no -weighing of epididymis, sperm mobility measurement, vagina histology
Rat developmental study	2	Uterine deaths, abortions ↑dystension of renal pelvis and ureter, retardation of skeletal ossification of os metacarpale	The underlying mechanism for the reproductive effects are unclear.	10 (Maternal toxicity) 10 (Developmental)	-	-
Rabbit developmental study	2	↓ food consumption Dead foetuses, resorptions and abortions	The underlying mechanism for the reproductive effects are unclear.	6.3 (Maternal toxicity) 6.3 (Development)	20	-
Mouse embryos in culture developmental and dysmorphogenic	2	Embryotoxicity Morphological defects in craniofacial Growth retardation ↑ embryolethality	The underlying mechanism for the reproductive effects are unclear.	-	-	-

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	The adverse reproductive effects seen in acceptable studies could potentially be related to endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	At present, there are no studies which link a mechanism of endocrine disruption to the reproductive toxicity seen. While disruption of the female reproductive hormone system is plausible, there are no known mechanisms by which glufosinate-ammonium reacts with such systems.
Are the effects judged to be relevant to humans?	Yes	Like glyphosate, the toxic effects of glufosinate-ammonium are based on the inhibition of glutamine synthetase (mainly in the brain) rather than acetylcholinesterase in the organophosphates. Glufosinate-ammonium has reproductive effects; reduced litter size, pre- and post-implantation losses, vaginal bleeding, abortions and dead foetuses which may be relevant to humans. The mechanism underlying these reprotoxic effects is unclear at present and there is no evidence to indicate that endocrine systems are being disrupted although this is a possibility. Connection between the inhibition of glutamine synthetase with such reproductive effects is not obvious and there have been no specific endocrine disruption assays conducted on glufosinate-ammonium.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No/NA	

Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**No** (if yes complete the sections below)	-

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Not required						

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Not required	-
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Not required	-
Are the effects judged to be relevant to fish, bird and/or mammalian populations?	Not required	-
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Not required	-
Grouping of the substance regarding its endocrine disrupting properties	***Not required***	

Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data

Group	Response (Yes/No)	Comments
(A) Substances requiring further information	**Yes**	**At present, there are data to suggest reproductive toxicity but no mechanistic studies to indicate how glufosinate-ammonium might affect hormonal systems.**
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.

(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.9 Endocrine Disruption Evaluation for Glyphosate

Substance details		
Substance Name	**Glyphosate**	
Substance Synonyms	N-(phosphonomethyl)glycine	
Substance CAS Number	1071-83-6	
Substance EC Number	213-997-4	
Data Source(s)	European Union Draft Assessment Report (2005)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xi; R41 N; R51-53 Eye Dam. Aquatic Chronic 2	 Risk of serious damage to eyes Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Causes serious eye damage Toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
Rat 90-day oral toxicity study	2	↑glucose and alkaline phosphatase	No information reported	150	1500	No evidence of an endocrine effect.
Mouse 90-day study	2	↓body weight gain	No information reported	2000	10000	No evidence of an endocrine effect.
Beagle dog 12-month study, capsule admin.	1/2	Clinical signs, equivocal ↓body wt. gain	No information reported	300	1000	No evidence of an endocrine effect.

Rat 2-year study	1/2	Salivary gland (histological lesions, ↑organ wt.), weak liver toxicity (clinical chemistry, ↓organ wt.), ↓body wt.	No information reported	10	100	No evidence of an endocrine effect.
Mouse 2-year study	1/2	↓body wt., histological changes in liver and urinary bladder	No information reported	160	800	No evidence of an endocrine effect.
Rat 2-generation study	1/2	Parental salivary gland changes. No reproductive or offspring effects	No information reported	80 (parental) 800 (reproduction and offspring)	800	No evidence of an endocrine effect.
Mouse teratology study	1/2	No evidence of teratogenicity	No information reported	300 (maternal and developmental)	1000	No evidence of an endocrine effect.
Rabbit teratology study	1/2	Visceral and skeletal abnormalities at maternally toxic levels	No information reported	20 (maternal) 100 (developmental)	500	No evidence of an endocrine effect.
Mechanistic reproductive studies in rats and mice	4	↓sperm but within normal variation. ↑oestrus cycle length in rats at high dose 50000 ppm	No information reported	-	-	Sperm count and motility, testes, epididymal and caudal wt. ↑Oestrus cycle length significance unknown, not considered adverse reproductive effect in isolation. No effects in mice.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects from a full set of toxicological data do not indicate an endocrine mode of action.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence is available to suggest an endocrine mode of action.
Are the effects judged to be relevant to humans?	N/A	Effects resulting from endocrine disruption are not present in the available studies. The effects observed are relevant to humans.

Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Effects resulting from endocrine disruption are not present in the available studies.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (If yes complete the sections below)	**-**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Algal *Nitzschia palea* growth inhibition test (96 hour exposure to technical glyphosate, purity >94%)	1/2	Inhibition of algal growth	No information reported	1.0	<4.5	Effects are evidently not endocrine mediated
Invertebrate *Daphnia magna* reproduction test	1/2	Reduction in juvenile production Increase in adult mortality	No information reported	9 95	30 300	Effects are evidently not endocrine mediated
Fish rainbow trout *Oncorhynchus mykiss* growth test (21 day exposure to technical glyphosate, purity >94%)	1/2	Decrease in growth Increase in mortality	No information reported	50 ≥100	100	Effects could be endocrine mediated
Fish early life stage test	No data reported	-	-	-	-	-
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish fathead minnow *Pimephales promelas* life cycle test (254 day exposure to technical glyphosate, purity >94%)	1/2	Effect not stated	No information reported	25.7	Not stated	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (17 week exposure to technical glyphosate, purity not stated)	1/2	Changes in other reproductive and adult health effects	No information reported	>1000 mg a.s./kg diet	Not relevant	No reproductive or adult health effects are evident at the highest test dose

Bobwhite quail (*Coilinus virginianus*) reproduction test (17 week exposure to technical glyphosate, purity not stated)	1/2	Reduction in egg weight Changes in other reproductive and adult health effects	No information reported	200 mg a.s./kg diet >1000 mg a.s./ kg diet	1000 mg a.s./kg diet Not relevant	Effects could be endocrine mediated

Evaluation of the available ecotoxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for glyphosate, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the effects in the rainbow trout growth test could be endocrine-mediated and could affect populations. For birds the one generation study in bobwhite quail reported reproductive effects that could be endocrine-mediated and could affect populations
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies
Are the effects judged to be relevant to fish, bird and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint for aquatic species is the inhibition of algal growth which is not evidently endocrine-mediated. The effect concentration for macrophytes is greater than a factor of 50 lower than those reported in fish. For birds reproductive effects on egg weight in bobwhite quail were evident at a lower test dose than those causing or adult health effects.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information*** ***A detailed ecotoxicological assessment was carried out in Stage 2 (see Appendix C) to assess the potential implications for grouping of having additional relevant endocrine disruption data from the open literature (where available).***	

Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, glyphosate is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.10 Endocrine Disruption Evaluation for Linuron

Substance details		
Substance Name	**Linuron**	
Substance Synonyms	-	
Substance CAS Number	330-55-2	
Substance EC Number	206-356-5	
Data Source(s)	European Union Draft Assessment Report (2003)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	 Repr. Cat. 2; R61 Repr. Cat. 3; R62 Carc. Cat. 3; R40 Xn; R22-48/22 N; R50-53	 May cause harm to the unborn child. Possible risk of impaired fertility. Limited evidence of a carcinogenic effect. Harmful: danger of serious damage to health by prolonged exposure if swallowed. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Repr. 1B Carc. 2 Acute Tox. 4 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	May damage the unborn child. Suspected of damaging fertility. Suspected of causing cancer. Harmful if swallowed. May cause damage to organs through prolonged or repeated exposure. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**Yes (For the feasibility study the assessment has been completed)**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
Rat oral 13 week study	1	↓ Bodyweight gain at top dose ↓ Food consumption at top dose Haemolytic anaemia at mid and top dose Alteration of clinical chemistry at mid and top dose Alteration of urinalysis data at top dose Haemosiderin in liver at top dose	No information reported	1.9 males 2.1 females	15.2 males 16.8 females	No evidence of endocrine disruption.
Dog oral 13 week study	1	Haemolytic effects at mid and top dose Haemosiderin in liver at top dose	No information reported	0.8-1.0	4-5	No evidence of endocrine disruption.
Dog oral 52 week study	1	Haemolytic anaemia at top dose Alteration of clinical chemistry at mid and top dose ↑ liver and spleen weight at top dose Haemosiderin in liver, spleen and kidney at top dose	No information reported	0.9	4.5	No evidence of endocrine disruption.
Rat oral 27 month study	1/2	↑ testis tumours at mid and top dose ↓ pituitary tumours in males at all doses Red cell effects at mid and top dose ↓ bodyweight gain at top dose	Mode of action possibly hormonal changes	1.6 (females)	1.3 (males)	Evidence of endocrine perturbation causing a decrease in pituitary tumours in males.
Mouse oral 2 year study	2	↓ bodyweight gain at mid and top dose ↓ red cell count at top dose Haemosiderin in liver at top dose ↑ hepatocellular adenomas at top dose Hepatic lesions at top dose	No information reported	6.5	19.5	No evidence of endocrine disruption.
Rat oral 2-generation study	1	↓ bodyweight gain and food intake at mid and top dose Clinical signs at top dose Ocular effects at top dose Adverse effects on male reproductive tissues and fertility at top dose ↓ birth weight, bodyweight gain, litter	Inhibition of androgen response elements.	Systemic toxicity 0.8 (males) 1.0 (females) Reproduction 6.8 (males) 8.3 (females)	Systemic toxicity **6.8** males 8.3 females Reproduction 42.5 males 51.9 females	Anti-androgenic. Limited evidence of an effect on the endocrine system.

		size, viability at top dose				
Rat oral developmental toxicity	1	↓ bodyweight gain and food intake at top dose ↓ food intake at mid dose ↑ kidney (top dose) and spleen weights (mid and top dose) Delayed ossification at mid and top dose group Early death *in utero at* top dose ↓ bodyweight in pups at top dose ↑ sternal abnormalities at top dose	No information reported	20 (Maternal toxicity) 20 (Foetal toxicity)	60 (Maternal toxicity) 60 (Foetal toxicity)	Feototoxicity occurred at maternally toxic doses, therefore secondary to maternal effects. No evidence of endocrine disruption.
Rabbit oral developmental toxicity study	1	↓ food and water intake and bodyweight gain at top dose ↓ food and water intake at mid dose Abortions and maternal death at top dose (patchy coloured livers) Early death *in utero* at top dose	No information reported	10 (Maternal toxicity) 25 (Foetal toxicity)	25 (Maternal toxicity) 62.5 (Foetal toxicity)	Feototoxicity occurred at maternally toxic doses, therefore secondary to maternal effects. No evidence of endocrine disruption.
Equine *in vitro* mechanistic study	2	↓ in aromatase and 17-20 desmolase ↑ 17-kerosteroid reductase	Reduction in enzymes relevant to steroid synthesis	500 µM	-	Evidence of endocrine perturbation.
Rat oral mechanistic study	2	No evidence of androgenic or oestrogenic action in young rats	No evidence of androgenic or oestrogenic action in young rats	-	-	No evidence of endocrine disruption.
Rat oral mechanistic study	2	No alteration in testosterone or progesterone synthesis in testes No alteration in LH levels in pituitary ↓ in LHRH binding in the pituitary	Reduction in LHRH receptor sites in the pituitary	-	-	Evidence of endocrine perturbation.
Rat oral mechanistic study	2	↓ serum testosterone ↑ testicular testosterone secreting capacity ↑ testicular testosterone content No consistent effect on pituitary receptor binding for LHRH or adrenal corticosterone content	Effects on testes, but mechanism and relation to pituitary function are unclear	-	-	Report states that the effects of linuron are species specific.
Rat oral mechanistic study	2	↓ in accessory sex organ weights ↑ serum oestradiol and LH levels Competition for binding to androgen receptor	Antiandrogenic – weak androgen receptor agonist	-	-	Evidence of endocrine perturbation.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Increases in testicular tumours and effects on male fertility, and decreases in thyroid tumours have been found in rats in standard toxicological studies in rodent species for linuron.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	Subsequent mechanistic studies have demonstrated that linuron competitively binds to androgen receptors, manifesting anti-androgenic properties.
Are the effects judged to be relevant to humans?	Yes	The postulated mechanism of action is not rodent specific, and as the pathways that constitute the mechanism of action exist in humans, the effects observed are judged to be relevant in humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	Yes	A LOAEL of 1.3 mg/kg bw/day has been identified in male rats, based on increases in testis tumours at mid and top dose and decrease in pituitary tumours in males at all doses in a lifetime study. This LOAEL of 1.3 mg/kg bw/day is below the guidance value proposed in the Joint DE-UK position paper for STOT-RE cat 1 for oral chronic studies (5 mg/kg bw/day).
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**No** (If yes complete the sections below)	-

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Not required						

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Not required	-
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Not required	-

Are the effects judged to be relevant to fish, bird and/or mammalian populations?	Not required	-
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Not required	-
Grouping of the substance regarding its endocrine disrupting properties	***Not required***	
Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	Standard toxicological studies and mechanistic studies are available.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	**Yes**	**A LOAEL of 1.3 mg/kg bw/day has been identified in male rats, based on increases in testis tumours at mid and top dose and decrease in pituitary tumours in males at all doses in a lifetime study.** **This LOAEL of 1.3 mg/kg bw/day is below the guidance value proposed in the Joint DE-UK position paper for STOT-RE cat 1 for oral chronic studies (5 mg/kg bw/day).Therefore, linuron can be considered as an endocrine disruptor more likely to pose a risk.**
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	-
(D) Substances not considered to be endocrine disrupters based on currently available data	No	Effects on the endocrine system have been observed in standard toxicological studies and in mechanistic studies.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.11 Endocrine Disruption Evaluation for Mecoprop

Substance details		
Substance Name	**Mecoprop** (ISO)	
Substance Synonyms	2-(4-chloro-o-tolyloxy) propionic acid (RS)-2-(4-chloro-o-tolyloxy)propionic acid 2-(4-chloro-2-methylphenoxy)propionic acid	
Substance CAS Number	7085-19-0	
Substance EC Number	230-386-8	
Data Source(s)	European Union Draft Assessment Report (1999) EU DAR (2002) Council Directive 91/414/EEC - EU Review Programme Draft Assessment Report – Mecoprop: Ecotoxicology Annex(es). EA (2007). Proposed EQS for Water Framework Directive Annex VIII Substances – Mecoprop. Water Framework Directive - United Kingdom Technical Advisory Group (WFD-UKTAG) Report.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	 Xn; R22 Xi; R38-41 N; R50-53	 Harmful if swallowed Irritating to skin, Risk of serious damage to eyes Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Acute Tox. 4 * Skin Irrit. 2 Eye Dam. 1 Aquatic Acute 1 Aquatic Chronic 1	Harmful if swallowed Causes skin irritation Causes serious eye damage Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
Rat 90-day study	1/2	↓thymus wt. ↑kidney wt.	No information reported	0.8	8	No evidence of an endocrine effect.
Dog 90-days study	1/2	haematological changes, ↑liver and kidney wt.	No information reported	16	64	No evidence of an endocrine effect.
Rat 2-year long-term toxicity and carcinogenicity study	1/2	No histopathological or neoplastic changes were found. ↑kidney wt.	No information reported	5.5	27.5	No evidence of an endocrine effect.
Rat 2-generation study	1/2	↑pup death and ↓pup and body weight gain	No information reported	10 (maternal) 10 (foetal)	50 (maternal) 50 (foetal)	No evidence of an endocrine effect.
Rat and rabbit teratogenicity studies	1/2	↑number of late resorptions, reduced crown/rump length, delayed ossification, and reduced foetal wt.	No information reported	50 (maternal) 50 (foetal)	100 (maternal) 100 (foetal)	No evidence of an endocrine effect.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects from a full set of toxicological data do not indicate an endocrine mode of action.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence is available to suggest an endocrine mode of action.
Are the effects judged to be relevant to humans?	N/A	Effects resulting from endocrine disruption are not present in the available studies. The effects observed are relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Effects resulting from endocrine disruption are not present in the available studies.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (If yes complete the sections below)	-

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Algal *Pseudokirchneriella subcapitata*) growth inhibition test (72 hour exposure to mecoprop-p, purity 92.2%)	1	Inhibition of growth	No information reported	27	81	Effects are evidently not endocrine mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to MCPP as DMA salt, purity 91.6%)	1	Reduction in juvenile production	No information reported	22.2	66.7	Effects are evidently not endocrine mediated
Fish rainbow trout *Oncorhynchus mykiss* sub-lethal test (28 day exposure to mecoprop-p acid, purity 92.2%)	1	Fish growth (as weight and length)	No information reported	50	100	Effects could be endocrine mediated
Fish early-life stage test	No data reported	-	-	-	-	-
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Japanese quail *Cotumix japonica* reproduction test (6 week exposure to Mecoprop-P-DMA, 765.7 g/l)	1	Reproductive and adult health endpoints	No information reported	>1000 mg a.s./kg diet	Not applicable	No dose related effects were observed in the reproductive endpoints even at the highest dose tested

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for glyphosate, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the effects in the rainbow trout sub-lethal test could be endocrine-mediated and could affect populations. For birds the one generation study in japanese quail reported no reproductive effects that could be

		endocrine-mediated and could affect populations
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies
Are the effects judged to be relevant to fish, bird and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	For aquatic species there is evidently similar sensitivity of the sub-lethal endpoints in algae, invertebrates and fish. For birds no reproductive and adult health effects were evident at the highest test concentrations.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information***	
Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, mecoprop is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Insecticides

Table A.12 Endocrine Disruption Evaluation for Chlorpyrifos

Substance details		
Substance Name	**Chlorpyrifos** (ISO)	
Substance Synonyms	*O*,*O*-diethyl *O*-3,5,6-trichloro-2-pyridyl phosphorothioate	
Substance CAS Number	2921-88-2	
Substance EC Number	220-864-4	
Data Source(s)	European Union Draft Assessment Report (1999) Colborn T (2006) A case for revisiting the safety of pesticides: a closer look at neurodevelopment EHP, 114, 10-17. Eaton *et al*. (2008) Review of the toxicology of chlorpyrifos with an emphasis on human exposure and neurodevelopment. *Crit. Rev Toxicol*. **82**, 1-125. De Angelis *et al*. (2009) Developmental exposure to chlorpyrifos induces alterations in thyroid and thyroid hormone levels without other toxicity signs in Cd1 mice. *Toxicol. Sci*. **108**, 311-319. Viswanath *et al*. (2010) Anti-androgenic endocrine disrupting activities of chlorpyrifos and piperophos. *J Steroid Biochem. Mol. Biol*. **120**, 22-29 (seen in Abstract only)	
Legislation		
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/2008	 T; R25 N; R50-53 Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	 Toxic if swallowed Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Toxic if swallowed Very toxic to aquatic life Very toxic to aquatic life with long lasting effects

Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
90-day dog study using capsules	1/2	↓plasma and erythrocyte cholinesterase activity	Cholinesterase inhibition.	0.01	0.22	A number of further oral, dermal and inhalation studies in rat and mice also indicate that ↓plasma and erythrocyte cholinesterase activity is major effect.
2-year rat systemic toxicity and oncogenicity	1/2	↓body wt, ↓brain cholinesterase activity; cataracts, retinal atrophy in females. No evidence of carcinogenicity.	No information reported	0.3 (Systemic toxicity >6.1 (Oncogenicity)	6.1 (Systemic toxicity) Oncogenicity: no effect at top dose	Similar effects observed in mice and Beagle dogs.
Two-generation Rat reproductive study with dietary administration	1/2	Parental: ↓brain cholinesterase activity, adrenal gland alteration Neonatal: ↓growth and survival Reproductive: None	No information reported	1 (parental) 1 (neonatal) >5 (reproductive)	5 (parental) 5 (neonatal) No reproductive toxicity at top dose	-
Rat Oral Developmental toxicity study by gavage	1/2	Parental: tremors, ↓weight and food consumption Developmental: ↑implants loss	No information reported	2.5 (parental) 2.5 (developmental)	15 (parental) 15 (developmental)	-
Rabbit Oral Developmental Toxicity by gavage	1/2	Foetal: ↓foetal size and ↑post-implantations loss Maternal: ↓body wt. Teratogenicity: None	No information reported	81 (foetal) 81 (maternal) No teratogenicity at top dose	141 (foetal) 141 (maternal)	-
Mouse embryonal and foetal development study	1/2	↑total major malformations, exencephaly, and sternebrae anomalies ↓body wt. and crown-rump length Maternal: Cholinergic effects.	No information reported	<1 (teratogenicity|), 10 (embryonal) 1 (maternal)	25 (teratogenicity) 10 (maternal)	-

Neurodevelopmental studies in man and experimental animals (Eaton et al., 2008)	Information is not available to assess reliability	*In vitro* Neurodevelopmental effects have been observed at concentrations below those which inhibit cholinesterase.	As the main effects are on the nervous system, cholinesterase inhibition is thought to be the main mechanism of action. No endocrine disrupter mechanisms suggested. Some evidence that chlorpyrifos inhibits some DNA binding factors and nuclear transcription factors.	Current levels of background (non-occupational) exposure to chlorpyrifos not expected to inhibit cholinesterase in humans.		A review by Eaton *et al* (2008) examined the toxicological and epidemiological evidence for neurodevelopmental effects.
Developmental mouse study to examine effects on thyroid and adrenal glands. (De Angelis et al., 2009)	1/2	In dams, ↓T4, ↑cell height in thyroid, slightly ↑vacuolisation in X-zone of adrenals In F1, short-term morphological modifications (↓follicular size at PND2), long-term morphological and biochemical alterations (↑necrotic follicular cells, ↓serum T4) at PND150. Higher vulnerability in males.	Evidence of effects on thyroid system at levels below those which inhibit cholinesterase suggesting a further effect of chlorpyrifos.	-	-	Single study to examine the potential short- and long-term effects of low level chlorpyrifos on thyroid and adrenal glands during gestational; and/or postnatal vulnerable phases.
Anti-androgenic activities *in vitro (seen in abstract only)* (*Viswanath et al., 2010)*	Published but non-regulatory systems	↓Human androgen receptor binding by testosterone (in mouse cells), ↓testosterone synthesis in rat Leydig cells, ↓expression of key steroidogenic enzymes, ↓LH receptor stimulated cAMP production	Conclusion of authors that chlorpyrifos pose serious threat to male reproductive system by interfering at various levels of androgen biosynthesis.	-	-	Chlorpyrifos-methyl has also been shown to have anti-androgenic effects including a positive Hershberger test.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response(Yes/ No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No/Yes (?)	No adverse effects related to endocrine disruption have been identified in the range of regulatory toxicological tests. These indicate that the major toxicological effect is decreased cholinesterase activity. However, there are some recent but non-regulatory studies that indicate that chlorpyrifos has effects on both the thyroid and male reproductive systems. There has been a study in mice showing perturbation of thyroid hormones in dams, but there is no information in this study on adverse effects manifested from these alterations. (Some preliminary *in vitro* data on possible effects on the androgen system also exist).

Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No/Yes(?)	There is insufficient evidence of any endocrine disruption mode of action at present. The range of regulatory toxicological tests did not yield any evidence and cholinesterase inhibition appeared to be the major toxicological effect. More recent non-regulatory studies have suggested that chlorpyrifos may have effects on both the thyroid and male reproductive systems.
Are the effects judged to be relevant to humans?	N/A	The mechanism behind possible effect of chlorpyrifos on the thyroid is unclear at present. The effect on the male reproductive system has only been seen *in vitro* at present.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	-
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**No** (If yes complete the sections below)	-

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Not required						

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Not required	-
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Not required	-
Are the effects judged to be relevant to fish, bird and/or mammalian populations?	Not required	-
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Not required	-
Grouping of the substance regarding its endocrine disrupting properties	***Not required here – However, a detailed ecotoxicological assessment was carried out in Stage 2 (see Appendix C) to assess the potential implications for grouping of having additional relevant endocrine disruption data from the open literature (where available).***	

Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response(Yes/ No)**	**Comments**
(A)Substances requiring further information	**Yes**	**No sign of any endocrine disruption in the full range of toxicological tests available but more recent specific studies have suggested perturbation of both the thyroid and male reproductive systems.**
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects

Table A.13 Endocrine Disruption Evaluation for Cyflumetofen

Substance details		
Substance Name	**Cyflumetofen**	
Substance Synonyms	-	
Substance CAS Number	400882-07-7	
Substance EC Number	Not assigned	
Data Source(s)	European Union Draft Assessment Report (2011)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 No data No data	 No data No data
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
Rat 13 weeks oral	1	Vacuolation (males) and hypertrophy of adrenal cortex (females).	No information reported	16.5 (males) 19.0 (females	54.5 (males) 62.8 (females)	Adrenals are part of the endocrine system.
Mouse 13 weeks oral	1	Vacuolation and hyoertrophy of adrenal cortex.	No information reported	117 (males) 150 (females)	348 (males) 447 (females)	Adrenals are part of the endocrine system.
Dog 13 weeks oral	1	Reduced bodyweight gain, increased adrenal and testis weight, vacuolation of adrenal cortex	No information reported	300	1000	Effects on organs that are part of the endocrine system.

Dog 1 year oral	1	Vacuolation and degradation of adrenal cortex.	No information reported	30	300	Adrenals are part of the endocrine system.
Rat 12 months oral	1	Increased adrenal weights, vacuolation (males) and hypertrophy (females) of adrenal cortical cells, vacuolation of interstitial ovary cells	No information reported	18.8 (males) 23.2 (females)	56.8 (males) 69.2 (females)	Effects on organs that are part of the endocrine system.
Rat 24 months oral	1	Hypertrophy of adrenal cortical cells, luminal dilation of the gland in the uterine horn.	No information reported	16.5 (males) 20.3 (females)	49.5 (males) 61.9 (females)	Effects on organs that are part of the endocrine system.
Mouse 18 months oral	1	Vacuolation of adrenal cortical cells.	No information reported	156 (males) 144 (females)	537 (males) 483 (females)	Adrenals are part of the endocrine system.
Rat 2 generation oral	1	Parental: increased adrenal weight and hypertrophy of adrenal cortical cells. Developmental: increased adrenal weight and hypertrophy of adrenal cortical cells.	No information reported	10 (Parental) 10 (Developmental) >100 (Reproduction)	34. 6 (Parental) 34.6 (Developmental) Reproduction: -	Adrenals are part of the endocrine system.
Rat developmental oral	1	Maternal: increased adrenal weight and vacuolation of adrenal cortical cells. Developmental: delayed ossification.	No information reported	50 (Maternal) 50 (Developmental)	250 (Maternal) 250 (Developmental)	Adrenals are part of the endocrine system.
Rabbit development oral	1	Maternal: decreased body weight gain. Developmental: incomplete ossification, hyoid changes and reduced foetal weight.	No information reported	50 (Maternal) 50 (Developmental)	50 (Maternal) 50 (Developmental)	-

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes effects, but not severely adverse.	Increases in organ weights and hypertrophy and/or vacuolation of cells in organs that are part of the endocrine system (particularly to adrenals) are increased in most chronic toxicological studies following exposure to cyflumetofen. These effects do not result in severe adverse effects that would be classifiable as STOT (even if the effect levels were below the cut-off values).

Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	A mode of action cannot be determined from the data available.
Are the effects judged to be relevant to humans?	Yes	The occurrence in humans of the effects observed is plausible. There are no species specific differences relating to the effects manifested in the available studies.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Serious endocrine disrupting effects are not observed in the available studies.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (If yes complete the sections below)	**-**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Algal *Pseudokirchneriella subcapitata* growth inhibition test (72 hour exposure to OK5101, purity 98.0%)	1	Inhibition of growth	No information reported	>0.040 mg a.s./l	Not relevant	No effects on growth at the single test concentration
Invertebrate *Daphnia magna* reproduction test (21 day exposure to OK5101, purity 98.0%)	2/3	Reduction in juvenile production Reduction in adult survival	No information reported	≥0.151 mg a.s./l 0.065 mg a.s./l	Not relevant 0.151 mg a.s./l	Effects were potentially compromised by high mortality in controls
Fish fathead minnow *Pimephales promelas* early life stage test (8 day exposure to OK5101, purity 98.0%)	1	Reduced egg hatching and larval survival	No information reported	≥0.145 mg a.s./l	Not relevant	No effects on egg hatching rate and larval survival at the highest concentration tested
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard *Anas platyrhynchos* reproduction test	No data reported	-	-	-	-	-

Bobwhite quail *Coilinus virginianus* reproduction test (20 week exposure to cyflumetofen, purity 98.4%)	1	Reproductive and adult health effects	No information reported	≥1000 mg a.s/ diet (≥84.4 -86.0 mg a.s./kg bw/day)	Not relevant	No reproductive and adult health effects are evident at the highest dose tested

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	No	The human health assessment for cyflumetofen, which is relevant to mammalian wildlife species, indicated that "*Increases in organ weights and hypertrophy and/or vacuolation of cells in organs that are part of the endocrine system (particularly to adrenals) are increased in most chronic toxicological studies following exposure to cyflumetofen. These effects do not result in severe adverse effects that would be classifiable as STOT (even if the effect levels were below the cut-off values)*" None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish no effects in the early life stage test with fathead minnows are evident at the highest exposure concentration. For birds the one generation study in bobwhite quail reported no reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.
Are the effects judged to be relevant to fish, bird and/or mammalian populations?	No	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint for aquatic species is reduced survival in the invertebrate *Daphnia magna*. For birds no reproductive and adult health effects are evident at the highest dose tested.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information***	

Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	Mechanistic data may inform on the process involved in adrenal enlargement.

(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	While effects on organs associated with the endocrine system occur in animal studies, mechanistic data do not exist, and effects are not deemed to be of a severe nature that would result in STOT classification (if effects were below the cut off levels). Cyflumetofen is not considered an ED more or less likely to pose a risk based on mammalian data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	See above
(D) Substances not considered to be endocrine disrupters based on currently available data	**No**	**Cyflumetofen is not considered an ED more or less likely to pose a risk based on mammalian data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.14 Endocrine Disruption Evaluation for Cypermethrin

Substance details		
Substance Name	**Cypermethrin**	
Substance Synonyms	-	
Substance CAS Number	52315-07-8	
Substance EC Number	257-842-9	
Data Source(s)	European Union Draft Assessment Report (1999) Kakko I, Toimela T and Tähti H, (2004) Oestradiol potentiates the effects of certain pyrethroid compounds in the MCF7 human breast carcinoma cell line. ATLA, 32, No. 4, 383–390. Kim I Y, Shin J H, Kim H S, Lee S J, Kang I H, Kim T S, Moon H J, Choi K S, Moon A and Han S Y, (2004) Assessing estrogenic activity of pyrethroid insecticides using in vitro combination assays. Journal of Reproduction and Development, 50, 245– 255.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Xn; R20/22 Xi; R37 N; R50-53	Harmful by inhalation and if swallowed. Irritating to respiratory system. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Acute Tox. 4 * Acute Tox. 4 * STOT SE 3 Aquatic Acute 1 Aquatic Chronic 1	Harmful if inhaled. Harmful if swallowed. May cause respiratory irritation. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90 day rat oral	1	Increased liver and kidney weight, increased urea, neurotoxicity at week 1	No information reported	20	80	No effects relating to endocrine disruption.
90 day rat oral	2	Increased kidney weight.	No information reported	5	20	No effects relating to endocrine disruption.
90 day dog oral	1	Neurotoxicity.	No information reported	12.5	37.5	No effects relating to endocrine disruption.
2 year dog oral	2	Decreased bodyweight, neurotoxicity.	No information reported	7.5	15	No effects relating to endocrine disruption.
2 year rat oral	2	Decreased bodyweight, decreased food consumption, increased blood urea.	No information reported	5	50	No effects relating to endocrine disruption.
101 week mice oral	2	Decreased bodyweight gain, altered haematology	No information reported	66	266	No effects relating to endocrine disruption.
3 generation rat oral	2	Decreased bodyweight and food consumption, decreased litter size and pup weight.	No information reported	Parental: 10 Developmental:10	Parental: 50 Developmental:50	No effects relating to endocrine disruption.
Developmental rat oral	2	Neurological disturbance	No information reported	Maternal: 17.5 Foetal:70	Maternal:35 Foetal: -	No effects relating to endocrine disruption.
Developmental rabbit oral	2	No adverse effects at highest dose tested.	No information reported	Maternal: 120 Foetal: 120	Maternal: - Foetal: -	No effects relating to endocrine disruption.
Cell proliferation assay using human breast cancer MCF-7 cells – Kakko *et al*. (2004)	2	Increase in cell proliferation relative to controls	The results suggest that cypermethrin has an oestrogenic (proliferative) effect on MCF7 cells which can be further augmented by oestradiol itself	<0.0416 (<0.1 µM)	0.0416 (0.1 µM)	-
Cell proliferation assay using human breast cancer MCF-7 cells – Kim *et al*. (2004)	2	No increase in cell proliferation relative to controls	The results suggest that cypermethrin has no oestrogenic (proliferative) effect on MCF7 cells	No data given	No data given	-

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects relate to neurotoxicity.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No definitive evidence is available to suggest an endocrine mode of action.
Are the effects judged to be relevant to humans?	Yes (but not ED effects)	Effects resulting from endocrine disruption are not present in the available studies. The effects observed are relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Effects resulting from endocrine disruption are not present in the available studies.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (If yes complete the sections below)	**-**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Algal *Pseudokirchneriella subcapitata* growth inhibition test	1/2	Inhibition of growth	No information reported	100	>100	Effects are evidently not endocrine mediated
Invertebrate *Daphnia magna* reproduction test	1/2	Reduction in juvenile production	No information reported	0.0001	0.0003	Effects are evidently not endocrine mediated
Fish fathead minnow *Pimephales promelas* early life stage test	1/2	Reduction in embryo/larval survival Reduction in larval growth	No information reported	0.00003 0.00017	0.00012 >0.00017	Effects could be endocrine mediated
Fish short-term reproduction test	No data provided	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data provided	-	-	-	-	-
Amphibian metamorphosis assay	No data provided	-	-	-	-	-

Mallard (*Anas platyrhynchos*) reproduction test	No data provided	-	-	-	-	-
Bobwhite quail (*Coilinus virginianus*) reproduction test (21 week exposure to cypermethrin, 96.5%)	1	Reproductive and adult health effects	No information reported	1000 mg a.s./diet (92 mg/kg bw/day)	>1000 mg a.s./diet	No reproductive or adult health effects at any test concentration

Evaluation of the available ecotoxicogical data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for cypermethrin, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*". None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test in fathead minnows reported effects on embryo-larval survival and larval growth that could be endocrine-mediated and could affect populations. For birds the one generation study in bobwhite quail did not report any reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.
Are the effects judged to be relevant to fish and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	The most sensitive endpoint for aquatic species is the effect on embryo-larval survival in fathead minnows. However effects on juvenile production in the invertebrate *Daphnia magna* occur at similar exposure concentrations. For birds no reproductive and adult health effects are evident at the highest dose tested.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information*** ***A detailed ecotoxicological assessment was carried out in Stage 2 (see Appendix C) to assess the potential implications for grouping of having additional relevant endocrine disruption data from the open literature (where available).***	

Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, cypermethrin is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.15 Endocrine Disruption Evaluation for Dimethoate

Substance details		
Substance Name	**Dimethoate**	
Substance Synonyms	-	
Substance CAS Number	60-51-5	
Substance EC Number	200-480-3	
Data Source(s)	Andersen HR, Vinggaard AM, Rasmussen TH, Gjermandsen IM, and Bonefeld-Jorgensen EC (2002) Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro. Toxicology and Applied Pharmacology, 179, 1-12. European Union Draft Assessment Report (2004) Walsh L P, Webster D R and Stocco D M (2000) Dimethoate inhibits steroidogenesis by disrupting transcription of the steroidogenic acute regulatory (StAR) gene. Journal of Endocrinology, 167, No. 2, 253–263.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xn; R21/22 Acute Tox. 4 * Acute Tox. 4 *	 Harmful in contact with skin and if swallowed. Harmful in contact with skin. Harmful if swallowed
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
Dog 1 year oral	1	Decrease in erythrocyte AChE	AChE inhibition reported	0.18	4.2	No evidence of endocrine effects
Rat 2 year oral	2	Decrease in brain AChE	AChE inhibition reported	0.01	0.1	No evidence of endocrine effects

Mouse 2 year oral	2	Decrease in erythrocyte AChE	AChE inhibition reported	-	3.6	No evidence of endocrine effects
Rat 2 generation oral	2	Decrease in brain and erythrocyte AChE Decreased pregnancy rate and 'productivity index' Mortality in offspring.	AChE inhibition reported	Systemic: 0.08 Reproduction: 1.2 Offspring: 1.2	Systemic: 1.2 Reproduction: 5 Offspring: 5	Reproductive and developmental effects occurred at doses above that which caused toxicity (decreased brain AChE) in parental animals, therefore these effects are deemed to be secondary to parental toxicity and not due to endocrine disruption. No evidence of endocrine effects
Rat developmental oral	1	Clinical signs and decreased bodyweight	No information reported	Maternal: 6 Foetal: 18	Maternal: 18 Foetal: -	Effects in pups occurred at doses above that which caused toxicity in dams, therefore these effects are deemed to be secondary to parental toxicity and not due to endocrine disruption. No evidence of endocrine effects
Rabbit developmental oral	1	Clinical signs and bodyweight. Delayed development (wavy ribs).	AChE inhibition reported	Maternal: 10 Foetal: 40	Maternal: 20 Foetal: -	Effects in pups occurred at doses above that which caused toxicity in dams, therefore these effects are deemed to be secondary to parental toxicity and not due to endocrine disruption. No evidence of endocrine effects
Cell proliferation assay using human breast cancer MCF-7 cells – Andersen *et al*. (2002)	2	No cell proliferation at noncytotoxic concentrations	-	>35,0 (>100 µM)	Not relevant	The results indicate no estrogenic response was induced

Estrogen receptor transactivation assay using human breast cancer MCF-7 cells – Andersen *et al*. (2002)	2	No estrogen receptor transactivation at non-cytotoxic concentrations	-	>35,0 (>100 µM)	Not relevant	The results indicate no estrogenic response was induced
Androgen receptor transactivation assay using Chinese hamster ovary cells (CHO K1) – Andersen *et al*. (2002)	2	Inhibition of AR trans-activation	-	17.5 (50 µM)	35,0 (100 µM)	The results indicate the substance did not react as an androgen agonist
Aromatase assay based on placental microsomes – Andersen *et al*. (2002)	2	No significant change from the control	-	17.5 (50 µM)	No data	The results indicate the substance did not cause inhibiting effects on aromatase activity
Steroidogenesis using mouse MA-10 Leydig tumor cell line – Walsh *et al*. (2000)	2	Inhibition of steroid-genesis	-	25	50	The results suggest that dimethoate inhibits steroidgenesis primarily by blocking transcription of the steroid-genic acute regulatory (StAR) gene.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects relate to acethylcholinesterase (AChE) inhibition.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No definitive evidence is available to suggest an endocrine mode of action.
Are the effects judged to be relevant to humans?	Yes – but no ED effects	Effects resulting from endocrine disruption are not present in the available studies. The effects observed are relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Effects resulting from endocrine disruption are not present in the available studies.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (If yes complete the sections below)	**-**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Algal *Pseudokirchneriella subcapitata* growth inhibition test (72 hour exposure to dimethoate, purity not stated)	1	Inhibition of growth	No information reported	30.5	No data	Effects are evidently not endocrine mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to dimethoate, purity, 99.0%)	1	Reduction in juvenile production Juvenile growth Parental survival	No information reported	0.04	0.1	Effects are evidently not endocrine mediated
Fish rainbow trout *Oncorhynchus mykiss* early life stage test (96 day exposure to dimethoate, purity 99.1%)	1	Larval growth Egg hatchability and fry survival	No information reported	1.5 3.0	3.0 6.0	Effects could be endocrine- mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (22 week exposure to dimethoate, purity 99.1%)	1	Reduction in number of eggs laid and 14 day old survivors Parental bodyweight	No information reported	35.4 mg a.s./kg diet (5.8 mg a.s./kg bw/day)	152 mg a.s./kg diet	No test substance-related gross lesions were observed at necropsy Effects could be endocrine- mediated
Bobwhite quail (*Coilinus virginianus*) reproduction test (22 week exposure to dimethoate, purity 99.1%)	1	Reduction in number of eggs laid and 14 day old survivors Parental bodyweight	Gross necropsy of surviving females showed increased incidence of hens with regressed or regressing ovaries	10.1 mg a.s./kg diet (1.0 mg a.s./kg bw/day)	35.4 mg a.s./kg diet	Effects could be endocrine- mediated

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for dimethoate, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the rainbow trout early life stage test reported effects on growth that could be endocrine-mediated and could affect populations. For birds the one generation studies in bobwhite quail and mallard reported reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.
Are the effects judged to be relevant to fish and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, birds and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	The most sensitive endpoint is the reduction in juvenile production and juvenile growth in *Daphnia magna* which are evidently not endocrine-mediated. The effects concentration for invertebrates is a factor of 30 lower than those reported in fish. For birds no reproductive or adult health effects were evident at the same test dose.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information*** ***A detailed ecotoxicological assessment was carried out in Stage 2 (see Appendix C) to assess the potential implications for grouping of having additional relevant endocrine disruption data from the open literature (where available).***	
Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.

(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, dimethoate is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.16 Endocrine Disruption Evaluation for Malathion

Substance details		
Substance Name	**Malathion**	
Substance Synonyms	-	
Substance CAS Number	121-75-5	
Substance EC Number	204-497-7	
Data Source(s)		
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	 Xn; R22 R43 N; R50-53	 Harmful if swallowed. May cause sensitization by skin contact. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Acute Tox. 4 * Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	Harmful if swallowed. May cause an allergic skin reaction. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
Rat 2 year oral	2	Decrease in erythrocyte AChE. Hepatocellular adenoma at top dose.	AChE inhibition reported	4	29	No evidence of endocrine effects
Mouse 18 month oral	2	Decrease in erythrocyte AChE. Hepatocellular hypertrophy and adenoma at mid dose.	AChE inhibition reported	100 ppm	800 ppm	No evidence of endocrine effects
Rat 2 generation oral	1	Decreased pup weight.	AChE inhibition reported	132	5000 ppm	No evidence of endocrine effects
Rat developmental toxicity oral	1	No developmental effects.	-	800	-	No evidence of endocrine effects
Rabbit developmental toxicity oral	1	Increased incidence of resorptions.	AChE inhibition reported	25	50	No evidence of endocrine effects

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects relate to acetylcholinesterase (AChE) inhibition.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence is available to suggest an endocrine mode of action.
Are the effects judged to be relevant to humans?	Yes – but no ED effects	Effects resulting from endocrine disruption are not present in the available studies. The effects observed are relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Effects resulting from endocrine disruption are not present in the available studies.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (If yes complete the sections below)	

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Algal *Pseudokichneriella subcapitata* growth inhibition test (72 hour exposure to malathion, purity 96.4%)	1	Inhibition of growth (growth rate) Inhibition of growth (biomass)	No information reported	2.30 0.81	8.16 2.30	Effects are evidently not endocrine mediated
Invertebrate *Daphnia magna* reproduction test	1	Reduction in juvenile production Juvenile growth Parental survival	No information reported	0.00006 0.00006 0.00025	0.0001 0.0001 0.00046	Effects are evidently not endocrine mediated
Fish rainbow trout (*Oncorhynchus mykiss*) early life stage test (97 day exposure to malathion, purity 94.0%)	1	Fry survival and morphology exophthalmia, spinal curvature and distended abdomen	No information reported	0.021	0.044	Effects could be endocrine- mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (20 week exposure to malathion, purity 94.0%)	1	Reproductive effects (reduced number of eggs and viability)	No information reported	1200 mg a.s./kg diet	2400 mg a.s./kg diet	Effects could be endocrine- mediated
Bobwhite quail (*Coilinus virginianus*) reproduction test (21 week exposure to malathion, purity 96.4%)	1	Necropsy of surviving females (regressing ovary) Reproductive effects (reduced number of eggs and viability)	No information reported	110 mg a.s./kg diet (13.5 mg a.s./kg bw/day) 350 mg a.s./kg diet (42.9 mg a.s./kg bw/day)	350 mg a.s./ kg diet	Effects could be endocrine- mediated
Estrogenic activity using the yeast two hybrid assay – Nishihara *et al*. (2000)	2	Evidence of estrogenic activity	-	33.0 mg/l (REC10) (>0.1 mM (REC10)	Not relevant	The result is not considered to show positive estrogenic activity because the activity of the test substance was less than 10% of the activity of 10^{-4} mM E2,

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for malathion, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test in rainbow trout reported effects on fry survival and morphology that could be endocrine-mediated and could affect populations. For birds the one generation studies in bobwhite quail and mallard reported reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.
Are the effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint is the reduction in juvenile production and juvenile growth in *Daphnia magna* which are evidently not endocrine-mediated. The effects concentration for invertebrates is a factor of 440 lower than those reported in fish. For birds reproductive effects were evident at a lower test dose than adult health effects.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information*** ***A detailed ecotoxicological assessment was carried out in Stage 2 (see Appendix C) to assess the potential implications for grouping of having additional relevant endocrine disruption data from the open literature (where available).***	
Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption

(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, malathion is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.17 Endocrine Disruption Evaluation for Methiocarb

Substance details		
Substance Name	**Methiocarb**	
Substance Synonyms	-	
Substance CAS Number	2032-65-7	
Substance EC Number	217-991-2	
Data Source(s)	European Union Draft Assessment Report (2004)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	T; R25 N; R50-53	Toxic if swallowed. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	Toxic if swallowed. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
Rat 2 year oral	2	Reduction in bodyweight.	No information reported	9.3	28	No evidence of endocrine effects
Mouse 2 year oral	2	Increase in ALT, indicating liver toxicity.	No information reported	14.6	57	No evidence of endocrine effects

Dog 2 year oral	2	Vomiting, reduced feed consumption, trembling associated with reduced cholinesterase activity.	AChE inhibition reported	2.2	8.6	No evidence of endocrine effects
Rat 2 generation oral	1	Reduced bodyweight gain in parents and reduced litter size.	No information reported	4.3	12.5	The reduced litter size is most likely to be a result of the reduced bodyweight gain in parental animals, and not a specific endocrine mediated effect. No evidence of endocrine effects
Rat developmental oral	1	Cholinergic signs, muscular fasciculation in dams.	AChE inhibition reported	Maternal: 0.5 Developmental: 5	Maternal: 1.5 Developmental: 5	No evidence of endocrine effects
Rabbit developmental oral	2	Clinical signs of toxicity in dams.	No information reported	3	10	No evidence of endocrine effects

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects relate to acetylcholinesterase (AChE) inhibition.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence is available to suggest an endocrine mode of action.
Are the effects judged to be relevant to humans?	Yes – but no ED effects	Effects resulting from endocrine disruption are not present in the available studies. The effects observed are relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Effects resulting from endocrine disruption are not present in the available studies.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (If yes complete the sections below)	**-**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Algal *Scenedesmus subspicatus* growth inhibition test (72 hour exposure to methiocarb, purity 99.3%)	1	Inhibition of growth (growth rate) Inhibition of growth (biomass)	No information reported	No data 0.052	No data No data	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to methiocarb, purity 99.7%)	1	Reduction in juvenile production Parental survival	No information reported	0.0001 0.0013	0.00017 >0.0013	Effects are evidently not endocrine-mediated
Fish rainbow trout *Oncorhynchus mykiss* early life stage test (56 day exposure to methiocarb, purity 97.0%)	1	Intoxication Larval growth Fry survival Hatching success	No information reported	0.05 0.1 0.1 0.4	0.1 0.2 0.2 >0.4	Certain effects could be endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard *Anas platyrhynchos* reproduction test (19 weeks exposure to methiocarb, purity 97.0%)	1	Adult health effects Reproductive effects	Inhibition of AChE activity	50 mg a.s./kg diet (4.51 mg a.s./ kg bw/day) >1000 mg a.s./kg diet	100 mg a.s./kg diet Not relevant	Effects are evidently not endocrine-mediated
Bobwhite quail *Coilinus virginianus* reproduction test (25 weeks exposure to methiocarb, purity 97.0%)	1	Reproductive and adult health effects	No information reported	≥50 mg a.s./kg diet ≥4.95 mg a.s./kg bw/day	Not relevant	No reproductive or adult health effects at the highest dose tested

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for methiocarb, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test in rainbow trout reported effects on fry survival and larval growth that could be endocrine-mediated and could affect populations. For birds the one generation studies in bobwhite quail and mallard reported reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.
Are the effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint is the reduction in juvenile production and juvenile growth in *Daphnia magna* which are evidently not endocrine-mediated. The effects concentration for invertebrates is a factor of 440 lower than those reported in fish. For birds reproductive effects were evident at the same or higher test doses than those causing adult health effects.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information***	

Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.

(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, methiocarb is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table A.18 Endocrine Disruption Evaluation for Pirimicarb

Substance details		
Substance Name	**Pirimicarb**	
Substance Synonyms	-	
Substance CAS Number	23103-98-2	
Substance EC Number	245-430-1	
Data Source(s)	European Union Draft Assessment Report (2003)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 T; R25 N; R50-53 Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	 Toxic if swallowed. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Toxic if swallowed. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
Dog 12 month oral	2	Reduced bodyweight gain, biochemical changes and increased haemosiderin deposition. Reduced brain AChE activity, tremors	AChE inhibition reported	10 (males) 3.5 (females)	25 (males) 10 (females)	No evidence of endocrine effects.

Rat 2 year oral	1	Decreased bodyweight and food consumption, clinical chemistry alterations, liver and kidney effects.	No information reported	Non-neoplastic 3.7 (males) 4.7 (females) Carcinogenic 37.3 (males) 47.4 (females)	Non-neoplastic 250 ppm Carcinogenic 750 ppm	No evidence of endocrine effects.
Mouse 80 week oral	2	Reduced bodyweight and food consumption, increased incidence of lung tumours.	No information reported	Non-neoplastic 26.2 (males) 37.1 (females) Carcinogenic 200 ppm	Non-neoplastic 700 ppm Carcinogenic 700 ppm	No evidence of endocrine effects.
Rat multi-generation oral	1	Reduced bodyweight gain and food consumption in adults. Reduced foetal weight.	No information reported	Parental 21.7 9males) 22.5 (females) Reproductive 750 ppm	Parental 750 ppm Reproductive: 700 ppm	No evidence of endocrine effects.
Rat developmental oral	1	Reduced bodyweight gain and food consumption. Reduced foetal weight and skeletal effects.	No information reported	Maternal: 25 Developmental: 25	Maternal: 75 Developmental: 75	No evidence of endocrine effects.
Rabbit developmental oral	1	Death, reduced bodyweight gain and food consumption in dams. Skeletal effects in pups.	No information reported	Maternal: 10 Developmental: 10	Maternal: 60 Developmental: 60	No evidence of endocrine effects.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects relate to acetylcholinesterase (AChE) inhibition.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence is available to suggest an endocrine mode of action.
Are the effects judged to be relevant to humans?	Yes – but no ED effects	Effects resulting from endocrine disruption are not present in the available studies. The effects observed are relevant to humans.

Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Effects resulting from endocrine disruption are not present in the available studies.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (If yes complete the sections below)	**-**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Algal *Pseudokirchneriella subcapitata* growth inhibition test (96 hour exposure to	1	Inhibition of growth (growth rate) Inhibition of growth (biomass)	No information reported	50	100	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to pirimicarb, purity 96-98%)	1	Reduction juvenile production Reduction in juvenile growth	No information reported	0.0009	0.002	Effects are evidently not endocrine-mediated
Fish fathead minnow *Pimephales promelas* early life stage test (36 day exposure to pirimicarb, purity 96-98%)	1	Reduced larval growth	No information reported	10	20	Effects could be endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard *Anas platyrhynchos* reproduction test (26 week exposure to pirimicarb, purity 98.6%)	1	Reproductive effects (reduction in the number of eggs laid) Adult health effects (bodyweight gain)	No information reported	60 mg a.s./kg diet 300 mg a.s./kg diet	300 mg a.s./kg diet 750 mg a.s./kg diet	Effects could be endocrine-mediated
Bobwhite quail *Coilinus virginianus* reproduction test (26 week exposure to pirimicarb, purity 98.6%)	1	Reproductive effects Adult health effects (reduction in parental food consumption and bodyweight)	No information reported	750 mg a.s./kg diet 300 mg a.s./kg diet	$\geq$750 mg a.s./kg diet 750 mg a.s./kg diet	Effects are evidently not endocrine-mediated

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for pirimicarb, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test in fathead minnows reported effects on larval growth that could be endocrine-mediated and could affect populations. For birds the one generation studies in bobwhite quail and mallard reported reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.
Are the effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint is the reduction in juvenile production and juvenile growth in *Daphnia magna* which are evidently not endocrine-mediated. The effects concentration for invertebrates is a factor of 10000 lower than those reported in fish. For birds reproductive effects were evident at lower test doses than those causing adult health effects.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information***	
Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.

(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, pirimicarb is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Plant growth regulators

Table A.19 Endocrine Disruption Evaluation for Chlormequat

Substance details		
Substance Name	**Chlormequat**	
Substance Synonyms	-	
Substance CAS Number	999-81-5	
Substance EC Number	213-666-4	
Data Source(s)	European Union Draft Assessment Report (2007)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xn; R21/22 Acute Tox. 4 * Acute Tox. 4 *	 Harmful in contact with skin and if swallowed. Harmful in contact with skin. Harmful if swallowed.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
Dog 12 month oral	1	Neurological effects (increased salivation, diarrhoea).	CNS effects	4	8	No evidence of endocrine effects
Rat 2 year oral	1	Reduced bodyweight gain and food consumption.	No information reported	42	125	No evidence of endocrine effects

Mouse 110 week oral	1	No adverse effects.	No information reported	336	-	No evidence of endocrine effects
Rat multi generation oral (combination of 3 studies)	1	Reduced conceptions per mating and mean number of pups per litter. Reduced bodyweight gain, clinical signs during lactation and anaemia in adults. Reduced bodyweight gain during lactation and focal dystrophy of the muscles.	No information reported	Reproductive: 211 Adult: 75 Offspring: 41	Reproductive: 2700 ppm Adult: 2500 ppm Offspring: 2500 ppm	No evidence of endocrine effects
Rat developmental oral	1	Decreased bodyweight and food consumption in dams.	No information reported	Maternal: 75 Developmental: 225	Maternal: 225 Developmental: -	No evidence of endocrine effects
Rabbit developmental oral	1	Clinical signs and decreased bodyweight in dams.	No information reported	Maternal: 20 Developmental: 40	Maternal: 40 Developmental: -	No evidence of endocrine effects

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects relate to CNS effects and general toxicity.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence is available to suggest an endocrine mode of action.
Are the effects judged to be relevant to humans?	Yes – but no ED effects	Effects resulting from endocrine disruption are not present in the available studies. The effects observed are relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Effects resulting from endocrine disruption are not present in the available studies.
Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (If yes complete the sections below)	**-**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Algal *Pseudokirchneriella subcapitata* growth inhibition test (96 hour exposure to 'BAS 062 W' 66.1% w/w chlormequat-chloride)	1	Inhibition of growth	No information reported	100	>100	No effects on growth at highest test concentration
Macrophyte *Lemna minor* growth inhibition test (7 day exposure to chlormequat-chloride, purity 75.3%)	1	Inhibition of growth (as growth rate and biomass)	No information reported	0.1	0.32	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to chlormequat-chloride 72.0%)	1	Reduction in juvenile production	No information reported	2.4	18.62	Effects are evidently not endocrine-mediated
Fish early life stage test	No data reported	-	-	-	-	-
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard *Anas platyrhynchos* reproduction test	No data reported	-	-	-	-	-
Bobwhite quail *Coilinus virginianus* reproduction test	No data reported	-	-	-	-	-
Japanese quail *Coturnix japconia* reproduction test (6 week exposure to chlormequat chloride, purity 66.9%)	1	Reproductive effects (normal hatchings and 14-day old survivors as percentage of eggs set and the number of normal hatchings and 14 day old survivors per hen per day) Adult health effects	No information reported	400 mg a.s/kg diet 54.8 mg a.s./kg bw / day 1000 mg a.s./kg diet	1000 mg a.s./kg diet >1000 mg a.s./kg diet	Effects could be endocrine-mediated

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for chlormequat, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For birds the one generation studies in japanese quail reported reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.
Are the effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint is the reduction in growth in the macrophyte *Lemna minor* which is evidently not endocrine-mediated. For birds reproductive effects were evident at lower test doses than those causing adult health effects.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information***	
Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, chlormequat is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Insect growth regulator

Table A.20 Endocrine Disruption Evaluation for Methoprene

Substance details		
Substance Name	**Methoprene**	
Substance Synonyms	1-methylethyl (E,E)-11- methoxy-3,7,11-trimethyl- 2,4-dodecadienoate	
Substance CAS Number	40596-69-8	
Substance EC Number	-	
Data Source(s)	No European Union Draft Assessment Report available JMPR (2001) United States Environmental Protection Agency Ecotox Database (Available at http://cfpub.epa.gov/ecotox/report.cfm?type=short)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	- -	- -
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
Dog 90 day oral	2	Increased liver weight and increased alkaline phosphatase activity.	No information reported	8.6	86	No evidence of an endocrine effect.
Rat 2 year oral	2	Focal accumulation of macrophages in the liver.	No information reported	44	220	No evidence of an endocrine effect.

Rat multi-generation	2	Reductions in weight gain and mean pup weight and increased mean number of pups born dead per litter.	No information reported	29	140	The adverse effects in pups is secondary to the parental toxicity and not due to endocrine mediated effects. No evidence of an endocrine effect.
Mouse developmental toxicity oral	2	Increased absolute liver, kidney and lung weights in pups.	No information reported	Maternal: 570 Foetotoxicity:570 Offspring: 190	Maternal: - Foetotoxicity: - Offspring: 570	No evidence of an endocrine effect.
Rabbit developmental toxicity oral	2	Reduced weight gain in dams and abortions. Increased percentage of foetal deaths.	No information reported	Maternal: 190 Foetotoxicity:190	Maternal: 1900 Foetotoxicity:1900	No evidence of an endocrine effect.
Endocrine activity in mammals (female mice, male rats)	2	No increase in uterus:bodyweight ration in females. No increase in organ:bodyweight ration of seminal vesicles, ventral prostate or levator ani. No effect on thymus:bodyweight ratio.	No information reported	-	-	No evidence of an endocrine effect.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects do not indicate an endocrine mode of action.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence is available to suggest an endocrine mode of action.
Are the effects judged to be relevant to humans?	Yes – but no ED effects	Effects resulting from endocrine disruption are not present in the available studies. The effects observed are relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Effects resulting from endocrine disruption are not present in the available studies.

Is it necessary to carry out an ecotoxicological assessment, i.e. the substance is not an ED more or less likely to pose a risk?	**Yes** (If yes complete the sections below)	

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Algal blue green growth inhibition test	1/2	Inhibition of growth	No information reported	<0.5	0.5	Effects are evidently not endocrine mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to methoprene, purity 96.6%)	1/2	Reduction in juvenile production	No information reported	0.01	0.051	Effects could be endocrine mediated
Fish fathead minnow *Pimephales promelas* early life stage test (37 day exposure to methoprene, purity 91.4%)	1/2	Inhibition of larval growth	No information reported	0.048	0.084	Effects could be endocrine mediated
Fish short-term reproduction test	No data located	-	-	-	-	-
Fish sexual development test	No data located	-	-	-	-	-
Fish life cycle test	No data located	-	-	-	-	-
Amphibian metamorphosis assay	No data located	-	-	-	-	-
Mallard *Anas platyrhynchos* reproduction test	1/2	Reproductive and adult health effects	No information reported	≥30 mg/kg diet	Not relevant	No reproductive effects are evident at the highest test dose
Bobwhite quail *Coilinus virginianus* reproduction test	1/2	Reproductive and adult health effects	No information reported	≥30 mg/kg diet	Not relevant	No reproductive effects are evident at the highest test dose

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for methoprene, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test in fathead minnows reported effects on larval growth that could be endocrine-mediated and could affect populations.

		For birds the one generation studies in bobwhite quail and mallards reported no reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies. This indicates that effects on invertebrates such as *Daphnia magna* are due to effects on the regulation of growth
Are the effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint is the reduction in juvenile production in the *i*nvertebrate *Daphnia magna* which could be endocrine-mediated. For birds no reproductive effects were evident at lower test doses than those causing adult health effects.
Grouping of the substance regarding its endocrine disrupting properties	***Substances requiring further information***	
Overall grouping of the substance regarding its endocrine disrupting properties based on mammalian toxicology data		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Category is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, methoprene is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Appendix B Human Health Assessment Datasheets for the eighty one identified substances

Fungicides

Table B.1 Human Health Endocrine Disruption Evaluation for Azoxystrobin

Substance details		
Substance Name	**Azoxystrobin (ISO)**	
Substance Synonyms	methyl (E)-2-{}{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}}-3-methoxyacrylate	
Substance CAS Number	131860-33-8	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (1997). A brief search for recent relevant studies did not find any further information.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 T; R23 N; 50-53 Acute Tox. 3 * H331 Aquatic Acute 1 H400 Aquatic Chronic 1 H400	 Toxic by inhalation Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Toxic if inhaled Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	Liver (↑organ wt, pathology), ↓body wt gain, clinical chemistry (↑GGT, ↓cholesterol and triglycerides), haematology	No information reported	20.4 (male) 22.4 (female)	200	No evidence of endocrine disruption.
1-year dog oral study	1/2	Clinical signs, clinical chemistry (↑GGT and alkaline phosphatase), ↑liver wt.	No information reported	3	25	No evidence of endocrine disruption.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	Mortality, bile duct (distension, histological changes) and liver effects (e.g. biliary hyperplasia), clinical chemistry (↓AST, ALT, alkaline phosphatase), ↓body wt. No carcinogenic potential.	No information reported	18.2 (male) 22.3 (female)	100 (↓ to 50 after 1 year due to ↑mortality)	No evidence of endocrine disruption.
2-generation rat oral reproduction study	1/2	No evidence of reproductive toxicity. Retardation of pup body wt development with parental toxicity.	No information reported	32 (parental) 32 (reproduction)	Approx 150 Approx150	No evidence of endocrine disruption.
Rat oral developmental and teratogenicity study	1/2	No teratogenic effects, slightly ↑minor skeletal defects at parental toxic levels.	No information reported	25 (parental) 25 (reproduction)	100 100	No evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1/2	No teratogenic effects. Maternal: ↓body wt and clinical signs.	No information reported	50 (parental) 500 (reproduction)	150 -	No evidence of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	No evidence of endocrine disruption in a full range of regulatory tests.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence of endocrine disruption in a full range of regulatory tests.

Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	No evidence of endocrine disruption in a full range of regulatory tests.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in the available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in the available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, azoxystrobin is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.2 Human Health Endocrine Disruption Evaluation for Boscalid

Substance details						
Substance Name	**Boscalid**					
Substance Synonyms	Nicobifen					
Substance CAS Number	**188425-85-6**					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2002), Addendum (2006)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
Rat 90-day oral study	1	Altered clinical chemistry and haematological parameters. Increased thyroid weight, follicular cell hypertrophy and hyperplasia. Increased liver weight and centrilobular hypertrophy.	No information reported	34 males 40 females	137 males 159 females	The increased thyroid weight could be due to increased stimulation of the thyroid. This could be due to an endocrine mode of action, but without further information, this cannot be confirmed.

Mouse 90-day oral study	1	Increased cholesterol and liver weight. Altered clinical chemistry parameters.	No information reported	29 males 42 females	197 males 277 females	No evidence of effects on the endocrine system.
Dog 90-day oral study	1	Increased weight. Changes in clinical chemistry and haematology. Decreased bodyweight and bodyweight gain. Increased thyroid weight.	No information reported	7.6 males 8.1 females	78 males 82 females	The increased thyroid weight could be due to increased stimulation of the thyroid. This could be due to an endocrine mode of action, but without further information, this cannot be confirmed.
Dog 1-year oral study	1	Vomitus. Decreased bodyweight and altered clinical chemistry. Increased thyroid and liver weight.	No information reported	22 males 22 females	57 males 58 females	The increased thyroid weight could be due to increased stimulation of the thyroid. This could be due to an endocrine mode of action, but without further information, this cannot be confirmed.
Rat 24-month oral long-term toxicity and carcinogenicity study	1	Clinical chemistry changes. Increased hepatocellular hypertrophy. Decreased bodyweight Anaemia Increased pathological changes in thyroid and liver. Increased thyroid follicular cell adenomas.	Increased metabolism of thyroid hormones (T3 and T4) due to increased conjugative metabolism. This triggers an increase in TSH causing chronic thyroid stimulation.	4.4 males 5.9 females	22 males 30 females	The thyroid changes are due to increased liver metabolism resulting in chronic stimulation of the thyroid. Therefore, the initial mechanism is not endocrine mediated, but an endocrine effect is observed secondary to the initial mechanism
Mouse 18-month oral study	1	Decreased bodyweight. Increased absolute and relative liver weights. Hepatocellular hypertrophy.	No information reported	13 males 90 females	65 males 443 females	No evidence of effects on the endocrine system.
Rat 2-generation oral reproduction study	1	Increased hepatocellular hypertrophy. Decreased bodyweight gain and feed intake. Increased liver weight and hepatocyte degeneration. Increased male pup mortality.	No information reported	11 parental 1165 fertility 11 offspring	113 parental - 113 offspring	Toxicity in offspring occurred at doses where parental toxicity was evident. No effects were observed on fertility.

Rat oral developmental and teratogenicity study	1	Increase incomplete ossification of the thoracic centrum.	No information reported	1000 maternal 300 developmental	- 1000 developmental	Although effects on the developing foetus occurred at doses where maternal toxicity was not present, there is no clear link to the effects observed and endocrine disruption.
Rabbit oral developmental and teratogenicity study	1	Abortion. Reduced/discoloured faeces. Decreased food intake and bodyweight. Increase incomplete ossification of the thoracic centrum.	No information reported	100 maternal 300 developmental	300 maternal 1000 developmental	Developmental toxicity was observed in the presence of overt maternal toxicity. Again, there is no clear link to the effects observed and endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There are potential endocrine effects demonstrated by increased thyroid weight and cell changes.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	The postulated mechanism of action is increased metabolism causing a decrease in T3 and T4, which in turn over stimulates TSH, resulting in thyroid hypertrophy. An endocrine mode of action has been demonstrated.
Are the effects judged to be relevant to humans?	No	The effects are not of relevance to humans, as there are proven significant quantitative differences in thyroid homeostasis between adult rats and adult humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	As the effects are judged not to be relevant to humans, this question is not applicable. However, the LOAELs identified in the regulatory studies for thyroid effects are above the recommended STOT RE Category 1 cut – off guidance values proposed in the joint German UK paper.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	Although the thyroid effects could be relevant to wildlife mammals, it is not clear whether they would have an effect on populations

Overall grouping of the substance regarding its endocrine disrupting properties

Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	Information to complete a human health assessment is available
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	The effects on the thyroid and thyroid hormones seen in rats are not considered to be relevant to humans owing to the differences in thyroid homeostasis seen in adult rats and adult human.

(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	The effects on the thyroid and thyroid hormones seen in rats are not considered to be relevant to humans owing to the differences in thyroid homeostasis seen in adult rats and adult humans.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**There is no evidence of endocrine disruption that is relevant to humans.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.3 Human Health Endocrine Disruption Evaluation for Bupirimate

Substance details						
Substance Name	**Bupirimate**					
Substance Synonyms	5-butyl-2-ethylamino-6-methylpyrimidin-4-yl dimethylsulfamate					
Substance CAS Number	41483-43-6					
Substance EC Number	255-391-2					
Data Source(s)	European Union Draft Assessment Report (2007)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1	Decreased bodyweight gain, increased liver weight, increased thyroid weight.	-	50	1700	Weight changes in the thyroid. Some evidence of endocrine disruption.

90-day dog oral study	1	Increased thyroid weight.	-	3	15	Weight changes in the thyroid. Some evidence of endocrine disruption.
2-year rat oral study	2	Decreased bodyweight gain, increased relative kidney, liver and thyroid weight, increased incidence of thyroid follicular adenoma and fibroma in the skin.	Disturbances in the HPT axis.	25	156	Thyroid effects due to an endocrine mechanism of action.
2-year dog oral long-term toxicity and carcinogenicity study	2	Decreased bodyweight and bodyweight gain. Increased liver weight with associated clinical chemistry and histopathology.	No information reported	5	20	No evidence of an endocrine effect.
Multi-generation rat oral reproduction study	2	Increased relative liver and kidney weight, decreased bodyweight (parent and offspring) and delay in physical development.	No information reported	Parental 20 Offspring 20	Parental 200 Offspring 200	Effects in offspring occur at maternally toxic doses. No evidence of endocrine disruption.
Rat oral developmental and teratogenicity study	1	Slight increase in clinical signs of toxicity. Decreased maternal bodyweight gain. Minor skeletal defects.	No information reported	Maternal - Developmental 50	Maternal 50 Developmental 150	Effects in offspring occur at maternally toxic doses. No evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1	Decreased bodyweight gain and food consumption. Increased abortions. Increase in un ossified skeleton and increase in supernumerary ribs.	No information reported	Maternal 20 Developmental 80	Maternal 80 Developmental 320	Effects in offspring occur at maternally toxic doses. No evidence of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Effects on the thyroid are seen in a 2 year oral study in rats.

Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	Information from 2 year studies had indicated that the thyroid adenomas are due to perturbation of the HPT axis.
Are the effects judged to be relevant to humans?	Yes	Effects may occur in humans, although rats are more sensitive to this pathway. It is not known if the thyroid effects are due to liver enzyme induction.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Increased relative thyroid weight and increased incidence of thyroid follicular adenoma occur at 156 mg/kg bw/day in a 2 year rat oral study, which is above the cut-off for STOT RE category 1 for long term studies of 5 mg/kg bw/day.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and evidence of endocrine disruption in the thyroid.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as ED effects occur at high dose levels above the STOT-RE Cat 1 guidance values.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	**Yes**	**Group is appropriate as ED effects occur above the STOT-RE Cat 1 guidance values.**
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is evidence from a full range of regulatory toxicology tests of buprimate causing endocrine disruption in the thyroid.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.4 Human Health Endocrine Disruption Evaluation for Captan

Substance details						
Substance Name	**Captan (ISO)**					
Substance Synonyms	1,2,3,6-tetrahydro-N-(trichloromethylthio)phthalimide					
Substance CAS Number	133-06-2					
Substance EC Number	205-087-0					
Data Source(s)	European Union Draft Assessment Report (2003)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Carc. Cat. 3; R40 T; R23 Xi; R41 R43 N; R50 Carc. 2 H351 Acute Tox. 3 * H331 Eye Dam. 1 H318 Skin Sens. 1 H317 Aquatic Acute 1 H400	 Limited evidence of a carcinogenic effect Toxic by inhalation Risk of serious damage to eyes May cause sensitization by skin contact Very toxic to aquatic organisms Suspected of causing cancer Toxic if inhaled Causes serious eye damage May cause an allergic skin reaction Very toxic to aquatic life				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
1-year dog oral study	1/2	No treatment-related gross pathological changes, absolute organ wt unaffected, ↑liver wt considered to	No information reported	300	300	No 90-day rat oral study. 90-day rat inhalation study showed respiratory effects

		be related to the lower body wt and not treatment-related. No treatment-related histopathological changes.				consistent with intake of particulate irritant. No evidence of endocrine disruption.
2-year rat oral long-term toxicity and carcinogenicity study (2 studies)	1/2	↓Body wt, ↑mean absolute and relative liver and kidney wt related to significant hepatocellular hypertrophy of a centrilobular, focal, multifocal or diffuse nature, no microscopic changes in kidney. No ↑incidence of microscopic neoplastic and non-neoplastic lesions or toxicologically significant ↑any tumour type, total tumours, total benign tumours or total malignant tumours.	No information reported	25	100	No evidence of endocrine disruption.
2-year mouse oral long-term toxicity and carcinogenicity study	1/2	Alopecia, ↓body wt. ↑duodenal hyperplasia, benign and malignant tumours (adenomas and adenocarcinomas).	No information reported			Non-genotoxic duodenal tumours due to irritant changes in the gastrointestinal tract. No evidence of endocrine disruption.
3-generation rat oral reproduction study	1/2	Parental ↓body wt Reproduction no effects on fertility, length of gestation or litter size at birth. ↓Pup survival, pup wt, ↓foetal body wt in an F2. No ↑incidence of gross abnormalities. There were no indications of any cumulative effects of treatment in successive generations.	No information reported	Parental toxicity: 25 Fertility: >500 Pup survival: 100 Pup toxicity: <25	100 - 250 100	No evidence of endocrine disruption.
Rat oral developmental and teratogenicity study	1/2	Maternal: ↓body wt, food consumption Foetotoxicity: ↓foetal body weight, ↑incidence of small foetuses and skeletal defects classified as variants The incidence of major malformations was not adversely affected by treatment.	No information reported	18 (maternal) 90 (foetal)	90 450	The observed axial skeletal abnormalities could be related to the gastro-intestinal maternal toxicity and, as a consequence, to an embryonic nutrient imbalance. There is no evidence of endocrine disruption.

Rabbit oral developmental and teratogenicity study (3 studies)	1/2	Maternal: ↓body wt gain, body wt. Embryotoxicity: ↑post-implantation loss, ↓body weight, ↑incidence of skeletal abnormalities classified as variants, ↑incidence of major abnormalities and minor visceral.	No information reported	10 (maternal) 10 (foetal)	30 30	No mechanistic studies were performed, but suggested that the observed foetal axial alterations could be related to maternal gastro-intestinal damages and consequently to an imbalance on nutrients reaching the developing embryo. No evidence of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	There is no evidence of endocrine disruption in a full range of regulatory tests. The main toxic effect appears to be an irritant effect on the GI tract.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no evidence of endocrine disruption in a full range of regulatory tests.
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	There is no evidence of endocrine disruption in a full range of regulatory tests.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.

Overall grouping of the substance regarding its endocrine disrupting properties

Group	Response (Yes/No)	Comments
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.

(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in the available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in the available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, captan is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.5 Human Health Endocrine Disruption Evaluation for Cyazofamid

Substance details						
Substance Name	**Cyazofamid (ISO)**					
Substance Synonyms	4-chloro-2-cyano-N,N-dimethyl-5-p-tolylimidazole-1-sulfonamide					
Substance CAS Number	120116-88-3					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2001). A brief search for more recent relevant studies did not yield any further information.					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 N; R50-53 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Very toxic to aquatic life Very toxic to aquatic life with long lasting effects				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	Kidney basophilic tubules. ↑mean relative kidney wt	No information reported	M) 29.5 (F) 33.3	295 338	No changes suggesting an effect on endocrine function
1-year dog oral study	1/2	No treatment-related effects were observed	No information reported	1000	Highest dose tested	No changes suggesting an effect on endocrine function
2-year rat long-term toxicity and carcinogenicity study	1/2	↑urine volume, chloride levels and kidney and liver wt. No evidence of carcinogenicity	No information reported	17.1 (males) 20.2 (females)	171.1 (males) 207.8 (females)	No changes suggesting an effect on endocrine function

18-month mouse long-term toxicity and carcinogenicity study	1/2	No treatment related adverse effects. No evidence of carcinogenicity	No information reported	985 (males) 1203 (females)	Highest dose tested	No changes suggesting an effect on endocrine function
2-generation rat reproduction study	1/2	↓body wt in females. No reproductive effects observed in any animals	No information reported	936 (males) 134 (F0 females)	Top dose tested 1000	No changes suggesting an effect on endocrine function
Rat oral developmental and teratogenicity study	1/2	No treatment related effects were observed	No information reported	1000	Top dose tested	No changes suggesting an effect on endocrine function
Rabbit oral developmental and teratogenicity	1/2	No treatment related effects were observed	No information reported	1000	Top dose tested	No changes suggesting an effect on endocrine function

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	No changes suggesting an effect on endocrine function in a full range of regulatory tests.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No changes suggesting an effect on endocrine function in a full range of regulatory tests.
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	No changes suggesting an effect on endocrine function in a full range of regulatory tests.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	No changes suggesting an effect on endocrine function in a full range of regulatory tests.
(B**)** Endocrine disrupter more likely to pose a risk based on currently available data	No	Group not appropriate as there is no evidence of endocrine disruption in the available data.
(C) Endocrine disrupter less likely to pose a	No	Group not appropriate as there is no evidence of endocrine disruption in the available data.

risk based on currently available data		
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**No changes suggesting an effect on endocrine function in a full range of regulatory tests. Therefore, cyazofamid is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.6 Human Health Endocrine Disruption Evaluation for Cymoxanil

Substance details		
Substance Name	**Cymoxanil**	
Substance Synonyms	2-cyano-N-[(ethylamino)carbonyl]-2-(methoxyimino)acetamide cymoxanil (ISO)	
Substance CAS Number	57966-95-7	
Substance EC Number	261-043-0	
Data Source(s)	European Union Draft Assessment Report (2007)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Xn; R22 R43 N; R50-53	Harmful if swallowed. May cause sensitization by skin contact. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Acute Tox. 4 * Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	Harmful if swallowed. May cause an allergic skin reaction. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2-year rat oral long-term toxicity and carcinogenicity study	1	Hyper activity Reduced bodyweight and body weight gain Degenerative/inflammation changes in liver, lung, testes, pancreas, retina and nerves	No information reported. Effect on reproductive organs	4.08: males 5.36: females	30.3: males 38.4: females	Changes in testis could be due to an endocrine mode of action.
2 year oral rat	1	Reduced bodyweight and body weight gain Alterations in haematology and clinical chemistry Histological changes in the lung, colon, rectum and testes	No information reported	4.7: males 31.6: females	23.5: males 67.3: females	Changes in testis could be due to an endocrine mode of action.
18-month mouse oral long-term toxicity and carcinogenicity study	1	Clinical findings Reduced bodyweight and body weight gain Alterations in haematological parameters Increased liver weight Histological findings in the liver, stomach, intestine, testes and epididymides	No information reported.	4.19: males 5.83: females	42.0: males 58.1: females	Changes in testis could be due to an endocrine mode of action.
18-month mouse oral long-term toxicity and carcinogenicity study	1	Changes in differential leukocyte count Pathological findings in mesenterical lymph nodes and ovary	No information reported.	91.4: males 91.9: males	178.3: males 179.1: females	Changes in ovary could be due to an endocrine mode of action.
2-generation rat oral reproduction study	1	Parental: Reduced bodyweight and weight gain Decreased food consumption Increased testis weight Offspring: Reduced 0-4 day viability Reduced pup weights	No information reported	Parental: 6.5 Reproductive: 97.9	Parental: 94 Reproductive: -	No evidence of endocrine disruption.

2-generation rat oral reproduction study	1	Parental: Reduced bodyweight Decreased food consumption Offspring: Reduced pup weights Reproductive: Reduced percentage of live births Reduced mean number of corpora lutea Reduced number of implantations Increased percentage of post-implantation loss	No information reported	Parental: 10.5 Reproductive: 31.6	Parental: 31.6 Reproductive: 94	The reproductive effects could be due to endocrine disruption
Rat oral developmental and teratogenicity study	1	Maternal: Reduced bodyweight gain Reduced food consumption Foetal: Increased incidence of variations Increased incidence of malformations	No information reported	Maternal: 10 Foetal:10	Maternal: 25 Foetal:25	No evidence of endocrine disruption
Rat oral developmental and teratogenicity study	1	Maternal: Reduced bodyweight and weight gain Reduced food consumption Increased late resorptions Increased post implantation loss Increased number of dams with any resorption Foetal: Increased incidence of anomalies (dumbbell shaped thoracic vertebra)	No information reported	Maternal: 60 Foetal:-	Maternal: 120 Foetal: -	No evidence of endocrine disruption
Rat oral developmental and teratogenicity study	1	Maternal: None Foetal: Increased incidences of skeletal malformations (vertebra/rib alterations linked with scoliosis)	No information reported	Maternal: 8 Foetal: 16	Maternal: 16 Foetal: 32	No evidence of endocrine disruption

Rabbit oral developmental and teratogenicity study	1	Maternal: None Foetal: Increased incidences of visceral malformations (hydrocephaly and cleft palates)	No information reported	Maternal: >32 Foetal: 8	Maternal: - Foetal: 32	No evidence of endocrine disruption
Rabbit oral developmental and teratogenicity study	1	Maternal: Reduced bodyweight gain Reduced food consumption Foetal: Increased incidence of visceral and skeletal variants Increased incidence of minor skeletal anomalies Increased incidence of visceral malformation (dilation of heart ventricles)	No information reported	Maternal: 15 Foetal:15	Maternal: 25 Foetal: 25	No evidence of endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Effects on reproductive organs (ovaries and testes) were observed in multiple long term studies in rats and mice. Also, decreased fertility occurred in one 2 generation study in rats.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no information on mechanism of action to determine if the observed effects are due to an ED MOA.
Are the effects judged to be relevant to humans?	Yes	It is plausible that the effects that occurred in animals can occur in man.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	There is no mechanistic information to establish whether cymoxanil is an endocrine disrupter
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**The effects observed in regulatory tests raise a concern for endocrine disruption but mode of action information is lacking.**
(B) Endocrine disrupter more likely to pose a risk based on currently available data	No	Cymoxanil is not an established endocrine disrupter.
(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	Cymoxanil is not an established endocrine disrupter
(D) Substances not considered to be endocrine disrupters based on currently available data	No	At present it cannot be excluded whether or not cymoxanil is an endocrine disrupter

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.7 Human Health Endocrine Disruption Evaluation for Cyprodinil

Substance details		
Substance Name	**Cyprodinil**	
Substance Synonyms	4-cyclopropyl-6-methyl-*N*-phenylpyrimidin-2-amine	
Substance CAS Number	121552-61-2	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (2004)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	R43 N; R50-53	May cause sensitization by skin contact. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	May cause an allergic skin reaction. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
90-day rat oral study	1	Liver: increased weight, hepatocellular hypertrophy and necrosis. Thyroid: increased weight,	No information reported	3	19	Effects on the thyroid and pituitary, however, not functional effects observed.

		hypertrophy of follicular epithelium; Pituitary cell hypertrophy; Kidney: chronic tubular lesion (males only)				
1-year dog oral study	1	Reduced bodyweight gain and food consumption	No information reported	65	449	No endocrine effects observed.
2-year rat oral study	1	Increased relative liver weight and degenerative changes. Increased relative kidney weight.	No information reported	2.7 male 3.22 female	35.6 male 41.2 female	No endocrine effects observed.
18-month mouse oral long-term toxicity and carcinogenicity study	1	Reduced bodyweight gain. Increased liver weight. Increased relative kidney weight in females.	No information reported	212.4 male 196.3 female	629.9 male 558.1 female	No endocrine effects observed.
2-generation rat oral reproduction study	1	Parental: Reduced bodyweight gain, increased relative liver and kidney weight. Pups: Reduced bodyweight gain.	No information reported	51-144 males 70-153 females	217-153 males 292-633 females	No endocrine effects observed.
Rat oral developmental and teratogenicity study	1	Maternal: Reduced bodyweight gain and food consumption. Foetal: Decreased bodyweight and delayed ossification.	No information reported	Maternal 200 Foetal 200	Maternal 1000 Foetal 1000	No endocrine effects observed.
Rabbit oral developmental and teratogenicity study	1	Maternal: Reduced bodyweight development and food consumption Foetal: None	No information reported	Maternal 150 Foetal -	Maternal 400 Foetal -	No endocrine effects observed.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	There are no adverse effects that could be due to endocrine disruption in standard studies.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	-

Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	-
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Category	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, cyprodinil is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.8 Human Health Endocrine Disruption Evaluation for Dimethomorph

Substance details						
Substance Name	**Dimethomorph**					
Substance Synonyms	4-(3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl)morpholine					
Substance CAS Number	110488-70-5					
Substance EC Number	404-200-2					
Data Source(s)	European Union Draft Assessment Report (2004)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 N; R51-53 Aquatic Chronic 2	 Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Toxic to aquatic life with long lasting effects.				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1	Increased liver weight in females.	No information reported	16	73	No evidence of endocrine effects.
90-day dog oral study	1	Increased alkaline phosphatase activity (males); Decreased prostrate weights (males); prostatic interstitial fibrosis (males) Increased liver weights	No information reported	15	43	Possible evidence of endocrine effects on the prostate. No functional effects reported.

		(absolute and relative) (females)				
1-year dog study	1	Increased liver and testes weights.	No information reported	5	15	Possible evidence of endocrine effects on the prostate. No functional effects reported.
2-year rat oral long-term toxicity and carcinogenicity study	1	Decreased bodyweight gain.	No information reported	9	34	No evidence of endocrine effects.
2-year mouse oral long-term toxicity and carcinogenicity study	1	Decreased bodyweight gain.	No information reported	10	97	No evidence of endocrine effects.
2-generation rat oral reproduction study	1	Decreased parental bodyweight gain and reduced duration of pregnancy.	No information reported	Parental 20	Parental 67	Possible endocrine effects (reduced duration of pregnancy), but occurring in the presence of maternal toxicity.
Rat oral developmental and teratogenicity study	1	Decreased maternal bodyweight gain and food consumption. Slightly increased early resorption rate.	No information reported	Maternal 60 Foetal 60	Maternal 160 Foetal 160	No evidence of endocrine effects. The early resorptions are likely to be the consequence of maternal toxicity.
Rabbit oral developmental and teratogenicity study	1	Decreased food consumption, bodyweight gain, slightly increased abortion rate.	No information reported	Maternal 300 Foetal 300	Maternal 650 Foetal 650	Possible endocrine effects (abortions), but occurring in the presence of maternal toxicity.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Functional effects potentially relating to an endocrine mechanism of action are not present in standard toxicity studies.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no evidence of an endocrine effect.
Are the effects judged to be relevant to humans?	N/A	There is no evidence of an endocrine effect.

Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	There is no evidence of an endocrine effect.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B)Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, dimethomorph is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.9 Human Health Endocrine Disruption Evaluation for Fenhaxamid

Substance details						
Substance Name	**Fenhexamid**					
Substance Synonyms	*N*-(2,3-dichlor-4-hydroxyphenyl)-1-methylcyclohexancarboxamid					
Substance CAS Number	126833-17-8					
Substance EC Number	422-530-5					
Data Source(s)	European Union Draft Assessment Report (approximately 2000). A brief search for recent relevant studies located the following paper which is summarised below: Orton F, Rosivatz E, Scholze M and Kortenkamp A (2011) Widely used pesticides with previously unknown endocrine activity revealed as *in vitro* antiandrogens. EHP 119, 794-800					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 N; R51-53 Aquatic Chronic 2	 Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Toxic to aquatic life with long lasting effects				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day dog oral study	1/2	↑Heinz bodies, ↑blood alkaline phosphatase, ↑liver wt, No histological correlation.	No information reported	33	Approximately 230	This study had the lowest NOAEL of the subchronic studies. No rodent studies or the 1-year dog study gave additional toxicological information. No study gave any

						evidence of endocrine disruption.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	Caecal mucosal hyperplasia, thyroid follicular colloid alteration, slightly ↑cataracts. No carcinogenic potential.	No information reported	28	290	Slight evidence of thyroid effects but no seen in other studies.
2-generation rat oral reproduction study	1/2	Maternal: blood chemistry, ↑body wt gain, marginal organ wt changes. Foetal: No adverse effects on reproductive parameters, impairment of pup growth at dose levels where maternal toxicity was seen	No information reported	38 (maternal and pup)	350	No evidence of endocrine disruption.
Rat oral developmental and teratogenicity study	1/2	Maternal: Slightly ↓body wt gain and food consumption. Developmental: marginal ↑pre- and post-implantation losses at a maternally-toxic dose.	No information reported	1000 (maternal and developmental)	-	No evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1/2	No evidence of teratogenicity. Maternal: ↓body wt gain, Foetal: ↓placental weights.	No information reported	100 (maternal and foetal)	300	No evidence of endocrine disruption.
In vitro screen for anti-androgen activity	2	-	Anti-androgen activity in 2 *in vitro* systems (Human breast cancer cells with androgen-responsive element and reporter gene. Yeast cells with transfected androgen receptor). These are screening assays and potency as compared to androgens not addressed	Antiandrogen IC_{20} 2.02 µM	Most potent Pyrimethanil 27.2 µM Least potent Fenitrothion 0.098 µM	Stated as being previously unknown for having endocrine activity (2011).

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Slight effect on thyroid in rat long-term study, not seen in other studies. Hence, no convincing evidence of effects raising a concern for endocrine disruption from *in vivo* regulatory studies.

Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	*In vitro* assays suggest anti-androgen activity. However, no adverse effects potentially caused by this activity have been observed.
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	No evidence for endocrine disruption in a full range of regulatory tests. Recent *in vitro* assay suggests anti-androgenic activity but this does not appear to be expressed *in vivo*..
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, fenhexamid is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.10 Human Health Endocrine Disruption Evaluation for Fenpropimorph

Substance details		
Substance Name	**Fenpropimorph**	
Substance Synonyms	-	
Substance CAS Number	67564-91-4 67306-03-0	
Substance EC Number	266-719-9	
Data Source(s)	European Union Draft Assessment Report Revision (2007)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	 Repr. Cat. 3; R63 Xn; R22 Xi; R38 N; R51-53	 Possible risk of harm to the unborn child. Harmful if swallowed. Irritating to skin. Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Repr. 2 Acute Tox. 4 * Skin Irrit. 2 Aquatic Chronic 2	Suspected of damaging the unborn child. Harmful if swallowed. Causes skin irritation. Toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
1-year dog oral study	1	Increased alkaline phosphatase and alanine aminotransferase.	No information reported	0.8	3.2	The effects do not suggest involvement of the endocrine system.

2-year rat oral long-term toxicity and carcinogenicity study	1	Reduced bodyweights Reduced brain and plasma AChE. Increased liver weights in males with centrilobular liver enlargement. Multinucleate hepatocytes.	No information reported	0.3 males 0.4 females	1.7 males 2.7 females	The effects do not suggest involvement of the endocrine system.
95-week mouse oral long-term toxicity and carcinogenicity study	1	Reduced bodyweight gain. Increased liver weight.	No information reported	16 males 17 females	106 males 118 females	The effects do not suggest involvement of the endocrine system.
2-generation rat oral reproduction study	1	No effects on fertility; possible effect on duration of pregnancy; slight effect on postnatal pup growth. Effects on food consumption, bodyweights, liver weights and serum cholinesterase.	No information reported	16 reproductive 4 developmental 4 general toxicity	-reproductive 8 developmental 8 general toxicity	The effects do not suggest involvement of the endocrine system.
Rat oral developmental and teratogenicity study	1	No effects on pregnancy rate. Effects on embrofoetal and postnatal growth. Reduced food consumption, bodyweight gain and serum AChE.	No information reported	15 reproductive <5 developmental <5 general toxicity	-reproductive 5 developmental 5 general toxicity	The effects do not suggest involvement of the endocrine system.
Rabbit oral developmental and teratogenicity study	1	Reduced foetal weight, limb/skeletal anomalies, sternal fusions and cleft palate. Decreased food consumption, bodyweight and anal swelling.	No information reported	15 embryotoxicity 15 anomalies 15 maternal toxicity	30 embryotoxicity 30 anomalies 30 maternal toxicity	Individual animal data demonstrate skeletal effects at a dose causing pronounced maternal toxicity. It is questionable if the embrytoxicity observed is due to maternal toxicity or exposure. Data are not available to assess whether the embryo-toxicity is due to treatment, however, if it is, it is unlikely that the effects observed are due to endocrine mediated mechanisms.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects relate to AChE inhibition .There is no evidence of effects mediated by an endocrine mode of actions.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no information indicating that an endocrine mode of action occurs.
Are the effects judged to be relevant to humans?	N/A	Endocrine mediated effects are not observed.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	Endocrine mediated effects are not observed.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, fenpropimorph is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.11 Human Health Endocrine Disruption Evaluation for Fluazinam

Substance details						
Substance Name	**Fluazinam**					
Substance Synonyms	3-chloro-N-(3-chloro-5-trifluoromethyl-2-pyridyl)-?α?α?α- trifluoro-2, 6-dinitro-p-toluidine (IUPAC) 3-chloro-N-[3-chloro-2, 6-dinitro-4-trifluoromethyl) phenyl]-5-(trifluoromethyl)-2-pyridinamine (CA)					
Substance CAS Number	79622-59-6					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2005) EFSA Scientific Report (2008) 137, 1-82, Conclusion on the peer review of fluazinam					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day oral rat study	1/2	Haematological findings ↑relative liver wt, ↑higher absolute and relative lung and uterus wt, histopathological changes in the liver	No information reported	4.1	41	Effect on uterus wt may be indicative of endocrine disruption
90-day oral dog study	1/2	↓food consumption and body wt gain, grey pigmentation of the tapetal fundus of the retina, clinical chemical findings, ↑absolute and relative liver wt,	No information reported	10	100	No changes suggesting an effect on endocrine function

		histopathological changes in the liver				
2-year long-term toxicity and carcinogenicity oral rat study	1/2	↑liver, testes and epididymides wt, histopathological changes in liver, pancreas, lungs and ↑testicular atrophy and spermatocele granuloma.	No information reported	.9 (males) 2.4 (females)	3.9 (males) 4.9 (females)	Effects on testes may be indicative of endocrine disruption
2-year long-term toxicity and carcinogenicity oral mouse study	1/2	↑liver weights, histopathological changes in liver, liver cell tumours, vacuolation of white matter in brain and spinal cord	No information reported	1.12 (males) 1.16 (females)	10.72 11.72	No changes suggesting an effect on endocrine function
Two generation reproduction oral rat study	1/2	Parental: ↑body weight and body wt; relative liver weight Offsprings: gestation length; implantation sites and litter sizes	No information reported	Parental and Reproductive 1 (males) 1.4 (females)	 5 6.7	No reproductive toxicity at doses below parental toxicity
Rat oral developmental and teratogenicity study	1/2	Maternal: food consumption; wt gain Developmental: foetal and placental wt; ossification incomplete; gross morphological foetal abnormalities	No information reported	10 (maternal) 10 (developmental)	50	No developmental toxicity at doses below maternal toxicity
Rabbit oral developmental and teratogenicity study	1/2	Maternal: food consumption Developmental: ossification incomplete	No information reported	1 (maternal) 1 (developmental)	3	No developmental toxicity at doses below maternal toxicity

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Effects on testicular and uterine weight have been observed which could be due to endocrine disruption. However, there is no mechanistic evidence of endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	Effects on testes and uterine weight have been observed which could be due to endocrine disruption. However, there is no mechanistic evidence of endocrine disruption.
Are the effects judged to be relevant to humans?	Yes	There is no evidence that the effects on testicular and uterine weight are due to a mechanism not relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	Effects on testicular and uterine weight have been observed which could be due to endocrine disruption. However, there is no mechanistic evidence of endocrine disruption.

Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**Effects on testicular and uterine weight have been observed which could be due to endocrine disruption. However, there is no mechanistic evidence of endocrine disruption and further studies are required to resolve this uncertainty.**
(B**)** Endocrine disrupter more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.12 Human Health Endocrine Disruption Evaluation for Fludioxonil

Substance details		
Substance Name	**Fludioxonil**	
Substance Synonyms	-	
Substance CAS Number	**131341-86-1**	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (2005)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
2-year rat oral study	1	Reduced bodyweight and bodyweight gain. Mild anaemia. Histopathological and gross necropsy findings in the liver and kidney.	No information reported	37 males 44 females	113 males 141 females	The effects observed do not indicate an endocrine mode of action.
18-month mouse oral long-term toxicity and carcinogenicity study	1	Reduced survival at top dose. Body weight and bodyweight gain decreased.	No information reported	112 males 133 females	360 males 417 females	The effects observed do not indicate an endocrine mode of action.

		Anaemia. Increased liver weight and bile duct hyperplasia. Nephropathy.				
Two-generation rat oral reproduction study	1	Decreased bodyweight in parental animals and pups. No reproductive effects.	No information reported	21 Maternal 212 Reproduction	212 maternal -reproduction	The effects observed do not indicate an endocrine mode of action.
Rat oral developmental and teratogenicity study	1	Reduced bodyweight gain and food consumption in dams. No effects in foetuses.	No information reported	100 maternal 1000 developmental	1000 maternal -developmental	The effects observed do not indicate an endocrine mode of action.
Rabbit oral developmental and teratogenicity study	1	Reduced bodyweight gain in dams. No effects in foetuses.	No information reported	10 maternal 300 developmental	100 maternal -developmental	The effects observed do not indicate an endocrine mode of action.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects do not indicate that an endocrine mode of action is responsible for any toxicity associated with this substance.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	An endocrine mode of action is not plausible.
Are the effects judged to be relevant to humans?	No	No endocrine mediated effects have been observed.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	No endocrine mediated effects have been observed.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, fludioxinil is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.13 Human Health Endocrine Disruption Evaluation for Fluoxastrobin

Substance details						
Substance Name	**Fluoxastrobin**					
Substance Synonyms	-					
Substance CAS Number	361377-29-9 193740-76-0					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2003)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2-year rat oral long-term toxicity and carcinogenicity study	1	Reduced bodyweight gain.	No information reported	53 males 35 females	272 males 181 females	No evidence of an endocrine effect.
18-month mouse oral long-term toxicity and c carcinogenicity study	1	Increased liver weight. Reduced plasma ALT.	No information reported	135 males 30 females	776 males 204 females	No evidence of an endocrine effect.

2-generation rat oral reproduction study	1	Reduced bodyweight gain. Increased liver weight. Reduced thymus weight in dams and pups.	No information reported	74-87 parental 742-764 reproductive 16 developmental	764-871 parental >742-764 reproductive 171 developmental	No evidence of an endocrine effect.
Rat oral developmental and teratogenicity study	1	No adverse effects.	No information reported	1000 maternal 1000 developmental	>1000 maternal >1000 developmental	No evidence of an endocrine effect.
Rabbit oral developmental and teratogenicity study	1	Reduced food consumption, increased incidence of weight loss. Dilation of brain ventricles.	No information reported	25 maternal 100 developmental	100 maternal 400 developmental	No evidence of an endocrine effect.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects do not indicate an endocrine mode of action.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence is available to suggest an endocrine mode of action.
Are the effects judged to be relevant to humans?	No	Effects resulting from endocrine disruption are not present in the available studies.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Adverse effects do not indicate an endocrine mode of action.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Category	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.

(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, fluoxastrobin is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.14 Human Health Endocrine Disruption Evaluation for Fosetyl ammonium

Substance details						
Substance Name	**Fosetyl aluminium**					
Substance Synonyms	Aluminium triethylphosphonate					
Substance CAS Number	39148-24-8					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2004)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	Not classified Not classified	Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1	No effects observed.	No information reported	1424	-	No effects observed.
90-day dog oral study	1	No effects observed.	No information reported	1377	-	No effects observed.
2-year dog oral long-term toxicity and carcinogenicity study	1	Testicular degeneration.	No information reported	309 male 288 female	609 male 632 female	Possible endocrine effects.
2-year mouse oral long-term toxicity and carcinogenicity study	1	No effects observed.	No information reported	3956 male 4549 female	- -	No effects observed.

2 year rat oral long-term toxicity and carcinogenicity study	1	Uroliths and hyperplasia of the urinary bladder. Urinary bladder neoplasms secondary to chronic irritation.	Functional alterations and histopathological changes in the kidney, including imbalance of calcium/ phosphorous metabolism, formation of calculi and hyperplasia of the urinary tract.	348 male 450 female	1372 male 1786 female	No evidence of endocrine mediated effects.
Rat oral developmental and teratogenicity study	1	No evidence of reproductive effects. Decreased pup bodyweight.	No information reported	Reproductive 1782 male 1997 female Maternal and Foetal 439 male 520 female	Reproductive - - Maternal and Foetal 820 approx 960 approx	No evidence of endocrine mediated effects.
Rat oral developmental and teratogenicity study	1	Maternal mortality and bodyweight loss. Minor changes in litter parameters. Increased incidence of malformation and minor abnormalities.	No information reported	Maternal 1000 Foetal 1000	Maternal 4000 Foetal 4000	Toxicity in the presence of maternal effects, suggesting a secondary cause.
Rabbit oral developmental and teratogenicity study	1	-	No information reported	Maternal 300 Foetal 300	-	No evidence of toxicity.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Testicular degeneration was observed in a 2 year study in dogs.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no evidence to determine whether an endocrine mechanism of action is plausible.
Are the effects judged to be relevant to humans?	Yes	The effects could be relevant for humans.

Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	No mechanistic studies are available, therefore the testicular degeneration observed in dogs cannot be conclusively attributed to an endocrine mechanism of action. Effects are observed at 609 mg/kg bw/day, which is above the cut-off point for STOT-RE.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**Further information on the mechanism of testicular degeneration in dogs is necessary to determine if this is due to an endocrine mechanism of action.**
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.14 Human Health Endocrine Disruption Evaluation for Hymexazol

Substance details		
Substance Name	**Hymexazol (ISO)**	
Substance Synonyms	3-hydroxy-5-methylisoxazole	
Substance CAS Number	10004-44-1	
Substance EC Number	233-000-6	
Data Source(s)	European Union Draft Assessment Report (2007). A brief search for recent relevant studies did not locate any further information.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xn; R22 Xi; R41 R52-53 Acute Tox. 4 * H302 Eye Dam. 1 H318 Aquatic Chronic 3 H412	 Harmful if swallowed Risk of serious damage to eyes Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment Harmful if swallowed Causes serious eye damage Harmful to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	↓Body wt gain, ↑liver wt, blood biochemical changes, centrilobular hepatocyte enlargement	No information reported	371(male) 450 (female)	1694 (male) 2084 (female)	Liver toxicity with no evidence of endocrine disruption.

1-year dog oral study	1/2	↑Liver wt.	No information reported	17.00 (male) 18.18 (female)	87(male) 91 (female)	Liver toxicity with no evidence of endocrine disruption.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↓Body wt gain, ↓relative thyroid wt.	No information reported	20 (male) 28 (female) Carcinogenicity 532(male) 769 (female)	99/149 -	Only potential endocrine effect was decrease in thyroid weight.
2-generation rat oral reproduction study	1/2	Slightly extended gestation length (F0 and F1) and ↓litter size at birth due to ↑postimplantation loss (F0 and F1).	No information reported	Adult and Offspring: 159 (males) 192 (females) Reproduction 31 (F0 males) 38 (F0 females)	 - - 159 192	EU DAR considered classification for fertility and development. Indications of disturbed oestrous cyclicity were also observed in the range-finding study. Disruption of reproduction at levels below maternal toxicity which could be due to endocrine disruption.
Rat oral developmental and teratogenicity study	1/2	↓foetal wts, ↑incidence skeletal variations	No information reported	500 (maternal) 100 (embryotoxicity/teratogenicity)	- 500	No clear evidence of potential endocrine effects.
Rabbit oral developmental and teratogenicity study	1/2	↑postimplantation loss, ↓litter size and litter weight, ↑number of foetuses with malformations and variations variant sternebrae. Malformations affecting heart, great vessels and face	No information reported	150 (maternal): 150 (embryotoxicity/teratogenicity)	450 450	There was no NOEL for variant sternebrae. Malformations affecting heart, great vessels and face were observed at ≥ 150 mg/kg. Overall, no explicit evidence of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There is evidence of adverse effects on reproduction (oestrous cycle, gestation length) which may be indicative of endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	Endocrine disruption may be responsible for adverse effects although there are no measured effects on hormones or mechanistic studies to demonstrate this.
Are the effects judged to be relevant to humans?	N/A	The adverse effects may be relevant to humans. The EU DAR did consider classification of hymexazol for adverse effects on fertility and development and there is no reliable evidence for endocrine disruption.

Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	There is no reliable evidence that the substance is an endocrine disrupter.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**Adverse effects on reproduction have been observed but to confirm endocrine disruption, further information on hormone levels and potential mechanisms are required.**
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.15 Human Health Endocrine Disruption Evaluation for Imazaquin

Substance details						
Substance Name	**Imazaquin**					
Substance Synonyms	2-[(RS)-4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl]quinoline-3-carboxylic acid (IUPAC) 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-3-quinolinecarboxylic acid (CAS)					
Substance CAS Number	81335-37-7					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2007)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	No adverse effects.	No information reported	800 (highest dose)	-	In general, low toxicity in subchronic and long-term toxicity tests. No evidence of endocrine disruption

1-year dog oral study	1/2	↑clinical signs, ↑skeletal myopathy, ↑anaemia, and ↑related haematological and clinical chemical alterations.	No information reported	25	125	No evidence of endocrine disruption
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↑urine stains, and marginal ↓body wt (gain). No carcinogenic potential.	No information reported	250	500	No evidence of endocrine disruption
78-week mouse oral long-term toxicity and carcinogenicity study	1/2	↓body wt parameters. No carcinogenic potential.	No information reported	150	600	No evidence of endocrine disruption
3-generation rat reproduction study	1/2	↑kidney pelvis calcification in females.	No information reported	469 (parental) 917 (foetal)	917 -	No evidence of endocrine disruption
Rat oral developmental and teratology study	1/2	Maternal: ↑mortality, ↑clinical signs. Developmental: ↓foetal wt, ↑reduced ossifications	No information reported	500 (maternal and developmental)	2000	No evidence of endocrine disruption
Rabbit oral developmental and teratology study	1/2	Maternal: ↑mortality, ↓body wt change	No information reported	250 (maternal) 500 (developmental)	500 -	No evidence of endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	In a full range of regulatory toxicity tests, there is no evidence of endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	In a full range of regulatory toxicity tests, there is no evidence of endocrine disruption.
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	In a full range of regulatory toxicity tests, there is no evidence of endocrine disruption.

Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, imazaquin is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.16 Human Health Endocrine Disruption Evaluation for Iprodione

Substance details		
Substance Name	**Iprodione (ISO)**	
Substance Synonyms	3-(3,5-dichlorophenyl)-2,4-dioxo-N-isopropylimidazolidine-1-carboxamide	
Substance CAS Number	36734-19-7	
Substance EC Number	253-178-9	
Data Source(s)	European Union Draft Assessment Report (1996) – This is an older DAR with older studies and less easy to obtain study details. The studies summarised were carried out to GLP and guidelines and so are considered to be Klimisch 1/2. A brief search for recent relevant studies located the following papers which are summarised below: Blystone CR, Lambright CS, Furr J, Wilson VS, Gray LE (2007) Iprodione delays male rat pubertal development, reduces serum testosterone levels, and decreases ex vivo testicular testosterone production. *Toxicol Lett*. **174**, 74-81. Blystone CR, Lambright CS, Cardon MC, Furr J, Rider CV, Hartig PC, Wilson VS and Gray LE (2009) Cumulative and antagonistic effects of a mixture of the antiandrogens vinclozolin and iprodione in the pubertal male rat. *Toxicol Sci*, **111**, 179-188. Ghisari, M and Bonefeld-Jorgensen, E.C (2005) Impact of environmental chemicals on the thyroid hormone function in pituitary rat GH3 cells. *Molecular and Cellular Endocrinology*, **244(1-2)**, 31-41. Vinggaard, A M , Breinholt, V, Larsen, J C (1999) Screening of selected pesticides for oestrogen receptor activation *in vitro. Food Additives and Contaminants,* **16(12),** 533-542	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Carc. Cat. 3; R40 N; R50-53 Carc. 2 H351 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	 Limited evidence of a carcinogenic effect Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Suspected of causing cancer Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	2	↓body wt gain, food consumption, clinical signs, ↑liver wt, microscopic liver changes, ↓uterus, ovary wt, atrophic changes in uterus, ↓corpora lutea	No information reported	20.5-23.7	Approximately 60	The NOAEL is derived by EU DAR from a series of rat, mouse and dog 90-day studies, some of which date from before GLP. Effects on uterus and ovaries (wt and histopath) could be due to endocrine disruption.
1-year dog oral study	1/2	Transient ↑Heinz bodies, ↓prostate wt, slight microscopic changes adrenals (↑depth *zona fasciculata* and *zona glomerulosa,* with large cells and "watery" cell cytoplasm), kidneys, histopathological changes liver, adrenals and bladder.	No information reported	12.4 (males) 13.1 (females)	17.5 18.4	Effects on the prostate and adrenals which may be due to endocrine disruption
2-year rat oral long-term toxicity and carcinogenicity study	1/2	Non-carcinogenic effects: testes, ↑atrophied seminiferous tubules, ↑interstitial cell hyperplasia; epididymides, ↓sperm; ↑prostate atrophy; seminal vesicles, ↑absence of secretory colloid; spleen ↑minimal haemosiderosis; adrenals ↑general/focal enlargement of cells/vacuolation of cells of *zona glomerulosa.* Interstitial cell tumours in testes.	No information reported	7.25 (non-carcinogenic) 15 (carcinogenic)	Approx 15 Approx 750	Severe effects on the male reproductive system including tumours. These effects and those on the adrenals could be due to endocrine disruption.
2-generation rat oral reproduction study	1/2	Maternal: ↓body wt gain, food consumption. Development: ↓pup viability and wt. Reproduction: no adverse effects.	No information reported	Parental: 18.5 (males) 22.8 (females) Development: Approx 60 Reproduction: Approx 200	 60 120 -	No adverse effects on reproduction. Overall, no evidence of endocrine disruption.

Rat oral developmental and teratogenicity study	1/2	No maternal toxicity No teratogenic effects. Delayed foetal development.	No information reported	90 (delayed embryofoetal toxicity)	200	No adverse effects on reproduction. Overall, no evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1/2	Maternal ↓body wt gain No teratogenic effects. ↑abortions and post-implantation loss.	No information reported	20 (maternal) 60 (embryofoetal toxicity)	60 200	Some effects that could be due to endocrine disruption but at doses causing maternal toxicity.
Further more recent studies effects on the prepubertal male rat Blystone *et al*. (2007) Blystone *et al*. (2009)	2 2	↓ Serum testosterone levels, serum 17alpha-hydroxyprogesterone and androstenedione, serum LH unaffected. Delayed preputial separation and decreased androgen sensitive seminal vesicle and epididymides weights. Binds to human androgen receptor, ↓androgen-dependent gene expression, ↓androgen-sensitive tissue wt in castrated male rats (Hershberger assay).	Iprodione affects steroidogenesis within the testis, not through disruption of LH signaling, but possibly through enzyme inhibition of the steroidogenic pathway before CYP17. More direct anti-androgenic effects demonstrated *In vitro* data also indicate potential for endocrine disruption	N/A	N/A	Iprodione may act as an antiandrogen both directly through androgen receptor and androgen-specific pathways and through inhibition of the steroidogenic pathways.
Mechanistic (*in vitro* and *in vivo*) data Activation of the estrogen receptor using the MCF cell proliferation assay – Vinggaard *et al*. (1999)	2	No effect on MCF cell proliferation assay	-	>3.3 mg/l (10 µM)	Not relevant	No activation of the estrogen receptor
Androgen receptor binding in the hAR COS cell binding assay - Blystone *et al*. (2009)	2	Binding to the androgen receptor (AR)	-	3.3 mg/l (10 µM)	>3.3 mg/l (>10 µM)	Iprodione binds to the androgen receptor
Thyroid hormone function - Proliferation of the rat pituitary GH3 cell line – Ghisari and Bonefeld-Jorgensen (2005)	2	Inhibition of cell growth	-		Max inhibition (75%) at 0.033 mg/l (0.1 µM)	Iprodione interferes with the function of thyroid hormones (THs). U shaped dose response curve reported

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	The long-term test indicates clear effects on the male reproductive system.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	More recent studies show antiandrogen effects in the rat and binding to the human androgen receptor.
Are the effects judged to be relevant to humans?	Yes	It cannot be excluded that the effects on the male reproductive system are relevant to humans..
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	The effects which could potentially be due to endocrine disruption occur at doses above the STOT Category 1 guidance values for subchronic and chronic studies: uterus and ovary in 90-day rat oral study 60 mg/kg bw/day; adrenals in 1-year dog oral study, 17.5 mg/kg bw/day; testes and epididymis in 2-year rat oral study, 15 mg/kg bw/day.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is a full range of regulatory tests plus further recent specific studies on the male endocrine system.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	The reprotoxic effects occur at doses above the STOT Category 1 guidance values for subchronic and chronic studies.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	**Yes**	**The reprotoxic effects occur at doses above the STOT Category 1 guidance values for subchronic and chronic studies.**
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The long-term test indicates clear effects on the male reproductive and this is supported by more recent studies showing antiandrogen effects in the rat and binding to the human androgen receptor.

Notes:
[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?
[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.17 Human Health Endocrine Disruption Evaluation for Kresoxim-methyl

Substance details	
Substance Name	**Kresoxim-methyl**
Substance Synonyms	methyl (E)-methoxyimino[α-(o-tolyloxy)-o-tolyl]acetate (IUPAC) methyl (αE)-α-(methoxyimino)-2-[(2-methylphenoxy)methyl]benzeneacetate (CA)
Substance CAS Number	143390-89-0
Substance EC Number	-
Data Source(s)	European Union Draft Assessment Report (1997 revised in 2010) EFSA Journal (2010) Conclusion on the peer review of the pesticide risk assessment of the active substance kresoxim-methyl. 18, 1-88

Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
90-day oral rat study	1/2	↑GGT, ↑relative liver wt, ↓body wt gain	No information reported	146 (male) 172 (female)	577 672	No evidence of endocrine disruption
1-year oral dog study	2	↓body wt	No information reported	138 (male) 761 (female)	714 -	No evidence of endocrine disruption
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↓body wt, ↑liver wt, eosinophilic and basophilic foci, spongiosis/ peliosis, periportal hypertrophy in liver, hepatocellular adenoma and carcinoma	At carcinogenic doses it produced hepatic cell proliferation together with mild hepatic toxicity, both being reversible. Kesoxim-	-	752.1 (male) 1021.6 (female)	No evidence of endocrine disruption

			methyl is a non-genotoxic carcinogen in the rat, acting as a promoter for which a threshold dose exists.			
18-month mouse oral long-term toxicity and carcinogenicity study	1/2	↓body weight; papillary necroses (kidneys); ↑number of females with amyloidosis (liver) No evidence of carcinogenicity	Liver tumours are in single-species, reinforcing possible non-genotoxic mechanism	304 (male) 81 (female)	1308 400	No evidence of endocrine disruption
2-generation oral rat reproduction study	1/2	F0: ↓body weight; ↑serum GGT; ↓liver fat storing cells F1b pup: retarded morphological development. No reproductive effects	No information reported	100	424	Some evidence of toxicity and retarded morphological development at doses with parental toxicity
Rat oral developmental and teratogenicity study	1/2	No effects	No information reported	1000 (maternal and foetal)	-	No evidence of endocrine disruption
Rabbit developmental and teratogenicity study	1/2	No effects	No information reported	1000 (maternal and foetal)	-	No evidence of endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	There is no evidence of endocrine disruption in a full range of regulatory tests
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no evidence of endocrine disruption in a full range of regulatory tests
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	There is no evidence of endocrine disruption in a full range of regulatory tests
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	Yes	No detailed assessment has been carried out as part of the project as stipulated with HSE.

Overall grouping of the substance regarding its endocrine disrupting properties		
Category	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is sufficient reliable information with which to categorise the substance.
(B**)** Endocrine disrupter more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**There is no evidence of endocrine disruption in a full range of regulatory tests**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.18 Human Health Endocrine Disruption Evaluation for Mandipropamid

Substance details		
Substance Name	**Mandipropamid**	
Substance Synonyms	(RS)-2-(4-chlorophenyl)-N-[3-methoxy-4-(prop-2-ynyloxy)phenethyl]-2-(prop-2-ynyloxy)acetamide (IUPAC) 4-chloro-N-[2-[3-methoxy-4-(2-propynyloxy)phenyl]ethyl]-α-(2-propynyloxy)benzeneacetamide (CAS)	
Substance CAS Number	374726-62-2	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (2006)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	↓body wt, ↓body wt gain, haematological and clinical chemical findings, ↑liver weight, periportal hypertrophy/eosinophilia, ↑kidney wt, tubular basophilia	No information reported	41.1 (male) 44.7 (female)	260	No evidence of endocrine disruption

1-year dog oral study	1/2	↓body wt, haematological and clinical chemical findings, ↑liver wt, porphyrin deposition.	No information reported	5	40	No evidence of endocrine disruption
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↓body wt, ↓body wt gain, haematological and clinical chemical findings, ↑liver wt, periportal hypertrophy/ eosinophilia, chronic progressive nephropathy, osteo-renal syndrome including hyperplasia of the parathyroid. No carcinogenic potential.	No information reported	15.2 (male) 17.6 (female)	61.3 69.7	Chronic renal failure is accompanied by bone disease. Vitamin D cannot be synthesised, therefore Calcium falls and parathyroid hormone (PTH) increases with subsequent effects on bone. Therefore the primary effect, chronic nephropathy caused by the substance, may potentially lead to a secondary increase in PTH. This may be considered evidence of potential endocrine disruption, although by a secondary or even tertiary mechanism, No actual measurement of PTH but hyperplasia of the parathyroid.
2-generation rat oral reproduction study	1/2	Parental and offspring: ↓body wt, ↑liver wt.	No information reported	20 (parental) 120 (reproductive|) 20 (developmental)	120 - 120	No evidence of endocrine disruption
Rat oral developmental and teratogenicity study	1/2	Maternal: ↓plasma total protein, ↓total bilirubin, ↑albumin/globulin ratio Developmental: liver cysts, slightly ↓kidneys, slightly dilated ureters and kinked ureters	No information reported	200 (maternal) 200 (developmental)	1000 1000	No evidence of endocrine disruption
Rabbit oral developmental and teratogenicity study	1/2	Maternal and developmental: no effects	No information reported	1000 (maternal and developmental)	-	No evidence of endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Osteo-renal syndrome observed in rat long-term study involving the parathyroid (hyperplasia) - secondary consequence of chronic renal nephropathy. No actual PTH measurements.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	The osteo-renal syndrome observed may involve the parathyroid, but as no actual PTH measurements are available, an ED MOA has not been shown. The osteo-renal syndrome could be a direct cytotoxic effect of the substance.
Are the effects judged to be relevant to humans?	Yes	Renal failure is accompanied by bone disease in humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	The evidence establishes that the substance is not an endocrine disrupter.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**There are data available from a rat long-term study which may be indicative of endocrine disruption (potentially via increased PTH). However, further information is necessary.**
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	There is evidence of potential endocrine disruption but further study is necessary.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is evidence of potential endocrine disruption but further study is necessary.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is evidence of potential endocrine disruption but further study is necessary.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.19 Human Health Endocrine Disruption Evaluation for Metalaxyl-M

Substance details		
Substance Name	**Metalaxyl-M**	
Substance Synonyms	metalaxyl-M (ISO) (*R*)-2-[(2,6-dimethylphenyl)-methoxyacetylamino]propionic acid methyl ester mefenoxam	
Substance CAS Number	70630-17-0	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (1999)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xn; R22 Xi; R41 Acute Tox. 4 * Eye Dam. 1	 Harmful if swallowed. Risk of serious damage to eyes. Harmful if swallowed. Causes serious eye damage.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2-year rat oral long-term toxicity and carcinogenicity study	1	Increased liver weight Periacinar fatty vacuolation	No information reported	2	9.43	No evidence of endocrine effects

2-year mouse oral long-term toxicity and carcinogenicity study	1	Decreased bodyweight gain	No information reported	25	129	No evidence of endocrine effects
3- generation rat oral reproduction study	1	Hepatomegaly in adult F2B females	No information reported	Reproductive: >58 Systemic: 13	Reproductive: - Systemic: 58	No evidence of endocrine effects
Rat oral developmental and teratogenicity study	1	Decreased bodyweight gain and food consumption in dams	No information reported	Maternal: 10 Developmental:250	Maternal:50 Developmental: 0	No evidence of endocrine effects
Rat oral developmental and teratogenicity study	1	Clinical signs Decreased bodyweight in dams	No information reported	Maternal: 50 Developmental: >400	Maternal: 250 Developmental: -	No evidence of endocrine effects
Rabbit oral developmental and teratogenicity study	1	Decreased bodyweight gain and food consumption in dams	No information reported	Maternal: 150 Developmental: >300	Maternal:300 Developmental: -	No evidence of endocrine effects

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects occur in the liver in long term studies and reduced bodyweight is observed in reproductive and developmental studies. These effects do not demonstrate that an endocrine mode of action is taking place.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are the effects judged to be relevant to humans?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	No effects potentially related to an endocrine mechanism of action were observed.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is sufficient reliable information with which to categorise the substance.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**There is no evidence of endocrine disruption in a full range of regulatory tests.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.20 Human Health Endocrine Disruption Evaluation for Metrafenone

Substance details		
Substance Name	**Metrafenone**	
Substance Synonyms	-	
Substance CAS Number	**220899-03-6**	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (2003)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2-year rat oral long-term toxicity and carcinogenicity study	1	Decreased bodyweight gain. Increased relative liver weights. Increased incidence of histopathological findings in the liver. Increased kidney weights and increased incidence and severity of chronic nephropathy. Increased incidence of	No information reported	25-30	260-320	No evidence of an effect on the endocrine system.

		hepatocellular adenomas.				
18-month mouse oral long-term toxicity and carcinogenicity study	1	Increased liver weights and increased incidence of hepatocellular hypertrophy and chronic nephropathy. Increased incidence of liver neoplasms.	No information reported	39-53	156-223	No evidence of an effect on the endocrine system.
Two-generation rat oral reproduction study	1	Increased liver weights in parents and increased incidence and severity of hepatocellular hypertrophy. Decreased pup weights. No effects on reproductive parameters.	No information reported	39 parental 79 offspring 79 reproductive	79 parental 811 offspring 811 reproductive	No evidence of an effect on the endocrine system.
Rat oral developmental and teratogenicity study	1	No effects.	No information reported	1000	-	No evidence of an effect on the endocrine system.
Rabbit oral developmental and teratogenicity study	1	Decreased maternal bodyweights and food consumption. Increased liver weights and histopathological effects in the liver. Single incidence of premature delivery.	No information reported	50 maternal 50 developmental 700 teratogenicity	350 maternal 350 developmental -teratogenicity	The premature delivery may have been caused by endocrine effects, but as this was a single incident and mechanistic data is not available to indicate any plausible endocrine mechanism.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects do not indicate an endocrine mode of action.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence is available to suggest an endocrine mode of action.
Are the effects judged to be relevant to humans?	N/A	Effects resulting from endocrine disruption are not present in the available studies. The effects observed are relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	Effects resulting from endocrine disruption are not present in the available studies.

Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, metrafenone is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.21 Human Health Endocrine Disruption Evaluation for Myclobutanil

Substance details		
Substance Name	**Myclobutanil (ISO)**	
Substance Synonyms	2-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)hexanenitrile	
Substance CAS Number	88671-89-0	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (2005). A brief search for recent relevant studies found the following additional information: Goetz A K, Ren H, Schmid J E, Blystone C R, Thillainadarajah, I, Best D S, Nichols H P, Strader, L F, Wolf D C, Narotsky, M G, Rockett J C and Dix, D J (2007) Disruption of testosterone homeostasis as a mode of action for the reproductive toxicity of triazole fungicides in the male rat. *Toxicological Sciences*, 95(1), 227-239 Okubo T, Yokoyama Y, Kano K, Soya Y and Kano, I (2004) Estimation of Estrogenic and Antiestrogenic Activities of Selected Pesticides by MCF-7 Cell Proliferation Assay. *Archives of Environmental Contamination and Toxicology*, 46(4), 445-453.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	 Repr. Cat. 3; R63 Xn; R22 Xi; R36 N; R51-53	 Possible risk of harm to the unborn child Harmful if swallowed Irritating to eyes Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Repr. 2 H361d*** Acute Tox. 4 * H302 Eye Irrit. 2 H319 Aquatic Chronic 2 H311	Suspected of damaging the unborn child Harmful if swallowed Causes serious eye irritation Toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	↓Body wt, hepatocellular cell necrosis, kidney epithelial pigmentation, ↑number of small follicles in the thyroid, vacuolation of adrenal cortex	No information reported	51.5	158	Effects on the thyroid and adrenal could indicate endocrine disruption.
1-year dog oral study	1/2	Histopathological findings in liver; slight clinical chemistry and slight haematological effects	No information reported	14.3	54.2	No evidence of endocrine disruption
2-year rat oral long-term toxicity and carcinogenicity study (2 studies)	1/2	Testicular atrophy Testes: aspermatogenesis Epididymides: hypospermia cellular debris	No information reported	2.5 -	9.9 106	Adverse effects on the male reproductive system could be due to endocrine disruption
2-generation rat oral reproduction study	1/2	↓females delivering litters, ↑still-born pups, ↓wt gain offspring's during lactation. Testicular, epididymides lesions, prostate atrophy, slight ↓body wt in P2 males prior to mating, single liver cell necrosis.	No information reported	16 (reproduction) 16 (systemic)	80 80	Adverse effects on the male and the female reproductive systems /functions could be due to endocrine disruption
Rat oral developmental and teratogenicity study	1/2	Maternal: clinical signs of toxicity. Developmental: altered viability index.	No information reported	94 (maternal) 31 (developmental)	312.6 93.8	No clear evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1/2	Maternal: clinical signs, ↓body wt. Developmental: ↑number of resorptions/litter, ↑abortions and resorptions, ↓viability index	No information reported	60 (maternal) 60 (developmental)	200 200	Developmental toxicity in the presence of maternal toxicity. Overall, no clear evidence of endocrine disruption.
Other *in vivo* data from published literature Wistar male rats exposed to myclobutazin – Goetz *et al*. (2007)	2	Reduced litter survival Impaired insemination and fertility Increased serum testosterone at PND92/99	The potential mechanism is demasculinisation of the spinal nucleus of the bulbocavernosus (SNB) The potential mechanism is increased testicular steroidogenesis	500 mg/kg diet 500 mg/kg diet 5.3.1 5.3.2	5.3.8 5.3.9 2000 mg/kg diet 2000 mg/kg diet 5.3.10	5.3.16 5.3.17 These reproductive effects are consistent with the disruption of testosterone homeostasis as a key event in triazole-induced reproductive toxicity

		Increased relative liver weight at Postnatal day (PND) 1, 50 and 92		5.3.3 5.3.4 500 mg/kg diet 5.3.5 5.3.6 500 mg/kg diet 5.3.7	5.3.11 5.3.12 5.3.13 2000 mg/kg diet 5.3.14 5.3.15 2000 mg/kg diet	
Mechanistic (*in vitro* and *in vivo*) data Activation of the estrogen receptor using the MCF cell proliferation assay – Okubo *et al*. (2004)	2	No effect on MCF cell proliferation assay Suppressive effect on cell proliferation induced by 30 pM 17β-estradiol	No activation of the estrogen receptor Myclobutanil has the capacity to bind to ERα a and may exert its activity by competing at the level of ERα	28.88 mg/l (≥100 µM) 2.89 mg/l (10 µM)	5.3.18 5.3.19 Not relevant 28.88 mg/l (100 µM)	No effect at the highest concentration tested Myclobutazin was found to have strong antiestrogenic activity

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There is evidence of adverse effects on the male reproductive system (and the female reproductive system to a lesser extent) which could be due to endocrine disruption. The effects on thyroid and adrenal are equivocal as they were seen in the rat in the 90-day study but not in longer studies.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	There is some mechanistic information to show an endocrine mediated mode of action for myclobutanil in mammals, possibly through increased testicular steroidogenesis.
Are the effects judged to be relevant to humans?	Yes	There are no reasons to suggest that the effects on the male reproductive system are not relevant to humans
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	The toxic effects that may be due to endocrine disruption are not observed at or below the STOT-RE Category 1 guidance values

Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	An detailed ecotoxicological assessment has been carried out on this substance as part of the project
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is evidence of adverse effects on the male reproductive system (and the female system to a lesser extent) which could be due to endocrine disruption with also some mechanistic information.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Although there are effects that raise a concern for endocrine disruption, these are not at or below the STOT-RE Category guidance values and there is limited information on the mode of action.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	**Yes**	**There are effects that raise a concern for endocrine disruption and there is limited information on a possible mode of action.**
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The substance is considered to be an endocrine disrupter based on the available data.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.22 Human Health Endocrine Disruption Evaluation for Prochloraz

Substance details						
Substance Name	**Prochloraz**					
Substance Synonyms	N-Propyl-N-(2,4,6-trichlorophenoxy)ethyl-imidazole-1-carboxamide					
Substance CAS Number	67747-09-5					
Substance EC Number	266-994-5					
Data Source(s)	European Union Draft Assessment Report (2007) OECD (2011) Guidance Document (GD) on Standardized Test Guidelines for Evaluating Chemicals for Endocrine Disruption (No. 150). Case Studies using example chemicals – Prochloraz. ENV/JM/TG/EDTA(2011)12					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xn; R22 N; R50-53 Acute Tox. 4 * Aquatic Acute 1 Aquatic Chronic 1	 Harmful if swallowed. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Harmful if swallowed. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1	↑liver wt, ↑ovary wt, thyroid wt, ↓prostate, seminal vesicle wt.	No information reported	25	100	Effects on ovaries, prostate and thyroid could be due to endocrine disruption.
2-year rat oral long-term toxicity and carcinogenicity study	1	Increased liver weight and histopathological changes.	No information reported	5.1 males 6.4 females	21.5 males 28 females	No evidence of endocrine mediated effects.

18-month mouse oral long-term toxicity and carcinogenicity study	1	Increased liver weight, histopathological changes and tumours.	No information reported	7.5 males 8.8 females	33 males 36 females	No evidence of endocrine mediated effects. This could be due to the fact that they are older studies using lower doses than the recent more endocrine disrupter-specific studies.
2-generation rat oral reproduction study	1	Increased parental mortality, impairment of bodyweight gain and bodyweight, increased adverse clinical signs and increased liver weight in males. Increased gestation and dystocia. Decreased mean litter size and weight, increased total litter loss, decreased live birth index and viability index, impaired growth and adverse effects on organ weights (liver, brain an thymus).	No information reported	Parental 13 males 14 females Reproductive 14 males 18 females Developmental 13 males 14 females	Parental 57 males 58 females Reproductive 57 males 58 females Developmental 57 males 58 females	Effects occurred at doses where there is generalised toxicity. However, the effects could be due to endocrine disruption.
Rat oral developmental and teratogenicity study	1	Increased maternal salivation and nose rubbing. Decreased food consumption and bodyweight gain. Increased liver weight. Decreased litter size, implantation and viability index and increased number of dead foetuses. Decreased mean foetus weight. Calcification of sternebrae.	No information reported	25 maternal 25 development	100 maternal 100 development	Effects occurred at doses where there is generalised toxicity. However, the effects could be due to endocrine disruption.
Rabbit oral developmental and teratogenicity study	1	Decreased maternal food consumption and bodyweight gain. Increased liver weight. Increased number of non-pregnant animals and increased total litter loss. Increased foetal resorption.	No information reported	40 maternal 40 development	160 maternal 160 development	Effects occurred at doses where there is generalised toxicity. However, the effects could be due to endocrine disruption.

In vitro endocrine disruption studies	2	AR binding, antagonism ER reporter gene assays, antagonism H295 steroidogenesis assay, ↓testosterone, E2 Aromatase, inhibition	Both androgenic and oestrogenic antagonism, steroidogenesis disruption			Specific *in vitro* tests for endocrine disruption using human receptors and cells indicate that endocrine disruption could have an effect on reproductive systems.
In vivo endocrine disruption studies	1/2	Hershberger, ↓sexual accessory tissues (SAT), ↓T4 and TSH. Pubertal development and thyroid function, ↓SAT, ↓testosterone, ↑progesterone and hydroxyprogesterone	Effects consistent with effects on reproductive systems and thyroid hormones.	- 7.8	50 15.6	Specific *in vivo* tests for endocrine disruption suggest that endocrine disruption is having an effect on reproductive systems and thyroid hormones.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	The results of regulatory tests indicate some effects that could be due to endocrine disruption. More specific *in vitro* and *in vivo* tests for endocrine disruption indicate effects on reproduction and thyroid function due to endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	The specific *in vitro* and *in vivo* tests for endocrine disruption demonstrate that endocrine disruption is a plausible explanation for the effects on the reproduction systems (oestrogen and androgen antagonism and disruption of steroidogenesis) and the thyroid (effects on T4 and TSH).
Are the effects judged to be relevant to humans?	Yes	Differences in thyroid function between humans and rats may indicate that the effects on thyroid hormones are less relevant to humans. However, the relevance to humans of the repro effects cannot be excluded..
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Serious endocrine disrupting effects have not been observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	A detailed assessment has been carried out as part of the project. In agreement with HSE.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is a full range of regulatory tests and specific in vitro and in vivo tests for endocrine disruption available.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Serious endocrine disrupting effects have not been observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	**Yes**	**ED-mediated adverse effects occurred above the STOT-RE Cat 1 guidance values.**
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The substance is considered an endocrine disrupter on the basis of the available data.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.23 Human Health Endocrine Disruption Evaluation for Propamocarb hydrochloride

Substance details	
Substance Name	**Propamacarb hydrochloride**
Substance Synonyms	Propyl 3-(dimethylamino)propylcarbamate hydrochloride (IUPAC) Propyl N-[3-(dimethylamino)propyl]carbamate hydrochloride (1:1) (CAS)
Substance CAS Number	25606-41-1
Substance EC Number	-
Data Source(s)	European Union Draft Assessment Report (2004). A brief search for recent relevant studies located the following *in vitro* study which is summarised below: Bretveld RW, Thomas CM, Scheepers PT, Zielhaus GA and Roeleveld N (2006) Pesticide exposure: the hormonal function of the female reproductive system disrupted? *Reproductive Biology and Endocrinology*, **4**, 30.

Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	Vacuolation of the choroid plexus and the lacrimal glands, ↓Body wt and body wt gain.	No information reported	104 (male) 130 (female)	434 540	No evidence of endocrine disruption
1-year dog oral study	1/2	Vacuolar alteration in duodenum (Brunner's glands), tracheal glands, stomach (pyloric glands), lungs (bronchial glands).	No information reported	Impossible to determine	39 (male); 42 (female)	No evidence of endocrine disruption

2-year rat oral long-term toxicity and carcinogenicity study	1/2	↓body wt, body wt gain, food & water consumption; Vacuolation of the choroid plexus and lacrimal gland. No carcinogenic potential.	No information reported	84-118 (male) 112-158 (female)	682-985 871-1223	Two further long-term rat studies were carried out. One gave similar results while the older study observed no treatment-related effects. No evidence of endocrine disruption.
2-generation rat oral reproduction study	1/2	Parental: ↓F0, female body wt and food consumption Reproductive: ↓ in gestation length (not considered relevant by study authors and DAR as marginal and within historical records) Development ↓mean pup wt in F1 and F2 offspring Day14 & 21 lactation	No information reported	57.6 (parental male) 15 (parental female) 366.2 (reproductive male) 568.8 (reproductive female) 57.6 (developmental male) 90.1 (developmental female)	336.2 90.1 Reproductive cannot be estimated 366.2 568.8	No clear evidence of endocrine disruption.
2-generation rat oral reproduction study	1/2	↓F0, F1 female body wt gain ↓food consumption in F0 female , F1 male. Specific vacuolar changes in epithelial cells of the choroid plexus in F0, F1 ↓Sperm concentration and count in F1 epididymis, ↓F1 offspring pup viability, mean pup wt and body wt at vaginal opening, ↓F2 pup viability	No information reported	37.5 (parental) 37.5 (reproductive) 150.1 (developmental)	150.1 150.1 750.5	Some evidence of disruption of the male reproductive system (sperm concentration and count), but same findings not seen in previous 2-generation study.
Rat oral developmental and teratology study	1/2	Maternal: ↓body wt, body wt gain, uterus wt and corrected body wt gain. Developmental: ↑number of small foetuses. ↓Wt of live foetuses.	No information reported	123 (maternal.) 31 (developmental)	453 123	No clear evidence of endocrine disruption. The decreased uterus weight is most likely a sign of generalised toxicity.

Rabbit oral developmental and teratology study	1/2	Maternal: body wt, corrected body wt gain, food and relative food consumption.	No information reported	76 (maternal) 269 (developmental)	269 Developmental LOAEL could not be estimated	No evidence of endocrine disruption
In vitro assays	2		Weak stimulation of CYP19 aromatase activity *in vitro.* Increase in oestrogen biosynthesis.	N/A	N/A	Very weak response on aromatase activity in vitro.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	The only effects possibly related to endocrine disruption were effects on sperm. However, these effects were not repeated in another 2-generation study.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	The weak response in the *in vitro* aromatase assay does not demonstrate an ED MOA.
Are the effects judged to be relevant to humans?	N/A	There is no reliable evidence of an endocrine disruption effect.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	There is no reliable evidence of an endocrine disruption effect.
***Would there be benefits to carry out an ecotoxicological endocrine disruption assessment*?**	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is no clear evidence of endocrine disruption effects
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests.**

endocrine disrupters based on currently available data		**Therefore, propamocarb hydochloride is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.24 Human Health Endocrine Disruption Evaluation for Prothioconazole

Substance details	
Substance Name	**Prothioconazole (ISO)**
Substance Synonyms	(RS)-2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-2,4-dihydro-1,2,4-triazole-3-thione (IUPAC)
Substance CAS Number	178928-70-6
Substance EC Number	-
Data Source(s)	European Union Draft Assessment Report (2007)

Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
90 day study in Dogs	1/2	Kidney histopathological changes and liver ↑ALT and liver wt. but no liver histological findings ↓TSH and T4	Thyroid hormone changes could secondary to liver changes	25	100	Similar liver and kidney findings in short-term studies in rats and dogs
2 year rat (gavage), long-term and carcinogenicity study	1/2	Gross necropsy and microscopic findings in the kidneys including ↑weight and severity of chronic progressive nephropathy. Gross necropsy	No information reported	5	50	A further rat and mouse gavage studies gave similar results indicating liver and kidney effects.

		and microscopic findings in the liver Slight ↓T4 and inconsistent changes in T3 and TSH No carcinogenic effects				
2-generation study in rats (gavage)	1/2	Slight body wt and organ wt effects ↓pup wt gain, ↓pup spleen wt and delayed preputial separation Disruption to the oestrus cycle, ↓implantation sites and litter size, ↑time to insemination and ↑duration of gestation	No information reported	Parental animals: 9.7 Offspring: 95.6 Reproductive effects: 95.6	Parental toxicity: 95.6 Offspring: 726 Reproductive effects: 726	Some European Member States suggested that the disruption to the oestrus cycle should be considered to be adverse.
Developmental toxicity study in rats (gavage)	1/2	↓body wt gains, ↑water consumption ↓foetal wt, ↑incidence of engorged placentas, renal pelvis dilatation and incomplete ossification, ↑incidence of microphthalmia and rudimentary supernumerary ribs.	No information reported	Maternal toxicity: 80 Foeto- and developmental toxicity: 500	Maternal toxicity: 500 Foeto- and developmental toxicity: 1000	-
Developmental toxicity study in rats (gavage) using a strain with a virtually zero incidence of microphthalmia	1/2	↓net body wt gain, ↑water consumption, ↓food consumption and clinical chemical indications for functional impairments of kidneys and liver. Foetal supernumerary rudimentary ribs (secondary to maternal toxicity).	No information reported	Maternal toxicity: 80 Foeto- and developmental toxicity: 80	Maternal toxicity: 750 Foeto- and developmental toxicity: 750	An overall developmental NOAEL of 20 mg/kg bw/day was agreed by the experts.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There are slight alterations to thyroid hormone in 90-day and 2-year studies in experimental animals. It is suggested that the thyroid effects may be secondary to changes in the liver and reproductive/developmental effects (delayed preputial separation and reduction in implantation sites) might be due to generalised toxicity. There is disruption to the oestrus cycle in a 2-generation reproductive study. However, there is no available evidence for a mechanism of endocrine disruption action.

Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	The results indicate a potential endocrine disruption effect on thyroid and reproduction but there is no available data on a possible mode of action.
Are the effects judged to be relevant to humans?	Yes	There is no evidence to suggest that effects may not be relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	The substance is not an established endocrine disrupter.
***Would there be benefits to carry out an ecotoxicological endocrine disruption assessment*?**	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**There are slight effects on the thyroid and on reproduction but no information is available on a possible mode of action. Therefore more information is required on a possible mechanism of action.**
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	The evidence is insufficient to suggest that the substance is an endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	The evidence is insufficient to suggest that the substance is an endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	Further information is required.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.25 Human Health Endocrine Disruption Evaluation for Pyraclostrobin

Substance details		
Substance Name	**Pyraclostrobin**	
Substance Synonyms	-	
Substance CAS Number	**175013-18-0**	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (2002)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
24-month rat oral long-term toxicity and carcinogenicity study	1	Reduced bodyweight and food consumption, liver necrosis.	No information reported	3.4 male 4.6 female	9 male 12.3 female	No evidence of an endocrine effect.
18-month mouse oral long-term toxicity and carcinogenicity study	1	Reduced bodyweight.	No information reported	4.1 male 4.8 female	17.2 male 20.5 female	No evidence of an endocrine effect.

2-generation rat oral reproduction study	1	Reduced food consumption and bodyweight gain in parents. Reduced pup bodyweight gain, organ weight changes and a delay in vaginal opening.	No information reported	8.2 parental 8.2 reproductive	32.6 parental 32.6 reproductive	Effects occurred at doses where maternal toxicity was manifested, therefore are most likely to be secondary to such toxicity.
Rat oral developmental and teratogenicity study	1	Reduced food consumption and bodyweight gain in dams. Increased variations in pups.	No information reported	10 maternal 25 developmental	25 maternal 50 developmental	Effects occurred at doses where maternal toxicity was manifested, therefore are most likely to be secondary to such toxicity.
Rabbit oral developmental and teratogenicity study	1	Reduced food consumption and bodyweight gain in dams. Increased skeletal malformations, increased resorptions and postimplantation losses, reduced number of live foetuses.	No information reported	<5 maternal 5 developmental	5 maternal 10 developmental	Effects occurred at doses where maternal toxicity was manifested, therefore are most likely to be secondary to such toxicity.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects do not indicate a concern for endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence is available to suggest an endocrine mode of action.
Are the effects judged to be relevant to humans?	N/A	Effects resulting from endocrine disruption are not present in the available studies.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	Adverse effects do not indicate an endocrine mode of action.
***Would there be benefits to carry out an ecotoxicological endocrine disruption assessment*?**	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, pyraclostrobin is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.26 Human Health Endocrine Disruption Evaluation for Silthiofam

Substance details						
Substance Name	**Silthiofam**					
Substance Synonyms	4,5-Dimethyl-2-trimethylsilanyl-thiophene-3-carboxylic acid allylamide (IUPAC) 4,5-Dimethyl-N-(2-propenyl)-2-(trimethylsilyl)-3-thiophenecarboxamide (CA)					
Substance CAS Number	175217-20-6					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2000). A brief search for more recent relevant studies did not yield further information.					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day oral rat study with pilot reproduction phase	1/2	↑organ weight, enzymes (ALP, AST, ALT and GGT), bilirubin and cholesterol, and/or microscopic changes that involved hepatocytes, Kupffer cells and the biliary system. ↑platelet counts. Kidneys of abnormal colour, ↑organ weight and/or blood urea nitrogen. No effects on reproduction.	No information reported	NOELs 15 (males) 18 (females) Reproductive toxicity 290 (males) 334 (females)	 150 -	No evidence of endocrine disruption.

1-year oral dog study	1/2	↓serum potassium and phosphorous, ↑liver weight, ↑marker enzymes	No information reported	20 (NOAEL) 5 (NOEL)	80 20	No evidence of endocrine disruption.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↑liver wt, increased serum ↑GT (males) and/or microscopic changes. Microscopic change included hepatocellular vacuolization and hypertrophy, eosinophilic foci and/or cystic degeneration. ↑increase in incidence of hepatocellular and thyroid tumours in high dose males.	No information reported	6.4 (NOAEL females) 50.5 (NOEL) NOEL for carcinogenicity 52 (males) 195 (females)	50 150 150	The detection of thyroid tumours may indicate an endocrine effect.
18-month mouse oral long-term toxicity and carcinogenicity study	1/2	Effects on the liver and gall bladder, ↑hepatocellular adenoma in females at the high dose level (855 mg/kg bw/day) which was also hepatotoxic.	Liver only tumours at hepatotoxic dose may indicate a non-genotoxic mechanism of carcinogenicity based on response to necrosis.	NOELs 141 (males) 203 (females)		No evidence of endocrine disruption.
2-generation rat oral reproduction study	1/2	Systemic toxicity: effects on the liver and adrenal glands (cortical vacuolation). No reproductive toxicity	No information reported	Systemic toxicity 25 (males) 30 (females) Reproductive toxicity 256.5 (males) 292.6 (females)		Effects on the adrenals may indicate an endocrine effect.
Rat oral developmental and teratogenicity study	1/2	Maternal: ↑liver wt. Developmental (all at maternal toxicity dose): ↓foetal wt, ↑incidence of a single malformation (cleft palate) and, ↓/↑certain skeletal variations were considered related to treatment. slight ↑dead foetuses.	No information reported	Maternal 50 Developmental toxicity 500	1000	No evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1/2	No treatment related effects were identified	No information reported	Maternal and developmental 60	-	No evidence of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Thyroid tumours and effects on adrenal gland may be indicative of endocrine disruption but no mechanistic evidence.

Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	Effects on thyroid and adrenals may be indicative of endocrine disruption, but mechanistic information not available.
Are the effects judged to be relevant to humans?	Yes	No evidence that the effects are not relevant to humans, although rats are generally more susceptible to thyroid effects than humans
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	-
Would there be benefits to carry out an ecotoxiological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Category	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**As the risk assessment is over 10 years old it may be prudent to investigate possible endocrine effects using more recent techniques for thyroid hormones and adrenals.**
(B**)** Endocrine disrupter more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	A weight of evidence suggests that it is not an endocrine disrupter but evaluation of more recent techniques might be prudent.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.27 Human Health Endocrine Disruption Evaluation for Tebuconazole

Substance details		
Substance Name	**Tebuconazole**	
Substance Synonyms	1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazol-1-ylmethyl)pentan-3-ol	
Substance CAS Number	**107534-96-3**	
Substance EC Number	403-640-2	
Data Source(s)	European Union Draft Assessment Report (2006) Hass U, Christiansen M, Boberg J and 6 others (2012) Evaluation of tebuconazole, triclosan, methylparaben and ethylparaben according to the Danish proposal for criteria for endocrine disrupters. Danish Centre on Endocrine Disrupters. Kjaerstad MB, Taxvig C, Nelleman C, Vinggard AM and Andersen (2010) Endocrine disrupting effects *in vitro of conazole anti-fungals used as pesticides and pharmaceuticals. Reproductive Toxicology, 30, 573-582.* Sanderson JT, Boerma J, Lansbergen GW and van den Berg (2002) Induction and inhibition of aromatase (CYP19) activity by various classes of pesticides in H295R human adrenocortical carcinoma cells. Toxicology and Applied Pharmacology, 182, 44-54. Taxvig C, Hass U, Axelstad M, Dalgaard M, Boberg J, Andeasen HR and Vingaard AM (2007) Endocrine-disrupting activities in vivo of the fungicides tebuconazole and epoxiconazole. Toxicol. Sci. 100, 464-473. Taxvig C, Vingaard AM Hass U, Axelstad M, Metzdorff S and Nelleman C (2008) Endocrine-disrupting properties *in vivo* of widely-used azole fungicides. Int. J. Andrology. 31, 170-176.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	 Repr. Cat. 3; R63 Xn; R22 N; R51-53	 Possible risk of harm to the unborn child. Harmful if swallowed. Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Repr. 2 Acute Tox. 4 * Aquatic Chronic 2	Suspected of damaging the unborn child. Harmful if swallowed. Toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2-year rat oral long-term and carcinogenicity study	1	Increased incidence of pigment deposits in Kupffer star cells. Increased food consumption.	No information reported	15.9 males 22.8 females	55 males 86.3 females	No evidence of endocrine mediated effects.
21-month mouse oral long-term toxicity and carcinogenicity study	1	Increased incidence of liver tumours. Pronounced liver toxicity.	No information reported	<85 males <103 females	280	No evidence of endocrine mediated effects.
2-generation rat oral reproduction study	1	Decreased litter size and food consumption decreased weight gain and organ weights.	No information reported	21.6 male 27.8 female	72 male 97 female	No evidence of endocrine mediated effects.
Rat oral developmental and teratogenicity study	1	Reduced weight gain and liver affection. Increased number of resorptions, malformations and runts. Decreased number of live foetuses and foetal body weight.	No information reported	10 maternal 30 foetal	30 maternal 100 foetal	Effects occurred at doses where maternal toxicity was manifested, therefore are most likely to be secondary to such toxicity.
Rat oral developmental and teratogenicity study	1	Decreased food consumption and weight gain in dams. Malformation (external and skeletal).	No information reported	30 maternal 10 foetal	100 maternal 30 foetal	Effects in foetuses occurred at a lower dose than maternal toxicity, suggesting that the effects are not secondary to maternal toxicity. In the absence of further mechanistic data, perturbation of the endocrine system cannot be discounted.
Mouse oral developmental and teratogenicity study	1	No maternal toxicity. Increased number of runts.	No information reported	100 maternal 10 foetal	-maternal 30 foetal	Effects in foetuses occurred at a lower dose than maternal toxicity, suggesting that the effects are not secondary to maternal toxicity. In the absence of further mechanistic data, perturbation of the endocrine system cannot be discounted.

Mouse oral developmental and teratogenicity study	1	Increased enzyme activity in livers. Increased post-implantation loss. Increased external, skeletal and visceral anomalies.	No information reported	10 maternal 30 foetal	30 maternal 100 foetal	Effects occurred at doses where maternal toxicity was manifested, therefore are most likely to be secondary to such toxicity.
In vitro endocrine disruption studies	2	Studies on H295R human adrenocortical carcinoma cells: ↓aromatase, ↑progesterone, ↓testosterone and oestradiol, enzyme inhibition. MCF-cell proliferation assay: Anti-oestrogenic effect, Inhibited response induced by 17β-oestradiol and testosterone. Anti-androgenic in androgen receptor reporter gene assay.	Anti-oestrogenic and anti-androgenic mode of action in vitro	-	-	*In vitro* results that could explain reproductive and developmental toxicity.
In vivo endocrine disruption studies	2	Hershberger assay no effect on reproductive organ wt or on hormone levels. Pregnant females dosed from GD (gestation day) 7 to GD 21: ↑gestational length ↑plasma progesterone in the mothers, ↑anogenital distance (AGD) in pups indicating a virilising effect on the females. No effect on AGD was seen in the newborn male pups. ↓testosterone in testis from the male foetuses, ↑progesterone and 17α-hydroxyprogesterone levels. ↑number of nipples in the male pups and a tendency towards ↓plasma testosterone concentration in male pups. Pregnant dams were exposed from GD 7 to PND: ↑gestation length and pup mortality, virilised female pups, (↑AGD) and demasculinised the male pups (↑retained nipples)	Virilisation of females and feminisation of male pups.	50	100	These *in vitro* and *in vivo* results together with the observations from the regulatory tests indicate that there is a plausible mode of action for effects on the male and female reproductive systems involving endocrine disruption

		and affected steroid hormone levels in dams				

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Adverse reproductive effects could be related to endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	The adverse effects on reproduction and development could be explained by an endocrine disruption mode of action as suggested by the results of recent *in vitro* and *in vivo* data.
Are the effects judged to be relevant to humans?	Yes	The human relevance of the repro effects observed cannot be excluded.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	The endocrine disruption-mediated adverse effects were not observed at or below the STOT-RE Category 1 guidance values.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	A detailed assessment has been carried out as part of the project.
Overall grouping of the substance regarding its endocrine disrupting properties		
Category	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There are a full range of regulatory tests together with specific endocrine disruption assays *in vitro* and *in vivo*
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	The endocrine disruption-mediated adverse effects were not observed at or below the STOT-RE Category 1 guidance values.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	**Yes**	The endocrine disruption-mediated adverse effects were observed above the STOT-RE Category 1 guidance values.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The substance is considered an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.28 Human Health Endocrine Disruption Evaluation for Thiophanate-methyl

Substance details		
Substance Name	**Thiophanate-methyl**	
Substance Synonyms	1,2-di-(3-methoxycarbonyl-2-thioureido)benzene	
Substance CAS Number	23564-05-8	
Substance EC Number	245-740-7	
Data Source(s)	European Union Draft Assessment Report (2003)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Muta. Cat. 3; R68 Xn; R20 R43 N; R50-53 Muta. 2 Acute Tox. 4 * Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	 Possible risk of irreversible effects. Harmful by inhalation. May cause sensitization by skin contact. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Suspected of causing genetic defects. Harmful if inhaled. May cause an allergic skin reaction. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1	Anaemia. Increased thyroid, liver and kidney weight.	No information reported	14	140	Some evidence of endocrine disruption on thyroid hormones.

		Adrenal fatty degeneration.				
1-year dog oral study	1	Increased thyroid weight and histopathological changes. Increased liver weight.	No information reported	8	40	Some evidence of endocrine disruption on thyroid hormones and thyroid pathology.
2-year rat oral long-term toxicity and carcinogenicity study	1	Reduced bodyweight, clinical chemistry and urinalysis changes, increased kidney, liver and thyroid weights, increased mortality, anaemia and increased incidence of thyroid follicular cell adenomas.	Effect on thyroid hormone (T3 and T4) production or release.	8.8 male 10.2 female	60 approx	Some evidence of endocrine disruption on thyroid hormones and thyroid pathology.
18-month mouse oral long-term toxicity and carcinogenicity study	1	Increased mortality, bodyweight reduction, increased liver and thyroid weight and histopathological changes, hepatocellular adenomas.	No information reported	23.7 male 28.7 female	120 approx	Effects on the thyroid could be related to endocrine disruption.
2-generation rat oral reproduction study	1	Reduced bodyweight gain in parents and offspring, target organs, liver and thyroid.	No information reported	Parental and reproduction 15 male 18 female	Parental and reproduction 46 males 55 females	Effects on the thyroid could be related to endocrine disruption.
Rat oral developmental and teratogenicity study	1	Slight reduction in maternal bodyweight gain.	No information reported	Maternal 300 Developmental 1000	Maternal 1000 Developmental -	No effects that can be attributed to endocrine disruption.
Rabbit oral developmental and teratogenicity study	1	Reduced bodyweight gain, increased skeletal variations, slightly increased incidence of total litter loss.	No information reported	Maternal 1000 Developmental 1000	Maternal - Developmental -	Effects on the litter occurred at maternally toxic doses. Overall, no evidence of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Thyroid changes and adenomas have been observed in long term studies.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	Mechanistic studies have demonstrated hormonal disruption in the thyroid.

Are the effects judged to be relevant to humans?	Yes	There is no clear mechanistic information to dismiss human relevance.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	The thyroid effects occur above the STOT-RE Cat 1 guidance values.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is sufficient data from regulatory tests to show that the substance is an endocrine disrupter.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as the thyroid effects occur above the STOT-RE Cat 1 guidance values.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	**Yes**	**Group is appropriate as effects on the thyroid occur above the STOT-RE Cat 1 guidance values.**
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is sufficient data from regulatory tests to show that the substance is an endocrine disrupter..

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.29 Human Health Endocrine Disruption Evaluation for Thiram

Substance details		
Substance Name	**Thiram**	
Substance Synonyms	tetramethylthiuram disulphide	
Substance CAS Number	137-26-8	
Substance EC Number	205-286-2	
Data Source(s)	WHO (1992) Mastorakos, G., Karoutsou, E.I., Mizamtsidi, M., Creatsas, G. (2007) The menace of endocrine disruptors on thyroid hormone physiology and their impact on intrauterine development. *Endocrinology*, **31(3),** 219-237.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	 Xn; R20/22-48/22 Xi; R36/38 R43 N; R50-53	 Harmful by inhalation and if swallowed. Harmful: danger of serious damage to health by prolonged exposure if swallowed. Irritating to eyes and skin. May cause sensitization by skin contact. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Acute Tox. 4 * Acute Tox. 4 * STOT RE 2 * Eye Irrit. 2 Skin Irrit. 2 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	Harmful if inhaled. Harmful if swallowed. May cause damage to organs through prolonged or repeated exposure . Causes serious eye irritation. Causes skin irritation. May cause an allergic skin reaction. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2-year rat oral long-term toxicity and carcinogenicity study	1	Thyroid C cell hyperplasia. Reduced LH surge	No information reported	1.5	7.3	Evidence of endocrine effects.
2-generation rat oral reproduction study	1	Reduced bodyweight.	No information reported	9	-	No evidence of endocrine effects.
Rat oral developmental and teratogenicity study	1	Decreased foetal weight. Reduced ossification. Increase in subcutaneous oedema. Reduced 13th rib size.	No information reported	7.5	15	Evidence of endocrine effects.
Rabbit oral developmental and teratogenicity study	1	Reduced bodyweight gain.	No information reported	Maternal: 2.5 Foetal: 5	Maternal; 5 Foetal: -	No evidence of endocrine effects.
In vitro study using hamsters – Marinovic *et al.*(1997) cited in Mastorakos *et al.*(2007)	4	Effect on the activity of hyperoxidase or disorders in the iodization of thyroglobin	-	<2.40 (<10 µM)	2.40 10 µM	-

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Effects on LH surge and thyroid adenomas were observed
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no conclusive evidence that an ED mode of action is operative for thiram
Are the effects judged to be relevant to humans?	Yes	Effects could be relevant for humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	The substance is not an established endocrine disrupter.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	A detailed assessment has been carried out as part of the project.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**Further information on the mechanism of tumour formation and alteration in LH surge are required.**
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.30 Human Health Endocrine Disruption Evaluation for Toclofos-methyl

Substance details						
Substance Name	**Toclofos-methyl**					
Substance Synonyms	o-(2,6-Dichloro-4-methylphenyl) o,o-dimethyl phosphorothioate					
Substance CAS Number	78617-90-1					
Substance EC Number	260-515-3					
Data Source(s)	European Union Draft Assessment Report (2003)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1	Increased liver weight. Hypertrophy of hepatocytes. Decreased body weight gain. Decreased cholinesterase levels. Decreased food consumption. Several changes of haematological and clinical chemistry parameters.	No information reported	66	653	No evidence of endocrine mediated effects.

1-year dog oral study	1	Increased liver and pancreas weight Decreased prostate weight Increased hepatocytic hypertrophyl Increased alkaline phophatase	No information reported	11	59	Decreased prostate weight occurred, however no functional endocrine effects were observed.
2-year rat oral long-term toxicity and carcinogenicity study	1	No reported adverse effects.	No information reported	42	-	No evidence of endocrine mediated effects.
2-year mouse oral long-term toxicity and carcinogenicity study	1	Decreased cholinesterase levels. Increased glucose. Increased pituitary weight. Decreased thymus weight.	No information reported	32.2	134	Alterations in pituitary and thymus weight may be suggestive of an endocrine mechanism of action.
3-generation rat oral reproduction study	1	No reported adverse effects.	No information reported	Parental 198 Reproduction 198	Parental - Reproduction -	No evidence of endocrine mediated effects.
Rat oral developmental and teratogenicity study	1	Decreased implantation efficiency in the presence of maternal toxicity.	No information reported	Maternal 50 Developmental 50	Maternal - Developmental -	No evidence of an endocrine effect.
Rabbit oral developmental and teratogenicity study	1	Decreased bodyweight gain. Delayed ossification.	No information reported	Maternal 300 Developmental 300	Maternal 1000 Developmental 1000	No evidence of an endocrine effect.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	The effects on pituitary and thymus weights in the mouse without any histopathology cannot be considered clearly related to endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	The available reliable evidence for a full range of regulatory tests does not suggest endocrine disruption. There is no mechanistic information available.
Are the effects judged to be relevant to humans?	No	-

Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	The available reliable evidence for a full range of regulatory tests does not suggest endocrine disruption.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of functional endocrine disruption.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, toclofos-methyl is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.31 Human Health Endocrine Disruption Evaluation for Triazoxide

Substance details		
Substance Name	**Triazoxide**	
Substance Synonyms	1,2,4-Benzotriazine, 7-chloro-3-(1H-imidazol-1-yl)-, 1-oxide	
Substance CAS Number	72459-58-6	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (2007)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
2-year rat oral long-term toxicity and carcinogenicity study	1	Darkly coloured spleens in both sexes.	No information reported	1.25 (males)	>1.25 (males)	No evidence of an endocrine effect
21-month mouse oral long-term toxicity and carcinogenicity study	1	Increased incidence of luphoid hyperplasia in the thymus. Round cell infiltration of the sciatic nerve. Hyperplasia of the lung.	No information reported	0.28 (males)	1.5 (males)	No evidence of an endocrine effect

Multi-generation rat oral reproduction study	1	Parental: Increased spleen weight Offspring: Increased ovarian weight	No information reported	Reproduction: 2.04 (males) Parental: 0.09 (males) Offspring: 0.11	Reproduction: >2.04 (males) Parental: 0.42 (males) Offspring: 0.57	Possible limited evidence of an endocrine effect (ovarian weight in offspring)
Rat oral developmental and teratogenicity study	1	Reduced bodyweight gain in dams.	No information reported	Maternal: 3 Developmental: 10	Maternal: 10 Developmental: >10	No evidence of an endocrine effect
Rabbit oral developmental and teratogenicity study	1	No adverse effects.	No information reported	Maternal: 10 Developmental: 10	Maternal: >10 Developmental: >10	No evidence of an endocrine effect

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Possibly	Increased ovarian weight was observed in a multi generation study in rat offspring. This is the only effect that may be related to endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	The evidence is not strong enough to demonstrate that an endocrine disruption mode of action is plausible.
Are the effects judged to be relevant to humans?	Yes	There is nothing to demonstrate that effects observed are not relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	At present, there is no convincing evidence that triazoxide in an ED
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	Yes	No detailed assessment has been carried out as part of the project as stipulated with HSE

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	Although ovarian weight was increased in rat offspring in a 2-generation study, there was no other finding indicating potential endocrine disruption. Further information is not justified.
(B) Endocrine disrupter more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, triazoxide is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Herbicides

Table B.32 Human Health Endocrine Disruption Evaluation for Bentazone

Substance details		
Substance Name	**Bentazone**	
Substance Synonyms	3-isopropyl-2,1,3-benzothiadiazine-4-one-2,2-dioxide	
Substance CAS Number	25057-89-0	
Substance EC Number	246-585-8	
Data Source(s)	European Union Draft Assessment Report (2003)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Xn; R22 Xi; R36 R43 R52-53	Harmful if swallowed. Irritating to eyes. May cause sensitization by skin contact. Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Acute Tox. 4 * Eye Irrit. 2 Skin Sens. 1 Aquatic Chronic 3	Harmful if swallowed. Causes serious eye irritation. May cause an allergic skin reaction. Harmful to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1	Mortality, decreased bodyweight gain, altered haematological and clinical chemistry parameters.	No information reported	25	75 (approx.)	No evidence of an endocrine effect.
1-year dog oral study	1	Transient decreases in bodyweight, changes in haematological parameters.	No information reported	13	60 (approx.)	No evidence of an endocrine effect.
2-year rat oral long-term toxicity and carcinogenicity study	1	Reduced bodyweight. Effects on blood coagulation, impairment of liver and kidney function.	No information reported	10	40 approximately	No evidence of an endocrine effect.
2-year mouse oral long-term toxicity and carcinogenicity study	1	Transient reduction in bodyweight gain. Impaired blood coagulation, increased testicular calcification (equivocal), proliferative lesions in the liver.	No information reported	12	48 approximately	No evidence of an endocrine effect.
2-generation rat oral reproduction study	2	Reduced parental bodyweight. Reduced pup bodyweight.	No information reported	Parental 56 Offspring 14	Parental 150 approximately Offspring 56	No evidence of an endocrine effect.
Rat oral developmental and teratogenicity study	2	Reduced maternal food consumption and bodyweight. Slightly reduced foetal weight.	No information reported	Maternal 180 Foetal 180	Maternal 360 Foetal 360	No evidence of an endocrine effect.
Rabbit oral developmental and teratogenicity study	2	No substance related findings.	No information reported	Maternal 150 Foetal 150	Maternal - Foetal -	No evidence of an endocrine effect.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	There are no adverse effects potentially linked to endocrine disruption in standard toxicity tests.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	-

Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	-
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, bentazone is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.33 Human Health Endocrine Disruption Evaluation for Bromoxynil

Substance details		
Substance Name	**Bromoxynil**	
Substance Synonyms	3,5-dibromo-4-hydroxybenzonitrile, bromoxynil phenol	
Substance CAS Number	1689-84-5	
Substance EC Number	216-882-7	
Data Source(s)	European Union Draft Assessment Report (2001)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Repr. Cat. 3; R63 T+; R26 T; R25 R43 N; R50-53	Possible risk of harm to the unborn child. Very toxic by inhalation. Toxic if swallowed. May cause sensitization by skin contact. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Repr. 2 Acute Tox. 2 * Acute Tox. 3 * Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	Suspected of damaging the unborn child. Fatal if inhaled. Toxic if swallowed. May cause an allergic skin reaction. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	2	Decreased bodyweight gain. Hepatic enzyme induction.	No information reported	10	40 (approx.)	No evidence of endocrine effects.
1-year dog oral study	2	Increased liver weights, panting and effects on bodyweight gain	No information reported	0.3	1.5	No evidence of endocrine effects.
2-year rat oral long-term toxicity and carcinogenicity study	1	Effects on bodyweight and increased liver weight. Increased incidence of eosinophilic cellular alteration and spongiosis hepatis in the liver.	No information reported	2.6	8.2 approximately	No evidence of endocrine effects.
18-month mouse oral long-term toxicity and carcinogenicity study	1	Increased incidence of combined hepatocellular adenoma/carcinoma. Hepatocellular hypertrophy and degeneration, pigment accumulation in hepatocytes and Kupffer cells.	No information reported	-	3.1	No evidence of endocrine effects.
2-generation rat oral reproduction study	1	Slight adverse effects on somatic growth. Slight retardation of offspring. Slight increase in relative liver and kidney weights.	No information reported	2	6 approximately	No evidence of endocrine effects.
Rat oral developmental and teratogenicity study	1	Decreased maternal uterus weight. Malformations including increases of supernumerary ribs.	No information reported	Maternal 12.5 Foetal 4	Maternal 40 Foetal 12.5	Supernumerary ribs are is unlikely to be linked to endocrine disruption. The decreased uterus weight is a sign of maternal toxicity and not linked to endocrine disruption. Overall, therefore, no evidence of endocrine effects.
Rabbit oral developmental and teratogenicity study	1	No significant effects observed	No information reported	Maternal - Foetal -	Maternal - Foetal -	No evidence of endocrine effects.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	No adverse effects relating to endocrine disruption were observed in the standard toxicity studies.

Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	-
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	-
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, bromoxynil is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.34 Human Health Endocrine Disruption Evaluation for Chloridazon

Substance details						
Substance Name	**Chloridazon (ISO)**					
Substance Synonyms	5-amino-4-chloro-2-phenylpyridazine-3-(2H)-one					
Substance CAS Number	1698-60-8					
Substance EC Number	216-920-2					
Data Source(s)	European Union Draft Assessment Report (2004)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 R43 N; R50-53 Skin Sens. 1 H317 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	 May cause sensitization by skin contact Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment May cause an allergic skin reaction Very toxic to aquatic life Very toxic to aquatic life with long lasting effects				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	Several animals sacrificed prematurely, retardation of growth, emaciation or loss of use of hind limbs. ↓food consumption and body wt gain. ↓erythrocyte and haemoglobin values in females, altered clinical chemical changes.	No information reported	20.7 (males) 23.5 (female's)	83 84.8	No evidence of endocrine disruption.

		Liver: ↑wt (centrilobular hepatocyte enlargement, ↓glycogen content				
1-year dog oral study	1/2	Slightly ↓food consumption, slight ↓body wt gain. Slightly ↓body wt gain, ↑inorganic phosphate, ↓bilirubin. Target organs, kidneys, gastric mucosa possibly due to irritation.	No information reported	< 186 mg/kg bw	241	No evidence of endocrine disruption.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↓body wt in both sexes, ↓red blood cell parameters. ↓thromboplastin time. Slightly altered clinical chemical parameters. No carcinogenic potential.	No information reported	13 (males) 18 (females)	43 60	No evidence of endocrine disruption.
2-generation rat oral reproduction study	1/2	Effects on body wt and body wt gain, triglycerides, liver (wt and histology) in dams. ↓pup body wt and growth. No effect on reproductive function.	No information reported	37 (parental) 37 (systemic toxicity offspring) 148 (reproductive function)	148 148 -	No evidence of endocrine disruption.
Rat oral developmental and teratogenicity study	1/2	Effects on food consumption, body wt, body wt gain and clinical symptom's (piloerection) in dams. No embryo-/foetotoxicity or malformations at any dose levels.	No information reported	10 (maternal) 250 (prenatal) 250 (anomalies)	50 - -	No evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1/2	Effects on food consumption, body wt, body wt gain in dams. No embryo-/foetotoxicity or malformations at any dose levels.	No information reported	55 (maternal) 495 (prenatal toxicity) 495 (anomalies)	165 - -	No evidence of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	In a full range of regulatory toxicity tests, there is no evidence of endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	In a full range of regulatory toxicity tests, there is no evidence of endocrine disruption.
Are the effects judged to be relevant to humans?	N/A	-

Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	In a full range of regulatory toxicity tests, there is no evidence of endocrine disruption.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, chloridazon is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.35 Human Health Endocrine Disruption Evaluation for Chlorpropham

Substance details		
Substance Name	**Chlorpropham (ISO)**	
Substance Synonyms	isopropyl 3-chlorocarbanilate	
Substance CAS Number	101-21-3	
Substance EC Number	202-925-7	
Data Source(s)	European Union Draft Assessment Report (1999). A brief search for recent relevant studies located the following paper which is summarised below: Kojima H, Takeuchi S and Nagai T (2010) Endocrine disrupting potential of pesticides via nuclear receptors and aryl hydrocarbon receptor. *J Health Science*, **56**, 374-386.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Carc. Cat. 3; R40 Xn; R48/22 N; R51-53 Carc. 2 H351 STOT RE 2 * H373** Aquatic Chronic 2 H411	 Limited evidence of a carcinogenic effect Harmful: danger of serious damage to health by prolonged exposure if swallowed Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Suspected of causing cancer May cause damage to organs through prolonged or repeated exposure Toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
90-day rat oral study	1/2	↓red blood cell count, ↑MetHb	No information reported	10	50	No evidence of endocrine disruption.

60-week dog oral study	1/2	↑thyroid wt., enlarged thyroid lobes, ↑thyroid activity, decreased T4 levels in TSH stimulation test.	No information reported	5	50	Main effects on the thyroid. Evidence of potential endocrine disruption.
18-month mouse oral long-term toxicity and carcinogenicity study	1/2	Bluish extremities, dark eyes, microscopic changes in spleen, ↑cellularity of bone-marrow. No carcinogenic potential.	No information reported	100	500	Bluish extremities suggesting MebHb. No evidence of endocrine disruption.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	Slight microscopic changes in liver, spleen and bone-marrow. ↑thyroid and testes wt at highest dose. Significantly ↑incidence of benign Leydig cell tumours in the testes seen at the highest dose in the rat study	No information reported	-	30	Limited evidence for carcinogenicity in laboratory animals based on a significantly increased incidence of benign Leydig cell tumours seen at the highest dose in the rat study only and the absence of a carcinogenic effect in the mouse study. Leydig cell tumours are benign and generally related to a disturbance of the hormonal control mechanism of the testes. Therefore this represents evidence of potential endocrine disruption.
2-generation rat oral reproduction study	1/2	Parental: body wt, ↑spleen and liver wt, microscopic changes in spleen, liver, kidneys and bone-marrow. Developmental: ↓survival, body wt, ↓spleen wt and dark spleens.	No information reported	Parental and developmental 44.5 (males) 60.8 (females)	 131.2 188.5	No evidence of endocrine disruption.
Rat oral developmental and teratogenicity study	1/2	Maternal: ↓growth and food consumption Developmental: ↓foetal wt, retarded ossification	No information reported	Parental and developmental 200	 800	No evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1/2	Maternal: mortality, ↓food consumption and body wt gain. ↑spleen weight. Developmental: slightly ↓foetal weight and slightly retarded ossification.	No information reported	125 (parental) 250 (developmental)	250 500	No evidence of endocrine disruption.

In vitro studies	2	*In vitro* studies showed binding to the aryl hydrocarbon receptor, Pregnane X receptor and androgen receptor agonism	This binding to nuclear receptors indicates some potential mechanisms for endocrine disrupting effects			These *in vitro* assays show some potential for binding to nuclear receptors which may be of relevance to human endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There are inconsistent results indicating a potential effect on the testes and thyroid which could be due to endocrine disruption. The major thyroid effects are only seen in a 60-week dog study and the testes effects only in a long-term rat study with no effects observed in reproduction and developmental studies.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	The effects seen on the thyroid and testes could be due to endocrine disruption but there is very limited mechanistic information to confirm an ED MOA.
Are the effects judged to be relevant to humans?	N/A	If there was reliable evidence for an endocrine disruption mechanism for the effects seen on the thyroid and testes, these could be relevant for humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	The evidence for endocrine disruption is not sufficient to assess against this criterion.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**Although there is evidence for effects which could be due to endocrine disruption, these effects are inconsistent and an endocrine disrupter mechanism of action has not been shown. Further studies measuring hormone levels and possible mechanisms are required.**
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.

(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.36 Human Health Endocrine Disruption Evaluation for Clomazone

Substance details						
Substance Name	**Clomazone**					
Substance Synonyms	2-(2-chlorobenzyl)-4,4-dimethyl-1,2-oxazolidin-3-one (IUPAC)					
Substance CAS Number	81777-89-1					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2005)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	↑increased a/r liver wt, ↓reduced body wt, ↑cholesterol. Significant change in hepatocytes in forms of megalocytosis The liver was the target organ.	Liver is the target organ	200	400	No evidence of endocrine disruption
1-year dog oral study	1/2	↑serum cholesterol and some inconsistent, however considered treatment-related, organ weight changes (a/r liver wt, a/r ovary and relative brain).	No information reported	12.5	62.5	No evidence of endocrine disruption

		Signs of transient mild anaemia in the high dose group up till 6 month. The liver was the target organ.				
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↑absolute liver wt, relative liver wt was not statistically elevated, but still regarded as toxicological relevant, since the elevation in the both the absolute and relative liver weight was increased in a dose-related manner. Hepatocytomegaly was more frequent in treated animals but not dose-related. The liver was the target organ. No indication of neoplastic or non-neoplastic changes.	Liver is the target organ.	50	100	No evidence of endocrine disruption
2-generation rat oral reproduction study	1	↓maternal body wt, maternal body wt gain and food consumption in parental animals. No significant effects on offspring. No significant effects on reproduction.	No information reported	~50 (parental) ~400 (offspring) ~400 (reproduction)	~150 (parental)	No significant effects on reproduction. No evidence of endocrine disruption
Rat oral developmental and teratogenicity study	1/2	Maternal toxicity: ↓food consumption and clinical signs as abdominogenital staining and ↓locomotion Embryo/foetotoxicity: ↓female foetal body wt, Significant ↑incidence of foetal skeletal malformations (delayed ossifications) and in visceral anomalies (increased incidence of hydroureter). Developmental effects only at maternally toxic doses	No information reported	100 (maternal) 100 (foetal)	300 (maternal) 300 (foetal)	Developmental effects only at maternally toxic doses. No evidence of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	There is no evidence of endocrine disruption in a full range of regulatory tests
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no evidence of endocrine disruption in a full range of regulatory tests
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	There is no evidence of endocrine disruption in a full range of regulatory tests
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupter more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**There is a full range of regulatory toxicology tests and no evidence of endocrine disruption. Therefore, clomazone is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.37 Human Health Endocrine Disruption Evaluation for Clopyralid

Substance details						
Substance Name	**Clopyralid (ISO) often described as Clorpyralid**					
Substance Synonyms	3,6-dichloropyridine-2-carboxylic acid					
Substance CAS Number	1702-17-6					
Substance EC Number	216-935-4					
Data Source(s)	European Union Draft Assessment Report (2005) EFSA Scientific Report (2005) Conclusion regarding the peer review of the pesticide risk assessment, of the active substance, clopyralid 50, 1-65.					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xi; R41 Eye Dam. 1 H318	 Risk of serious damage to eyes Causes serious eye damage				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
Rat 90-day oral study	1/2	Males: ↑relative liver and kidney weights at all doses. Females: ↓bodyweight, food consumption.	No information reported	<300 (males) 300 (females)	M: 300 F: 1500	No evidence of endocrine disruption.
Dog 12-months oral study	1/2	Haematological effects (↓RBC, Haematocrit, total haemoglobin) and ↑ liver wt	No information reported	100	320	No evidence of endocrine disruption.

Rat 2-year long-term toxicity and carcinogenicity study	1/2	Lesions of the gastric limiting Ridge. No carcinogenic potential.	No information reported	15	150	-No evidence of endocrine disruption.
Rat 2-generation reproductive study	1/2	Adult: ↓body wt, ↓food consumption, stomach lesions Offspring: ↓pup wt and ↑pup liver wt in F1 generations.	No information reported	Adult 150 (females) 500 (males), Offspring 500 Reproduction >1500	 500 1500 1500 Highest dose tested	Supplementary histopathological examinations on samples collected in the above study Adults: No treatment-related histopathological effects in reproductive organs and accessory sex glands in randomly selected adult F0 and F1 rats/sex at 1500 mg/kg bw/day or in major organs of randomly selected F2B weanlings/sex at 1500 mg/kg bw/day.
Rat teratogenicity and developmental study	1/2	Maternal: ↓liver wt and food consumption Embryotoxicity/teratogenicity: malformed foetuses detected were considered incidental)	No information reported	15 (maternal) >250 (Embryotoxicity/ Teratogenicity)	75 Highest dose tested	Effects only at maternally toxic doses
Rabbit teratogenicity and developmental study	1/2	Maternal: ↓body wt and body wt gain, gastric lesions, clinical signs and morbidity Embryotoxicity/teratogenicity: ↓mean foetal weight, slightly ↑spontaneous malformations	No information reported	110 (maternal) 110 (Embryotoxicity/ Teratogenicity)	250	Effects only at maternally toxic doses

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	No endocrine disruption in a full range of toxicological tests
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No endocrine disruption in a full range of toxicological tests
Are the effects judged to be relevant to humans?	N/A	-

Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	No endocrine disruption in a full range of toxicological tests
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**There is a full range of regulatory toxicology tests and no evidence of endocrine disruption. Therefore, clorpyralid is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.38 Human Health Endocrine Disruption Evaluation for Dimethenamid-P

Substance details						
Substance Name	**Dimethenamid-P**					
Substance Synonyms	(S)-2-Chloro-N-(2,4-dimethyl-2-thienyl)-N-(2-methoxy-1-methylethyl)acetamide					
Substance CAS Number	163515-14-8					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2000)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	- -	- -				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1	Decreased bodyweight and bodyweight gain, increased liver weight and hepatocellular hypertrophy, increased cholesterol.	No information reported	37	100 (approx.)	No evidence of endocrine effects.
1-year dog oral study	1	Decreased bodyweight gain, hepatocyte enlargement and vacuolation, increased liver weight, altered clinical chemistry.	No information reported	10	60 (approx.)	No evidence of endocrine effects.

2-year rat oral long-term toxicity and carcinogenicity study	1	Decreased food consumption and bodyweight gain. Lenticular opacities. Changes in chemistry. Stomach hyperplasia. Altered hepatocytes, bile duct hyperplasia, parathyroid hyperplasia.	No information reported	5	35	Parathyroid effects possibly due to endocrine effects.
2-year mouse oral long-term toxicity and carcinogenicity study	1	Decreased bodyweight gain, increased relative liver and kidney weight. Increased incidence of stomach hyperkeratosis.	No information reported	40	120	No evidence of endocrine effects.
2-generation rat oral reproduction study	1	Decreased food intake and bodyweight gain. Increased liver weight. Decreased bodyweight gain during lactation.	No information reported	Parental 50 Pups 50 Reproduction 150	Parental 150 Pups 150 Reproduction -	No evidence of endocrine effects.
Rat oral developmental and teratogenicity study	1	Decreased maternal bodyweight gain and food consumption. Increased liver weight. Slightly lower foetal weights. Increased incidence of delayed ossification	No information reported	Maternal - Foetal 25	Maternal 25 Foetal 150	Foetal effects occurred in the presence of maternal toxicity. No clear evidence of potential endocrine effects.
Rabbit oral developmental and teratogenicity study	1	Decreased maternal bodyweight gain and food intake. Abortions in 2 animals.	No information reported	Maternal 37.5 Foetal 75	Maternal 75 Foetal 150	Foetal effects occurred in the presence of maternal toxicity. No clear evidence of potential endocrine effects.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	No substantial adverse effects related to endocrine disruption have been demonstrated. However, parathyroid hyperplasia was observed, which may indicate that the levels of parathyroid hormones could be altered,
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no mechanistic evidence to suggest perturbation of parathyroid hormones.
Are the effects judged to be relevant to humans?	N/A	-

Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	-
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**There is data available from a full range of regulatory toxicology tests and some evidence of potential endocrine disruption. Parathyroid hyperplasia has been observed, but this has not been linked to an endocrine disruption mode of action. Further information is required.**
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no conclusive evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no conclusive evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	Further mechanistic information is required.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.39 Human Health Endocrine Disruption Evaluation for Diquat

Substance details		
Substance Name	**Diquat**	
Substance Synonyms	9,10-dihydro-8a,10a-diazoniaphenanthrene ion	
Substance CAS Number	85-00-7	
Substance EC Number	201-579-4	
Data Source(s)	IUCLID (1997) Review report (2000)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	T+; R26 T; R48/25 Xn; R22 Xi; R36/37/38 R43 N; R50-53	Harmful if swallowed Very toxic by inhalation Irritating to eyes, respiratory system and skin May cause sensitization by skin contact Toxic: danger of serious damage to health by prolonged exposure if swallowed Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Acute Tox. 2 * STOT RE 1 Acute Tox. 4 * Eye Irrit. 2 STOT SE 3 Skin Irrit. 2 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	Fatal if inhaled Causes damage to organs through prolonged or repeated exposure Harmful if swallowed Causes serious eye irritation May cause respiratory irritation Causes skin irritation May cause an allergic skin reaction Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2-year rat oral long-term toxicity and carcinogenicity study	1	Cataracts.	No information reported	0.2	0.6	No evidence of an endocrine effect.
2-generation rat oral reproduction study	1	Cataract formation.	No information reported	Parental: 1.4	80ppm	No evidence of an endocrine effect.
Rat oral developmental and teratogenicity study	1	Decreased maternal food consumption. Delayed skeletal ossification.	No information reported	Parental: 4 Developmental: 12	Parental: 12 Developmental: 10	Developmental toxicity occurred in the presence of maternal toxicity.
Rabbit oral developmental and teratogenicity study	1	Decreased maternal food consumption. Delayed skeletal ossification.	No information reported	Parental: 1 Developmental: 1	Parental: 3 Developmental: 3	Developmental toxicity occurred in the presence of maternal toxicity.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	No effects related to endocrine disruption occur.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are the effects judged to be relevant to humans?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	No effects potentially related to an endocrine mechanism of action were observed.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, diquat is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.40 Human Health Endocrine Disruption Evaluation for Ethofumasate

Substance details		
Substance Name	**Ethofumesate**	
Substance Synonyms	(±)-2-ethoxy-2,3-dihydro-3,3-dimethylbenzofuran-5-yl methanesulfonate	
Substance CAS Number	26225-79-6	
Substance EC Number	247-525-3	
Data Source(s)	European Union Draft Assessment Report (2002). A brief search for recent relevant studies did not find any further information.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 N; R51-53 Aquatic Chronic 2	 Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
90-day rat oral study	1/2	↑body wt gain, food consumption, ↑liver wt, ↑ovary wt, ↑serum sodium	No information reported	200	2000	Increase in ovary weight might be indicative of endocrine disruption; however it was not seen in other studies. Also, no histopathology was noted. Possibly, it is a chance finding..

2-year Sprague-Dawley rat oral long-term toxicity and carcinogenicity study	1/2	↓body wt gain, ↑liver wt, hepatocyte hypertrophy, ↑testicular adenoma, focal hypertrophy, slight increase over controls	No information reported	100	1000	Slight effects on testes which may be indicative of endocrine disruption.
2-year Wistar rat oral long-term toxicity and carcinogenicity study	1/2	↓body wt gain, ↑mortality (males)	No information reported	6.9-9.8	100	No evidence of endocrine disruption
3-generation Wistar rat oral reproduction study	1/2	Parental: ↓body wt gain P_0: ↓litter size, no. of male pups, implantations P_1: ↑litter size	No information reported	50	500	Some slight effects on reproduction which could indicate endocrine disruption
Rat oral developmental study	1/2	No adverse effects on dams or litters.	No information reported	1000	-	No evidence of endocrine disruption
Rabbit oral developmental study	1/2	No adverse effects on embryonic or foetal development.	No information reported	600 (maternal) 1200 (foetal)	1200 -	No evidence of endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There are some slight effects in rats (testes, reduced no of implantation, reduced no of male pups) which could be indicative of endocrine disruption
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no mechanistic information..
Are the effects judged to be relevant to humans?	N/A	
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	

Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**This is a borderline case between no endocrine disruption and some slight effects which may be attributable to endocrine disruption, but further mechanistic investigation is required.**
(B) Substances more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Substances less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	Further information is required.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.41 Human Health Endocrine Disruption Evaluation for Fluazifop-p-butyl

Substance details		
Substance Name	**Fluazifop-P-butyl (ISO)**	
Substance Synonyms	Butyl (R)-2-[4-(5-trifluoromethyl-2-pyridyloxy)phenoxy]propionate	
Substance CAS Number	79241-46-6	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (2007) EFSA Journal (2010) Conclusion on the peer review of the pesticide risk assessment of the active substance fluazifop-P (evaluated variant fluazifop-P-butyl);8(11):1905, 1-76	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Repr. Cat. 3; R63 N; R50-53 Repr. 2 H361d*** Aquatic Acute 1 H400 Aquatic Chronic 1 H410	 Possible risk of harm to the unborn child Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Suspected of damaging the unborn child Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	Liver; kidney; spleen; ¯ cholesterol levels	No information reported	9	166	No evidence of endocrine disruption.
1-year dog oral study	1/2	Liver; corneal opacity, bilateral cataract; ↓haematocrit, haemoglobin, RBC; cholesterol levels	No information reported	25	125	No evidence of endocrine disruption.

2-year rat oral long-term toxicity and carcinogenicity study	1/2	Kidney (nephropathy) ovary; ↑plasma cholesterol; ↓haematocrit, RBC No carcinogenic potential	No information reported	0.47	3.79	Effects on liver, kidney and ovaries.
98-week mouse oral long-term toxicity and carcinogenicity study	1/2	Kidney, liver (hypertrophy, pigmentation, fatty vacuolation) No carcinogenic potential	No information reported	1.86	7.71	Effects on liver and kidneys.
80-week hamster oral long-term toxicity and carcinogenicity study	1/2	Kidney, liver; testis, eye (cataract); ↓haematocrit, haemoglobin, RBC. No carcinogenic potential	No information reported	12.5 (male) 12.1 (female)	47.4 45.5	Effects in liver and kidneys. Tubular degeneration in the testes.
2-generation rat oral reproduction study	1/2	↓testis and epididymal wt ↓litter size; ↓gestation length; ↓spleen, testis, epididymal, pituitary and uterine wt; ↑ovary, liver & kidney wt	No information reported	0.8 (parental) 7 (reproductive) 0.8 (offspring)	7 Approximately 20 7	Effects on the male and female reproductive systems.
Rat oral developmental and teratogenicity study	1/2	Maternal: Kidney Developmental: Delayed ossification; kinked ureter	No information reported	20 (maternal) 2 (developmental)	300 20	Other investigative studies also showed delayed ossification.
Investigative studies on some of the endpoints of the Reproductive study	2	Testicular histology was re-examined on the 2-gen study and indicated no abnormal pathology and no reduction in testes volume nor seminiferous tubule length. Minor delay in reproductive organ maturation at 20 mg/kg bw/d	No information reported	N/A	N/A	Re-examination of the histology did not find major effects on the testes.
Investigative study using recombinant yeast strains with human androgen and oestrogen receptors	2	Binding studies showed no oestrogenic, ant-oestrogenic, androgenic or anti-androgen activity.	No direct oestrogenic or androgenic activity	N/A	N/A	No direct oestrogenic or androgenic activity

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There are a number of effects on both the male and female reproductive development (e.g. testes, ovary and uterine weight) which raise a concern for endocrine disruption. However, there is no binding to either the human oestrogen receptor or the androgen receptor *in vitro*, hence the need for further studies to investigate the underlying mode of action of these effects.

Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There are clear effects on the male and female reproductive systems but an ED mode of action has not been identified.
Are the effects judged to be relevant to humans?	N/A	Although there is no binding to the human oestrogen or androgen receptors *in vitro*, there is no reason why the effects on the reproductive system cannot be relevant to humans via a different mechanism.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	The substance is not an established endocrine disrupter.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**There are a number of effects on both the male and female reproductive development (e.g. testes, ovary and uterine weight). However, there is no binding to either the human oestrogen receptor or the androgen receptor *in vitro*, hence the need for further studies to investigate the underlying mode of action of these effects.**
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	There is insufficient information to indicate that the substance is an endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is insufficient information to indicate that the substance is an endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	Further information is required.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.42 Human Health Endocrine Disruption Evaluation for Flufenacet

Assessment not carried out due to the absence of a suitable regulatory dossier

Table B.43 Human Health Endocrine Disruption Evaluation for Fluroxypur

Substance details						
Substance Name	**Fluroxypyr (ISO) and fluroxypyr-meptyl (MHE) variant**					
Substance Synonyms	Fluroxypyr 4-amino-3,5-dichloro-6-fluoro-2-pyridyloxyacetic acid Fluroxypyr-meptyl (RS)-1-methylheptyl 4-amino-3,5-dichloro-6-fluoro-2-pyridyloxyacetate					
Substance CAS Number	Fluroxypyr 69377-81-7 Fluroxypyr-meptyl 81406-37-3					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (1997) SERA (2009) Fluroxypyr Human Health and Ecological Risk Assessment, USDA Forest Service					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 R52-53 Aquatic Chronic 3 H412	 Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment Harmful to aquatic life with long lasting effects				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	Severe clinical findings and mortality, kidney pathological changes and clinical parameters, not fully reversed after 24 weeks	No information reported	80	750	Kidney toxicity is the major effect but not seen to this extent in 90-day mouse and 1-year dog studies. No evidence of endocrine disruption.

2-year rat oral long-term toxicity and carcinogenicity oral study	1/2	No carcinogenic potential. Nephrosis.	No information reported	80	320	The kidney effects from the subacute and subchronic studies were confirmed. No evidence of endocrine disruption.
2-generation rat oral reproduction study	1/2	No effect on fertility or reproductive performance.	No information reported	500 (maternal or parental) 500 (reproduction)	Top dose tested	No evidence of endocrine disruption.
Rat oral developmental and teratogenicity study	1/2	↓food intake and body wt gain, ↑kidney wt in mothers. ↓sternebrae ossification	-	250 (maternal and foetal)	500	No evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1/2	Marked maternal toxicity. Sl ↑resorptions and pre- and post-implantation losses.	-	250 (maternal) 100 (foetal)	400 250	No evidence of endocrine disruption.
SERA Review (2009)	N/A	Review in 2009 confirmed kidney effects as the major toxicity and did not identify any endocrine disruption, although there is mention of ovarian lesions and testes wt change (due to low testes wt in control group) in one earlier studies these were not observed in any other studies.	-	-	-	-

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	There are no endocrine effects in the vast majority of studies. However, in one study testes and ovarian effects were observed but these were not seen in other studies.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There are no endocrine effects in the vast majority of studies including all the reproductive and developmental studies.
Are the effects judged to be relevant to humans?	N/A	There are no endocrine effects in the vast majority of studies including all the reproductive and developmental studies.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	There are no endocrine effects in the vast majority of studies including all the reproductive and developmental studies.

Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Although none of the reproductive studies indicate any signs of endocrine disruption, there are testes and ovarian effects reported in one study.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.44 Human Health Endocrine Disruption Evaluation for Ioxynil

Substance details		
Substance Name	**Ioxynil (ISO)**	
Substance Synonyms	4-hydroxy-3,5-diiodobenzonitrile	
Substance CAS Number	1689-83-4	
Substance EC Number	216-881-1	
Data Source(s)	European Union Draft Assessment Report (2001)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	 Repr. Cat. 3; R63 T; R23/25 Xn; R21-48/22 Xi; R36 N; R50-53	 R63 Possible risk of harm to the unborn child R23/25Toxic by inhalation and if swallowed R21 Harmful in contact with skin; Harmful: danger of serious damage to health by prolonged exposure if swallowed R36Irritating to eyes R50-53 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Repr. 2 Acute Tox. 3 * Acute Tox. 3 * Acute Tox. 4 * STOT RE 2 * Eye Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H361d Suspected of damaging the unborn child H331 Toxic if inhaled H301Toxic if swallowed. H312 Harmful in contact with skin H373 May cause damage to organs through prolonged or repeated exposure H319 Causes serious eye irritation H400 Very toxic to aquatic life H410 Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	↑increased the basal metabolic rate (↑food consumption and hyperactivity of the thyroid). ↑ wt and histopathology of the liver. haematology (WBC) and organ histopathology (thyroid, heart).	Effects on thyroid indicate an increase in basal metabolism – an uncoupling of oxidative phosphorylation. Effects on liver indicate enzyme induction.	NOEL 0.7 to 1.4	10	There appears to be an increase in basal metabolism and an effect on the thyroid.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	Effects on blood parameters (albumin and T4) at lowest dose, incidence of thyroid enlargements, nodules and masses and incidence of uterus polyps and masses.	No information reported	Carcinogenicity 0.2-0.3. Long-term toxicity < 0.2-0.3	2.9-4.8	Possible tumourigenic activity in the thyroid and in the uterus.
18-month mouse oral long-term and carcinogenicity study	1/2	↑mortality, ↓body wt, ↑organ weight (thyroid, liver, adrenal and kidney), ↑incidence of amyloidosis and liver tumours (in males only).	No information reported	NOAEL1.3 NOEL for Carcinogenicity 3.9 (males) NOEL < 3.9		No thyroid tumours in the mouse.
2-generation rat oral reproduction study	1/2	No effects on mating performance or pregnancy rate. Dose-related general retardation of growth of adults and offspring. Effects observed on liver and body wt had no effect on reproductive performance.	No information reported	2.5	8	No effects ion reproductive performance
Rat oral developmental and teratogenicity study	1/2	Developmental: Deleterious effect on morphogenesis (microphthalmia, anophthalmia and skeletal variations). Maternal: ↓body weight and food consumption in the 36 mg/kg female group.	No information reported	4 (developmental) 12 (NOEL maternal)	12 36	Some evidence of developmental toxicity
Rabbit oral developmental and teratogenicity study	1/2	Developmental: ↑major malformation and minor anomaly (microphthalmia/ anophthalmia, hydrocephaly, rib, skull and spine ossification defects) indicating a teratogenic effect. Foetal:	No information reported	15 (developmental) <15 (foetal) 15 (maternal)	30	Some evidence of teratogenicity and foetotoxicity.

		↑(not statistically significant) late uterine deaths may indicate a degree of foetotoxicity. Maternal toxicity ↓body wt gain and food consumption				
3- or 6-month oral rat study – effect on thyroid hormones	2	Morphological changes characteristic of early hyperthyroidism. Results tended to show ↑Plasma TSH and T4 and ↓T3	-		Effects seen at the lower dose 5.3 (males), 6.1 (females)	The results from this study may suggest that the mechanism of Ioxynil-induced thyroid carcinogenesis in the rat is a result of perturbation of thyroid hormone homeostasis leading to a decrease in circulating thyroid hormones. Under these conditions, the pituitary increases thyroid stimulating hormone (TSH) secretion which stimulates the thyroid. This leads to a predictable set of responses, including cellular hypertrophy and hyperplasia. Sustained hyperplasia of the thyroid eventually results in nodular hyperplasia and, finally, neoplasia. Study in DAR
Effects of Ioxynil on the binding of 125I-thyroxine (T4) to rat plasma proteins *in vitro*	2	Significant displacement of bound ^{125}I-thyroxine from rat plasma proteins for all concentrations of test compound between 1 to 1000 µM.	Ioxynil bound significantly to human thyroxine-binding prealbumin (TBPA) but not to thyroxine-binding globulin (TBG), nor albumin and that Ioxynil had the ability to displace T4 from TBPA but not from TBG, the major thyroid transport protein in human. This suggests that the rat, which has TBPA but not TBG, may be particularly sensitive to the action of Ioxynil.	-	-	Evidence of a direct effect on the thyroid system in the rat although this effect on TBPA may not be relevant to humans. Study in DAR

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There is evidence from a number of studies that Ioxynil has effects on the thyroid system including overactivity of the thyroid gland, changes in thyroid hormone levels and the formation of thyroid tumours. Also, a carcinogenic response was seen in the uterus.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	There is evidence from regulatory tests and from mechanistic studies that ioxynil causes perturbation of thyroid hormone homeostasis leading to a decrease in circulating thyroid hormones. Under these conditions, the pituitary increases thyroid stimulating hormone (TSH) secretion which stimulates the thyroid. This leads to a predictable set of responses, including cellular hypertrophy and hyperplasia. Sustained hyperplasia of the thyroid eventually results in nodular hyperplasia and, finally, neoplasia.
Are the effects judged to be relevant to humans?	Yes	Although the rat is more sensitive to changes in the thyroid than humans and ioxynil binds to the PBPA but not TGB, the main thyroid transport protein in humans, there is still evidence of a major effect on the thyroid which may be relevant to humans. There is also uncertainty about effects on development in the young. In addition, the human relevance of the uterus tumours cannot be excluded.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	Yes	A number of effects on the thyroid were observed below the STOT-RE Category 1 guidance values: overactivity of the thyroid (10 mg/kg bw/day in rat oral 90-day study), the formation of thyroid tumours (2.9 mg/kg bw/day in rat oral 2-year study) and the effects on thyroid hormone levels (5.3 mg/kg bw/day in 3-6 month rat oral study; 0.2 mg/kg bw/day in rat oral 2-year study).
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	No	A detailed assessment has been carried out as part of the project.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is sufficient reliable information with which to categorise the substance together with some further studies on thyroid hormone levels and thyroid protein binding.
(B) Endocrine disrupter more likely to pose a risk based on currently available data	**Yes**	**There is evidence of major effects on the thyroid system, including the formation of tumours at dose levels below the STOT-RE Category 1 guidance values.**
(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	The ED-mediated adverse effects occur below the STOT-RE Category 1 guidance values.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The substance is an established endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?
[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?**?**

Table B.45 Human Health Endocrine Disruption Evaluation for Isoxaben

Substance details		
Substance Name	**Isoxaben (ISO)**	
Substance Synonyms	N-[3-(1-ethyl-1-methylpropyl)-1,2-oxazol-5-yl]-2,6-dimethoxybenzamide	
Substance CAS Number	82558-50-7	
Substance EC Number	407-190-8	
Data Source(s)	European Union Draft Assessment Report (2006)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	R53 Aquatic Chronic 4 H413	May cause long-term adverse effects in the aquatic environment May cause long lasting harmful effects to aquatic life
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
90-day rat oral study	1/2	↑liver weight with minimal hepatocyte hypertrophy, ↓body wt, ↑(reversible) hepatic metabolising activity, changes in clinical chemistry parameters	No information reported	290 (male) 950 (female)	850 (male) 950 (female	No evidence of endocrine disruption.
1-year dog oral study	1/2	↑relative liver wt, ↑hepatic metabolising activity, ↑Alkaline phosphatase activity	No information reported	1000 (male) 100 (female)	1000 1000	No evidence of endocrine disruption.

2-year rat oral long-term toxicity and carcinogenicity study	1/2	Chronic renal failure (↑wt, disrupted BUN, creatinine, cholesterol and phosphorus), ↓Survival, ↑benign tumours (hepatocellular adenoma, benign adrenal phaeochromocytomas) ↓body wt and body wt gain, ↑progressive glomerular nephritis. No carcinogenic effects evident.	No information reported	51 (male) 62 (female)	527 647	No evidence of endocrine disruption.
3-generation rat oral reproduction study	1/2	Parental toxicity: ↓body wt, ↑liver wt. Offspring: no adverse effects	No information reported	40 (parental) 200 (offspring)	200 1000	No evidence of endocrine disruption.
Rat oral developmental and teratogenicity study	1/2	Maternal: ↓body wt gain, Litter: No toxic effects, ↓body wt	No information reported	1000 (maternal) 1000 (litter)	1000 1000	No evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1/2	Maternal: Single death and single abortion, ↓Food consumption and body wt for dead/aborted animals. Litter: None	No information reported	320 (maternal) ≥ 1000 (litter)	1000 ≥ 1000	No evidence of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	No evidence of endocrine disruption in a full range of regulatory tests.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence of endocrine disruption.
Are the effects judged to be relevant to humans?	N/A	No evidence of endocrine disruption.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	No evidence of endocrine disruption.

Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, isoxaben is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.46 Human Health Endocrine Disruption Evaluation for Lenacil

Substance details						
Substance Name	**Lenacil**					
Substance Synonyms	3-Cyclohexyl-6,7-dihydro-1H-cyclopentapyrimidine-2,4-(3H,5H)-dione					
Substance CAS Number	2164-08-1					
Substance EC Number						
Data Source(s)	European Union Draft Assessment Report (2007)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	- -	- -				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1	Leucopenia, increased excretion of urinary proteins; lipofuscin staining in thyroid follicular epithelium	No information reported	40	412	Thyroid effects could be due to endocrine disruption.
90-day dog oral study	1	Increased relative liver weight in female dogs, increased relative thyroid and parathyroid weight, centrilobular/midzonal hepatocyte hypertrophy	No information reported	44	221	Thyroid effects could be due to endocrine disruption.

2-year rat oral long-term toxicity and carcinogenicity study	1	Reduced bodyweight gain. Reduced motor activity, organ weight effects, thyroid discolouration, increased thyroidal luminal concretions, centrilobular hepatocyte hypertrophy and vacuolation, mammary gland tumours.	No effect on ability of thyroid to take up and organify iodide. Slight decrease in T4 and T3.	139	1390	Thyroid effects and mammary gland tumours could be due to endocrine disruption.
2-year mouse oral long-term toxicity and carcinogenicity study	1	Hepatocellular adenomas, lung alveolar tumours.	No information reported	332	1358	No evidence of an endocrine effect.
2-generation rat oral reproduction study	1	Parental thyroid toxicity. Decreased offspring bodyweight during lactation. Altered lactation at top dose.	No information reported	Systemic 81 Offspring 89 Reproduction 1727	Systemic 810 Offspring 897 Reproduction 8635	Thyroid effects could be due to endocrine disruption.
Rat oral developmental and teratogenicity study	1	No effects reported	No information reported	Maternal - Developmental -	Maternal - Developmental -	No evidence of an endocrine effect.
Rabbit oral developmental and teratogenicity study	1	Clinical signs and altered bodyweight changes in dams.	No information reported	Maternal 1000 Developmental 4000	Maternal 4000 Developmental -	No evidence of an endocrine effect.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Thyroid effects and mammary gland tumours could be due to an endocrine mechanism of action.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	Mechanistic studies to show conclusively that the thyroid function has been altered or to establish and endocrine disrupter mode of action for the mammary gland tumours are not available.
Are the effects judged to be relevant to humans?	Yes	On the basis of the available evidence, the relevance to humans of the effects on the thyroid and mammary gland cannot be excluded. However, the evidence is insufficient to establish the substance as an endocrine disrupter.

Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	The evidence is insufficient to establish the substance as an endocrine disrupter.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**There is evidence of thyroid effects and mammary gland tumours in regulatory tests. Further studies are required to clarify the mode of action.**
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.47 Human Health Endocrine Disruption Evaluation for Mesosulfuron-methyl

Substance details						
Substance Name	**Mesosulfuron-methyl (provisional ISO)**					
Substance Synonyms	methyl2-[3-(4,6-dimethoxypyrimidin-2-yl)¬ureidosulfo¬nyl]-4-methanesulfonamidomethylben-zoate (IUPAC)					
Substance CAS Number	208465-21-8					
Substance EC Number	Not allocated					
Data Source(s)	European Union Draft Assessment Report (2001)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day dog oral study	1	Some minor biochemical changes not considered adverse. No adverse effects.	No information reported	Males: 648 Females: 734	Top dose was NOAEL	No evidence of endocrine disruption
12-month dog oral study	1	No adverse effect seen in general health, food consumption, organ wt or histopathology	No information reported	Males: 574 mg/kg bw Females: 646 mg/kg bw	Top dose was NOAEL	No evidence of endocrine disruption

2-year rat oral long-term toxicity and carcinogenicity study	1	No adverse macroscopic findings	No information reported	865 (male) 1056 (female)(chronic toxicity) 764 (male) and 952 (female) (oncogenicity)	Top dose was NOAEL	No evidence of endocrine disruption
18-month mouse oral long-term toxicity and carcinogenicity study	1	No carcinogenic potential. ↓body wt gains in females	No information reported	103 (males) 130 (females)	Approximately 1000	No evidence of endocrine disruption
2-generation rat oral reproduction study	1	No substance related adverse findings	No information reported	1175 (males) 1388 (females)	Top dose was NOAEL	No evidence of endocrine disruption
Rat and rabbit oral developmental and teratogenicity study	1/2	No teratogenic potential and is not a developmental toxicant	No information reported	1000 (maternal and foetal)	Top dose was NOAEL	No evidence o f endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	No adverse toxicological effects were seen except for a decreased female weight gain.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No adverse toxicological effects were seen except for a decreased female weight gain.
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	-
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, mesosulfuron-methyl is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.48 Human Health Endocrine Disruption Evaluation for s-Metalochlor

Substance details		
Substance Name	**S-metolachlor**	
Substance Synonyms	Mixture of : (aRS, 1 S)-2-chloro-N-(6-ethyl-o-tolyl)-N-(2-methoxy-1-methylethyl)acetamide (80-100%) and: (aRS, 1 R)-2-chloro-N-(6-ethyl-o-tolyl)-N-(2-methoxy-1-methylethyl)acetamide (20-0%)	
Substance CAS Number	87392-12-9	
Substance EC Number	203-625-9	
Data Source(s)	European Union Draft Assessment Report (2003). A brief search for recent relevant studies located the following which are summarised below: Laville N, Balaguer P, Brion F, Hinfray N, Casellas C, Porcher JM and Ait-Aissa S (2006) Modulation of aromatase activity and mRNA by various selected pesticides in the human choriocarcinoma JEG-3 cell line. Toxicology, 228, 98-108. Mathias FT, Romana RM, Sleiman HK, de Oliveira CA and Romano MA (2012) Herbicide metolachlor causes changes in reproductive endocrinology of male Wistar rats. Toxicology ePubl. Doi:10.5402/2012/130846	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 R43 N; R50-53 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	 May cause sensitization by skin contact. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. May cause an allergic skin reaction. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day dog oral study	1/2	↑relative liver wt.	No information reported	15.1	31.1	No evidence of endocrine disruption. This subchronic study derived the lowest NOAEL, and the rodent short-term and dog 1-year studies also gave no additional information on toxicity and no evidence of endocrine disruption.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↓body wt, ↑liver focal lesions. No carcinogenic potential.	No information reported	14 (male) 17 (female)	139 178	No evidence of endocrine disruption.
2-generation rat oral reproduction study	1/2	Parental: ↓food consumption. Foetal: ↓body wt in F1 and F2 litters	No information reported	24 (parental) 24 (foetal)	76	No evidence of endocrine disruption.
Rat oral developmental study	1/2	Maternal: ↓body wt, body wt gain, food consumption, ↑clinical signs Foetal: ↓body wt	No information reported	100 (maternal) 300 (foetal)	300 -	No evidence of endocrine disruption.
Rabbit oral developmental study	1/2	Maternal: ↓body wt, body wt gain, food consumption Foetal: ↑foetal malformations at top dose in one litter with maternal toxicity.	No information reported	100 (maternal) 100 (foetal)	500 500	No evidence of endocrine disruption.
In vitro study on aromatase activity in JEG-3 choriocarcinoma cell line	2	.	Induction of aromatase activity. Aromatase converts testosterone to oestrogen and increased activity might lead to alterations in oestrogen, testosterone and DHT.	-	-	*In vitro* activation of a human enzyme connected to sex hormone modulation. Therefore in vitro evidence of endocrine activity.
Rat oral male reproduction study (Mathias *et al*. 2012, paper available by ePub at	2 (only in epub at present)	↑serum testosterone, oestradiol, FSH, ↓DHT. No effect on LH. ↑fluid in seminal vesicles,	The authors speculated that changes could be due to an effect on aromatase (as seen *in vitro*) or	Effects at 5 and 50 mg/kg bw/day but not good dose	-	Prepubertal male rats treated PND23-53, 0, 5 or 50 mg/kg bw/day.

present).		precocious puberty, changes in morphology of seminiferous epithelium.	modulation of other male hormonal pathways.	response.		Not a regulatory study but evidence of disruption to male sex hormones and development. Not good dose response except for oestradiol.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes/No	No evidence of endocrine disruption in regulatory tests but there is recent *in vivo* evidence of endocrine activity (sex hormone levels) and effects on male development. However, these effects were not seen in the 2-generation study.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	The recent *in vitro* and *in vivo* evidence does suggest an endocrine disruption mode of action on the male reproductive system.
Are the effects judged to be relevant to humans?	Yes	There is no evidence to suggest that the effects should not be relevant to humans
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	There is no reliable evidence of serious endocrine disruption in regulatory tests. Further studies are required.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	A detailed assessment has been carried out as part of the project.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**There is no evidence of endocrine disruption in the full range of regulatory tests but recent studies indicate endocrine disrupting effects on the male reproductive system. It is suggested that further evidence is required to substantiate these recent findings.**
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	There is no reliable evidence of serious endocrine disruption in regulatory tests. Further studies are required.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is no reliable evidence of serious endocrine disruption in regulatory tests. Further studies are required.

(D) Substances not considered to be endocrine disrupters based on currently available data	No	Further information is required.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.49 Human Health Endocrine Disruption Evaluation for Metamitron

Substance details						
Substance Name	**Metamitron (ISO)**					
Substance Synonyms	4-amino-3-methyl-6-phenyl-1,2,4-triazin-5-one					
Substance CAS Number	41394-05-2					
Substance EC Number	255-349-3					
Data Source(s)	EU Draft Assessment Report, 2007. EFSA Scientific Report (2008) Conclusion regarding the peer review of the pesticide risk assessment of the active substance metamitron. 185, 1-43					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xn; R22 N; R50 Acute Tox. 4 * H302 Aquatic Acute 1 H400	 Harmful if swallowed Very toxic to aquatic organisms Harmful if swallowed Very toxic to aquatic life				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	Clinical pathology and histopathology suggestive of effects on liver function (↑cholesterol and bilirubin, ↓triglyceride and morphology (single cell necrosis of hepatocytes and enlarged cell nuclei).	No information reported	18.4 (males) 22.8 (females)	36.6 (males) 42.8 (females)	No evidence of endocrine disruption

1-year dog oral study	1/2	Haematology and clinical chemistry effects indicative of liver toxicity (↑ALAT, cholesterol, bile acids, triglycerides)	No information reported	1.1 (males) 1.2 (females)	13.6(males) 12.7 (females)	No evidence of endocrine disruption
2-year dog oral long-term toxicity study	1/2	↑clinical chemistry effects indicative of liver toxicity (↑ALAT, cholesterol, bilirubin)	No information reported	3	11.3	No evidence of endocrine disruption
2-year rat oral long-term toxicity and carcinogenicity study	1/2	Changes in the liver and ↓Hb and haematocrit. No carcinogenic potential	No information reported	4.9 (males) 6.0 (female)	19.5 24.9	No evidence of endocrine disruption -
2-generation rat oral reproduction study	1/2	Developmental and Parental: ↓body wt in parental animals and offspring Reproduction: No evidence of reproductive toxicity.	No information reported	Developmental and Parental: 3.9 (males) 4.6 |(females) Reproduction: 97.2 (males) 136 (females)	Developmental and Parental: 19.8 (males) 24.1 (females). Reproduction: >97.2 (males) >136 (females)	No evidence of endocrine disruption
2-generation rat oral reproduction study	1/2	↓Body weight development in parental animals and offspring ↓mean number of corpora lutea and implantations in both generations and reduction in survival index in pups after standardisation.	No information reported	Developmental and Parental: 7.3 (males) 11.3 (females) Reproduction: 36.4 (males) 53.8 (females)	Developmental and Parental: 36.4 (males) 53.8 (females). Reproduction: 239 (males) 306 (females).	Effects on reproduction could raise a concern for endocrine disruption, but seen only in the presence of parental toxicity
Rat oral developmental and teratogenicity study	1/2	↓body wt No developmental toxicity.	No information reported	10 (maternal) ≥100 (developmental)	30 >100	-

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Slight reproductive toxicity in one 2-generation study but in the presence of parental toxicity. Also not seen in another similar study. Overall, no convincing evidence of endocrine disruption in a full range of regulatory tests.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No mode of action information available. However, no firm evidence of endocrine disruption in a full range of regulatory tests.
Are the effects judged to be relevant to humans?	N/A	No firm evidence of endocrine disruption in a full range of regulatory tests.

Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	No firm evidence of endocrine disruption in a full range of regulatory tests.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, metamitron is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.50 Human Health Endocrine Disruption Evaluation for Metazochlor

Substance details						
Substance Name	**Metazachlor**					
Substance Synonyms	2-chloro-N-(pyrazol-1-ylmethyl)acet-2',6'-xylidide (IUPAC)					
Substance CAS Number	67129-08-2					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2005)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	Clinical chemistry, ↑liver wt	No information reported	16.7 (male) 20 (female)	84 98	No evidence of endocrine disruption
1-year dog oral study	1/2	Bodyweight, haematology, clinical chemistry, ↑liver and kidney wt, mainly liver pathology changes.	No information reported	30	144	No evidence of endocrine disruption
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↓Bodyweights & food consumption, ↑bilirubin	No information reported	8.5 (male) 11.6 (female)	87 114	No evidence of endocrine disruption

3-generation rat oral reproduction study	1/2	Reproductive: ↓corpora lutea, implantations & litter size Adults: ↓body wt Offspring: ↓body wt and survival.	No information reported	Reproductive 151 and 192 in males and females respectively Adults: 151 and 20.0 in males and females respectively Offspring: 20	Approximately 800 192 192	The effects on corpora luteum, implantation and litter size at the highest dose are the only effects seen involving an endocrine system, probably due to adult toxicity.
Rat oral developmental and teratogenicity study	1/2	↓weight gain ↓ossification	No information reported	250 (maternal) 250 (developmental)	500 500	No evidence of endocrine disruption
Rabbit oral developmental and teratogenicity study	1/2	Mortality and clinical signs. Lung agenesis	No information reported	30 (maternal) 120 (developmental)	120 300	No evidence of endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	In a 3-generation reproduction study, effects on corpora luteum, implantation and litter size were reported. However, it is likely that these were due to generalised toxicity at the highest dose.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No mode of action information available.
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	No evidence of endocrine disruption in a full range of regulatory tests.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, metazochlor is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.51 Human Health Endocrine Disruption Evaluation for Metribuzin

Substance details						
Substance Name	**Metribuzin**					
Substance Synonyms	4-amino-6-tert-butyl-3-methylthio-1,2,4-triazin-5(4H)-one 4-amino-4,5-dihydro-6-(1,1-dimethylethyl)-3-methylthio-1,2,4-triazin-5-one					
Substance CAS Number	21087-64-9					
Substance EC Number	244-209-7					
Data Source(s)	European Union Draft Assessment Report (2004) Nishihara T, Nishikawa J, Kanayama T, Dakeyama F, Saito,K, Imagawa M, Takatori S, Kitagawa Y, Hori S and Utsumic H (2000) Estrogenic Activities of 517 Chemicals by Yeast Two-Hybrid Assay. *Journal of Health Science*, **46(4),** 282-298.					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xn; R22 N; R50-53 Acute Tox. 4 * H320 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	 Harmful if swallowed Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Harmful if swallowed Very toxic to aquatic life Very toxic to aquatic life with long lasting effects				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	↑liver wt. histopathology. changes in thyroid (loss of colloid, variations in follicular size and desquamation) and pituitary gland, liver: ↓RBC, ↑reticulocyte	No information reported	≤ 5	15	Some changes in the thyroid indicative of endocrine disruption.

		count and cholesterol, ↓body wt and body wt gain, ↓Hb + platelet count, ↑Alk Phos, total bilirubin, ALAT, ASAT activation, BUN, creatinine, thyroid, spleen, liver wt.				
90-day dog oral study	1/2	↑UDP-glucuronyltransferase activity), ↑protein in urine, ↑liver wt., chronic inflammation and Kupffer cell aggregates in liver. ↓RBC, Hct, Hb, ↑ALAT, ASAT. GGT. Alphas activity, ↑bilirubin, bile acid conc., ↑protein in urine, ↑liver wt., histopathological findings in liver	No information reported	1.9	8	No evidence of endocrine disruption
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↓body wt gain, ↑thyroid follicular cell hyperplasia, ↓T3, ↑T4. No evidence of a carcinogenic potential	No information reported	13 (male) 16 (female)	15	Changes in thyroid hormones and follicular cell hyperplasia are indicative of endocrine disruption
2-year dog oral long-term toxicity and carcinogenicity study	1/2	High mortality, ↓food consumption, ↓body wt, ↑organ wt, clinical chemistry, anaemia. No evidence of a carcinogenic potential	No information reported	3.5	50	No evidence of endocrine disruption
2-generation rat oral reproduction study	1/2	Parental: ↓body wt. gain, ↑γGT, ↓food consumption hepatocellular hypertrophy, Reproductive: ↑pup mortality until day 4, ↓pup wt.	No information reported	2.2 (parental and reproductive)	12	No evidence of endocrine disruption
Rat oral developmental and teratogenicity study	1/2	Maternal: ↓body wt. (gain), food consumption, hypoactivity, ptosis, ataxia, Developmental: ↓foetal wt, ↓placental wt. skeletal retardations No evidence for teratogenicity	No information reported	maternal: < 25 70 (developmental)	70 200	No evidence of endocrine disruption
Rabbit oral developmental and teratogenicity study	1/2	Maternal: no effects Developmental: : 'seal heart', lung and heart development, skeletal retardation. No evidence for teratogenicity	No information reported	maternal: > 100 developmental: 10	- 30	No evidence of endocrine disruption

Estrogenic activity using the yeast two hybrid assay – Nishihara *et al*. (2000)	2	Evidence of estrogenic activity	-	64.3 mg/l (REC10) (0.3 mM (REC10)		The result is not considered to show positive estrogenic activity because the activity of the test substance was less than 10% of the activity of 10^{-4} mM E2,

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There is some evidence of disruption of the thyroid hormone and the thyroid in the regulatory studies.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	The effects on the thyroid in the rat appear to be due to perturbation of the thyroid hormone homeostasis.
Are the effects judged to be relevant to humans?	Yes	There is no clear mechanism of action information to exclude relevance to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	The thyroid effects occur at dose above the STOT-RE Cat 1 guidance values.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	A detailed assessment has been carried out as part of the project.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is evidence of thyroid disruption from regulatory studies.
(B**)** Endocrine disrupter more likely to pose a risk based on currently available data	No	The substance is not an ED more likely to pose a risk and the thyroid effects are above the STOT-RE Category guidance values..
(C) Endocrine disrupter less likely to pose a risk based on currently available data	**Yes**	**The substance is an endocrine disrupter less likely to pose a risk (low potency).**
(D) Substances not considered to be endocrine disrupters based on currently available data	**No**	There is evidence of thyroid disruption from regulatory studies indicating the substance is an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.52 Human Health Endocrine Disruption Evaluation for Metsulfuron-methyl

Substance details							
Substance Name	**Metsulfuron-methyl**						
Substance Synonyms	2-(4-methoxy-6-methyl-1,3,5-triazin-2-ylcarbamoylsulfamoyl) benzoic acid metsulfuron-methyl (ISO)						
Substance CAS Number	74223-64-6						
Substance EC Number	-						
Data Source(s)	European Union Draft Assessment Report (1997) Additional literature search has been performed for endocrine disruption.						
Data on the classification of the substance							
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**					
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	N; R50-53 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Very toxic to aquatic life Very toxic to aquatic life with long lasting effects					
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**						
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)							
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**	
90-day rat oral study	1/2	No gross or microscopic lesions. ↓female body wt and body wt gain, total protein; ↓male mean liver wt	No information reported	68 (male) 84 (female)	520 (male) 659 (female)	Low toxicity	
2-year rat oral long-term toxicity and carcinogenicity study	1/2	No carcinogenic potential Slight ↓body wt gain	No information reported	23 (male) 30 (female)	120 (male) 157 (female)	No evidence of endocrine disruption	

2-generation rat oral reproduction study	1/2	Slight body wt effects in adults. No reproductive effects	No information reported	39-43 (maternal and reproductive toxicity)		No evidence o f endocrine disruption
Rat oral developmental and teratogenicity study	1/2	No teratogenic activity.	No information reported	1000 (developmental effects) 40 (maternal)	1000 (Highest dose tested) 400	-
Rabbit oral developmental and teratogenicity study	1/2	No teratogenic activity.	-	>700 (developmental effects) 25 (maternal)	(Highest dose) tested) 250	No evidence of endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	No evidence of endocrine disruption in a full range of toxicological tests or in a subsequent literature search according to the methodology
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence of endocrine disruption in a full range of toxicological tests or in a subsequent literature search according to the methodology
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	No evidence of endocrine disruption in a full range of toxicological tests or in a subsequent literature search according to the methodology
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Category	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.

(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, metsulfuron-methyl is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.53 Human Health Endocrine Disruption Evaluation for Napropamide

Substance details						
Substance Name	**Napropamide**					
Substance Synonyms	N,N-Diethyl-2-(1-naphthyloxy)propanamide.					
Substance CAS Number	15299-99-7					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2005)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1	No adverse effects	No information reported	50	-	No evidence of an endocrine effect.
1-year dog oral study	1	Vomiting, reduced bodyweight gain, increased liver weights, altered clinical chemistry.	No information reported	50	250	No evidence of an endocrine effect.
2-year rat oral long-term toxicity and carcinogenicity study	1	Decreased bodyweight and food consumption. Haematological changes.	No information reported	10	47	No evidence of an endocrine effect.

18-month mouse oral long-term toxicity and carcinogenicity study	1	Reduced bodyweight and bodyweight gain. Increased relative liver weight.	No information reported	55	455	No evidence of an endocrine effect.
3-generation rat oral reproduction study	1	Reduced parental and pup bodyweight.	No information reported	Parental 30 Pups 30 Fertility 100	Parental 100 Pups 100 Fertility -	No evidence of an endocrine effect.
Rat oral developmental and teratogenicity study	1	Reduced maternal food consumption and bodyweight gain.	No information reported	Maternal 300 Foetal 1000	Maternal 1000 Foetal -	No evidence of an endocrine effect.
Rabbit oral developmental and teratogenicity study	1	Decreased maternal bodyweight and food consumption.	No information reported	Maternal 300 Foetal 1000	Maternal 1000 Foetal -	No evidence of an endocrine effect.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Effects attributable to endocrine disruption did not occur in standard toxicity studies.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	-
Are the effects judged to be relevant to humans?	No	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	-
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, napropamide is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Table B.54 Human Health Endocrine Disruption Evaluation for Oxadiazon

Substance details						
Substance Name	**Oxadiazon (ISO)**					
Substance Synonyms	3-[2,4-dichloro-5-(1-methylethoxy)phenyl]-5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2(3H)-one					
Substance CAS Number	19666-30-9					
Substance EC Number	243-215-7					
Data Source(s)	European Union Draft Assessment Report (2006) Revised 2009					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 N; R50-53 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Very toxic to aquatic life Very toxic to aquatic life with long lasting effects				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	↓Body wt, ↑liver wt, haematological changes, clinical chemistry and pathological changes associated with liver toxicity, protoporphyrin accumulation in liver and kidneys	No information reported	18	60	No evidence of endocrine disruption. Liver is the main target for toxicity.
1-year dog oral study	1/2	Mortality, ↓body wt, and body wt gain, ↑cholesterol and blood biochemical changes, ↑liver wt and	No information reported	20	60	No evidence of endocrine disruption.

		hepatocytic vacuolation, ↑serum AST.				
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↑incidence of hepatocellular centrilobular swelling in males. ↑incidence of hepatocellular neoplasms in males (adenomas and combined adenomas/carcinomas at 4.2 mg/kg/day and carcinomas at 39 mg/kg/day).		0.36 (males) 4.2 (females)	3.6 42	No evidence of endocrine disruption.
2-generation rat oral reproduction study	1/2	Parent/progeny: no adverse effects. Pup development: no adverse effects. Reproduction: no impairment of fertility and reproductive performance, prolonged gestation.	No information reported	15 (parental) 15 (development) 5 (reproduction)	- - 15	No evidence of endocrine disruption.
Rat oral developmental and teratogenicity study	1/2	Maternal: ↓body wt. Foetal: ↓pup wt and marginally delayed ossification	No information reported	12 (maternal) 12 (foetal)	40 40	No evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1/2	Maternal: ↓food intake and body wt gain Foetal: small foetuses	No information reported	20 (maternal) 60 (foetal)	60 180	No evidence of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	There is no evidence of endocrine disruption in a full range of regulatory tests.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no evidence of endocrine disruption in a full range of regulatory tests.
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	There is no evidence of endocrine disruption in a full range of regulatory tests.

Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, oxadiazon is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.55 Human Health Endocrine Disruption Evaluation for Phenmedipham

Substance details						
Substance Name	**Phenmedipham (ISO)**					
Substance Synonyms	methyl 3-(3-methylcarbaniloyloxy)carbanilate					
Substance CAS Number	13684-63-4					
Substance EC Number	237-199-0					
Data Source(s)	European Union Draft Assessment Report (2003)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 N; R50-53 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Very toxic to aquatic life Very toxic to aquatic life with long lasting effects				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1	Haematological effects suggestive of sight anaemia. ↑Spleen wt, ↑deposition of haemosiderin in liver and kidneys. ↓Relative uterus wt and absolute and relative thymus wt	Methaemoglobinaemia appears to be the major toxic effect.	<30	60	Other studies in rats and dogs with similar haematological effects reported

1-year rat oral study	1/2	Haematological effects (↓Hb, RBC and HCT), blood pigment positive urine suggesting renal postrenal damage, Haemosiderin was detected in liver, kidneys and spleen.	Methaemoglobinaemia appears to be the major toxic effect.	3.4 (males) 4.6 (females)	Approximately 20	No evidence of endocrine disruption
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↓body wt and body wt gain, transient haematological changes, ↓adrenal and kidney wt. No carcinogenic potential	No information reported	5 (males) 7(females)	Approximately 35	This and other long-term studies had a high mortality not related to dose.
2-generation rat oral reproduction study	1/2	↓body wt gain in F0 and F1 No effects on fertility	No information reported	75 (paternal) <25 (maternal) 5 (progeny) 225 (reproductive)	225 75 25 Highest dose tested	No evidence of endocrine disruption
Rabbit oral developmental and teratogenicity study	1/2	↓foetal body wt and retarded cranial ossification, No increased incidences of major abnormalities (malformations) were observed,	No information reported	225 (maternal and foetal)	1000	A number of other teratogenicity studies in rats showed some skeletal with slight developmental effects in rats, in the form of reduced skeletal ossification

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	There is a single observation of a decrease in uterus weight but no further evidence of reproductive or developmental effects.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No mode of action information available.
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	-

Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, phenmedipham is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.56 Human Health Endocrine Disruption Evaluation for Pinoxaden

Substance details						
Substance Name	**Pinoxaden**					
Substance Synonyms	2-dimethyl-Propanoic acid 8-(2,6-diethyl-4-methylphenyl)-1,2,4,5-tetrahydro-7-oxo-7H-pyrazolo[1,2-d][1,4,5]oxadiazepin-9-yl ester					
Substance CAS Number	**243973-20-8**					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2006)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2-year rat oral long-term toxicity and carcinogenicity study	2	Histopathological changes in the kidneys and associated changes in water intake/urine volume. Chronic progressive nephropathy. Osteo-renal syndrome	Secondary hyper-parathyroidism associated with parathyroid gland hyperplasia.	10	100 Renal effects from 250	Osteo-renal syndrome caused by secondary hyperparathyroidism, suggestive of an endocrine mode of action.
18-month mouse oral long-term toxicity and carcinogenicity study	2	Mortality. Lung tumours. Increased liver weight and	Possible administration error.	5	40	No explicit evidence of endocrine

		glycogen deposits.				disruption
2-generation rat oral reproduction study	1	Increased parental liver weight. Chronic nephropathy and tubular atrophy of the kidneys in parents. Decreased pup weight.	No information reported	Parental: 10 Reproductive: 500 Neonatal: 250	Parental: 50 Reproductive: - Neonatal:500	No explicit evidence of endocrine disruption
Rat oral developmental and teratogenicity study	2	Reduced maternal food consumption and bodyweight gain. Retarded ossification in pups.	No information reported	Maternal: 30 Developmental: 30	Maternal: 300 Developmental: 300	No explicit evidence of endocrine disruption
Rabbit oral developmental and teratogenicity study	1	Diaphragmatic hernia and fissure in foetuses. Reduced maternal bodyweight gain and food consumption. Reduced foetal weight.	No information reported	Maternal: 30 Developmental: 10	Maternal: 100 Developmental: 30	No explicit evidence of endocrine disruption
Rabbit oral developmental and teratogenicity study	1	Reduced maternal bodyweight gain. Death. Abortion. Increased early resorptions.	No information reported	Maternal: 10 Developmental: 30	Maternal: 30 Developmental: 100	No explicit evidence of endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Osteo-renal syndrome occurred in rats in a 2 year oral study. This effect is caused by secondary parathyroid hyperactivity
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	This osteo-renal syndrome involves parathyroid gland hyperplasia, fibrous osteodystrophy and metastatic mineralization. It results from hyperparathyroidism and increase in parathyroid hormone. However, although there was parathyroid hyperplasia and bone effects are often seen with renal failure, parathyroid hormone was not measured and so there is no robust evidence of an endocrine effect.
Are the effects judged to be relevant to humans?	Yes	Osteo-renal syndrome can occur in humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	Osteo-renal syndrome effects seen from 250 mg/kg bw/day in a 2 year study. These dose levels are above the STOT-RE Category 1 guidance values of the CLP Regulation.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	No	-

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**There is data available from a full range of regulatory toxicology tests and the osteo-renal effect may be due to endocrine disruption but further evidence of endocrine disruption is required such as changes in parathyroid hormone concentrations.**
(B) Endocrine disrupter more likely to pose a risk based on currently available data	No	Group is not appropriate as endocrine disrupter effects occur above STOT-RE Cat 1 guidance values.
(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	Although effects on the parathyroid have been observed that may be indicative of endocrine disruption, this requires further evidence.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There is data available from a full range of regulatory toxicology tests that the substance may an endocrine disrupter, although this requires further information.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.57 Human Health Endocrine Disruption Evaluation for Propyzamide

Substance details						
Substance Name	**Propyzamide**					
Substance Synonyms	3,5-dichloro-*N*-(1,1-dimethylprop-2-ynyl)benzamide					
Substance CAS Number	23950-58-5					
Substance EC Number	245-951-4					
Data Source(s)	European Union Draft Assessment Report (1998)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Carc. Cat. 3; R40 N; R50-53 Carc. 2 Aquatic Acute 1 Aquatic Chronic 1	 Limited evidence of a carcinogenic effect. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Suspected of causing cancer. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2 year rat oral	2	Decreased bodyweight gain. Increased liver weight and liver hypertrophy. Increased thyroid follicle cell adenoma. Enlarged testes and benign testes interstitial tumours.	No information reported	8.46	42.59	Effects potentially caused by disruption of endocrine systems were observed (thyroid and testicular tumours and ovarian hyperplasia).

		Ovarian sertoliform hyperplasia.				
2 year mouse oral	2	Heptaocellular carcinomas and adenomas	No information reported	20 ppm	100 ppm	No endocrine mediated effects were observed.
3 generation rat oral	1	Decrease in maternal and offspring bodyweight gain.	No information reported	Parental: 15-18	Parental	No endocrine mediated effects were observed.
Developmental rat oral	1	Reduced maternal bodyweight gain.	No information reported	Maternal: 20 Foetal: 160	Maternal: 80 Foetal: -	No endocrine mediated effects were observed.
Developmental rabbit oral	2	Reduced maternal bodyweight. Mortality.	No information reported	Maternal: 5 Foetal: 80	Maternal: 20 Foetal: -	No endocrine mediated effects were observed.
Thyroid tumour mechanism study rat	2	Increased liver and thyroid weights. Hypertrophy of cells of the thyroid and pituitary. Decreased serum T4 Increased TSH	Induction of liver enzymes, decreasing circulating thyroid hormones, increasing TSH production.	3	Approximately 800	Evidence of endocrine disruption leading to formation of thyroid tumours.
Testicular tumour mechanism rat	2	Enlarged livers Pituitary hypertrophy Increased LH, FSH, oestradiol and corticosterone and metabolism of testosterone.	Increased metabolism of testosterone in the liver.	-	329	Evidence of endocrine disruption leading to formation of testicular tumours.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Thyroid and testis tumours and ovarian hyperplasia were observed in long term studies.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	Mechanistic studies have been conducted that demonstrate the thyroid tumours observed are due to the induction of liver enzymes, subsequently decreasing circulating thyroid hormones, leading to increased TSH production. The testis tumours also involve hormonal disruption.
Are the effects judged to be relevant to humans?	Yes	The thyroid tumours appear to be induced by increased catabolism of thyroid hormones due to increased liver enzyme activity (liver hypertrophy was observed) and this mechanism is considered not to be relevant to humans (due to quantitative differences between rats and humans in thyroid hormone homeostasis), However, the human relevance of the testis tumours and ovarian hyperplasia cannot be excluded..
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	A LOAEL of 42.59 mg/kg bw/day was reported in a 2 year oral study in rats, where effects potentially caused by disruption of endocrine systems were observed. This is above the STOT-RE Category 1 guidance values proposed in the UK-DE position paper.

Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	**Yes**	**Effects on the endocrine system, that have a defined mechanism which may plausibly occur in humans, have been observed at a dose above the STOT-RE category 1 guidance value. While the thyroid effects may not be relevant to humans, there are also effects on the testes.**
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The evidence suggests that the substance is an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.58 Human Health Endocrine Disruption Evaluation for Prosulfocarb

Substance details		
Substance Name	**Prosulfocarb**	
Substance Synonyms	*S*-benzyl *N*,*N*-dipropylthiocarbamate	
Substance CAS Number	52888-80-9	
Substance EC Number	401-730-6	
Data Source(s)	European Union Draft Assessment Report (2005)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xn; R22 R43 N; R51-53 Acute Tox. 4 * Skin Sens. 1 Aquatic Chronic 2	 Harmful if swallowed. May cause sensitization by skin contact. Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. May cause an allergic skin reaction. Toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
2-year rat oral long-term toxicity and carcinogenicity study	2	Decreased bodyweight gain Changes in urinalysis and haematological parameters	No information reported	1.9 (males) 0.5 (females)	17 (males) 2.3 (females)	No evidence of endocrine effects
18-month mouse oral long-term toxicity and carcinogenicity study	2	Decreased bodyweight	No information reported	269 (males) 350 (females)	>269 (males) >350 (females)	No evidence of endocrine effects

2-generation rat oral reproduction study	1	Parental: Decreased bodyweight Increased kidney weight Histopathological changes in the kidney Pups: Decreased weight	No information reported	Parental: 0.5 Reproduction: >50 Developmental: 5	Parental: 5 Reproduction:- Developmental: 50	No evidence of endocrine effects
Rat oral developmental and teratogenicity study	1	Maternal: Decreased food consumption and bodyweight gain Increased kidney and liver weights Pups: Decreased pup weights	No information reported	Maternal: 10 Developmental: 50	Maternal: 50 Developmental: 250	No evidence of endocrine effects
Rabbit oral developmental and teratogenicity study	1	Maternal: Gastrointestinal effects and decreased urination Increased abortions Pups: Single incidence of microphtalmia	No information reported	Maternal: 50 Developmental: 50	Maternal: 250 Developmental: 250	No evidence of endocrine effects

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Adverse effects occur in the kidney and liver and reduced bodyweight is observed in reproductive and developmental studies. These effects do not demonstrate that an endocrine mode of action is taking place.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are the effects judged to be relevant to humans?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	No effects potentially related to an endocrine mechanism of action were observed.

Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, prosulfocarb is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.59 Human Health Endocrine Disruption Evaluation for Pyridate

Assessment not carried out due to the absence of a suitable regulatory dossier

Table B.60 Human Health Endocrine Disruption Evaluation for Tepraloxydim

Substance details		
Substance Name	**Tepraloxydim (ISO)**	
Substance Synonyms	(RS)-(EZ)-2-{1-[(2E)-3-chloroallyloxyimino]propyl}-3-hydroxy-5-perhydropyran-4-ylcyclohex-2-en-1-one	
Substance CAS Number	149979-41-9	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (1999) BAS 620 - Tepraloxydim A brief search for more recent relevant studies did not locate any further information.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Carc. Cat. 3; R40 Repr. Cat. 3; R62-63	Limited evidence of a carcinogenic effect R62 Possible risk of impaired fertility R63 Possible risk of harm to the unborn child
Regulation (EC) No 1272/ 2008	Carc. 2 H351 Repr. 2 H361fd	Suspected of causing cancer Suspected of damaging fertility. Suspected of damaging the unborn child
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	↓body wt, ↑cholesterol and ↓chloride, ↑total proteins, ↓glucose and food consumption. Histopathological findings in kidneys.	No information reported	Ca 24	240	Main effects appear to involve liver and kidneys.

90-day dog oral study	1/2	Haematological findings, ↑wts of liver and thyroid gland, histopathological findings in spleen and bone marrow.	No information reported	Ca. 14	Ca. 66	Effects on the weight of thyroid gland may be indicative of endocrine disruption.
1-year dog oral study	1/2	Slight disturbance in lipid metabolism, wts of liver and thyroid gland, epididymides wt, hyperplasia of transitional epithelium of urinary bladder.	No information reported	12	58	Effects on the weights of thyroid gland and epididymis may be indicative of endocrine disruption.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↑total protein, albumin and cholesterol in females; ↓liver wt. (female). ↑eosinophilia Foci in the liver. No carcinogenic potential	No information reported	6	33	No effects indicative of endocrine disruption
18-month mouse oral long-term toxicity and carcinogenicity study	1/2	↓Body wt., body wt., change, relative liver wt. in males and at top dose ↑non neoplastic lesions (sclerosis of endometrial stroma, muscularis and perivascular areas) in uterus, ↓activities in ovaries, ↓secretory activity in seminal vesicles and preputial glands. No carcinogenic potential.	No information reported	45	45	Some lesions in the uterus.
2-generation rat oral reproduction study	1/2	Parental toxicity: 2500 ppm decreased food consumption reduced body wets and body wt. gains, ↑albumin and cholesterol, ↓triglycerides, ↑white blood cell count. Developmental toxicity ↓body wets and ↓body wt. gains, delayed eye opening.	No information reported	11(parental) 53 (development) 268 (reproduction):	53 (parental) 268 (development)	No reproductive toxicity in the absence of maternal toxicity.
Rat oral developmental and teratogenicity study	1/2	Maternal toxicity: ↓food consumption, ↓body wt. gain, ↓uterus wets Developmental toxicity: Slightly ↓mean foetal body wets, slightly ↑rate of skeletal retardation Reproduction toxicity increased resumptions and post,	No information reported	120 (maternal) 40 (development) 120 (reproduction)	360 (maternal) 120 (development) 360 (reproduction	Again effects on the uterus weight.

		implantation loss, lower mean, percentage of live foetuses, lower mean placental wt.				
Rabbit oral development and teratogenicity	1/2	Maternal: ↓food intake, impaired body wt. gain Embryofoetotoxicity: No test substance-related changes	No information reported	60 (maternal) 180 (development)	180 (maternal	No substance related changes detected.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Effects on the thyroid and epididymis weights in the dog and on uterus (weights and histopathology) in the mouse raise a concern for endocrine disruption but no mechanistic evidence is available.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There are effects seen on the thyroid and on organs under endocrine control (uterus and epididymis), but no endocrine disruption mode of action has been shown.
Are the effects judged to be relevant to humans?	Yes	There is no evidence that the effects on thyroid, epididymis and uterus are not relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	At present it is unclear whether or not tepraloxydim is an endocrine disrupter.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Category	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**Although there are some effects on organs producing or reacting to hormones, there is no mechanistic evidence that tepraloxydim is an endocrine disrupter.**
(B) Endocrine disrupter more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.

(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There are effects seen in a full set of regulatory tests that could be due to endocrine disruption but further evidence would be required on a potential mechanism.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.61 Human Health Endocrine Disruption Evaluation for Terbuthylazine

Substance details	
Substance Name	**Terbuthylazine**
Substance Synonyms	N-tert-butyl-6-chloro-N'-ethyl-1,3,5-triazine-2,4-diamine (IUPAC)
Substance CAS Number	5915-41-3
Substance EC Number	-
Data Source(s)	European Union Draft Assessment Report (2007); A brief search for recent relevant studies located the following papers: EFSA (2011) Conclusion on the peer review of the pesticide risk assessment of the active substance terbuthylazine, 9, 1969; Creusot N, Kinoni S, Balaguer P, Tapie N, LeMenach K, Maillot-Maréchel E, Pocher JM, Budzinski H, Aït-Aïssa S (2010) Evaluation of a hPXR reporter gene assay for the detection of aquatic emerging pollutants: screening for chemicals and application to water samples. *Anal Bioanal Chem,* **396**, 569-583.

Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
90-day rat oral study	1/2	↓wt gain, haematology and clinical chemistry	No information reported	2.08 (male) 2.13 (female)	7.11 7.18	No evidence of endocrine disruption
1-year dog oral study	1/2	↓body wt and food consumption	No information reported	0.4 (male) 0.4 (female)	1.8 1.6	No evidence of endocrine disruption

2-year rat oral long-term toxicity and carcinogenicity study	1/2	↓body wt and food consumption, absence of corpora lutea; uterine, cervical and mammary gland hyperplasia. Haematology & histopathology. ↑mammary adenomas and carcinomas	The EU DAR considered that some of these effects were consistent with a hormonal effect.	0.4 (male) 0.6 (female)	1.7 2.4	A number of these effects are consistent with hormonal disruption of the female reproductive system.
2-generation rat oral reproduction study	1/2	Reproductive: ↓fertility in females Adult: ↓body wt Offspring: ↓pup wt and viability	No information reported	4.5 (reproductive) 0.4 (adults) 0.4 (offspring)	21.8 4.5 4.5	Reduced fertility in females associated with parental toxicity. It was judged by the EFSA Conclusion that there was insufficient evidence to trigger a classification proposal regarding reproduction. Therefore, as the fertility effects were considered secondary to the parental toxicity, they do not raise a concern for endocrine disruption.
Rat oral developmental and teratology study	1/2	Maternal: clinical signs, ↓body wt and food consumption. Developmental: interventricular septal defect	No information reported	5 (maternal) 5 (developmental)	25 25	Minor foetal skeletal effects considered to be secondary to maternal toxicity. Overall, no evidence of endocrine disruption.
Rabbit oral developmental and teratology study	1/2	↓body wt and food consumption	No information reported	1.5 (maternal) 5 (developmental)	5 -	No evidence of endocrine disruption.
In vitro study	2		Weak to moderate human PXR activation. Human pregnane X receptor (hPXR) agonist	N/A	N/A	No evidence of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There are effects consistent with endocrine disruption of the female reproduction system. However, these are inconsistent across a range of studies such that EFSA concluded that there was insufficient evidence to classify the substance for reproduction.

Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no mechanistic information to indicate an endocrine disrupter mode of action.
Are the effects judged to be relevant to humans?	N/A	The substance is not an established endocrine disrupter.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	The substance is not an established endocrine disrupter.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Category	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**Further mechanistic information is required to establish whether there is an endocrine disruption mode of action.**
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	There is no robust evidence that the substance is an endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is no robust evidence that the substance is an endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	Further information is required.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.62 Human Health Endocrine Disruption Evaluation for Triallate

Substance details						
Substance Name	**Triallate**					
Substance Synonyms	S-2,3,3-trichloroallyl diisopropyl(thiocarbamate) (IUPAC) S-(2,3,3-trichloro-2-propen-1-yl) N,N-bis(1-methylethyl)carbamothioate (CAS)					
Substance CAS Number	2303-17-5					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2007). A brief search for more recent relevant studies located the following paper, which is summarised below: Rawlings NC; Cook SJ; Waldbillig D (1998). Effects of the pesticides carbofuran, chlorpyrifos, dimethoate, lindane, triallate, trifluralin, 2,4-D, and pentachlorophenol on the metabolic endocrine and reproductive endocrine system in ewes. *J Toxicol Environ Health*, **54**, 21-36					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	↓body wt and body wt gain, renal toxicity attributed to alpha2µ-globulin deposits and subsequent nephropathy, slight anaemia.	No information reported	6.7 (male) 8.1 (female)	33.3 40.5	No evidence of endocrine disruption.
1-year dog oral study	1/2	Clinical chemistry changes (↑Alk Phos), ↑liver wt.	No information reported	2.5	15	No evidence of endocrine disruption.

2-year rat oral long-term toxicity and carcinogenicity study	1/2	↑mortality, ↓mean body wt and body wt gain, testicular atrophy (macroscopic and microscopically) in males that died or were sacrificed in extremis after the interim kill most likely secondary due to the severe toxicity (increased mortality) observed at this dose level. Chronic progressive nephropathy, slightly ↑severity in males considered most likely due to alpha2µ-globulin accumulation No carcinogenic potential.	No information reported	2.5 (males) 3.1 (females)	13 16	Testicular atrophy may be due to endocrine disruption but most likely to be due to severe generalised toxicity (e.g. increased mortality).
2-generation rat oral reproduction study	1/2	↓body wt during lactation in dams in F0 and F1. ↓pup birth wt and pre-weaning wt.	No information reported	Parental and developmental: 9 (male) 12.2 (females) Reproduction: 9 (male) 12.2 (females)	Parental and developmental: 30.74 Reproduction: 30.74	No direct evidence of endocrine disruption
Rat oral developmental study	1/2	Parental: mortality, clinical signs including circling movements and ↓maternal body wt gain. Developmental: foetotoxicity, ↓foetal birth wt and ↑incidence in retarded ossification of the skull and malaligned sternebrae.	No information reported	30 (parental) 30 (developmental)	90 90	No direct evidence of endocrine disruption
Rabbit oral developmental study	1/2	Maternal:↓body wt gain during gestation Developmental: ↓foetal body wt. ↑incidence of fused sternebrae. No teratogenic effect	No information reported	15 (parental) 15 (developmental)	45 45	No direct evidence of endocrine disruption
Effects of triallate, on the metabolic endocrine and reproductive endocrine system in ewes (36 day treatment (5 mg/kg))	2	↑serum insulin, ↑serum LH, ↑severity of oviductal intraepithelial cysts.	No information reported	-	-	Older study not quoted in EU DAR but in other reviews. Suggests some endocrine effects but unusual study in non-conventional species.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	The regulatory studies show no evidence of endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	With the exception of a non-conventional study in ewes, there is no mechanistic information.
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	The evidence suggests that the substance is not an endocrine disrupter.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, triallate is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.63 Human Health Endocrine Disruption Evaluation for Triclopyr

Substance details		
Substance Name	**Triclopyr**	
Substance Synonyms	3,4,6-trichloro-2-pyridinyloxyacetic acid	
Substance CAS Number	55335-06-3	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (2003)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	- -	- -
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
90-day rat oral study	1	Increased relative kidney weight.	No information reported	30	100	No evidence of an endocrine effect.
1-year dog oral study	1	None	No information reported	5	>5	No evidence of an endocrine effect.
2-year rat oral long-term toxicity and carcinogenicity study	1	Increased kidney weights.	No information reported	3	12	No evidence of an endocrine effect.

2-year mouse oral long-term and carcinogenicity study	1	Minimal kidney and liver effects.	No information reported	5	27	No evidence of an endocrine effect.
2-generation rat oral reproduction study	1	Increased parental nephrotoxicity, decreased mating, conception and fertility indices, decreased litter size, pup bodyweight and survival.	No information reported	Parental 5 Reproductive 25 Developmental 25	Parental 25 Reproductive 250 Developmental 250	Reprotox effects occurred in the presence of maternal toxicity. Overall, no clear evidence of endocrine disruption.
Rat oral developmental and teratogenicity study	1	Decreased maternal bodyweight gain. Increased litter effects, visceral and skeletal anomalies.	No information reported	Maternal 5 Developmental 5	Maternal 30 Developmental 30	Foetal effects occurred in the presence of maternal toxicity. Overall, no clear evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1	Two maternal mortalities. Increased resorption, early embryonic death and post implantation loss. Increased sternebral centres, decreased ossification, extra ribs.	No information reported	Maternal 30 Developmental 30	Maternal 100 Developmental 100	Foetal effects occurred in the presence of maternal toxicity. Overall, no clear evidence of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Effects potentially caused by endocrine disruption did not occur.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No mechanistic information is available.
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	-
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, triclopyr is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects.

Insecticides

Table B.64 Human Health Endocrine Disruption Evaluation for Abamectin

Substance details		
Substance Name	**Abamectin**	
Substance Synonyms	mixture of (10E,14E,16E)-(1R,4S,5′S,6S,6′R,8R,12S,13S,20R,21R,24S)-6′-[(S)-sec-butyl]-21,24-dihydroxy-5′,11,13,22-tetramethyl-2-oxo-(3,7,19-trioxatetracyclo[15.6.1.14,8.020,24]pentacosa-10,14,16,22-tetraene)-6-spiro-2′-(5′,6′-dihydro-2′H-pyran)-12-yl 2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl-α-L-arabino-hexopyranosyl)-3-O-methyl-α-L-arabino-hexopyranoside and (10E,14E,16E)-(1R,4S,5′S,6S,6′R,8R,12S,13S,20R,21R,24S)-21,22-dihydroxy-6′-isopropyl-5′,11,13,22-tetramethyl-2-oxo-(3,7,19-trioxatetracyclo[15.6.1.14,8.020,24]pentacosa-10,14,16,22-tetraene)-6-spiro-2′-(5′,6′-dihydro-2′H-pyran)-12-yl 2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl-α-L-arabino-hexopyranosyl)-3-O-methyl-α-L-arabino-hexopyranoside (IUPAC)	
Substance CAS Number	71751-41-2	
Substance EC Number	265-610-3	
Data Source(s)	European Union Draft Assessment Report (2005). A brief search for recent relevant studies found the following additional information; Celik-Ozenci C, Tasatargil A, Tekcan M, Sati L, Gungor E, Isbir M and Demir, R. Effects of abamectin exposure on male fertility in rats: Potential role of oxidative stress-mediated poly(ADP-ribose) polymerase (PARP) activation. *Regulatory Toxicology and Pharmacology*, **61 (3)**, 310-317 Elbetieha A and Da'as S I (2003) Assessment of antifertility activities of abamectin pesticide in male rats. *Ecotoxicology and Environmental Safety*, **55(3)**, 307-13.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
18-week dog oral study with Avermectin B1a	1	Mortality, clinical signs of toxicity - ataxia, tremors, mydriasis (dilation of pupils), ptyalism (excessive salivation), ↓wt gain, histopathological changes in the liver	No information reported	0.25	0.5	No evidence of endocrine disruption. There was only an 8-week range finding study in rats so only the 18-week and 52-week studies in dog were considered relevant.
1-year dog oral study	1	Absent or ↓pupil reflex (death at 1.0 mg/kg bw/day)	No information reported	0.25	0.5	No evidence of endocrine disruption
2-year rat long-term toxicity and carcinogenicity study	1	Increased mortality in males, clinical signs (tremors, unthrifty appearance). No carcinogenic potential.	No information reported	1.5	2	No evidence of endocrine disruption
2-generation rat oral reproduction study	1/2	Parent: ↑mating time, ↓number of males and females mating, increased duration of cohabitation, ↑number of dams with prolonged interoestrus, less females littering Foetuses/pups: ↑pup mortality, retarded weight gain pups (F1 and F2), ↑incidence of total litter loss, ↓lactation index, ↑incidence of retinal anomaly in the eyes of pups (F1 and F2)	No information reported	0.12	0.4	There are a number of effects that may be indicative of endocrine disruption in both the dams and pups, e.g. effects on lactation and oestrus. Maternal and reproduction toxicity occurred at similar dose levels.
Rat oral developmental and teratogenicity study	1/2	Cleft palate, lumbar rib and lumbar count variation	No information reported	1.6 (maternal) 0.8 (developmental)	>1.6 1.6	No evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1/2	Maternal: ↓water and food consumption and weight loss during gestation, ↑number of resorptions. Developmental: cleft palate, omphalocele, clubbed fore-feet and delayed ossification.	No information reported	1.0 (maternal) 1.0 (developmental)	2.0 2.0	No evidence of endocrine disruption
Other *in vivo* data from published literature Male fertility in Sprague Dawley rats (6 week	2	Reduced male fertility as number of females impregnated by them	The pregnancy rate and the number of viable	<1.19 mg/animal/ day	1.19 mg/animal/ day	The results suggest that exposure to the pesticide

exposure to abamectin, purity not stated) - Elbetieha and Da'as (2003)		was significantly reduced Reduction in number of viable foetuses Significant increases in the total number of resorptions and the number of females with resorptions in females mated with the exposed males Increase in the absolute weight of testes	foetuses were significantly reduced in females impregnated by abamectin-exposed males. The serum level of testosterone was decreased, while the level of FSH was reduced in males that ingested abamectin. The observed decrease in male fertility could be explained by the fact that the pesticide acted directly on the testes and affected the androgen biosynthesis pathway. An agent acting directly on the brain, hypothalamus, or anterior pituitary gland will indirectly affect the testes and will possibly affect sexual activity (see mechanistic data) The increased weight of testes may be attributed to the accumulation of interstitial connective tissue around the seminiferous tubules.	1.19 mg/animal/ day <1.19 mg/animal/ day <1.19 mg/animal/ day	1.87mg/animal/ day 1.19mg/animal/ day 1.19 mg/animal/ day	abamectin would have adverse effects on fertility and reproduction in adult male rats and possible other mammalian wildlife which are evidently endocrine mediated.
Male fertility in rats (1-6 week exposure to abamectin, purity not stated) - Celik-Ozenci *et al*. (2011)	2	Change in testes weights Decreased sperm count and motility Increased seminiferous tubule damage	The results showed that abamectin exposure induces testicular damage and affects sperm dynamics. It was suggested that oxidative stress-mediated PARP activation could be one of the possible mechanism(s) underlying testicular damage induced by abamectin	≥4 mg/kg bw/day <1 mg/kg bw/day <1 mg/kg bw/day	Not relevant 1 mg/kg bw/day 1 mg/kg bw/day	The results suggest that exposure to the pesticide abamectin would have adverse effects on fertility and reproduction in adult male rats

Mechanistic (*in vitro* and *in vivo*) data Male fertility in Sprague Dawley rats (6 week exposure to abamectin, purity not stated) - Elbetieha and Da'as (2003)	2	Decreased epididymal and testicular sperm counts and daily sperm production Decreased serum level of testosterone Increased serum level of follicle-stimulating hormone Change in lutenizing hormone	-	<1.19 mg/animal/ day <2.3 mg/animal/ day <2.3 mg/animal/ day 2.3 mg/animal/ day	1.19 mg/animal/ day 2.3 mg/animal/ day 2.3 mg/animal/ day >2.3 mg/animal/ day	The reductions may be caused by a direct effect of the pesticide on testicular Leydig and Sertoli cells, causing a decrease in testosterone production.
Male fertility in rats (1-6 week exposure to abamectin, purity not stated) - Celik-Ozenci et al. (2011)	2	Change in serum testosterone and lutenising hormone concentrations Reduction in follicle stimulating hormone concentration Significant elevations in the 4-hydroxy-2-nonenal (4-HNE)-modified proteins and poly(ADP-ribose) (PAR) expression as markers for oxidative stress and poly(ADP-ribose) polymerase (PARP) activation	-	>4 mg/kg bw/day <1 mg/kg bw/day <1 mg/kg bw/day	Not relevant 1 mg/kg bw/day 1 mg/kg bw/day	Exposure to abamectin may lead to ATP failure and testicular damage as a result of increased PARP enzyme activity. The activation of PARP results in a rapid depletion of intracellular ATP, a source of energy for the forward movement of spermatozoa. Full ATP pool is also crucial for normal spermatozoal movement and a slight deprivation of ATP leads to reduction in motility, which may cause infertility. Thus, marked inhibition of sperm motility after ABM exposure may be related with low levels of ATP content as a consequence of increased enzymatic activity of PARP.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There are a number of effects on lactation and oestrus and male reproductive function which could potentially be related to endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	In some recent studies, effects on the levels of testosterone, FSH and LH have been observed. Although it is unclear whether these hormonal changes are the cause or the consequence of the toxic effects seen in the reproductive organs, an endocrine disruption mechanism of action is plausible.
Are the effects judged to be relevant to humans?	Yes	The reported effects could be relevant to humans although rat hormonal control is different to human.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	Yes	endocrine disrupter-mediated adverse effects have been observed at relatively low dose levels below the STOT-RE Cat 1 guidance values.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	A detailed assessment has been carried out as part of the project.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	The evidence establishes the substance as an endocrine disrupter.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	**Yes**	**There are clear toxic effects due to endocrine disruption observed at or below the STOT-RE Category 1 guidance value in regulatory tests (2-generation rat oral reproduction test).**
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	The endocrine disruption effects observed give rise to concerns over potential risks.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The endocrine disruption effects observed give rise to concerns over potential risks.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.65 Human Health Endocrine Disruption Evaluation for Clothianidin

Substance details		
Substance Name	**Clothianidin (ISO)**	
Substance Synonyms	3-[(2-chloro-1,3-thiazol-5-yl)methyl]-2-methyl-1-nitroguanidine	
Substance CAS Number	210880-92-5	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (2003)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xn; R22 N; R50-53 Acute Tox. 4 * H302 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	 Harmful if swallowed Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Harmful if swallowed Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	↓body wt, body wt gain, ↑ovary / uterus wt	No information reported	19.7 (male) 24.0 (female)	96.0 (male) 119.0 (female)	When another similar study was conducted the effects on ovarian and uterus wt were not observed so these results must be taken with caution.

1-year rat oral study	1/2	↓WBC, neutrophils.	No information reported	36.3 (males) 40.1 (females)	46.4 (males) 52.9 (females)	No evidence of endocrine disruption.
2-year rat oral long-term toxicity and carcinogenicity oral study	1/2	↓feed consumption, body wt effects, interstitial ovarian gland hyperplasia	No information	9.7 157 (carcinogenicity, highest doses tested)	32.5	Effects on the female reproductive system.
2-year mouse oral long-term toxicity and carcinogenicity oral study	1/2	body weight effects, clinical signs, liver cell hypertrophy, cervix hyperplasia	No information reported	47.2 (male) 251.9 (female)	171.4	Effects on the female reproductive system.
2-generation rat oral reproduction study	1/2	Parent offspring toxicity: Body wt effects, preputial separation/vaginal opening patency, thymus wt Reproductive toxicity: stillborns, sperm motility and morphology effects No reproductive toxicity	No information reported	Parental/offspring toxicity 10.2 Reproduction toxicity 32.7	Parental/offspring toxicity 32.7 Reproduction toxicity 179.6 d	Effects on the female and male reproductive system.
Rabbit oral developmental and teratogenicity study	1/2	Maternal: mortality, clinical signs Foetal: abortions, premature deliveries foetal wt, intermediate lung lobe absence, sternal ossification centres	No information reported	10 (maternal) 25 (foetal/developmental)	25 (maternal) 75 (foetal/developmental)	-
Investigation on enzyme induction	4	Slight enzymatic induction potential in the liver; no influence on thyroid hormone activity (T3, T4, TSH) in 90d rat study.	There was some suggestion that induction of aromatase though the CYP-isoform, CYP19 might possibly responsible for reprotoxicity but this shows only weak induction and there is no further evidence.	N/A	N/A	-

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There are male and female reproductive effects (ovarian gland and cervix hyperplasia, preputial separation/vaginal opening, sperm motility) which might suggest endocrine disruption although this is only present at high doses at which there is generalised toxicity. The suggestion that enzyme induction in the liver might lead to increased aromatase activity is not proven.

Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	Although an endocrine disruption mode of action is plausible, it is possible that the observed adverse effects are secondary to generalised toxicity and the suggestion that enzyme induction in the liver might lead to increased aromatase activity is not proven. Given this uncertainty, further mode of action information would be needed.
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	-
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	**-**
Overall grouping of the substance regarding its endocrine disrupting properties		
Category	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**There are some effects suggestive of endocrine disruption. However, these are at high doses and further studies would be necessary to confirm the effects and investigate a potential mechanism of action.**
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There are some effects suggestive of endocrine disruption. However, these are at high doses and further studies would be necessary to confirm the effects and investigate a potential mode of action.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.66 Human Health Endocrine Disruption Evaluation for Beta-cyfluthrin

Substance details		
Substance Name	**Beta-cyfluthrin**	
Substance Synonyms	α-cyano-4-fluoro-3-phenoxybenzyl-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate	
Substance CAS Number	68359-37-5	
Substance EC Number	269-855-7	
Data Source(s)	European Union Draft Assessment Report (2003). A brief search for recent relevant studies found the following additional information: Hayes T B, Case P, Chui S, Chung D, Haeffele C, Haston K, Lee M, Mai V P, Marjuoa Y, Parker J and Tsui M (2006) Pesticide mixtures, endocrine disruption, and amphibian declines: Are we underestimating the impact? *Environmental Health Perspectives*, **114(S-1)**, 40-50. Zhang, J., Zhu, W., Zheng, Y., Yang, J., Zhu, X. (2008) The antiandrogenic activity of pyrethroid pesticides cyfluthrin and β-cyfluthrin. *Reproductive Toxicology*, **25(4),** 491-496.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 T+; R26/28 N; R50-53 Acute Tox. 2 * Acute Tox. 2 * Aquatic Acute 1 Aquatic Chronic 1	 Very toxic by inhalation and if swallowed. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Fatal if inhaled. Fatal if swallowed. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
2 year rat oral	1	Decreased bodyweight.	No information reported	2.02	Approx: 6	No evidence of an endocrine effect.

2 year mouse oral	1	Decreased bodyweight. AP increased.	No information reported	11.6	Approx: 40	No evidence of an endocrine effect.
3 generation rat oral	1	Reduced bodyweight Reduced pup viability.	No information reported	3.74	3.74	No evidence of an endocrine effect.
Developmental rat oral	1	Clinical signs of toxicity in dams.	No information reported	3	30	No evidence of an endocrine effect.
Developmental rabbit oral	1	Increased miscarriage rate.	No information reported	15	45	No evidence of an endocrine effect.
Other *in vivo* data from published literature Castrated male Wistar rats in the Hershberger assay (exposure to cyfluthrin, purity 92.6% and ß-cyfluthrin, purity 97.0%) - Zhang *et al*. (2008)	2	Decreases in the weight of seminal vesicle, ventral prostate, dorsolateral prostate, LABC and Cowper's glands Change in glans penis weight Maternal weight gain Decrease in seminal vesicle weight Decreases in the weight of seminal vesicle, ventral prostate, dorsolateral prostate, LABC and Cowper's glands Maternal weight gain	No information reported	6 mg a.s./kg (cyfluthrin) 54 mg a.s./kg (cyfluthrin) 54 mg a.s./kg (cyfluthrin) 4 mg a.s./kg (ß-cyfluthrin) 12 mg a.s./kg (ß-cyfluthrin) 36 mg a.s./kg (ß-cyfluthrin)	18 mg a.s./kg (cyfluthrin) Not relevant Not relevant 12 mg a.s./kg (ß-cyfluthrin) 36 mg a.s./kg (ß-cyfluthrin) Not relevant	Effects could be endocrine-mediated
Mechanistic (*in vitro* and *in vivo*) data Androgen receptor antagonistic effects using a stably transfected, androgen-responsive cell line, MDA-kb2 – Zhang *et al*. (2008)	2	Reduced DHT-induced transcriptional activation	-	0.0434 mg/l	0.434 mg/l	The results suggest that beta-cyfluthrin has low potency as androgen receptor antagonists

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Although in recent papers effects on the male reproductive organs (Heshberger assay) have been reported, these have not been confirmed in the apical studies, Overall, there is no clear evidence of adverse effects indicating a concern for endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	There is some limited information *in vitro* and *in vivo* screening assays indicating a potential for endocrine activity, but this activity does not lead to clear adverse effects.
Are the effects judged to be relevant to humans?	N/A	No adverse effects potentially related to an endocrine mechanism of action were observed.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	A detailed assessment has been carried out as part of the project.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**Regulatory studies show no evidence of endocrine disruption, but some recent mechanistic data indicate a potential for endocrine activity. There is concern that the apical studies were not performed in accordance with recent guidelines and did not include more sensitive endocrine endpoints. Further information is required.**
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Evidence has not established this substance as an endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Evidence has not established this substance as an endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	Further information is required.

Notes:
[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?
[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.67 Human Health Endocrine Disruption Evaluation for Lamda-cyhalothrin

Substance details		
Substance Name	**Lambda-cyhalothrin (ISO)**	
Substance Synonyms	reaction mass of (S)-α-cyano-3-phenoxybenzyl(Z)-(1R)-cis-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate and (R)-α-cyano-3-phenoxybenzyl (Z)-(1S)-cis-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate (1:1)	
Substance CAS Number	91465-08-6	
Substance EC Number	415-130-7	
Data Source(s)	EU (2011) Directive 98/8/EC concerning the placing biocidal products on the market Inclusion of active substances in Annex I or IA to Directive 98/8/EC, Assessment Report, lambda-cyhalothrin Product-type 18, (Insecticide) Zhao, M., Zhang, Y., Liu, W., Xu, C., Wang, L., Gan, J. (2008) Estrogenic activity of lambda-cyhalothrin in the MCF-7 human breast carcinoma cell line. *Environmental Toxicology and Chemistry*, **27(5),** 1194-1200. Nishihara T, Nishikawa J, Kanayama T, Dakeyama F, Saito,K, Imagawa M, Takatori S, Kitagawa Y, Hori S and Utsumic H (2000) Estrogenic Activities of 517 Chemicals by Yeast Two-Hybrid Assay. *Journal of Health Science*, **46(4),** 282-298.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	 T+; R26 T; R25 Xn; R21 N; R50-53	 Very toxic by inhalation Toxic if swallowed Harmful in contact with skin Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Acute Tox. 2 * H330 Acute Tox. 3 * H301 Acute Tox. 4 * H312 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	Fatal if inhaled Toxic if swallowed Harmful in contact with skin Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	↓body wt gain, liver effects (↑liver weight, proliferation of smooth endoplasmic reticulum and ↑hepatic aminopyrine-N-demethylase activity)	Liver effects were considered to represent an adaptive response to ↑liver workload since reversibility of effects was demonstrated during a recovery period in a 28 day rat study.	3	14	No evidence of endocrine disruption.
1-year dog oral study	1/2	Neurological effects (unsteadiness, lack of muscular co-ordination), gastro-intestinal effects and ↓ food intake.	No information reported	0.5	3.5	Neurological effects common in dogs. No evidence of endocrine disruption.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	No evidence of carcinogenicity. ↓body wt gain	No information reported	1.8	9	No evidence of endocrine disruption.
2-year mouse oral long-term carcinogenicity oral study	1/2	Increased incidence of mammary adenocarcinomas in female mice (above incidence in concurrent and historical controls). Neurological effects.	The results of the studies performed do not give sufficient evidence for classification as a carcinogenic substance.		11 (lowest dose with tumours)	No evidence of a role for endocrine disruption in the mammary tumours found only in mice..
3-generation rat oral reproduction study	1/2	↓body wt with associated effects on mean litter wt. No adverse effects on adult fertility or reproduction	No information reported	Parental reproductive: 2 Offspring 2	5 5	Similar results found in rabbits
Rat oral developmental and teratogenicity study	1/2	No adverse foetal findings/↓maternal body wt gain and food intake, uncoordinated movements observed in two adult animals	No information reported	10 (maternal)	>15 (developmental, highest dose tested)	Similar results found in rabbits
Estrogenic activity using the yeast two hybrid assay – Nishihara *et al*. (2000)	2	Evidence of estrogenic activity	-	100 mg/l (REC10) (>0.3 mM (REC10)	Not relevant	The result is not considered to show positive estrogenic activity because the activity of the test substance was less than 10% of the activity of 10^{-4} mM

						E2,
Estrogenic activity using the cell proliferation assay with the MCF-7 human cell line – Zhao *et al*. (2008)	2	2 times increase in cell proliferation, relative proliferative effect of 45% Increased expression of the pS2 and PR mRNA by 2 and 1.5 times	-	<0.045 (<0.1 µM) <0.045 (<0.1 µM)	0.045 (0.1 µM) 0.045 (0.1 µM)	The results suggest lambda cyhalothrin possesses estrogenic properties and may function as a xeno-estrogen
EU Statement on Endocrine Disruption	4	-	Initial work carried out under the EU Strategy for Endocrine Disruptors included cyhalothrin in Group III of a list of 553 candidate priority substances with the potential to act as endocrine disruptors in both humans and animals. In a follow-up to the first prioritising exercise, further information was gathered and presented for chemicals not previously prioritised. Substances were categorized specifically in relation to human health and wildlife. Overall, cyhalothrin was identified as Category 1. As part of the evaluation of the application for the inclusion of lambda-cyhalothrin in Annex I of the Biocidal Products Directive (98/8/EC) toxicology and ecotoxicology data are assessed. It is concluded that there was no clear evidence of endocrine disruption effects from these studies. However, it should be noted that due to limitations in the test guidelines available at the time, the potential for endocrine effects may not have been fully investigated. The RMS recommends that the potential for endocrine disruption is reconsidered when EU	-		-

			harmonised guidance is established based on the work and final conclusions of the EC work on defining criteria to identify endocrine disrupting substances.			

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Mammary adenocarcinomas were detected in mice but there were no reproductive or developmental effects in rats or rabbits (no studies in mice).
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is limited evidence from published studies that the substance has weak oestrogenic activity *in vitro*. However, it is unclear whether this activity is responsible for the mammary tumours.
Are the effects judged to be relevant to humans?	N/'A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	-
***Would there be benefits to carry out an ecotoxicological* endocrine disruption assessment?**	**No**	A detailed assessment has been carried out as part of the project.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**Further mechanistic information is required to clarify the aetiology of the mammary tumours.**
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as evidence has not the substance as an endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as evidence has not established the substance as an endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	Further information is required.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.68 Human Health Endocrine Disruption Evaluation for Diflubenzuron

Substance details		
Substance Name	**Diflubenzuron**	
Substance Synonyms	N-[(4-Chlorophenyl)carbamoyl]-2,6-difluorobenzamide (IUPAC)	
Substance CAS Number	35367-38-5	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (2008)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
90-day rat oral study	1/2	↑Increase in MetHb,↑liver wt	No information reported	4	50	Anaemia is the main toxic effect due to the formation of metHb and sulphurHb. No evidence of endocrine disruption
1-year dog oral study	1/2	↑Increase in MetHb ↑Increase in SulphurHb Changes on organ wt and histopathological changes.	No information reported	2	10	No evidence of endocrine disruption

2-year rat oral long-term toxicity and carcinogenicity study	1/2	↑metHb, ↑sulphurHb ↑spleen wt both sexes adjusted liver wt, females No carcinogenic potential.	No information reported	7.8	120	No evidence of endocrine disruption
2-generation rat oral reproduction study	1/2	↑metHb ↑liver and spleen wt and histopathological changes No effect on reproduction.	No information reported	< 30	≤ 30	No evidence of endocrine disruption
rat oral developmental and teratogenicity study	1/2	No maternal toxicity or any evidence of embryotoxicity	No information reported	≥ 1 000	≥1 000	No evidence of endocrine disruption
rabbit oral developmental and teratogenicity study	1/2	No maternal toxicity or any evidence of embryotoxicity	No information reported	≥ 1 000	≥ 1 000	No evidence of endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	There is no evidence of endocrine disruption in a full range of regulatory tests.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no evidence of endocrine disruption in a full range of regulatory tests.
Are the effects judged to be relevant to humans?	N/A	-
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	There is no evidence of endocrine disruption in a full range of regulatory tests.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupter more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**There is no evidence of endocrine disruption in a full range of regulatory tests**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.69 Human Health Endocrine Disruption Evaluation for Fenoxycarb

Substance details	
Substance Name	**Fenoxycarb**
Substance Synonyms	ethyl [2-(4-phenoxyphenoxy)ethyl]carbamate
Substance CAS Number	72490-01-8
Substance EC Number	276-696-7
Data Source(s)	European Union Draft Assessment Report (2010)

Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 N; R50-53 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
90-day rat oral study	1/2	↑cholesterol, ↑liver weight, large liver, hepatocellular centrilobular hypertrophy, follicular hypertrophy in thyroid.	No information reported	9.71 (male) 10.1 (female)	45.1 (male) 49.6 (female)	Effects on the thyroid which may be indicative of endocrine disruption.
1-year dog oral study	1/2	↓body weight gain, ↑relative liver weight.	No information reported	< 25	25	No evidence of endocrine disruption.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	Clinical biochemistry changes, mostly liver enzymes, liver weights, hypertrophy, focal necrosis	No information reported	8.1 (male) 10.9 (female)	24.7 (male) 33.1 (female)	No evidence of endocrine disruption.

18-month mouse oral long-term toxicity and carcinogenicity study	1/2	Pulmonary and hepatocellular tumours, hepatic foci of cellular change. Carcinogenic potential in male mice.	No information reported	5.8 (male) 5.3 (female)	55.4 (male) 51.5 (female)	No evidence of endocrine disruption.
2-generation rat oral reproduction study	1/2	Parental: ↑liver weight. Developmental: ↓body wt and ↑liver weight. Reproduction: No effects on reproduction.	No information reported	13 parental) 13 (developmental) ≥ 119 (reproduction)	40 40 -	No evidence of endocrine disruption.
Rat oral developmental and teratogenicity study	1/2	Maternal: Increased incidence of nervousness. Development: No effects. Teratogenicity: No effects	No information reported	50 (maternal) ≥ 500 (developmental) ≥ 500 (teratogenicity)	150 - -	No evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1/2	Maternal: ↓body wt gain. Developmental: No effects. Teratogenicity: ↑incidence of spina bifida	No information reported	100 (maternal) ≥ 300 (developmental) 200 (teratogenicity)	200 - 300	No evidence of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	The only evidence for endocrine disruption was follicular hypertrophy in the thyroid in a 90-day study but this observation has not been repeated in other studies.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no significant evidence of an endocrine disruption mode of action.
Are the effects judged to be relevant to humans?	N/A	There is no significant evidence of endocrine disruption
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	There is no significant evidence of endocrine disruption
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	A detailed assessment has been carried out as part of the project.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupter more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**There is a full range of regulatory toxicology tests and no evidence of endocrine disruption. Therefore, fenoxycarb is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.70 Human Health Endocrine Disruption Evaluation for Imidacloprid

Substance details	
Substance Name	**Imidacloprid**
Substance Synonyms	1-(6-chloropyridin-3-ylmethyl)-*N*-nitroimidazolidin-2-ylidenamine
Substance CAS Number	138261-41-3
Substance EC Number	428-040-8
Data Source(s)	European Union Draft Assessment Report (2006)

Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xn; R22 N; R50-53 Acute Tox. 4 * Aquatic Acute 1 Aquatic Chronic 1	 Harmful if swallowed. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Harmful if swallowed. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2-ear rat oral long-term toxicity and carcinogenicity study	1	Reduced bodyweight gain. Decreased plasma cholesterol. Mineralisation of thyroid follicles.	No information reported	5.7 (males) 24.9 (females)	Approx 24.9 (males) Approx 75 (females)	No evidence of endocrine effect.
18-month mouse oral long-term toxicity and carcinogenicity study	1	Reduced bodyweight gain. Liver effects. CNS effects.	No information reported	65.6 (males) 103.6 (females)	Approx: 195 (males) Approx: 300	No evidence of endocrine effect.

		Decreased plasma cholesterol. Mineralisation of the thalamus.			(females)	
2-generation rat oral reproduction study	1	Reduced food consumption and bodyweight gain. Reduced birth weights and weight gain in pups.	No information reported	Parental: 20 Fertility:50 Offspring:40	Parental: 50 Fertility:- Offspring:120	No evidence of endocrine effect.
Rat oral developmental and teratogenicity study	1	Reduced food consumption and bodyweight gain in dams. Wavy rib.	No information reported	Maternal: 30 Foetal: 30	Maternal: 100 Foetal: 100	No evidence of endocrine effect. Foetal effects occurred in the presence of maternal toxicity and are probably due to this factor.
Rabbit oral developmental and teratogenicity study	1	Reduced bodyweight gain in dams and pups. Delayed ossification.	No information reported	Maternal:8 Foetal: 24	Maternal: 24 Foetal: 72	No evidence of endocrine effect. Foetal effects occurred in the presence of maternal toxicity and are probably due to this factor.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Mineralisation of the thyroid was not attributable to perturbation of the endocrine system.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are the effects judged to be relevant to humans?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	No effects potentially related to an endocrine mechanism of action were observed.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated by HSE.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, imidacloprid is not considered an endocrine disrupter based on currently available mammalian toxicology data**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.71 Human Health Endocrine Disruption Evaluation for Indoxacarb

Assessment not carried out due to the absence of a suitable regulatory dossier

Table B.72 Human Health Endocrine Disruption Evaluation for Pymetrozine

Substance details						
Substance Name	**Pymetrozine**					
Substance Synonyms	(*E*)-4,5-dihydro-6-methyl-4-(3-pyridylmethyleneamino)-1,2,4-triazin-3(2*H*)-one					
Substance CAS Number	123312-89-0					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (1998)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Carc. Cat. 3; R40 R52-53 Carc. 2 Aquatic Chronic 3	 Limited evidence of a carcinogenic effect. Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Suspected of causing cancer. Harmful to aquatic life with long lasting effects.				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2-year rat oral long-term toxicity and carcinogenicity study	1	Liver toxicity. Benign hepatomas.	No information reported	3.7	Approx 37	No evidence of an endocrine effect.
18-month mouse oral long-term toxicity and carcinogenicity	1	Liver toxicity. Tumours.	No information reported	11.4	Approx 230	No evidence of an endocrine effect.

2-generation rat oral reproduction study	1	Reduced bodyweight in parents and offspring.	No information reported	Parental: 10 Offspring: 10	Parental:100 Offspring:100	No evidence of an endocrine effect.
Rat oral developmental and teratogenicity study	1	Maternal toxicity and pelvic anomalies and delayed ossification.	No information reported	Maternal:30 Foetal:30	Maternal:100 Foetal:100	Developmental effects occurred, however, this cannot be directly related to endocrine disruption.
Rabbit oral developmental and teratogenicity study	1	Maternal toxicity. Embryo toxicity, pelvic anomalies and delayed ossification.	No information reported	Maternal:10 Foetal:10	Maternal:75 Foetal:75	Developmental effects occurred, however, this cannot be directly related to endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Developmental effects occurred, however, this cannot be directly related to endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are the effects judged to be relevant to humans?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	No effects potentially related to an endocrine mechanism of action were observed.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.

(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, pymetrozine is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.73 Human Health Endocrine Disruption Evaluation for Spinosad

Substance details		
Substance Name	**Spinosad (ISO) (reaction mass of spinosyn A and spinosyn D in ratios between 95:5 to 50:50)**	
Substance Synonyms	reaction mass of 50-95% of (2R,3aS,5aR,5bS,9S,13S,14R,16aS,16bR)-2-(6-deoxy-2,3,4-tri-O-methyl-α-l-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-d-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-14-methyl-1H-8-oxacyclododeca[b]as-indacene-7,15-dione and 50-5% (2S,3aR,5aS,5bS,9S,13S,14R,16aS ,16bS)-2-(6-deoxy-2,3,4-tri-O-methyl-α-l-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-d-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-4,14-dimethyl-1H-8-oxacyclododeca[b]as-indacene-7,15-dione	
Substance CAS Number	131929-60-7 (Spinosyn A) 131929-63-0 (Spinosyn D)	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (2001). A brief search for recent relevant studies did not locate any further information.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	N; R50-53 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	Hepatotoxicity, anaemia and clinical chemistry changes, ↑organ weights (liver, heart, spleen), vacuolation of the thyroid gland	No information reported	8.6	42.7	Effect on the thyroid gland but no further evidence of endocrine disruption

90-day dog oral study	1/2	↓body wt, food consumption, vacuolation in several tissues, minor microscopic changes	No information reported	4.38	9.73	Vacuolation of organs appears to be a major effect.
90-day mouse oral study	1/2	Vacuolation and necrosis in several tissues including lymphoid organs, kidneys, liver, stomach, ovary, female genital tract, epididymis, and skeletal muscle. Alterations in liver, kidneys, and stomach	No information reported	7.5	22.5	Vacuolation seen in some reproductive organs could be indicative of an effect on endocrine disruption and no evidence
1-year dog oral study	1/2	Vacuolated cell aggregation in several tissues including parathyroid and lymphoid tissue.	No information reported	2.68	8.22	Effect on parathyroid gland but not the thyroid in this study.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	Vacuolation of the thyroid gland. No carcinogenic potential.	No information reported	2.4	9.5	Effect on the thyroid gland but no further evidence of endocrine disruption
2-generation rat oral reproduction study	1/2	Parental: mortality, dystocia, vaginal bleeding, changes in body and organ wt, histological changes in several organs Developmental: decreased gestation survival, litter size, pup wt, and neonatal survival Reproductive: dystocia, vaginal bleeding, decreased litter size	No information reported	10 (parental) 10 (developmental) 10 (reproductive)	100 (parental) 100 (developmental) 100 (reproductive)	There are changes observed which may be indicative of endocrine disruption such as vaginal bleeding, dystocia, decreased litter size.
Rat oral developmental and teratogenicity study	1/2	Maternal: ↓body wt gain. No other effects	No information reported	50 (maternal) >=200 (developmental) >=200 (teratogenicity)	200 (maternal) - -	No evidence of endocrine disruption
Rabbit oral developmental and teratogenicity study	1/2	Maternal: ↓body wt gain, feed consumption, and faecal output, abortions. No other effects	No information reported	10 (maternal) >=50 (developmental) >=50 (teratogenicity)	50 (maternal) - -	No evidence of endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There are effects on the thyroid, reproductive organs and reproductive performance that may indicate endocrine disruption.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There are effects on the thyroid, reproductive organs and reproductive performance that may indicate endocrine disruption, but no mechanistic information is available.
Are the effects judged to be relevant to humans?	Yes	Rats are more sensitive than humans to effects on the thyroid but otherwise there is no reason that the effects seen are not relevant to humans
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	At present it is unclear whether spinosad is an endocrine disrupter or not.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**There are effects seen in a full set of regulatory tests that could be due to endocrine disruption but further evidence would be required on a potential mechanism.**
(B) Endocrine disrupter more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There are effects seen in a full set of regulatory tests that could be due to endocrine disruption but further evidence would be required on a potential mechanism.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.74 Human Health Endocrine Disruption Evaluation for Spiromesifen

Substance details	
Substance Name	**Spiromesifen**
Substance Synonyms	3-mesityl-2-oxo-1-oxaspiro[4.4]non-3-en-4-yl 3,3-dimethylbutanoate (IUPAC) Butanoic acid, 3,3-dimethyl-, 2-oxo-3-(2,4,6-trimethylphenyl)-1-oxaspiro[4.4]non-3-en-4-yl ester (9CI) (CA)
Substance CAS Number	283594-90-1
Substance EC Number	-
Data Source(s)	European Union Draft Assessment Report (2004)

Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Not classified	Not classified
Regulation (EC) No 1272/ 2008	Not classified	Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study (with 28-dy recovery)	1/2	↓body wt gain and water intake, ↑thromboplastin time, ↑Alkaline phosphatase activity, ↓plasma cholesterol and triglycerides, a tendency to ↑TSH values, ↑relative kidney wts), white jejunal mucosa coverings and cytoplasmic vacuolation of the jejunal mucosa, and ↑incidences	Clear effects on the thyroid foliicular cells and ↑TSH	6.3	32	Evidence of disruption of the thyroid and its hormones

		of thyroidal follicular cell hypertrophy (females) and thyroidal colloidal alterations (males).				
90-day dog oral study	1/2	↑liver wt, ↑alkaline phosphatase and GGT activity, ↑triglycerides. Marginal effects on T4 and hepatic enzyme induction		9.2	71	Evidence of disruption of the thyroid and its hormones.
1-year dog oral study	1/2	↓body wt gain, ↓T4, ↑serum alkaline phosphatase, hepatic inclusions/vacuoles (hyaline bodies), small cell type in adrenocortical zona fasciculata. Hepatic enzyme induction with ↑activity of hepatic enzymes; N-demethylase and Cytochrome P-450.	In the dog, induction of liver enzymes is the primary effect which may lead to effects on thyroid hormones with ↑TSH and ↓T4.	11.5 (male) 10.8 (females)	109 (male) 117 (female)	Evidence of disruption of the thyroid and its hormones and of the adrenals.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	Clinical signs (increased girth, vaginal bleeding),↓body wt, ↓plasma cholesterol, ↑ TSH) and thyroidal colloidal alteration (and uterus dilation and inflammation (endometritis/metritis). No carcinogenic potential.	No information reported	6	15	Evidence of disruption of the thyroid and its hormones and possible endocrine disruption of the female reproductive system.
2-generation rat oral reproduction study	1/2	Parental toxicity: ↓body wt. in F1 males and in F0 and F1 females, changes in organ wt. parameters, slight effects on the thyroid gland (follicular cell hypertrophy, altered follicular colloid), ↓vacillation of the adrenal zone glomerulus cells and ↓hepatic perioral fat content in F0 females Neonatal toxicity: ↓body wt. (F1, F2, F2b) during lactation and respective secondarily ↓absolute (F1 males, F2 males and females) and ↑relative (F1 and F2 males and females) brain wt., ↓absolute spleen and thymus wt. (F1 and F2 males and females, F2b males) and on ↓absolute thymus wt. in	No information reported	Parental toxicity: 10.2 (F0 males) 14.7 (F0 females) Reproductive toxicity: 46.5 (F0 males) 55.9 (F0 females) Neonatal toxicity: 10.2	 46.5 55.9 - -	Some effects on the thyroid.

		F2b females.				
2-generation rat oral reproduction study	1/2	Parental toxicity: ↓body wt Reproductive toxicity: reduced oestrus cycling frequency in F0 females ↑number of ovarian primordial follicles in F1 females Neonatal toxicity: effects on body wt during lactation	No information reported	Parental toxicity: 3.3 (F0 males) 4.6 (F0 females). Reproductive toxicity 14.2 (F0 females) Neonatal toxicity: 3.3 (F0 males) 4.6 (F0 females)	14.2 64 14.2	Evidence of reproductive toxicity, with potential endocrine disruption of the female reproductive system (oestrus cycle and ovaries).
Rat developmental and teratogenicity study	1/2	Maternal toxicity: ↓feed intake and body wt development Developmental toxicity: slightly more advanced ossification of phalangeal and single skull bones	No information reported	10(maternal) 10 (developmental)	70	No evidence of endocrine disruption
Rabbit developmental and teratogenicity study	1/2	Maternal: ↓feed intake and amount of faeces, ↓transient body wt loss, ↓body wt gain and ↓corrected body wt gain	No information reported	5 (maternal) 250 (developmental)	35 - -	No evidence of endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Evidence of effects on the thyroid system (via hepatic enzyme induction) and the female reproductive system which may be due to endocrine disruption
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes (thyroid)/No (adrenals and female reproduction)	There are effects on thyroid hormone levels which may be driven by hepatic enzyme induction. There are also effects on the rat female reproductive system and dog adrenals which may be due to endocrine disruption, but no mechanistic information is available.
Are the effects judged to be relevant to humans?	Yes	Although the rat is more sensitive than humans to effects on the thyroid, effects were seen also in the dog. Moreover, the MOA for these effects has not been completely elucidated. Therefore the human relevance of these thyroid effects cannot be excluded, In addition, the effects on the adrenals (dog) and rat female reproductive system must be considered relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	The effects on the thyroid gland and its hormones were observed at levels above the STOT-RE Category 1 guidance values

Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is sufficient data on the effects on the thyroid to indicate endocrine disruption. Further mechanistic data may be useful in relation to the effects on the adrenals and female reproduction.
(B**)** Endocrine disrupter more likely to pose a risk based on currently available data	No	The effects on the thyroid gland and its hormones were observed at levels above the STOT-RE Category 1 guidance values.
(C) Endocrine disrupter less likely to pose a risk based on currently available data	**Yes**	**There are sufficient data on the effects on the thyroid to indicate endocrine disruption. However, these effects were observed at levels above the STOT-RE Category 1 guidance values.**
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There are sufficient data on the effects on the thyroid to indicate endocrine disruption.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.75 Human Health Endocrine Disruption Evaluation for Spirotetremat

Substance details						
Substance Name	**Spirotetramat**					
Substance Synonyms	cis -4 - (ethoxycarbonyloxy)-8-methoxy-3-(2,5-xylyl)-1-azaspiro [4.5] dec-3-en-2-one (IUPAC)					
Substance CAS Number	203313-25-1					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2008)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	↓body wt, ↓absolute testicular wt, testicular tubular degeneration, abnormal epididymal spermatozoa and hypospermia, and ↑accumulation of alveolar macrophages in both sexes.	No information reported	148 (male) 188 (female)	616 (male) 752 (female)	Effects on the male reproductive system observed indicative of endocrine disruption.
90-day dog oral study	1/2	↓body wt during the first two weeks of the study. No marked toxicity was determined in the	Based on the total response of the animals to the thyroid profile that emerged over 90	81 (male) 72 (female) NOEL 9 (male)	- - 33 (male)	Effects seen on circulating thyroid hormones but these were

		present study, ↓thyroid hormone but no changes in thyroid wt, thyroid pathology, no compensating increases in TSH, or no clinical observations (e.g., neurological signs) suggestive of thyroid compromise were detected in either sex.	days, the compound-induced changes in circulating thyroid hormones, though significant in magnitude, were judged to be non-adverse. This conclusion was confirmed when a similar thyroid and toxicological profile emerged in the 1-year chronic dog study (see below).	10 (female)	33 (female)	considered not adverse as there was no accompanying increase in TSH, thyroid weight or pathology.
1-year dog oral study	1/2	↓thyroid hormones, but no changes in thyroid wt, thyroid pathology, no compensating increases in TSH, or no clinical observations (e.g., neurological signs) indicative of thyroid toxicity. Based on the total response of the animals to the thyroid profile over one year, the isolated compound-induced changes in circulating thyroid hormones, though significant in magnitude, were judged to be non-adverse..	Based on non-adverse declines in T4 at 0 mg/kg bw/day in males and 19 mg/kg bw/day in females, the overall NOEL for beagle dogs in a chronic one year dog study was 5 mg/kg bw/day.	NOEL 5	20	More evidence in a longer study that the changes in thyroid hormones were not adverse.
2-year rat oral long-term toxicity and carcinogenicity study	1/2	Male: ↑ accumulation of alveolar macrophage, testicular toxicity histopathologically, with testicular tubular degeneration and germ cell debris in epididymis. Female: ↓body wt and body wt gain, yellow and brown staining in the perigenital area and tail, discoloration of the lung and increased incidence of accumulation of alveolar macrophages. No carcinogenic potential.	No information reported	13 (male) 255 (female)	189 (male) 890 (female)	Effects on the male reproductive system observed indicative of endocrine disruption.
2-generation rat oral reproduction study	1/2	Parental: ↓body wt gain, ↓terminal body wt, ↑renal multifocal tubular dilatation Reproduction: abnormal sperm cell morphology. No female effects.	No information reported	Parental: 70.7 (male) 82.5 (female) Reproductive: 71 (male) 485 (female)	Parental : 419.3 (male) 484.7(female)l Reproductive: 719 (male) -	Effects on the male reproductive system observed indicative of endocrine disruption.

		Offspring: ↓body wt gain		Offspring: 70.7 (male) 82.5 (female)	Offspring: 419 (male) 485 (female)	
Rat oral developmental and teratogenicity study	1/2	maternal ↓placental wt, ↓foetal wt, slightly ↑incidence of common unspecific malformations, ↑incidence of skeletal variations (wavy ribs, 14th ribs, combined osseous and cartilaginous findings), ↑incidence of retarded ossification. No evidence for a primary embryotoxic or teratogenic potential	No information reported	140 (maternal and developmental)	1000 (maternal and developmental)	No evidence of developmental toxicity indicative of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1/2	Maternal: abortion, clinical signs, impaired food and water consumption and body weight loss. Developmental: no evidence for a teratogenic effect.	No information reported	10 (maternal 160 (developmental)	40 -	No evidence of developmental toxicity indicative of endocrine disruption.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	There are effects on the male reproductive system in the rat indicative of a potential endocrine disruption mechanism. However, effects ion thyroid hormone levels in the dog were not considered to be adverse as there was no effect on TSH, thyroid weight or pathology,
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	There is no mechanistic information to indicate that an endocrine disrupter mechanism of action is the basis of the effects in the male reproductive organs.
Are the effects judged to be relevant to humans?	Yes	There is no obvious reason why the effects observed in animals would not be relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	At present, there are no mechanistic studies to show that effects seen in the regulatory tests are due to endocrine disruption.

Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**There are effects on the male reproductive system, seen in the full range of regulatory tests, which raise a concern for endocrine disruption. However, more mechanistic studies would be needed to confirm the initial concern.**
(B**)** Endocrine disrupter more likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	There is insufficient information upon which to make a judgement on endocrine disruption.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	There are effects seen in a full set of regulatory tests that could be due to endocrine disruption but further evidence would be required on a potential mechanism.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.76 Human Health Endocrine Disruption Evaluation for Tebufenpyrad

Substance details		
Substance Name	**Tebufenpyrad**	
Substance Synonyms	N-(4-tert-Butylbenzyl)-4-chloro-3-ethyl-1-methylpyrazole-5-carboxamide (IUPAC) 4-Chloro-N-[[4-(1,1-dimethylethyl)phenyl]]methyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide	
Substance CAS Number	119168-77-3	
Substance EC Number	-	
Data Source(s)	European Union Draft Assessment Report (2008)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
90-day rat oral study	1/2	Some evidence of liver and kidney toxicity (↑organ weight, changes in clinical chemistry parameters), ↓body wt gain, food and water consumption, haematological, urinary and histological liver findings.	No information reported	0.7	6.8	No evidence of endocrine disruption

90-day dog oral study	1/2	Vomiting and loose stool/diarrhoea; initial body wt losses and/or ↓body wt gain, focal mucosal congestion (stomach and intestines)	No information reported	2	10	No evidence of endocrine disruption
1-year dog oral study	1/2	Vomiting and loose stool/diarrhoea, local irritation in stomach; ↓body wt development.	No information reported	1	6	No evidence of endocrine disruption
2-year rat oral long-term toxicity and carcinogenicity study	1/2	↓body wt gain, food consumption and efficiency; slight haematological changes mainly in females (haematocrit, haemoglobin, ↓MCH, ↑spherocytes, hepatotoxicity (↑organ weight, hepatocyte hypertrophy, ↑Alk phosphatase, albumin and A/G-ratio , ↑Cyt P450, ↓cholesterol). No carcinogenic potential.	No information reported	0.8	6.5	No evidence of endocrine disruption
2-generation rat oral reproduction study	1/2	Adults: ↓body wt development and food consumption (mainly males) Pups: ↓body wt development, delayed vaginal opening	No information reported	NOAEL8 (systemic) NOEL 17 (reproduction): NOAEL 8 (offspring)	17 (systemic) -(reproduction) 17 (offspring)	No indication of reproductive toxicity in the absence of paternal toxicity. No evidence of endocrine disruption
Rat oral developmental and teratogenicity study	1/2	Dams: ↓body wt development and food consumption, ↑water consumption Foetuses: ↓body wt, ↑incidence of 14th pair of ribs.	No information reported	15 (maternal and foetal)	50	There was no indication of a teratogenic potential in developmental rats. No evidence of endocrine disruption
Rabbit oral developmental and teratogenicity study	1/2	Dams: ↓body wt development and food consumption, abortions	No information reported	NOAEL 15 (maternal) NOEL 40 (foetal)	40 (maternal) -(foetal)	There was no indication of a teratogenic potential in developmental rabbits. No evidence of endocrine disruption

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	No evidence of endocrine disruption in a full range of regulatory tests.

Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No evidence of endocrine disruption in a full range of regulatory tests.
Are the effects judged to be relevant to humans?	N/A	No evidence of endocrine disruption in a full range of regulatory tests.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	N/A	No evidence of endocrine disruption in a full range of regulatory tests.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption
(B**)** Endocrine disrupter more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupter less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**There is a full range of regulatory toxicology tests and no evidence of endocrine disruption. Therefore, tebufenpyrad is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.77 Human Health Endocrine Disruption Evaluation for Thiacloprid

Substance details						
Substance Name	**Thiacloprid**					
Substance Synonyms	(3-((6-Chloro-3-pyridinyl)methyl)-2-thiazolidinylidene)cyanamide					
Substance CAS Number	111988-49-9					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (2001)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2-year rat oral long-term toxicity and carcinogenicity study	1	Liver and thyroid effects and neuropathy. Uterine tumours and thyroid tumours.	In rats, the hepatic enzyme induction, especially aromatase induction, resulted in elevated oestradiol levels, which produced an increased incidence of uterine tumours in old females.	1.23 (males) 3.3 (females)	2.5 (males) 33 (females)	Evidence of endocrine disruption.

18-month mouse oral long-term toxicity and carcinogenicity study	1	Liver effects. Ovarian tumours.	Hepatic enzyme induction.	5.7 (males) 10.9 (females)	Approx: 240 (males) Approx: 460 (females)	Evidence of endocrine disruption.
2-generation rat oral reproduction study	1	Dystocia. Decreased pup weight.	No information reported	2.6	16.4	Evidence of endocrine disruption.
Rat oral developmental and teratogenicity study	1	Decreased bodyweight. Reduced implantations, litter size and foetal weight, increased resorptions, skeletal variations.	No information reported	Maternal: 10 Foetal: 10	Maternal: 50 Foetal: 50	Possible evidence of endocrine disruption.
Rabbit oral developmental and teratogenicity study	1	Decreased bodyweight and pup weight.	No information reported	Maternal: 2 Foetal: 2	Maternal: 10 Foetal: 10	No clear evidence of endocrine disruption.
Mechanistic investigations			Strong hepatic enzyme inducer, especially in rodents. The enzyme induction showed a severe enzyme induction at dose levels >500 ppm. Aromatase induction (key enzyme in estradiol synthesis) was evident in rat and mouse liver. No aromatase induction was evident in the ovaries of rats. Aromatase induction resulted in hormonal changes, especially to estradiol levels. No direct inhibitory effect on thyroid peroxidase. Did not inhibit the enzymes involved in steroid degradation. However, induction of the enzymes that catalyse testosterone to androstenedione was evident. No effects on cervical extensibility, collagen content, uterine contractility or contraction force, uterine electrophysiology or interuterine	-	-	Evidence of endocrine disruption.

			pressure. No effects on the uterine alpha-1 adrenergic receptor levels or oestrogen and progesterone receptor levels.			

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	Yes	Adverse effects raising a concern for endocrine disruption (thyroid, ovarian and uterine tumours, effects on reproduction) are observed in multiple studies
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	Yes	An endocrine mode of action is plausible as aromatase induction was observed.
Are the effects judged to be relevant to humans?	Yes	Effects are relevant to humans.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	Yes	Effects occur below 5 mg/kg bw/day.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**No**	-
Overall grouping of the substance regarding its endocrine disrupting properties		
Category	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and evidence of endocrine disruption.
(B) Endocrine disrupters more likely to pose a risk based on currently available data	**Yes**	**Group is appropriate as endocrine mediated adverse effects occur in multiple studies at low doses below the STOT-RE guidance values of the UK-DE position paper.**
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as endocrine mediated adverse effects occur in multiple studies at low doses, below the STOT-RE guidance values of the UK-DE position paper.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The substance is an established endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Plant growth regulators

Table B.78 Human Health Endocrine Disruption Evaluation for Maleic hydrazide

Substance details						
Substance Name	**Maleic hydrazide**					
Substance Synonyms	1,2-Dihydro-3,6-pyridazinedione, 3,6-Dihydroxypyridazine					
Substance CAS Number	123-33-1					
Substance EC Number	204-619-9					
Data Source(s)	European Union Draft Assessment Report (2002)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2-year rat oral long-term toxicity and carcinogenicity study	1	Reduced bodyweight.	No information reported	25 (males) 500 (females)	500 (males) 1000 (females)	No evidence of endocrine effects
2-year mouse oral long-term toxicity and carcinogenicity study	1	No effects.	No information reported	1545 (males) 1811 (females)	- -	No evidence of endocrine effects

2-generation rat oral reproduction study	1	Reduced bodyweight. Reduced weight and weight gain in pups.	No information reported	Parental: 550 Offspring: 550	Parental: 1650 Offspring: 1650	No evidence of endocrine effects
Rat oral developmental and teratogenicity study	1	No effects.	No information reported	1000	-	No evidence of endocrine effects
Rabbit oral developmental and teratogenicity study	1	No effects.	No information reported	1000	-	No evidence of endocrine effects

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Reduced bodyweight is observed in reproductive and long term studies. These effects do not demonstrate that an endocrine mode of action is taking place.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are the effects judged to be relevant to humans?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	No effects potentially related to an endocrine mechanism of action were observed.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.

(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, maleic hydrazide is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.79 Human Health Endocrine Disruption Evaluation for Paclobutrazol

Substance details		
Substance Name	**Paclobutrazol**	
Substance Synonyms	(2RS,3RS)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl)-pentan-3-ol	
Substance CAS Number	76738-62-0	
Substance EC Number	266-325-7	
Data Source(s)	European Union Draft Assessment Report (2006)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Not classified Not classified	 Not classified Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOAEL (mg/kg bw/day)	Reported LOAEL (mg/kg bw/day)	Remarks
2-year rat oral long-term toxicity and carcinogenicity study	1	Centrilobular hypertrophy and steatosis. Increased liver weights. Decreased body weight gain.	No information reported	2.2 (male) 14 (female)	11 (male) 72 (female)	No evidence of an endocrine effect.
2-year mouse oral long-term toxicity and carcinogenicity study	1	Increased liver weights and steatosis. Reduced serum cholesterol and triglyceride levels.	No information reported	14 (male) 16 (female)	81 (male) 89 (female)	No evidence of an endocrine effect.

2-generation rat oral reproduction study	1	Increased relative liver weights and histopathology. Thickened eyelids and twisted snout.	No information reported	Parental: 23.2 Reproductive: >108 Offspring: 23.2	Parental: 108 Reproductive: - Offspring: 108	No evidence of an endocrine effect.
Rat oral developmental and teratogenicity study	1	Increase in skeletal abnormalities.	No information reported	Maternal: 100 Developmental:10	Maternal:- Developmental:40	Possible effects occurring without maternal toxicity.
Rabbit oral developmental and teratogenicity study	1	Decreased bodyweight gain.	No information reported	Maternal:75 Developmental:125	Maternal:125 Developmental:-	No evidence of an endocrine effect.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Skeletal abnormalities were observed in developmental studies, however, these effects were considered to be minor abnormalities. These effects do not demonstrate that an endocrine mode of action is taking place.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are the effects judged to be relevant to humans?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	No effects potentially related to an endocrine mechanism of action were observed.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.
(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.

(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, paclobutrazol is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table B.80 Human Health Endocrine Disruption Evaluation for Prohexadione-calcium

Substance details						
Substance Name	**Prohexadione-calcium**					
Substance Synonyms	-					
Substance CAS Number	127277-53-6					
Substance EC Number	-					
Data Source(s)	European Union Draft Assessment Report (1999)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	Not classified Not classified	Not classified Not classified				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
Mammalian toxicology data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOAEL (mg/kg bw/day)**	**Reported LOAEL (mg/kg bw/day)**	**Remarks**
2-year rat oral long-term toxicity and carcinogenicity study	2	Slight reduction in bodyweight Hyperplastic changes in the stomach Slight changes in chemical parameters	No information reported	93.9 (males) 114 (females)	Approx 470 Approx. 570	No evidence of an endocrine effect.
2-year mouse oral long-term toxicity and carcinogenicity study	2	Bodyweight reduction Organ weight changes Haematological parameters Proliferation of stomach	No information reported	279 9males) 351 (females)	Approx 2790 Approx 3510	No evidence of an endocrine effect.

		epithelium				
2-generation rat oral reproduction study	2	Reduced bodyweight	No information reported	Parental: 500 ppm Reproductive: 50000 ppm Offspring: 500 ppm	Parental: 5000 Reproductive: - Offspring: 5000	No evidence of an endocrine effect.
Rat oral developmental and teratogenicity study	2	No effects	No information reported	Maternal: 1000 Developmental:1000	Maternal:- Developmental:-	No evidence of an endocrine effect.
Rabbit oral developmental and teratogenicity study	2	Death and stomach erosion in dams Abortions	No information reported	Maternal:40 Developmental:200	Maternal:200 Developmental:750	Effects on pups were a result of the severe toxicity observed in dams.

Evaluation of the available mammalian toxicology data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there adverse effects potentially[1] related to endocrine disruption in intact organisms in acceptable studies?	No	Reduced bodyweight is observed in reproductive and long term studies. These effects do not demonstrate that an endocrine mode of action is taking place.
Does the available evidence[2] demonstrate that an endocrine disruption mode of action in animals is plausible?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are the effects judged to be relevant to humans?	No	No effects potentially related to an endocrine mechanism of action were observed.
Are serious endocrine disrupting effects observed at or below the STOT-RE Category 1 guidance values of the CLP Regulation?	No	No effects potentially related to an endocrine mechanism of action were observed.
Would there be benefits to carry out an ecotoxicological endocrine disruption assessment?	**Yes**	No detailed assessment has been carried out as part of the project as stipulated with HSE.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	There is data available from a full range of regulatory toxicology tests and no evidence of endocrine disruption.

(B**)** Endocrine disrupters more likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(C) Endocrine disrupters less likely to pose a risk based on currently available data	No	Group is not appropriate as there is no evidence of endocrine disruption in available data.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**Adverse effects caused by an endocrine mode of action were not observed in standard toxicity tests. Therefore, prohexadione-calcium is not considered an endocrine disrupter based on currently available mammalian toxicology data.**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Appendix C Detailed Ecotoxicological Assessment Datasheets for the Twenty Identified Substances

Fungicides

Table C.1 Ecotoxicological Endocrine Disruption Evaluation for Carbendazim

Substance details		
Substance Name	**Carbendazim**	
Substance Synonyms	-	
Substance CAS Number	10605-21-7	
Substance EC Number	EEC: 613-048-00-8; EINECS: 234-232-0	
Data Source(s)	European Union Draft Assessment Report (2009) Kim D-J, Seok S-H, Baek M-W, Lee H-Y, Na Y-R, Park S-H, Lee H-K, Dutta N-K, Kawakami K and Park J-H (2009) Benomyl induction of brain aromatase and toxic effects in the zebrafish embryo, *Journal of Applied Toxicology*. **29**, 289–294. Lu, S.Y., Liao, J.W., Kuo, M.L., Wang, S.C., Hwang, J.S., Ueng, T.H., (2004) Endocrine disrupting activity in carbendazim-induced reproductive and developmental toxicity in rats. *Journal of Toxicology and Environmental Health Part A: Current Issues,* **67**, 1501–1515. Yoon C S, Jin J-H, Park J-H, Yeo C-Y, Kim S-J, Hwang Y-G, Hong S-J and Cheong S-W (2008) Toxic Effects of Carbendazim and n-Butyl Isocyanate, Metabolites of the Fungicide Benomyl, on Early Development in the African Clawed Frog, *Xenopus laevis*, Inc. *Environmental Toxicology*, **23**, 131–144. Yu G, Guo Q, Xie L, Liu and Wang X (2009) Effects of subchronic exposure to carbendazim on spermatogenesis and fertility in male rats, *Toxicology and Industrial Health*, **25**, 41–47.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Muta. Cat. 2; R46 Repr. Cat. 2; R60-61 N; R50-53	May cause heritable genetic damage. May impair fertility. May cause harm to the unborn child. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Muta. 1B Repr. 1B Aquatic Acute 1 Aquatic Chronic 1	May cause genetic defects May damage fertility. May damage the unborn child. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.

Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**Yes**
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group A - Substances requiring further information**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Scenedesmus subspicatus* growth inhibition test (72 hour exposure to carbendazim, 99% purity ,	1	Inhibition of growth	No information reported	8.0	>8.0	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to carbendazim, 99.5% purity)	1	Reduction in juvenile production	No information reported	0.0015	0.0046	Effects are evidently not endocrine-mediated
Fish rainbow trout *Oncorhynchus mykiss* early-life stage test (79 day exposure to technical grade carbendazim)	1	Reduced embryo-survival	No information reported	0.011	0.034	Effects could be endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard *Anas platyrhynchos* reproduction test (21 week exposure to benomyl, which is metabolized to carbendazim)	1	Reduction in fertility	No information reported	212 mg/kg diet (26.4 mg/kg bw/day)	474 mg/kg diet (59.0 mg/kg bw/day)	Effects could be endocrine-mediated
Bobwhite quail *Coilinus virginianus* reproduction test (22 week exposure to benomyl)	1	Reproductive and adult health endpoints	No information reported	2370 mg/kg diet	>2370 mg/kg diet	No reproductive or adult health effects are evident at any test dose

Wildlife (*in vivo*) data from published literature						
Fish zebrafish *Danio rerio* early-life stage test (3 day exposure to benomyl) – Kim *et al*. (2008)	2	Reduced hatching rate	Carbendazim stimulated zebrafish brain aromatase gene expression at 191 µg/l (1.0 µM)	1912 µg/l (10 µM)	3824 µg/l (20 µM)	-
Amphibian African clawed frog *Xenopus laevis* early development test – Yoon *et al*. (2008)	2	Increased incidence of ten different types of malformations in embryos	Carbendazim inhibited the differentiation of neural tissue at 764.8 µg/l (4 µM)	573.6 µg/l (3 µM)	>573.6 µg/l (3 µM)	-
Mechanistic (*in vitro* and *in vivo*) data						
In vitro rat testis extract - Lu *et al.* (2004)	2	Inhibition of [3 H]-5-dihydro-testosterone to androgen receptor	-	956 µg/l (5 µM)	9560 µg/l (50 µM)	The results suggest that androgen- and androgen receptor-dependent mechanisms are possibly involved in carbendazim-induced toxicity in mammals.
In vivo rat fertility study (80 days exposure to carbendazim) – Yu *et al.* (2009)	2	Decreasing luteinizing hormone (LH) levels Follicle stimulating hormone (FSH) and testosterone (T) levels	-	100 mg/kg 200 mg/kg	200 mg/kg >200 mg/kg	The results suggest that carbendazim has adverse effects on meiotic transformation and spermatogenesis, resulting in reduced fertility in male rats.
In vivo rat fertility study (60 days exposure to carbendazim) – Yu *et al*. (2009)	2	Decreased stem cell factors (SCF)s levels Increased amyloid beta protein (ABP) levels	-	20 mg/kg 20 mg/kg	100 mg/kg 100 mg/kg	The results suggest that alterations of Sertoli cell morphology and function were involved in spermatogenic failure

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for carbendazim, which is relevant to mammalian wildlife species, indicated that "*There are a number of adverse effects on the male reproductive system (relating to testes and sperm production) that may indicate endocrine disruption but no mechanism has been identified to suggest that carbendazim disrupts endocrine systems.* " For fish the early-life stage test in rainbow trout reported effects on embryo-larval survival which could be endocrine-mediated and could affect populations. For birds the one generation study in mallard reported reproductive effects that could be endocrine-mediated and could affect populations.

Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is some data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies, but these are not conclusive.
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	There is no definitive evidence from the available reliable studies that other systemic effects are seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed. The most sensitive endpoint for aquatic species is the reduction in juvenile production in the invertebrate *Daphnia magna* which is not evidently endocrine-mediated. The effects concentration for invertebrates is a factor of 7.3 lower than those reported in fish.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**The currently available evidence does not allow a definitive conclusion to be drawn on the endocrine-mediated effects of carbendazim on wildlife species.**
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that carbendazim is an established endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that carbendazim is an established endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow carbendazim to be excluded for consideration as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.2 Ecotoxicological Endocrine Disruption Evaluation for Chlorothalonil

Substance details		
Substance Name	**Chlorothalonil**	
Substance Synonyms	Tetrachloroisophthalonitrile	
Substance CAS Number	1897-45-6	
Substance EC Number	217-588-1	
Data Source(s)	Andersen HR, Vinggaard AM, Rasmussen TH, Gjermandsen IM, and Bonefeld-Jorgensen EC (2002) Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity *in vitro*. *Toxicology and Applied Pharmacology*, **179**, 1-12. Environment Canada (2004) Pesticides in Ontario: A critical assessment of potential toxicity of urban use products to wildlife, with consideration for endocrine disruption. Volume 3: Phenoxy herbicides, chlorothalonil and chloropyrifos. Canadian Wildlife Service, Environment Conservation Branch, Ontario Region, European Union Draft Assessment Report (2003) McMahon T, Halstead N, Johnson S, Raffel TR, Romansic JM, Crumrine PW, Boughton RK, Martin LB, Rohr JR. (2011) The fungicide chlorothalonil is nonlinearly associated with corticosterone levels, immunity, and mortality in amphibians. *Environmental Health Perspectives*, **119(8)**,1098-1103. Teather K, Jardine C, and Gormley K (2005) Behavioral and sex ratio modification of Japanese medaka (Oryzias latipes) in response to environmentally relevant mixtures of three pesticides. *Environmental Toxicology*, **20**, 110-117. US EPA (2004) Chlorothalonil: Notice of filing a pesticide petition to establish a tolerance for a certain pesticide chemical in or on food. Available from http://www.epa.gov/fedrgstr/EPA-PEST/2004/August/Day-20/p19032.htm.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Directive 67/548/EEC	Carc. Cat. 3; R40 T+; R26 Xi; R37-41 R43 N; R50-53	Limited evidence of a carcinogenic effect Very toxic by inhalation Irritating to respiratory system Risk of serious damage to eyes May cause sensitization by skin contact Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Carc. 2 Acute Tox. 2 * STOT SE 3 Eye Dam. 1 Skin Sens. 1	Suspected of causing cancer Fatal if inhaled May cause respiratory irritation Causes serious eye damage May cause an allergic skin reaction

	Aquatic Acute 1 Aquatic Chronic 1	Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group D - Substances not considered to be endocrine disrupters based on currently available data**	

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Navicula pelliculosa* growth inhibition test (120 hour exposure to chlorothalonil, 98.1%)	1	Inhibition of cell growth	No information reported	0.0035	0.007	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to Chlorothalonil 75WG, 500 g/l)	1	Reduction in juvenile production Reduced adult survival	No information reported No information reported	0.019 0.0006	0.075 0.018	Effects are evidently not endocrine-mediated
Fish early life stage test	No data reported	-	-	-	-	-
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish fathead minnow *Pimephales promelas* one generational test (297 day exposure to chlorothalonil, 96.0%)	1	Reduced hatchability and fry survival of the F0 eggs Reduced reproduction success of F0 fish Reduced hatchability of second generation F1 eggs	No information reported No information reported No information reported	0.0065 0.0065 0.003	0.016 0.016 0.0065	Effects could be endocrine- mediated
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard *Anas platyrhynchos* reproduction test (18 week exposure to technical grade chlorothalonil)	1	Reproductive and adult health effects	No information reported	10000 mg a.s./kg diet	>10000 mg a.s./kg diet	No reproductive or adult health effects were measured at any test concentration

Bobwhite quail *Coilinus virginianus* reproduction test (22 week exposure to Chlorothalonil 75WG, 500 g/l)	1	Reduction in number of eggs laid and number of 14 day survivors per female	No information reported	160 mg a.s./kg diet (reproduction) 640 mg a.s./kg diet (adult health)	640 mg a.s./kg diet (reproduction)	No treatment related effects at necropsy Effects could be endocrine-mediated
Wildlife (*in vivo*) data from published literature						
Fish zebrafish *Danio rerio* early-life stage test (non-standard procedure) – Teacher *et al*. (2005)	3	Change in sex ratio (increased proportion of females) relative to control	Mechanism not known	Not relevant	0.00006 (0.06 µg/l, single exposure concentration)	Sex ratio (male: female) changed from 1.13:1.0 in controls to 1.0:1.86 in the test concentration
Amphibian cuban tree frog *Osteopilus septentrionalis* early life stage test – McMahon *et al*. (2011)	2	Increased corticosterone levels Decreased melanomacrophages and granulocytes	Mechanism not known	0.000164 (0.164 µg/l) 0.0000164 (0.0164 µg/l)	0.0164 (16.4 µg/l) 0.000164 (0.164 µg/l)	The concentration-effect relationships observed were non-monotonic in nature
Mechanistic (*in vitro* and *in vivo*) data						
Cell proliferation assay using human breast cancer MCF-7 cells – Andersen *et al*. (2002)	2	Marked effects were evident at low exposure concentrations due to cytotoxicity	Assay not suitable for evaluating potential hormone disrupting effects of the substance	No data reported	>1329.5 µg/l (>5 µM) (cytotoxicity)	The presence of four electrophilic groups means the substance is extremely reactive towards intra-cellular thiol groups causing high cytotoxicity
Estrogen receptor transactivation assay using human breast cancer MCF-7 cells – Andersen *et al*. (2002)	2	Marked effects were evident at low exposure concentrations due to cytotoxicity	Assay not suitable for evaluating potential hormone disrupting effects of the substance	No data reported	>1329.5 µg/l (>5 µM) (cytotoxicity)	
Androgen receptor transactivation assay using Chinese hamster ovary cells (CHO K1) – Andersen *et al*. (2002)	2	Marked effects were evident at low exposure concentrations due to cytotoxicity	Assay not suitable for evaluating potential hormone disrupting effects of the substance	No data reported	>265.9 µg/l (>1 µM) (cytotoxicity)	
Aromatase assay based on placental microsomes – Andersen *et al*. (2002)	2	Marked effects were evident at low exposure concentrations due to cytotoxicity	Assay not suitable for evaluating potential hormone disrupting effects of the substance	No data reported	13295 µg/l 50 µM (cytotoxicity)	

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for chlorothalonil, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*." For fish the one generation study in fathead minnow reported effects on reproduction and development which could be endocrine-mediated and could affect populations.

		Teather *et al*. (2005) reported toxicity to the Japanese medaka *Oryzias latipes* in the form of reduced activity and a skewed sex ratio compared to the controls. The fish were exposed for 7 days to a single test concentration of 0.00006 mg/l (0.06 µg/l) of an un-named commercial formulation containing chlorthalonil and at this concentration no effects were seen on survival, time to hatch or foraging ability. These tests were of intermediate duration, were non-standard concentration-response studies, and there was no analytical confirmation of the test concentration. Therefore the results are not readily interpretable and cannot be taken as definitive evidence of endocrine disruption. For birds the one generation study in bobwhite quail reported reproductive effects that could be endocrine-mediated.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies. Cellular assays are not suitable for evaluating the potential hormone-disrupting effects of chlorothalonil owing to four electrophilic chlorine atoms that are very reactive toward intracellular thiol groups and result in cytotoxicity even at low exposure concentrations. Environment Canada (2004) concluded that "*Chlorothalonil does not appear to have a direct effect on the endocrine system. However, it does have the ability to react with sulfhydryl groups of proteins and enzymes like GAPDH and NADPH oxidase and so may interfere with other enzymes or hormones that have free sulfhydryl groups*."
Are the potential ED-mediated effects judged to be relevant to fish, bird and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	There is no definitive evidence from the available reliable studies that other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed. The most sensitive endpoint for aquatic species is the reduction in juvenile production in the invertebrate *Daphnia magna* which is not evidently endocrine-mediated, though algal growth inhibition effects and fish growth effects are evident at similar concentrations.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(1) Substances requiring further information	**Yes**	**The currently available evidence does not allow a definitive conclusion to be drawn on the endocrine-mediated effects of chlorothalonil on wildlife species.** **Environment Canada (2004) stated that "*Chlorothalonil may qualify as an endocrine disruptor since it has the potential to interfere with endogenous hormones/neurohormones and enzymes, and is an immunomodulator*." In contrast the United States Environmental Protection Agency (2004) stated that "*Chlorothalonil does not belong to a class of chemicals known or suspected of having adverse effects on the endocrine system. Developmental toxicity studies in rats and rabbits and a reproduction study in***

		***rats gave no indication that chlorothalonil might have any effects on endocrine function related to development and reproduction. The subchronic and chronic studies also showed no evidence of a long-term effect related to the endocrine system*.”**
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that chlorothalonil is an established endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that chlorothalonil is an established endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow chlorothalonil to be excluded as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.3 Ecotoxicological Endocrine Disruption Evaluation for Iprodione

Substance details		
Substance Name	**Iprodione**	
Substance Synonyms	3-(3,5-dichlorophenyl)-N-isopropyl-2,4-dioxoimidazolidine-1-carboxamide	
Substance CAS Number	36734-19-7	
Substance EC Number	253-178-9	
Data Source(s)	Blystone C R, Lambright C S, Furr J, Wilson V S and Gray L E Jr (2007) Iprodione delays male rat pubertal development, reduces serum testosterone levels, and decreases *ex vivo* testicular testosterone production. *Toxicology Letters*,**174(1-3),** 74-81 Blystone, C R, Lambright C S, Cardon M C, Furr J, Rider C V, Hartig P C, Gray L E, and V S Wilson (2009) Cumulative and antagonistic effects of a mixture of the antiandrogrens vinclozolin and iprodione in the pubertal male rat. Toxicological Sciences. Society of Toxicology, **111(1)**, 179-188 European Union Draft Assessment Report (2009) Ghisari, M and Bonefeld-Jorgensen, E.C (2005) Impact of environmental chemicals on the thyroid hormone function in pituitary rat GH3 cells. *Molecular and Cellular Endocrinology*, **244(1-2)**, 31-41. Vinggaard, A M , Breinholt, V, Larsen, J C (1999) Screening of selected pesticides for oestrogen receptor activation *in vitro. Food Additives and Contaminants,* **16(12),** 533-542	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Carc. Cat. 3; R40 N; R50-53	Limited evidence of a carcinogenic effect Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Carc. 2 Aquatic Acute 1 Aquatic Chronic 1	Suspected of causing cancer Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

What is the grouping for the substance from the human health assessment of endocrine disruption?	Group C - Endocrine disrupters less likely to pose a risk

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Pseudokirchneriella subcapitata* growth inhibition test (120 hour exposure to ipriodone, purity 96.2%)	1	Inhibition of growth	No information reported	0.13	0.23	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 days exposure to ipriodone, purity %)	1	Reduction in juvenile production Parental survival	No information reported	0.17 0.33	0.33 0.71	Effects are evidently not endocrine-mediated
Fish fathead minnow *Pimephales promelas* early life stage test (34 days exposure to ipriodone, purity 100%)	1	Reduced embryo-larval survival Reduction in larval growth	No information reported	0.26	0.55	Effects could be endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (22 week exposure to ipriodone, purity 95.5%)	1	Reduction in reproductive endpoints (number of eggs hatchling body weights and % of hatchlings per egg set) Adult health effects	No information reported	300 mg a.s./diet (36.2mg a.s./kg bw/day) ≥1000 mg a.s./ diet	1000 mg a.s./ diet Not relevant	Effects could be endocrine-mediated
Bobwhite quail (*Coilinus virginianus*) reproduction test (22 week exposure to ipriodone, purity 95.5%)	1	Reduction in reproductive endpoints (number of 14 day survivors) Adult health effects	No information reported	300 mg a.s./diet (33.7mg a.s./kg bw/day) ≥1000 mg a.s./ diet	1000 mg a.s./ diet Not relevant	Effects could be endocrine-mediated
Wildlife (*in vivo*) data from published literature						
Weanling Sprague Dawley male rats exposed to iprodione – Blystone *et al*. (2007)	2	Delayed onset of puberty as the progression of preputial separation (PPS) Decreased androgen sensitive seminal vesicle and epididymides	The results suggest that in mammals iprodione affects steroidogenesis within the testis, not through disruption of LH	50 mg a.s./ kg diet 100 mg a.s./ kg diet	100 mg a.s./ kg diet 200 mg a.s./ kg diet	-

		weights Increased adrenal and liver weights Decreased serum testosterone 17alpha-hydroxyprogesterone and androstenedione levels No change in serum lutenizing hormone (LH) levels Reduced *ex vivo* testis production of testosterone Reduced ex vivo testis production of progesterone	signaling, but possibly through enzyme inhibition of the steroidogenic pathway before CYP17	100 mg a.s./ kg diet <50 mg a.s./ kg diet ≥200 mg a.s./ kg diet 50 mg a.s./ kg diet 100 mg a.s./ kg diet	200 mg a.s./ kg diet 50 mg a.s./ kg diet >200 mg a.s./ kg diet 100 mg a.s./ kg diet 200 mg a.s./ kg diet	
Immature male (castrated) rats exposed to iprodione – Blystone *et al*. (2009)	2	Reducing androgen-dependent gene expression Reducing paired adrenal and ventral prostate weight	Iprodione acts as an AR antagonist *in vivo*.	33.03 mg/l (100 µM) 100 mg a.s./ kg diet	99.09 mg/l (300 µM) 200 mg a.s./ kg diet	-
Mechanistic (*in vitro* and *in vivo*) data						
Activation of the estrogen receptor using the MCF cell proliferation assay – Vinggaard *et al*. (1999)	2	No effect on MCF cell proliferation assay	-	>3.3 mg/l (10 µM)	Not relevant	No activation of the estrogen receptor
Androgen receptor binding in the hAR COS cell binding assay - Blystone *et al*. (2009)	2	Binding to the androgen receptor (AR)	-	3.3 mg/l (10 µM)	>3.3 mg/l (>10 µM)	Iprodione binds to the androgen receptor
Thyroid hormone function - Proliferation of the rat pituitary GH3 cell line – Ghisari and Bonefeld-Jorgensen (2005)	2	Inhibition of cell growth	-		Max inhibition (75%) at 0.033 mg/l (0.1 µM)	Iprodione interferes with the function of thyroid hormones (THs). U shaped dose response curve reported

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for iprodione, which is relevant to mammalian wildlife species, indicated that it was an endocrine disrupter less likely to pose a risk. None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test in fathead minnow reported effects on embryo-larval and larval growth which could be endocrine-mediated and could affect populations.

		For birds the one generation studies in bobwhite quail and mallard reported reproductive effects that could be endocrine-mediated and could affect populations. Effects observed in rats are evidently endocrine mediated and could affect mammalian populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Yes	There is evidence that the mechanisms responsible for the adverse effects in mammals are potentially related to endocrine disruption Iprodione acts as an AR antagonist *in vivo*.
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	The most sensitive endpoint for aquatic species is the inhibition of growth in the alga *Pseudokirchneriella subcapitata* which is not evidently endocrine-mediated. This effect concentration for alga is within a factor of 3 of those reported for fish. Reproductive effects in birds occur below those causing adult health effects.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	The currently available evidence allows a definitive conclusion to be drawn on the endocrine-mediated effects of iprodione on wildlife species.
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	**Yes**	**There is evidence that iprodione is an endocrine disrupter more likely to pose a risk in mammals based on the most sensitive endpoint.**
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is evidence that iprodione is not an endocrine disrupter less likely to pose a risk based on the most sensitive endpoint
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow iprodione to be excluded for consideration as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.4 Ecotoxicological Endocrine Disruption Evaluation for Myclobutanil

Substance details		
Substance Name	**Myclobutanil**	
Substance Synonyms	2-p-Chlorophenyl-2-(1H-1,2,4-triazol-1-ylmethyl)hexanenitrile	
Substance CAS Number	88671-89-0	
Substance EC Number	410-400-0	
Data Source(s)	Goetz A K, Ren H, Schmid J E, Blystone C R, Thillainadarajah, I, Best D S, Nichols H P, Strader, L F, Wolf D C, Narotsky, M G, Rockett J C and Dix, D J (2007) Disruption of testosterone homeostasis as a mode of action for the reproductive toxicity of triazole fungicides in the male rat. *Toxicological Sciences*, 95(1), 227-239 European Union Draft Assessment Report (2007) Okubo T, Yokoyama Y, Kano K, Soya Y and Kano, I (2004) Estimation of Estrogenic and Antiestrogenic Activities of Selected Pesticides by MCF-7 Cell Proliferation Assay. *Archives of Environmental Contamination and Toxicology*, 46(4), 445-453.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Repr. Cat. 3; R63 Xn; R22 Xi; R36 N; R51-53 Repr. 2 Acute Tox. 4 * Eye Irrit. 2 Aquatic Chronic 2	 Possible harm to the unborn child Harmful if swallowed Irritating to eyes Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Suspected of damaging the unborn child Harmful if swallowed Cause serious eye irritation Toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group 3 - Endocrine disrupter less likely to pose a risk**	

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Pseudokirchneriella subcapitata* growth inhibition test (120 hour exposure to myclobutanil, purity 93.0%)	1	Inhibition of growth	No information provided	0.56	1.1	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 days exposure to myclobutanil, purity 90.0%)	1	Reduction in juvenile production	No information provided	1.0	>1.0	No reproductive or parental effects at any test concentration
Fish fathead minnow *Pimephales promelas* early life stage test (35 day exposure to myclobutanil, purity 91.9%)	1	Larval growth	No information provided	0.98	2.2	Effect could be endocrine-mediated
Fish short-term reproduction test	No data provided	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data provided	-	-	-	-	-
Amphibian metamorphosis assay	No data provided	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (22 week exposure to myclobutanil, purity 94.2%)	1	Reproductive and adult health effects	No information provided	260 mg a.s./kg diet (31.6 mg a.s./kg bw day)	>260 mg a.s./kg diet (>31.6 mg a.s./kg bw day)	No reproductive or adult health effects were measured at any test concentration
Bobwhite quail (*Coilinus virginianus*) reproduction test (22 week exposure to myclobutanil, purity 94.2%)	1	Reproductive and adult health effects	No information provided	260 mg a.s./kg diet (24.2 mg a.s./kg bw day)	>260 mg a.s./kg diet (>24.2 mg a.s./kg bw day)	No reproductive or adult health effects were measured at any test concentration
Wildlife (*in vivo*) data from published literature						
Wistar male rats exposed to myclobutanil – Goetz *et al*. (2007)	2	Reduced litter survival Impaired insemination and fertility Increased serum testosterone at PND92/99 Increased relative liver weight	 The potential mechanism is demasculinisation of the spinal nucleus of the bulbocavernosus (SNB) The potential mechanism is increased testicular steroidogenesis	500 mg/kg diet 500 mg/kg diet 500 mg/kg diet 500 mg/kg diet	2000 mg/kg diet 2000 mg/kg diet 2000 mg/kg diet 2000 mg/kg diet	These reproductive effects are consistent with the disruption of testosterone homeostasis as a key event in triazole-induced reproductive toxicity

		at Postnatal day (PND) 1, 50 and 92				
Mechanistic (*in vitro* and *in vivo*) data						
Activation of the estrogen receptor using the MCF cell proliferation assay – Okubo *et al*. (2004)	2	No effect on MCF cell proliferation assay Suppressive effect on cell proliferation induced by 30 pM 17β-estradiol	No activation of the estrogen receptor Myclobutanil has the capacity to bind to ERα a and may exert its activity by competing at the level of ERα	28.88 mg/l (≥100 µM) 2.89 mg/l (10 µM)	Not relevant 28.88 mg/l (100 µM)	No effect at the highest concentration tested Myclobutanil was found to have strong antiestrogenic activity

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for myclobutanil, which is relevant to mammalian wildlife species, indicated that the substance is an endocrine disrupter less likely to pose a risk. None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test in fathead minnow reported effects on larval growth which could be endocrine-mediated and could affect populations. For birds the one generation studies in bobwhite quail and mallard reported no reproductive effects that could be endocrine-mediated and could affect populations. Effects observed in rats are probably endocrine mediated and could affect mammalian populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Yes	There is evidence that disruption of testosterone homeostasis is a key event in myclobutanil-induced reproductive toxicity. Myclobutanil has been found to have strong antiestrogenic activity *in vitro*.
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	The most sensitive endpoint for aquatic species is the inhibition of growth in the alga *Pseudokirchneriella subcapitata* which is not evidently endocrine-mediated. This effect concentration for alga is within a factor of 3 of those reported for fish. For birds no reproductive or adult health effects were evident at the highest dose tested.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	The currently available evidence allows a definitive conclusion to be drawn on the endocrine-mediated effects of myclobutanil on wildlife species.
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	**Yes**	**There is evidence that myclobutanil is an endocrine disrupter more likely to pose a risk in mammals based on the most sensitive endpoint.**
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is evidence that myclobutanil is not an endocrine disrupter less likely to pose a risk based on the most sensitive endpoint
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow myclobutanil to be excluded for consideration as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.5 Ecotoxicological Endocrine Disruption Evaluation for Prochloraz

Substance details		
Substance Name	**Prochloraz**	
Substance Synonyms	N-propyl-N-[2-(2,4,6-trichlorophenoxy)ethyl]imidazole-1-carboxamide	
Substance CAS Number	67747-09-5	
Substance EC Number	266-994-5	
Data Source(s)	European Union Draft Assessment Report (2007) OECD (2011) Guidance Document (GD) on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption - Case Studies using Prochloraz	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Xn;R22 N; R50-53	Harmful if swallowed. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Acute Tox. 4 * Aquatic Acute 1 Aquatic Chronic 1	Harmful if swallowed Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group C - Endocrine disrupters less likely to pose a risk**	

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Desmodesmus subspicatus* growth inhibition test (72 hour exposure to prochloraz, purity 99.0%)	1	Inhibition of growth	No information reported	0.0032 (biomass and growth rate)	0.0056 (biomass and growth rate)	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to radiolabelled prochloraz, purity 92.0%)	1	Reduction in juvenile production and juvenile growth	No information reported	0.022	0.050	Effects are evidently not endocrine-mediated
Fish fathead minnow *Pimephales promelas* early life stage test (36 day exposure to prochloraz, purity 96.2%)	1	Embryo-larval hatching and larval growth	No information reported	≥0.0485	Not relevant	No effects on hatching and larval growth are evident at the highest test concentration
Fish short-term reproduction test	No data provided	-	-	-	-	-
Fish sexual development test	No data provided	-	-	-	-	-
Fish fathead minnow *Pimephales promelas* life cycle test (189 day exposure to prochloraz, purity not stated)	1	Effects not stated	No information reported	0.0249		Effects could be endocrine-mediated
Amphibian metamorphosis assay	No data provided	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test	No data provided	-	-	-	-	-
Bobwhite quail (*Coilinus virginianus*) reproduction test (20 week exposure to prochloraz, purity 96.7%)	1	Reproductive effects (reduction in the proportion of viable embryos of eggs set, the proportions of normal hatchlings of eggs set and of viable embryos, the proportions of 14-day survivors of normal hatchlings and of eggs laid, and the number of 14-day survivors per adult female Adult health effects	No information reported	160 mg a.s./kg diet (14.2 mg a.s./kg bw/day) 1000 mg a.s./kg diet	1000 mg a.s./kg diet (87.4 mg a.s./kg bw/day) >1000 mg a.s./kg diet	Effects could be endocrine-mediated

Wildlife (*in vivo*) data from published literature						
Fish Short Term Reproduction Assay (FSTRA) using fathead minnows *Pimephales promelas* (exposure duration and prochloraz purity not stated) - Ankley *et al*. (2005) cited in OECD (2011)	2	Increase in fecundity Decrease in vitellogenin level in females	No information reported	0.03 0.03	0.1 0.1	Effects are endocrine-mediated
Fish Short Term Reproduction Assay (FSTRA) using fathead minnows *Pimephales promelas* (exposure duration and prochloraz purity not stated) - Jensen and Ankley (2006) cited in OECD (2011)	2	Decrease in secondary sexual characteristics (tubercle score) Decrease in vitellogenin level in females	No information reported	0.034 <0.02	0.144 0.020	Effects are endocrine-mediated
Fish Short Term Reproduction Assay (FSTRA) using fathead minnows (exposure duration and prochloraz purity not stated) - Biever *et al*. (2007) cited in OECD (2011)	2	Increase in fecundity	No information reported	0.016	0.058	Effects are endocrine-mediated
Fish Sexual Development Test (FSDT) using zebrafish *Danio rerio* (exposure duration and prochloraz purity not stated) - Kinnberg *et al*. (2007) cited in OECD (2011)	2	Increase in proportion of males in offspring Decrease in vitellogenin level in females	No information reported	0.064 0.064	0.202 0.202	Effects are endocrine-mediated
Fish Sexual Development Test (FSDT) using fathead minnows *Pimephales promelas* and zebrafish *Danio rerio* (exposure duration and prochloraz purity not stated) – OECD (2007) cited in OECD (2011)	2	Decrease in the proportion of females in fathead minnow offspring Decrease in vitellogenin level in female fathead minnows Decrease in the proportion of females in zebrafish offspring Decrease in vitellogenin level in female zebrafish	No information reported	0.101 <0.03 0.058 0.04	0.292 0.03 0.138 0.124	Effects are endocrine-mediated
Fish acute test using medaka *Oryzias latipes* (7 day exposure to prochloraz, purity not stated) - Zhang *et al*. (2008) cited in OECD (2011)	2	Reduction in fecundity	Up-regulation of ovarian CYP17 and 19A genes, and down-regulation of various female hepatic genes including ERα, VTG I and II, and several choriogenin genes was	-	0.03	Effects are endocrine-mediated

			observed.			
Fish acute test using adult fathead minnow *Pimephales promelas (*8 day exposure to prochloraz with 8 day post-exposure period, purity not stated) - Ankley *et al*. (2009) cited in OECD (2011)	2	Transient depression of *ex-vivo* ovarian estradiol production in females Permanent E2 and VTG depression in females Depression of testosterone production in males	Several genes associated with steroidogenesis were upregulated in both sexes.	<0.03 0.03 <0.03	0.03 0.3 0.03	Effects are endocrine-mediated
Fish acute test using adult female zebrafish *Danio rerio* (48 hour exposure to prochloraz, purity not stated) – Liu *et al.* (2011) cited in OECD (2011)	2	Decreased plasma T and E2 concentrations and corticotrophin-releasing hormone (CRH)	The decrease in plasma E2 caused by prochloraz was correlated with the down-regulation of CRH mRNA expression.	<0.3	0.3	Effects are endocrine-mediated
Fish acute test using adult female fathead minnow *Pimephales promelas* (24 hour exposure to prochloraz, purity not stated) - Skolness *et al*.(2011) cited in OECD (2011)	2	Decrease in plasma E2 levels Decreased *ex vivo* plasma E2 levels	The results are consistent with compensation of the HPG axis to inhibition of steroidogenesis by prochloraz.	<0.3	≤0.3	Effects are endocrine-mediated
Fish (Medaka) Multi-Generation Test (MMGT) (exposure duration and prochloraz purity not stated) - Unpublished US EPA data (2011) cited in OECD (2011)	2	Decreased anal fin papillae in F1 generation sub adult males Decreased anal fin papillae in F2 generation sub-adult males Decrease in vitellogenin level in F1 and F2 generation sub-adult females Decreased fecundity in adult females: F0 generation F1 generation F2 generation	No information reported	0.005 0.017 0.005 0.025 >0.025 0.017	0.009 Not reported 0.009 0.041 Not stated 0.025	Effects are endocrine-mediated
Common frog (*Rana temporaria*) metamorphosis assay with exposure of prochloraz from hatch to metamorphosis (exposure duration and prochloraz purity not stated) - Brande-Lavridsen *et al*. (2008) cited	2	Increased proportion of males and decreased proportion of hermaphrodites Reduced whole body testosterone levels	The results suggested that enzymes upstream of aromatase were being affected in addition to aromatase itself.	0.011 0.011	0.155 0.155	Effects are endocrine-mediated

in OECD (2011)						
Mechanistic (*in vitro* and *in vivo*) data						
Cell proliferation assay using human breast cancer MCF-7 cells – Andersen *et al*. (2002) cited in OECD (2011)	2	47% of maximum response for 0.01 nM 17ß-estradiol response	-	Not relevant	0.377 (1.0 µM)	No estrogen agonism was detected with estrogen addition Estrogen antagonism was evident with estrogen addition
Estrogen receptor transactivation assay using human breast cancer MCF-7 cells – Andersen *et al*. (2002)	2	47% of maximum response for 10 nM 17ß-estradiol response	-	Not relevant	3.77 (10 µM)	No estrogen agonism was detected with estrogen addition Estrogen antagonism was evident with estrogen addition
Androgen receptor transactivation assay using Chinese hamster ovary cells (CHO K1) – Andersen *et al*. (2002)	2	37% of 0.1 nM R1881 induced response	-	Not relevant	3.77 (10 µM)	Anti-androgenic response was evident
Aromatase assay based on placental microsomes – Andersen *et al*. (2002)	2	8% of control level	-	Not relevant	18.9 (50 µM)	Potent inhibition of aromatase activity was observed

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for prochloraz, which is relevant to mammalian wildlife species, indicated that "*The substance is an endocrine disruptor less likely to pose a risk*". For fish the Short Term Reproduction Assay (FSTRA), Sexual Development Test (FSDT) and life cycle tests reported effects on fecundity and the sex ratio of the offspring which are endocrine-mediated and could affect populations. For birds the one generation studies in bobwhite quail reported reproductive effects that could be endocrine-mediated and could affect populations. Effects observed in rats are probably endocrine mediated and could affect mammalian populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Yes	There is evidence that the mechanisms responsible for the adverse effects in fish and mammals are potentially related to endocrine disruption.

Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	The most sensitive endpoint for aquatic species is the inhibition of algal growth which is not evidently endocrine-mediated. However, effects in fish which are evidently endocrine mediated have been reported at similar exposure concentrations.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	The currently available evidence allows a definitive conclusion to be drawn on the endocrine-mediated effects of prochloraz on wildlife species.
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	**Yes**	**There is evidence that prochloraz is an endocrine disrupter more likely to pose a risk in fish and mammals based on the most sensitive endpoint.**
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is evidence that prochloraz is not an endocrine disrupter less likely to pose a risk based on the most sensitive endpoint.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow prochloraz to be excluded for consideration as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.6 Ecotoxicological Endocrine Disruption Evaluation for Tebuconazole

Substance details		
Substance Name	**Tebuconazole**	
Substance Synonyms	alpha-[2-(4-chlorophenyl)ethyl]-alpha-(1,1-dimethylethyl)- 1H-1,2,4-triazole-1-ethanol	
Substance CAS Number	80443-41-0	
Substance EC Number	403-640-2	
Data Source(s)	Cericato, L., Machado, J.G., Fagundes, M., Kreutz, L.C., Quevedo, R.M., Finco, J., da Rosa, J.G.S., Koakoski, G., Centenaro, L., Pottker, E., Anziliero, D., and Barcellos, L.J.G. (2008) Cortisol response to acute stress in jundia Rhamdia quelen acutely exposed to sub-lethal concentrations of agrichemicals. *Comparative Biochemistry and Physiology C-Toxicology and Pharmacology*, **148**, 281-286. European Union Draft Assessment Report (2008) Sancho, E., Villarroel, M.J., Fernandez, C., Andreu, E., and Ferrando, M.D. (2010) Short-term exposure to sublethal tebuconazole induces physiological impairment in male zebrafish (*Danio rerio*). *Ecotoxicology and Environmental Safety*, **73**, 370-376. Taxvig, C., Hass, U., Axelstad, M., Dalgaard, M., Boberg, J., Andeasen, H.R., and Vinggaard, A.M., (2007) Endocrine-disrupting activities *in vivo* of the fungicides tebuconazole and epoxiconazole. *Toxicological Sciences*, **100**, 464-473. Taxvig, C., Vinggaard, A.M., Hass, U., Axelstad, M., Metzdorff, S., and Nellemann, C., (2008) Endocrine disrupting properties *in vivo* of widely used azole fungicides. *International Journal of Andrology*, **31**, 170-176.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Repr. Cat. 3; R63 Xn; R22 N; R51-53	Possible risk of harm to the unborn child. Harmful if swallowed. Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Repr. 2 Acute Tox. 4 * Aquatic Chronic 2	Suspected of damaging the unborn child. Harmful if swallowed. Toxic to aquatic life with long lasting effects.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

What is the grouping for the substance from the human health assessment of endocrine disruption?	Group C – Endocrine disrupters less likely to pose a risk

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Desmodesmus subspicatus* growth inhibition test (72 hour exposure to tebuconazole, purity 97.5%)	1	Inhibition of growth (growth rate) Inhibition of growth (biomass)	No information reported	1.0 0.32	1.8 0.56	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to tebuconazole, purity 99.6%)	1	Reduction in juvenile production	No information reported	0.01	0.03	Effects are evidently not endocrine-mediated
Fish rainbow trout *Oncorynchus mykiss* early life stage test (83 day exposure to tebuconazole, purity 96.3%)	1	Reduction in larval survival and growth	No information reported	0.012	0.025	Effects could be endocrine-mediated
Fish short-term reproduction test	No data provided	-	-	-	-	-
Fish fathead minnow *Pimephales promelas* sexual development test (122-125 day exposure to tebuconazole, purity 96.8%)	1	Degenerative liver toxicity in both sexes (at day 122-125) Female gonad changes (at day 122-125) Morphological and behavioural effects (spinal column deformations)	No information reported	0.0063 0.0063 0.0125	0.0125 0.0063 0.025	Observed effects which could be interpreted as endocrine effects are considered more likely to be secondary effects based on systemic toxicity in the organisms caused by liver degeneration
Fish life cycle test (203 day exposure to tebuconazole, purity 96.4%)	1	F0 larval growth F1 larval growth Reduction in F0 reproductive success	No information reported	0.0436 0.0469 0.0986	0.0967 0.0978 0.196	Effects could be endocrine-mediated
Amphibian metamorphosis assay	No data provided	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (19 week exposure to tebuconazole, purity 96.9%)	1	Reproductive effects (14 day old survivors per hen)	No information reported	157 mg a.s./kg diet (16.4 mg a.s./kg bw/day)	320 mg a.s./kg diet (33.4 mg a.s./kg bw/day)	Effects could be endocrine-mediated
Bobwhite quail (*Coilinus virginianus*) reproduction test (21 week exposure to tebuconazole, purity 97.0%)	1	Reproductive effects (reduction in body weight of hatchlings and 14 day survivor body weights)	No information reported	<156 mg a.s./kg diet (<12.4 mg a.s./kg bw/day)	<156 mg a.s./ kg diet (<12.4 mg a.s./kg	Effects could be endocrine-mediated

					bw/day)	
Wildlife (*in vivo*) data from published literature						
Fish jundia *Rhamdia quelen* acute study (96 hour exposure to tebuconazole as Folicur200CE, purity not stated) – Cericato *et al*. (2008)	2	Plasma cortisol concentrations Behavioural responses	No information reported	≥2.65	Not relevant	No endocrine-mediated effects are evident at any test concentration
Fish zebrafish *Danio rerio* short-term study (7 to 14 day exposure to tebuconazole, purity 96.0%) – Sancho *et al*. (2010)	2	Increased vitellogenin level (Vitellogenin level continued to increase after 14 days recovery) Increased levels of glucose, lactate, cholesterol and triglycerides	No information reported	<0.23	0.23 (Only concentration tested)	Effects are endocrine-mediated
Pregnant female Wistar rats in an *in utero* test (exposure to tebuconazole from gestational day 3 to postnatal day 16, purity 98.0%) – Taxvig *et al*. (2007)	2	Increased maternal body weight gain, gestation length, % post-implementation loss, % perinatal loss and % postnatal death in dams Increased T3 and progesterone levels in dams at GD21 Change in T4 and testosterone levels in dams at GD21 Change in litter size, number of live offspring and % males Increased nipple retention in male offspring and anogenital distance in female offspring Increases in maternal body weight, % post-implementation loss and male and female foetal weight in females at GD21 (caesarean section) Increased 17α-hydroxyprogesterone and progesterone levels in male foetuses at GD21 Increased testosterone levels in male foetuses at GD21	No information reported	50 mg/kg bw/ day 50 mg/kg bw/ day >100 mg/kg bw/ day ≥100 mg/kg bw/ day 50 mg/kg bw/ day 50 mg/kg bw/ day <50 mg/kg bw/ day 50 mg/kg bw/ day	100 mg/kg bw/ day 100 mg/kg bw/ day Not relevant Not relevant 100 mg/kg bw/ day 100 mg/kg bw/ day 50 mg/kg bw/ day 100 mg/kg bw/ day	Effects are endocrine-mediated. The overall suggested outcome is that tebuconazole virilises the females and feminises the male pups.

Pregnant female Wistar rats in an *in utero* test (exposure to tebuconazole from gestational day 7 to 21, purity 98.0%) – Taxvig *et al*. (2008)	2	Increased frequency of post-implantation loss Change in number of implantations, number of live foetuses, % of late resorptions, % of very late resorptions and % of male foetuses Change in anogenital distance in male and female foetuses Increased serum progesterone levels in male foetuses Increased serum oestradiol levels in male foetuses	No information reported	<50 mg/kg bw/ day ≥50 mg/kg bw/ day >50 mg/kg bw/ day <50 mg/kg bw/ day <50 mg/kg bw/ day	50 mg/kg bw/ day Not relevant Not relevant 50 mg/kg bw/ day 50 mg/kg bw/ day	Effects are endocrine-mediated. The overall suggested outcome is that tebuconazole virilises the females and feminises the male pups.
Castrated male Wistar rats in the Hershberger assay (exposure to tebuconazole, purity 98.0%) – Taxvig *et al*. (2008)	2	Increase in liver weight Changes in weights of ventral prostate, seminal vesicles✓ coagulation gland, levator ani ⁄ bulbocavernosus muscles (LABC) and bulbourethral glands Changes in serum LH, FSH and T4 levels	Tebuconazole does not act as an anti-androgen	100 mg/kg bw/ day ≥150 mg/kg bw/ day ≥150 mg/kg bw/ day	150 mg/kg bw/ day Not relevant Not relevant	No endocrine--mediated (anti-androgenic) effects at any test dose
Mechanistic (*in vitro* and *in vivo*) data						
No specific information located	-	-	-	-	-	-

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for tebuconazole, which is relevant to mammalian wildlife species, indicates that "*The substance is an endocrine disruptor less likely to pose a risk*". None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test in fathead minnow reported effects on larval growth which could be endocrine-mediated and could affect populations.

		For birds the one generation studies in bobwhite quail and mallard reported reproductive effects that could be endocrine-mediated and could affect populations. Effects observed in rats are probably endocrine mediated and could affect mammalian populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Yes	There is evidence that the mechanisms responsible for the adverse effects in mammals are potentially related to endocrine disruption. Vitellogenin induction was observed in fish after acute exposure. The observed effects in the fathead minnow *Pimephales promelas* sexual development test which could be interpreted as endocrine effects are considered more likely to be secondary effects based on systemic toxicity in the organisms caused by liver degeneration.
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	The most sensitive endpoint for aquatic species is female gonad changes (at day 122-125) in a fathead minnow *Pimephales promelas* sexual development test. These effects which could be interpreted as endocrine effects are considered more likely to be secondary effects based on systemic toxicity in the organisms caused by liver degeneration. Effects on F0 and F1 larval growth and F0 reproductive success are also evident at low tebuconazole exposure concentrations in a fish life cycle test.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	The currently available evidence allows a definitive conclusion to be drawn on the endocrine-mediated effects of tebuconazole on wildlife species.
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	**Yes**	**There is evidence that tebuconazole is an endocrine disrupter more likely to pose a risk in fish and mammals and based on the most sensitive endpoint.**
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is evidence that tebuconazole is not an endocrine disrupter less likely to pose a risk based on the most sensitive endpoint
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow tebuconazole to be excluded as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.7 Ecotoxicological Endocrine Disruption Evaluation for Thiram

Substance details		
Substance Name	**Thiram**	
Substance Synonyms	tetramethylthiuram disulfide	
Substance CAS Number	137-26-8	
Substance EC Number	205-286-2	
Data Source(s)	European Union Draft Assessment Report (2003) Mastorakos, G., Karoutsou, E.I., Mizamtsidi, M., Creatsas, G. (2007) The menace of endocrine disruptors on thyroid hormone physiology and their impact on intrauterine development. *Endocrinology*, **31(3),** 219-237.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Xn; R20/22-48/22 Xi; R36/38 R43 N; R50-53	Harmful by inhalation and if swallowed Harmful: danger of serious damage to health by prolonged exposure if swallowed Irritating to eyes and skin May cause sensitization by skin contact Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Acute Tox. 4 * Acute Tox. 4 * STOT RE 2 * Eye Irrit. 2 Skin Irrit. 2 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	Harmful if inhaled Harmful if swallowed May cause damage to organs through prolonged or repeated exposure Causes serious eye irritation Causes skin irritation May cause an allergic skin reaction Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

What is the grouping for the substance from the human health assessment of endocrine disruption?	Group A - Substances requiring further information

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal growth inhibition test (120 hour exposure to thiram, purity not stated)	1	Inhibition of growth	No information reported	<0.065	Not stated	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to thiram, purity not stated)	1	Reduction in juvenile production	No information reported	<0.008	Not stated	Effects are evidently not endocrine-mediated
Fish rainbow trout *Oncorhynchus mykiss* early life stage test (28 day exposure to Thiram 80WG, 4 applications at 7 day intervals in a water-sediment system, purity = 81.2% followed by a 14 day recovery period)	1	Reduction in mean growth rate at day 28 Mean growth rate at day 42 Increased mortality	No information reported	0.012 ≥0.020 0.020	0.020 Not relevant 0.031	Effects could be endocrine-mediated
Fish short-term reproduction test	No data provided	-	-	-	-	-
Fish sexual development test	No data provided	-	-	-	-	-
Fish life cycle test	No data provided	-	-	-	-	-
Amphibian metamorphosis assay	No data provided	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test	No data provided	-	-	-	-	-
Bobwhite quail (*Coilinus virginianus*) reproduction test (23 week exposure to thiram, purity not stated)	1	Reproductive effects Adult health effects	No information reported	500 mg a.s./kg diet (37.5 mg a.s./kg bw/ day) ≥2500 mg a.s./kg diet	2500 mg a.s./kg diet	Effects could be endocrine-mediated Reversibility of the effects on reproduction were observed at 2500 mg a.s./kg diet
Wildlife (*in vivo*) data from published literature						
No specific information located	-	-	-	-	-	-

Mechanistic (*in vitro* and *in vivo*) data						
In vitro study using hamsters – Marinovic *et al.* (1997) cited in Mastorakos *et al.* (2007)	4	Effect on the activity of hyperoxidase or disorders in the iodization of thyroglobin	-	<2.40 (<10 µM)	2.40 10 µM	-

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for thiram, which is relevant to mammalian wildlife species, indicated that "*Effects on LH surge and thyroid adenomas were observed*". None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test reported effects on larval growth which could be endocrine-mediated and could affect populations. For birds the one generation study in bobwhite quail reported reproductive effects that could be endocrine-mediated and could affect populations. Effects observed in rats are probably endocrine mediated and could affect mammalian populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is some evidence that the mechanisms responsible for the adverse effects in mammals are potentially related to endocrine disruption but this is not conclusive.
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	The most sensitive endpoint is the reduction in juvenile production and juvenile growth in *Daphnia magna* which are evidently not endocrine-mediated. However, effects which could be endocrine mediated are evident in fish at similar concentrations. For birds the reproductive effects were evident at a lower test dose than those causing adult health effects.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**The currently available evidence does not allow a definitive conclusion to be drawn on the endocrine-mediated effects of thiram on wildlife species.**

(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that thiram is an established endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that thiram is an established endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow thiram to be excluded as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Herbicides

Table C.8 Ecotoxicological Endocrine Disruption Evaluation for 2,4-D

Substance details		
Substance Name	**2,4-D (ISO)**	
Substance Synonyms	2,4-dichlorophenoxyacetic acid	
Substance CAS Number	94-75-7	
Substance EC Number	202-361-1	
Data Source(s)	European Union Draft Assessment Report (2001) IPCS (1984) 2,4-D Environmental Health Criteria Monograph 29 Liu R C (1996) The direct effects of hepatic peroxisome proliferators on rat Leydig cell function *in vitro*. *Fundamental Applied Toxicology*, **30**, 102–108. USDI (1962) Pesticide Wildlife Studies: A Review of Fish and Wildlife Service Investigations during 1961 and 1962. United States Department of the Interior, Fish and Wildlife Service Circular 167. WHO (2003) 2,4-D in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*;	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Xn; R22 Xi; R37-41 R43 R52-53	Harmful if swallowed Irritating to respiratory system, Risk of serious damage to eyes May cause sensitization by skin contact Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Acute Tox. 4 * STOT SE 3 Eye Dam. 1 Skin Sens. 1 Aquatic Chronic 3	Harmful if swallowed May cause respiratory irritation Causes serious eye damage May cause an allergic skin reaction Harmful to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group A - Substances requiring further information**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Pseudokirchneriella subcapitata* growth inhibition test (5 day exposure to 2,4-D, purity 96.1%)	1	Inhibition of growth	No information reported	26.4	49.5	Effects are evidently not endocrine-mediated
Macrophyte *Lemna gibba* growth inhibition (14 day exposure to 2,4-D Dimethylamine salt, purity 66.7%)	1	Inhibition of growth	No information reported	0.27	0.50	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to 2,4-D, purity 97.5%)	1	Reduction in juvenile production Reduced parental survival	No information reported	46.2 100	100 215	Effects are evidently not endocrine-mediated
Fish fathead minnow *Pimephales promelas* early life stage test (32 day exposure to 2,4-D, purity not stated)	1	Embryo hatching and larval growth Larval survival	No information reported	102 63.4	>102 102	Effects could be endocrine- mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay						
Mallard (*Anas platyrhynchos*) reproduction test (21 week exposure to 2,4-D, purity not stated)	1	Reproductive and adult health effects	No information reported	1000 mg a.s./kg	>1000 mg a.s./kg	No reproductive or adult health effects at any test concentration
Bobwhite quail (*Coilinus virginianus*) reproduction test	No data reported	-	-	-	-	-
Wildlife (*in vivo*) data from published literature						
Fish bluegill sunfish (*Lepomis macrochirus*) mesocosm test (12 week exposure to Esteron 99, propylene glycol butyl ether ester of 2,4-D) – USDI (1962)	2	Delayed spawning in females No change in fry production	No information reported	5 10	10 >10	Effects could be endocrine- mediated
Mechanistic (*in vitro* and *in vivo*) data						
In vitro leydig cell function test – Liu (1996)	2	Effect of peroxisome proliferators on the hCG stimulated release of testosterone from 24-hr cultures of		No data	No data	No minimum effective concentration established

		Leydig cells Effect of peroxisome proliferators on the non-stimulated release of testosterone from 24-hr cultures of Leydig cells Effect of peroxisome proliferator on the baseline release of estradiol from 2l-hr cultures of Leydig cells		No data 22.1 (100 µM)	No data 110.5 (500 µM)	No minimum effective concentration established

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for 2,4-D, which is relevant to mammalian wildlife species, indicated that "*There is some evidence of effects on thyroid weight and thyroxine levels in long-term toxicity studies. However, no modern studies to indicate whether this is due to any direct disrupting effects on the thyroid system*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the effects in the fathead minnow early stage test and bluegill sunfish mesocosm study could be endocrine-mediated and could affect populations. For birds the one generation study in bobwhite quail did not report any reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint for aquatic species is the inhibition of growth in the macrophyte *Lemna minor* which is not evidently endocrine-mediated. The effects concentration for *Lemna* is a factor of 200 lower than those reported in fish. For birds no reproductive or adult health effects were evident at the highest dose tested.

Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**The currently available evidence does not allow a definitive conclusion to be drawn on the endocrine-mediated effects of 2,4-D on wildlife species.**
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that 2,4-D is an established endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that 2,4-D is an established endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow 2,4-D to be excluded as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.9 Ecotoxicological Endocrine Disruption Evaluation for Glyphosate

Substance details		
Substance Name	**Glyphosate**	
Substance Synonyms	N-(phosphonomethyl)glycine	
Substance CAS Number	1071-83-6	
Substance EC Number	213-997-4	
Data Source(s)	European Union Draft Assessment Report (2005) Roshon R D (1997) A toxicity test for the effects of chemicals on the non-target submersed aquataic macrophyte, *Myriophyllum sibiricum* Komarov. PhD thesis. University of Guelph, Guelph, Ontario, Canada. SERA (2002) Syracuse Environmental Research Associates, Inc. Neurotoxicity, Immunotoxicity, and Endocrine Disruption with Specific Commentary on Glyphosate, Tricloopyr, and Hexazinone: Final Report: SERA TR 01-43-08-04a. Submitted to USDA Forest Service, Riverdale, MD, USA. Soso AB, Barcellos LJG, Ranzani-Paiva MJ, Kreutz LC, Quevedo RM, Anziliero D, Lima M, Bolognesi da Silva L, Ritter F, Bedin AC and Finco JA (2007) Chronic exposure to sub-lethal concentration of a glyphosate-based herbicide alters hormone profiles and affects reproduction of female Jundiá (*Rhamdia quelen*). *Environmental Toxicology and Pharmacology*, **23**, 308-313.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	 Xi; R41 N; R51-53 Eye Dam. Aquatic Chronic 2	 Risk of serious damage to eyes Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment Causes serious eye damage Toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group D - Substances not considered to be endocrine disrupters based on currently available data**	

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Nitzschia palea* growth inhibition test (96 hour exposure to technical glyphosate, purity >94%)	1/2	Inhibition of algal growth	No information reported	1.0	<4.5	Effects are evidently not endocrine mediated
Invertebrate *Daphnia magna* reproduction test	1/2	Reduction in juvenile production Increase in adult mortality	No information reported	9 95	30 300	Effects are evidently not endocrine mediated
Fish rainbow trout *Oncorhynchus mykiss* growth test (21 day exposure to technical glyphosate, purity >94%)	1/2	Decrease in growth Increase in mortality	No information reported	50 ≥100	100	Effects could be endocrine mediated
Fish early life stage test	No data reported	-	-	-	-	-
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish fathead minnow *Pimephales promelas* life cycle test (254 day exposure to technical glyphosate, purity >94%)	1/2	Effect not stated	No information reported	25.7	Not stated	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (17 week exposure to technical glyphosate, purity not stated)	1/2	Changes in other reproductive and adult health effects	No information reported	≥1000 mg a.s./ kg diet	Not relevant	No reproductive or adult health effects are evident at the highest test dose
Bobwhite quail (*Coilinus virginianus*) reproduction test (17 week exposure to technical glyphosate, purity not stated)	1/2	Reduction in egg weight Changes in other reproductive and adult health effects	No information reported	200 mg a.s./kg diet ≥1000 mg a.s./ kg diet	1000 mg a.s./kg diet Not relevant	Effects could be endocrine mediated
Wildlife (*in vivo*) data from published literature						
Marcophyte *Myriophyllum sibiricum* growth inhibition test (14 day exposure to glyphosate, purity 97%)	2	Inhibition of growth	No information reported	0.33	0.996	Effects are evidently not endocrine mediated

Fish jundi´a (*Rhamdia quelen*) reproduction study (40 day exposure to Roundup®WG, 640 g glyphosate/kg) – Soso *et al*. (2007)	3	Reduced number of swim-up fry Decreased serum E2 concentrations (after 40 days) Increased serum cortisol concentrations (after 40 days) Change in serum testosterone concentration (after 40 days)	The results suggest and effect on E2 production and/or release	<3.6 <3.6 <3.6 ≥3.6	3.6 3.6 3.6 Not relevant	Effects could be endocrine mediated. This study was carried out using a formulated product. No details are available on the surfactant present in the formulation and it is possible that this substance may have contributed to the effects seen.
Mechanistic (*in vitro* and *in vivo*) data						
No specific information located	-	-	-	-	-	-

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes and No	The human health assessment for glyphosate, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the effects in the rainbow trout growth test could be endocrine-mediated and could affect populations. For birds the one generation study in bobwhite quail reported reproductive effects that could be endocrine-mediated and could affect populations A report submitted to the USDA Forest Service concluded that extensive testing in experimental animals and wildlife provided reasonably strong evidence that glyphosate is not an endocrine disruptor (SERA 2002).
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is some data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms but this is not conclusive and is from a poor quality study.
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations

Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint for aquatic species is the inhibition of macrophyte growth which is not evidently endocrine-mediated. The effect concentration for macrophytes is greater than a factor of 100 lower than those reported in fish. For birds reproductive effects on egg weight in bobwhite quail were evident at a lower test dose than those causing or adult health effects.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	The currently available evidence allows a definitive conclusion to be drawn on the endocrine-mediated effects of glyphosate on wildlife species
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that glyphosate is an established endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that glyphosate is an established endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	**Yes**	**The available evidence allows glyphosate to be excluded as an endocrine disrupter**

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.10 Ecotoxicological Endocrine Disruption Evaluation for Ioxynil

Substance details		
Substance Name	**Ioxynil**	
Substance Synonyms	4-hydroxy-3,5-diiodobenzonitrile	
Substance CAS Number	1689-83-4	
Substance EC Number	216-881-1	
Data Source(s)	Akiyoshi S, Sai G, Yamauchi K (2012) Species-dependent effects of the phenolic herbicide ioxynil with potential thyroid hormone disrupting activity: Modulation of its cellular uptake and activity by interaction with serum thyroid hormone-binding proteins. *Journal of Environmental Sciences*, **24(5)**, 949-955 European Union Draft Assessment Report (2003) Morgado I, Campinho M A, Costa R, Jacinto R, Power, D M (2009) Disruption of the thyroid system by diethylstilbestrol and ioxynil in the sea bream (*Sparus aurata*). *Aquatic Toxicology*, **92(4)**, 271-280.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Repr. Cat. 3; R63 T; R23/25 Xn; R21-48/22 Xi; R36 N; R50-53	R63 Possible risk of harm to the unborn child R23/25Toxic by inhalation and if swallowed R21 Harmful in contact with skin; Harmful: danger of serious damage to health by prolonged exposure if swallowed R36Irritating to eyes R50-53 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Repr. 2 Acute Tox. 3 * Acute Tox. 3 * Acute Tox. 4 * STOT RE 2 * Eye Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H361d Suspected of damaging the unborn child H331 Toxic if inhaled H301Toxic if swallowed. H312 Harmful in contact with skin H373 May cause damage to organs through prolonged or repeated exposure H319 Causes serious eye irritation H400 Very toxic to aquatic life H410 Very toxic to aquatic life with long lasting effects

Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group B – Endocrine disrupters more likely to pose a risk**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Wildlife (*in vivo*) data from European Union Draft Assessment Report						
Algal *Navicula pelliculosa* growth inhibition test (72 hour exposure to ioxynil octanate, purity 93.7%)	1	Inhibition of growth	No information reported	0.012	0.027	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to ioxynil octanate, purity 94.2%)	1	Reduction in juvenile production Increase in immobilisation	No information reported	0.03 0.01	0.1 0.03	Effects are evidently not endocrine-mediated
Fish fathead minnow *Pimephales promelas* early life stage test (36 day exposure to ioxynil octanate, purity 94.2%)	1	Reduction in larval growth	No information reported	0.0022	0.0042	Effects could be endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test	No data reported	-	-	-	-	-
Bobwhite quail (*Coilinus virginianus*) reproduction test	No data reported	-	-	-	-	-
Japanese quail (*Coturnix japonica*) reproduction test (8 week exposure to ioxynil phenol, purity 98.7%)	1	Adult health effects (increased male liver weight) Reproductive effects	No information reported	100 mg a.s./kg diet 300 mg a.s./kg diet	300 mg a.s./kg diet >300 mg a.s./kg diet	No reproductive effects at the highest dose tested

Wildlife (*in vivo*) data from published literature						
Fish sea bream (*Sparus aurata*) thyroid disruption study (21 day exposure to ioxynil) – Morgada *et al*. (2009)	2	No effect on thyroid hormone (T3 and T4) levels Increased transthyretin (TTR) plasma levels Changes in thyroid histology	The results indicated follicular hyperstimulation in all treatments It appears therefore, that in *vitro* TTR-binders, ioxynil, can strongly influence several components of the fish thyroid system *in vivo* but that the thyroid axis may have the ability to maintain or re-establish plasma TH homeostasis.	1 mg/kg diet >1 mg/kg diet >1 mg/kg diet	>1 mg/kg diet Not relevant Not relevant	-
Mechanistic (*in vitro* and *in vivo*) data						
Serum thyroid hormone-binding protein assay in rainbow trout, bullfrog tadpoles, chickens and rats – Akiyoshi *et al*. (2012)	2	Inhibition of T3 antagonist activity in the T3 responsive reporter gene assay – tadpoles Inhibition of T3 antagonist activity in the T3 responsive reporter gene assay - rat	The results suggest that ioxynil interferes with TH homeostasis in plasma and with a step of cellular TH-signaling pathway other than TH-uptake system, in a species-specific manner. This may be modulated by serum binding proteins, depending on their binding affinity and capacity for ioxynil. This could be one of the reasons for greater ecotoxicity of ioxynil in fish and amphibians than in birds and mammals	<0.371 mg/l (<1.0 µM) ≥0.371 mg/l (≥1.0 µM)	0.371 mg/l (1.0 µM) Not relevant	-

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment, which is relevant to mammalian wildlife species, indicates that "*There is evidence of major effects on the thyroid system, including the formation of tumours at dose levels below the STOT-RE Category 1 guidance values*". None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects For fish the effects in the fathead minnow early stage test could be endocrine-mediated and could affect

		populations. For birds the one generation study in japanese quail did not report any reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Yes	The available evidence indicates that effects in fish could be due to interference with TH homeostasis in plasma and with a step of cellular TH-signaling pathway other than TH-uptake system, in a species-specific manner
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	There is no definitive evidence from the available reliable studies that other systemic effects are seen at concentration levels orders of magnitude below those at which endocrine effects are observed. The most sensitive endpoint for aquatic species is the reduction of larval growth in the fathead minnow early life stage test which could be endocrine-mediated. For birds no reproductive or adult health effects were evident at the highest dose tested.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	The currently available evidence allow a definitive conclusion to be drawn on the endocrine-mediated effects of ioxynil on wildlife species.
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	**Yes**	**There is evidence that ioxynil is an endocrine disrupters more likely to pose a risk in fish and mammals based on the most sensitive endpoint**
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is evidence that ioxynil is not an endocrine disrupters less likely to pose a risk based on the most sensitive endpoint.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow ioxynil to be excluded as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.11 Ecotoxicological Endocrine Disruption Evaluation for s-Metolachlor

Substance details		
Substance Name	**s-Metolachlor**	
Substance Synonyms	Mixture of : (aRS, 1 S)-2-chloro-N-(6-ethyl-o-tolyl)-N-(2-methoxy-1-methylethyl)acetamide (80-100%) and: (aRS, 1 R)-2-chloro-N-(6-ethyl-o-tolyl)-N-(2-methoxy-1-methylethyl)acetamide (20-0%)	
Substance CAS Number	87392-12-9	
Substance EC Number	203-625-9	
Data Source(s)	European Union Draft Assessment Report (2004) Jin Y, Chen R, Wang L, Liu J, Yang Y, Zhou C, Liu W and Fu Z (2011) Effects of metalochlor on transcription of thyroid system-related genes in juvenile and adult Japanese medaka (*Oryzias latipes*). *General and Comparative Endocrinology*, 170(3), 487-493. Hayes T B, Case P, Chui S, Chung D, Haeffele C, Haston K, Lee M, Mai V P, Marjuoa Y, Parker J and Tsui M (2006) Pesticide mixtures, endocrine disruption, and amphibian declines: Are we underestimating the impact? *Environmental Health Perspectives*, 114(S-1), 40-50. Mathias F T, Romano R M, Sleiman H K, de Oliveira C A and Romano M A (2012) Herbicide metalochlor causes changes in reproductive endocrinology of male wistar rats ISRN Toxicology, Volume 2012 Article ID 130846.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	R43 N; R50-53	May cause sensitization by skin contact R50-53 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	May cause an allergic skin reaction H400 Very toxic to aquatic life H410 Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

What is the grouping for the substance from the human health assessment of endocrine disruption?	Group A – Substances requiring further information

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Pseudokirchneriella subcapitata* growth inhibition test (120 hour exposure to metolachlor, purity 97.6%)	1	Inhibition of growth	No information reported	0.003	0.0055	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to metolachlor, purity 96.4%)	1	Reduction in juvenile production	No information reported	3.0	15.0	Effects are evidently not endocrine-mediated
Fish sheepshead minnows *Cyprinodon variegatus* early life stage test	Study not considered reliable	-	-	-	-	-
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish fathead minnow *Pimephales promelas* life cycle test (266 day exposure to metalochlor, purity 97.3%)	1/2	Reduced survival of first generation larvae Growth of first generation larvae Hatchability of second generation eggs and larval growth		0.78 ≥1.6 1.6	1.6 Not relevant 3.4	Effects could be endocrine-mediated
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (20 weeks exposure to metolachlor, purity 97.3%)	1	Reproductive and adult health effects	No information reported	≥800 mg a.s./kg diet	Not relevant	No reproductive or adult health effects at any test concentration
Bobwhite quail (*Coilinus virginianus*) reproduction test (23 weeks exposure to metolachlor, purity 97.3%)	1	Reproductive and adult health effects	No information reported	≥800 mg a.s./kg diet	Not relevant	No reproductive or adult health effects at any test concentration
Wildlife (*in vivo*) data from published literature						
Fish Japanese medaka *Oryzias latipes* chronic study (14 day exposure to s-metalochlor, purity not stated) – Jin *et al.* (2011)	2	Induction of transcription of genes related to the thyroid system, including thyrotropin releasing hormone (Trh), deiodinase 2 (Dio2), thyroid hormone receptor α	No information reported			The results suggest that s-metalochlor has the potential to influence several steps of the hypothalamus-pituitary-thyroid (HPT) axis

		(Thrα), and thyroid hormone receptor β (Thrβ) in - Brain and liver tissue of juvenile fish - Brain of adult female fish Increased (Thrα) and (Thrβ) gene transcription in male juvenile medaka in presence of 100 ng/L E2		<0.01 0.01 <0.1	0.01 0.1 0.1	homeostasis and to disrupt the thyroid system in medaka.
Amphibian leopard frogs *Rana pipiens* chronic study (Exposure to metalochlor from 2 days post-hatching until complete tail reabsorption, purity ≥98%) – Hayes *et al*. (2006)	2	Change in the time to initiate metamorphosis (FLE) and time to complete metamorphosis (TR) Change in size at metamorphosis (SVL) and body weight (BW)	-	≥0.0001 (>0.1 µg/l) >0.0001 (>0.1 µg/l)	Not relevant Not relevant	No endocrine-mediated effects were evident at the test concentration
Wistar rat chronic exposure study (30 day exposure to s-metalochlor, purity 96%) – Mathias *et al*. (2012)	2	Increase in serum concentration of testosterone and estradiol Change in serum DHT and LH concentrations Increased epithelial height of seminiferous epithelium	-	<5 mg/kg >50 mg/kg >50 mg/kg	5 mg/kg Not relevant Not relevant	The results were considered to indicate that exposure promotes endocrine problems in reproductive parameters and these changes are reflected by altering the serum concentrations of testosterone, DHT, estradiol, and FSH as well as by causing morphological alterations in androgen-targeted tissues
Mechanistic (*in vitro* and *in vivo*) data						
No specific information located	-	-	-	-	-	-

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment, which is relevant to mammalian wildlife species, indicates that further information is required. None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the effects in the life cycle test in fathead minnow could be endocrine-mediated and could affect populations. For birds the one generation studies in bobwhite quail and mallard did not report any reproductive effects that could be

		endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint for aquatic species is the inhibition of algal growth which is not evidently endocrine-mediated. The effects concentration for alga is greater than a factor of 290900 lower than those reported in fish. For birds no reproductive or adult health effects were evident at the highest dose tested.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**The currently available evidence does not allow a definitive conclusion to be drawn on the endocrine-mediated effects of s-metalochlor on wildlife species.**
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that s-metalochlor is an established endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that s-metalochlor is an established endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow s-metalochlor to be excluded as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.12 Ecotoxicological Endocrine Disruption Evaluation for Metribuzin

Substance details		
Substance Name	**Metribuzin**	
Substance Synonyms	4-amino-6-tert-butyl-4,5-dihydro-3-methylthio-1,2,4-triazin-5-one	
Substance CAS Number	21087-64-9	
Substance EC Number	244-209-7	
Data Source(s)	European Union Draft Assessment Report (2004) Nishihara T, Nishikawa J, Kanayama T, Dakeyama F, Saito,K, Imagawa M, Takatori S, Kitagawa Y, Hori S and Utsumic H (2000) Estrogenic Activities of 517 Chemicals by Yeast Two-Hybrid Assay. *Journal of Health Science*, **46(4),** 282-298. Porter W P, Green S M, Debbink N L and Carlson I (1993) Groundwater pesticides: interactive effects of low concentrations of carbamates aldicarb and methomyl and the triazine metribuzin on thyroxine and somatotropin levels in white rats. *Journal of Toxicology and Environmental Health*, **40(1)**,15-34.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Xn; R22 N; R50-53	Harmful if swallowed Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Acute Tox. 4 * Aquatic Acute 1 Aquatic Chronic 1	Harmful if swallowed Hazardous to the aquatic environment Very toxic to aquatic life with long- lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group C – Endocrine disrupters less likely to pose a risk**	

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal growth inhibition test (96 hour exposure to metribuzin, purity 91.8%)	1	Inhibition in growth	No information provided	0.0018	0.0032	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to metribuzin, purity 93.0%)	1	Reduction in juvenile production	No information provided	0.32	1.0	Effects are evidently not endocrine-mediated
Fish rainbow trout *Oncorhynchus mykiss* early life stage test (95 days exposure to metribuzin, purity 94.0%)	1	Reduction in larval growth	No information provided	5.7 4.4 (EC_{10})	11.7	Effects could be endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (22 weeks exposure to metribuzin, purity 93.5%)	1	Reproductive and adult health effects	No information provided	≥368 mg a.s./kg diet (≥31 mg a.s./kg bw/ day)	Not relevant	No reproductive or adult health effects at the highest dose tested
Bobwhite quail (*Coilinus virginianus*) reproduction test (22 weeks exposure to metribuzin, purity 93.5%)	1	Reproductive and adult health effects	No information provided	≥385 mg a.s./kg diet (≥28.3 mg a.s./kg bw/ day)	Not relevant	No reproductive or adult health effects at the highest dose tested
Wildlife (*in vivo*) data from published literature						
Sprague Dawley rat thyroid function study (6 week exposure for females and 16 week exposure to males) – Porter *et al*. (1993)	2	Increased free thyroxine index	-	<10 mg/l	10 mg/l	The results indicate that the rats showed hyperthyroidism after exposure
Mechanistic (*in vitro* and *in vivo*) data						
Estrogenic activity using the yeast two hybrid assay – Nishihara *et al*. (2000)	2	Evidence of estrogenic activity	-	64.3 mg/l (REC10) (0.3 mM (REC10)		The result is not considered to show positive estrogenic activity because the activity of the test substance was less

						than 10% of the activity of 10^{-4} mM E2,

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment, which is relevant to mammalian wildlife species, indicates that "*The substance is an endocrine disruptor less likely to pose a risk*". None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the effects in the rainbow trout early stage test could be endocrine-mediated and could affect populations. For birds the one generation study in bobwhite quail and mallard did not report any reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Yes	There is some data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact mammals in acceptable studies.
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The thyroid effects measured in the chronic studies in mammals are not relevant to populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint for aquatic species is the inhibition of algal growth which is not evidently endocrine-mediated. The effects concentration for alga is greater than a factor of 3500 lower than those reported in fish. For birds no reproductive or adult health effects were evident at the highest dose tested.
Overall grouping of the substance regarding its endocrine disrupting properties		
Category	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**The currently available evidence does not allow a definitive conclusion to be drawn on the endocrine-mediated effects of metribuzin on wildlife species.**
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that metribuzin is an established endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that metribuzin is an established endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow metribuzin to be excluded as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Insecticides

Table C.13 Ecotoxicological Endocrine Disruption Evaluation for Abamectin

Substance details		
Substance Name	**Abamectin**	
Substance Synonyms	Avermectin B1a	
Substance CAS Number	71751-41-2	
Substance EC Number	-	
Data Source(s)	Celik-Ozenci C, Tasatargil A, Tekcan M, Sati L, Gungor E, Isbir M and Demir, R. Effects of abamectin exposure on male fertility in rats: Potential role of oxidative stress-mediated poly(ADP-ribose) polymerase (PARP) activation. *Regulatory Toxicology and Pharmacology*, **61 (3)**, 310-317 Elbetieha A and Da'as S I (2003) Assessment of antifertility activities of abamectin pesticide in male rats. *Ecotoxicology and Environmental Safety*, **55(3)**, 307-13. European Union Draft Assessment Report (2008)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Not classified	Not classified
Regulation (EC) No 1272/ 2008	Not classified	Not classified
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group B – Endocrine disrupter more likely to pose a risk**	

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Pseudokirchneriella subcapitata* growth inhibition test (72 hour exposure to abamectin, purity 87.6%)	1	Inhibition of growth	No information provided	9.0	>9.0	No effects at the highest test concentration
Invertebrate *Daphnia magna* reproduction test (21 day exposure to abamectin, purity 89.3%)	1	Reduction in juvenile production	No information provided	0.01	0.02	Effects are evidently not endocrine-mediated
Fish rainbow trout *Oncorhynchus mykiss* early life stage test (72 day exposure to abamectin, purity 91.0%)	1	Reduction in larval growth	No information provided	0.52	0.96	Effects could be endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (18 week exposure to abamectin, purity 94.7%)	1	Reproductive and adult health effects	No information provided	12 mg a.s./kg diet (1.33 – 1.49 mg a.s./kg bw/day)	>12 mg a.s./kg diet	No reproductive or adult health effects at the highest dose tested
Bobwhite quail (*Coilinus virginianus*) reproduction test (20 week exposure to abamectin, purity 90.2%)	1	Reproductive and adult health effects	No information provided	20 mg a.s./kg diet (2.0 mg a.s./kg bw/day)	>20mg a.s./kg diet	No reproductive or adult health effects at the highest dose tested
Wildlife (*in vivo*) data from published literature						
Male fertility in Sprague Dawley rats (6 week exposure to abamectin, purity not stated) - Elbetieha and Da'as (2003)	2	Reduced male fertility as number of females impregnated by them was significantly reduced Reduction in number of viable foetuses Significant increases in the total number of resorptions and the number of females	The pregnancy rate and the number of viable foetuses were significantly reduced in females impregnated by abamectin- exposed males. The serum level of testosterone was decreased, while the level of FSH was reduced in males that ingested abamectin. The observed decrease in male	<1.19 mg/animal/ day 1.19 mg/animal/ day <1.19 mg/animal/ day	1.19 mg/animal/ day 1.87mg/animal/ day 1.19mg/animal/ day	The results suggest that exposure to the pesticide abamectin would have adverse effects on fertility and reproduction in adult male rats and possible other mammalian wildlife which are evidently endocrine mediated.

		with resorptions in females mated with the exposed males Increase in the absolute weight of testes	fertility could be explained by the fact that the pesticide acted directly on the testes and affected the androgen biosynthesis pathway. An agent acting directly on the brain, hypothalamus, or anterior pituitary gland will indirectly affect the testes and will possibly affect sexual activity (see mechanistic data) The increased weight of testes may be attributed to the accumulation of interstitial connective tissue around the seminiferous tubules.	<1.19 mg/animal/ day	1.19 mg/animal/ day	
Male fertility in rats (1-6 week exposure to abamectin, purity not stated) - Celik-Ozenci *et al*. (2011)	2	Change in testes weights Decreased sperm count and motility Increased seminiferous tubule damage	The results showed that abamectin exposure induces testicular damage and affects sperm dynamics. It was suggested that oxidative stress-mediated PARP activation could be one of the possible mechanism(s) underlying testicular damage induced by abamectin	≥4 mg/kg bw/day <1 mg/kg bw/day <1 mg/kg bw/day	Not relevant 1 mg/kg bw/day 1 mg/kg bw/day	The results suggest that exposure to the pesticide abamectin would have adverse effects on fertility and reproduction in adult male rats and possible other mammalian wildlife. However, it is not clear that these effects are endocrine mediated.
Mechanistic (*in vitro* and *in vivo*) data						
Male fertility in Sprague Dawley rats (6 week exposure to abamectin, purity not stated) - Elbetieha and Da'as (2003)	2	Decreased epididymal and testicular sperm counts and daily sperm production Decreased serum level of testosterone Increased serum level of follicle-stimulating hormone	-	<1.19 mg/animal/ day <2.3 mg/animal/ day <2.3 mg/animal/ day	1.19 mg/animal/ day 2.3 mg/animal/ day 2.3 mg/animal/ day	The reductions may be caused by a direct effect of the pesticide on testicular Leydig and Sertoli cells, causing a decrease in testosterone production.

		Change in lutenizing hormone		2.3 mg/animal/ day	>2.3 mg/animal/ day	
Male fertility in rats (1-6 week exposure to abamectin, purity not stated) - Celik-Ozenci et al. (2011)	2	Change in serum testosterone and lutenising hormone concentrations Reduction in follicle stimulating hormone concentration Significant elevations in the 4-hydroxy-2-nonenal (4-HNE)-modified proteins and poly(ADP-ribose) (PAR) expression as markers for oxidative stress and poly(ADP-ribose) polymerase (PARP) activation	-	>4 mg/kg bw/day <1 mg/kg bw/day <1 mg/kg bw/day	Not relevant 1 mg/kg bw/day 1 mg/kg bw/day	Exposure to abamectin may lead to ATP failure and testicular damage as a result of increased PARP enzyme activity. The activation of PARP results in a rapid depletion of intracellular ATP, a source of energy for the forward movement of spermatozoa. Full ATP pool is also crucial for normal spermatozoal movement and a slight deprivation of ATP leads to reduction in motility, which may cause infertility. Thus, marked inhibition of sperm motility after ABM exposure may be related with low levels of ATP content as a consequence of increased enzymatic activity of PARP.

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment, which is relevant to mammalian wildlife species, indicates that the substance is an endocrine disrupter more likely to pose a risk based on ED-mediated adverse effects on rat reproduction .

		None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the rainbow trout early life stage test reported effects on growth that could be endocrine-mediated and could affect populations. For birds the one generation studies in bobwhite quail and mallard did not report reproductive effects that could be endocrine-mediated and could affect populations. For rats effects on male fertility are evident that are evidently endocrine-mediated and could affect mammalian populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Possibly	There is evidence in rats of the effects of abamectin on testosterone and FSH levels which suggests an endocrine-mediated response. However, it is not clear whether this is a primary endocrine disruption mode of action or whether the effects are secondary to the effects on sperm production. Overall, there is a plausible/reasonable link between sex hormone disruption and reproductive effects in mammals.
Are the potential ED-mediated effects judged to be relevant to fish, bird and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, birds and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint is the reduction in juvenile production and juvenile growth in *Daphnia magna* which are evidently not endocrine-mediated. The effects concentration for invertebrates is a factor of 50 lower than those reported in fish. For birds no reproductive or adult health effects were evident at the highest dose tested.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	The substance is an endocrine disrupter in mammals
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	No	The substance is not an endocrine disrupter of concerns over potential risks based on the most sensitive endpoint.
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	**Yes**	**The substance is an endocrine disrupter less likely to pose a risk in mammals based on the most sensitive endpoint**
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The substance is an endocrine disrupter in mammals

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.14 Ecotoxicological Endocrine Disruption Evaluation for Chlorpyrifos

Substance details		
Substance Name	**Chlorpyrifos (ISO)**	
Substance Synonyms	*O*,*O*-diethyl *O*-3,5,6-trichloro-2-pyridyl phosphorothioate	
Substance CAS Number	2921-88-2	
Substance EC Number	220-864-4	
Data Source(s)	Andersen HR, Vinggaard AM, Rasmussen TH, Gjermandsen IM, and Bonefeld-Jorgensen EC (2002) Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro. Toxicology and Applied Pharmacology, 179, 1-12. Bernabo I, Gallo L, Sperone E, Tripepi S and Brunelli E (2011) Survival, development, and gonadal differentiation in *Rana dalmatina* chronically exposed to chlorpyrifos. *Journal of Experimental Zoology A: Ecology Genetics and Physiology*, **315(5)**, 314-326. European Union Draft Assessment Report (1999)	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	T; R25 N; R50-53 Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	Toxic if swallowed Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Toxic if swallowed Very toxic to aquatic life Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group A - Substances requiring further information**	

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal growth inhibition test (72 hour exposure to Dursban 5G)	1	Inhibition of growth	No information reported	0.027	0.065	Effects are evidently not endocrine-mediated
Invertebrate *Daphnia magna* reproduction test	1	Reduction in juvenile production	No information reported	0.056	0.1	Effects are evidently not endocrine-mediated
Fish fathead minnow *Pimephales promelas* early life stage test (32 days exposure to chlorpyrifos)	2	Embryo-larval growth and survival	No information reported	0.0016	0.0022	Effects could be endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish fathead minnow *Pimephales promelas* one generation test (exposure of <24 hour old embryos to chlorpyrifos through to 32 day old F1 generation)	2	Parental growth and reproduction Parental and F1 survival	No information reported	0.0011 0.00057	>0.0011 0.0011	Effects could be endocrine-mediated.
Fish fathead minnow *Pimephales promelas* two generation test (Two generation exposure to Dursban)	2	First generation fish survival First generation fish growth after 30 days First generation fish growth after 60 days First generation fish maturation First generation fish reproduction Second generation fish growth	Certain effects may have been due to inhibition of brain acetylcholinesterase (AChE) activity which was significantly inhibitied at 0.00027 mg/l and above	0.0012 0.0012 0.00063 <0.00012 0.00027 <0.00012	0.0027 0.0027 0.0012 0.00012 0.00063 0.00012	Certain effects could be endocrine-mediated.
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (18 week exposure to chlorpyrifos)	1	Reproductive effects (reduction in eggs/hen/day, shell thickness and egg weight)	No information reported	<80 mg/kg diet	80 mg/kg diet	Effects could be endocrine-mediated
Mallard (*Anas platyrhynchos*) reproduction test (17 week exposure to chlorpyrifos)	1	Reproductive and adult health effects	No information reported	25 mg/kg diet	125 mg/kg diet	Effects could be endocrine-mediated
Bobwhite quail (*Coilinus virginianus*) reproduction test (26 week exposure to chlorpyrifos)	1	Reproductive effects	No information reported	125 mg/kg diet	>125 mg/kg diet	No reproductive or adult health effects at any test concentration

Wildlife (*in vivo*) data from published literature						
Amphibian agile frog *Rana dalmatina* early life stage test (57 day exposure to chlorpyrifos, purity 99.5%) – Bernabo *et al*. (2011)	2	Change in the developmental rate of tadpoles Increased incidence of intersex in 1 month old froglets (0% in controls, 20-25% in treatments)	The results suggested that chlorpyrifos acted as an antiandrogen and induced partial feminization (induction and growth of oocytes) or demasculinization in the gonads of exposed males	0.05 mg/l <0.025 mg/l	>0.05 mg/l 0.025 mg/l	No effect at the highest test concentration
Mechanistic (*in vitro* and *in vivo*) data						
Cell proliferation assay using human breast cancer MCF-7 cells – Andersen *et al*. (2002)	2	Cell proliferation	-	No data	8.77 (25 µM)	The results indicate a weak estrogenic response was induced
Estrogen receptor transactivation assay using human breast cancer MCF-7 cells – Andersen *et al*. (2002)	2	Estrogen receptor transactivation	-	No data	17.5 (50 µM)	The results indicate a weak estrogenic response was induced
Androgen receptor transactivation assay using Chinese hamster ovary cells (CHO K1) – Andersen *et al*. (2002)	2	No significant change from the control	-	No data	No data	The results indicate the substance did not react as an androgen agonist
Aromatase assay based on placental microsomes – Andersen *et al*. (2002)	2	No significant change from the control		17.5 (50 µM)	No data	The results indicate the substance did not cause inhibiting effects on aromatase activity

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for chlorpyrifos , which is relevant to mammalian wildlife species, indicated that "*No adverse effects related to endocrine disruption have been identified in the range of regulatory toxicological tests. These indicate that the major toxicological effect is decreased cholinesterase activity. However, there are some recent but non-regulatory studies that indicate that chlorpyrifos has effects on both the thyroid and male reproductive systems. There has been a study in mice showing perturbation of thyroid hormones in dams, but there is no information in this study on adverse effects manifested from these alterations*." For fish the one and two generation study in fathead minnow reported effects on reproduction and development could be endocrine-mediated and could affect populations. For amphibians the effects on sexual development of froglets could be endocrine mediated and could affect populations. For birds the one generation studies in mallard reported reproductive effects that could be endocrine-mediated

		and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.
Are the potential ED-mediated effects judged to be relevant to fish, bird and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, birds and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	There is no evidence from the available reliable studies that other systemic effects are seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed. The most sensitive endpoint(s) for aquatic species are effects on first generation fish maturation and second generation fish growth in a two generation fathead minnow *Pimephales promelas* test which could be endocrine mediated.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**The currently available evidence does not allow a definitive conclusion to be drawn on the endocrine-mediated effects of chlorpyrifos on wildlife species.**
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that chlorpyrifos is an established endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that chlorpyrifos is an established endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow chlorpyrifos to be excluded as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.15 Ecotoxicological Endocrine Disruption Evaluation for Beta cyfluthrin

Substance details		
Substance Name	**Beta cyfluthrin**	
Substance Synonyms	(1RS,3RS;1RS,3SR)-3- (2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (SR)--cyano- (4-fluoro-3-phenoxy-phenyl)methyl ester	
Substance CAS Number	68359-37-5	
Substance EC Number	269-855-7.	
Data Source(s)	European Union Draft Assessment Report (2002) Hayes T B, Case P, Chui S, Chung D, Haeffele C, Haston K, Lee M, Mai V P, Marjuoa Y, Parker J and Tsui M (2006) Pesticide mixtures, endocrine disruption, and amphibian declines: Are we underestimating the impact? *Environmental Health Perspectives*, **114(S-1)**, 40-50. Zhang, J., Zhu, W., Zheng, Y., Yang, J., Zhu, X. (2008) The antiandrogenic activity of pyrethroid pesticides cyfluthrin and β-cyfluthrin. *Reproductive Toxicology*, **25(4),** 491-496.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	T+; R28 T; R23 N; R50-53	Very toxic if swallowed Toxic by inhalation. R50-53 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Acute Tox. 2 * Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	Fatal if swallowed Toxic if inhaled H400 Very toxic to aquatic life H410 Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group A – Substance requiring further information**	

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Scenedesmus subspicatus* growth inhibition test (96 hour exposure to cyfluthrin, purity not stated)	1	Inhibition of growth	No information reported	>0.010	>0.010	No effects are evident at the highest test concentration
Invertebrate *Daphnia magna* reproduction test (21 day exposure to cyfluthrin, purity not stated)	1	Reduction in juvenile production Reduction in juvenile growth	No information reported	0.02	0.041	Effects are evidently not endocrine-mediated
Fish rainbow trout *Oncorhynchus mykiss* early life stage test (58 day exposure to cyfluthrin, purity not stated)	1	Effect not stated	No information reported	0.01	0.018	Not known if effects could be endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish fathead minnow *Pimephales promelas* life cycle test (307 day exposure to cyfluthrin, purity not stated)	1	Increased F0 mortality Increased F1 mortality	No information reported	0.14	0.29	Effects could be endocrine-mediated
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (24 week exposure to cyfluthrin, purity not stated)	1	Reproductive effects (reduction in number of eggs laid and decrease in hatching)	No information reported	250 mg a.s./kg diet	1000 mg a.s./kg diet	Effects could be endocrine-mediated
Bobwhite quail (*Coilinus virginianus*) reproduction test (23 week exposure to cyfluthrin, purity not stated)	1	Reproductive effects (reduction in number of eggs laid and decrease in hatching) Adult health effects (decrease in adult body weight)	No information reported	1000 mg a.s./kg diet	4000 mg a.s./kg diet	Effects could be endocrine-mediated
Wildlife (*in vivo*) data from published literature						
Amphibian leopard frogs *Rana pipiens* chronic study (Exposure to cyfluthrin from 2 days post-hatching until complete tail reabsorption, purity ≥98%) – Hayes *et al*. (2006)	2	Change in the time to initiate metamorphosis (FLE) and time to complete metamorphosis (TR) Decrease in size at metamorphosis (SVL) Change in body weight (BW)	-	≥0.0001 (>0.1 µg/l) <0.0001 (<0.1 µg/l) >0.0001 (>0.1 µg/l)	Not relevant 0.0001 (0.1 µg/l) Not relevant	Potential endocrine-mediated effects are evident at the test concentration

Castrated male Wistar rats in the Hershberger assay (exposure to cyfluthrin, purity 92.6% and ß-cyfluthrin, purity 97.0%) - Zhang *et al*. (2008)	2	Decreases in the weight of seminal vesicle, ventral prostate, dorsolateral prostate, LABC and Cowper's glands	No information reported	6 mg a.s./kg (cyfluthrin)	18 mg a.s./kg (cyfluthrin)	Effects could be endocrine-mediated
		Change in glans penis weight		54 mg a.s./kg (cyfluthrin)	Not relevant	
		Maternal weight gain		54 mg a.s./kg (cyfluthrin)	Not relevant	
		Decrease in seminal vesicle weight		4 mg a.s./kg (ß-cyfluthrin)	12 mg a.s./kg (ß-cyfluthrin)	
		Decreases in the weight of seminal vesicle, ventral prostate, dorsolateral prostate, LABC and Cowper's glands		12 mg a.s./kg (ß-cyfluthrin)	36 mg a.s./kg (ß-cyfluthrin)	
		Maternal weight gain		36 mg a.s./kg (ß-cyfluthrin)	Not relevant	
Mechanistic (*in vitro* and *in vivo*) data						
Androgen receptor antagonistic effects using a stably transfected, androgen-responsive cell line, MDA-kb2 – Zhang *et al*. (2008)	2	Reduced DHT-induced transcriptional activation	-	0.0434 mg/l	0.434 mg/l	The results suggest that beta-cyfluthrin has low potency as androgen receptor antagonists

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes and No	The human health assessment for beta-cyfluthrin, which is relevant to mammalian wildlife species, indicated that further information is required to explain the anti-androgen activity of the substance observed in vitro and in vivo. None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the life cycle test in fathead minnow reported effects on embryo-larval mortality which could be endocrine-mediated and could affect populations. For birds the one generation studies in bobwhite quail and mallard reported reproductive effects that could be endocrine-mediated and could affect populations. Effects observed in rats in the Heshberger assay indicate endocrine activity.

Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is evidence of endocrine activity but no clear evidence of adverse effects in mammals in apical studies.
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which endocrine effects are observed?	No	The most sensitive standard endpoint for aquatic species is the inhibition of growth in the invertebrate *Daphnia magna* which is not evidently endocrine-mediated. Potential endocrine mediated effects have been reported in amphibians at a single lower exposure concentration.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**The currently available evidence does not allow a definitive conclusion to be drawn on the endocrine-mediated effects of ß-cyfluthrin on wildlife species.**
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that ß-cyfluthrin is an established endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that ß-cyfluthrin is an established endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow ß-cyfluthrin to be excluded for consideration as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.16 Ecotoxicological Endocrine Disruption Evaluation for Lambda cyhalothrin

Substance details		
Substance Name	**Lambda cyhalothrin**	
Substance Synonyms	reaction product comprising equal quantities of (R)-α-cyano-3-phenoxybenzyl (1S,3S)-3-[(Z)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate and (S)-α-cyano-3-phenoxybenzyl (1R,3R)-3-[(Z)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate or of (R)-α-cyano-3-phenoxybenzyl (1S)-cis-3-[(Z)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate and (S)-α-cyano-3-phenoxybenzyl (1R)-cis-3-[(Z)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate	
Substance CAS Number	91465-08-6	
Substance EC Number	415-130-7	
Data Source(s)	European Union Draft Assessment Report (2000) Hayes T B, Case P, Chui S, Chung D, Haeffele C, Haston K, Lee M, Mai V P, Marjuoa Y, Parker J and Tsui M (2006) Pesticide mixtures, endocrine disruption, and amphibian declines: Are we underestimating the impact? *Environmental Health Perspectives*, **114(S-1),** 40-50. Saravanan, R., Revathi, K., Balakrishna Murthy, P. (2009) Lambda cyhalothrin induced alterations in *Clarias batrachus*. *Journal of Environmental Biology*, **30(2),** 265-270. Zhao, M., Zhang, Y., Liu, W., Xu, C., Wang, L., Gan, J. (2008) Estrogenic activity of lambda-cyhalothrin in the MCF-7 human breast carcinoma cell line. *Environmental Toxicology and Chemistry*, **27(5),** 1194-1200.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	T+; R26 T; R25 Xn; R21 N; R50-53	Very toxic by inhalation Toxic if swallowed Harmful in contact with skin Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Regulation (EC) No 1272/ 2008	Acute Tox. 2 * H330 Acute Tox. 3 * H301 Acute Tox. 4 * H312 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	Fatal if inhaled Toxic if swallowed Harmful in contact with skin Very toxic to aquatic life Very toxic to aquatic life with long lasting effects

Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group A - Substances requiring further information**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Pseudokirchneriella subcapitata* growth inhibition test (96 hours exposure to lambda cyhalothrin, purity 96.5%)	2/3	Inhibition of growth	No information provided	>0.3	Not relevant	No effects are evident at the highest test concentration
Invertebrate *Daphnia magna* reproduction test (21 day exposure to radiolabelled lambda cyhalothrin, purity 97-98%))	1	Reduction in juvenile production	No information provided	0.0000002 (0.0002 µg/l)	0.00000038 (0.00038 µg/l)	Effects are evidently not endocrine mediated
Fish sheepshead minnow *Cyprinodon variegatus* early life stage test (28 day exposure to lambda cyhalothrin, purity 96.6%)	1	Larval growth Hatchability and larval survival	No information provided	0.00025 ≥0.00038	0.00038 Not relevant	Effects could be endocrine mediated
Fish short-term reproduction test	No data provided	-	-	-	-	-
Fish sexual development test	No data provided	-	-	-	-	-
Fish life cycle test	No data provided	-	-	-	-	-
Amphibian metamorphosis assay	No data provided	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (20 week exposure to cyhalothrin, purity 96.6%)	1	Reproductive and adult health effects	No information provided	>30 mg a.s./kg diet (>3 mg a.s./kg bw/ day)	Not relevant	No reproductive or adult health effects are evident at the highest test dose
Bobwhite quail (*Coilinus virginianus*) reproduction test	No data provided	-	-	-	-	-

Wildlife (*in vivo*) data from published literature						
Fish catfish *Clarias batrachus* chronic study (45 days exposure to cyhalothrin, purity 95%)	2	Decreased plasma T3and T4 and Decreased plasma testosterone concentrations Increased plasma cortisol concentration	The results suggest cyhalothrin may have directly impaired the hormone synthesis and release The result may be due to disruption of the feed back mechanisms existing between the hypothalamic-pituitary-gonadal axis Exposure to cyhalothrin may favour gluconeogenesis	<5.77 <5.77 <5.77	5.77 (only test concentration) 5.77 5.77	Effects could be endocrine mediated
Amphibian leopard frogs *Rana pipiens* chronic study (Exposure to cyhalothrin from 2 days post-hatching until complete tail reabsorption, purity ≥98%) – Hayes *et al*. (2006)	2	Change in the time to initiate metamorphosis (FLE) and time to complete metamorphosis (TR) Change in size at metamorphosis (SVL) and body weight (BW)	-	≥0.0001 (>0.1 µg/l) >0.0001 (>0.1 µg/l)	Not relevant Not relevant	Effects could be endocrine mediated
Mechanistic (*in vitro* and *in vivo*) data						
Estrogenic activity using the yeast two hybrid assay – Nishihara *et al*. (2000)	2	Evidence of estrogenic activity	-	100 mg/l (REC10) (>0.3 mM (REC10)	Not relevant	The result is not considered to show positive estrogenic activity because the activity of the test substance was less than 10% of the activity of 10^{-4} mM E2,
Estrogenic activity using the cell proliferation assay with the MCF-7 human cell line – Zhao *et al*. (2008)	2	2 times increase in cell proliferation, relative proliferative effect of 45% Increased expression of the pS2 and PR mRNA by 2 and 1.5 times	-	<0.045 (<0.1 µM) <0.045 (<0.1 µM)	0.045 (0.1 µM) 0.045 (0.1 µM)	The results suggest lamda cyhalothrin possesses estrogenic properties and may function as a xeno-estrogen

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for lamda cyhalothrin, which is relevant to mammalian wildlife species, indicated that the mammary tumours in mice could be due to the weak oestrogenic activity of the substance, but further information is required as reproductive toxicity was not affected.in rats and rabbits (mice not investigated). None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test in sheepshead minnow reported effects on larval growth that could be endocrine-mediated and could affect populations. For birds the one generation study in mallard did not report reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is some data suggesting oestrogenic activity that could be linked to the mammary tumours in mice but this is not conclusive.
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	No	The effects measured in the chronic studies in mammals are not relevant to populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	Yes	The most sensitive endpoint is the reduction in juvenile production and juvenile growth in *Daphnia magna* which are evidently not endocrine-mediated. The effects concentration for invertebrates is a factor of 1000 lower than those reported in fish. For birds no reproductive or adult health effects were evident at the highest test dose.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**The currently available evidence does not allow a definitive conclusion to be drawn on the endocrine-mediated effects of lamda cyhalothrin on wildlife species.**
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint.	No	There is no evidence that lamda cyhalothrin is an established endocrine disrupter.

(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that lamda cyhalothrin is an established endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow lamda cyhalothrin to be excluded as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.17 Ecotoxicological Endocrine Disruption Evaluation for Cypermethrin

Substance details		
Substance Name	**Cypermethrin**	
Substance Synonyms	-	
Substance CAS Number	52315-07-8	
Substance EC Number	257-842-9	
Data Source(s)	European Union Draft Assessment Report (1999) Kakko I, Toimela T and Tähti H, (2004) Oestradiol potentiates the effects of certain pyrethroid compounds in the MCF7 human breast carcinoma cell line. *ATLA*, **32, No. 4**, 383–390. Kim I Y, Shin J H, Kim H S, Lee S J, Kang I H, Kim T S, Moon H J, Choi K S, Moon A and Han S Y, (2004) Assessing estrogenic activity of pyrethroid insecticides using *in vitro* combination assays. *Journal of Reproduction and Development*, **50**, 245– 255. Moore A and Waring C P (2001) The effects of a synthetic pyrethroid pesticide on some aspects of reproduction in Atlantic salmon (*Salmo salar* L.). *Aquatic Toxicology*, **52**, 1–12.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Xn; R20/22 Xi; R37 N; R50-53	Harmful by inhalation and if swallowed. Irritating to respiratory system. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Acute Tox. 4 * Acute Tox. 4 * STOT SE 3 Aquatic Acute 1 Aquatic Chronic 1	Harmful by inhalation Harmful if swallowed May cause respiratory irritation. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	

What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group D - Substances not considered to be endocrine disrupters based on currently available data**

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)

Study	Reliability of the data	Adverse effects	Mechanistic information	Reported NOEC (mg/l)	Reported LOEC (mg/l)	Remarks
Wildlife (*in vivo*) data from European Union Draft Assessment Report						
Algal *Pseudokirchneriella subcapitata* growth inhibition test	1/2	Inhibition of growth	No information reported	100	>100	Effects are evidently not endocrine mediated
Invertebrate *Daphnia magna* reproduction test	1/2	Reduction in juvenile production	No information reported	0.0001	0.0003	Effects are evidently not endocrine mediated
Fish fathead minnow *Pimephales promelas* early life stage test	1/2	Reduction in embryo/larval survival Reduction in larval growth	No information reported	0.00003 0.00017	0.00012 >0.00017	Effects could be endocrine mediated
Fish short-term reproduction test	No data provided	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data provided	-	-	-	-	-
Amphibian metamorphosis assay	No data provided	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test	No data provided	-	-	-	-	-
Bobwhite quail (*Coilinus virginianus*) reproduction test (21 week exposure to cypermethrin, 96.5%)	1	Reproductive and adult health effects	No information reported	1000 mg a.s./diet (92 mg/kg bw/day)	>1000 mg a.s./diet	No reproductive or adult health effects at any test concentration
Wildlife (*in vivo*) data from published literature						
Fish Atlantic salmon (*Salmo salar*) olfaction and milt priming test - Moore and Waring (2001)	2	Reduced effect of exposure to the female pheromone on male milt expression Reduced egg fertilisation success	It is suggested that cypermethrin exposure probably acted directly on the sodium channels, inhibiting nervous transmission within the olfactory system and resulting in the male salmons' inability to detect and respond to the pheromone.	<0.000004 0.000028	No data 0.0001	The results of the study suggest that low levels of cypermethrin in the aquatic environment may have a significant effect on Atlantic salmon populations through disruption of reproductive functions.

Mechanistic (*in vitro* and *in vivo*) data						
Cell proliferation assay using human breast cancer MCF-7 cells – Kakko *et al*. (2004)	2	Increase in cell proliferation relative to controls	The results suggest that cypermethrin has an oestrogenic (proliferative) effect on MCF7 cells which can be further augmented by oestradiol itself	<0.0416 (<0.1 µM)	0.0416 (0.1 µM)	-
Cell proliferation assay using human breast cancer MCF-7 cells – Kim *et al*. (2004)	2	No increase in cell proliferation relative to controls	The results suggest that cypermethrin has no oestrogenic (proliferative) effect on MCF7 cells	No data given	No data given	-

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for cypermethrin, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*". None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the fathead minnow early life stage test reported effects on growth that could be endocrine-mediated and could affect populations. For birds the one generation study in bobwhite quail did not report any reproductive effects that could be endocrine-mediated and could affect populations. Moore and Waring (2001) investigated the effects of cypermethrin on olfaction and milt priming in Atlantic salmon (*Salmo salar*). Exposure of mature male parr for a 5 day period to a water concentration of <0.004 µg/l cypermethrin significantly reduced or inhibited the olfactory response to a priming pheromone in female salmon urine F-type prostaglandin (PGF2α). In addition, exposure of male parr to cypermethrin significantly reduced their ability to respond to the priming effect of the pheromone. The priming effect on milt and plasma 17,20 β-dihydroxy-4-pregnen-3-one levels were abolished at water concentrations of <0.004 and 0.028 µg/lcypermethrin, respectively. The effect of cypermethrin on the priming response did not appear to be due to a direct effect on the testes, since the ability of testes to respond to pituitary extract stimulation *in vitro* was not impaired in males exposed to cypermethrin. In addition, exposure of salmon milt and eggs to a concentration of 0.1 µg/l cypermethrin during fertilisation subsequently reduced the number of fertilised eggs
Does the available evidence demonstrate that an endocrine disruption mode of action in fish and/or	Yes	There is data that there is an endocrine disruption based mode of action to effects observed in fish (i.e. via inhibition of the olfactory response to priming pheromones in male and female salmon).

mammals is reasonably linked to the adverse effects?[2]		
Are the potential ED-mediated effects judged to be relevant to fish and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	There is no evidence from the available reliable studies that other systemic effects are seen at concentration levels orders of magnitude below those at which endocrine effects are observed. The most sensitive endpoint is the effect on olfaction and milt priming in Atlantic salmon that is evidently endocrine-mediated and has population consequences.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	The currently available evidence allows a definitive conclusion to be drawn on the endocrine-mediated effects of cypermethrin on wildlife species.
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	**Yes**	**There is evidence that cypermethrin is an endocrine disrupter more likely to pose a risk in fish based on the most sensitive endpoint.**
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is evidence that cypermethrin is not an endocrine disrupter less likely to pose a risk based on the most sensitive endpoint.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow cypermethrin to be excluded as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.18 Ecotoxicological Endocrine Disruption Evaluation for Dimethoate

Substance details		
Substance Name	**Dimethoate**	
Substance Synonyms	-	
Substance CAS Number	60-51-5	
Substance EC Number	200-480-3	
Data Source(s)	Aboul-Eta I A and Khalil M T (1987) The chronic toxicity of three pollutants upon the freshwater snail *Helisoma trivolvis*. *Proceedings of the Zoological Society of the Arab Republic of Egypt*, **13**, 17–29. Andersen HR, Vinggaard AM, Rasmussen TH, Gjermandsen IM, and Bonefeld-Jorgensen EC (2002) Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro. Toxicology and Applied Pharmacology, 179, 1-12. European Union Draft Assessment Report (2004) Walsh L P, Webster D R and Stocco D M (2000) Dimethoate inhibits steroidogenesis by disrupting transcription of the steroidogenic acute regulatory (StAR) gene. *Journal of Endocrinology*, **167, No. 2**, 253–263.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC Regulation (EC) No 1272/ 2008	Xn; R21/22 Acute Tox. 4 * Acute Tox. 4 *	Harmful in contact with skin and if swallowed. Harmful in contact with skin. Harmful if swallowed.
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group D - Substances not considered to be endocrine disrupters based on currently available data**	

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC(mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Pseudokirchneriella subcapitata* growth inhibition test (72 hour exposure to dimethoate, purity not stated)	1	Inhibition of growth	No information reported	30.5	No data	Effects are evidently not endocrine mediated
Invertebrate *Daphnia magna* reproduction test (21 day exposure to dimethoate, purity, 99.0%)	1	Reduction in juvenile production Juvenile growth Parental survival	No information reported	0.04	0.1	Effects are evidently not endocrine mediated
Fish rainbow trout *Oncorhynchus mykiss* early life stage test (96 day exposure to dimethoate, purity 99.1%)	1	Larval growth Egg hatchability and fry survival	No information reported	1.5 3.0	3.0 6.0	Effects could be endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (22 week exposure to dimethoate, purity 99.1%)	1	Reduction in number of eggs laid and 14 day old survivors Parental bodyweight	No information reported	35.4 mg a.s./kg diet (5.8 mg a.s./kg bw/day)	152 mg a.s./kg diet	No test substance-related gross lesions were observed at necropsy Effects could be endocrine-mediated
Bobwhite quail (*Coilinus virginianus*) reproduction test (22 week exposure to dimethoate, purity 99.1%)	1	Reduction in number of eggs laid and 14 day old survivors Parental bodyweight	Gross necropsy of surviving females showed increased incidence of hens with regressed or regressing ovaries	10.1 mg a.s./kg diet (1.0 mg a.s./kg bw/day)	35.4 mg a.s./kg diet	Effects could be endocrine-mediated
Wildlife (*in vivo*) data from published literature						
Invertebrate snail *Helisoma trivolvis* (63 day exposure to technical grade dimethoate) - Aboul-Eta and Khalil (1987)	3	Reduction in number of eggs produced Changes in the shape of the eggs and the egg masses		<0.0075	0.0075	Effects could be endocrine-mediated

Mechanistic (*in vitro* and *in vivo*) data						
Cell proliferation assay using human breast cancer MCF-7 cells – Andersen *et al*. (2002)	2	No cell proliferation at noncytotoxic concentrations	-	>35,0 (>100 µM)	Not relevant	The results indicate no estrogenic response was induced
Estrogen receptor transactivation assay using human breast cancer MCF-7 cells – Andersen *et al*. (2002)	2	No estrogen receptor transactivation at non-cytotoxic concentrations	-	>35,0 (>100 µM)	Not relevant	The results indicate no estrogenic response was induced
Androgen receptor transactivation assay using Chinese hamster ovary cells (CHO K1) – Andersen *et al*. (2002)	2	Inhibition of AR trans-activation	-	17.5 (50 µM)	35,0 (100 µM)	The results indicate the substance did not react as an androgen agonist
Aromatase assay based on placental microsomes – Andersen *et al*. (2002)	2	No significant change from the control	-	17.5 (50 µM)	No data	The results indicate the substance did not cause inhibiting effects on aromatase activity
Steroidogenesis using mouse MA-10 Leydig tumor cell line – Walsh *et al*. (2000)	2	Inhibition of steroidogenesis	-	25	50	The results suggest that dimethoate inhibits steroid-genesis primarily by blocking transcription of the steroid-genic acute regulatory (StAR) gene.

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties		
Question	**Response (Yes/No)**	**Summary**
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for dimethoate, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the rainbow trout early life stage test reported effects on growth that could be endocrine-mediated and could affect populations. For birds the one generation studies in bobwhite quail and mallard reported reproductive effects that could be endocrine-mediated and could affect populations. Aboul-Eta and Khalil (1987) reported on the chronic effects of technical grade dimethoate on the snail *Helisoma trivolvis* found that exposure to the insecticide not only caused a decrease in the number of eggs produced, but also changes in the shape of the eggs and the egg masses. It was found that, as early as the fourth or fifth day of the experiment, abnormal egg masses were evident in test vessels at all test

		concentrations (nominal values of 7.5, 30 and 120 µg/l) and many of these had eggs containing more than the single egg cell normally found. In other egg masses, only elements of the egg membrane were left and sometimes they were entirely absent. The egg cells were then surrounded only by the jelly mass and the outer egg-mass membrane. It was concluded that these results indicated a dimethoate induced effect on the ability of parts of the oviductal tract to carry out their secretory function. In particular the pars contorta, which lays down these membranes, may be sensitive to insecticides such as dimethoate. There are issues with the reliability of this study as there was no analytical confirmation of the exposure concentrations and it needs to be recognised that these data are not necessarily evidence of endocrine disruption.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies.
Are the potential ED-mediated effects judged to be relevant to fish, bird and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, birds and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	The most sensitive endpoint is the reduction in juvenile production and juvenile growth in *Daphnia magna* which are evidently not endocrine-mediated. The effects concentration for invertebrates is a factor of 30 lower than those reported in fish. For birds no reproductive or adult health effects were evident at the same test dose.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**The currently available evidence does not allow a definitive conclusion to be drawn on the endocrine-mediated effects of dimethoate on wildlife species.**
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that dimethoate is an established endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	There is no evidence that dimethoate is an established endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow dimethoate to be excluded as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.19 Ecotoxicological Endocrine Disruption Evaluation for Fenoxycarb

Substance details						
Substance Name	**Fenoxycarb**					
Substance Synonyms	ethyl N-[2-(4-phenoxyphenoxy)ethyl]carbamate					
Substance CAS Number	72490-01-8					
Substance EC Number	276-696-7					
Data Source(s)	Arnold K E, Wells C and Spicer J I (2008) Effect of an insect juvenile hormone analogue, Fenoxycarb on development and oxygen uptake by larval lobsters *Homarus gammarus* (L.). *Comparative Biochemistry and Physiology, Part C*, doi:10.1016/j.cbpc.2008.09.007. European Union Draft Assessment Report (2010)					
Data on the classification of the substance						
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**				
Classification of the substance: Directive 67/548/EEC	N; R50-53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.				
Regulation (EC) No 1272/ 2008	Aquatic Acute 1 H400 Aquatic Chronic 1 H410	Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.				
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**					
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group D - Substances not considered to be endocrine disrupters based on currently available data**					
Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Pseudokirchneriella subcapitata* growth inhibition test (72 hour exposure to formulated, 25.6%	1	Inhibition of growth	No information reported	0.064 (biomass) 0.12 (growth rate)	0.12 (biomass) 0.25 (growth rate)	Effects are evidently not endocrine-mediated

fenoxycarb content)						
Invertebrate *Daphnia magna* reproduction test (21 day exposure to fenoxycarb, purity 97.7%)	1	Delay in time to first brood	No information reported	0.0032	0.013	Effects are evidently not endocrine-mediated
Fish rainbow trout *Oncoryhchus mykiss* early life stage test (96 day exposure to fenoxycarb, purity 94.8%)	1	Reduction in larval growth	No information reported	0.048	0.1	Effects could be endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (19 week exposure to fenoxycarb, purity 94.8%)	1	Reproductive effects (reduced hatchability)	No information reported	160 mg a.s./kg diet (17.7-18.4 mg a.s./ kg bw/day)	4000 mg a.s./kg diet	Effects could be endocrine-mediated
Bobwhite quail (*Coilinus virginianus*) reproduction test (21 week exposure to fenoxycarb, purity 94.8%)	1	Reproductive and adult health effects	No information reported	400 mg a.s./kg diet (35.9-39.2 mg a.s./ kg bw/day)	>400 mg a.s./kg diet (35.9-39.2 mg a.s./ kg bw/day)	No reproductive or adult health effects are evident at the highest test dose
Wildlife (*in vivo*) data from published literature						
Invertebrate lobster *Homarus gammarus* development test (12 day exposure to Insegar containing 25% fenoxycarb) – Arnold *et al*. (2008)	2	Reduced larval growth Increased intermoult duration	The results may indicate that fenoxycarb acts to interfere with the moult cycle	<0.05 <0.05	0.05 0.05	Effects are evidently endocrine-mediated
Mechanistic (*in vitro* and *in vivo*) data						
No specific information located	-	-	-	-	-	-

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for fenoxycarb, which is relevant to mammalian wildlife species, indicated that "*The only evidence for endocrine disruption was follicular hypertrophy in the thyroid in a 90-day study but this observation has not been repeated in other studies".* None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test in rainbow trout reported effects on larval growth that could be endocrine-mediated and could affect populations.

		For birds the one generation study in mallard reported reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	Yes	There is definitive data on an ED MOA responsible for the adverse effects seen in invertebrate studies (i.e. that fenoxycarb acts as an insect juvenile hormone analogue). However, no such endocrine-mediated effects have been reported in fish, birds or mammals.
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine effects are observed?	No	The most sensitive endpoint is the reduction in the time to first brood in *Daphnia magna* which are evidently endocrine-mediated. The effects concentration for invertebrates is a factor of 7.7 lower than those reported in fish. For birds reproductive effects were evident in mallard at a lower test dose that that causing adult health effects.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	No	The currently available evidence does allow a definitive conclusion to be drawn on the endocrine-mediated effects of fenoxycarb on wildlife species. Potential endocrine-mediated effects are evident in invertebrates and, therefore, the substance has not been classified as an endocrine disrupter.
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint	**Yes**	**There is evidence that fenoxycarb is an endocrine disrupter more likely to pose a risk in invertebrates based on the most sensitive endpoint.**
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint	No	Group not appropriate as the substance is an endocrine disrupter of concerns over potential risks in invertebrates.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	Group not appropriate as the substance is an endocrine disrupter in invertebrates.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Table C.20 Ecotoxicological Endocrine Disruption Evaluation for Malathion

Substance details		
Substance Name	**Malathion**	
Substance Synonyms	diethyl [(dimethoxyphosphino-thioyl)thio]butanedioate	
Substance CAS Number	121-75-5	
Substance EC Number	204-497-7	
Data Source(s)	European Union Draft Assessment Report (2003) Nishihara T, Nishikawa J, Kanayama T, Dakeyama F, Saito,K, Imagawa M, Takatori S, Kitagawa Y, Hori S and Utsumic H (2000) Estrogenic Activities of 517 Chemicals by Yeast Two-Hybrid Assay. Journal of Health Science, 46(4), 282-298. Ozmen G and Akay M T (1993) The effects of malathion on some hormone levels and tissues secreting these hormones in rats. *Veterinary and Human Toxicology*, **35(1),** 22-24.	
Data on the classification of the substance		
Legislation	**Hazard class/classification**	**Hazard statement/risk phrase**
Classification of the substance: Directive 67/548/EEC	Xn; R22 R43 N; R50-53	Harmful if swallowed. May cause sensitization by skin contact. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Regulation (EC) No 1272/ 2008	Acute Tox. 4 * Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	Harmful if swallowed. May cause an allergic skin reaction. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects
Is the substance already classified as CMR Category 1A or 1B under the CLP Regulation?	**No**	
What is the grouping for the substance from the human health assessment of endocrine disruption?	**Group D - Substances not considered to be endocrine disrupters based on currently available data**	

Ecotoxicological data for the evaluation of the endocrine disrupting properties of the substance (informative studies)						
Study	**Reliability of the data**	**Adverse effects**	**Mechanistic information**	**Reported NOEC (mg/l)**	**Reported LOEC (mg/l)**	**Remarks**
Wildlife (*in vivo*) data from the European Union Draft Assessment Report						
Algal *Pseudokichneriella subcapitata* growth inhibition test (72 hour exposure to malathion, purity 96.4%)	1	Inhibition of growth (growth rate) Inhibition of growth (biomass)	No information reported	2.30 0.81	8.16 2.30	Effects are evidently not endocrine mediated
Invertebrate *Daphnia magna* reproduction test	1	Reduction in juvenile production Juvenile growth Parental survival	No information reported	0.00006 0.00006 0.00025	0.0001 0.0001 0.00046	Effects are evidently not endocrine mediated
Fish rainbow trout (*Oncorhynchus mykiss*)early life stage test (97 day exposure to malathion, purity 94.0%)	1	Fry survival and morphology exophthalmia, spinal curvature and distended abdomen	No information reported	0.021	0.044	Effects could be endocrine-mediated
Fish short-term reproduction test	No data reported	-	-	-	-	-
Fish sexual development test	No data reported	-	-	-	-	-
Fish life cycle test	No data reported	-	-	-	-	-
Amphibian metamorphosis assay	No data reported	-	-	-	-	-
Mallard (*Anas platyrhynchos*) reproduction test (20 week exposure to malathion, purity 94.0%)	1	Reproductive effects (reduced number of eggs and viability)	No information reported	1200 mg a.s./kg diet	2400 mg a.s./kg diet	Effects could be endocrine-mediated
Bobwhite quail (*Coilinus virginianus*) reproduction test (21 week exposure to malathion, purity 96.4%)	1	Necropsy of surviving females (regressing ovary) Reproductive effects (reduced number of eggs and viability)	No information reported	110 mg a.s./kg diet (13.5 mg a.s./kg bw/day) 350 mg a.s./kg diet (42.9 mg a.s./kg bw/day)	350 mg a.s./ kg diet	Effects could be endocrine-mediated
Wildlife (*in vivo*) data from published literature						
Swiss rat chronic exposure study (15 week exposure to malathion, purity 94%) – Ozmen *et al*. (1992)	2	Serum levels of T3, T4, estradiol, testosterone, aldosterone and cortisol	The results are taken to suggest that malathion might inhibit hydroxyl-steroid dehydrogenase	≥100 mg/kg	Not relevant	No change in a range of serum hormones at all the test doses

		Histopathology of the ovaries, testes and adrenal and thyroid glands	or aromatase enzyme activities responsible for estrogen synthesis or may act indirectly to suppress the secretion of gonadotropin.	>100 mg/kg	Not relevant	No histopathological changes in ovaries and thyroid glands. Slight changes were present in the testisand adrenals of the dosed rats
Mechanistic (*in vitro* and *in vivo*) data						
Estrogenic activity using the yeast two hybrid assay – Nishihara *et al*. (2000)	2	Evidence of estrogenic activity	-	33.0 mg/l (REC10) (>0.1 mM (REC10)	Not relevant	The result is not considered to show positive estrogenic activity because the activity of the test substance was less than 10% of the activity of 10^{-4} mM E2,

Evaluation of the available ecotoxicological data for the grouping of the substance regarding its endocrine disrupting properties

Question	Response (Yes/No)	Summary
Are there population relevant adverse effects potentially related to endocrine disruption in intact organisms in acceptable studies?[1]	Yes	The human health assessment for malathion, which is relevant to mammalian wildlife species, indicated that "*Effects resulting from endocrine disruption are not present in the available studies*." None of the chronic studies in fish and birds described in the regulatory dossier specifically addressed the substances potential endocrine disrupting effects. For fish the early life stage test in rainbow trout reported effects on fry survival and morphology that could be endocrine-mediated and could affect populations. For birds the one generation studies in bobwhite quail and mallard reported reproductive effects that could be endocrine-mediated and could affect populations.
Does the available evidence demonstrate that an endocrine disruption mode of action in fish, birds and/or mammals is reasonably linked to the adverse effects?[2]	No	There is no definitive data on the mechanisms responsible for the adverse effects potentially related to endocrine disruption in fish and birds.
Are the potential ED-mediated effects judged to be relevant to fish, birds and/or mammalian populations?	Yes	The effects measured in the chronic studies are relevant to fish, bird and/or mammalian populations.
Are other systemic effects seen at concentration levels orders of magnitude below those at which potential endocrine	Yes	The most sensitive endpoint is the reduction in juvenile production and juvenile growth in *Daphnia magna* which are evidently not endocrine-mediated. The effects concentration for invertebrates is a factor of 440 lower than those reported in fish.

effects are observed?		For birds reproductive effects were evident at a lower test dose than adult health effects.
Overall grouping of the substance regarding its endocrine disrupting properties		
Group	**Response (Yes/No)**	**Comments**
(A) Substances requiring further information	**Yes**	**The currently available evidence does not allow a definitive conclusion to be drawn on the endocrine-mediated effects of malathion on wildlife species.**
(B) Endocrine disrupters more likely to pose a risk based on the most sensitive endpoint.	No	There is no evidence that malathion is an established endocrine disrupter.
(C) Endocrine disrupters less likely to pose a risk based on the most sensitive endpoint.	No	There is no evidence that malathion is an established endocrine disrupter.
(D) Substances not considered to be endocrine disrupters based on currently available data	No	The available evidence does not allow malathion to be excluded as an endocrine disrupter.

Notes:

[1] - In acceptable studies in intact organisms, are there adverse effects of a type that, considered in isolation, might initially suggest a possible link to endocrine disruption?

[2] - From all the available information, taken together, does it appear plausible that an ED mode of action in animals is responsible for these adverse effects?

Appendix D Substance ED grouping (likelihood of posing a risk) for Group A substances based on the assessment of mammalian toxicity apical data, assuming positive endocrine mechanistic data

Substance type	Substance	Substance ED grouping (more or less likely to pose a risk) based on the assessment of mammalian toxicology apical data, assuming positive endocrine mechanistic data				Comments
		Further information required	Adverse effects potentially related to an endocrine MoA (underlined)	LOAEL mg/kg bw/day	Likelihood of posing a risk (</>STOT RE 1)	
Fungicides	Carbendazim	**Yes**	**2-generation rat oral reproduction study** Infertility males, ↓Sperm numbers, testicular atrophy and absence of spermatogenesis.	100 (NOAEL highest dose tested)	**Low** (this is conservative as it is based on NOAEL rather than LOAEL)	Disruption of male reproduction system.
	Cymoxanil	**Yes**	**2-generation rat oral reproduction study** ↓percentage of live births, ↓mean number of corpora lutea, ↓number of implantations, ↑percentage of post-implantation loss **2-year long-term toxicity and carcinogenicity rat oral study** ↓bodyweight and body weight gain, Alterations in haematology and clinical chemistry, Histological changes in the lung, colon, rectum and testes	94 23.5	Low **Low**	The reproductive effects could be due to endocrine disruption. Changes in testis could be due to an endocrine mode of action.
	Fluazinam	**Yes**	**90-day rat oral study** Haematological findings, ↑relative liver wt, ↑higher absolute and relative lung and uterus wt, histopathological changes in the liver.	41	Low	Effect on uterus wt may be indicative of endocrine disruption.

Substance type	Substance	Substance ED grouping (more or less likely to pose a risk) based on the assessment of mammalian toxicology apical data, assuming positive endocrine mechanistic data				Comments
		Further information required	Adverse effects potentially related to an endocrine MoA (underlined)	LOAEL mg/kg bw/day	Likelihood of posing a risk (</>STOT RE 1)	
			2-year rat oral long-term toxicity and carcinogenicity study ↑liver, testes and epididymides wt, histopathological changes in liver, pancreas, lungs and ↑testicular atrophy and spermatocele granuloma.	3.9	**High**	Effects on testes may be indicative of endocrine disruption.
	Fosetyl aluminium	**Yes**	**2-year dog oral long-term toxicity and carcinogenicity study** Testicular degeneration.	609	**Low**	Effects on testes may be indicative of endocrine disruption.
	Hymexazol	**Yes**	**2-year rat oral long-term toxicity and carcinogenicity study** ↓Body wt gain, ↓relative thyroid wt. **2-generation rat oral reproduction study** Slightly extended gestation length (F0 and F1) and ↓litter size at birth due to ↑postimplantation loss (F0 and F1).	99 192 (female)	Low **Low**	Only potential endocrine effect was decrease in thyroid weight. Indications of disturbed oestrous cyclicity were also observed in the range-finding study. Disruption of reproduction at levels below maternal toxicity which could be due to endocrine disruption.
	Mandipropamid	**Yes**	**2-year rat oral long-term toxicity and carcinogenicity study** ↓body wt, ↓body wt gain, haematological and clinical chemical findings, ↑liver wt, periportal hypertrophy/ eosinophilia, chronic progressive nephropathy, osteo-renal syndrome including hyperplasia of the parathyroid. No carcinogenic potential.	61.3	**Low**	Chronic renal failure is accompanied by bone disease. Vitamin D cannot be synthesised, therefore Calcium falls and parathyroid hormone (PTH) increases with subsequent effects on bone. Therefore the primary effect, chronic nephropathy caused by the substance, may potentially lead to a secondary increase in PTH. This may be considered evidence of

Substance type	Substance	Substance ED grouping (more or less likely to pose a risk) based on the assessment of mammalian toxicology apical data, assuming positive endocrine mechanistic data				Comments
		Further information required	Adverse effects potentially related to an endocrine MoA (underlined)	LOAEL mg/kg bw/day	Likelihood of posing a risk (</>STOT RE 1)	
						potential endocrine disruption, although by a secondary or even tertiary mechanism, No actual measurement of PTH but hyperplasia of the parathyroid.
	Prothioconazole	**Yes**	**90 day dog oral study** Kidney histopathological changes and liver ↑ALT and liver wt. but no liver histological findings, ↓TSH and T4 **2-generation rat oral reproduction study** Slight body wt and organ wt effects ↓pup wt gain, ↓pup spleen wt and delayed preputial separation. Disruption to the oestrus cycle, ↓implantation sites and litter size, ↑time to insemination and ↑duration of gestation	100 726 (reproductive effects)	Low **Low**	Thyroid hormone changes could be secondary to liver changes but indicative of endocrine disruption. Some European Member States suggested that the disruption to the oestrus cycle should be considered to be adverse.
	Silthiofam	**Yes**	**2-generation rat oral reproduction study** Systemic toxicity: effects on the liver and adrenal glands (cortical vacuolation). No reproductive toxicity **2-year rat oral long-term toxicity and carcinogenicity study** ↑liver wt, increased serum ↑GT (males) and/or microscopic changes. Microscopic change included hepatocellular vacuolization and hypertrophy, eosinophilic foci and/or cystic degeneration. ↑increase in	250 150 (LOAEL for carcinogenicity)	Low **Low**	Effects on the adrenals may indicate an endocrine effect. The detection of thyroid tumours may indicate an endocrine effect.

Substance type	Substance	Substance ED grouping (more or less likely to pose a risk) based on the assessment of mammalian toxicology apical data, assuming positive endocrine mechanistic data				Comments
		Further information required	Adverse effects potentially related to an endocrine MoA (underlined)	LOAEL mg/kg bw/day	Likelihood of posing a risk (</>STOT RE 1)	
			incidence of hepatocellular and thyroid tumours in high dose males.			
	Thiram	**Yes**	**2-year rat oral long-term toxicity and carcinogenicity study** Thyroid C cell hyperplasia. ↓LH surge	7.3	Low	Evidence of endocrine effects.
Herbicides	2,4-D	**Yes**	**90-day mouse oral study** ↓glucose level in females, ↓thyroxine activity in males and ↑absolute and/or relative kidney wt in males. **2-year rat oral long-term toxicity and carcinogenicity study** ↓body wt gains and food consumption, ↑serum alanine and aspartate aminotransferase activities, ↓thyroxine concentrations, ↑absolute and relative thyroid wts and histopathological lesions in the eyes, kidneys, liver, lungs and mesenteric fat. There was no evidence of carcinogenicity.	100 75	Low **Low**	Effect on thyroid hormone. Effect on thyroid wt and thyroid hormone.
	Chlorpropham	**Yes**	**60-week dog oral study** ↑thyroid wt., enlarged thyroid lobes, ↑thyroid activity, decreased T4 levels in TSH stimulation test. **2-year rat oral long-term toxicity and carcinogenicity study** Slight microscopic changes in liver, spleen and bone-marrow. ↑thyroid and testes wt at highest dose. Significantly ↑incidence of benign Leydig cell tumours in the testes seen at the highest dose	50 30	Low **Low**	Main effects on the thyroid. Evidence of potential endocrine disruption. Limited evidence for carcinogenicity in laboratory animals based on a significantly increased incidence of benign Leydig cell tumours seen at the highest dose in the rat. Leydig cell tumours are benign and generally related to a disturbance of

Substance type	Substance	Substance ED grouping (more or less likely to pose a risk) based on the assessment of mammalian toxicology apical data, assuming positive endocrine mechanistic data				Comments
		Further information required	Adverse effects potentially related to an endocrine MoA (underlined)	LOAEL mg/kg bw/day	Likelihood of posing a risk (</>STOT RE 1)	
						the hormonal control mechanism of the testes. Therefore this represents evidence of potential endocrine disruption.
	Dimethenamid-P	**Yes**	**2-year rat oral long-term toxicity and carcinogenicity study** ↓food consumption and bodyweight gain. Lenticular opacities. Changes in chemistry. Stomach hyperplasia. Altered hepatocytes, bile duct hyperplasia, parathyroid hyperplasia.	35	**Low**	Parathyroid effects possibly due to endocrine effects
	Ethofumesate	**Yes**	**90-day rat oral study** ↑body wt gain, food consumption, ↑liver wt, ↑ovary wt, ↑serum sodium **2-year rat oral long-term toxicity and carcinogenicity study** ↓body wt gain, ↑liver wt, hepatocyte hypertrophy, ↑testicular adenoma, focal hypertrophy, slight increase over controls **3-generation rat oral reproduction study** Parental: ↓body wt gain P_0: ↓litter size, no. of male pups, implantations P_1: ↑litter size	2000 1000 500	Low Low **Low**	Increase in ovary weight might be indicative of endocrine disruption Slight effects on testes which may be indicative of endocrine disruption. Some slight effects on reproduction which could indicate endocrine disruption
	Fluazifop-p-butyl	**Yes**	**2-year rat oral long-term toxicity and carcinogenicity study** Kidney (nephropathy), ovary wt; ↑plasma cholesterol; ↓haematocrit, RBC, No carcinogenic potential **80-week hamster oral long-term toxicity and carcinogenicity study** Effects on kidney, liver; testis (wt and	3.79 47.4 (male)	**Low** Low	Effect on the ovary wt which could be indicative of endocrine disruption. Tubular degeneration in the testes which could be indicative of endocrine

Substance type	Substance	Substance ED grouping (more or less likely to pose a risk) based on the assessment of mammalian toxicology apical data, assuming positive endocrine mechanistic data				Comments
		Further information required	Adverse effects potentially related to an endocrine MoA (underlined)	LOAEL mg/kg bw/day	Likelihood of posing a risk (</>STOT RE 1)	
			tubular degeneration), eye (cataract); ↓haematocrit, haemoglobin, RBC. No carcinogenic potential **2-generation rat oral reproduction study** ↓testis and epididymal wt ↓litter size; ↓gestation length; ↓spleen, testis, epididymal, pituitary and uterine wt; ↑ovary wt, liver & kidney wt.	20 (reproductive)	Low	disruption. Effects on the male and female reproductive systems which could be indicative of endocrine disruption.
	Glufosinate-ammonium	**Yes**	**2-generation rat oral reproduction study** ↑kidney wt., ↓litter size. **Rat oral developmental and teratogenicity study** Uterine deaths, abortions, ↑dystension of renal pelvis and ureter, retardation of skeletal ossification of os metacarpale	22.3 50	Low **Low**	The underlying mechanism behind the effects on reproduction is unclear at present but could be due to endocrine disruption.
	Lenacil	**Yes**	**90-day dog oral study** ↑relative liver weight in female dogs, ↑relative thyroid and parathyroid weight, centrilobular/midzonal hepatocyte hypertrophy **2-year rat oral long-term toxicity and carcinogenicity study** ↓bodyweight gain. ↓motor activity, organ weight effects, thyroid discolouration, ↑thyroidal luminal concretions, centrilobular hepatocyte hypertrophy and vacuolation, mammary gland tumours. **2-generation rat oral reproduction study** Parental thyroid toxicity. ↓offspring	221 1390 810 (systemic)	**Low** Low Low	Thyroid and parathyroid effects could be due to endocrine disruption. Thyroid effects and mammary gland tumours could be due to endocrine disruption. Thyroid effects could be due to endocrine disruption.

Substance type	Substance	Substance ED grouping (more or less likely to pose a risk) based on the assessment of mammalian toxicology apical data, assuming positive endocrine mechanistic data				Comments
		Further information required	Adverse effects potentially related to an endocrine MoA (underlined)	LOAEL mg/kg bw/day	Likelihood of posing a risk (</>STOT RE 1)	
			bodyweight during lactation. Altered lactation at top dose.			
	S-metolachlor	**Yes**	**Rat oral male reproduction study** (Mathias *et al*. 2012). ↑serum testosterone, oestradiol, FSH, ↓DHT. No effect on LH. ↑fluid in seminal vesicles, precocious puberty, changes in morphology of seminiferous epithelium.	5 (but no good dose response)	**High**	**No relevant LOAELs in the standard regulatory tests.** Prepubertal male rats treated PND23-53, 0, 5 or 50 mg/kg bw/day. Not a regulatory study but evidence of disruption to male sex hormones and development. No good dose response except for oestradiol.
	Pinoxaden	**Yes**	**2-year rat oral long-term toxicity and carcinogenicity study** Histopathological changes in the kidneys and associated changes in water intake/urine volume, chronic progressive nephropathy, osteo-renal syndrome	250	**Low**	Osteo-renal syndrome caused by secondary hyperparathyroidism, suggestive of an endocrine mode of action.
	Tepraloxydim	**Yes**	**90-day dog oral study** Haematological findings, ↑wts of liver and thyroid gland, histopathological findings in spleen and bone marrow.	ca66	Low	Effects on the weight of thyroid gland may be indicative of endocrine disruption.
			1-year dog oral study Slight disturbance in lipid metabolism, wts of liver and thyroid gland, epididymides wt, hyperplasia of transitional epithelium of urinary bladder.	58	Low	Effects on the weights of thyroid gland and epididymis may be indicative of endocrine disruption.
			18-month mouse oral long-term toxicity and carcinogenicity study ↓Body wt., body wt., change, relative liver wt. in males and at top dose ↑non neoplastic lesions (sclerosis of	45	**Low**	Some lesions in the uterus, ovaries, seminal vesicles and preputial gland are indicative of endocrine

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			endometrial stroma, muscularis and perivascular areas) in uterus, ↓activities in ovaries, ↓secretory activity in seminal vesicles and preputial glands. No carcinogenic potential.			disruption.
	Terbuthylazine	**Yes**	**2-year rat oral long-term toxicity and carcinogenicity study** ↓body wt and food consumption, absence of corpora lutea; uterine, cervical and mammary gland hyperplasia. Haematology & histopathology. ↑mammary adenomas and carcinomas	2.4 (female)	**High**	A number of these effects are consistent with hormonal disruption of the female reproductive system.
Insecticides	Chlorpyrifos	**Yes**	**Developmental mouse study to examine effects on thyroid and adrenal glands.** (De Angelis et al., 2009) In dams, ↓T4, ↑cell height in thyroid, slightly ↑vacuolisation in X-zone of adrenals In F1, short-term morphological modifications (↓follicular size at PND2),of the thyroid; long-term morphological and biochemical alterations (↑necrotic follicular cells, ↓serum T4) of the thyroid at PND150. Higher vulnerability in males.	3	**High**	**No relevant LOAELs in the standard regulatory tests.** Single study to examine the potential short- and long-term effects of low level chlorpyrifos on thyroid and adrenal glands during gestational and/or postnatal vulnerable phases. Evidence of effects on thyroid system at levels below those which inhibit cholinesterase suggesting a potential endocrine disrupting effect of chlorpyrifos.
	Clothianidin	**Yes**	**2-year rat oral long-term toxicity and carcinogenicity oral study** ↓feed consumption, body wt effects,	32.5	Low	Effects on the female reproductive system.

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		Further information required	Adverse effects potentially related to an endocrine MoA (underlined)	LOAEL mg/kg bw/day	Likelihood of posing a risk (</>STOT RE 1)	
			interstitial ovarian gland hyperplasia. **2-generation rat oral reproduction study** Parent/offspring toxicity: Body wt effects, preputial separation/vaginal opening patency, thymus wt Reproductive toxicity: stillborns, sperm motility and morphology effects	Parental/offspring toxicity 32.7 Reproduction toxicity 179.6	**Low**	There are male and female reproductive effects which might suggest endocrine disruption, although these were only present at high doses, at which there is generalised toxicity.
	Beta-cyfluthrin	**Yes**	**Castrated male Wistar rats in the Hershberger assay** (Zhang *et al*. 2008) ↓seminal vesicle weight, ↓weight of seminal vesicle, ventral prostate, dorsolateral prostate, LABC and Cowper's glands, maternal weight gain	12	**Low**	**No relevant LOAELs in the standard regulatory tests.** Effects on male reproductive system in castrated rats (i.e. not intact organisms) which may be due to endocrine disruption
	Lamda-cyhalothrin	**Yes**	**2-year mouse oral long-term carcinogenicity oral study** ↑incidence of mammary adenocarcinomas in female mice (above incidence in concurrent and historical controls). Neurological effects.	11 (lowest dose with tumours)	**Low**	Mammary tumours could be due to endocrine disruption
	Spinosad	**Yes**	**90-day mouse oral study** Vacuolation and necrosis in several tissues including lymphoid organs, kidneys, liver, stomach, ovary, female genital tract, epididymis, and skeletal muscle. Alterations in liver, kidneys, and stomach	22.5	Low	Vacuolation seen in some reproductive organs could be indicative of an effect on endocrine disruption.

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		Further information required	Adverse effects potentially related to an endocrine MoA (underlined)	LOAEL mg/kg bw/day	Likelihood of posing a risk (</>STOT RE 1)	
			2-year rat oral long-term toxicity and carcinogenicity study Vacuolation of the thyroid gland. No carcinogenic potential.	9.5	**Low**	Effect on the thyroid gland which may be due to endocrine disruption
			2-generation rat oral reproduction study Parental: mortality, dystocia, vaginal bleeding, changes in body and organ wt, histological changes in several organs Developmental: decreased gestation survival, litter size, pup wt, and neonatal survival Reproductive: dystocia, vaginal bleeding, decreased litter size	100 (parental/ developmental/reproductive)	Low	There are changes observed which may be indicative of endocrine disruption such as vaginal bleeding, dystocia, decreased litter size.
	Spirotetremat	**Yes**	**90-day dog oral study** ↓body wt during the first two weeks of the study. No marked toxicity was determined in the present study, ↓thyroid hormone but no changes in thyroid wt, thyroid pathology, no compensating increases in TSH, or no clinical observations (e.g., neurological signs) suggestive of thyroid compromise were detected in either sex.	33	Low	Effects seen on circulating thyroid hormones may be due to endocrine disruption.
			1-year dog oral study ↓thyroid hormones, but no changes in thyroid wt, thyroid pathology, no compensating increases in TSH, or no clinical observations (e.g., neurological signs) indicative of thyroid toxicity.	20	**Low**	Effects seen on circulating thyroid hormones may be due to endocrine disruption.
			2-gen rat study ↓oestrus cycling in F0 females; ↑ no ovarian primordial follicles in F1	70	Low	Effects on the female reproductive system were

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			females			observed at higher doses.