Bundesinstitut für Risikobewertung

JOINT DE – UK POSITION PAPER

REGULATORY DEFINITION OF AN ENDOCRINE DISRUPTER IN RELATION TO POTENTIAL THREAT TO HUMAN HEALTH

Proposal applicable in the regulatory context of
Plant Protection Products, Biocidial Products, and Chemicals targeted within REACH

16. Mai 2011

Background

1. The prompt for this work 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 (see Appendix 1).

2. A similar approval exclusion criterion has been introduced in the proposed new EU Biocidal Products Regulation (5604/1/11 ENV, REV 1 of 2nd March 2011; See Appendix 1).

3. 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 Art 57(f) may lead to their inclusion in the list of substances of very high concern (SVHCs) as possible candidates for Authorisation (see Appendix 1). In addition, in accordance with Art 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.

4. Despite these stipulations, at the present time there is no set of criteria within these pieces of legislation, by which to identify EDs of very high regulatory concern. The aim of this paper is to propose a definition and associated interpretative criteria that can be applied in a regulatory context.

5. The proposal aims at identifying EDs of very high regulatory concern for which legislative action can be taken within the provisions of the current legislative framework. As such, the proposal has been developed to be generally applicable to data-rich chemicals such as those tested to meet the requirements of the pesticide or biocide regulations and those prioritised for Authorisation under REACH (most likely high-volume, extensively investigated substances).

6. An important perspective from which to begin is the recognition that within these pieces of legislation, the consequence of identification of a substance as an ED of very high regulatory concern is potentially of great commercial impact. Stringent measures – including prohibition – may well arise. Hence this paper takes the position that the assigning of the ED identifier to a substance should be reserved for those substances where such a property is clearly established, the substance is potent in this respect, and the endocrine-disrupting property is a prominent feature of the hazard profile of the substance.

7. In this document, the focus is on human health considerations only.

Argument

8. A number of definitions for EDs have been proposed (Kavlock, 1996; NRDC, 1998; Weybridge, 1996, WHO/IPCS, 2002 – see Appendix 2). Some of these definitions (e.g. Kavlock, 1996; NRDC, 1998) are ambiguous and, for regulatory purposes, are overly inclusive, in that they fail to discriminate between alterations of the endocrine system which fall within the physiological balance/homeostatic capabilities of the body, and adverse effects that disturb an organism’s endocrine system to an extent beyond that compatible with normal function.

This has led to the development of more restrictive definitions (e.g. Weybridge, 1996, WHO/IPCS, 2002) that readily account for the fact that many alterations of the endocrine system can be regarded as adaptive, falling within a range for which compensation can occur readily, and which pose no threat to the normal functioning of the organism.

9. Still, even the more restrictive definitions remain quite general. A definition of an ED for regulatory use and application requires further development and elaboration (Marx-Stoelting et al. 2011).

10. The widely accepted scientific definition of ED by WHO/IPCS is proposed as a starting point for characterising an ED for regulatory purposes. This is a well-established and widely recognised definition produced by a global, authoritative organisation through a world-wide initiative of highly scientific rigour (WHO/IPCS, 2002). In addition, it is supported by a number of organisations and regulatory bodies around the world, including the US EPA, the Canadian Centre for Occupational Health and Safety (CCHOS) and the International Union of Pure and Applied Chemistry (IUPAC). Furthermore, it is noted that this definition is already included in the REACH guidance (guidance for preparation of an annex XV dossier on the identification of substances of very high concern).

11. “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.”

12. This definition embodies two key elements on which one can build criteria for identifying an ED of regulatory importance: adversity and intact organism observations.

13. With regard to adversity, it is proposed that the global and widely accepted definition produced by WHO/IPCS in 2004 is used to determine whether effects caused by exposure to a chemical are adverse:

14. “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).”

15. This is a generic definition of adversity which is not specific to the endocrine system. Therefore, assessing adversity via endocrine perturbation may require to take account of some additional considerations. By definition, an endocrine disruptor perturbs the normal endocrine homeostasis, for instance, by changing the circulating levels of a particular hormone. However, such perturbation *in itself* is not considered to be an adverse effect, as the endocrine system is naturally dynamic and responsive to various stimuli as part of its normal functioning. In this context, endocrine perturbation is considered as a mode/mechanism of action, potentially on a pathway to other outcomes, rather than a toxicological endpoint in itself. Crucially, to consider that a substance might require attention for regulatory purposes, any endocrine perturbation must result in adverse effects, such as pathology or functional impairment. This approach is entirely consistent with other areas of regulatory assessment. For instance, in hazard identification for classification and labelling purposes for most endpoints, chemicals are only classified where there is a clear induction of adverse effects; they are not classified simply because the substance acts via a particular mode of action known to have the potential to lead to an adverse effect; the adverse consequences must be demonstrated to occur.

16. Another important element in this definition is that the ED effect must be observed in an intact organism. This reinforces the requirement that an ED-mediated “whole-animal” adverse effect must be observed, rather than simply inferred from results obtained in a simpler test system designed to explore the possibility that a substance can express a property relating to potential endocrine disruption. For example, observations from screening tests in ovariectomised or castrated animals cannot be considered as adverse effects in the intact animal as the integrity of the physiological homeostasis of the whole organism has been altered to maximise the test objective.

17. A tiered evaluation scheme to identify EDs of very high regulatory concern is described below (Figure 1). The scheme builds upon the WHO/IPCS definition but extends it with consideration of parameters of relevance from a regulatory perspective.

18. Before one starts to assess a substance using this proposed ED evaluation scheme, one should consider whether or not the substance meets the conditions for Carcinogen, Mutagen or Reprotoxicant (CMR) categories 1A or 1B (under the CLP Regulation). If it does, the stringent regulatory consequences that pertain to ED substances in PPPR, REACH and draft BPR already apply. Hence, in most cases, there is no additional value in pursuing the ED issue for CMR 1A or 1B substances. However, it should be noted that in the context of REACH, as the Authorisation process addresses only the hazard property for which inclusion on the SVHC list was proposed, it may still be appropriate to assess whether the CMR 1A or 1B substance is also an ED.

Evaluate all available data: are there adverse effects in intact organisms in acceptable studies?

19. EDs can be identified in standard toxicology tests that are routinely performed to fulfil the requirements of various regulatory programmes. In particular, ED-mediated toxicity can be detected in repeated-dose, reproductive and developmental toxicity, and carcinogenicity studies, although supplementary and more focussed ad-hoc studies, such as mechanistic studies, may be necessary to decide whether a relationship between the observed adverse effects and an ED mode/mechanism of action is plausible. Given the wide ranging functions of the endocrine system, ED-mediated adverse effects could manifest in various organs and tissues and in different ways. In some cases, a pattern of response characterised by a spectrum/syndrome of effects forming a coherent toxicological picture may be present. Expert judgement is generally required to assess the toxicological significance of such changes.

20. The criteria for acceptability of any such whole-animal toxicity studies follow general principles. The study must be conducted to an acceptable protocol and to good standards and be well reported. The study should have used relevant routes of exposure (oral, dermal or inhalation). Toxicity studies using parenteral routes are not generally appropriate and should not override results from well performed studies using a more relevant route of exposure.

21. Additional *in vivo* and *in vitro* mode-of-action or mechanistic studies may provide extremely valuable information which sheds light on the specific mode-of-action or mechanism of a substance, e.g. demonstrating binding to a hormone receptor. These should be evaluated on their merits on a case by case basis. However, it is noted that such studies demonstrate mechanism/mode of action and do not, on their own, provide conclusive proof of ED-induced adverse effects in an intact organism.

Mode-of-action link to endocrine disruptive activity

22. In order to conclude that a substance is an ED there must be a reasonable evidence base for the supposition that there is a plausible/coherent link between the induced endocrine perturbation/activity and the adverse effects seen in the intact organism studies. Such evidence usually comes from a combination of findings from standard toxicity tests, which identify the adverse effect, and mode-of-action/mechanistic studies, which provide supporting evidence. Such a mechanistic link could be established, for example, using information from the *in vitro* and *in vivo* screening assays (levels 2 and 3) of the current OECD conceptual framework for testing and assessment of EDs (Appendix 3) or from more ad-hoc studies. The OECD ED *in vitro* screening assays (level 2) are capable of identifying binding to the oestrogen or androgen receptor, alterations in the synthesis of steroid hormones and inhibition of aromatase (the enzyme responsible for the conversion of androgens to oestrogens). The OECD ED *in vivo* screening assays (level 3) can detect oestrogenic, androgenic, anti-androgenic and anti-thyroid activity. These screening assays are likely to provide varying degrees of evidence of endocrine disrupting activity of the substance which may explain the occurrence of the original adverse effects seen in the intact organism studies; they are less likely to provide a full sequence of biochemical and cellular events leading to the adverse effects, i.e. the mode/mechanism of action of the substance. Therefore, where a more robust mode-of-action/mechanistic link is sought, other, more specific/targeted investigations may be required to show this.

23. In relation to establishing that an endocrine-disrupting process applies to a particular toxic effect it is proposed that a structured framework, e. g. the IPCS mode of action framework (Boobis et al., 2008) is used to carry out a weight of evidence evaluation of the available information to reach a transparent and robust conclusion. Where a definitive conclusion cannot be reached, then the evaluation should highlight where additional studies may help provide the necessary clarification.

24. Where ED screening assays or other ad-hoc mode-of-action/mechanistic studies are not available, then they should be requested. Under the PPPR (point 5.8.2 of Annex II of the Data Requirement Regulation) and the draft BPR (points 8.13.3 and 8.13.5 of Annex II), these additional investigations can be required by the regulatory authority performing the evaluation of the substance. Under REACH, additional studies can be requested within the context of “Substance Evaluation” by the Member State assessing the substance (Art 46 of REACH). Before studies involving testing in vertebrates are requested, consideration should be given to the dose levels at which the adverse effects potentially related to ED were first seen. If these dosages are relatively high (the substance being of low potency for the potentially ED-related effect), then it may be justifiable not to conduct such additional studies (see below “Potency considerations”).

Relevance to humans

25. The default assumption of any adverse effect seen in regulatory toxicity studies is that the effect is relevant to humans. This assumption can be rebutted with sound scientific data showing non-relevance.

26. It is proposed that a structured framework, e.g the IPCS human relevance framework (Boobis et al., 2008), is used to analyse the available evidence to facilitate that a robust and transparent conclusion is reached.

27. It is noted that even when effects are not relevant to humans, they could still be relevant to non-target species in the environment. This is of potential value to determining whether or not a substance merits consideration as an ED in relation to potential effects on other environmental species, but is outside of the scope of this paper.

Potency considerations

28. In general terms, toxic effects are only of regulatory relevance when they occur at relevant dose levels. Toxic effects that occur at excessively high dose levels (above the Maximum Tolerated Dose) tend to represent the unspecific and generalised response of the body to the chemical insult e.g. arising from the saturation of kinetic processes. Mostly, these effects are not realistically relevant to humans and are not used to drive regulatory action. This concept is applied in various regulatory approaches, such as hazard classification and labelling.

29. As for any other type of toxicity, the dose-response curve must be considered to determine if the effects occur at a relevant dose level. It is proposed that the relevance of the dose level causing the ED-induced adverse effects should be judged using the same well established approach used for hazard classification.

30. [Note: This approach is based around the identification of overt toxicity, usually in standard regulatory tests conducted at relatively high doses. There are claims that at least some EDs show non-monotonic dose-response curves. Advocates suggest that EDs might cause effects at very low dose levels, in a manner that would not be detected by current testing approaches (e.g. Welshons et al., 2003). The effects may be of such a low magnitude that standard tests do not have the power to detect them, or the effects may be of a type that will not be detected by standard observations (e.g. epigenetic changes). At the moment this is still an area of research; it is surrounded by much controversy and inconsistency in reported findings (e. g. Ashby, 2003). It is therefore premature to introduce these ideas into a regulatory approach. Further developments in this field will be monitored and the approach described in this paper should be modified if the balance of scientific opinion merits this].

31. 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). It is proposed that the dose thresholds for STOT Repeated Exposure-RE should be used to determine whether or not the hazardous property of “endocrine disruption” should be identified for regulatory purposes.

32. 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 as:

For sub-acute and other short-term studies (e.g. developmental toxicity studies):

	STOT-RE Cat 2	STOT-RE Cat 1
Oral	300 mg/kg bw/day	30 mg/kg bw/day
Dermal	600 mg/kg bw/day	60 mg/kg bw/day
Inhalation (vapour)	3 mg/l/6h/day	0.6 mg/l/6h/day
Inhalation (dust/mist/fume)	0.6 mg/l/6h/day	0.06 mg/l/6h/day

For subchronic and other medium-term studies (e.g. 2-generation studies):

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

There are no guidance values in the CLP Regulations for chronic studies, but it is prop here that they should be half the subchronic study values (by applying the subchronic t chronic extrapolation assessment factor of 2 recommended in the REACH guidance or information requirements and chemical safety assessment, chapter R8), ie:

	STOT-RE Cat 2	STOT-RE Cat 1
Oral	50 mg/kg bw/day	5 mg/kg bw/day
Dermal	100 mg/kg bw/day	10 mg/kg bw/day
Inhalation (vapour)	0.5 mg/l/6h/day	0.1 mg/l/6h/day
Inhalation (dust/mist/fume)	0.1 mg/l/6h/day	0.01 mg/l/6h/day

33. 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.

34. 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.

35. 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 of very high regulatory concern requiring severe action (consideration for non-approval in the context of the PPP or draft BP regulations and consideration for inclusion in the list of SVHCs as possible candidates for Authorisation in the context of REACH). Where a substance produces endocrine disruption at a dose level above these discriminatory guidance levels, it should be noted that the substance is still to be regulated through standard risk assessment and risk management methodologies. Safe use is still to be demonstrated. In addition, a combined

risk assessment for exposure to a mixture of substances acting through a similar mode of action is still to be performed.

36. In the context of REACH and the draft BPR, this is further justified by the fact that only EDs of equivalent concern to carcinogens, mutagens or reproductive (CMR) toxicants Category 1A or 1B (under the CLP Regulation) may be included in the list of SVHCs as possible candidates for Authorisation under REACH and be considered for non-approval under the draft BPR. CMR cat 1A or 1B substances possess serious, well-established and specific hazard properties.

37. The focus of this proposal is on animal data, as human studies showing ED-induced adverse effects causally associated with exposure to a chemical substance are rarely available. However, where such human evidence were to exist, the application of the STOT-RE Cat 1 discriminatory guidance values should be performed with great care, by taking into account the severity of the effects and the relevance of the exposure conditions.

Conclusion and proposal

38. In relation to potential human health concerns, it is proposed that a substance is regarded as an ED of very high regulatory concern when it satisfies the following definition and associated criteria:

39. It should be 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.

40. And in doing so satisfies the following criteria (each of which is expanded on in the paper above):

- 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.
- a plausible mode-of-action/mechanistic link between the toxic effects of concern and endocrine disruption.
- the effects seen in experimental animals to be judged to be of potential relevance to human health.
- 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 & labelling.

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REACH Guidance on information requirements and chemical safety assessment, chapter R17. http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r17_en.pdf?vers=20_08_08

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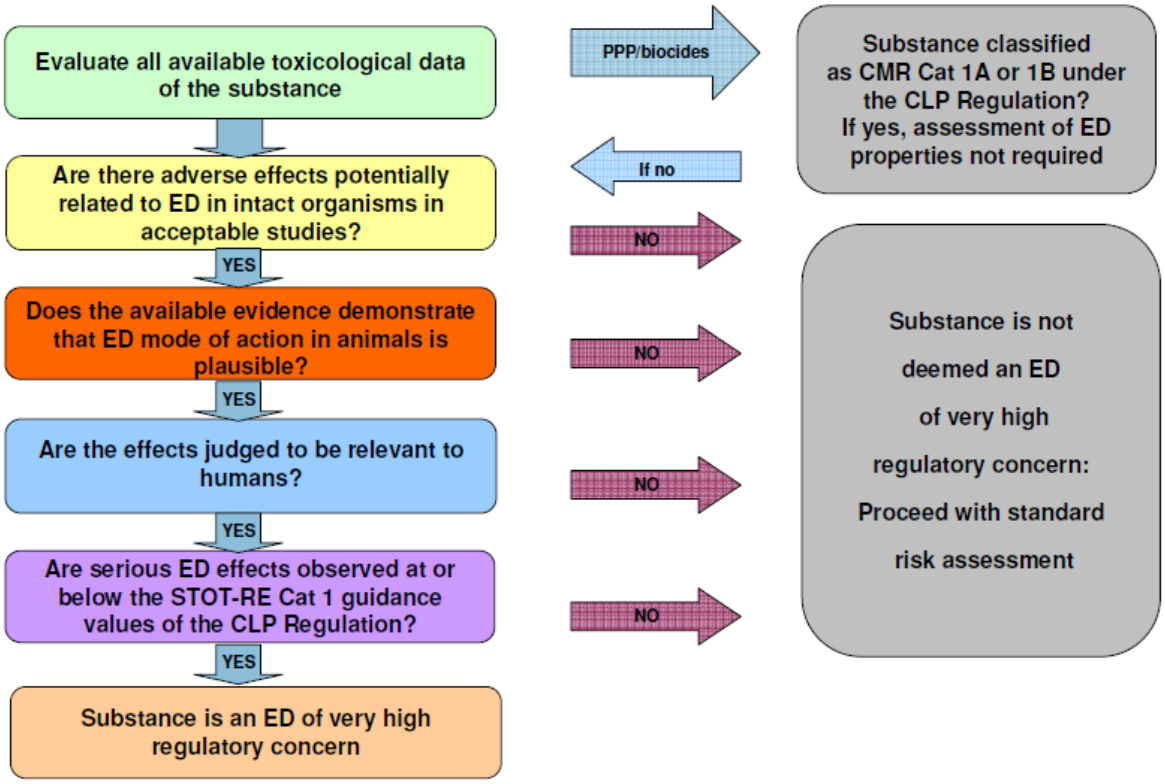
Abbreviations

BPR:	Biocidal Products Regulation
CLP:	Classification, Labelling and Packaging
CMR:	Carcinogenic, Mutagenic or Reprotoxic
ED:	Endocrine Disruptor
EPA:	Environmental Protection Agency
EU:	European Union
GHS:	Globaly Harmonised System
IPCS:	International Program on Chemical Safety
MTD:	Maximum Tolerated Dose
OECD:	Organisation for Economic Co-operation and Development
PPP:	Plant Protection Product
PPPR:	Plant Protection Products Regulation
RE:	Repeated Exposure
REACH:	Registration, Evaluation, Authorisation and Restricion of Chemicals
STOT:	Specific Target Organ Toxicity
SVHC:	Substance of Very High Concern
WHO:	World Health Organisation

FIGURE 1


Evaluate all available toxicological data of the substance
Are there adverse effects potentially related to ED in intact organisms in acceptable studies?
YES
Does the available evidence demonstrate that ED mode of action in animals is plausible?
YES
Are the effects judged to be relevant to humans?
YES
Are serious ED effects observed at or below the STOT-RE Cat 1 guidance values of the CLP Regulation?
YES
Substance is an ED of very high regulatory concern
PPP/biocides
Substance classified as CMR Cat 1A or 1B under the CLP Regulation? If yes, assessment of ED properties not required
If no
NO
NO
NO
NO
Substance is not deemed an ED of very high regulatory concern: Proceed with standard risk assessment

APPENDIX 1

Regulation 1107/2009 for placing plant protection products on the market – substance approval criteria

Human health

3.6.5 An active substance, safener or synergist shall only be approved if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not considered to have endocrine disrupting properties that may cause adverse effect in humans, unless the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, i.e. the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with point (b) of Article 18(1) of Regulation (EC) No 396/2005.

Environment

3.8.2 An active substance, safener or synergist shall only be approved if, on the basis of the assessment of Community or internationally agreed test guidelines, it is not considered to have endocrine disrupting properties that may cause adverse effects on non-target organisms unless the exposure of non-target organisms to that active substance in a plant protection product under realistic proposed conditions of use is negligible.

REACH (Regulation 1907/2006) – substances to be included in Annex XIV (substances subject to Authorisation)

Article 57 (f) : substances – such as those having endocrine disrupting properties or those having . . . . . - for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those other substances listed in points (a) to (e) and which are identified on a case-by-case basis in accordance with the procedure set out in Article 59

[points (a) to (e) cover category 1A and 1B carcinogens, mutagens, and/or substances toxic to reproduction; and/or (very) persistent, (very) bioaccumulative, toxic (PBT or vPvB) substances]

Draft Biocidal Product Regulation (5604/1/11 ENV, REV 1 of 2nd March 2011) – Chapter II (Approval of active substances), Art 5 (Exclusion criteria)

Art 5(1) – The following active substances shall not, subject to paragraph 2, be approved:
(d) active substances identified in accordance with Articles 57(f) and 59(1) of Regulation (EC) No 1907/2006 (REACH) as having endocrine disrupting properties.

Art 5(2) – However, without prejudice to Article 4(1), active substances referred to in paragraph 1 may be approved if it is shown that at least one of the following conditions is met:

(a) the risk to humans or the environment from exposure to that active substance in a biocidal product, under realistic worst case conditions of use, is negligible, in particular where the product is used in closed systems or strictly controlled conditions; or
(b) the active substance is essential to prevent or to control a serious danger to public or animal health or the environment; or
(c) not approving the active substance would cause disproportionate negative impacts for society when compared with the risk to human health or the environment arising from the use of the substance.

When deciding that an active substance may be approved in accordance with the first subparagraph, the availability of suitable and sufficient alternative substances or technologies shall also be taken into account.

APPENDIX 2

Definitions of EDs

Kavlock, 1996:

“An ED is an exogenous agent that interferes with the production, release, transport, metabolism, binding, action or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes.”

NRDC, 1998:

“EDs are synthetic chemicals that when absorbed into the body either mimic or block hormones and disrupt the body’s normal functions through altering hormone levels, halting or stimulating the production of hormones, or changing the way hormones travel through the body.”

Weybridge, 1996:

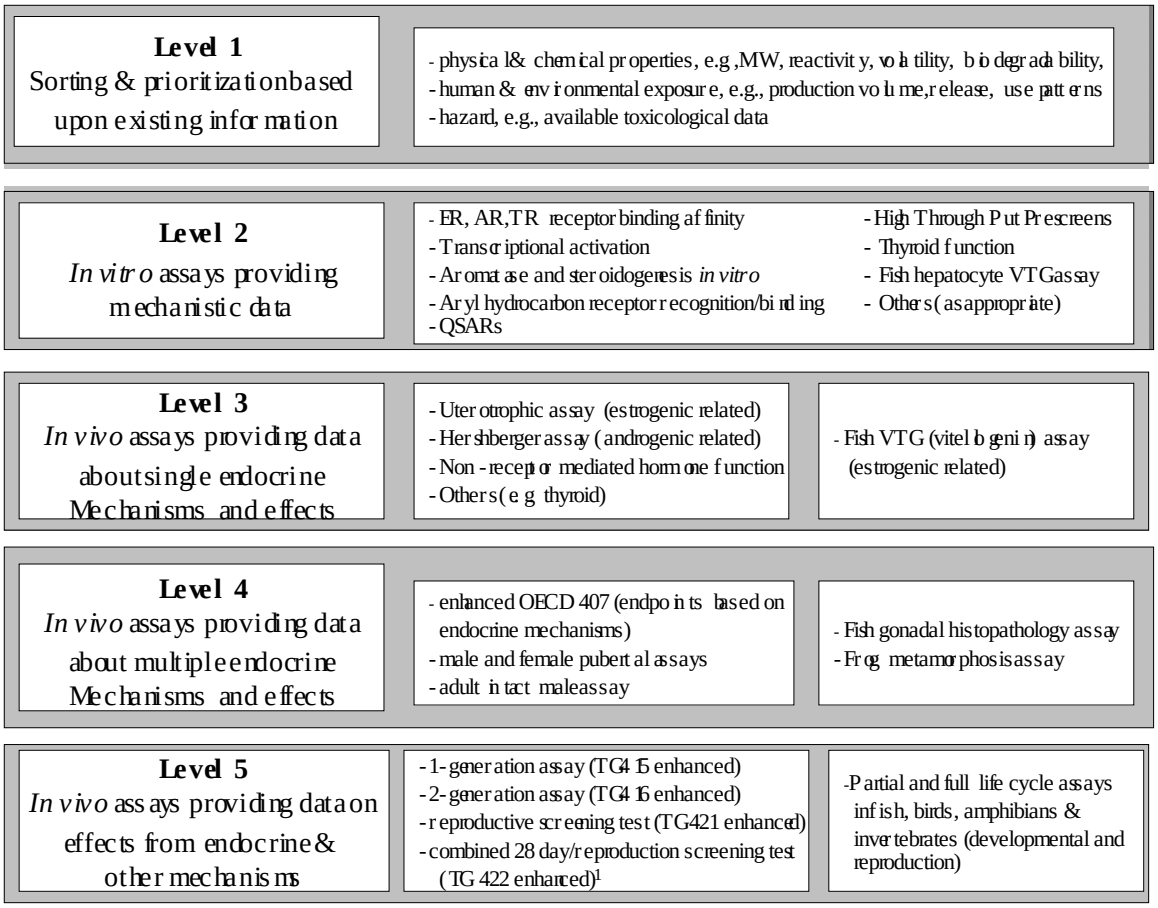
“An ED is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function. A potential ED is a substance that possesses properties that might be expected to lead to endocrine disruption in an intact organism.”

WHO/IPCS, 2002:

“An ED 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.”

APPENDIX 3

OECD Conceptual Framework for the Testing and Assessment of Endocrine Disrupting Chemicals



Note: Document prepared by the Secretariat of the Test Guidelines Programme based on the agreement reached at the 6th Meeting of the EDTA Task Force (The framework is currently under revision.)

Notes to the Framework

Note 1: Entering at all levels and exiting at all levels is possible and depends upon the nature of existing information needs for hazard and risk assessment purposes

Note 2: In level 5, ecotoxicology should include endpoints that indicate mechanisms of adverse effects, and potential population damage

Note 3: When a multimodal model covers several of the single endpoint assays, that model would replace the use of those single endpoint assays

Note 4: The assessment of each chemical should be based on a case by case basis, taking into account all available information, bearing in mind the function of the framework levels.

Note 5: The framework should not be considered as all inclusive at the present time. At levels 3,4 and 5 it includes assays that are either available or for which validation is under way. With respect to the latter, these are provisionally included. Once developed and validated, they will be formally added to the framework.

Note 6: Level 5 should not be considered as including definitive tests only. Tests included at that level are considered to contribute to general hazard and risk assessment.