Maisons-Alfort, 27 March 2012

The Director General

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

regarding a request for scientific and technical support for the revising of the European strategy on endocrine disruptors

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.

On 3 February 2012, ANSES received a formal request from the French Directorate General for Food[1], Directorate General for Health[2], Directorate General for Risk Prevention[3], Directorate General for Competition, Consumer Affairs and Fraud Control[4], and the Directorate General for Labour[5] regarding a request for scientific and technical support for the revision of the European strategy on endocrine disruptors (EDs).

BACKGROUND AND PURPOSE OF THE REQUEST

In the framework of EU work on revising the European strategy for endocrine disruptors, the European Commission set up an *ad hoc* group consisting of representatives of the competent authorities from the different Member States (MSs). This group, led by the DG Environment, has the primary objective of defining criteria for identifying substances as endocrine disruptors, which may then be used in European regulations such as the REACh, Biocides and Plant Protection Products Regulations. The European *ad hoc* group calls on a sub-group of experts appointed by the competent authorities of the Member States.

In this context, the European Commission ordered a state-of-the-art report on the assessment of endocrine disruptors. This report was published in its final version[6] on 23 December 2011.

This report, in interim form, as well as the separate action plan provided for[7] by the European Commission and the proposals by the Member States were presented at information meetings on

[1] of the Ministry of Agriculture, Food, Fisheries, Rural and Regional Planning
[2] of the Ministry of Labour, Employment and Health
[3] of the Ministry for Ecology, Sustainable Development, Transportation and Housing
[4] of the Ministry of Labour, Employment and Health
[5] of the Ministry of Economy, Finance and Industry
[6] STATE OF THE ART ASSESSMENT OF ENDOCRINE DISRUPTERS Final Report Project Contract Number 070307/2009/550687/SER/D3 Andreas Kortenkamp, Olwenn Martin, Michael Faust, Richard Evans, Rebecca McKinlay, Frances Orton and Erika Rosivatz 23.12.2011 [cited on p 3 overleaf]
[7] COMMISSION STAFF WORKING PAPER 4th Report on the implementation of the "Community Strategy for Endocrine Disrupters" a range of substances suspected of interfering with the hormone systems of humans and wildlife (COM (1999) 706) Brussels, 10.8.2011 SEC(2011) 1001 final

26 November 2010 and 19 May 2011, and at the most recent meetings of the *ad hoc* group and its sub-group of experts in November 2011. A review of this work is summarised in an Opinion issued by ANSES on 7 November 2011[8].

In this context, the above five Directorate Generals, representing ANSES's supervisory ministries, asked the Agency to:

1. extend the analytical work it has been conducting on various plant protection substances as part of the Directorate General for Food's formal request of 6 September 2011 (Opinion 2011-SA-0237 of 7 November 2011) to a selection of chemicals suspected of being endocrine disruptors (EDs) and subject to the regulation of biocides and of chemicals covered by REACh;

2. give a reasoned opinion on the "ED" criteria already proposed (Germany-UK, Denmark and certain stakeholders) and the positions to come;

3. propose, if necessary, other relevant endocrine disruption criteria that can be applied to the relevant regulations.

[8] ANSES Opinion 2011-SA-0237 of 7 November 2011 on a request for scientific and technical support regarding the European strategy for endocrine disruptors

ORGANISATION OF THE EXPERT APPRAISAL

This expert appraisal was carried out in accordance with the French standard NF X 50-110 "Quality in Expertise - General Requirements of Competence for Expert Appraisals (May 2003)".

The response to this request for scientific and technical support was produced by ANSES's Regulated Products Department together with the Risk Assessment Department. The Expert Committees (CESs) on Plant protection products (chemical substances and preparations), on chemicals under REACh and Biocides Regulations and on assessment of the risks related to chemicals, and the working group on endocrine disruptors, which met respectively on 25 January, 2 February, 15 March, 8 March, and 6 February, 2012, participated in the discussions.

The documents examined in the context of this request were as follows:

- ANSES Opinion 2011-SA-0237 of 7 November 2011 on a request for scientific and technical support regarding the European strategy for endocrine disruptors
- *State of the art assessment of endocrine disrupters. Final Report*, Project Contract Number 070307/2009/550687/SER/D3, PART 1 Summary of the state of the science. Richard Evans, Andreas Kortenkamp, Olwenn Martin, Rebecca McKinlay, Frances Orton, Erika Rosivatz
- WHO/IPCS (International Programme on Chemical Safety). *Global assessment of the state-of-the-science of endocrine disrupters.* WHO, 2002
- OECD *Test Guidelines Programme - Draft guidance document on the assessment of chemicals for endocrine disruption* - ENV/JM/TG(2011)4
- Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACh), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC
- Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC
- ECHA (2007). *Guidance for the preparation of an Annex XV dossier on the identification of substances of very high concern*
- Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006
- Joint DE-UK position paper: *Regulatory definition of an endocrine disrupter in relation to potential threat to human health*, BfR, May 2011
- *Establishment of criteria for endocrine disruptors and options for regulation*, Danish Ministry of the Environment, Environmental Protection Agency, May 2011
- *PAN Europe position paper on criteria for endocrine disrupting pesticides*, May 2011
- *CHEM Trust's Contribution to the Ongoing Debate on Criteria for EDCs*, September 2011 and CHEM Trust and WWF-EPO proposals for the regulation of chemicals with endocrine disrupting properties under REACh (EC No 1907/2006) and under the Plant Protection Products Regulation (EC No 1107/2009), December 2010
- Guidance on Identifying Endocrine Disrupting Effects, ECETOC Technical Report no. 106, June 2009 and Bars R. *et al.*, *Science based guidance for the assessment of endocrine disrupting properties of chemicals*, Regulatory Toxicology and Pharmacology 59 (2011) 37-46

SUMMARY OF ANALYTICAL WORK

1 SCIENTIFIC CONTEXT

In 2002, the World Health Organization (WHO) issued a fir*st rep*ort[9] on the state of knowledge relating to endocrine disruptors. Very recently, the European Commission decided to bring this knowledge up to date and instructed a consultant to produce a new state-of-the-art report, in view of possible regulatory changes, according to scientific advances in this field.

The first part of this work was the subject of a detailed scientific report[10] by Kortenkamp *et al.* (2011), whose final version was published on 23 December 2011. A summary containing the main points of the January 2011 version, with the conclusions reflecting the views of the authors, is given in the ANSES Opinion SA-2011-0237 of 7 November 2011. In particular, this document states the definitions available at international level, including that of the WHO/IPCS (2002), which results from an international consensus and defines an endocrine disruptor and a potential endocrine disruptor as follows:

- *An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.*
- *A potential endocrine disrupter is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations*.

It should be noted that extensive studies, being finalised by the OECD within the EDTA[11] workgroup, are aiming to establish a testing strategy for different living organisms in the event of suspected endocrine disrupting effects.

However, many issues related to endocrine disruption remain under discussion within the research community. Some of these have been the subject of debates within ANSES's competent CESs and in the working group on endocrine disruptors.

The following scientific issues were discussed and the following answers have been provided.

Definition of an endocrine disruptor
The choice of a definition from those of the WHO/IPCS and US EPA, or from any other definition or complement to a definition, was discussed by the experts of the working group on endocrine disruptors and reprotoxic substances.

Concept of an ED effect in the presence of other toxic effects
When both endocrine disruption effects and other toxic effects are observed, should the adverse ED effect appear at the lowest dose (lead effect) in order to be taken into account? When a substance induces various toxic effects that are independent of each other, the risk assessment is performed on the critical effect occurring at the lowest dose, adding appropriate safety factors in a protective approach. Conversely, the identification of a hazardous property such as ED should not be restricted to the most evident effects occurring at the lowest doses. It should be stressed that this is the approach advocated by the CLP Regulation, especially for CMR (Carcinogenic, Mutagenic or Toxic for Reproduction) effects, and is not intended to systematically exclude hazards occurring at the same dose levels as the other toxic effects.

[9] WHO/IPCS. *Global assessment of the state-of-the-science of endocrine disruptors*. WHO, 2002.
[10] *State of the art assessment of endocrine disrupters*. Final Report, Project Contract Number 070307/2009/550687/SER/D3, PART 1 Summary of the state of the science. Richard Evans, Andreas Kortenkamp, Olwenn Martin, Rebecca McKinlay, Frances Orton, Erika Rosivatz
[11] EDTA: *Endocrine Disruptor Testing and Assessment*

The experts believe that when the observed adverse ED effect is secondary to toxicity induced by other non-ED effects, the latter should not be taken into account.

In general, it is commonly accepted that the secondary ED effects observed in the presence of other toxic non-ED effects are adequately covered by the regulations, whether in terms of hazards (identified by classification if appropriate) or risks which, by protecting from the primary effect, also protects from potential hormonal disruption consequences. Only specific ED effects, not secondary to non-ED toxicity, must be taken into account.

Hormonal systems involved (concepts, definitions and consequence)

Certain ED modes of action (particularly related to reproductive functions) have thus far received more attention and been the subject of more studies and development of test methods. However the concerns raised by EDs largely exceed this framework, and it is important to include the different endocrine systems in the definition. Accordingly, all endocrine systems (such as those related to steroid, thyroid, parathyroid and pancreatic hormones, etc.) of potentially exposed organisms should be taken into account, not only humans but also organisms living in the environment.

Detection tools

Discussions took place to determine the tools for which models are available and how these studies are relevant and validated (in terms of feasibility, sensitivity, specificity and also from an economic point of view).

It is important to use the most suitable tools for establishing scientific evidence of endocrine disruption effects. Uncertainties remain, for example, on the interpretation of results obtained in some models, such as *in vitro* tests.

Moreover, the issue of the use of intact organisms was raised. Some tests for identifying an adverse effect are conducted on castrated or ovariectomised animals (e.g. the level 3 tests of the OECD framework). The models concerned, which are internationally recognised and have undergone inter-laboratory validation, have been developed specifically to identify certain ED modes of action and have the advantage of providing a response *in vivo,* for which physiological damage is measured and which takes all the regulations into account. However, even if they can be used to identify mechanisms of action *in vivo,* it is still unclear whether the observed response can be fully extrapolated to unmodified conditions, because of the specificity of these experimental models. Some experts therefore believe that the notion of intact organism should not be taken into account in the general definition of an ED but that it should be considered for the plausibility of an effect. In this context, transgenic animals and castrated animals are not regarded as intact organisms.

Some experts do not consider the use of an osmotic pump as a means of exposure that alters the integrity of the treated organism, like parenteral injections or co-exposures with a carcinogen.

Concept of adverse effects and low doses

Among the effects related to endocrine disruption, the issue of adverse effects was raised. The experts believe that it is necessary to consider the plausibility of a precursor effect that is part of a continuum of effects (e.g. subclinical signs, preneoplastic lesion, etc.). An effect's plausibility can be discussed with justification on a case-by-case basis.

Concept of effect level/potency

The experts discussed whether the dose at which the ED effect was shown should be taken into account. In the current state of knowledge, a number of experts believe that it is not possible to comment generally on the determination of a threshold effect.

In particular, it should be emphasised that the studies being conducted within the regulatory framework cannot necessarily be used to identify an ED substance's complete dose-response relationship. This notion of no-effect level or no adverse effect level is not shared by the entire scientific community.

Nor is the concept of the potency of endocrine disruptors shared by all the experts.

The idea of a "cut-off" level is not supported by scientific evidence, but could potentially be introduced within a regulatory framework.

Levels of evidence
It is necessary to define the level of evidence at which a substance can be considered as having endocrine disrupting effects. Expert judgment is essential to decide on the harmful nature of certain effects on a case-by-case basis, because the observed effects must primarily involve the occurrence of functional impairment. Furthermore, the mode of action must be taken into account to explain the adverse effects observed. To do this, additional information such as toxicokinetic data may be used, as well as data on compounds that are similar in structure or in their suspected mode of action. Furthermore, the question is raised about the possibility of referring to an overall analysis of the relative weight of the evidence, especially in the absence of *in vivo* evidence.

Routes of exposure
The routes of exposure are highly relevant with regard to the potential exposure of organisms. Routes of exposure that are not representative of human or environmental exposure introduce uncertainty as to the possibility of extrapolating the observed effect to relevant exposure conditions, mainly for humans, so cannot generally be used to identify a recognised adverse effect, especially not ED. On a case-by-case basis, the toxicokinetic data that complements the available studies could support the data obtained by these routes, enabling them to be used to identify a recognised ED effect. The available data from all routes of exposure may be relevant and could provide information on the mode of action. Consistency between the information available on the mode of action and on the adverse effects will in any case be discussed to determine the plausibility of the link between the two.

Other points
Some points raised by the scientific community still need to be explored. While the concept of window of exposure seems to be commonly accepted, other issues such as very low doses or non-monotonic dose-effect relationships are under discussion. Work is underway at the ANSES and at international level to address this issue. Research should be conducted to clarify these concepts before including them in a regulatory framework.

2 REGULATORY CONTEXT

2.1 REACh Regulation

Substances identified as having endocrine disrupting properties may be subject to the authorisation procedure in the framework of the European Union REACh Regulation[12] (EC) no 1907/2006.

Authorisation may apply, with no tonnage limits, to Substances of Very High Concern (SVHC) under Article 57 of the REACh Regulation, i.e. substances classified as Carcinogenic, Mutagenic or Toxic

[12] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACh), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

for Reproduction, Category 1 or 2, Persistent, Bioaccumulative and Toxic (PBT) substances, very Persistent and very Bioaccumulative (vPvB) substances as defined by Annex XIII of the REACh Regulation and substances which give rise to an equivalent level of concern to the aforementioned effects and particularly endocrine disruptors.

If the substance is initially identified as an SVHC and subsequently subjected to authorisation, then any manufacturer, importer or downstream user must not, after a certain date, place that substance on the market for a use, or use it itself without prior authorisation, unless the use has been exempted. An authorisation may be granted if it has been shown that the risks arising from the use of the substance are adequately controlled or there are no suitable alternative substances or technologies and the socio-economic benefits outweigh the risk(s) identified.

Article 57(f) of the REACh Regulation more specifically applies to substances having endocrine disrupting properties, as it states that Substances of Very High Concern include "*substances – such as those having endocrine disrupting properties [...] for which there is scientific evidence of probable serious effects to human health [...] which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e)*" of the said Article, and particularly substances classified as Carcinogenic, Mutagenic or Toxic for Reproduction, Category 1A or 1B.

The guidance document that was written for the competent authorities for the preparation of a dossier on the identification of Substances of Very High Concern[13] gives a general interpretation of this Article and considers that a key part of the definition of a substance with an "*equivalent level of concern*" relates to there being scientific evidence of serious effects to humans or the environment. Moreover, it specifies that an additional aspect to be considered is the uncertainty of standard risk assessment for such substances and the health consequences of the risk assessment being wrong.

2.2 Plant Protection Products Regulation

Substances regarded as having endocrine disrupting properties that may be harmful to humans or non-target organisms, unless the exposure is negligible under the conditions of use, cannot be authorised pursuant to Regulation (EC) no. 1107/2009[14]. Article 4(7)[15] indicates the conditions and situations that might justify an exemption and also the measures to mitigate them, while also informing the European Commission. Moreover, by no later than 14 December 2013, the Commission is required to present proposed measures concerning specific scientific criteria for the determination of endocrine disrupting properties (Annex II, Point 3.6.5 of Regulation (EC) no. 1107/2009).

[13] ECHA. (2007). *Guidance for the preparation of an Annex XV dossier on the identification of substances of very high concern* (p. 58)

[14] Regulation (EC) no. 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC.

[15] Regulation (EC) no. 1107/2009, Article 4(7): By way of derogation from paragraph 1, where on the basis of documented evidence included in the application an active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, such active substance may be approved for a limited period necessary to control that serious danger but not exceeding five years even if it does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II, provided that the use of the active substance is subject to risk mitigation measures to ensure that exposure of humans and the environment is minimised. For such substances maximum residue levels shall be set in accordance with Regulation (EC) No 396/2005.
This derogation shall not apply to active substances which are or have to be classified in accordance with Regulation (EC) No 1272/2008, as carcinogenic category 1A, carcinogenic category without a threshold, or toxic for reproduction category 1A.
Member States may authorise plant protection products containing active substances approved in accordance with this paragraph only when it is necessary to control that serious danger to plant health in their territory.
At the same time, they shall draw up a phasing out plan concerning the control of the serious danger by other means, including non-chemical methods, and shall without delay transmit that plan to the Commission.

However, pending the adoption of these criteria, substances that are or have to be classified, pursuant to the provisions of Regulation (EC) no. 1272/2008[16], as Carcinogenic Category 2 or Toxic for Reproduction Category 2, shall be considered as having endocrine disrupting properties.

In addition, substances such as those that are or have to be classified, pursuant to the provisions of Regulation (EC) no. 1272/2008, as Toxic for Reproduction Category 2 and which have toxic effects on the endocrine organs may be considered as having such endocrine disrupting properties.

2.3 Biocides Regulation

Biocidal substances are not approved if they have endocrine disrupting properties. They are identified using the criteria described in Article 57 (f) of the REACh Regulation. This non-approval does not apply if the risk to humans and the environment is negligible, if the substance is essential to combat a serious health risk, or if such non-approval would result in disproportionate negative impacts on society relative to the risks to humans and the environment.

Specifications for the establishment of scientific criteria for the determination of endocrine disrupting properties must be proposed no later than 13 December 2013. In the meantime, endocrine disrupting substances are considered to be those substances which, under the provisions of Regulation (EC) No 1272/2008, are - or should be - classified as:

- carcinogenic category 2 and toxic for reproduction category 2;
- toxic for reproduction category 2 and which have toxic effects on the endocrine organs;
- or substances that have been identified as having endocrine disrupting properties under Articles 57 (f) and 59 (1) of Regulation (EC) No. 1907/2006.

[16] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

3 PRESENTATION AND COMMENTS ON THE PROPOSED DEFINITIONS AND AVAILABLE CRITERIA FOR ENDOCRINE DISRUPTION

This section presents the different proposals by Member States, non-governmental organisations and industry on the definition of endocrine disruption. These various proposals are then analysed and compared, referring in particular to the critical points (see Section 3.5) selected for identifying EDs.

3.1 Proposals from Member States

3.1.1 Summary of the joint Germany/United Kingdom[17] (DE-UK) proposal on the regulatory definition of an endocrine disruptor in relation to potential effects on human health

A substance shall be regarded as an endocrine disruptor when it satisfies the following definition (proposed by the WHO/IPCS in 2002) and associated criteria.

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 and satisfies the following criteria:

- 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 1[18]) classification under Regulation (EC) no. 1272/2008 on classification, labelling and packaging of substances and mixtures.

3.1.2 Summary of the Denmark proposal[19] (DK) on the establishment of criteria for endocrine disruptors and options for regulation

Substances are divided into two groups:

- **Category 1: confirmed endocrine disruptors**
  This category corresponds to the WHO's definition of endocrine disruptor.

  Substances are placed in category 1 when they are known to have caused ED-mediated adverse effects in humans or animal species living in the environment or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to cause adverse ED effects in humans or animals living in the environment.

[17] Joint DE-UK position paper: *Regulatory definition of an endocrine disrupter in relation to potential threat to human health*, BfR, May 2011.
[18] Specific Target Organ Toxicity (Repeated Exposure) Category 1.
[19] *Establishment of criteria for endocrine disruptors and options for regulation*, Danish Ministry of the Environment, Environmental Protection Agency, May 2011.

The animal studies must provide clear evidence of ED effects in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effects should be considered not to be a secondary non-specific consequence of other toxic effects.

However, when there is mechanistic information that raises doubt about the relevance of the effect for humans or the environment, category 2a may be more appropriate.

Substances can be allocated to this category based on:

- adverse *in vivo* effects where an ED mode of action is highly plausible;
- ED mode of action *in vivo* that is clearly linked to adverse effects *in vivo* (e.g. by read-across).

- **Category 2: potential endocrine disruptors**
  The definition of potential endocrine disruptors, also proposed by the WHO, is as follows: a potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations. This category is divided into two sub-categories: category 2a for suspected EDs and category 2b for substances with indications of ED properties. Further data must be provided for these substances placed in category 2a or 2b.

  - **Category 2a: suspected endocrine disruptors**
    Substances are placed in category 2a when there is some evidence for ED effects from humans or experimental animals, and where the evidence is not sufficiently convincing to place the substance in category 1.
    For example, when there are limitations in the study or studies that make the evidence less convincing, category 2a may be more appropriate.

    These endocrine disrupting effects should be observed in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effect should be considered not to be a secondary non-specific consequence of other toxic effects.

    Substances can be allocated to this category based on:

    - adverse effects *in vivo* where an ED mode of action is suspected;
    - ED mode of action *in vivo* that is suspected to be linked to adverse effects *in vivo* (e.g. by read-across);
    - ED mode of action *in vitro* combined with toxicokinetic *in vivo* data (and relevant non-test information such as read-across, chemical categorisation and (Q)SAR predictions).

  - **Category 2b: substances with indication of endocrine disrupting properties**
    Substances are placed in category 2b when there is some *in vitro/in silico* evidence indicating a potential for endocrine disruption in intact organisms.

    The evidence could also be observed effects *in vivo* where there is general but not specific evidence relating those to ED (i.e. that may, or may not, be ED-mediated).

3.2 Summary of proposals from certain stakeholders (non-governmental organisations and industry)

ANSES's analysis focused on published documents.

3.2.1 Summary of the proposals of the Pesticide Action Network Europe[20] (PAN EUROPE) on pesticides with endocrine disrupting properties

[20] PAN Europe position paper on criteria for endocrine disrupting pesticides, May 2011

A substance should be considered as having endocrine disrupting properties when effects on the endocrine system are observed, including effects secondary to other toxic effects. A known mechanism of action is not necessary.

The approach should be based on the hazard and not on risk assessment.

An in-depth review of the scientific literature should be undertaken for a hazard assessment of the studied substance. Data from independent organisations are preferred.

A modern study protocol needs to be developed by independent scientists working on endocrine disruption. In order to identify substances having endocrine disrupting properties, it is necessary to study all hormonal systems, perform low-dose testing, consider the notion of exposure window and therefore administer the substance to animals during their development.

Regarding the interpretation of study results, the effects observed in animals should by default be considered relevant for humans. The notion of threshold should not be used for endocrine disrupting properties. If there is doubt about the adverse effects of chemicals with endocrine disrupting properties, the precautionary principle must be used and the chemical withdrawn from the market until further studies are evaluated.

3.2.2 Summary of the proposals of the Chemical Health and Environment Monitoring Trust (CHEM Trust) and WWF European Policy Office[21] on the regulation of active substances with endocrine disrupting properties under REACh and the Plant Protection Products Regulations

In order to identify substances with endocrine disrupting properties, the proposed criteria are similar to those developed by PAN Europe. A classification of these substances is also proposed.

Substances are divided into four categories: The substances placed in category 1 (1A, 1B and 1C) are considered as having endocrine disrupting properties.

- **Category 1**
  - **Category 1A**
    Substances are placed in category 1A when there is enough evidence to be sure that the adverse effect observed is a direct consequence of disruption of the endocrine system. The causal mechanism has therefore been established with certainty.

  - **Category 1B**
    Category 1B can apply to substances as defined in category 1A, but where the causal mechanism is not known with certainty, although the adverse effect observed is strongly suspected to be mediated via disruption of the endocrine system.

  - **Category 1C**
    Category 1C can apply to substances as defined in category 1B, but where there is less evidence for endocrine-mediated effects, and/or where endocrine disruption is strongly suspected or known but where there is debate over whether the effects reported should be considered adverse. It would also include substances considered as having endocrine disrupting properties *in vivo* (e.g. effects on hormone levels, hormone-sensitive tissues, endocrine glands, auxiliary systems).

- **Category 2**

[21] CHEM Trust's Contribution to the Ongoing Debate on Criteria for EDCs, September 2011 and CHEM Trust and WWF-EPO proposals for the regulation of chemicals with endocrine disrupting properties under REACh (EC 1907/2006) and under the Plant Protection Products Regulation (EC no.1107/2009), December 2010

Substances are placed in category 2 when there are suspected endocrine disrupting effects on the basis of *in vitro* tests (e.g. receptor binding assays) or non-validated (quantitative) structure–activity relationship (Q)SAR models, unless there are sufficient data to negate the concerns.

3.2.3 Proposal from industry (European Centre for Ecotoxicology and Toxicology of Chemicals[22]) (ECETOC): Guidance document on the identification of endocrine disrupting effects

It should be noted that the ECETOC position proposes defining different scenarios depending on the type of evidence available, but this approach is proposed with the aim of initiating a risk assessment and not in the context of defining regulatory ED criteria as such.

It is considered that there is evidence of endocrine disrupting properties when the adverse effects observed in regulatory toxicology studies may be explained by screening/mechanistic studies, or *vice-versa*, when the indications of endocrine disrupting activity observed in screening/mechanistic studies may be confirmed by adverse effects found in regulatory toxicology studies. Various factors can be used to discriminate between endocrine disruptors according to their level of concern: relevance of the endocrine disrupting mechanism of action to humans, specificity of endocrine effects in relation to other potential toxic effects, potency of the substance to induce endocrine toxicity and exposure level.

A decision tree was developed in order to determine, using the various types of study available for a substance, whether it has endocrine disrupting properties, according to the definition of an endocrine disruptor issued at the Weybridge [UK] workshop in 1996: an endocrine disruptor is an exogenous substance that causes adverse effects in an intact organism, or its progeny, secondary to changes in endocrine function.

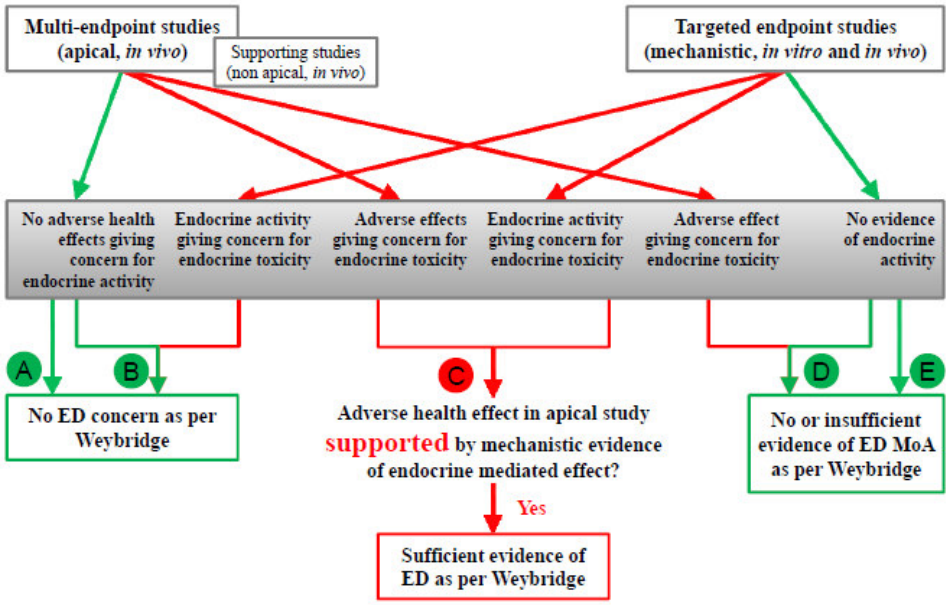
- **Scenarios A, B, D and E**: no ED concern or insufficient evidence of ED effects
  - **Scenario A**: no adverse effects on endocrine activity in general *in vivo* toxicology studies
  - **Scenario B**: no adverse effects on endocrine activity in general *in vivo* toxicology studies and positive results in targeted studies (mechanistic, *in vitro* or *in vivo*)
  - **Scenario D**: adverse effects on endocrine activity in general *in vivo* toxicology studies and no evidence of endocrine disrupting activity in targeted studies (mechanistic, *in vitro* or *in vivo*)
  - **Scenario E**: in the absence of other data, negative results in targeted studies (mechanistic, *in vitro* or *in vivo*)

- **Scenario C**: sufficient evidence of endocrine disrupting effects in laboratory animals
  Adverse effect(s) on endocrine activity in general *in vivo* toxicology studies and evidence of endocrine disrupting activity in mechanistic studies (*in vitro*, *in vivo*).

  The next step is to consider this effect's specificity, relevance to humans and potency:
  - If the adverse effect is not specific or is specific but not relevant to humans, the risk assessment will be based on non-endocrine disrupting effects. A specific adverse effect is defined as an adverse effect on the endocrine system occurring at dose levels lower than any other forms of adverse effects (e.g. neuro-, hepato-, cardio-toxicity).
  - If the adverse effect is specific and relevant to humans, and exposure is not negligible, the risk assessment will be based on the endocrine disrupting effect(s), applying variable safety factors based on the potency of the effect. The potency of an effect depends on several factors: dose at which the effect occurs, duration of exposure required to induce the effect, type and severity of endocrine effects, number of species affected.

[22] *Guidance on Identifying Endocrine Disrupting Effects,* ECETOC Technical Report no.106, June 2009 and Bars R. *et al.*, *Science based guidance for the assessment of endocrine disrupting properties of chemicals*, Regulatory Toxicology and Pharmacology 59 (2011) 37-46

Figure 1 (taken from ECETOC Technical report 106): Decision Tree for toxicology to determine whether a substance should be considered an endocrine disruptor according to the Weybridge definition (1996).



3.4 Summary of the regulatory consequences of the different proposals

Table 1 below provides a summary of the regulatory consequences of the different existing proposals for substances meeting the criteria established in each one, as described in Section 3.1, 3.2 and 3.3.

Table 1: Summary of the regulatory consequences of the different existing proposals

	Member States		NGOs		Industry
	UK-Germany	**Denmark**	**CHEM Trust**	**PAN Europe**	**ECETOC**
REACh	Identification as SVHC that may lead to an authorisation procedure	Cat 1: identification as SVHC that may lead to an authorisation procedure Cat 2: assessment	Identification as SVHC that may lead to an authorisation procedure	Identification as SVHC that may lead to an authorisation procedure	Assessment procedure
Biocides	Non-approval but exemption according to the rules defined in Article 5 (2)	Cat 1: non-approval but exemption according to the rules defined in Article 5 (2) Cat 2: assessment	Non-approval but exemption according to the rules defined in Article 5 (2)	Non approval but exemption according to the rules defined in Article 5 (2)	Risk assessment
Plant Protection Products	Non-approval	Cat 1: non-approval Cat 2: assessment (Art. 24 for substitution)	Non-approval	Non-approval	Risk assessment

3.5 Critical points and comparisons of the various proposals

The following critical points developed in the proposals were compared.

- ***Consideration of the concept of adverse effect***
  All the proposals agree on the need, if an ED is to be identified from a regulatory perspective, for this mode of action to give rise to effects considered as adverse. However, this notion of adverse effects is not defined in the same way in the various positions: PAN Europe believes that all biochemical alterations can be considered as harmful, while the other proposals (DK, DE-UK, CHEM Trust and ECETOC) are based on the IPCS[23] or Weybridge[24] definitions of EDs, and agree that the adverse effect must be a functional alteration of an intact organism.

- ***Consideration of ED effects in the presence of other toxic effects***
  This point is not discussed by the DE-UK position. The DK position proposes taking ED effects into consideration only if they occur either in the absence of other toxic effects, or in the presence of a toxic effect which is unlikely to be responsible for the ED effect. The ECETOC position also states, in its discussion of the assessment of ED properties, that it is necessary to differentiate the intrinsically specific ED effects from the non-specific ED effects. For PAN-Europe, an adverse effect should not be excluded because it is not the most sensitive (”lead effect”). This opinion is also shared by the CHEM Trust position, which states, however, in its proposal that the observed adverse effect must be a direct consequence of endocrine disruption.

[23] 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.

[24] 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.

- ***Consideration of the mode of action***
  All the positions state that it is necessary to have evidence of an ED mode of action. However, there are great differences in the level of evidence and type of data considered necessary to meet this criterion. PAN-Europe believes, for instance, that *in vitro* data are sufficient, whereas the ECETOC position is based on a developed definition of the mode of action requiring a detailed understanding of the sequence of events involved.

  It is emphasised in most positions that, given the complexity of the ED modes of action, it is extremely difficult to establish a mechanism of action fully and with certainty. The regulatory decision should not be based on too-high a level of evidence and understanding. However, the strictest regulatory consequences should be reserved for substances for which this ED type of mode of action can be established with a sufficient level of certainty.

- ***Relationship between adverse effects and mode of action***
  The PAN-Europe position does not clearly differentiate the concepts of adverse effect and ED mode of action, while the other positions mention that the relationship between these two concepts is an important discussion point. The DE-UK and ECETOC positions consider that this link should be biologically plausible and consistent. The DK and CHEM Trust positions rely on different levels of certainty to define the different (sub)categories (distinction between 1 and 2A for DK, between 1A and 1B for CHEM Trust). In line with this concept, they discuss the influence of the type of evidence available *(in vivo/in vitro/in silico*) on every aspect on the level of categorisation.

- ***Scope of the ED effects considered***
  The ECETOC position limits its analysis (which is not a proposal of criteria) to the best-studied hypothalamic-pituitary-gonad/thyroid axes. PAN-Europe recommends taking into account the effects on all the different hormonal targets, and interference with gene regulation and expression. The other proposals do not address this point.

- ***Consideration of the relevance to humans and non-target organisms in the environment***
  PAN-Europe believes that the experimental results should always be considered as relevant. The CHEM Trust and DE-UK positions mention that this relevance by default can be questioned in the event of contrary evidence. In the system of (sub)categories proposed by DK, this point and the doubts that may arise are taken into account in the categorisation.

- ***Consideration of the potency of the effects and/or a "cut-off" level***
  The DE-UK position prescribes considering as EDs any substances inducing these effects at doses below a "cut-off" level. This position is mainly based on the observation that assessment within a regulatory framework should not target effects occurring at excessive doses that are unrealistic for humans, and that a greater concern is to consider EDs with effects at levels close to exposure doses.

  It is noted that the CMR criteria do not include the concept of dose. The guidelines used, however, limit in practice the dose usually tested to 1000 mg/kg bw/day and it is only above this limit dose that the dose is considered to be excessive and not relevant to humans.

  The "cut-off" level proposed in the DE-UK position incorporates the existing regulatory threshold for the STOT-RE 1 category of the CLP Regulation (10 mg/kg bw/day for a 90-day toxicity study). Conversely, the DK position considers that the potency of the effect should not be taken into consideration in the criteria, by analogy with the identification of CMRs, which is based on the level of evidence and not the potency of the effect.

  This position is shared by CHEM Trust and PAN-Europe, which believe that the identification of an ED should be based on a hazard and is therefore independent of the dose producing the effects.

- ***Restriction to potential routes of exposure that are relevant for humans and organisms in the environment***
  The DE-UK position only takes into account the adverse effects identified by physiological routes of exposure (oral, dermal, inhalation), while PAN-Europe recommends not excluding any route of exposure. The DK position believes that data obtained by artificial routes should only be used to identify suspected or potential ED effects.

- ***Categorisation of substances based on effects***
  The DE-UK and PAN Europe positions propose the definition of a single ED category to which the different regulations would apply.

  The DK and CHEM Trust positions propose defining several categories and sub-categories. Both identify the level of available evidence as one of the main discriminators between the (sub)categories and propose defining different regulatory consequences according to the (sub)categories, with the most strictest consequences (identification as a SVHC in REACh, non-approval for biocides and plant protection products) being applied to the highest categories.

  It is noted that the ECETOC position also proposes defining different scenarios depending on the type of evidence available, but this approach is proposed with the aim of initiating a risk assessment and not in the context of defining regulatory ED criteria as such. This position is generally opposite to regulatory action that is not based on risk.

- ***Consideration of effects on the environment***
  Only the DE-UK position restricts itself to the definition of ED criteria for human health alone. The other proposals include the environmental aspect, but do nevertheless seem to apply more specifically to human health.

- ***Exclusion of CMR 1A/1B substances (Regulation (EC) no. 1272/2008)***
  The DE-UK position prescribes excluding CMR 1A/1B substances since they are already subject to the regulatory constraints stipulated for EDs in the three relevant regulations. The other proposals do not stipulate them.

Table 2 below summarises the various critical points considered in each proposal.

Table 2: Summary of critical points considered in the existing proposals

	Member States		NGOs		Industry
Critical points	**Germany-UK**	**Denmark**	**CHEM Trust**	**PAN Europe**	**ECETOC**
Categorisation of substances based on effects	Not addressed	Yes	Yes (depending on level of evidence)	Not addressed	Yes (different scenarios considered but no regulatory sub-categorisation proposed)
Consideration of effects on the environment	Not addressed	Yes	Yes	Yes (global approach but most comments seem rather to target human health)	Yes
Consideration of the potency of the effects and/or a "cut-off" level	Yes (STOT-RE 1 threshold)	No (analogy with the WHO definitions, OECD guide and CMRs and greater importance of the exposure window than the dose)	No (identification based on the hazard; independent of the dose producing the effects)	No (non-monotonic dose response, high individual variability and possible cumulative exposure, hazard-based approach)	Yes (considered in the risk assessment by assessment factors: for health, takes into account dose, duration of exposure, nature, incidence and severity of effects, the number of species affected)
Consideration of the concept of adverse effect	Yes	Yes	Yes (always necessary for category 1A or 1B)	Yes	Yes
Definition of the adverse effect and Adverse effect identified only on an intact animal	Yes (IPCS definition)	Yes (IPCS definition)	Yes (IPCS definition)	Yes (IPCS definition)	Yes (Weybridge definition)
Consideration of ED effects in the presence of other toxic effects	Not addressed	Yes (effects in the absence of other effects or not secondary to other effects)	Yes (consideration of ED effects even if it is not the critical effect)	Yes (consideration of ED effects secondary to other effects)	Yes (need to differentiate specific effects from non-specific effects)
Consideration of the mode of action	Yes	Yes	Yes	Yes (sufficient *in vitro* data)	Yes (mode of action = plausible described sequence of biological events, assessed according to specific criteria)

	Member States		NGOs		Industry
Critical points	**Germany-UK**	**Denmark**	**CHEM Trust**	**PAN Europe**	**ECETOC**
Relationship between adverse effects and mode of action (MoA)	Yes ("plausible/ coherent link", only in the discussion)	Yes (the level of plausibility between the adverse effect and the ED MoA distinguishes Cat. 1 from Cat. 2A) (no need for direct *in vivo* evidence of the adverse effect and the MoA)	Yes (the level of certainty of the ED MoA defines the 1A/1B/1C sub-categories)	No clear distinction is made between the two concepts	Yes (biological plausibility of the link)
Exclusion of CMR 1A/1B substances	Yes	Not addressed	Not addressed	Not addressed	Not addressed
Consideration of the quality of the studies	Yes (for identifying adverse effect)	Yes (study limitations to be discussed for Cat. 2A vs. 1)	Yes (all studies to be considered in the Weight of Evidence)	Not addressed	Yes (relevance, reliability and quality of data to be considered in the discussion)
Restriction to relevant routes of exposure	Yes (restriction to inhalation, oral and dermal routes and exclusion of parenteral route for identifying adverse effect)	Yes (subcutaneous, intravenous, intraperitoneal or other routes only taken into account for establishing a suspected or potential ED)	Not addressed	No (all relevant exposure routes without discussion)	Not addressed
Consideration of the relevance to humans and non-target organisms in the environment	Yes (for humans, presumed by default in the absence of contrary data)	Yes (doubts to be discussed during categorisation)	Yes (relevant by default, unless strong evidence to the contrary)	Yes (always relevant without discussion)	Yes (assessed in the mode of action)
Scope of the ED effects considered	Not addressed	Not addressed	Not addressed	Yes (all hormonal systems, including epigenetic changes)	Yes (guide considering only the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-thyroid axes)

4 IMPACT OF THE PROPOSALS MENTIONED IN SECTION 3: CASE STUDY APPLIED TO 24 CHEMICALS

The purpose of this case study is not to identify endocrine disrupting substances but to assess the impact of the positions described above in order to class substances according to the degree of certainty of their ED nature.

A categorisation of 24 active substances was established using the criteria proposed by some Member States, NGOs and industry (ECETOC), based on the available assessment reports, regulatory data (notably harmonised classifications of substances) and the literature. These chemicals were selected according to their toxicological properties that could be related to a mechanism of endocrine disruption.

The results shown in Table 3 are based on toxicological data and the mechanism of action, enabling the active substances to be classified in the different categories proposed.

As the active substances of plant protection products have already been addressed by a formal request (ANSES Opinion No. 2011-SA-0237 of 7 November 2011), those substances have not been included in this comparative study.

Table 3: Case study results

No.	Substance	CLP classification	Consequences according to the different proposals on the definition of endocrine disruption				
			DE-UK proposal	DK proposal	NGO proposals		Industry proposal (ECETOC)
					CHEM Trust /WWF	PAN-Europe	
1	DEHP 117-81-7	Repr. 1B; H360FD	No (yes if the cut-off is adjusted for duration of exposure)	Cat. 1	Cat. 1B	yes	Scenario C
2	DiBP 84-69-5	Repr. 1B, H360D; Repr. 2, H361f	No	Cat. 1	Cat. 1A	yes	Scenario C
3	Butyl-paraben 94-26-8	None	No (yes if the cut-off is adjusted for duration of exposure)	Cat. 1	Cat. 1B	yes	Scenario C
4	Bitertanol 55179-31-2	STOT RE 2 *, H373; Repr. 1B, H360D	Yes	Cat. 1	Cat. 1A	yes	Scenario B
5	Bisphenol A 80-05-7	Repr. 2, H361f; STOT SE 3, H335; Eye Dam. 1, H318; Skin Sens. 1, H317	Yes	Cat. 1	Cat. 1B	yes	Scenario C
6	Methyl tert-butyl ether 1634-04-4	Flam. Liq. 2, H225; Skin Irrit. 2, H315	No	Cat. 1/2A depending on appraisal of the data	Probable Cat.1B	yes	Scenario C
7	DBP (Dibutyl phthalate) 84-74-2	Repr. 1B H360Df	Yes	Cat. 1	Cat. 1A	yes	Scenario C

No.	Substance	CLP classification	Consequences according to the different proposals on the definition of endocrine disruption				
			DE-UK proposal	DK proposal	NGO proposals		Industry proposal (ECETOC)
					CHEM Trust /WWF	PAN-Europe	
8	4-nitro-phenol 100-02-7	STOT RE 2, H373; Acute Tox. 4, H332, 312, H302	Yes/No Depending on choice of endpoint and only if intact organism considered	Cat. 1/2A	Cat. 1A	yes	Scenario C
9	Bisphenol S 80-09-1	None	No	Cat. 2A	Probable Cat. 1C	yes	Scenario C
10	Bisphenol F 620-92-8	None	No	Cat. 2A	Probable Cat. 1B	yes	Scenario D?
11	Bisphenol B 77-40-7	None	No	Cat. 2A	Probable Cat. 1B	non	Scenario B
12	Isobutylparaben 4247-02-3	None	Yes/No (if the cut-off is adjusted for duration of exposure and if MoA confirmed)	Cat. 1/2A	Cat. 1B	yes	Scenario C
13	Propylparaben 94-13-3	None	No	Cat. 1/2A	Cat. 1B	yes	Scenario C

No.	Substance	CLP classification	Consequences according to the different proposals on the definition of endocrine disruption				
			DE-UK proposal	DK proposal	NGO proposals		Industry proposal (ECETOC)
					CHEM Trust /WWF	PAN-Europe	
14	DiNP 28553-12-0, 68515-48-0	None	No	Cat. 2B	Cat. 1C	yes	Probable Scenario D
15	DiDP 26761-40-0, 68515-49-1	None	No	Cat. 2B	Cat. 1C	yes	Probable Scenario D
16	p-tert butylphenol 98-54-4	None (proposed Repr 2; H361f in progress)	No	Cat. 2A	Probable Cat. 1C	yes	No categorisation possible
17	Bisphenol A Diglycidyl Ether 1675-54-3	Eye Irrit. 2, H319 Skin Irrit. 2, H315 Skin Sens. 1, H317	No	Cat. 2B	Cat. 2	yes	Probable Scenario B/D
18	Chlorocresol 59-50-7	Acute Tox. 4, H312 Acute Tox. 4, H302 Eye Dam. 1, H318 Skin Sens. 1 H317 Aquatic Acute 1, H400	No	Cat. 2B	Cat. 2	yes?	Probable Scenario E
19	Quaternium 15 cis/trans isomer 4080-31-3	None	No	No	No	no	Scenario A
20	Quaternium 15 cis isomer 51229-78-8	None	No	No	Probable Cat. 1C	no	Probable Scenario D

No.	Substance	CLP classification	Consequences according to the different proposals on the definition of endocrine disruption				
			DE-UK proposal	DK proposal	NGO proposals		Industry proposal (ECETOC)
					CHEM Trust /WWF	PAN-Europe	
21	n-Hexane 110-54-3	Flam. Liq. 2, H225 Repr. 2, H361f Asp. Tox. 1, H304 STOT RE 2 *, H373 Skin Irrit. 2, H315 STOT SE 3, H336 Aquatic Chronic 2, H411	No	Cat. 2B	No	yes	Scenario A
22	DEGME (Diethylene glycol monomethyl ether) 113-77-3	Repr. 2 – H361d	No	Cat. 2B	No	yes	Scenario A
23	Cybutryne 28159-98-0	Not classified	No	Cat. 2A	Cat. 2	yes	Scenario D
24	Toluene 108-88-3	Flam. Liq. 2, H225 Repr. 2, H361d Asp. Tox. 1, H304 STOT RE 2 *, H373 Skin Irrit. 2, H315 STOT SE 3, H336	No	No	Cat. 2	no	Scenario D

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Conclusions of the case study

The categories that only use the dose at which adverse effects appear as the discriminating criterion cannot be used to identify as endocrine disruptors substances that can be selected on the basis of other critical points. In the proposals based on weight of evidence, the analysis relies heavily on expert opinion, depending on the available data, and it is important to note the difficulties of categorising substances correctly in relation to the proposed criteria. Nevertheless, taking the weight of evidence into account overcomes the problem of identifying the relevant data to be used to define the LOAEL, or whether or not to adjust it depending on the exposure time, since the potency of the endocrine disrupting effect is not then compared with a threshold.

The use of several categories enables the regulatory response to be graduated.

It is important to note the differences that may be encountered in the amount and quality of available data according to the regulations, uses, quantities produced and data published in the literature.

Consequently, in all situations, studies dedicated to improved detection of an effect and an endocrine disruptor mechanism are needed, and changes in the regulatory requirements might be necessary.

In both cases (lack of adverse effects observed in a high-quality regulatory study, or difficulty in defining the endocrine disruption mode of action), the Danish proposal to identify endocrine disruptors as suspected (corresponding to category 2) and for which additional information may be required, appears relevant.

5 ANSES PROPOSAL ON SETTING CRITERIA FOR ENDOCRINE DISRUPTORS

5.1 Definition of an endocrine disruptor

ANSES presented to the different expert groups the definitions proposed by the WHO/ICPS, which are as follows:

- An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.

- A **potential** endocrine disrupter is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations.

Some experts said during the discussions that, for an endocrine disruptor, the definition “Exogenous substance or mixture that interferes[25] with the endocrine system, resulting in adverse effects on the health of an organism and/or its progeny" seemed more scientifically relevant.

In this situation, ANSES concluded that the definitions proposed by the WHO/ICPS for endocrine disruptors, cited above, are a credible basis for regulatory work.

5.2 Proposed criteria

Taking into account the critical points listed in Section 3.5, ANSES’s choice tends towards a proposal combining the following points:

5.2.1 Proposed scientific criteria

- Combination of different categories for considering graduated regulatory responses while proposing a general framework for implementing a broad regulatory strategy,
- Inclusion of environmental effects,
- Need to identify both the adverse effects on animals and information on the mode of action,
- Consideration of adverse effects on intact animals only. However, the mechanism of action may be identified in all the available experimental models.
- Consideration of endocrine disrupting effects when they occur in the absence of other toxic effects, or, if there is another toxic effect, the endocrine disruption effect should not appear secondary to the toxic effect,
- Consideration of the level of evidence of effects by preferring *in vivo* compared to *in vitro* assays,
- Not excluding 1A and 1B CMRs from a possible identification as EDs,
- Restriction to relevant routes of exposure for considering a proven endocrine disruption effect. On a case-by-case basis, toxicokinetic data that complement the available studies can support the data obtained by routes other than those representative of human and environmental exposures and allow them to be used for identifying a proven ED effect.

[25] According to these experts, the concept of interference must be understood as an interaction between a substance and the endocrine system; the interaction may occur with one or more of the steps involved in hormone regulation: synthesis, secretion, transport, bioavailability, receptor binding, transduction, regulation.

It should be noted however that some experts wished to make additional comments. According to them:

- if a compound has effects other than ED at low doses and shows ED effects at the higher dose tested, this can lead to this substance being classified as an ED compound. However, the risk assessment will be performed on the critical effect appearing at the lowest dose.
- any type of exposure route, including the subcutaneous route, may nevertheless be used insofar as the bioequivalence factors can be calculated, thus enabling the internal dose to be estimated.

ANSES's proposal for the scientific criteria for identifying an endocrine disruptor that are applicable to the REACh, Biocides and Plant Protection Products Regulations is based on that of the Danish Authorities[26] which separates the endocrine disrupting substances into two categories, confirmed and potential, with this second category being further divided into two sub-categories:

- ***Category 1: confirmed endocrine disruptors***

  Substances are placed in category 1 when they are known to have caused ED-mediated adverse effects in humans or animal species living in the environment or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to cause adverse ED effects in humans or animals living in the environment.

  The animal studies must provide clear evidence of ED effects in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effects should be considered not to be a secondary non-specific consequence of other toxic effects.

  However, when there is mechanistic information that raises doubt about the relevance of the effect for humans or the environment, category 2a may be more appropriate.

  Substances can be allocated to this category based on:

  - adverse *in vivo* effects where an ED mode of action is highly plausible;
  - ED mode of action *in vivo* that is clearly linked to adverse effects *in vivo* (e.g. by read-across).

- ***Category 2: potential endocrine disruptors***

  The definition of **potential** endocrine disruptors is based on the one proposed by the WHO.

  Category 2 is divided into two sub-categories:

  - Category 2a for suspected endocrine disruptors;
  - Category 2b for substances with an indication of endocrine disrupting properties.

  - ***Category 2a: suspected endocrine disruptors***

    Substances are placed in category 2a when there is some evidence for ED effects from humans or experimental animals, and where the evidence is not sufficiently convincing to place the substances in category 1. For example, when there are limitations in the study or studies that make the evidence less convincing, category 2a may be more appropriate.

[26] Establishment of criteria for endocrine disruptors and options for regulation, Danish Ministry of the Environment, Environmental Protection Agency, May 2011

These endocrine disrupting effects should be observed in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effect should be considered not to be a secondary non-specific consequence of other toxic effects.

Substances can be allocated to this category based on *:

- adverse effects observed *in vivo* and presumed to be caused by an ED mode of action;
- ED mode of action observed *in vivo* that is presumed to be linked to adverse effects *in vivo* (e.g. by read-across);
- ED mode of action identified *in vitro* combined with toxicokinetic *in vivo* data (and other relevant information such as read-across, chemical categorisation and (Q)SAR predictions).

* Some experts highlighted the need to clarify that substances could be allocated to this category if any of the conditions stated above were met.

- ***Category 2b: substances with indication of endocrine disrupting properties***

Substances are placed in category 2b when there is some *in vitro/in silico* evidence indicating a potential for endocrine disruption in living organisms.

The evidence could also be observed effects *in vivo* where there is general but not specific evidence relating those to ED (i.e. that may, or may not, be ED-mediated).

5.2.2 **Proposed criteria adapted to regulatory assessment**

ANSES recommends ensuring the consistency of the regulatory impact for the same substance, despite the differences between the texts concerned (Regulation EC No 1107/2009 for plant protection products on the one hand, and the REACh and Biocides Regulations on the other). Indeed, the existence of very strict non-approval criteria for plant protection substances should not lead to the exclusion of substances that may remain on the market for other uses, in a benefit/risk rationale. Harmonisation of the regulations therefore seems desirable.

In the current situation, ANSES proposes adding to the Danish position a regulatory criterion from the joint proposal by the United Kingdom and German authorities; **a limit applicable only to plant protection substances**. Substances with harmful endocrine disrupting effects, observed in mammals at a dose lower than 10 mg/kg bw/day, are placed in Category 1 and thus cannot be approved under the Regulation. This value, established to facilitate decision-making, is based on the CLP Regulation (STOT-RE 1 effect, see the table below, from Regulation (EC) No 1272/2008, Point 3.9.2.9.6., Table 3.9.2.), in which it applies to 90-day studies in mammals. For the endocrine disruption criteria, this value would apply regardless of the duration of the study. It could also be applied to birds.

Guidance values to assist in Category 1 classification

Route of exposure	Units	Guidance values (dose/concentration)
Oral (rat)	mg/kg body weight/day	C ≤ 10
Dermal (rat or rabbit)	mg/kg body weight/day	C ≤ 20
Inhalation (rat)gas	ppmV/6h/day	C ≤ 50
Inhalation (rat)vapour	mg/litre/6h/day	C ≤ 0,2
Inhalation (rat) dust/mist/fume	mg/litre/6h/day	C < 0,02

This effect limit for plant protection substances facilitates decision-making by limiting the scope for expert interpretation, thus respecting the principle enshrined in Regulation (EC) No 1107/2009: for a plant protection substance identified as having endocrine disrupting effects, non-approval applies unless it can be demonstrated that exposure is negligible. Characterising the effects reported at low doses would mean the exclusion of substances with the endocrine disrupting effects of greatest concern. For substances whose effects are observed above this dose, a risk assessment will be conducted, after which it will be established whether the risks are acceptable or unacceptable, within the meaning of Regulation (EC) No 1107/2009. If they are deemed to be acceptable, this could lead to the substance being approved, if appropriate in the category of substances that are candidates for substitution. Otherwise, the substance would not receive approval. The regulatory consequences for substances in this category would thus be equivalent to those for substances covered by the Biocides and REACh regulations.

Regarding the environment, the criteria for endocrine disrupting effects must be established on the basis of the assessment of tests based on the guidelines adopted at Community or international level. However, the methodologies for identifying a substance's endocrine disrupting nature for other non-target organisms are less developed and complete than for mammals. Indeed, the tests currently available are not always appropriate, especially considering the wide variety of species potentially affected. As these range from vertebrates to invertebrates, the endocrine mechanisms may differ (see the 2011 Report whose main points are listed in ANSES's Opinion No. 2011-SA-0237). In the current state of knowledge, the effect limit cannot therefore be applied to organisms in the environment.

The Regulation on plant protection products nevertheless offers the possibility, for the substances concerned, of requesting additional tests (on the mechanism of action, on different species, etc.) before approval. Work is being finalised in the OECD's EDTA working group, which is proposing a testing strategy for different living organisms in the case of suspected endocrine disrupting effects. This group also offers testing protocols specifically developed to show the effects of endocrine disruption on non-target organisms such as invertebrates, amphibians and fish. The OECD paper on the ranking of tests is referred to in Regulation (EC) No 1107/2009. It may therefore be used, when endocrine disrupting effects are suspected, to further knowledge of the potential effects in non-target organisms in the environment.

Moreover, the environmental protection objectives are targeted at populations. Yet in some cases it is not possible to establish a relationship between the causes of disruption and the effects observed *in situ.* Extrapolating effects observed in the laboratory to the field is difficult or impossible. Similarly, the observation of some effects in the laboratory can lead to false positives if no precautions are taken when interpreting the results. Indeed, some parameters may vary in the field due to natural changes (e.g. spermatogenesis). In such cases it can be difficult to distinguish these natural alterations from disruption due to chemical compounds. It may therefore be necessary to integrate field data.

Thus, the terms of the proposal are as follows:

- ***Category 1: confirmed endocrine disruptors***

  Substances are placed in category 1 when they are known to have caused ED-mediated adverse effects in humans or animal species living in the environment or when there is evidence from animal studies, possibly supplemented with other information, authorising a strong presumption that the substance has the capacity to cause adverse ED effects in humans or animals living in the environment.

  The animal studies must provide clear evidence of ED effects in the absence of other toxic effects or, if occurring together with other toxic effects, the ED effects should be considered not to be a secondary non-specific consequence of other toxic effects.

  However, when there is mechanistic information that raises doubt about the relevance of the effect for humans or the environment, category 2a may be more appropriate.

  Substances can be allocated to this category based on:

  - adverse *in vivo* effects where an ED mode of action is highly plausible;
  - and ED mode of action *in vivo* that is clearly linked to adverse effects *in vivo* (e.g. by read-across).

  Active plant protection substances whose adverse effects (observed *in vivo* in mammals and possibly in birds) are very plausibly caused by an endocrine disrupting mode of action after administration at doses less than or equal to 10 mg/kg bw/d, corresponding to STOT-RE 1 of Regulation (EC) No 1272/2008, are placed in Category 1[27]. The plant protection substances placed in this category cannot be approved under Regulation (EC) No 1107/2009 (plant protection products).

- ***Category 2: potential endocrine disruptors***

  The definition of **potential** endocrine disruptors is based on the one proposed by the WHO.

  Category 2 is divided into two sub-categories:

  - Category 2a for suspected endocrine disruptors;
  - Category 2b for substances with an indication of endocrine disrupting properties.

  - ***Category 2a: suspected endocrine disruptors***

    Substances are placed in category 2a when there is some evidence for ED effects from humans or experimental animals, and where the evidence is not sufficiently convincing to place the substances in category 1. For example, when there are limitations in the study or studies that make the evidence less convincing, Category 2a may be more appropriate.

    These endocrine disrupting effects should be observed in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effect should be considered not to be a secondary non-specific consequence of other toxic effects.

    Substances can be allocated to this category based on:

    - adverse effects observed *in vivo* and presumed to be caused by an ED mode of action;

[27] Addition from the joint United Kingdom and Germany proposal, applying only to plant protection products (Regulation (EC) No 1107/2009) in the context of this proposal.

- ED mode of action observed *in vivo* that is presumed to be linked to adverse effects *in vivo* (e.g. by read-across);

- ED mode of action identified *in vitro* combined with toxicokinetic *in vivo* data (and other relevant information such as read-across, chemical categorisation and (Q)SAR predictions);

- plant protection products' active substances whose adverse effects (observed *in vivo* in mammals and possibly in birds) are very plausibly caused by an endocrine disrupting mode of action after administration at doses higher than 10 mg/kg bw/d.

▪ ***Category 2b: substances with indication of endocrine disrupting properties***

Substances are placed in category 2b when there is some *in vitro/in silico* evidence indicating a potential for endocrine disruption in living organisms.

The evidence could also be observed effects *in vivo* where there is general but not specific evidence relating those to ED (i.e. that may, or may not, be ED-mediated).

5.3 Consequences of the criteria adapted for use in regulatory assessment proposed by ANSES for each of the three regulations

5.3.1 Consequences in the context of the Plant Protection Products Regulation

The regulatory consequences for plant protection substances according to the criteria based on the Danish proposal, with the addition of a regulatory criterion by ANSES, are shown in Table 4.

Table 4: Consequences in the context of the Plant Protection Products Regulation

Categories			**Criteria**	**Regulatory consequence**
1	Confirmed endocrine disruptors		- clear evidence of ED effects *in vivo* at doses less than or equal to 10 mg/kg bw/d[28] in the absence of other toxic effects, or jointly but not secondary. - no doubt about the relevance to humans or the environment based on information available on the mechanism	Active substances not approved
2	Potential endocrine disruptors	2A: Suspected endocrine disruptors	- in the absence of other toxic effects, or jointly but not secondary. - adverse effects *in vivo* with a presumed ED mode of action, or clear evidence of an ED effect observed at doses above 10 mg/kg bw/d - ED mode of action *in vivo* presumably linked to the adverse effects *in vivo* - ED mode of action *in vitro* associated with *in vivo* toxicokinetics data	Further tests Substance that may fall within the category of substances that are candidates for substitution
		2B: Substances with indication of endocrine disrupting properties	*in vitro/in silico* evidence	

The results of the case study on plant protection substances[29] including the criteria proposed by ANSES, are shown in Table 5 below.

[28] From tests on mammals and possibly birds
[29] Case study presented in the ANSES Opinion 2011-SA-0237 of 7 November 2011

Table 5: Results of the case study for plant protection substances

A substance cannot be authorised under Regulation (EC) No 1107/2009 if it belongs to one of the following categories:
- Category 1 according to the Danish proposal
- Category 1 according to the ANSES proposal
- Category "Yes" according to the DE-UK proposal.
- Categories 1A, 1B, 1C according to the CHEM Trust/WWF proposal

Substance	Former classification	New classification	Consequences according to the different proposals on the definition of endocrine disruption					
			DE-UK proposal	ANSES proposal	DK proposal	NGO proposals		Industry proposal (ECETOC)
						CHEM Trust /WWF	PAN-Europe	
Myclobutanil CAS: 88671-89-0	Xn, Repr. Cat. 3 R63 R22 R36 *	Acute toxicity, Cat 4, H302 Eye irritation, Cat 2, H319 Toxic for reproduction, Cat 2, H361d *	Yes	Cat. 1	Cat. 1	Cat. 1A	Yes	Scenario C (*risk assessment based on endocrine endpoint with a suitable safety factor)*
Flusilazole CAS: 85509-19-9	T, Carc. Cat. 3 R40 R22 R61 *	Acute toxicity, Cat 4, H302 Carcinogenicity, Cat 2, H351 Toxic for reproduction, Cat 1B, H360D *	Yes	Cat. 1	Cat. 1	Cat. 1A	Yes	Scenario C *(risk assessment based on endocrine endpoint with a suitable safety factor)*
Iprodione CAS: 36734-19-7	Xn, Carc. Cat. 3 R40 *	Carcinogenicity, Cat 2, H351 *	No	Cat. 2A	Cat. 1	Cat. 1A	Yes	Scenario C *(risk assessment based on endocrine endpoint with a suitable safety factor)*
Propyzamide CAS: 23950-58-5	Xn, Carc. Cat. 3 R40 *	Carcinogenicity, Cat 2, H351 *	No	Cat. 2A	Cat. 1	Cat. 1A	Yes	Scenario C *(risk assessment based on endocrine endpoint with a suitable safety factor)*

Substance	Former classification	New classification	Consequences according to the different proposals on the definition of endocrine disruption					
			DE-UK proposal	ANSES proposal	DK proposal	NGO proposals		Industry proposal (ECETOC)
						CHEM Trust /WWF	PAN-Europe	
Linuron CAS: 330-55-2	T, Carc. Cat. 3 R40 Repr. Cat. 2 R61 Repr. Cat. 3 R62 R22 R48/22 *	Acute toxicity, Cat 4, H302 Carcinogenicity, Cat 2, H351 Toxic for reproduction, Cat 1B(Df), H360Df Specific target organ toxicity - Repeated exposure, Cat 2, H373 *	Yes	Cat. 1	Cat. 1	Cat. 1A	Yes	Scenario C *(risk assessment based on endocrine endpoint with a suitable safety factor)*
Triflusulfuron-methyl CAS: 126535-15-7	Xn, Carc. Cat. 3 R40 §	Carcinogenicity, Cat 2, H351 §	No	Cat. 2A	Cat. 1	Cat. 1A	Yes	Scenario C *(risk assessment based on endocrine endpoint with a suitable safety factor)*
Chlorsulfuron CAS: 64902-72-3	Not classified *	Not classified *	No	Cat. 2A	Cat. 1	Cat. 1A	Yes	Scenario C *(risk assessment based on endocrine endpoint with a suitable safety factor)*
Propargite[$] CAS: 2312-35-8	T, Carc. Cat. 3 R40 R23 R38 R41 *	Acute toxicity, Cat 3, H331 Carcinogenicity, Cat 2, H351 Serious eye damage, Cat 1, H318 Skin irritation, Cat 2, H315 *	No	Cat. 2B	Cat. 2B	Cat. 1B	Yes	Scenario D
Glyphosate CAS: 1071-83-6	Xi, R41 *	Serious eye damage, Cat 1, H318 *	No	No	No	No	Yes	Scenario E

Substance	Former classification	New classification	Consequences according to the different proposals on the definition of endocrine disruption					
			DE-UK proposal	ANSES proposal	DK proposal	NGO proposals		Industry proposal (ECETOC)
						CHEM Trust /WWF	PAN-Europe	
Imazalil CAS: 3554-44-0	Xn, R20/22 R41 *	Acute toxicity, Cat 4, H302 Acute toxicity, Cat 4, H332 Serious eye damage, Cat 1, H318 *	No	Cat. 2B	Cat. 2B	Cat. 2	Yes	Scenario B
Carbetamide CAS: 16118-49-3	Xn, Carc. Cat. 3 R40 Repr. Cat. 3 R63 R22 §	Acute toxicity, Cat 4, H302 Carcinogenicity, Cat 2, H351 Toxic for reproduction, Cat 2, H361d §	No	Cat. 2B	Cat. 2B	Cat. 1B	Yes	Scenario D

* Harmonised classification (Regulation (EC) no. 1272/2008).
§ Non-harmonised classification, consolidated presentation in the Agritox database. The study took into account the October 2011 classifications. These may change depending on national and European assessments and the publication of harmonised classifications.
$ Unapproved substance

5.3.2 Consequences for products subject to REACh

For chemicals, the criteria proposed by ANSES are those of the Danish position. The regulatory consequences for products subject to REACh, according to the criteria based on it, are shown in Table 6.

Table 6: Consequences for products subject to REACh

Categories			Criteria	Regulatory consequence
1	Confirmed endocrine disruptors		- clear evidence of ED effects *in vivo* - in the absence of other toxic effects, or jointly but not secondary - no doubt about the relevance to humans or the environment from the information available on the mechanism	Substances that can be identified as SVHC (Article 57f) and that can therefore be subject to authorisation
2	Potential endocrine disruptors	2A: Suspected endocrine disruptors	- in the absence of other toxic effects, or jointly but not secondary - adverse effects *in vivo* with a presumed ED mode of action - ED mode of action *in vivo* presumably linked to the adverse effects *in vivo* - ED mode of action *in vitro* associated with *in vivo* toxicokinetics data	May be included in the CoRAP: Substances subject to Evaluation at the request of the MS/ECHA (not currently automatic)
		2B: Substances with indication of endocrine disrupting properties	*in vitro/in silico* evidence	

If the substances identified as confirmed endocrine disruptors can be identified as SVHCs thereby making them candidates for authorisation, for substances that are identified only as suspected endocrine disruptors, the only possible regulatory action is to be included in the CoRAP[30] at the initiative of a Member State or ECHA[31] so that the substance may be evaluated.

[30] CoRAP: Community Rolling Action Plan (triennial)
[31] ECHA: European CHemicals Agency

5.3.3 Consequences in the context of the Biocides Regulation

For biocidal products, the criteria proposed by ANSES are those of the Danish position. The regulatory consequences for biocidal products according to criteria based on this position are shown in Table 7.

Table 7: Consequences in the context of the Biocides Regulation

Categories			Criteria	Regulatory consequence
1	Confirmed endocrine disruptors		- clear evidence of ED effects *in vivo* in the absence of other toxic effects, or jointly but not secondary - no doubt about the relevance to humans or the environment from the information available on the mechanism	Non-approval but exemption according to the rules defined in Art 5 (2)
2	Potential endocrine disruptors	2A: Suspected endocrine disruptors	- in the absence of other toxic effects, or jointly but not secondary - adverse effects *in vivo* with a presumed ED mode of action - ED mode of action *in vivo* presumably linked to the adverse effects *in vivo* - ED mode of action *in vitro* associated with *in vivo* toxicokinetics data	Further tests
		2B: Substances with indication of endocrine disrupting properties	*in vitro/in silico* evidence	

Biocides are not approved if they have endocrine disrupting properties. They are identified using the criteria described in Article 57 (f) of the REACh Regulation.

AGENCY CONCLUSION AND RECOMMENDATIONS

Within the scientific community, there are a number of uncertainties and highly complex issues on which there is not currently a consensus about endocrine disruption. The level of knowledge is increasing, however, and any additional tests that may be required in a regulatory framework will help to improve it further. It should be noted that risk assessment is the most relevant scientific approach for estimating the effects on health and the environment, and should be the preferred approach in the regulations rather than the approach using hazard identification. As such, further integration of this approach in the regulation of plant protection products could be considered.

The proposal presented in Section 5 of this Opinion is based on the current state of scientific knowledge as well as regulatory requirements in terms of experimentation, including additional studies. It could be revised to reflect changes in the level of scientific knowledge, the development of new tests in particular on organisms in the environment, and regulatory requirements. Alternative *in vitro* methods, and molecular biology or modelling tools, could complement or substitute in some cases the *in vivo* methods, and research actions in these fields are required.

With regard to the current regulations, this proposal:

- for plant protection products' active substances, facilitates decision-making and enables substances with the endocrine disrupting effects of greatest concern to be excluded;
- for chemical substances (REACh), establishes procedures for identifying substances of very high concern (SVHC);
- for biocides, identifies the substances that should be excluded, while respecting the rules defined in Article 5 (2).

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