The Director General

Maisons-Alfort, 19 July 2016

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

on "the definition of scientific criteria for defining endocrine disruptors"

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES's public health mission involves ensuring 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 the necessary information concerning these risks as well as the requisite expertise 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 published on its website.
This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 19 July 2016 shall prevail.

On 9 May 2016, ANSES received a formal request from the Minister of the Environment, Energy and the Sea, responsible for international climate relations, to propose criteria for defining endocrine disruptors (EDs) that could be used to clarify the French contribution to current European Union discussions on this issue. While this request was being examined, on 15 June 2016 the European Commission (EC) announced a proposal for criteria for identifying EDs as well as several texts[1] proposing a draft amendment to the regulations in force concerning biocidal products and plant protection products, via draft delegated acts. ANSES therefore modified the scope of the original request in order to incorporate these draft delegated acts in the elements to be taken into account.

1. BACKGROUND AND PURPOSE OF THE REQUEST

In March 2012, ANSES published an opinion regarding a request for scientific and technical support for the revising of the European strategy on EDs. This opinion had been formulated following a request dated 3 February 2012 from the Directorate General for Food, the Directorate General for Health, the Directorate General for Risk Prevention, the Directorate General for Competition, Consumer Affairs and Fraud Control, and the Directorate General for Labour.

[1] Draft Commission Delegated Regulation (EU) No 528/2012. C(2016)3752 Project & Annex 1 / Commission Regulation (EC) No 1107/2009. C(2016)3751 Project & Annex 1 / COM (2016) 350 final / SWD (2016) 212 final.

Since 2012, various reports[2], position statements[3] and scientific publications[4] have added to the scientific, political and societal debate at EU level and among the Member States on the criteria for defining EDs.

A proposal by the European Commission (EC) was announced on 15 June 2016 concerning the definition of criteria for identifying EDs as well as several texts proposing a draft amendment to the regulations in force concerning biocidal products and plant protection products, via draft delegated acts.

In this context, the Minister of the Environment, Energy and the Sea, responsible for international climate relations, asked the Agency to participate in the EU discussions taking place on this subject. ANSES therefore decided to revise its opinion of 2012 in light of the evidence published since then, in particular the draft proposed by the EC.

The documents examined in the context of this request were therefore:

- The 2014 roadmap[5], which proposed four possible options for criteria for identifying EDs and three options relating to approaches to regulatory decision-making.
- The Communication by the EC and the draft delegated acts made public on 15 June 2016[6].

2. ORGANISATION OF THE EXPERT APPRAISAL

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

The response to this request was coordinated by the Risk Assessment Department and monitored by the Regulated Products Assessment Department. In view of the time constraints and the multiplicity of ANSES expert appraisal bodies concerned by this issue, it was decided to set up an Emergency Collective Expert Assessment Group (GECU) to deal with this request. This GECU met from 6 June 2016 to 4 July 2016.

[2] These include:

- EFSA, Scientific Opinion on the hazard assessment of endrocrine disruptors: scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. EFSA Journal, 2013, 11(3): 3132
- JRC scientific and policy reports: Key scientific issues relevant to the identification and characterization of endocrine disrupting substances. Report of the Endocrine Disrupters Expert Advisory Group, Sharon Munn and Marina Goumenou, 2013

[3] These include:

- Dietrich DR *et al.*, Chem Biol Interact. 2013 Sep 5;205(1):A1-5. Scientifically unfounded precaution drives European Commission's recommendations on EDC regulation, while defying common sense, well-established science and risk assessment principles.
- BfR workshop: Scientific principles for the determination of endocrine disrupting properties of chemicals – a consensus statement

[4] These include: Slama R et al., Environ Health Perspect; Scientific Issues Relevant to Setting Regulatory Criteria to Identify Endocrine Disrupting Substances in the European Union

[5] EC Roadmap.
http://ec.europa.eu/smart-regulation/impact/planned_ia/docs/2014_env_009_endocrine_disruptors_en.pdf

[6] Executive summary of the impact assessment. SWD(2016) 212 final.
Communication from the Commission to the European Parliament and the Council. COM(2016) 350 final
Draft Commission Delegated Regulation (EU) No 528/2012. C(2016)3752 project & Annex 1
Commission Regulation (EU) No 1107/2009. C(2016)3751 project & Annex 1

The Expert Committees (CESs) on "Plant protection products: chemical substances and preparations" (CES PPP), "Chemicals covered by the REACh and CLP Regulations" (CES REACh), "Characterisation of substance hazards and toxicity reference values" (CES Substances) and "Biocidal substances and products" (CES Biocides), and the Working Group on "Endocrine disruptors" (WG EDs) were all involved in the discussions.

3. ANALYSIS AND CONCLUSIONS OF THE GECU

The experts welcomed the publication on 15 June 2016 of the proposal by the European Commission (EC) for criteria for identifying endocrine disruptors (EDs). This proposal is based on the WHO/IPCS definition, taking into account the effects on humans and non-target organisms in the environment, which is essential for a comprehensive assessment of the effects of EDs. However, the experts expressed regret at the absence of a single, harmonised text on categorisation criteria applicable to all chemical substances, irrespective of their uses.

The experts noted that the proposal does not retain Option 1 as defined by the EC in the roadmap on EDs submitted for public consultation in 2014, which did not rely on any definition of EDs and maintained the interim criteria proposed by the regulations in force applicable to biocidal products and plant protection products. Option 4 was also excluded; the proposal thus rejects the principle of "potency". These two points are in phase with ANSES's previous opinions.

The current choice of the EC, corresponding in part only to Option 2, results in only "known" EDs and not "presumed" EDs being identified. The experts expressed regret at this choice. Option 3 differentiates the concepts of "known" EDs, "suspected" EDs and "endocrine active substances". This option would make it possible, for the identification of EDs, to take more fully into account the modes of action and data from *in vitro* approaches.

3.1. Analysis of the EC's proposed definition and criteria

3.1.1. Definition of EDs

The EC is proposing an identification of EDs based on a single category. However, as it reiterated in its roadmap, the WHO/IPCS definition of 2002[7], on which there is consensus, has two parts. Indeed, the WHO/IPCS defines an ED as:

"*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 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 second paragraph included in the WHO/IPCS definition defines a "suspected" ED (potential endocrine disruptor). The experts stress the importance of not separating these two components and retaining the identification of EDs in several categories.

Retaining the concept of a "presumed" ED (as proposed in Option 2 of the 2014 roadmap) is essential for more effectively taking uncertainties and the development of knowledge into account.

[7] Global assessment of the State of the Science of Endocrine Disruptors WHO/IPCS/EDC, 2002

In addition, breaking down this definition into three categories (as proposed in Option 3 of the roadmap) would enable a more flexible application of the regulations. Differentiated levels of management could thus be introduced depending on the uses and exposed populations. For example, a ban on "known" EDs, "presumed" EDs and "suspected" EDs could be considered in the regulations governing toys. In the case of the regulations applicable to plant protection products, only "known" and "presumed" EDs would be prohibited, and "suspected" EDs would be subject to management based on the risks.

3.1.2. The proposed criteria rejected by the GECU

3.1.2.1. EC proposal of 15 June 2016:

Concerning the criteria for identification, the rigorous application of only one part of the WHO/IPCS 2002 definition without taking "suspected" EDs into account leads to a very strict regulatory identification: a very high level of evidence is expected to define a substance as an ED and no uncertainty is permitted. The experts regret the lack of graduation in the level of evidence for demonstrating that a substance is an ED: often, the state of available knowledge is insufficient to be able to reach a firm and final conclusion at a given moment in spite of the body of presumptive evidence. The experts emphasise that the levels of evidence do not rely on the same types of studies[8], according to whether the focus is on the concept of adverse effect or the ED mode of action.

The EC proposes classifying an ED substance on the basis of the weight of scientific evidence by granting a very high credit to regulatory studies based on recognised international guidelines, to the detriment of non-standardised studies. It is therefore likely that only a few substances could be identified as ED by the strict application of these criteria, while models or experimental protocols that are not based on guidelines, used in good quality studies, could help identify ED substances and potentially ED substances.

In addition, despite the constant improvement in international guidelines, there is still a lack of relevant models and protocols for identifying some of the adverse effects and many of the endocrine disrupting mechanisms. Standardisation is a long process that results in a lag between scientific advances and their recognition at international level. These shortcomings have been identified by the Organisation for Economic Cooperation and Development (OECD) with regard to non-steroidal hormonal systems (OECD, 2012). They are even more obvious in environmental targets such as invertebrates. Indeed, the studies that follow the guidelines only concern vertebrates and therefore exclude 95% of biodiversity[9].

3.1.2.2. Option 1 of the 2014 roadmap:

This option equates to a status quo where the definition of an ED is not addressed, which is unacceptable in light of the scientific advances on the subject. This option, like the intermediate criteria, limits the concept of adverse effects to carcinogenic and/or reprotoxic effects, which is insufficient when attributing the occurrence of adverse effects to endocrine disruption. In particular, this option does not cover endocrine disruption in wild and domesticated animal species, which is unacceptable. By its very concept, ED classification should encompass humans and the environment (which includes all living species).

[8] Type of study means epidemiological studies, *in vivo* studies, *in vitro* studies, *in silico* studies, etc.

[9] Barnes, R.D., 1987. Invertebrate Zoology, 5th ed. Saunders, Philadelphia; Wilson, E.O., 1999. The diversity of life. Penguin, London. 406 pp.

3.1.2.3. Option 2 of the 2014 roadmap:

Option 2 is the one used as the basis for the EC's proposal. Nevertheless, Option 2 of the 2014 roadmap differs from the current proposal in that it integrates "presumed" EDs in addition to "known" EDs in the same category. The experts have not selected this option because it is binary and overlooks the uncertainties and graduations in the level of knowledge on chemicals, especially with regard to their ED nature.

3.1.2.4. Option 4 of the 2014 roadmap:

Option 4 is also excluded by the experts, who reject the principle of "potency", in agreement with ANSES's previous opinions. This concept, often related to the dose at which the effect appears (threshold effect), is complex and variable because it can also refer to the severity and/or amplitude of the effect.

In conclusion, the experts reject the EC's proposal relating to Options 1, 2 and 4 of the 2014 roadmap. Option 3 is the one that is recommended and discussed below by the experts.

3.1.3. The proposed criteria favoured by the GECU

3.1.3.1. The benefits of classification into several categories

Option 3 of the roadmap covers a number of key concepts on the identification of EDs that will be addressed in a specific section relating to the scientific issues (see section 4).
It mainly proposes distinguishing EDs into three categories ("known" EDs, "suspected" EDs or "endocrine active substances" that should be developed into "known", "presumed" or "suspected" EDs) and thus offers a better guarantee that all the data available on a substance at a given time are taken into account.

As with the current procedure for carcinogenic, mutagenic and reprotoxic (CMR) substances, a graduated approach would make it possible to more effectively take the uncertainties into account and facilitate the experts' judgment. In addition, this categorisation would allow tailored regulatory implementation. Different levels of management could thus be introduced according to the uses and exposed populations (for example, stricter regulations for toys, with a ban on "known", "presumed" and "suspected" EDs). Finally, as it is similar to the existing European classification system (see below), its application could be rapidly made operational.

3.1.3.2. Example of the classification system of Regulation (EC) No 1272/2008[10] known as the CLP Regulation

As an example, a substance is classified as a human reproductive toxicant in Category 1 when it is proved that it has adverse effects on sexual function and fertility or on the development of human beings (1A), or if there are data from animal studies providing a strong presumption that the substance is likely to have an adverse effect on human reproduction (1B).

It is classified in Category 2 when the results of human or animal studies are not sufficiently convincing to justify a classification in Category 1, but show an adverse effect on sexual function and fertility or on development.

[10] 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

The constant development of knowledge on the mode of action of substances justifies the establishment of several categories in order to be able to identify as early as possible a substance that may cause ED effects but with a level of evidence insufficient to classify it in Category 1.

3.1.3.3. Theoretical consequences of a CLP classification with only one category

If the level of evidence requested in the EC's proposal for EDs (one single category) were applied to the existing classification system (CLP Regulation No 1272/2008), few substances would be classified (see Table 1). Indeed, the level of evidence called for corresponds to a classification in Category 1A.

Table 1: Number of harmonised CMR substances until the 7th Adaptation to Technical Progress (ATP) of the CLP Regulation

Class / Category	C[1]	M[2]	R[3]
1A	239 (22%)	0	22 (8%)
1B	669 (61%)	422 (76%)	139 (47%)
2	183 (17%)	131 (24%)	132 (45%)

1/ Carcinogenic: induces tumours and/or cancer.
2/ Mutagenic: increases the frequency of inherited mutations in populations of cells and/or organisms.
3/ Reprotoxic: induces adverse effects on sexual function and fertility in adult men and women, as well as adverse effects on the development of their descendants.

Carcinogens are identified when the tested substance induces tumours. Despite the simple criteria, only 22% of substances with a harmonised classification for this hazard class are in Category 1A (see Table 1). For the hazard classes that are more complex to identify (that lack studies for indisputably identifying this hazard), no chemicals are classified in Category 1A for mutagenic substances, while 422 are in Category 1B and 131 in Category 2, and there are only 8% in Category 1A for reprotoxic substances.

As a comparison, if the CMR classification were only based on a single category as proposed by the EC for EDs, there would be no classification for substances such as formaldehyde (Category 2 mutagenic and Category 1B carcinogenic), tetrachloroethylene (Category 2 carcinogenic) and trichloroethylene (Category 2 mutagenic and Category 1B carcinogenic), despite the current consensus about their carcinogenic properties. Similarly, it would not have been possible to adopt the R1B classification of BPA for its presumed human reprotoxic effects.

Based on the harmonised CMR classifications of the CLP Regulation, it therefore seems likely that the criteria proposed by the EC would make it difficult or impossible to identify EDs.

3.2. Implementation of the identification of EDs

The EC's choice aims to define the criteria for identifying EDs according to specific constraints of implementation of the regulations on biocides and plant protection products. The EC proposal therefore goes beyond the single issue of identifying EDs in general, since it is accompanied by management recommendations in sectoral regulations. The EC's current proposal thus mixes the definition of criteria for identifying an ED with implementation.

For example, although necessary for plant protection product and biocide uses, the concept of non-target organism introduces a *de facto* distinction in how EDs are dealt with between these two regulations and the other European regulations (REACh, cosmetics, etc.). In addition, for plant

protection and biocide uses of the same chemical substance, the non-target organisms may differ. Lastly, for chemicals covered by the REACh Regulation, all species can be regarded as non-target.

Thus, with regard to biocides and plant protection products, the experts propose making a distinction between:

- The identification of an ED independently of its use, i.e. by not taking into account the concept of target or non-target organism,

- The conditions for the approval of plant protection or biocidal active substances that are ED for target organisms defined in each of the ad-hoc regulations.

In addition, the experts advocate that classification be performed by a single European body, which could be ECHA, to avoid any risk of divergence of classification for a given substance. The conditions for the authorisation of substances shall be the responsibility of the bodies or committees laid down by the various regulations concerned, on a common hazard identification basis on which there is a consensus.

It would also be desirable to propose more precise and operational criteria for classifying EDs in connection with the tools already available, such as the OECD conceptual framework for testing and assessment of endocrine disruptors[11]. This level of detail could be addressed in a subsequent guidance document. Indeed, the EC's current proposal incorporates elements that relate more to a technical guide that can be updated according to scientific advances than to more binding texts such as regulations.

Thus the level of evidence expected (and currently mentioned in Definition (3)(a), (b) and (c) of Sections A and B of the Biocides Regulation or 3.(3)(a), (b) and (c) of the Regulation governing plant protection products, (EC) No 1107/2009[12]) rather warrants clarification in this technical guide.

The level of evidence required for identifying certain adverse effects is defined in the CLP Regulation and described in its technical guide. It is the level of evidence of the ED mode of action that should be clarified in a dedicated technical guide. This work has been initiated by the OECD for oestrogenic, steroidal, thyroid and androgenic effects.

3.3. Regulatory application of ED criteria

The EC proposes amending the Regulation relating to plant protection products to introduce the concept of "negligible risks of exposure" for the approval of certain substances. This concept of approval in the event of "negligible risk of exposure" introduces additional ambiguity (given that this "negligible risk of exposure" is described as a lack of exposure of humans). In addition, the concept of negligible risk to the environment is not defined in the EC's proposed text.

With regard to biocides, this concept is already addressed in the regulations in force.

The experts are not in favour, for an ED, of the regulatory framework taking into account the concept of exposure or risk, given that it is difficult in the current state of knowledge to define a threshold below which the exposure or risk could be qualified as "negligible". These difficulties are due to specificities related to the modes of action of EDs ; the windows of vulnerability of exposed

[11] OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters (GD 150, August 2012)

[12] 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

populations (humans and other living species) and the possibility of non-monotonous dose-response relationships.

On the other hand, the experts are in favour of extending the principle of a regulatory framework for EDs based on the hazard for uses other than those applicable to biocides and plant protection products (cosmetic products, chemicals, etc.). Concerning "suspected" EDs, a risk assessment could be conducted prior to authorisation for the substance concerned.

3.4. With regard to the distinction between an ED effect for humans and the environment

The classification of an "endocrine disruptor" type substance is intended to cover humans and all other living species. It applies without distinction to human health and the environment, as was stressed in document C(2016)3751 and its annexes: "*Scientific criteria for the determination of endocrine disrupting properties of active substances, safeners and synergists, […], which are to ensure a high level of protection of both human and animal health and the environment*."

The characterisation of the adverse effects of biocidal and plant protection products is described in the annexes of the aforementioned documents in two separate sections relating to humans and non-target species. This semantic separation seems inadequate with regard to the state of the art of scientific knowledge and the experts therefore recommend that substances ultimately be classified as ED irrespective of whether they are ED for humans or ED for the environment.

In conclusion, it is important to distinguish:

- what relates to the identification, by a single body at European level, of an ED into different categories,
- what should be specified in a technical guide:
  - the level of evidence required for inclusion in each of the categories,
  - the type of study that can be used to assess the level of evidence,
- what relates to the management of the use of the EDs according to the exposed populations and what should be described in the dedicated regulations according to the uses. This includes:
  - the authorised substance categories (this may differ according to the regulations).
  - the target/non-target organisms.

4. RECOMMENDATIONS OF THE GECU

The experts furthermore recommend that the debate be continued on some of the aspects of definition and classification of EDs. These points are briefly mentioned below.

With regard to the delimitation of the hormonal system (concepts, definitions and consequences)

Certain endocrine disruptor modes of action (particularly related to reproductive functions) have thus far received attention and been the subject of much research and development of test methods. Accordingly, all endocrine functions (such as those related to steroid, thyroid, parathyroid and pancreatic hormones, etc.) of potentially exposed organisms should be taken into account, including humans and the species found in the environment. In addition, the concerns raised by EDs exceed the framework of reproduction, and it is important to integrate the different adverse effects in the identification of EDs by developing the necessary study protocols to allow this.

Finally, it seems necessary to clarify what is behind the term "endocrine system". Indeed, while a strict definition is given in the OECD guidance document, for example, the state of the art shows that it is today difficult to distinguish paracrine/autocrine/intracrine effects from endocrine effects. Thus, the hormone (or the chemical messenger) is not necessarily conveyed by the blood. The cells of a given organ interact through chemical signals that diffuse in the interstitial lymph fluid within the organ. These chemical signals can be what are known as "hormones" or "factors".

With regard to primary effects *versus* secondary effects

The experts agree that only the primary effects of endocrine disruption should be taken into account, and consider that when the observed adverse effect results from a non-ED mode of action, this should not be taken into consideration. However, in light of the tools available to identify the modes of action, the experts stress that it will be very difficult to demonstrate that an adverse effect is linked to a primary ED effect rather than being a secondary effect of a non-ED effect.

Nevertheless, the text of Option 3 should be simplified as follows: *"the experimental studies used to determine if a substance is an endocrine disruptor shall provide clear evidence that the endocrine-mediated adverse effects are not non-specific secondary consequences of other non-ED toxic effects".*

In addition, a substance showing an ED effect, not secondary to a toxic effect but at higher doses than another sign of toxicity (irritation for example), should still be identified as an ED. Indeed, taking into account the toxicity at the lowest dose will not necessarily protect from the identified ED effect, as the latter may have a non-monotonous dose-response curve.

5. AGENCY CONCLUSIONS AND RECOMMENDATIONS

ANSES endorses the conclusions and recommendations presented above on which there was a consensus within the Expert Group (GECU), whose members also sit on the following ANSES expert groups: the CESs on PPP, Biocides, REACh, Substances, and the WG on EDs.

ANSES thus recommends retaining the ED definition and identification criteria of Option 3 previously proposed in the Commission roadmap[13]. It also proposes, as stated in the National Endocrine Disruptor Strategy (SNPE), distinguishing EDs into three categories: "known" EDs, "presumed" EDs and "suspected" EDs.

This option draws on the WHO/IPCS definition of an ED while at the same time reflecting the level of uncertainty, outside any specific regulatory context. The Agency also recommends the application of criteria integrating the level of evidence, considering that such a scheme would enable the application of a single classification, and management tailored to the different regulatory contexts according to the uses and populations.

ANSES insists on the need to distinguish the definition and identification of an ED (with no distinction for humans or the environment), which should be carried out by a single body at European level, from the conditions for the approval of these substances according to their use.

[13] http://ec.europa.eu/smart-regulation/impact/planned_ia/docs/2014_env_009_endocrine_disruptors_en.pdf

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KEYWORDS

Endocrine disruptors, definition, criteria, classification, categories, target and non-target species, humans, environment.

ANNEX 1: PRESENTATION OF PARTICIPANTS

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisations.

EMERGENCY COLLECTIVE EXPERT APPRAISAL GROUP (GECU)

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