APPROVED: 16 December 2016

PUBLISHED: 20 December 2016

Outline of Draft Guidance Document for the Implementation of the Hazard-based Criteria to Identify Endocrine Disruptors

European Food Safety Authority

European Chemicals Agency

Acknowledgements: EFSA and ECHA wish to thank the Joint Research Centre for the support and preparatory work for this outline to the Guidance Document for the Implementation of the Hazard-based Criteria to Identify Endocrine Disruptors.

Table of contents

1. Introduction

In a letter addressed to both ECHA and EFSA, the European Commission (EC) requested both Agencies to develop a common Guidance Document for the implementation of the hazard-based criteria to identify endocrine disruptors (ED) in the context of Regulations (EC) No 1107/2009 and (EU) No 528/2012. The requested technical and scientific assistance is foreseen under Article 31 of Regulation (EC) No 178/2002 (for EFSA) and Article 76 (1) (d) of Regulation (EU) No 528/2012 (for ECHA). The scope of the request received from EC is limited to a Guidance Document on scientific hazard identification and does not cover other potential requests on issues potentially related to the evaluation of substances identified as endocrine disruptors.

According to the mandate from EC, ECHA and EFSA were asked to provide EC with an outline of the Guidance Document by the end of December 2016. This outline is shown below and was drafted jointly by both Agencies, in collaboration with the Joint Research Centre (JRC). It includes a detailed plan of the drafting process, including timelines, responsibilities, the foreseen consultations with relevant parties and information on the respective endorsement procedures of the Guidance by both EFSA and ECHA.

According to the mandate, the draft Guidance Document will be aligned with the agreed version of the criteria before it is released for public consultation will be initiated.

2. Scope of the Guidance Document

The Guidance Document will provide guidance for the implementation of the scientific criteria concerning the hazard-based identification of EDs in the context of Regulations (EC) No 1107/2009 and (EU) No 528/2012. The Guidance is intended be suitable for both applicants and regulatory authorities.

Although the (identical) criteria for EDs will formally apply only in the context of the Biocidal Products and Plant Protection Products legislation, the scientific approach(es) to be described in the joint Guidance could be relevant for other chemical substances, since the ED identification step will be based exclusively on the evaluation of the relevant hazardous properties of a substance.

The Guidance will focus on the data and information needed for ED hazard identification. It will also provide an indication on which information may be considered sufficient to conclude on the ED properties of a substance in accordance with the criteria. The evaluation approach will take toxicological and eco-toxicological information into account in an integrated manner and provide guidance for identifying data gaps that would trigger the need for additional data across the human health and environment domains.

With regard to the time available for developing the Guidance, best use will be made of available relevant documents/guidance and already developed tools in the context of EDs.

A limitation of the Guidance will be that its scope will only cover the so-called EATS pathways (Estrogen, Androgen, Thyroid and Steroidogenesis) which are the best characterized pathways. ECHA and EFSA are aware of the multitude of possible endocrine modes of action (MoA), however, the timeline provided by the mandate for drafting the Guidance is too short to include non-EATS pathways.

Regarding the groups of (non-target) organisms to be considered in the Guidance the coverage of the Guidance will be limited to vertebrates, including mammals, fish, birds, amphibians and reptiles. The main reason for this limitation is the short timeline provided by the mandate for drafting the Guidance.

3. Workplan and Responsibilities

3.1. The drafting process

The drafting process will be carried out by a joint team of scientific staff of ECHA and EFSA. They will receive scientific support from the JRC. The drafting process will involve face-to-face meetings in

order to harmonise a joint and efficient approach in the drafting process. The minutes of these meetings will be published. Several targeted consultations (see section 4) are envisaged during the drafting process. Once the draft Guidance has been completed it will undergo a public consultation. Following consideration of the comments received, the Guidance will be finalised by ECHA and EFSA.

3.2. Timelines

The time plan for the drafting process, consultations steps and finalisation of the draft for public consultation is presented in Table 1. In brief, the initial drafting process will last five months that will include at least one targeted consultation phase with an ad-hoc ECHA-EFSA ED Consultation Group (see section 4). Pending the adoption of the final criteria and conclusion of the scrutiny period by the European Parliament and the Council and the subsequent publication of the legislations defining the scientific criteria concerning the hazard-based identification of EDs in the context of Regulations (EC) No 1107/2009 and (EU) No 528/2012, the draft Guidance will be revised before undergoing public consultation. The time plan for the finalisation of the Guidance from the beginning of the public consultation is presented in Table 2.

4. Procedures for consultation of scientific bodies and information of Member States

An ad-hoc ECHA/EFSA ED Consultation Group will be created for supporting the drafting group. On ECHA's side the members of the Endocrine Disruptors Expert Group (EDEG) will be part of this Consultation Group. In order to ensure that experts with expertise in Plant Protection Products (PPP) are also involved in the process, EFSA will select an equivalent number of members representing MS risk assessment organisations and other stakeholders.

The drafting group will consult the Consultation Group on initial versions of (parts of) the draft Guidance Document. The drafting group may on specific issues also consult other scientific bodies, such as the EFSA Scientific Committee or the Plant Protection Products and their Residues (PPR) Panel and their working groups (WGs). No meetings of the Consultation Group are planned; written comments from the Consultation Group members will be considered by the drafting group. However, considering the time constraints, no responses to the individual comments will be made.

Member State Competent Authorities will be informed on the progress of the drafting at the regular meetings organised by the EC, in particular the Plants, Animals, Food and Feed (PAFF) meetings for pesticides and the Competent Authorities (CA) meetings for biocides. Furthermore, MS pesticides risk assessment organisations may also be updated on guidance development through the EFSA Pesticides Steering Network.

5. Procedures for consultation with stakeholders

This outline paper will be published for information.

The draft Guidance Document will be subject to a public consultation. This process ensures the opportunity for the public (including all relevant stakeholders) to comment and get involved in the development of this Guidance. The public consultation will be conducted by both Agencies together.

A report addressing the comments received during the public consultation will be prepared and published.

6. Procedures for adoption of the draft for consultation and of the final Guidance

The proposed process for the finalization of the Guidance Document is as follows.

a. Adoption of the draft Guidance Document for public consultation.
   Once the joint ECHA/EFSA/JRC drafting group considers that the draft Guidance Document is ready for public consultation it will be submitted for approval for public consultation by the management of both agencies. Each Agency will use its own internal procedure for this approval.

b. Public consultation.
The draft Guidance will be subject to public consultation. To this end, the draft Guidance will be made available on the Agencies' websites. Comments may be submitted using a webform that will be made available. Comments received will be considered for updating the Guidance after the public consultation.

c. Public event for presenting the draft Guidance.
The Agencies will consider with DG SANTE the feasibility of organising a public information event (meeting, webinar, etc.) at the beginning of the public consultation in order to present the draft Guidance.

d. Workshop with MS ED risk assessors.
A workshop with MS experts in evaluating endocrine disruption in the regulatory context will be organised for assessing the applicability of the Guidance. The workshop will be held shortly after the end of the public consultation. The outcome of the workshop will be published in the form of a report.

e. Follow up of the public consultation.
The drafting group will consider the comments from the public consultation and the feedback received from the workshop with MS ED assessors (see points b. and d. above) and will update the draft Guidance as necessary.

f. Consultation with the ECHA and EFSA scientific bodies.
Before the finalisation of the Guidance by the drafting group it is envisaged to have a consultation with the relevant scientific risk assessment bodies: the ECHA's Biocidal Products Committee, the EFSA Scientific Committee and PPR Panel, and the EFSA Pesticides Steering Network, for comments. The comments will be considered in the finalisation of the Guidance.

g. Endorsement as regulatory Guidance.
After agreement on the final document the drafting group will submit the guidance to both Agencies for approval. The Agencies will agree with DG SANTE on an ad-hoc procedure for endorsement in the regulatory context.

h. Publications.
As described above, the Guidance and three background documents will be prepared and published:
- Guidance on ED identification.
- Report on the Public Consultation, containing the received comments and the ways the comments have been addressed during the finalization of the Guidance Document.
- Report on the outcome of the workshop with MS risk assessors.
- Report describing the consultation with the Consultation Group.

7. Draft table of contents of the ED Guidance Document

I. Introduction and regulatory background

II. Scope

This section will outline the scope of the Guidance (as described above).

III. Definitions and general issues including reference to other Guidance Documents

In this section definitions of terms that are fundamental for the understanding of the Guidance will be provided, such as endocrine system; endocrine activity; endocrine disruption/disruptor (ED); endocrine mode of action (ED MoA); adverse effect; biological plausible link between endocrine disrupting activity and adverse effect; weight-of-evidence (WoE).

It is anticipated that there will be no need for development of new definitions. It presumably will be possible to draw on existing ones.

Reference will be made to publications relevant in the context of ED evaluation for regulatory purposes such as for example the reports of the EC ED expert advisory group, Guidance documents on biocides and pesticides, the EFSA Scientific Committee opinion on the hazard assessment of endocrine disruptors, the OECD Conceptual Framework (OECD CF) and Guidance Document (GD) 150, and relevant references on the use of systematic review methodology and WoE evaluation.

IV. Information sources for ED identification

This section will list the data and data sources that may inform on an ED MoA or (adverse) effect, covering both standard and non-standard test methods. This section will be built, to a large extent, on the *in vitro* and *in vivo* laboratory studies identified in OECD GD 150.

In this section, guidance will be provided on the main elements of applying systematic approaches in reviewing of the scientific literature.

IV.1. In vivo tests for identification of ED-relevant adverse effects

This section will describe the test methods relevant for the identification of adverse effects and associated endpoints possibly informative of an ED MoA. This will include an indication of which endpoint is informative on which of the EATS modalities.

In order to facilitate the evaluation of adverse effects, it will be described which apical adverse effects could be considered as (i) diagnostic for ED MoA and which could be considered as (ii) indicative for an ED MoA (i.e. possibly, but not exclusively linked to an ED MoA); and those adverse effects that in principle are (iii) not related to an ED MoA. These descriptions will be based on the OECD GD 150, updated with additional information sources and considering the JRC methodology. In this context, the currently ongoing revision of OECD GD 150 needs to be taken into account as well as the results of the workshop on thyroidal ED effects, which will take place in March 2017.

Two sub-sections are envisioned to cover human health and ecotoxicology. The sub-sections will identify which adverse effects (including targets and parameters) are indicative for endocrine activity for each of the EATS modalities.

IV.1.1. Human health

Mammalian and other toxicity studies relevant for human health evaluation, covering OECD CF levels 4 and 5.

IV.1.2. Ecotoxicology

Toxicity studies relevant for the evaluation of non-target vertebrates, covering OECD CF levels 4 and 5.

IV.2. Mechanistic information

Test methods informative on the ED MoA of a chemical will be identified, indicating the endocrine modalities/axes/pathways that each specific test is aimed at or informative on. As some test guidelines include optional endpoints, that are informative on alterations in the endocrine system, e.g. the level of hormones in the blood, the overview should therefore also indicate whether the endpoint is standard or optional (at least according to the test guideline(s)). Test guidelines identified in OECD GD 150 (focusing on EATS modalities) will be the main focus.

IV.2.1. Mechanistic in vitro tests

Covering OECD CF level 2 and other non-standardised studies

IV.2.2. Mechanistic in vivo tests

Covering OECD CF level 3, plus relevant mechanistic information from level 4 or 5 studies and other non-standardised studies.

IV.3. (Q)SAR, Read across and category approaches

This section will discuss the general approaches that are available, including chemical categories and read-across (e.g. OECD Toolbox), as well as available databases, (Q)SAR models and expert systems relevant to endocrine activity. The availability of several well-known software tools will be indicated (freely available, commercial package etc.).

IV.4. Epidemiological data, field studies and population models

This section will describe how epidemiology data can be used to support an association between an exposure and ED-related effects.

It will also be described how results from field studies, both from controlled field experiments as well as from field monitoring data, and from population modelling can be used in the evaluation.

V. Hazard identification strategy for endocrine disrupting properties

This section outlines a stepwise approach for hazard identification with regard to ED properties. The WoE methodology essentially follows the steps outlined by the scientific criteria for determining ED properties currently applicable to the Plant Protection Products (PPPs) (EC) No 1107/2009 and Biocidal Products (BPs) (EU) No 528/2012 Regulations.

The strategy aims to evaluate effects relevant to human health and non-target vertebrates in an integrative manner, recognising that there may be information available which is important for the evaluation of both.

The Guidance will describe ED hazard identification from two different starting points to ensure applicability of the proposed methodology for substances for which the available information differs in type. One approach will consider starting the evaluation with apical studies indicative of endocrine mediated adverse effects and will set out how to evaluate if, indeed, an endocrine mechanism would be the cause of the adverse effect observed. The second approach will consider starting the evaluation with ED-relevant mechanistic information and set out how to investigate whether the observed endocrine activity would result in adverse effects in intact organisms.

Evaluation of the information in a WoE approach

A schematic approach based on several steps will be developed as follows.

Gathering of relevant information with regard to adverse effect(s) and ED MoA(s) of action

In this section guidance will be given on the gathering of relevant data as described in section 4.

Evaluation of quality, reliability, reproducibility and consistency of the individual studies

In this section guidance will be provided on the evaluation of the relevant studies with regard to quality, reliability, reproducibility and consistency. For this purpose reference may be made to documents describing such evaluation approaches, as appropriate.

Evaluation and summary of the evidence for an adverse effect

This section will provide guidance on how to assess and conclude on the strength of evidence in terms of adversity relevant to (a) humans and (b) non-target vertebrates. This section will be written with the intention to apply to both human health and the environment, however, where differentiation with regard to humans and non-target vertebrates is required, these aspects will be considered separately.

Suggested content:

- how to evaluate conflicting results, e.g. both positive and negative results;
- consistency of the data;
- consideration of the pattern and coherence of the results between studies of a similar design and across different species;
- route of exposure, toxicokinetic and metabolism studies;
- concept of the limit dose, and international guidelines on maximum recommended doses and for evaluating confounding effects of excessive toxicity;
- evaluation of the relevance at population level for non-target vertebrates.

Evaluation and summary of the evidence for MoA(s)

This section will give guidance on how to assess and conclude on strength of evidence in terms of mode(s) of action for the EATS modalities. Evaluation of strength of evidence will consider both *in vitro* and *in vivo* mechanistic evidence.

This section will be written with the intention to apply to both human health and the environment. However, in each of the sub-sections below there may be need for a specific human health or environment section.

The following sub-sections are foreseen:

- how to evaluate mode of action for (anti)estrogenicity;
- how to evaluate mode of action for (anti)androgenicity;
- how to evaluate mode of action for thyroid effects;
- how to evaluate mode of action for steroidogenesis.

Integration of the evidence and evaluation of biological plausibility of a link between ED MoA and adverse effect

This section will provide guidance on how to integrate the available evidence on adverse effects for humans and non-target vertebrates with the evidence on (endocrine) MoA(s) in order to enable a conclusion on the existence of a biologically plausible link between the observed adverse effect(s) and the endocrine MoA(s).

Approaches will be described on how the available information on adversity and endocrine activity (*in silico*, *in vitro* and *in vivo* data including observational studies) should be considered together in a WoE approach, in order to conclude on the biological plausibility. The evaluation will cover human health and non-target vertebrates.

Identify uncertainties

This section will provide guidance on how to assess uncertainties. For this purpose reference will also be made to existing documents addressing this issue.

Conclusions on ED properties

This section will provide guidance on how to conclude on the ED properties of a substance in accordance with the ED criteria both with regard to human health and non-target vertebrates, considering WoE and identified uncertainties.

Indication will be provided on which information may be considered sufficient to conclude on the ED properties of a substance in accordance with the criteria.

For some substances the information identified as relevant may not be sufficient to reach a firm conclusion. For such cases, this section will provide guidance for different scenarios on what missing information should be generated in order to enable a conclusion on the ED properties of the substance in question in accordance with the criteria.

VI. Recommendations

As necessary

VII. References

Table 1. Time plan for the drafting process, consultations steps and finalisation of the draft ED Guidance for public consultation

Task	January	February	March	April	May	June
Drafting of Guidance Document by ECHA-EFSA-JRC ED Guidance team						
Consultation with the Consultation Group *						
Finalisation of draft Guidance for public consultation						

* Consultation with the Consultation Group: 14 d consultation period in April. Second consultation period in June optional, as necessary.

Table 2. Indicative time plan for the finalisation of the Guidance after the beginning of the public consultation

The draft Guidance will undergo public consultation after adoption of the legislations defining the scientific criteria concerning the hazard-based identification of endocrine disruptors in the context of Regulations (EC) No 1107/2009 and (EU) No 528/2012 by the European Parliament and the Council.
The lengths of the periods for public consultation and for revision of the draft Guidance after consultation periods may vary, depending on the period in which they may take place (holiday season covered) and on the amount of comments received.

Task	Months after beginning of the public consultation							
	1	2	3	4	5	6	7	8
Public consultation on the draft Guidance								
Public event for presenting the draft Guidance (if feasible)								
Consideration of comments from public consultation & revision of Guidance								
Workshop with Member State experts in assessing endocrine disruption *								
Consultation with ECHA and EFSA scientific bodies								
Consideration of comments received from the ECHA and EFSA scientific bodies								
Approval of the consolidated draft Guidance by EFSA and ECHA								
Launch of process for endorsement as regulatory Guidance								

***** Workshop with Member State experts in assessing endocrine disruption will take place in the indicated period