Identification of EDs under CLP

Criteria for hazard classification of EDs and allocation to hazard categories, incl. for Suspected EDs

March 2021

1 Introduction

The EU Commission announced in its communication on a Chemicals Strategy for Sustainability, on 14 October 2020[1], that it will propose legally binding criteria for the identification of endocrine disruptors (EDs) for application across all legislation to be included in the CLP Regulation. The Commission announced it will base this work on the WHO ED-definition and will build on the criteria already developed for endocrine disrupting biocides and plant protection products. Furthermore, it announced that the identification effort will be supported by efforts to get sufficient and appropriate information by strengthening the information requirements as well as screening and testing of substances.

In this briefing, we outline how horizontal ED criteria, including for suspected EDs, can be set up for the identification and classification of endocrine disruptors under the CLP Regulation, building on what was developed for the Biocidal Products and Plant Protection Products Regulations (BPR/PPPR). However, the BPR/PPPR ED criteria are set up to address known and presumed EDs only to meet the cut-off provision. They ignore suspected EDs, that is, substances for which there is some evidence of endocrine disrupting properties, but not sufficient to meet the ED criteria. This is a weakness which absolutely needs to be fixed when developing the new horizontal ED criteria. The latter should be in line with the approach for hazard identification and classification of carcinogenic and mutagenic substances, and substances toxic to reproduction (CMRs) under the CLP Regulation.

In addition, we also suggest classifying substances that show evidence for endocrine-active properties as this is a strong indicator of a potential for ED properties. This classification can serve as a tool to prioritize substances for evaluation of their ED properties, and to inform companies and the public about chemicals that may have the potential for being endocrine disruptors. For more details on how to better identify and regulate EDs and Suspected EDs, we refer to the publications from CHEM Trust, ClientEarth, and EDC-Free Europe mentioned below in section 2.1.

[1] https://ec.europa.eu/environment/pdf/chemicals/2020/10/Strategy.pdf

2 Horizontal ED classification criteria, including categories for Suspected EDs and substances showing endocrine activity

2.1 Background and context for horizontal ED identification

In September 2020, the coalition EDC-Free Europe presented its key recommendations[2] for a reformed European regulatory framework on endocrine disrupting chemicals (EDCs). These recommendations follow publications from coalition partners; CHEM Trust's policy paper: "A new path for EU control of Endocrine Disruptors"[3] and ClientEarth's action plan for the EU institutions and States: "3 actions to protect people and wildlife from EDCs"[4].

One central element in these papers is the establishment of horizontal criteria for the identification of substances with endocrine disrupting properties - endocrine disruptors (EDs) - as well as their categorisation according to the level of available evidence for these properties. Lack of data is particularly common for information relating to ED properties. Therefore, to reflect the level of evidence for ED properties, categories are needed for Known (Category 1 A), Presumed (Category 1 B) and Suspected EDs (Category 2). The latter concerns substances for which there is some evidence on endocrine disrupting properties, although not sufficient to meet the criteria for an ED Category 1A or 1B. To date, only criteria for the identification of endocrine disrupting biocides and plant protection products (herein referred to as pesticides) have been established under the BPR/PPPR.

Endocrine disrupting substances are also identified under the chemicals legislation REACH as Substances of Very High Concern (SVHC) on the basis of the WHO definition and recommendations from the Commission Endocrine Disrupters Expert Advisory Group (EU Commission Joint Research Centre (JRC) report)[5].

However, horizontal criteria for ED identification, including categorisation according to the level of evidence, that can be applied to chemical substances under all regulatory domains, have not yet been established. This creates a barrier to consistent and effective regulation of endocrine disrupting substances across all sectors of EU law, which an extension of the current REACH or BPR/PPPR approach would not be sufficient to overcome.

The process of establishing criteria for identification of endocrine disrupting biocides and pesticides has been lengthy and the subject of intensive discussions between authorities, industry, academia, NGOs and other stakeholders. Against this background, CHEM Trust proposed to use the current criteria for identification of endocrine disrupting biocides and pesticides and the accompanying guidance document[6] as the basis for setting up new horizontal ED criteria. However, this approach still has some limitations that should be addressed. This was confirmed recently by Boberg et al.[7],

[2] https://www.env-health.org/wp-content/uploads/2020/09/September-2020-EDC-Free-Europes-key-recommendations-for-a-reformed-European-regulatory-framework-on-EDCs.pdf
[3] https://chemtrust.org/wp-content/uploads/CHEMTrust-newEDPolicy-July2020.pdf
[4] https://www.documents.clientearth.org/wp-content/uploads/library/2020-09-16-3-actions-to-protect-people-and-wildlife-from-edcs-ce-en.pdf
[5] https://publications.jrc.ec.europa.eu/repository/bitstream/JRC79981/lbna25919enn.pdf

[6] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311

[7] https://doi.org/10.1016/j.envint.2020.105996

who experienced the limitations when using the approach for ED identification set under the pesticides regulation to evaluate the ED potential of the industrial chemical butylparaben.

2.2 The need for horizontal criteria acknowledging current data gaps hindering ED identification

The WHO definition for an ED is commonly accepted as the basis for the EU regulatory approach on EDs. However, in order to identify a substance as an ED in a regulatory context, it is useful - if not necessary - to specify the data requirements and the level of evidence for ED properties that need to be attained. Setting up such specific ED criteria facilitates a transparent, consistent, and coherent implementation of the law, and ensures that early scientific warnings are taken up in the regulatory domains.

However, for many chemical substances the lack of safety data is a common issue. This is particularly the case for information relating to ED properties. The lack of adequate data is due in part to general gaps in legislation on chemicals as for example, industry is not always obliged to produce or collect data on the chemicals they place on the market. And when data are available, many of them are old and/or from tests not conducted according to current standards or more importantly, they have not specifically examined ED properties. Furthermore, test methods to predict certain endocrine disrupting properties have only recently become available. However, these recent test methods do not cover all ED properties and in addition, chemical manufacturers or users have not yet been required to use the newest methods.

As a result, when data are available, they are often not sufficiently comprehensive to meet the existing BPR/PPPR ED criteria. This is the case for many biocide and pesticide substances lined up for assessment. It will take many years and a lot of resources to gather enough data enabling comprehensive assessments of substances to possibly meet the BPR/PPPR ED criteria. In the meantime, human health and the environment will not be adequately protected.

This is why new horizontal ED criteria must allow to reflect the current state of knowledge and offer more flexibility than the current biocides/pesticides ED criteria and the accompanying ECHA/EFSA guidance. Therefore, a category of suspected EDs should be part of the new horizontal ED criteria, implementing the full WHO ED-definition[8]. Substances for which there is some evidence for ED properties, but not enough to meet the criteria for a Known/Presumed ED, should be allocated to a category of Suspected EDs. This is fully in line with the approach for CMR-substances in the CLP Regulation.

[8] IPCS, 2002: *An endocrine disruptor 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 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.

2.3 The need for an integrated approach for human health and environment

It is well known that the hormonal system is well-conserved across vertebrate species with little variation[9]. Thus, effects on the endocrine system in one vertebrate species is predictive for endocrine disrupting effects in other vertebrate species, unless appropriate scientific evidence clearly demonstrates the opposite. Therefore, evidence based on human and animal data for the evaluation of human health effects may also be relevant for the evaluation of environmental effects, as well as animal data for the environmental assessment may also be relevant for the assessment of human health effects. And in general, when effects on the endocrine system are detected in one species, it should always be carefully considered whether it may be relevant to suspect endocrine disrupting effects in other species, regardless of whether these are vertebrates or invertebrates. ED effects are more uncertain when it comes to invertebrates. Since knowledge on endocrine disruption is mainly based on knowledge of the function of vertebrate hormones, which are often absent or are quite different in invertebrates, extrapolation of effects in invertebrates to vertebrate species can be challenging. Nevertheless, clear endocrine-related adverse effects are found in invertebrates after exposure to chemicals and should be examined as they may indicate that these chemicals have the potential to be endocrine disrupting for other species. As long as there are big gaps in our knowledge of invertebrate species, a more cautious approach is preferred that assumes that ED effects are relevant to invertebrates, unless the opposite has been clearly demonstrated.

Therefore, the new horizontal ED criteria should be based on an integrated approach for human health and the environment.

2.4 The need to address substances which show endocrine-active properties

Like adverse effects, endocrine activity is an important part of the current EU definition of an ED. Thus, endocrine activity is a strong indicator of a potential for endocrine disrupting properties. Standard information/data requirements under some pieces of EU legislation are currently being revised in order to include *in vitro* test methods for prediction of endocrine-active properties. This should make it possible to increase the evidence base for the identification of substances with endocrine-active properties, and to prioritise substances for the further evaluation.

Thus, in addition to the horizontal ED classification allocating substances to Category 1 and 2, a hazard category 3 for endocrine activity should be established. Substances showing endocrine-active properties in tests for endocrine activity not placed in Category 1 or 2, should be allocated to category 3 for endocrine activity. Such a Category 3 could trigger a more in-depth ED assessment process, increase awareness on possible adverse effects, and also be a tool to prioritize substances for evaluation of their ED properties. Furthermore, it will contribute to the provision of transparent information to companies and the public about chemicals that have shown endocrine-active properties, and which can be considered potential endocrine disruptors.

9 Ankley, G.T. and L.E. Gray (2013), https://doi.org/10.1002/etc.2151.

2.5 The proposal: integrated ED classification criteria with three hazard categories

According to the ED criteria in the BPR and PPPR and the ECHA/EFSA Guidance, a substance shall be considered as having endocrine disrupting properties that may cause adverse effects in humans "if it meets all of the following criteria, unless there is evidence demonstrating that the adverse effects identified are not relevant to humans (or non-target organisms):

a) *it shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;*

b) *it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;*

c) *the adverse effect is a consequence of the endocrine mode of action.*

Point (c) above should be understood as: *there is a biologically plausible link between the endocrine activity (the endocrine mode of action (MoA)) and the adverse effect.*

These criteria are based on the text of the WHO-definition of an ED and the WHO-definition of adverse effects and thus, only an introduction of these definitions into EU legislation. The interpretation on how to define the level of evidence required for a legally binding identification as ED is set by the accompanying ECHA/EFSA guidance document.

Thus, the WHO definitions and the guidance document are the natural starting points for defining ED criteria under the CLP. To ensure coherence and consistency in legislation, they, however, need to be refined in order to respect the approach followed by the CLP for the other hazard classes. This is in particular the case considering the level of evidence, and the subsequent allocation to hazard categories for being in line with the approach for CMR substances.

This means that the full WHO ED-definition, which also includes potential EDs, and the WHO definition of adverse effects, must form the basis of the new horizontal criteria for legally binding identification and classification of EDs, with allocation to hazard categories in line with the CMR criteria, and supported by a new guidance document. Furthermore, substances with evidence for endocrine activity may indicate a potential for endocrine disrupting properties and therefore be useful for the overall ED identification process. Therefore, they should also be classified and allocated to a hazard category 3.

For the purpose of classification, the hazard class, Endocrine Disruption, is differentiated into ED Category 1 & Suspected ED Category 2, and Category 3 for endocrine activity.

We therefore propose the following new horizontal ED criteria, which integrate the assessment for human health and environment and classify substances as an ED Category 1, including Known (Category 1A) and Presumed (Category 1B)) EDs, or as a Suspected ED, Category 2, according to the strength of evidence for the ED properties. See also fig. 1.

- Category 1: Endocrine Disruptor

  (Category 1A: Known ED & Category 1B: Presumed ED)

- Category 2: Suspected Endocrine Disruptor

Substances showing endocrine-active properties are allocated to Category 3 for endocrine activity:

- Substance showing endocrine activity

Substances that meet the ED criteria are allocated to one of two categories based on evidence available for the ED properties and additional considerations in a weight of evidence approach described in a targeted guidance document. The proposed criteria are based on the WHO definition, the current biocides and pesticides ED criteria and are in line with the current CMR criteria. In addition, the evidence of endocrine activity is captured by an additional Category 3. The criteria also recognize and take into account advances in science and new identification methods, meaning criteria are prepared for a future with an increased use of non-test methods to support or even replace animal testing. The criterion for an ED Cat. 1 corresponds to the ED criterion in the BPR/PPPR regulation.

PROPOSED CLASSIFICATION CRITERIA FOR ENDOCRINE DISRUPTION

For the purpose of hazard classification for endocrine disruption, substances are allocated to one of three categories.

CATEGORY 1: Endocrine Disruptor (ED)

Substances are classified in Category 1 for endocrine disruption when they are known or presumed to have produced endocrine-mediated adverse effects in humans or population-relevant endocrine-mediated adverse effects in animal species living in the environment, or when there is evidence from experimental studies (*in vivo*), possibly supported with other information (e.g. (Q)SAR, AOPs, analogue and category approaches), to provide a strong presumption that the substance has the capacity to cause endocrine-mediated adverse effects in humans or population-relevant endocrine-mediated adverse effects on animal species living in the environment.

A substance shall be considered as having endocrine disrupting properties, i.e. causing endocrine-mediated adverse effects, if:

a) *it shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;*

b) *it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;*

c) *there is a biologically plausible link between the endocrine activity and the adverse effect.*

The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily based on human data (Category 1A) or on animal data (Category 1B).

Category 1A: Known endocrine disruptor

The classification of a substances in Category 1A is largely based on evidence from humans /animal species living in the environment. This could e.g. be epidemiological studies, case-reports, or environmental field studies, possibly supplemented with other information.

Note: as for CMR-substances, for the vast majority of substances there will not be sufficient data for classification in Category 1A[10].

[10] An example of an exception is e.g. DES (Diethylstilboestrol) that in known to cause endocrine disrupting effects in humans.

Category 1B: Presumed endocrine disruptor

The classification of a substance in Category 1B is largely based on data from experimental studies *in vivo*. This could e.g. be animal experimental studies, possibly supplemented with other information.

Substances can be allocated to Category 1 based on:

- Reliable evidence from humans or from animal species living in the environment where it is plausible that the observed adverse effects are endocrine-mediated, or
- Experimental studies where it is plausible that the observed adverse effects are endocrine-mediated, or
- Experimental studies showing endocrine activity *in vivo* predicted to have a biological plausible link (e.g. through (Q)SAR, AOPs, analogue and category approaches) to adverse effects *in vivo*.

CATEGORY 2: Suspected Endocrine Disruptor

Substances are classified in Category 2 for endocrine disruption, when there is some evidence for endocrine-mediated adverse effects, i.e. relating to adverse effects, endocrine mode of action or to a plausible link - from humans, animal species living in the environment or from experimental studies, possibly supplemented with other information - and where the evidence is not sufficiently convincing to place the substance in Category 1.

If deficiencies in the study (or studies), or in demonstrating a biologically plausible link, make the quality of evidence less convincing, Category 2 could be the more appropriate classification.

Substances can be allocated to Category 2 based on:

- Evidence from humans or from animal species living in the environment where it is suspected that the observed adverse effect is endocrine-mediated, or
- Experimental studies where there is a biologically plausible link that the observed adverse effects are endocrine-mediated but where, for example, specific weaknesses in study design (e.g. limitations in relevant ED endpoints), or execution weaken this conclusion, or
- Experimental studies *in vivo* where it is suspected that the observed adverse effects are endocrine-mediated.
- Experimental studies showing endocrine activity *in vivo* which is suspected to be linked to adverse effects *in vivo* (e.g. through (Q)SAR, AOPs, analogue or category approaches), or
- Experimental studies *in vivo* showing endocrine activity but for which the link to an adverse effect is uncertain, or
- Experimental studies *in vitro* showing endocrine activity, combined with toxicokinetic *in vivo* data, linked to adverse effects in *vivo* (e.g. through Q(SAR), AOPs, analogue and category approaches) but for which the link is suspected.

CATEGORY 3: Substance showing endocrine activity

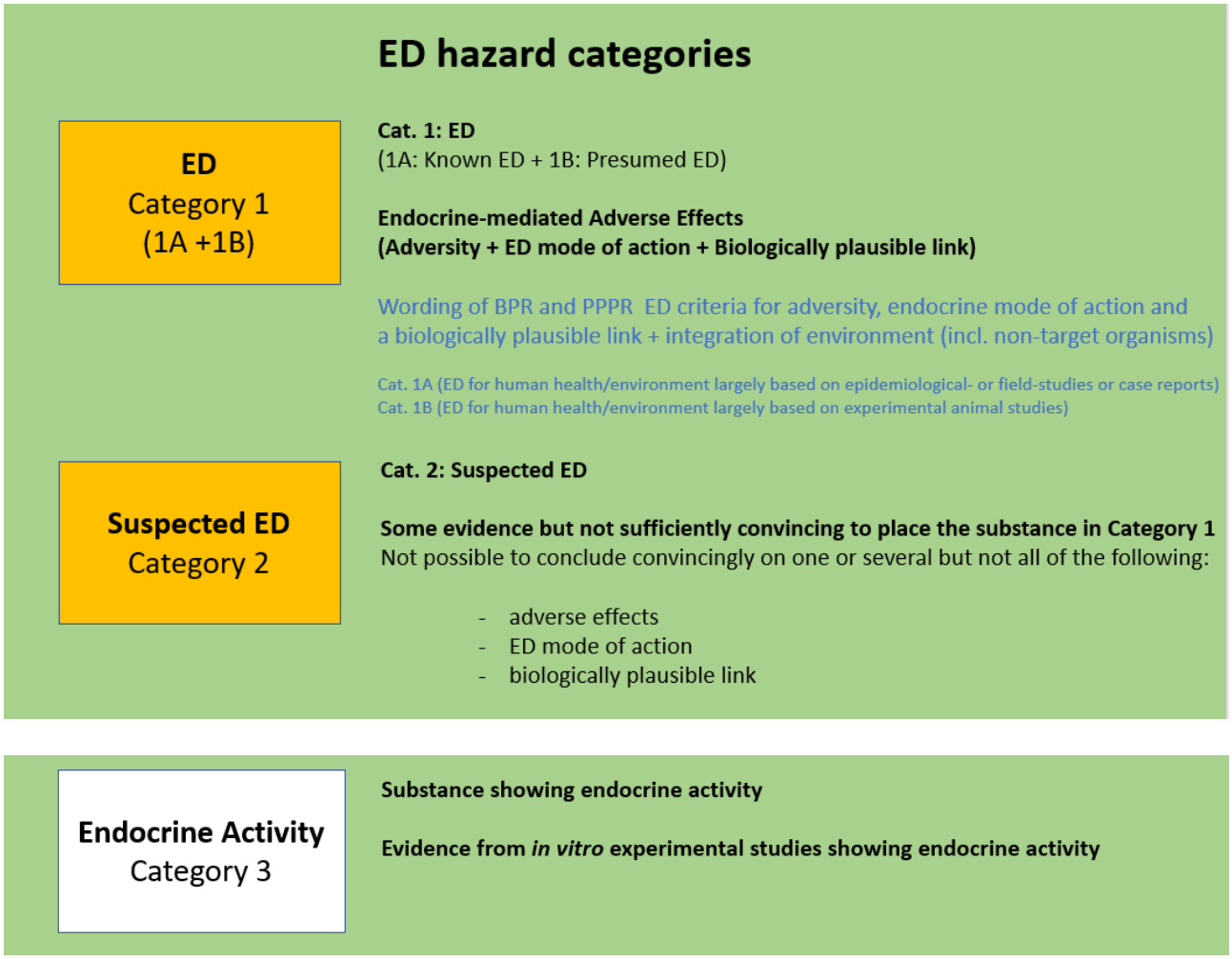
Substances are classified in the Category 3 for endocrine activity, if they have shown endocrine activity in vitro, and are not placed in Category 1 or 2.

Substances can be allocated to the Category 3 for endocrine activity based on:

- Evidence from *in vitro* experimental studies showing endocrine-active properties*.

  ** The evidence comes from the in vitro tests specified for ED modalities or similar tests in the information/data requirements (recently updated or under update).*

Fig. 1 – Simplified presentation of the ED Hazard Categories



2.6 Assessment of evidence & required level of evidence for ED hazard categories

Identification of ED properties should be based on **all available data**, which means that peer-reviewed academic studies must be included in the analysis alongside data from industry. Latest advances in science must be taken into account in the ED assessment.

The proposed approach for horizontal criteria is building on the current BPR/PPPR ED criteria and the accompanying guidance document which still have limitations, e.g. all hormonal axes and endocrine mechanisms and thus some aspects of endocrine disruption are not covered. The guidance focuses on a limited number of endocrine mechanisms operating via estrogenic/androgenic/thyroid/steroidogenic (EATS) modalities. Even though the guidance does not prevent including studies reporting adverse effects through other endocrine modalities (non-EATS) in the assessment, these are not currently part of the data/information requirements as there are no standardised test methods to specifically cover such adverse effects. These limitations should be reflected upon and the new horizontal criteria should consider all endocrine modalities.

All the available data should be evaluated based on the quality of each study as well as the type and level of evidence provided through the "weight of evidence approach", already used by the CLP Regulation for CMRs.

In the context of ED assessment, a good example is the assessment approach used by the Danish authorities for gathering scientific data for the assessment and identification of EDs. A subsequent ED listing was part of a joint Member States' initiative that resulted in the launch of a website making several lists of endocrine disruptors public[11].

The approach, as detailed by Hass et al.[12], is following the weight of evidence approach set by the CLP Regulation and the ECHA/EFSA ED Guidance.

Such approach entails that:

- the quality of a study is evaluated as low, medium, or high based on an expert judgement considering the strength and limitations of the study,
- the evidence in each paper is evaluated as weak, moderate, or strong based on an expert judgement considering consistency and magnitude of the results, the relevance of the effects studied etc., and
- the overall level of evidence for, respectively, endocrine-related adverse effects, *in vitro* ED mode of action, *in vivo* ED mode of action, and the biologically plausible link, is evaluated to be weak, moderate, or strong based on Weight of Evidence (WoE). This involves considering all of the findings, both positive and negative in each area, as well as the general knowledge for the biologically plausible link specifically (ref. to OECD Guidance Document 150).

[11] https://edlists.org/the-ed-lists/list-iii-substances-identified-as-endocrine-disruptors-by-participating-national-authorities
[12] http://www.cend.dk/files/DK_ED-list-final_2018.pdf

Therefore, and based on this approach:

- all the available information that bears on the endocrine-mediated effects, i.e. determination of adverse effects, the mode of action, and the biologically plausible link, should be considered together in a total WoE as outlined by the CLP regulation using expert judgement on all findings. The assessment of the biologically plausible link should be made in light of the most up-to-date scientific knowledge, current understanding of physiology, endocrinology and toxicology, and with consideration given to internationally agreed guidelines (as also referred to in the BPR/PPPR and the ECHA/EFSA guidance).
- relevance to humans of animal data should be assumed by default unless appropriate scientific data clearly demonstrate non-relevance.
- a single, positive study performed according to good scientific principles and with statistically or biologically significant positive results may justify classification.
- certain scientific aspects relating to the assessment of endocrine disruption should always be taken into account, e.g. sensitive windows of exposure, low dose effects, non-monotonicity, non-thresholds, test methods insensitive for ED endpoints, and combination effects.
- expert judgement related to ED identification and thus classification requires deep expert insight into the scientific aspects of endocrine disruption. Therefore, specific experts with expertise in endocrinology should be responsible for the expert judgement regarding ED classification. In the EU regulatory system, the current ECHA ED Expert group could for example be responsible for expert judgements related to ED classification.

2.7 Decision criteria – required level of evidence for ED hazard categorisation

The current state of science on EDs, the limited number of standardised ED test methods available, and the current lack of knowledge on substances' ED properties should be adequately reflected, as well as the precautionary principle should be taken into account in the criteria for hazard classification of EDs and the allocation to hazard categories.

Based on and inspired by the approach described by Hass et al. and the report of the Commission Endocrine Disrupter Expert Advisory Group[5], the following required level of evidence for ED classification and allocation to categories is proposed.

Required level of evidence for classification as ED Category 1

To fulfil the WHO definition of an ED and the horizontal criteria for a Category 1 ED based on the above considerations, the overall level of evidence for endocrine-mediated adverse effects should be assessed to be **at least moderate for the three elements**: 1) adverse effects, 2) an ED mode of action (*in vitro* or *in vivo*) as well as for 3) a biologically plausible link.

However, if the overall evidence for both adverse effects and an ED mode of action is strong, then the evidence for a plausible link is by default considered to be at least moderate, unless there is clear evidence for the absence of a plausible link.

Furthermore, in those cases where there is a strong evidence for *in vivo* ED MoA and weak evidence for adverse effects, and it is scientifically well known that this ED MoA causes adverse ED effects, the substance can be identified as an ED Cat. 1, when the bioavailability of the substance to reach the foetus cannot be excluded.

For example, if there is a strong evidence for thyroid disruptive MoA with decreased T4, but weak evidence for adversity, there is no need to require further developmental studies, as it is well known that decreased T4 may lead to detrimental effects in the developing child. The substance will be classified as an ED Cat. 1, if the bioavailability of the substance to reach the foetus cannot be excluded.

Required level of evidence for classification as ED Category 2

To fulfil the WHO definition of a potential ED and the horizontal criteria for a Category 2 Suspected ED, the overall level of evidence for endocrine-mediated adverse effects should be **at least moderate for at least ONE of the elements**: 1) adverse effects, 2) ED MoA (*in vitro* or *in vivo*) or for 3) a biologically plausible link.

If, for example, substantial data on adverse ED effects exist but there are some limitations in the study (or studies), or if the studies demonstrating the ED MoA or a biologically plausible link make the quality of evidence less convincing, then the substance can only be classified as a Suspected ED.

If the level of evidence is **weak for ALL elements,** then further information and/or investigation is needed before a substance can be evaluated according to the criteria and a conclusion can be drawn on the basis thereof.

In cases where an assessment for ED properties has shown that the level of evidence is weak for all elements, but where there is a support for ED properties from chemical structure activity relationships (QSAR) to Known/Presumed or Suspected EDs and from data showing bioavailability of the substance to reach the foetus, it is up to an expert judgement to decide whether the evidence supports classification as a Suspected ED.

In general, it should be emphasized that lack of data is not the same as evidence of lack of effects and therefore, a precautionary approach should always be taken when evaluating substances for ED properties.

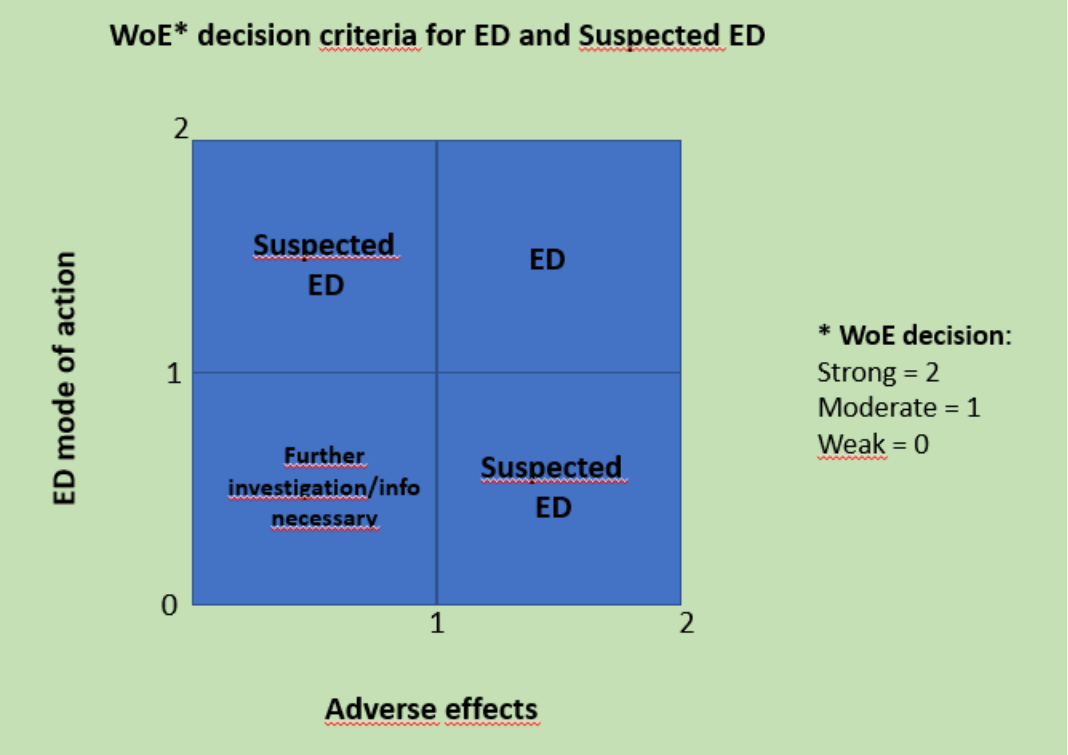
Required level of evidence for classification in Category 3 for Endocrine Activity

To classify and allocate a substance to Category 3 for Endocrine Activity requires **at least moderate** evidence for showing *in vitro* endocrine activity in at least one of the *in vitro* tests specified for ED modalities or in similar tests.

2.8 Application of the decision criteria for EDs and Suspected EDs

The decision criteria for EDs and Suspected EDs based on the level of evidence for the elements: 1) the endocrine related adverse effects, and 2) ED MoA (*in vitro* or *in vivo*) is illustrated in figure 2, where four scenarios are represented by the four quadrants in the matrix.

Fig. 2 – WoE decision criteria for ED Cat. 1 and Suspected ED Cat. 2.



(based on the JRC report[4], figure 1, p. 19)

For the elements 'adverse effects' and 'ED mode of action' the level of evidence is concluded to be weak, moderate, or strong which equals 0, 1 and 2, respectively, as indicated on the figure of the x- and the y-axis for adverse effects and mode of action, respectively.

When the level of evidence is at least moderate=1 for both elements the substance will be classified as a Cat. 1 ED, provided that the level of evidence for the biologically plausible link is also concluded to be at least moderate. Unless there is clear evidence for the opposite, in this case the level of evidence for the biologically plausible link is by default considered to be at least moderate. In case of uncertainties the substance will be classified as a Cat. 2 Suspected ED.

In cases where the level of evidence is at least moderate=1 for the ED mode of action, and it is scientifically well known that this mode of action leads to adverse ED effects, a substance can be classified as a Cat. 1 ED, provided that data are available that clearly show the substance is bioavailable and may reach the foetus.

When the level of evidence is weak=0 for one of the elements 'adverse effects' or 'ED MoA' and the level of evidence is at least moderate=1 for the other element, then the substance will be classified as a Cat. 2 Suspected ED. A biologically plausible link between adverse effects and the ED mode of action is considered default unless there is clear evidence of the opposite.

When the level of evidence is weak=0 for both elements 'adverse effects' and 'ED MoA' then further investigation is needed before the substance can be assessed according to the criteria. For example, if it is scientifically well known there is a plausible link between the specific ED MoA and the specific ED adverse effects or other supporting evidence, e.g. from QSAR, AOP and read across, then it is up to an expert judgement to decide whether the evidence supports classification as a Suspected ED.

In summary, the following decision criteria for ED classification apply in general:

Cat. 1: ED - if the level of evidence is **at least moderate=1 for all** of the elements**.**

Cat. 2: Suspected ED - if the level of evidence is **at least moderate=1 for one** of the three elements.

Cat. 3 for Endocrine Activity: - if there is **at least moderate=1** evidence for showing endocrine activity from specified or similar *in vitro* tests.

Further investigation needed - if the level of evidence is **weak=0 for all** of the elements then it is not possible to evaluate the substance according to the criteria without further information/investigation.

2.9 Examples illustrating outcomes of the decision criteria for ED classification

Case 1: For substance A there are substantial data on adverse effects on reproduction and some data showing ED MoA. An ED expert assessment of the substance concludes the level of evidence for ED adversity is strong, the level of evidence for an ED mode of action is moderate, and the level of evidence for a biologically plausible link between the ED adverse effects and the ED mode of action is moderate. The WoE expert judgement concludes that the overall level evidence meets the criteria for Category 1: ED.

Case 2: For substance B there are substantial data on adverse effects on reproduction and some data showing ED MoA. An ED expert assessment of the substance concludes the level of evidence for ED adversity is strong, the level of evidence for an ED mode of action is moderate, and the level of evidence for a biologically plausible link between the ED adverse effects and the ED mode of action is assumed by default to be considered moderate, unless there is clear evidence for the absence of a plausible link. The WoE expert judgement concludes that the overall level evidence meets the criteria for Category 1: ED.

Case 3: For substance C there are very few indications of adverse effects on reproductive organs and some data on ED MoA. An ED expert assessment of the substance concludes that the level of evidence for ED adversity is weak, the level of evidence for an ED mode of action is moderate, and the level of evidence for a biologically plausible link between the ED adverse effects and the ED mode of action

is weak. The WoE expert judgement concludes that the overall level of evidence meets the criteria for Category 2: Suspected ED.

Case 4: For substance D there are some data on effects on the thyroid and only scarce indications of an ED MoA. An ED expert assessment of the substance concludes that the level of evidence for ED-related adversity is moderate, the level of evidence for an ED mode of action is weak, and the level of evidence for a biologically plausible link between the ED adverse effects and the ED mode of action is weak. The WoE expert judgement concludes that the overall level of evidence meets the criteria for Category 2: Suspected ED.

Case 5: For substance E there are very few data indicating adverse effects on the male reproductive system. Data on ED MoA is not available. An ED expert assessment of the substance concludes that the level of evidence for ED adversity is weak, the level of evidence for an ED mode of action is weak and the level of evidence for a biologically plausible link between the ED adverse effects and the ED mode of action is also weak. The WoE expert judgement concludes that the level of evidence is not sufficient to evaluate the substance according to the ED criteria without further information/investigations.

Case 6: For substance F there are very few data indicating adverse effects on the male reproductive system. Data on ED MoA are scattered, and the level of evidence is weak. An ED expert assessment of the substance concludes that the level of evidence for ED adversity is weak, the level of evidence for an ED mode of action is weak and the level of evidence for a biologically plausible link between the ED adverse effects and the ED mode of action is also weak. However, there is support for ED properties from structure activity relationship to a known ED and an expert judgement concludes that the substances should be classified as a Category 2: Suspected ED.

3. Summary and Conclusion

New horizontal criteria for the hazard classification and categorisation of endocrine disruptors, in line with the current CMR criteria, should be included in the CLP Regulation.

In this briefing, we showed how such criteria based on the full WHO ED-definition and building on the BPR/PPPR criteria for endocrine disrupting biocides and pesticides can be set up to identify Endocrine Disruptors and Suspected Endocrine Disruptors. In addition, we proposed to address and classify substances showing endocrine-active properties accordingly.

Furthermore, by several examples we detailed how the criteria can be applied in practice.

In conclusion, new horizontal ED criteria, integrating the assessment for human health and environment, should classify substances as an ED, Category 1 (including Known (Category 1A) and Presumed (Category 1B)) or as a Suspected ED, Category 2, according to the strength of evidence for the ED properties. In addition, substances showing endocrine activity *in vitro* should be classified in Category 3 for endocrine activity, providing evidence for the further ED identification process. Such Category 3 can also serve as a watch-list for prioritising substances for further evaluation of their ED properties, and provide transparent information to the companies and the public on substances with a potential for being endocrine disruptors.

These ED criteria are prepared for a future where non-test methods to identify the inherent properties of chemicals will be more and more prominent to support animal test methods, or even

for their replacement. The criteria are integrated for human health and the environment, but they can be easily adapted in case a separate approach for human health effects and environmental effects is preferred.

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