

Public Consultation on Defining criteria for identifying Endocrine Disruptors in the context of the implementation of the Plant Protection Product Regulation and Biocidal Products Regulation

Fields marked with * are mandatory.

1. Information about you

All your answers to questions in sections 2, 3 and 4, are intended to be published on the web, together with some of your personal data (please read the specific [privacy statement](#) before answering the following questions). Please note that answers to questions 1.2 to 1.6, as well as 1.8 to 1.10 will not be published.

How would you like your contribution to appear?*

- Under the name supplied** (I consent to the publication of all the information in my contribution, and I declare that none of it is subject to copyright restrictions that would prevent publication)
- Anonymously** (I consent to the publication of all the information in my contribution, except my name/the name of my organisation, and I declare that none of it is subject to copyright restrictions that would prevent publication)
- I ask for confidential treatment of my contribution and do not give consent for publication** (the contribution will not be published and its content may not be taken into account. In any case, the contribution will be subject to the rules on access to documents, Regulation (EC) No 1049/2001)

1.1. Your full name:*

Peter Andrew Smith

1.2. Your e-mail address for correspondence:*

psm@cefic.be

1.3. Your gender:*

- Male Female

1.4. Your age:*

- 15-24 25-39 40-54 55-64 65+

1.5. Your level of education (highest degree obtained):*

- Primary school
 Secondary school
 Technical college or similar
 University
 Post-/University
 Still in full time education

1.6. Your occupation:*

- a. Self-employed
 b. Employee
 c. Not in formal working arrangement
 d. Other

1.6.b. If employee, please specify:*

- Professional (employed doctor, lawyer, accountant, architect)
 General management, director or top management
 Middle management
 Civil servant
 Office clerk
 Other employee (salesman, nurse, etc...)
 Manual worker
 Other

1.7. I'm replying as a(n):*

- a. Individual/citizen/consumer
 b. On behalf of an organization

1.7.b.1. If responding on behalf of a(n) organisation/association/authority/company/body, please provide the name:*

European Chemical Industry Council (Cefic)

1.7.b.2. Is your organisation listed in the EU transparency register?*

- a. Yes
 b. No
 c. Do not know

1.7.b.2.a. Please specify identification number *(optional)*:

64879142323-90

1.7.b. Please specify the organisation you represent:*

- i. Public authority
- ii. Academic/Research institution
- iii. Hospital / Health institution
- iv. Private company
- v. Agricultural producers (farmers)
- vi. Consumer / Non-Governmental Organisation
- vii. Industrial or trade association
- viii. Other

1.7.b.vii. If industrial or trade association, please specify:*

- International
- National

1.8. Your location:*

BE - Belgium

1.9. Would you say you live in a ...?*

- Metropolitan zone
- Other town/urban centre
- Rural zone
- Do not want to answer

1.10. Were you or your organisation involved in scientific issues in relation to endocrine disrupting chemicals in the last 3 years and in which way? *(more than one answer possible)**

- Direct experimental scientific research
- Review of scientific research
- Use of scientific research for safety assessments
- Use of scientific research for regulatory purposes
- Lobbying
- Other
- Not involved

1.11. Were you or your organization directly involved in/affected by the EU legislation mentioned below in the past 3 years? *(more than one answer possible)**

- Classification and Labelling (Regulation 1272/2008)
- REACH (Regulation 1907/2006)
- Plant Protection Products (Regulation 1107/2009)
- Biocides (Regulation 528/2012)
- Water Framework Directive (2000/60/EC)
- Cosmetics (Regulation 1223/2009)
- Chemicals Agents Directive (98/24/EC)
- Other
- Not involved

1.12. In what context have you been made aware of the discussions about endocrine disrupting chemicals?*

- Media for the general public
- Scientific publications
- As part of my profession
- Schools, universities, etc.

2. Options for criteria for determination of endocrine disrupting properties

The roadmap defines 4 different options for the establishment of criteria for determination of endocrine disrupting properties.

2.1. Questions regarding option 1 *(No policy change (baseline). The interim criteria set in the plant protection products and biocidal products regulations continue to apply. No other criteria are specified).*

2.1.1. Have you conducted or are you aware of an assessment of substances which would be identified as endocrine disruptors according to option 1?*

- Yes
- No

If yes, please describe the methodology(ies):*

4,000 character(s) maximum

Case-by-case assessment is inherent to identifying when an adverse effect results from an endocrine mode of action, including under Option 1. Cefic has not performed a comprehensive assessment for Option 1, as such assessments are integral to chemical hazard and safety assessment under existing EU legislation (REACH, medicinal products, foodstuffs,

cosmetics, toys, etc.). In particular, substances are currently being selected and reviewed as potential endocrine disruptors under REACH and estimates of the number of potential Substances of Very High Concern (SVHC) include endocrine disruptors.

For Biocidal Products and Plant Protection Products, interim criteria already exist that rely on the classification of substances as carcinogenic category 2 and reprotoxic category 2 irrespective of whether or not there is an endocrine disrupting mode of action. The European Chemicals Agency (ECHA) database of classified substances can be used to assess which substances would be identified using the interim criteria. These classifications can be applied to the 108 biocidal active substances for which assessment reports exist. For Plant Protection Products DG SANCO holds a data base of pesticide active substances against which the classifications can be checked to see if the active meets the criteria.

Beyond biocidal and plant protection products, regulatory provisions for assessing endocrine disrupting substances do not currently require criteria. Under REACH, endocrine disruptors fall within the scope of Art. 57 (f). REACH makes the provision for such substances to be included in the Candidate List and Annex XIV (substances subject to Authorisation). In this way, substances such as those having endocrine disrupting properties for which there is "scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern" as CMRs or PBTs or vPvBs can be identified as SVHC under REACH.

As indicated above, endocrine disruptors which are demonstrated also to be of an equivalent level of concern can be considered to all intents and purposes as SVHC and, therefore, fall under the processes foreseen in the Commission's SVHC Roadmap 2020. In turn, those substances meeting the conditions for equivalent concern can be added to the Candidate List and, if prioritised, onto the Authorisation List. To maintain the use of a substance on the Authorisation List (beyond its sunset date) requires a specific authorisation, as all other uses are prohibited. This process allows for public consultations as well as reviews by ECHA committees and expert groups to ensure all relevant safety data, together with the socio-economic impact, and the availability of safer alternatives are assessed. Application of the PACT-RMOA (Public Activities Coordination Tool-Risk Management Option Analysis) process, before initiating Authorisation, can also assure that the risk posed by a substance is thoroughly assessed to ensure the correct risk management option is implemented - e.g. restriction or authorisation.

REACH Evaluation also provides a mechanism for identifying substances with endocrine disrupting properties. If information in a REACH registration dossier is considered by ECHA or a Member State to be insufficient, then further information can be requested and/or the substance can be added to the Community Rolling Action Plan (CoRAP).

The outcome of such an evaluation can conclude that sufficient information is available or that further testing is needed to complete the evaluation of the substance.

All cosmetic ingredients are subject to a case by case assessment by the Scientific Committee for Consumer Safety (SCCS) under the responsibility of the European Commission (DG SANCO). This allows for expert assessment of any substance that is used in cosmetic applications to be completed including those substances for which there is any concern regarding possible endocrine activity.

If yes, please describe the outcome(s) of the assessment(s):*

4,000 character(s) maximum

The REACH procedures described above are relatively new. Therefore, the outcome of their application across all the substances registered for use in the EU (under REACH) will not be known until the actions resulting from SVHC Roadmap 2020 are complete. Even then, substances will continue to be added to the CoRAP list and new substances will be created and need to be registered. Therefore, the assessments of substances will continue to occur in the future.

All that said, there are some initial results which reveal that substances with potential endocrine disrupting properties are appearing at the different stages in the REACH assessment process including the recently developed PACT-RMOA which lists the substances for which a Risk Management Option Analysis is under development or else has been completed since the SVHC Roadmap began in 2013. This indicates that the process of identifying substances with endocrine disrupting properties under REACH is progressing (even in the absence of criteria).

REACH Instrument	Total Substances	Substances Identified on the basis of concern for Endocrine Disruptors
PACT-RMOA (5/12/2014)	88	10
Candidate List (17/12/2014)	161	5
Authorisation List	31	0
CoRAP List (2012-2017)	238	40

The majority of substances that are currently on the Candidate List are Cat 1 CMRs. Some of these substances may act via an endocrine disrupting mode of action. However, for CMR's (or other SVHC), the information about the mode of action is not needed to ensure that such a substance is thoroughly risk assessed and, if appropriate, its use(s) regulated in accordance with the authorisation procedures under REACH. The purpose of the substance evaluation (CoRAP) and authorisation (Candidate and Authorisation Lists) instruments in an endocrine disruptor context is to identify substances giving rise to an equivalent level of concern to (for example) CMRs purely because of their endocrine disrupting properties.

Please provide the reference(s) if possible

2.1.2. Are you aware of any assessment(s) of substitutability of the identified substances?*

- Yes
 No

If yes, please describe the methodology(ies):*

4,000 character(s) maximum

Actual substitution studies are handled by companies on a substance by substance basis. We are not aware of a systematic study of a group of substances compliant with the criteria and categorisation presented in the Commission's roadmap. That said, we want to underline the point that proposing automatic substitution of endocrine disruptors (as implied by this question) is not appropriate. This could lead to the loss of important substances which could otherwise be safely used based on risk assessment. With the potential loss of these substances, the benefits that they provide to society will also be lost (whilst incurring any associated competitiveness, economic and employment impacts). Against this background of safe use, there will be no improvement to human health and/or the environment when:

- o a hazardous substance is substituted for an equally or more hazardous substance;
- o a hazardous substance with low exposure potential is substituted for a less hazardous substance with higher exposure potential that results in higher risks;
- o a life cycle assessment of the substitution does not show overall health / environmental benefits;
- o adverse health effects associated with recession and unemployment that can result from loss of industrial competitiveness (e.g. Waddle & Burton, 2006).

Waddell, G., Burton, K. (2006) Is work good for your health and well-being? The Stationary Office, London.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/214326/hwwb-is-work-good-for-you.pdf

If yes, please describe the outcome(s) of the assessment(s):*

4,000 character(s) maximum

See comments above relating to individual company activities.

Please provide the reference(s) if possible

2.1.3. Are you aware of any assessment(s) of the socio-economic impact if the identified substances were regulated without further risk assessment?*

- Yes
- No

If yes, please describe the methodology(ies):*

4,000 character(s) maximum

Socio-economic analysis will only be conducted in conjunction with a comprehensive risk assessment and before deciding on the regulatory action to be taken on a particular substance. A socio-economic impact analysis, therefore, should not be conducted in the absence of such a risk assessment. The scenario referred to in the question will not occur in the context of REACH.

If yes, please describe the the outcome(s) of the assessment(s):*

4,000 character(s) maximum

Please see explanation above.

Please provide the reference(s) if possible

2.1.4. Please, provide us with any other comments you may have regarding option 1:

4,000 character(s) maximum

We are of the opinion that the interim criteria included in the plant protection products and biocidal products regulations are not suitable science based criteria for the regulation of endocrine disruptors. Since they are not scientifically based, they are not a reliable indicator of whether a substance should be regarded as an endocrine disruptor. As the interim criteria would additionally identify substances as endocrine disruptors which are already classified as carcinogenic category 2 and reprotoxic category 2 (C2+R2), this approach seems to be overprotective and not suitable for regulatory decision making

2.2. Questions regarding option 2 (WHO/IPCS definition to identify endocrine disruptors (hazard identification))

2.2.1. Have you conducted or are you aware of an assessment of substances which would be identified as endocrine disruptors according to option 2?*

- Yes
 No

If yes, please describe the methodology(ies):*

4,000 character(s) maximum

We are aware of the proposal (REACH Annex XV dossiers) from Denmark for the second listing of four classified low molecular weight phthalates (DEHP, DBP, BBP, DIBP) on the REACH Candidate List for endocrine disrupting properties. The following comments relate to the justification for these proposals:

- The four dossiers follow largely an approach of using the WHO/IPCS (2002) definition with reference to the JRC Ad Hoc Expert Group Report. Potency is not included nor is a rigorous approach taken to the definition of adverse effects

- While the WHO/IPCS (2002) definition is used, the dossiers fail to apply a scientifically robust weight of evidence process to integrate various kinds and lines of evidence and to gauge how/how well the collective evidence supports the conclusion. For instance, the OECD Conceptual Framework can be used to support a robust weight of evidence evaluation. Such an approach would identify methodological deficiencies of certain studies (e.g. testing above water solubility for ecotox tests, not employing replicates within treatment groups) - this was not done in the dossiers. In particular, there was no weighing of evidence to differentiate between robust and scientifically weak studies.

- A formal framework for assessing adversity, mode of action, human relevance and causation is not used (see IPCS Mode of Action / Human Relevancy Framework (Boobis, 2006, 2008, 2009; Meek, 2014 a, 2014b) which is an evolution of WHO/IPCS 2002 both of which were adapted from the Hill considerations (Hill, 1965). The Annex XV dossiers do not establish reasonable causation linkage between the proposed mode of action and the adverse effects - this is simply presumed to be "plausible". In many toxicological studies hormones may well change due to stress, due to adaptation, and general toxicity - such changes can also be potentially presumed to be a plausible link to observed effects, but without a systematic approach using the above frameworks and with documentation, this is speculative and without proper foundation.

- Although the dossiers cite the WHO/IPCS (2002) definition of an endocrine disruptor, the conclusions include the potential ability of substances to interact with the endocrine system. The important distinction between endocrine active and endocrine disruptive is overlooked.

- Identification of these substances with respect to endocrine disrupting effects for top predators, primates and other larger animals, based on reproductive effects in rodent laboratory studies is not justified. It is assumed that these species will be subject to a potential endocrine disrupting effect based on laboratory rodent studies. This is a stated "concern" in the dossiers without any substantiation with data. If the logic were to be followed then any substance showing an endocrine disrupting effect in laboratory rodent studies would be a threat to all wildlife. Concerns for primates, top predators and endangered species can only be considered valid where there are data to warrant such concerns (e.g. bioaccumulation data, actual studies on primates, evidence from environmental fate studies

that the hazard can be presented to these species).

In summary, these REACH Annex XV dossiers demonstrate the limitations and flaws of following a simplified hazard identification only approach for endocrine disruption. Rather they exemplify the need to follow a scientific evaluation process with full hazard characterisation to draw robust conclusions on the endocrine disrupting properties of substances.

If yes, please describe the outcome(s) of the assessment(s):*

4,000 character(s) maximum

The above comments (relating to methodologies) are supported by the outcome of the December 8 - 11, 2014 ECHA Member State Committee which evaluated the Annex XV dossiers from Denmark. Using a simplified hazard only identification approach, and relying on the endocrine activity for fish and not adverse effects, and with clear data showing a lack of concern for wildlife and mammals in the environment, and where causation between proposed modes of action and adverse effects has not been demonstrated, the ECHA MSC nevertheless identified DEHP as an Endocrine Disruptor with equivalent level of concern for its environmental effects.

Reference:

Annex XV Report Proposal for Identification of a Substance of Very High Concern on the basis of the criteria set out in REACH Article 57; DEHP, DBP, BBP, DIBP. Danish Environmental Protection Agency, 26 August 2014

Please provide the reference(s) if possible:

2.2.2. Are you aware of any assessment(s) of substitutability of the identified substances?*

- Yes
 No

If yes, please describe the methodology(ies):*

4,000 character(s) maximum

Actual substitution studies are handled by companies on a substance by substance basis. We are not aware of a systematic study of a group of substances compliant with the criteria and categorisation presented in the Commission's roadmap. That said, we want to underline the point that proposing automatic substitution of endocrine disruptors (as implied by this question) is not appropriate. This could lead to the loss of important substances which could otherwise be safely used based on risk assessment. With the potential loss of these substances, the benefits that they provide to society will also be lost (whilst incurring any associated competitiveness, economic and employment impacts). Against this background of safe use, there will be no improvement to human health and/or the environment when:

- o a hazardous substance is substituted for an equally or more hazardous substance;
- o a hazardous substance with low exposure potential is substituted for a less hazardous substance with higher exposure potential that results in higher risks;
- o a life cycle assessment of the substitution does not show overall health / environmental benefits;
- o adverse health effects associated with recession and unemployment that can result from loss of industrial competitiveness (e.g. Waddell & Burton, 2006).

Waddell, G., Burton, K. (2006) Is work good for your health and well-being? The Stationary Office, London.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/214326/hwwb-is-work-good-for-you.pdf

If yes, please describe the outcome(s) of the assessment(s):*

4,000 character(s) maximum

Authorisation has been recommended by RAC and SEAC for DEHP and DBP based on risk assessment and risk control and also socio-economic grounds. RAC recognised a threshold via DNELs for the adverse reproductive effects and based on the risk assessment has recommended Authorisation. If these same adverse reproductive effects are also to be identified as endocrine disrupting effects, then logically it would follow that a threshold approach would apply and that the substances would remain authorized based on risk control.

This underlines an important principle. Risk assessment should be applied to substances that are endocrine disruptors for which a threshold is demonstrated before deciding on risk management options. It should also be noted that applications for Authorisation of DIBP and BBP have not been made to date.

Please provide the reference(s) if possible:

2.2.3. Are you aware of any assessment(s) of the socio-economic impact if the identified substances were regulated without further risk assessment?*

- Yes
 No

If yes, please describe the methodology(ies):*

4,000 character(s) maximum

Socio-economic analysis will only be conducted in conjunction with a comprehensive risk assessment and before deciding on the regulatory action to be taken on a particular substance. A socio-economic impact analysis, therefore, should not be conducted in the absence of such a risk assessment. The scenario referred to in the question will not occur in the context of REACH.

If yes, please describe the outcome(s) of the assessment(s):*

4,000 character(s) maximum

Please see explanation above.

Please provide the reference(s) if possible

2.2.4. Please, provide us with any other comments you may have regarding option 2.

4,000 character(s) maximum

We support the WHO/IPCS definition; it is a starting point for the criteria. This is in line with EFSA's scientific opinion which "endorsed the WHO/IPCS 2002 definition of an ED implying that there must be reasonable evidence for a biologically plausible causal relationship between the endocrine activity and the induced adverse effect(s) seen in an intact organism or a (sub)population for a substance to be identified as an ED." The EFSA Scientific Committee concluded that the WHO/IPCS (2002) definition and the WHO/IPCS (2009) definition of an adverse effect should be endorsed as working definitions of their scientific opinion. We agree with the wording in Option 2 relating to the available evidence needing to support a strong presumption that an alteration of

the endocrine system is the basis for the observed effect and that the data provide clear evidence of endocrine-mediated adverse effects. This scientific definition is not sufficient for the purposes of regulatory decision making which requires consideration of hazard characterisation (see last paragraph) in a robust weight of evidence approach.

As part of a weight of evidence evaluation, causality between the mode of action and the adverse effects is established using the comprehensive frameworks such as; IPCS Mode of Action / Human Relevancy Framework (Boobis, 2006, 2008, 2009; Meek, 2014 a, 2014b) which is an evolution of WHO/IPCS 2002 and adapted from the Hill considerations (Hill, 1965). The OECD Conceptual Framework/OECD Guidance Document 150 can also be used to support the evaluation. Testing in line with this framework should be the basis for the assessment (TG407, 416, 443, 451, 452, 453, and 234), with consideration to the "route of exposure". Only adverse effects induced via relevant exposure route(s) should be considered when identifying endocrine disruptors. Qualified experts should be responsible for carrying out the weight of evidence assessments, as definition and criteria alone cannot compensate for this.

Severity of adverse effect describes the magnitude of an adverse effect and/or its nature. Severe adverse effects contribute to a greater level of concern.

(Ir)reversibility: Reversibility or irreversibility contributes to the severity assessment. Reversibility implies that recovery of the individual or population can occur after exposure has stopped.

Reversible adverse effects provide a lower level of concern.

Potency relates to the dose at which adverse effects are induced and the duration required. A highly potent substance produces a large effect at low concentrations, while a substance of low potency leads to a small effect at high concentrations. A potent substance may cause an adverse effect after a short exposure; a less potent substance may require longer exposure. Potency measures the strength of a substance's tendency to produce an adverse effect. It is a routine part of hazard characterisation, and is essential in identifying those substances of high regulatory concern.

Lead toxic effect considers the dose response of all the toxicity effects of a substance. It refers to the adverse effect that occurs at the lowest dose. This describes the most sensitive toxicological endpoint (critical effect) and drives the risk assessment. Risk management measures based on the lead toxic effect will be protective of all other adverse effects occurring at higher dose levels. For endocrine disruptors, the endocrine mediated adverse effect should be the lead toxic effect.

Specificity: For a substance to be considered to have endocrine disrupting properties, the adverse effect should occur as a consequence of a primary endocrine mode of action; it should not be the result of a secondary consequence of another toxic effect.

Human and population relevance

The endocrine mediated adverse effects must be relevant to humans or non-target populations. Relevance to humans is assumed in the absence of scientific data demonstrating non relevance.

2.3. Questions regarding option 3 (*WHO/IPCS definition to identify endocrine disruptors and introduction of additional categories based on the different strength of evidence for fulfilling the WHO/IPCS definition*)

2.3.1. Have you conducted or are you aware of an assessment of substances which, in addition to those identified according to option 2, would be identified as suspected endocrine disruptors or endocrine active substances (Categories II or III) according to option 3?*

- Yes
 No

If yes, please describe the methodology(ies):*

4,000 character(s) maximum

Option 3 in the Roadmap resembles a proposal for the identification of endocrine disruptors by the European Commission presented in early 2013. That proposal included a concept of categorisation of endocrine disruptors. Two categories were suggested, category 1 for “endocrine disruptors” and category 2 for “suspected endocrine disruptors”. We contracted FOBIG to undertake an ad hoc Impact Assessment of the criteria for ED proposed by DG ENV based on the existing European Commission database (“BKH list”). This study, therefore, went beyond the assessment according to Option 2 (WHO/IPCS definition) to include something similar to the second category in Option 3. We are not aware of any assessment encompassing the third category (or something similar) as included in Option 3. In our study only adverse effects on human health were considered.

The reason for using that (“BKH list”) database was that it contained a relatively large and publicly available collection of data that could be assessed quickly in a systematic way. The disadvantages of using this database were that it was largely developed in the early 2000s, was not intended to contain all available data at that time, and was not updated regularly. Therefore, the scope of this work was not to assess individual chemicals, but to perform a practicability check of the (DG ENV) proposed criteria.

To that end, the findings of the study can be summarised as follows (next section).

If yes, please describe the outcome(s) of the assessment(s):*

4,000 character(s) maximum

The proposed criteria for identifying endocrine disruptors are not precise enough for their purpose and require extensive interpretation by experts, resulting in differing categorisation of the same substances. This would create a major unpredictability and lack of consistency for industry and lead to more fragmented chemical regimes that could cause the unnecessary stigmatisation of many substances in the marketplace.

Based on the proposed criteria, it is impossible to determine if substances are endocrine disruptors.

To ensure that the endocrine disruptors' criteria can be implemented in practice, Cefic requests the Commission to include the use of the OECD testing guidelines and the OECD testing framework in its criteria and any guidance, as well as including potency and (ir)reversibility amongst other hazard characterisation criteria. The use of the WHO/IPCS Mode of Action / Human Relevance Framework is also essential to assess causality between the mechanism and the adverse effects, as well as human relevance (Boobis et al 2006, 2008, 2009; Meek et al 2014a, 2014b). The Commission's roadmap does not provide clarity on the regulatory purpose of the proposed additional categories. The relevant directives do not foresee multiple categories.

Therefore, we are of the opinion that only one single set of criteria, which clearly identifies endocrine disruptors, is required and these should include hazard characterisation. A multiple category system is not required. And for substances for which the status is unclear, the REACH process of substance evaluation (i.e. CoRAP) should suffice.

Please provide the reference(s) if possible:

2.3.2. Are you aware of any assessment(s) of substitutability of the identified substances?*

- Yes
 No

If yes, please describe the methodology(ies):*

4,000 character(s) maximum

Actual substitution studies are handled by companies on a substance by substance basis. We are not aware of a systematic study of a group of substances compliant with the criteria and categorisation presented in the Commission's roadmap. That said, we want to underline the point that proposing automatic substitution of endocrine disruptors (as implied by this question) is not appropriate. This could lead to the loss of important substances which could otherwise be safely used based on risk assessment. With the potential loss of these substances, the benefits that they provide to society will also be lost (whilst incurring any associated competitiveness, economic and employment impacts). Against this background of safe use, there will be no improvement to human health and/or the environment when:

- o a hazardous substance is substituted for an equally or more hazardous substance;
- o a hazardous substance with low exposure potential is substituted for a less hazardous substance with higher exposure potential that results in higher risks;
- o a life cycle assessment of the substitution does not show overall health / environmental benefits;
- o adverse health effects associated with recession and unemployment that can result from loss of industrial competitiveness (e.g. Waddell & Burton, 2006).

Waddell, G., Burton, K. (2006) Is work good for your health and well-being? The Stationary Office, London.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/214326/hwwb-is-work-good-for-you.pdf

If yes, please describe the outcome(s) of the assessment(s):*

4,000 character(s) maximum

See comments above relating to individual company activities.

Please provide the reference(s) if possible:

2.3.3. Are you aware of any assessment(s) of the socio-economic impact if the identified substances were regulated without further risk assessment?*

- Yes
 No

If yes, please describe the methodology(ies):*

4,000 character(s) maximum

Socio-economic analysis will only be conducted in conjunction with a comprehensive risk assessment and before deciding on the regulatory action to be taken on a particular substance. A socio-economic impact analysis, therefore, should not be conducted in the absence of such a risk assessment. The scenario referred to in the question will not occur in the context of REACH.

If yes, please describe the outcome(s) of the assessment(s):*

4,000 character(s) maximum

Please see explanation above.

Please provide the reference(s) if possible:

Please, provide us with any other comments you may have regarding option 3.

4,000 character(s) maximum

Option 3 foresees discrimination of multiple categories of endocrine disruptors based on the strength of evidence. Option 3 fails to describe the purpose of the categories in the context of the PPR and BPR both of which do not have provisions for multiple categories but only for Endocrine Disruptors. Therefore the categorisation in option 3 is not helping to identify ED substances of regulatory concern.

Substances should only be considered as endocrine disruptors of regulatory concern when there are clear adverse effects unambiguously caused by a well identified and empirically described mode of action. These adverse effects must be relevant to humans and wildlife populations, not to be secondary to other toxic effects, and occur at exposure levels indicative of significant potency. Based on these considerations, only one single set of criteria is required. By default, chemicals which do not meet these criteria will be subject to all other safety provisions of the PPPR, the BPR and REACH.

We, therefore, oppose the categorisation concept. Categorisation is used under CLP for CMR endpoints. However, CMRs represent well-defined adverse effects which are suitable to categorisation, while endocrine disruption is a generic terminology that artificially groups a collection of different modes of action and different adverse effects of variable nature, severity and concern.

For the consumer a sophisticated distinction between categories of, for example, endocrine disruptors and endocrine active substances is confusing. There will be an inevitable creation of "black lists" resulting from the categories which will be susceptible to misinterpretation and misuse and unwarranted additional primary or secondary regulation, in Europe and globally. Substances not considered as endocrine disruptors under the proposed scheme will still be labelled as "suspected endocrine disruptors" which would lead to stigmatisation and potential regulation, market de-selection and loss of beneficial substances for no benefit to health or the environment.

2.4. Questions regarding option 4 (*WHO/IPCS definition to identify endocrine disruptors and inclusion of potency as element of hazard characterisation (hazard identification and characterisation)*)

2.4.1. Have you conducted or are you aware of an assessment of substances which would be identified as endocrine disruptors according to option 4?*

- Yes
 No

If yes, please describe the methodology(ies), including the potency thresholds that applied:*

4,000 character(s) maximum

We are aware that the UK authorities (HSE-CRD) have studied the impact of including potency in criteria applied to approved pesticide active substances.

<http://sciencesearch.defra.gov.uk/Default.aspx?Menu=Menu&Module=More&Location=None&Completed=0&ProjectID=18083>

Under the Plant Protection Products Regulation (PPPR) 1107/2009, the criteria can be used as a cut-off for substances having endocrine disrupting properties. The study compares the results from the use of the WHO/IPCS definition (such as described in Option 2 in the Commission's Roadmap) and those obtained when potency is introduced as an element of hazard characterisation (using the potency threshold of the STOT-RE Category guidance provided in by the Classification, Labelling, and Packaging Regulation). The use of the STOT-RE potency threshold can be viewed as being indicative of Option 4 in the Roadmap. In this way, the study provides a means to make a comparison between criteria similar in design and intent to Option 2 and those similar to Option 4 (when applied to approved pesticide active substances).

If yes, please describe the outcome(s) of the assessment(s):*

4,000 character(s) maximum

There were 98 substances investigated in the study. 58 were not considered to be endocrine disruptors. 26 substances required additional data to make an informed assessment. The remaining 14 substances are considered to be endocrine disruptors according to the WHO/IPCS definition (similar to Option 2), of which 5 of these were identified as EDs more likely to pose a risk (similar to Option 4).

Reference:

<http://sciencesearch.defra.gov.uk/Default.aspx?Menu=Menu&Module=More&Location=None&Completed=0&ProjectID=18083>

Please provide the reference(s) if possible:

2.4.2. Are you aware of any assessment(s) of substitutability of the identified substances?*

- Yes
 No

If yes, please describe the methodology(ies):*

4,000 character(s) maximum

Actual substitution studies are handled by companies on a substance by substance basis. We are not aware of a systematic study of a group of substances compliant with the criteria and categorisation presented in the Commission's roadmap. That said, we want to underline the point that proposing automatic substitution of endocrine disruptors (as implied by this question) is not appropriate. This could lead to the loss of important substances which could otherwise be safely used based on risk assessment. With the potential loss of these substances, the benefits that they provide to society will also be lost (whilst incurring any associated competitiveness, economic and employment impacts). Against this background of safe use, there will be no improvement to human health and/or the environment when:

- o a hazardous substance is substituted for an equally or more hazardous substance;
- o a hazardous substance with low exposure potential is substituted for a less hazardous substance with higher exposure potential that results in higher risks;
- o a life cycle assessment of the substitution does not show overall health / environmental benefits;
- o adverse health effects associated with recession and unemployment that can result from loss of industrial competitiveness (e.g. Waddell & Burton, 2006).

Waddell, G., Burton, K. (2006) Is work good for your health and well-being? The Stationary Office, London.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/214326/hwwb-is-work-good-for-you.pdf

If yes, please describe the outcome(s) of the assessment(s):*

4,000 character(s) maximum

See comments above relating to individual company activities.

Please provide the reference(s) if possible:

2.4.3. Are you aware of any assessment(s) of the socio-economic impact if the identified substances were regulated without further risk assessment?*

- Yes
 No

If yes, please describe the methodology(ies):*

4,000 character(s) maximum

Socio-economic analysis will only be conducted in conjunction with a comprehensive risk assessment and before deciding on the regulatory action to be taken on a particular substance. A socio-economic impact analysis, therefore, should not be conducted in the absence of such a risk assessment. The scenario referred to in the question will not occur in the context of REACH.

If yes, please describe the outcome(s) of the assessment(s):*

4,000 character(s) maximum

Please see explanation above.

Please provide the reference(s) if possible:

2.4.4. Please, provide us with any other comments you may have regarding option 4.

4,000 character(s) maximum

Option 4 recognises that potency is an important element to identify substances that cause adverse effects at environmental relevant concentrations. We support the inclusion of potency in option 4 for the identification of ED's. However, there are insufficient hazard characterisation elements taken into account.

Recommendation

We feel confident that the development of a single set of criteria for the determination of endocrine disrupting properties, which uses the WHO-IPCS definition as a basis, but which also takes into account the relevance of the adverse effect (that is: severity of effect, (ir)reversibility of effect, potency and lead toxicity) ensures the correct identification of the relevant substances. Without these hazard characterisation elements, substances which pose little or no concern for human health or the environment could be considered to have endocrine disrupting properties and be unnecessarily regulated without any benefit to society.

Taking full account of the data on these additional elements is a routine part of chemicals evaluation as well as a structured weight of evidence approach considering both the quality and consistency of data, as well as determining a causal link between the mode of action and adverse effects, (human and population relevance). This approach is critical to be able to distinguish between those substances that should be of high regulatory concern from those that are not and so do not need to be regulated. Note, without these additional elements of hazard characterisation it is likely that many natural substances, including those found in food, feed and drinks would require regulating as they could demonstrate both endocrine active and endocrine disrupting properties.

An extended Option 4 approach has been developed by CEFIC and would be an appropriate and effective way to identify EDs of regulatory concern. It would ensure the use of the global OECD framework and fit into the regulatory context in Europe. Additionally, data and information on the above mentioned factors should be carefully assessed using a structured weight of evidence approach, considering quality and consistency of data.

A fully elaborated description of this scheme is provided below by way of a link to the Cefic public website as it exceeds the 4000 character limit for written responses.

<http://www.cefic.org/Documents/PolicyCentre/Endocrine/Elaboration-of-ED-Criteria-with-Full-Hazard-Characterisation-Nov2014.pdf>

This scheme is also provided as an uploaded file at the end of Qu. 4.1 (Other information).

3. Options for approaches to regulatory decision making

The roadmap defines 3 different options for approaches to regulatory decision making. Option A (no changes of the existing provisions in BPR and PPPR), Option B (introduction of further elements of risk assessment) where necessary and desirable to reduce potential socio-economic impacts, and Option C (introduction of further socio-economic considerations) where necessary and desirable to prevent adverse socio-economic impacts.

3.1. Have you conducted or are you aware of an assessment applying any of the 3 different options for regulatory approaches to decision making (option A-C) to substances identified as endocrine disruptors by any of the options for defining criteria (option 1-4)?*

- Yes
 No

3.2. Have you conducted or are you aware of an assessment of the socio-economic impact of the 3 different options for regulatory approaches to decision making (option A-C) for substances identified as endocrine disruptors by any of the options for defining criteria (option 1-4)?*

- Yes
 No

4. Other information

4.1. Please provide any other data or information that could help the Commission to conduct its impact assessment.

4,000 character(s) maximum

For the impact assessment, Cefic urges the Commission to include the criteria proposed in response to Q.2.4.4 ('extended Option 4'). This is because scientific assessments must consider and account for factors that can modulate endocrine systems and cause adverse effects on the endocrine system that are naturally occurring or resulting from confounding factors in laboratories or life, such as diet and stress.

In particular, a number of components that are present naturally in the diet as well as environmental conditions have endocrine disrupting properties. Three examples of different substance classes follow: phyto-oestrogens, mycotoxins, physical modulators:

Phyto-oestrogens are naturally occurring compounds in plants known to have oestrogenic properties. The majority of phyto-oestrogens belong to a large group of substituted phenolic compounds termed flavonoids. Three classes of flavonoids, the coumestans, the phenylated flavonoids, and the isoflavones are phyto-oestrogens that possess the most potent oestrogenic activity (COT, 2003). By definition phyto-oestrogens are

biologically active, and in vitro and in vivo animal studies support this. A classic example of a phyto-oestrogen is genistein and there are many studies describing the biological effects of genistein in mammalian systems, including effects on reproduction and development (Rozman et al, 2006). In addition the effects on the environment have also been discussed (Spengler et al 2001; Kiparissis et al, 2001, Kawanashi et al, 2004)

Certain fungal contaminants in natural foodstuffs such as the mycotoxin zearalenone are also known to have endocrine disrupting properties. A large number of studies, both in vitro and in vivo have shown the zearalenone binds to the ER, inducing oestrogenic effects and interfering with the reproductive process. For example, the adverse effects associated with the ingestion of mouldy feed by pigs include foetal death, infertility, reduced litter size and abortion (Nelson et al, 1966; Radnai, 1974)

Other natural stressors can also cause modulation of endocrine systems, with potential adverse effects. Physiological stresses such as parasitism (Allner et al, 2009; Jobling and Tyler, 2003; Schabuss et al, 2005), temperature (Kime, 1999), hypoxia (Thomas et al, 2007; Wu et al, 2003), caloric intake (Odum et al, 2004) and food restriction (Rehm et al, 2008) are known to induce adverse endocrine effects. Other physical interactions that can alter endocrine function include environmental conditions. For example, sex determination in many fish species can be influenced by environmental variables such as temperature, salinity, and/or pH (Baroiller et al, 1999).

Responses to physiological stress can also have effects on homeostasis with potential adverse effects on endocrine organs and reproduction, as is well documented in research (e.g. Everds et al., 2013). The concept of homeostasis originates from studies on stress that highlight how responses to exposure to exogenous agents occur in a background of constantly changing endocrine processes that are responding to many factors. This is an important consideration when evaluating potential endocrine effects caused by chemicals.

The above examples clearly demonstrate that the priority must be on effectively distinguishing between endocrine disruptors of regulatory concern and those substances that pose little or no concern for human health or the environment and that do not need to be regulated - including many natural substances. Inclusion of elements of hazard characterisation (i.e., potency, (ir)reversibility, severity, and lead toxicity) - as described in the proposed industry 'extended Option 4' - would allow for the correct identification of endocrine disruptors of regulatory concern by determining a causal link between the mode of action and adverse effects whilst taking into account the relevance of the adverse effect.

Please provide the reference(s) if possible:

1. a8589dd0-a67a-4c27-818c-31d327e8ac4e/ED Criteria Scheme With Explanatory Notes.pdf
2. 8daae9b4-cab8-4d72-b757-59ab00276ff2/References.docx

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