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# REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL AND THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE

## in accordance with Article 138(7) of REACH to review if the scope of Article 60(3) should be extended to substances identified under Article 57(f) as having endocrine disrupting properties with an equivalent level of concern to other substances listed as substances of very high concern

## 1) Introduction

The REACH Regulation[1] entered into force on 1 June 2007. Its main objectives are to ensure a high level of protection of human health and the environment, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation. The Regulation shifts the responsibility to manage chemicals risks from public authorities to industry. Those objectives are to be achieved via four processes, namely Registration, Evaluation, Authorisation and Restriction.

The authorisation process aims at ensuring the sound functioning of the internal market while assuring that the risks from substances of very high concern (SVHCs) included in Annex XIV are properly controlled and that these substances are progressively replaced by suitable alternative substances or technologies where these are economically and technically viable. Article 60(2) states that *"an authorisation shall be granted if the risk to human health or the environment [..] is adequately controlled"*. To this end, manufacturers, importers or downstream users have to apply for authorisation and to analyse the availability of alternatives, considering their risks and the technical and economic feasibility of substitution. According to Article 60(3), Article 60(2) shall not apply to substances that are carcinogenic, mutagenic or toxic to reproduction category 1A or 1B (CMR Cat. 1A/1B) or to substances meeting the criteria in Article 57(f) for which it is not possible to determine a threshold. Substances falling under Article 57(f) are inter alia 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 concern"* to CMR Cat. 1A/1B or to substances which are persistent, bioaccumulating and toxic or very persistent and very bioaccumulating (PBT/vPvB). For substances identified under Article 60(3), "*authorisation may only be granted if it is shown that socio-economic benefits outweigh the risk to human health or the environment*", as specified in Article 60(4) (the so-called 'Socio-Economic Route').

Article 138(7) of REACH requires that "*by 1 June 2013, the Commission shall carry out a review to assess whether or not, taking into account latest developments in scientific knowledge, to extend the scope of Article 60(3) to substances identified under Article 57(f) as having endocrine disrupting properties. On the basis of that review the Commission may, if appropriate, present legislative proposals*." In other words, the Commission has to review the way some SVHCs, namely substances "*having endocrine disrupting properties […] which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) [of Article 57]*"[2], that are CMR Cat. 1A/1B and PBT/vPvB substances, should be handled under the authorisation process and in particular whether endocrine disruptors should only be authorised through the Socio-Economic Route.

The review clause was inserted during the co-decision process, where the authorisation process was substantially changed from the Commission proposal. There was not enough time to find a detailed agreement on whether endocrine disruptors should be authorised in all circumstances through the Socio-Economic Route. Therefore this decision was entrusted to

[1] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L396, 30.12.2006, p. 1).

[2] Article 57 (f) of REACH.

the Commission through the review clause in Article 138(7) and postponed to 2013, as there was also an expectation that the scientific knowledge about endocrine disruptors might have evolved further to allow taking a clear position on this matter.

The purpose of this document is to review whether or not, based on the current scientific knowledge, there would be a need to change the legislative text as regards those substances, as required by Article 138(7).

The Commission's conclusions build on work with Member States, input from EU regulatory agencies[3], independent scientific committees advising the Commission, the Commission's in-house scientific body (the Joint Research Centre[4]), and from multilateral and bilateral scientific and regulatory cooperation with third countries, as well as extensive contacts with stakeholders over the past years[5].

## 2) Context

### - What is an Endocrine Disruptor?

For the purpose of this review the Commission is going to apply the WHO/IPCS definition of endocrine disruptor: "*A substance having endocrine disrupting properties means 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*". This is in line with the publication, on 15 June 2016, by the Commission of draft scientific criteria for the determination of endocrine disrupting properties pursuant to the legislation on biocidal products and plant protection products.[6]

Endocrine disrupting substances can be identified as SVHCs under REACH based on Article 57(f) provided that there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to CMRs Cat. 1A/1B and PBT/vPvBs. For an easier reading, it will be considered for the purpose of this document that the abbreviation "EDs" covers this requirement, i.e. that the substances concerned are considered as being of equivalent concern.

### - Application for authorisation for ED substances

Title VII of the REACH Regulation lays down the provisions governing the authorisation requirements for SVHCs listed in Annex XIV, the so-called 'Authorisation List', which may

[3] For example, European Food Safety Authority, Scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment, 28.2.2013, EFSA Journal 2013;11(3):3132, p. 17 ("EFSA(2013)").

[4] The most important Joint Research Centre scientific and policy reports are the reports of the endocrine disrupters expert advisory group: "Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances" (2013); and "Thresholds for endocrine disruptors and related uncertainties" (2013) (https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/thresholds-endocrine-disrupters-and-related-uncertainties; https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/key-scientific-issues-relevant-identification-and-characterisation-endocrine-disrupting).

[5] More information on the multitude of EU activities is available on the dedicated Commission web portal: http://ec.europa.eu/health/endocrine_disruptors/policy/index_en.htm.

[6] C(2016) 3751 projet and C(2016)3752 projet, 16 June 2016.

include EDs. General information on authorisation is described further on the website of the European Chemicals Agency (ECHA)[7].

Once a substance is included in Annex XIV, a manufacturer, importer or downstream user may not place on the market for a use or use such a substance unless an authorisation has been granted for that use or the use is exempted (Article 56(1)).

Applications for authorisation must be submitted to ECHA. The Risk Assessment Committee (RAC) and the Socio-economic Analysis Committee (SEAC) of ECHA are to assess the applications and issue an opinion. The decision to grant or refuse an authorisation is adopted by the Commission, in accordance with the examination procedure applicable to implementing acts.

For an authorisation to be granted, one of the following conditions must be fulfilled:

- the risks from the use of the substance arising from the intrinsic properties specified in Annex XIV are adequately controlled, as documented in the chemical safety report (commonly referred to as 'Adequate Control Route'), or
- it is shown that socio-economic benefits of continued use outweigh the risks to human health or the environment arising from the use of the substance and there are no suitable alternative substances or technologies (commonly referred to as 'Socio-Economic Route'). Only this second route applies to PBT/vPvB substances and substances of equivalent concern to these, as well as to CMR substances for which it is not possible to determine a threshold and to substances of equivalent concern to them. It was decided by the co-legislators that PBT/vPvB substances would be subject in all circumstances to the 'Socio-Economic Route', as they exhibit the potential to distribute within the environment and to contaminate environmental compartments distant to their source. This leads to uncertainties about the prediction of their environmental concentrations through the normal predictive models. Their persistence and their bioaccumulating properties invoke the expectation that concentrations in the environment, by continuous releases, will keep increasing and eventually lead to toxic effects on organisms in the environment.

**- What is understood by "threshold" in the context of application for authorisation?**

As indicated above, two routes for authorisation exist in REACH, depending on the possibility to determine a threshold or not for an SVHC (with the exception of PBT/vPvB, which are always subjected to the 'Socio-Economic Route').

For human health, as described in the ECHA guidance document R.8[8] "characterisation of dose (concentration)-response for human health", the Derived No Effect Level (DNEL) can be considered as an "overall" No-(Adverse)-Effect-Level (NOAEL) for a given exposure (route, duration, frequency) accounting for uncertainties/variability in these data and the human population exposed. Consequently, exposure of humans should not exceed the DNEL. The DNEL, where it can actually be derived, can be considered as a regulatory threshold under REACH for authorisation purposes.

For the environment, the concentration below which no adverse effects in the environmental sphere of concern are expected to occur is considered to be the Predicted No-Effect

[7] http://echa.europa.eu/web/guest/regulations/reach/authorisation.

[8] https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258.

concentration (PNEC). The PNEC, where it can actually be derived, can be considered as a regulatory threshold under REACH for authorisation purposes. More details can be found in the ECHA guidance document R.10[9] "characterisation of dose (concentration)-response for the environment".

In case of a non-threshold substance, RAC will not be in a position to give an opinion whether safe (or acceptable) exposure levels can be reached as it is not possible to determine a DNEL or PNEC, and therefore authorisation can be granted only if it is shown that the socio-economic benefits outweigh the risk to human health or the environment and no suitable alternative substances or technologies are available.

The analysis of whether or not a threshold can be set is the responsibility of the applicant, based on appropriate data to be provided in the application dossier. It is up to RAC to assess this evaluation and to give an opinion. In order to facilitate the Committee's evaluation of applications for authorisation, the RAC has occasionally derived 'reference' DNELs for substances already included in Annex XIV (e.g. for DEHP for its reprotoxic properties) and 'reference' dose-response curves for non-threshold carcinogens (arsenic and hexavalent chromium substances). Those reference values are not legally binding but have been developed by RAC mainly to provide predictability on how it would like the applicants' risk assessment documented.

Applicants for authorisation of uses involving non-threshold substances can describe the remaining risk (after application of proposed operational controls (OCs) and Risk Management Measures (RMMs)) quantitatively/semi-quantitatively based on information on dose-response, or qualitatively if dose-response information is not available. RAC is then expected to give an opinion on the appropriateness of the proposed OCs and RMMs and whether these are effective for attaining the exposure levels in the applicant's exposure assessment and assure that the exposure levels are as low as technically and practically possible. This information on the remaining risk is an input to the socio-economic analysis, which SEAC will use when developing its view on the health and environmental impacts and its subsequent opinion on whether these are outweighed by the benefits of continued use.

## 3) Scientific aspects: what the science tells us on determining thresholds

### ***3.1. Existence or not of threshold for EDs***

As indicated in section 2, the threshold in the REACH context is the biological or practical threshold (e.g. the NOAEL or other thresholds[10]) that can be determined by experimentation and under which no adverse effects are supposed to occur and to which uncertainty factors are applied to determine the regulatory threshold (DNEL/PNEC).

EFSA in 2013 stated that "*the presence of homeostatic and cytoprotective mechanisms, and the redundancy of cellular targets, mean that a certain degree of interaction of the substance with the critical sites or their occupancy must be reached in order to elicit a toxicologically relevant effect (Dybing et al., 2002). Below this critical (threshold) level of interaction, homeostatic mechanisms would be able to counteract any perturbation produced by xenobiotic exposure, and no structural or functional changes would be observed. In certain*

[9] https://echa.europa.eu/documents/10162/13632/information_requirements_r10_en.pdf/bb902be7-a503-4ab7-9036-d866b8ddce69.

[10] See footnote 13.

*developmental stages, homeostatic capacity is limited and this will affect the sensitivity of the organism*".[11]

The endocrine disrupters expert advisory group of the Joint Research Centre concluded in 2013 that "*most experts considered that thresholds of adversity are likely to exist for EDs but may be very low for individual EDs, depending on the mode of action, potency and toxicokinetics and that these thresholds may be particularly low during foetal development (i.e. critical windows of sensitivity) due to the immaturity of homeostatic mechanisms, the immature metabolism as well as the absence of some endocrine axes during sensitive periods of foetal life as compared to adult life stages. For these reasons some experts considered it uncertain whether there is a threshold during development. Several experts also expressed the view that, although thresholds may exist, it might be difficult to estimate with any confidence the biological thresholds of adversity based on currently available standard tests. In addition, small changes in hormone levels during development could have permanent serious consequences for the organism.*

*Other experts expressed the view that a threshold of adversity for EDs might be lower in the developing organism than in the adult and the nature of the effect might be different (severe, permanent change in the foetus versus a less severe effect in the adult), but a threshold of adversity must exist and can be estimated with appropriate testing (involving developmental exposure).*"[12]

## ***3.2. Related uncertainties***

Several uncertainties surrounding the determination of thresholds were highlighted in the debates between scientists. Some are specific to EDs, while most are common to all chemicals.

### *3.2.1 Testing methods*

The endocrine disrupters expert advisory group of the Joint Research Centre noted in 2013 "The limitation on the methods' sensitivity as well as the possible lack of inclusion of sensitive endpoints relevant to ED."[13]

EFSA in 2013 noted that "[…] *a reasonably complete suite of standardised assays (for testing the effects of EAS [endocrine active substances]) is (or will soon be) available for the oestrogen, androgen, thyroid and steroidogenesis (EATS) modalities in mammals and fish, with fewer tests available for birds and amphibians. While downstream effects of disruption of some non-EATS pathways/modalities may be detectable in some standardised apical vertebrate assays, it is important to recognise that standardised mechanistic assays for non-EATS modalities relevant to mammals, fish and other vertebrates are not or not yet available. For invertebrates, relevant mechanistic assays are lacking from the OECD testing suite, mainly due to poor understanding of invertebrate endocrinology. Finally, a range of major taxa, e.g. reptiles or echinoderms have not yet been considered by OECD for any endocrine assay development. It is unknown at present whether it will be possible to read-across to untested groups from tests with other taxa.*"[14]

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11 EFSA(2013), p. 16.

12 "Thresholds for endocrine disruptors and related uncertainties" (2013), p. 11.

13 "Thresholds for endocrine disruptors and related uncertainties" (2013), p. 10.

14 EFSA(2013), p. 2.

In addition, in relation to mammals, EFSA identified as the significant limitation that a weakness "*of the current suite of test methods available for the identification of EDs (and therefore an area for further developing it) is the lack of a single study involving exposure through the complete life cycle of a mammal, from conception to old age or a single study involving developmental exposure with follow-up into old age*". [15]

EFSA further mentioned, relating in general to developmental toxicants including EDs, that "*several recent review reports concluded that current mammalian tests do not cover certain endpoints that might be induced by exposure during foetal or pubertal development but emerge later in life like certain cancers (breast, prostate, testis, ovarian and endometrial) and effects on reproductive senescence*".[16]

### *3.2.2 Critical window of exposure*

EFSA in 2013 stresses that the issues of "*critical windows of exposure*" are "*not unique to EAS [endocrine active substances] but are equally applicable to substances with other mechanisms of action.*"[17]

The endocrine disruptors expert advisory group of the Joint Research Centre concluded in 2013 "[…] *that there is an important difference in maturity and functionality of the endocrine system between pre-and post-natal life. The major issue the absence or immaturity of the homeostatic mechanisms, the immature metabolism and the lack of feedback loops as well as the absence of fully developed endocrine axes during sensitive periods of foetal life […]. These facts increase significantly the concerns in relation to the existence of a threshold of adversity and the possibility, if it exists, to be determined with sufficient confidence. In addition, a small change in hormone levels during development could have permanent serious consequences for the organism.*

*Other experts [of the endocrine disruptors expert advisory group] expressed the view that a threshold of adversity for EDs might be lower in the developing organism than in the adult and the nature of the effect might be different (severe, permanent change in the foetus versus a less severe effect in the adult), but a threshold of adversity must exist and can be estimated with appropriate testing (involving developmental exposure). Finally other possibly sensitive life stages were mentioned like puberty, pregnancy and menopause for which there is a considerable lack of knowledge. Non-consideration of these life stages in testing protocols would be expected to increase the uncertainty in relation to threshold existence and/or reliable approximation of a threshold*".[18]

### *3.2.3 Non-monotonic dose responses and low dose effects*

EFSA in 2013 stresses that the issues of non-monotonic dose response (NMDR) relationships are "*not unique to EAS [endocrine active substances] but are equally applicable to substances with other mechanisms of action.*"[19] Concerning low doses, the endocrine disruptors expert advisory group (EDEAG) of the Joint Research Centre acknowledged in

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15 EFSA(2013), p. 30.
16 EFSA(2013), p. 37.
17 EFSA(2013), p. 46.
18 Thresholds for endocrine disruptors and related uncertainties" (2013), p. 9.
19 EFSA(2013), p. 46.

2013 "*that there is still a lack of scientific consensus on the evidence for 'low dose responses' and this was reflected in the lack of consensus in the EDEAG"*.[20] EFSA similarly "*notes the lack of consensus in the scientific community as to the existence and/or relevance of low-dose effects and NMDRCs [non-monotonic dose response curves] in (eco)toxicology in relation to endocrine disruption, or other endpoints/modes of action.*"[21]

## 4) Policy aspects for the routes for authorisation of EDs under REACH

The consequences in terms of possible regulatory action of whether a threshold for EDs exists can be separated into four main options:

a) All EDs do not have a threshold

b) EDs do not have a threshold, except where it can be demonstrated that a threshold exists

c) EDs have a threshold, except where it can be demonstrated that such a threshold does not exist

d) All EDs have a threshold

Both, options a) and d) are ruled out in the light of the on-going debate in scientific community as set out in section 3. Options b) and c) are not fundamentally different as they require a case-by-case assessment.

Based upon the information provided in the previous sections it may be difficult (albeit not impossible) to determine a safe threshold with reasonable certainty for EDs.

As is the case for all substances subject to the authorisation requirement under REACH, it is the responsibility of the applicant to demonstrate that a threshold exists and to determine that threshold in accordance with Annex I to REACH and it is up to the RAC to assess the validity of the assessment and ultimately decide on the possible existence or not of this threshold.

However, in order to increase predictability and legal certainty for applicants, RAC has set on a case-by-case basis reference DNELs for threshold substances, or reference dose-response curves for non-threshold substances, which industry can use when applying for authorisation. This practice applies for EDs as for other substances.

## 5) Conclusions

The current legislation in Article 60(3)(a) of REACH already lays down that for substances for which it is not possible to determine a threshold, the 'Adequate Control Route' for authorisation is not possible.

Based on the information provided in the previous sections, it is concluded that it is not appropriate to extend a-priori the scope of Article 60(3) to all substances identified under Article 57(f) as substances with endocrine disrupting properties which have an equivalent level of concern.

Consequently, Article 60(3) of REACH will continue to be applicable to those EDs for which it is not possible to determine a threshold. It remains the responsibility of applicants for

[20] Thresholds for endocrine disruptors and related uncertainties" (2013), p. 11.

[21] EFSA(2013), p. 46.

authorisation to demonstrate that a threshold exists and to determine that threshold in accordance with Annex I to REACH. Even though this might be particularly difficult for EDs, it cannot be excluded on the basis of current knowledge that it will be possible. It is up to RAC to assess the validity of the assessment and ultimately decide on the possible existence or not of this threshold. Furthermore, as for other substances, RAC may on a case-by-case basis set reference DNELs, or reference dose-response curves, which industry can use when applying for authorisation. Therefore, as under REACH as it stands today only the 'Socio-Economic Route' can be used when a threshold cannot be determined, and considering the conclusion of the REACH Review that regulatory stability is desirable, the Commission will not propose a change to the legislation.