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CHEM Trust's position on the REACH review of the authorization of Endocrine Disrupting Chemicals (EDCs)

Summary

The EU chemical legislation REACH mandates the EU Commission to review, before June 2013, whether a threshold or non-threshold approach to industrial chemicals with endocrine disrupting (ED) properties should be adopted within the REACH authorization procedure. In CHEM Trust's view endocrine disrupting chemicals (EDCs) should be treated as non-threshold substances equivalent to chemicals with PBT/vPvB[a] properties. This is because there is currently no scientific evidence that reliable threshold values for EDCs can be set with sufficient certainty. The rationale for adopting a non-threshold approach is based on the following:

- Current testing requirements in REACH are inadequate to identify EDCs and do not cover all ED relevant endpoints. For all but the high production volume chemicals, the tests do not even include the most relevant sensitive exposure time window, and therefore the tests are not sensitive to identify effects which may occur at low doses. Moreover, none of the tests currently in use include all potential adverse effects that may manifest later in life due to *in-utero* exposure.
- The known existence of i) non-monotonic dose responses (NMDRs) and ii) low dose adverse effects for some EDCs, casts doubt on the current mechanism of setting safe levels of exposure.
- Early life exposure to EDCs may cause lasting and severe irreversible damage, and such effects may even be carried over to subsequent generations that were not originally exposed.

Moreover, research has shown an alarming increase in the diseases which may be caused by hormone disruption in the population at large. Additionally, numerous animal studies and epidemiology have strengthened the concern that these adverse trends in the incidence of reproductive problems, hormone related cancers and other metabolic diseases are partly linked to exposure to EDCs. Furthermore, recent research has highlighted the likelihood that exposure to many EDCs, even at low levels, may give rise to additive effects. These developments in scientific research make the topic a matter of urgency that now requires a response at the political level. The European Commission and Member States should not miss this chance to reduce exposures to EDCs and require their substitution with safer alternatives, when available.

[a] PBT=Persistent, Bioaccumulative, Toxic; vPvB=very Persistent, very Bioaccumulative

The need to improve EU EDCs policies to ensure better protection

Current EU regulation does not adequately address the health threats of EDCs; measures to reduce exposures to protect people and ecosystems are long overdue. Health concerns related to EDCs include reproductive and fertility problems, hormone-related cancers, neurological impairment, and obesity and diabetes.[1-3] Biomonitoring studies have shown that the general European population is exposed to many different EDCs via food, water and indoor air.[4,5] Wildlife is also suffering from exposure to EDCs. Fish, birds, otters and even polar bears are showing adverse effects on reproduction in polluted areas all over the world.[1,2,6,7] Very worryingly, this means EDCs are threatening the survival of some populations of certain species.

The REACH EDC review

The EU chemicals law REACH regulates industrial chemicals and it aims to ensure a high level of health and environment protection whilst also encouraging innovation. The REACH review of the authorization of EDCs[b] presents an important opportunity to trigger substitution of EDCs with safer alternatives: By June 2013 the EU Commission is legally mandated to assess whether EDCs identified as substances of very high concern (SVHC) in REACH should generally be treated as non-threshold chemicals in authorization. The Commission shall *take into account latest development in scientific knowledge* and *present legislative proposals, if appropriate*.[b]

The REACH authorization procedure establishes a stricter regulatory control regime for SVHCs. EDCs are subject to the authorization procedure on a case-by-case basis when there is scientific evidence for probable serious effects (Article 57f).[c] Chemical manufacturers/importers then have, in principle, one of two ways to obtain an authorization. (i) The first option is based on deriving a safe level (DNEL/PNEC)[d] and demonstrating adequate control of the risk according to REACH Annex 1, section 6.4. (This is the so-called 'adequate control of the risk route'.) It is only open to those chemicals for which it is considered safe levels can be set, that is the chemicals for which thresholds for effects can be derived. (ii) The second option foresees that an authorization can only be granted if the socio-economic benefits outweigh the risk *and* if there is no available alternative. (This is the so-called 'socio-economic route'). This option applies to all substances where the risks cannot be adequately controlled, i.e. all SVHCs for which it is not possible to determine a threshold value according to Annex 1 (non-threshold chemicals) such as for PBTs/vPvBs and PBT/vPvB-like substances. As the legislation currently stands, the uses of an EDC may be authorized, based on a single substance risk assessment leading to a predicted safe "no

[b] REACH article 138 (7): *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.*

[c] REACH article 57f: "*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 to those of other substances listed in points (a) to (e) and which are identified on a case-by-case basis (…*).

[d] DNEL=Derived No Effect level, PNEC=Predicted No Effect Concentration

effect" - level. CHEM Trust considers that this approach is wrong because it ignores the difficulties of setting reliable threshold for effects from exposure to EDCs (see arguments outlined below). Moreover, it ignores the potential for combined effects due to exposure to many EDCs concurrently. Therefore, we propose that EDCs should only be authorized via the 'socio-economic route', when there are no available alternatives.

Setting thresholds for EDCs is undermining health and environment protection

If a threshold cannot be established for a SVHC using the methodologies of annex 1, section 6.4 (article 60.3.) it is excluded from the 'adequate control route.' CHEM Trust considers that it is not possible to definitively determine whether or not a threshold does or does not exist for EDCs largely because the power of experiments to determine such thresholds will always have significant limitations.[e] Thus, whether or not a threshold approach is taken, is based on the theoretical considerations of biological plausibility.

EDCs exert many different biological effects and many of them are unlikely to have a threshold, in particular when receptor binding is involved.[8] The Endocrine Society argues that in almost all situations, pre-existing endogenous hormone levels exist, and any additional exposure will increase this load in a threshold-independent manner.[9] Moreover, in recent epidemiological studies of very large populations, thresholds were not observed.[2] In contrast, others, including industry, argue that the known hormone receptor mediated interactions are threshold events and that homeostasis mechanisms prevent the occurrence of adversity in most cases. This overlooks the fact that during development *in-utero*, one of the periods of life most sensitive to endocrine disruption, the homeostatic control is not fully functional or not yet developed.[2,8]

In the deliberations for the REACH review, the important question is: can a safe no-effect level for an EDC be determined with sufficient certainty to protect human health and the environment, by using the specified methodology? Or, are there greater uncertainties for EDCs?

A key argument for adopting a non-threshold approach for EDCs is that the current risk assessment methods are inadequate to identify potential effects at the low dose range and therefore are not suited to identify thresholds. This will remain the case for quite a while for two major reasons:

a) The existence of the non-monotonic dose response (NMDR): It has been demonstrated in several studies and recent reviews that some EDCs do exhibit non-monotonic responses in *in-vitro* as well as *in-vivo* studies.[8, 10] Moreover, NMDRs are a well-known phenomenon that are taken into account when using certain endocrine disruptors (e.g. tamoxifen) in the pharmaceutical treatment of some diseases. Such NMDRs are not necessarily unique to EDCs, but are likely to be more common in EDCs as compared

[e] For the same reason, CHEM Trust believes that it is not possible to definitively determine whether there are thresholds of adverse effects for any other chemical.

to chemicals operating via other mechanisms, because of the way in which the endocrine system works. Unfortunately, the existence of NMDRs means that safe levels in the lower dose range are unsound if based on the usually applied extrapolation from high-dose testing to low doses and the assumption of a more classical dose response curve which does not change direction. Furthermore, it means that without testing at many low doses below the existing so-called no observed adverse effect levels (NOAELs), these NOAELs cannot be relied upon to be genuine. And with the EU drive to minimize costs to industry, as well as minimizing animal testing, adequate low dose testing is unlikely to be undertaken for each substance.

b) The lack of adequate test methods to identify ED properties: Research has pointed to the fact that currently available test methods are inadequate and do not cover all potential effects of EDCs.[2] The tests required under REACH, for chemicals below a production volume of 1000 tonnes per annum, do not even include the most important sensitive exposure windows of development. This means that adverse effects at lower dose levels may be missed. Hormones have very complex actions, simultaneously in various tissues, and can therefore affect several endpoints with different sensitivity. EDCs are most damaging in certain sensitive life stages, and exposure during early development can affect a person's health for their entire life time (developmental programming). For example, current test methods do not cover all effects which manifest at old age (such as hormone-related cancers due to *in-utero* exposure, nor effects on reproductive senescence (menopause)). This leaves major uncertainties for the reliability of setting NOAELs which usually form the basis for "no effect" levels.

Developments in scientific knowledge necessitate political action

According to the REACH legal text, the review of which route to authorization is most appropriate for EDCs must also take into account *the latest developments in scientific knowledge.*[b] CHEM Trust considers that there is a large and growing body of research which suggests that the characteristics of EDCs and the totality of exposures to them is having a negative impact on human health and is at least partly responsible for some adverse human health trends. The concerns that EDCs are linked to many adverse health trends, particularly including rising levels of obesity and diabetes, have strengthened in recent years and this increase in scientific knowledge warrants doing more to ensure that EDCs are substituted with safer alternatives.

Therefore, in addition to the scientific uncertainty that is evident in setting thresholds using the methodology outlined in Annex 1, there are additional reasons as to why there should be a political decision to adopt a non-threshold approach for EDCs. These include:

- **Adverse health trends linked to EDC exposures**: Adverse health trends over time are now confirmed for male reproductive health in many EU countries (including increased incidence of

genital birth defects in baby boys and decreased sperm counts). Indeed in many EU countries it is now considered that 1 in 5 young men are now sub-fertile. Moreover, research has shown that over the last 30 years hormone related cancers (including breast, testicular and prostate cancer) have increased dramatically, including a recent increase in breast cancer in young women.

- **Time lag of effects of EDCs:** The scientific knowledge of how EDC exposure during early development can have permanent effects has increased. Such perturbations of developmental programming may only become visible decades later. The potential for irreversible adverse effects following *in-utero* (and early childhood*)* exposure to EDCs highlights that there is too much at stake if the usual risk assessment is flawed. In the case of the PBT/vPvBs and PBT/vPvB-like substances, the added uncertainty in the risk assessment in relation to long-lasting and irreversible effects was the crucial argument for exempting them from the option of the 'adequate control route' to authorization. Similarly, for EDCs, if the risk assessment is wrong, and effects do come to light, due to their delayed effects there will be impacts for many years to come even after exposure has stopped.

- **Threat for future generations:** New research has shown the potential for some EDCs to affect future generations by negative effects on our genes being passed from mother to baby (trans-generational transmission of the altered gene programming). Such so-called epigenetic effects may manifest in the next generation and even over several subsequent generations.[11] If the effects of exposure can indeed be transmitted to subsequent generations, this would have major public health implications, as not only the current generation exposed *in-utero* is affected, but also their children and their grandchildren.

- **Mixture effects**: Humans and ecosystems are not exposed to one substance only but to many EDCs at the same time. The potential for mixture effects has been clearly demonstrated in animals and the knowledge on combined exposures to many EDCs has rightly caused concerns among policy makers (see Council conclusions on mixtures[12] and Danish study on 2 year old children[13]). Exposure to many EDCs concurrently cannot be taken into account using the methodology in Annex 1, which is a single substance approach. Nevertheless multiple exposures must influence the political decision to deal with these chemicals in a more robust way. Our proposal is therefore that the potential for mixture effects is a vital and necessary component of the rationale for the Commission's political decision to include EDCs in the scope of 60.3.

The way forward for better health of humans and wildlife

We therefore propose the addition of a new entry in Article 60.3. (d) "substances identified under Article 57 (f) having endocrine disrupting properties". This would effectively block EDCs from the 'adequate control of the risk' route to authorization and ensure that EDCs are to be treated as non-threshold chemicals under REACH authorization.

Introducing this change would be the best way to deliver the original aims and aspirations of the REACH authorization procedure, which is the progressive replacement of SVHCs: If EDCs are to be only authorized via the socio-economic route, it would mean that if there is a safer alternative, it would have to be used instead.

In a nutshell: CHEM Trust proposals for changes in REACH:

- Add a new Article 60.3(d) "substances identified under Article 57 (f) having endocrine disrupting properties" which would ensure EDCs would need a stringent socio-economic and 'alternatives' assessment, stimulating innovation and the development of safer alternatives.
- Update Annexes VII-X with new screening and testing requirements targeted to identifying EDCs (and at least finally include the new extended one generation test with endpoints on immune- and developmental toxicity).
- Update Annex I and introduce a separate EDC assessment, in analogy to a PBT assessment, with an obligation to minimize exposures and emissions to humans and the environment (when the guidance for the implementation of the EDC criteria is developed).
- Create a new Annex (e.g. XIII B) with the new EDC criteria, for industry to apply within their chemicals safety assessment according to Annex I (also following the development of guidance on EDC criteria).

Encouraging the replacement of EDCs with safer alternatives: a crucial step towards innovation

In conclusion, CHEM Trust considers there is no scientific evidence that a threshold for EDCs can be established with reasonable certainty taking into account current scientific knowledge. Given the adverse health trends linked to widespread EDC exposure, these findings warrant a clear political response within the REACH review.

There is now a wealth of new science for the EU Commission to take into account in their review (see Annex of this briefing for more details). Moreover, the European Parliament has strongly urged the EU Commission to amend legislation to reduce exposure to EDCs and made clear its view that current science does not allow safe levels to be set. A strong political push is also coming from several EU Member States: the recent decisions or announcements by individual Member States to act independently in restricting uses of EDCs (such as France on BPA, Denmark on parabens) illustrate the perceived lack of required minimum regulatory measures on EDCs at the EU level. As both the proper control of SVHCs and the good functioning of the EU internal market are key aims of the REACH authorization procedure, clear rules for the treatment of EDCs are required to avoid further distortions of the internal market.

People and ecosystems are continuously exposed to low doses of many EDCs concurrently and the lists of diseases and disorders that are linked to these exposures is growing. The health care costs for the treatment of such diseases will be significantly reduced if EDCs are adequately regulated. The costs for industry in the short term will actually be the initial investments in the transition to greener chemistry, and they will recoup these expenses in the medium- to long-term, through their innovative products.

The EU Commission and Member States have to make a serious choice: to carry on with business as usual and allow EDCs to remain on the market with flawed safety assumptions OR to update this law in view of the current scientific knowledge.

Annex

Widespread scientific support for tighter controls and substitution of EDCs

Many research organizations and scientists have been worried for several years about the potentially enormous implications of exposure to EDCs for human health, wildlife and future generations. If it was decided, say forty years ago, to start a deliberate global experiment of exposing the general population to EDCs, one would expect to see a very similar picture as is evident today: rising global trends of diseases linked to hormonal disorders, impaired reproduction in many species - including humans. In the last few years, the science investigating the links between EDC exposure and adverse reproductive outcomes, as well as effects on thyroid function, brain function, obesity, metabolism, and diabetes, has progressed. The EU Commission must take note of the wealth of science that exists and use it to inform their review.

Scientists globally raising concerns about EDCs: Policy lags too far behind science

The recent landmark report on EDCs from the **World Health Organization (WHO) and the United Nations Environmental Programme (UNEP)**[1] compiled by internationally respected scientists, published in February 2013, summarizes the state of the science. It highlights that the data from wildlife, laboratory studies, and epidemiological research, suggests a greater role for EDCs in the origin of diseases than previously thought. The report concludes that, based on current knowledge, no safe threshold can be assumed: *"there is no threshold for EDC effects due to the presence of active hormone pathways, and EDCs are likely to have effects at low doses"*.[14] The authors also published a consensus statement on the state of the science, pointing to the significance of early life exposures to EDCs and their consequences for the development of serious and irreversible diseases later in life.[15] Absence of safe thresholds and early life sensitivity shows how important it is to eliminate exposure such that serious and irreversible impacts are prevented. Treating EDCs as non-threshold chemicals, rather than setting arbitrary safety levels, is vital in achieving this.

The **Endocrine Society**, which is the international society of leading experts on the human endocrine system, provided an extensive summary of the science that justifies the concern about the effects of EDCs on humans and wildlife in their Scientific Statement, 2009.[16] In their 2012 statement[9] they reiterate that EDCs cannot be evaluated as if they are general toxic chemicals. They describe the importance of the developmental stage and the potential for very low-dose exposures to have serious and irreversible effects. Exposure to a presumptive "safe" dose of a chemical may impact a life stage when there is normally no endogenous hormone exposure. The Endocrine Society concludes that a threshold for EDCs cannot be assumed.

As early as 2006, prominent scientists signaled their worries about the risks from EDCs to human and wildlife health: 170 scientists adopted the **Prague declaration**[17]. At that time the scientists were advocating for a stronger focus on human and wildlife health in the context of the REACH negotiations. Now 7 years later in the newly released **Berlaymont declaration**[18] 89 leading public health scientists from around the world express their concerns that the prevalence of endocrine-related diseases is higher than it has ever been. They call on the EU Commission to implement a regulatory regime for EDCs that is based on sound scientific principles and that scientific uncertainty should not delay regulatory action. In addition, they strongly advocate for updating the testing requirements with adequate methods for identifying EDCs and for developing a targeted research strategy to fill knowledge gaps.

The **European Environment Agency (EEA) report** highlights in their report, **Weybridge + 15** from 2012[19], that EDCs typically have many characteristics that make risk assessment difficult, such as critical time windows for exposure, the long latency between exposure and effect, and the capacity for every similarly acting EDC to contribute to a 'mixture effect', i.e. add up together. In particular, they challenge the traditional risk assessment paradigm of being able to identify/set a threshold dose below which a chemical fails to produce effects.

Political calls for treating EDCs as non-threshold chemicals

The elected representatives of the European Parliament called on the EU Commission to amend existing legislation, or come forward with new legislative proposals, to reduce the public exposure to EDCs, and particularly that of vulnerable groups.

EU Parliament: EDCs should be treated as having no safe levels

In their Resolution from March 2013, **the EU Parliament**[20] *stresses that current science does not provide sufficient basis for setting a limit value below which adverse effects do not occur, and endocrine disrupters should therefore be regarded as 'non-threshold' substances, and that any exposure to such substances may entail a risk, unless the manufacturer can show scientific proof that a threshold can be identified, taking into account increased sensitivities during critical windows of development, and the effects of mixtures.*

Views from EU Member States

Several Member States have contributed to the debate by providing papers and reports to the EU Commission in the context of the discussion in the EDC Ad-hoc group and CARACAL meetings (the meetings of the Competent Authorities on REACH and Classification and Labeling). All papers are available on the circa database.

Sweden: The Swedish Chemicals Agency (KEMI) recently published a review on the question whether it is possible to determine thresholds for the effects of EDCs.[21] The report contains a summary of the

arguments based on scientific publications that have investigated this question. Based on this analysis KEMI concludes that, from a regulatory perspective, EDCs as a default, should be regarded as substances for which, in practice, it is not possible to determine safe threshold concentrations.

Denmark: The Danish Ministry of the Environment has formed their position based on a report by the Danish Centre on Endocrine Disrupters.[8] This report compiles the scientific evidence available on NMDRs and the uncertainties of deriving reliable thresholds for EDCs. Their report provides clear examples of chemicals which have opposite effects at high and low dose levels, which makes current risk assessment methodologies fatally flawed because they may miss low dose effects. Consequently, the Danish position is that safe no-effect levels cannot be determined for EDCs with sufficient certainty and that EDCs are of particular concern.

Spain and Lithuania are also of the opinion that thresholds cannot be set with sufficient certainty and that the scope of article 60.3 should be extended to EDCs. **Belgium** agrees that for the moment EDCs should be treated as non-threshold substances by default. However, they propose to include this consideration in the process of EDC identification instead of changing the REACH text.

Unfortunately, the UK has a totally different perspective. It asserts that thresholds "*surely exist*". CHEM Trust disagrees with this position (see detailed CHEM Trust critique of UK position).[22]

Global context

EDCs have long been on the international research agenda. Furthermore, in 2012, EDCs have been nominated as an issue of global importance under the UN process SAICM (Strategic Approach to Chemicals Management). The global community recognized *"…potential adverse effects of endocrine disruptors on human health and the environment"* and *"…the need to protect humans, and ecosystems and their constituent parts that are especially vulnerable."* One of the recommended actions specified the need to *"provide up-to-date information and scientific expert advice to relevant stakeholders for the purpose of identifying or recommending potential measures that could contribute to reductions in exposures to or the effects of endocrine-disrupting chemicals, in particular among vulnerable populations."*

The focus on the threats of EDCs in international fora such as SAICM will trigger the search for better solutions at the global level. The need to develop chemicals without ED properties is therefore an important challenge, which also provides business opportunities. Researchers have started looking into designing chemicals without ED properties and developed a stepwise approach which may prove useful to companies and academia.[23] Moreover, tools for finding alternatives such as the Green Screen[24] and substitution portals such as the EU SUBSPORT database[25] are becoming more widely available and provide assistance to manufacturers and chemical users for replacing chemicals of concern.

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