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CHEM Trust's Contribution to the Ongoing Debate on Criteria for EDCs¹

There are well-founded concerns about the effects of endocrine disrupting chemicals (EDCs) in wildlife, with sex-hormone disruption related effects having been reported in many species. Furthermore, EDCs are suspected of playing a role in disrupting human brain development, the deterioration of male reproductive health including defects of the genitals in baby boys, the increased incidence of male and female hormone related cancers and in the increase in cardiovascular disease, obesity and diabetes. In the current debate on suitable regulatory criteria in the context of REACH and the EU Plant Protection Products Regulation (EC No 1107/2009) (referred to in this document as the 'Pesticides Regulation') several proposals by national regulatory agencies have been made.

In section 1 of this paper, CHEM Trust has outlined its position on some of the main issues raised. Following this in section 2, a more detailed critique is provided of some of the suggestions relating to the criteria to identify chemicals with ED properties which have been put forward by various government departments in some Member States. Appendix I lists two other documents by CHEM Trust which relate specifically to the regulation of chemicals with ED properties. Firstly, an earlier discussion paper by CHEM Trust and WWF-EPO relating to proposed classification of EDCs, and secondly a position paper by several Environment and Health NGOs, Consumer Organisations & Trade Union's relating to overarching needs for the proper regulation of EDCs (dated April 2011). Details of the CHEM Trust web-sites where these two documents can be downloaded are also provided.

¹ **This paper has been developed with input from WWF European Policy Office.**

It should be realised that intrinsically linked to the interpretation of any criteria for the identification of chemicals with ED properties are the test methods which will provide the information to determine if the criteria are met. However, whilst new test methods have been developed or are under development at the OECD, most of these new test methods are not part of existing minimum standard information requirements for pesticides or for industrial chemicals under REACH. Unfortunately the current data base on existing chemicals, including pesticides, is therefore mostly populated with test methods, including out-dated versions, which do not include all relevant endpoints needed for the identification of chemicals with ED properties. Moreover, it is likely that many chemicals with endocrine disrupting properties disrupt biological processes for which test methods are not yet developed and to address this issue, the OECD are looking at 'novel endpoints'. We consider that research should focus on the development of non-animal test methods suitable for regulatory purposes.

Section 2 provides critiques of the following proposals:-

- i) The proposals of German Federal Institute for Risk Assessment (BfR) and the UK's Chemicals Regulation Directorate (CRD) entitled "Regulatory Definition of an Endocrine Disrupter in Relation to Potential Threat to Human Health" (dated 16th May 2011). This is referred to as the Joint De-UK Position Paper and abbreviated to the De-UK PP.
- ii) The proposals of the Danish Environmental Protection Agency, "Establishment of criteria for endocrine disruptors and options for regulation" (dated 17th May 2011).
- iii) The German Institute for Occupational Safety and Health (BAuA) proposals re human health criteria for endocrine disruption according to article 57(f) of the REACH Regulation (dated 20th October 2010).
- iv) The Danish EPA's Comments to BAuA document on human health criteria for endocrine disruption (ED) according to Art. 57 (f) of the REACH regulation (dated 30th November 2010).

- v) The response of the French ANSES (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail) to the German BAuA's proposal re 57(f) of REACH (dated 10th January 2011).
- vi) The German Federal Environment Agency's (UBA) "Discussion paper on the interpretation of Art 57(f) REACH with respect to substances having endocrine disrupting properties hazardous to the environment" (dated 26th May 2010).
- vii) The Proposal of the German Federal Environment Agency (UBA) entitled "Substances with endocrine disrupting properties in the environmental risk assessment under the new EU regulation on plant protection products (EC1107/2009) – A Proposal for a differentiated decision making" (Dr Tobias Frische) (dated 25th January 2010).
- viii) The UK Chemicals Regulation Directorate (CRD) proposal re "Definition of an ecotoxicological endocrine disrupter for regulatory purposes" (dated April 2011).

The Pesticides Regulation mandates the Commission to present a draft of the measures concerning scientific criteria for the determination of endocrine disrupting properties. This mandate relates to criteria to identify pesticides with ED properties relevant for human health, although these will no doubt have an important bearing on the criteria for pesticides with ED properties relevant for wildlife. Moreover, such criteria will likely serve as the basis for the identification of such chemicals under REACH and in other legislation where chemicals with ED properties are targeted.

CHEM Trust welcomes the attempts made by Member States to initiate discussions on this topic and would like to succinctly make the following main points in response.

Section 1: CHEM Trust's concerns regarding the criteria for chemicals with ED properties

CHEM Trust considers that the following principles should play a role when developing an assessment and identification scheme for EDCs:

1. Provide protection before damage occurs

Given the current scientific concerns relating to the potential contribution of EDCs to several serious diseases, many of which are on the rise in the population at large, a regulatory approach is needed which enables timely action rather than waiting for absolute proof that damage is linked to a particular chemical.

2. Must not wait for full knowledge of the mechanism of action

Exact knowledge about the mechanism of action of how the endocrine disrupting property is exerted should not justify delay of measures to minimize exposure, i.e. this should not be a prerequisite for the identification of a chemical with endocrine disrupting properties.

3. Definition of EDCs

We consider that the WHO/IPCS definition provides a useful scientific working definition. However, for protective legislation this requires too high a bar of proof that a substance, by disruption of the endocrine system, “**consequently** causes adverse health effects”. This is because mechanisms of action can take years or decades to establish, as exemplified by chemicals such as DDT or TBT. Of the definitions put forward by others in the EU, CHEM Trust therefore favours the definition put forward by experts at the Danish Centre on Endocrine Disrupters which still requires adverse effects but removes the word ‘consequently’. Thus, an endocrine disrupter “is an exogenous substance or mixture that alters function(s) of the endocrine system and causes adverse health effects in an intact organism, or its progeny, or (sub)populations.”

4. Need for better regulatory acceptance of *in vitro* information

In order to move away from animal testing, in future, regulation should be based on *in vitro/in silico* methods provided these are of such a standard that they are deemed sufficiently predictive. Until then, the evidence of ED properties in an intact organism, such as from *in vivo* screening tests in an intact animal or from other *in vivo* tests (i.e. *in vivo* evidence without details of the mechanism of action, but with some alterations in the endocrine system) should be sufficient to establish the chemical as having endocrine disrupting properties. *In vitro* information should be used as supporting evidence to avoid unnecessary testing.

5. Adverse effects must be reasonably predicted

Changes to the endocrine system in an organism following exposure to a substance should always be regarded as a concern. Both REACH and the Pesticides Regulation require a precautionary interpretation of whether or not the effects seen are adverse, because they stipulate 'probable serious effects' and 'may cause adverse effects' respectively. With regard to ecotoxicological EDCs, effects on sperm or egg-laying should certainly be considered likely to effect population levels.

6. Non GLP and non-internationally agreed test methods must be able to inform the hazard assessment

The assessment of ED properties should consider all available information based on a weight of evidence approach. Non OECD tests or non-internationally agreed tests which are well reported should be appropriately considered.

7. Hazard not risk based approach to identify ED properties

Potency considerations should not be part of the assessment as to whether a chemical has endocrine disrupting properties. As stipulated by the Pesticides Regulation, it has to be a hazard-based identification process such that potency considerations should not play a part in the identification of whether or not a substance possesses ED properties. Such an approach would mirror the requirements for the assessment of whether a chemical has CMR properties, where potency is also not taken into account. Data on the potency of a chemical could be taken into account for prioritization purposes under REACH, but should not influence any determination of whether or not a chemical possesses endocrine disrupting properties.

8. Need to recognize the potential effects of EDCs on the next generation

Specific emphasis in the assessment has to be given to the special properties of chemicals with ED properties, such as critical windows of vulnerable development as well as epigenetic effects.

9. Need to recognize other properties of EDCs, such as potential non-linear dose response curves and low dose effects, including possible lack of thresholds.

The identification of those chemicals considered to have ED properties needs to be based purely on the toxicological evidence of endocrine effects – irrespective of exposure or dose thresholds. It is unlikely that all chemicals with ED properties have a threshold dose below which there are no effects. It should also be recognized that chemicals with ED properties have been shown to exhibit non-linear dose response curves, such that ‘no effect levels’ or ‘low dose effects’ can not be predicted from testing at high doses.

10. A chemical with ED properties should trigger regulation even if these are not the ‘lead’ effect.

It should not be a prerequisite that the ED related adverse health effect is the most sensitive effect that has been identified and that it should be the lead effect driving classification. To require the ED effect to be the lead effect would ignore the potential for mixture effects, when it is well known that there is exposure to many substances with ED properties which have been shown to cause additive effects in laboratory studies. Furthermore, the situation should not be allowed to arise whereby a chemical with more potent ED properties is not subject to the cut off, just because there is another effect which manifests at lower dose levels, but which does not require such strict regulation – while on the other hand a chemical with less potent ED properties is banned because the endocrine effect is considered the ‘lead’ effect.

Section 2: CHEM Trust’s critique of various proposals by regulatory agencies of some Member States

- i) The proposal of the German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung BfR) and the UK’s Chemicals Regulation Directorate (CRD) entitled “Regulatory Definition of an Endocrine Disrupter in Relation to Potential Threat to Human Health” (dated 16th May 2011).**

The Joint De-UK Position Paper (abbreviated to the De-UK PP) related to the criteria to identify pesticides with ED properties relevant for human health, and did not address the criteria to identify pesticides with ED properties relevant for wildlife.

CHEM Trust disagrees that potency should be considered

The De-UK PP makes what CHEM Trust considers to be a fundamentally incorrect assumption that chemicals with ED properties should be defined as such only if the substance is potent in this respect (para 6). Such a requirement is neither specified in REACH, nor the Pesticides Regulation. Moreover, targeting only potent EDs would not address the crucial concern that exposure to many such substances, albeit each with relatively weak potency, may be causing effects in the population at large, because chemicals with endocrine disrupting properties could act additively to cause effects in vulnerable people.

Definition of 'endocrine disrupting properties'

The De-UK PP proposes using the restrictive WHO/IPCS definition as a starting point for characterising an ED for regulatory purposes. This definition requires that an adverse effect is caused in an intact organism, and furthermore, requires that this adverse effect is known to be a **consequence** of the altered endocrine function. It states that “an ED is an exogenous substance or mixture that alters function(s) of the endocrine system and **consequently** causes adverse health effects in an intact organism, or its progeny, or (sub) populations.” Furthermore, the De-UK PP accepted the following definition (WHO/IPCS 2004) of adversity: “A change in morphology, physiology, growth, reproduction, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences.” The De-UK PP considers that endocrine perturbation is not, in itself, an adverse effect, but rather a mechanism²/mode of action (MOA) of toxicity. They consider that to merit regulatory attention, the perturbation must result in adverse effects in an intact animal.

CHEM Trust would like to stress that the above WHO/IPCS definition of EDC does NOT equate to what is required to show 'endocrine disrupting properties', as stipulated in EU legislation. We consider that the WHO/IPCS definition provides a useful *scientific definition*, but it requires too high a level of proof for a protective regulation. The difficulty here is to prove beyond doubt that the adverse effect is a definite *consequence* of endocrine disruption rather than the observed endocrine disruption being a secondary effect of some other mechanism of toxicity. This could leave regulatory agencies vulnerable to laborious and difficult-to-defend legal challenges from industry, either at the outset, or as and when further information became available.

CHEM Trust considers that effects should not have to be proven to be a direct consequence of the endocrine disruption

We consider that the use of the term 'endocrine disrupting properties' as found in the Pesticides Regulation and REACH suggests that a lower level of proof is required, which is

² The BfR consider that mechanism of action should be defined as the totality of the mechanistic steps necessary for a certain toxic effect, while the term mode of action comprises a less detailed description of the mechanism or several key events within the mechanism (see Marx-Stoelting P et al. (2011) *Reprod Toxicol*).

needed for the regulatory setting in order to allow for timely action rather than regulation having to wait until damage has already occurred. It must be shown that the endocrine system is perturbed (to justify the term endocrine disrupting properties) but there is not a need to show that the adverse effects are a direct consequence of the perturbation of the endocrine system. Furthermore, the REACH legislation requires only that a chemical with ED properties must cause probable serious effects before it can be designated a SVHC, while the Pesticides Regulation requires evidence sufficient to determine that it may cause adverse effects. These requirements should not be made more burdensome during the actual implementation of the legislation.

It is clear that the use of the term ‘endocrine disrupting properties’, as used in REACH and the Pesticides Regulation, was not intended to only embrace chemicals which definitely ‘consequently cause adverse health effects’, otherwise the terms ‘probable serious effects’ or ‘may cause adverse effects’ would not have been included in REACH and the Pesticides Regulation, respectively. It is clear that the terms used in the EU legislation (probable and may) require a less definite adverse effect to be identified and moreover, do not require absolute certainty that the adverse effects are a consequence of the ED activity.

As noted in the UK CRD’s proposal of December 2010 relating to the definition of an ecotoxicological ED, which informed this joint DE-UK PP, “endocrine disruption in its widest sense is a perturbation of the normal endocrine homeostasis, for instance, a change in the circulating levels of a particular hormone. However, such perturbation in itself is not considered to be an adverse effect, as the endocrine system is naturally dynamic and responsive to various stimuli as part of its normal functioning. In this context, endocrine perturbation is considered as a mode of action, potentially on a pathway to other outcomes, rather than an ecotoxicological endpoint in itself. Crucially, to designate a substance as an ecotoxicological ED, any endocrine perturbation must result in, or be plausibly connected with,” an adverse effect (para 16). We concur with this, in that we agree the chemical must be shown to cause adverse effects in the laboratory or to cause effects which may be predicted to lead to adverse effects in the environment – and that it must be plausible that these effects are connected with the endocrine disruption observed. However, we conclude that given the difficulty of proving that the adverse effects seen are a direct **consequence** of the perturbation of the

endocrine system, rather than secondary to another mode of action, it would not be appropriate to enshrine the IPCS/WHO definition of an EDC in any legal text or guidance.

Chemicals with CMR and ED Properties

The De-UK PP suggests that since all endocrine disruptors do not represent the same hazard to humans, there is a need for a tiered evaluation to identify those of high regulatory concern. They suggest that substances should first be evaluated to see whether they meet the CMR criteria, because if any of these are met, then regulation equivalent to that of a substance with ED properties must already ensue, such that there is no additional value in pursuing the ED issue for CMR 1A or 1B substances. However, they do note that under REACH, as the authorisation process only addresses the hazard property for which inclusion on the SVHC list was proposed, it may still be appropriate to assess whether the CMR substance also has ED properties. We concur, but suggest that for industrial chemicals meeting the CMR criteria under REACH, their ED properties should always be examined if they are to be authorised on the basis of 'adequate control of the risk'. Therefore, we suggest that substances should be nominated for the REACH candidate list on the basis of both their R and ED properties. This is because a 2013 review of how chemicals with ED properties are treated under REACH (see Article 138(7) of REACH), might block the 'adequate control of the risk' route to authorisation for such chemicals. In addition, the identification of a carcinogenic substance as also having ED properties could be of regulatory importance if and when combined exposures to ED chemicals are addressed.

Data gathering and evaluation

We concur with the De-UK PP that all available data should be evaluated with regards to identifying whether there are ED properties. Furthermore, we note that they consider that the chemical must be shown to be able to cause adverse effects in a whole animal study, but we stress that as this is a hazard assessment, such effects in the animal study should not have to be manifest at exposure levels similar to those recorded in the environment or in the population at large, rather it is an assessment of whether such adverse effects can indeed be caused by that chemical in a laboratory setting. We accept that all information must be looked at to determine whether the effects noted are likely to

be mediated via disruption of the endocrine system, and that both *in vivo* and *in vitro* mode of action or mechanistic studies may provide valuable information to make such an assessment.

Thus, in conclusion, we do not accept that it is necessary to show beyond doubt that the adverse effects are a direct consequence of the perturbation of the endocrine system as the legislation only requires the substance to have 'endocrine disrupting properties' which can be established by the reporting of effects on hormone levels, or effects on endocrine organs. In the drive to eliminate unnecessary animal testing, it would not be appropriate to require definite proof that the adverse effects were a direct consequence of the perturbation. We are therefore concerned that in paragraph 23, the De-UK PP suggests, in relation to establishing whether endocrine disruption applies to the toxic effect, that "where a definitive conclusion cannot be reached, then the evaluation should highlight where additional studies may help provide the necessary clarification." Nevertheless, we accept that there must be scientific information to show that the chemical affects the endocrine system and that the OECD framework 'tool box' provides test methods which can provide such information. In this, it should be noted that it is not just OECD screens and tests which can provide this information, as there are many other test methods, often conducted in independent or academic laboratories which are undertaken and reported to a sufficient standard that they can be used to determine that a chemical affects or perturbs the endocrine system and therefore has endocrine disrupting properties. Indeed, we do not agree (point 19) that EDs can be identified in standard regulatory tests that are routinely performed to fulfil the requirements of various regulatory programmes. Some may be identified in standard regulatory tests, but some may require the development of new test methods to pick up their ED properties and may therefore be first flagged as having ED properties by the use of non standard tests. Therefore, non OECD studies that are well conducted and well reported should be considered in any hazard assessment using a weight of evidence approach.

Furthermore, even studies not using the relevant exposure route (oral/ dermal/ inhalation) should be taken into account during the identification of ED. This is because although absorption, metabolism and excretion may differ for the various routes, expert

judgement taking this into account, can be brought to bear in making any weight of evidence decisions.

The relevance of data for humans

For the protection of human health, the De-UK PP proposes that the default assumption is that any adverse effect seen in regulatory toxicity studies on mammalian animals should be taken as relevant for humans, but proposes that this can be rebutted with sound scientific data showing non-relevance (para 25). We similarly suggest that this default assumption should only be over-ridden if it is proven beyond doubt that the animal study is not relevant for humans. However, regulatory controls should ensue in any case for substances with ED properties likely to harm wildlife populations.

CHEM Trust considers that the chemical should not have to be shown to be of high potency

The De-UK PP in paragraph 24 suggests that before studies on vertebrate animals are conducted, consideration should be given to the dose levels at which the adverse effects potentially related to ED were first seen – and if these dosages were relatively high (the substance being of low potency for the potentially related ED effect) then it may not be justifiable to carry out additional studies. However, the identification of a substance with ED properties should be a hazard based approach, and we consider that even if the substance is of low potency, this should not absolve it from the regulatory impacts that the legislation requires for substances with ED properties. This is particularly because such substances can have additive effects with other substances with endocrine activity. Another possible problem with disregarding chemicals of low potency may be that the test method used had low power or low sensitivity for the particular endpoint investigated.

CHEM Trust strongly disagrees with the De-UK's position which is trying to require a risk based process for the identification and control of EDCs in the Pesticides Regulation (1107/2009). We strongly disagree that the dose response curve must be considered to determine if the effects occur at a relevant dose level (para 29). It is clear that the legislation does not require such a risk based approach, but instead mandates that if a substance is considered to have endocrine disrupting properties that may cause adverse effect in humans, then approval is only possible if the exposure of humans under realistic

proposed conditions of use is negligible. Such negligible exposure is already strictly defined by the Pesticides Regulation in Annex II point 3.6.5, and therefore it cannot be justified to interpret this otherwise.

The use of potency triggers, such as STOT-REs, is not scientifically defensible, and would leave many ED pesticides insufficiently regulated

The De-UK PP notes that the Classification, Labelling and Packaging Regulations contain discriminatory dose thresholds for use in determining whether or not a wide range of expressions of toxicity seen in single and repeated exposure (RE) studies, collectively termed “Specific Target Organ Toxicity (STOT)” should be identified by hazard classification and be assigned appropriate labelling. Furthermore, they propose that the dose thresholds for Specific Target Organ Toxicity -Repeated Exposure (STOT-RE) should be used to determine whether or not the hazardous property of endocrine disruption should be identified for regulatory purposes. For category 1 the STOT RE oral doses proposed for acute, sub-chronic and chronic studies are 30mg/kg bw/day, 10mg/kg bw/day, and 5mg/kg bw/day. They propose that only substances which produce endocrine disruption at a dose level at or below these guidance values should be the subject of the cut-off criteria under the Pesticides Regulation or subjected to the authorisation procedure of REACH under Article 57(f). We strongly disagree with this approach.

The DE-UK PP notes that these STOT-RE potency guidance values are pragmatic, and should not be used as strict demarcation values but taken into account along with severity of effects, dose spacing etc in a weight of evidence approach. However, even if these values are not taken as strict demarcation values, we consider that this approach is highly un-scientific and would not protect humans and wildlife from harm. We consider that these STOT-RE ‘cut-off’ values are too arbitrary and have no relevance to ED effects. EDC act on a system that is already biologically active, and it is therefore likely that there will not be a threshold for effects. Hormonally active chemicals act in concert with natural hormones, so the assumption of a threshold dose below which there are no effects is an unlikely one. Within a population, there will be people with varying levels of natural hormones. Even very small amount of a chemical with hormone disrupting properties might be sufficient to cause harm to those who are particularly susceptible.

Moreover, cumulative or 'additive' effects of chemicals with endocrine disrupting properties are possible and clearly demonstrated in literature; exposure to mixtures of endocrine-active chemicals are an everyday reality. It would be inappropriate to use thresholds while these cumulative effects are not taken into account.³ Furthermore, given that inverted U shaped dose response curves or non-monotonic curves have been reported for some EDCs, high dose testing may not predict low dose effects, and effects may occur at levels below those currently identified as NOAELs.

Data compiled by the Danish National Food Institute further illustrates the unsuitability of these thresholds of toxicity, which have been proposed both in the De-UK PP and in the position paper of the German health and safety agency (BAuA) (see below). For example, among a group of recognised endocrine disruptors comprising various phthalates, pesticides and chlorinated substances, only two of these (vinclozolin and PCB) would have LOAELs below the proposed 10 mg/kg bw/day limit and these are already classified and severely restricted (see paper by DK EPA). It is therefore clear that if such thresholds of toxicity were implemented it would severely thwart the future regulation of EDCs of concern. We therefore strongly oppose the joint proposal of the German BfR and the UK, as it is seeking to bring in a risk based approach which is in contravention to the intent of the Pesticides Regulation, which has already been agreed in the EU. Moreover, the identification of SVHC under REACH is also based only on intrinsic properties.

The De-UK PP suggests that if a pesticide is active at higher doses than the STOT-RE values, it would still need to be regulated through a standard risk assessment and moreover, a combined risk assessment for exposure to a mixture of substances acting through a similar mode of action would still need to be performed. However, such mixtures assessment would not be protective as it would not embrace all endocrine active substances (beyond just pesticides) and nor would it include substances acting on the same target organ via a mode of action which was not similar. The intent of the

³ Kortenkamp A. *et al.* State of the art report on mixture toxicity. Final report dated 22 December 2009. Study Contract No. 070307/2007/485103/ETU/D.1 (Contractor: School of Pharmacy, University of London). The document is accessible on the DG Environment website at http://ec.europa.eu/environment/chemicals/pdf/report_Mixture%20toxicity.pdf

pesticides regulation was rightly to eliminate exposure to chemicals with endocrine disrupting properties as the risks could not be adequately managed.

ii) The proposals of the Danish Environmental Protection Agency (EPA), “Establishment of criteria for endocrine disruptors and options for regulation” (dated 17th May 2011).

Definition of endocrine disruptors

The Danish EPA (Dk-EPA) considers that the same definition should apply for all EU legislation and, if possible, the same definition should also apply at the international level. Furthermore they note that there is generally wide acceptance of using the IPCS/WHO definitions (2002):

“An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and **consequently** causes adverse health effects in an intact organism, or its progeny, or (sub) populations.”

“A **potential** ED is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny or (sub) populations.”

The Dk-EPA consider that these 2 definitions imply the existence of a large difference in scientific evidence for categorising a substance as either an ED or potential ED, and therefore propose subdividing **potential EDs** into two categories, namely category 2a (**suspected ED** (mainly based on *in vivo* data) and Category 2b (substances with indications of ED properties (**indicated ED**) mainly based on *in vitro/in silico* data).

Such a need for expansion of the WHO definition of potential EDs was reflected at the April 2011 meeting of the OECD Advisory Group on Endocrine Disruptors, which put forward a new operational definition of a possible endocrine disrupting chemical in the context of the draft “Guidance document on standardised test guidelines for evaluating chemicals for endocrine disruption.” “A possible endocrine disrupter is a chemical that is able to alter the functioning of the endocrine system but for which information about possible adverse consequences of that alteration in an intact organism is uncertain.”

As noted in CHEM Trust's comments above to the De-UK PP we can accept the IPCS/WHO definition as a working scientific definition, but would have reservations with regard to its use as a starting point for identifying EDCs in EU policy context. It is clear that less evidence is required under REACH and under the Pesticides Regulation. If a definition was to be used as a basis for legislation or regulatory guidance, of the proposals made by experts of the Member States, we strongly prefer the definition suggested by the Danish Centre on Endocrine Disruptors, which took out the word 'consequently'. Thus, we could support the following definition:

An ED "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and causes adverse health effects in an intact organism, or its progeny, or (sub) populations." The rationale for this is explained fully under the heading '*Definition of 'endocrine disrupting properties'*' relating to the De-UK PP (i) above. In this definition, the term adverse effects relates to effects in a test system, and not effects at current exposure levels in humans or the environment.

It is noteworthy that EU legislation uses the term 'endocrine disrupting properties' and we consider it should be recognised that, in order to facilitate the goal of ultimately moving away from *in-vivo* testing to *in-vitro* testing, there will be a need to ensure that endocrine disrupting properties can encompass both those seen in vivo and in-vitro tests, when the latter are considered to be adequately predictive of effects in an intact animal. Similarly, interpretation of the words 'probable serious effects' and 'may cause adverse effects' must allow for the future use of *in-vitro* rather than *in vivo* assessment.

Criteria for classification

Whatever definition is used as a basis for a common understanding of the chemicals which we are trying to address, we agree that a more operational set of "level of evidence rules" or criteria are needed to allow industry and authorities to determine whether a substance should be considered to have endocrine disrupting properties.

We consider that the table put forward by the Dk-EPA as proposed criteria for endocrine disruptors, which is reproduced on page 18, is based on expert understanding and has much to recommend it. However, a central issue is what should result for each category

in terms of regulation, and in this we consider that the Danish proposal outlined below, requires too high a level of proof which would mean too much additional testing.

Regulatory outcomes under REACH for ED category 1 & 2 chemicals

The Dk-EPA suggests the following:

- Substances identified as ED category 1 should be considered to meet the criteria (Art.57(f)) for inclusion on the Candidate List. Dk suggests that category 2a and 2b similar to other types of SVHC should be identified and further evaluated. Depending on the likely use and exposure, the severity of effects and the potential risk (based on tonnage, uses, emissions, exposure potential and hazard (eg. potency) characteristics) – such potential EDs could be subject to regulation or prioritised for ‘substance evaluation’. The latter would allow that further targeted testing of prioritised potential EDs could be required from registrants.
- Alternatively, for substance not prioritised for substance evaluation under REACH – Member States, academia or NGO’s could on a voluntary basis perform the necessary targeting testing to confirm the ED categorisation.

For each ED category 1 substance identified as well as for potential EDs of higher priority, Dk consider that there should be an analysis of the need for Community Risk Management and where this is needed, a Risk Management Options analysis should be prepared.

Regulatory outcomes under the Pesticide Regulation for ED category 1 & 2 chemicals

Dk propose that confirmed EDs (category 1) pesticides should be subject to the cut-off criteria. For suspected EDs, Dk suggest that additional mechanistic studies *in vivo* and/or *in vitro* are necessary – but that the default assumption is that the mechanism is endocrine. Therefore, if no mechanistic data are provided, or if the mechanism is shown to be endocrine, the substance may be considered as being an ED category 1.

The cut off criteria for ED pesticides relate to those which have “ED properties that may cause adverse effects in humans, unless the exposure of humans ... under realistic proposed conditions of use, is negligible” (Annex II, 3.6.5). Negligible is further defined in this case as “the product is used in closed systems or in other conditions

excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005”.⁴ Similarly, cut-off criteria apply to a pesticide having “ED properties that may cause adverse effects on non-target organisms unless the exposure of non-target organisms to that active substance in a plant protection product under realistic proposed conditions of use is negligible.”

As the meaning of ‘negligible exposure’ is tightly defined for human health, it is clear that the legislation requires a hazard based approach in this case. The Dk EPA paper, however, points out that in relation to non-target organisms there is currently no specified definition of negligible exposure. Nevertheless, we would argue that a similar hazard based approach was intended to be applied across the board.

Dk consider that if there are data from tests which are not agreed OECD test and therefore not included in the OECD Conceptual Framework Level 5 tests, - which indicate an ED effect, but the available level 5 test investigating the relevant end point does not find effects,⁵ then the substance is not categorised as an ED unless there is other evidence indicating ED related adverse effects. Here we consider it crucial that the OECD study includes dose levels and endpoints that are the same as in the study where the effects were found. If on the other hand, the OECD test method does not include the end-point in the non-OECD test which suggested the chemical was an ED, then we would conclude that the non-OECD test should be given due weight, such that unless there were convincing data to show the non OECD test was erroneous, we would conclude that the pesticide should be subject to the cut-off criteria for ED. Moreover, we would prefer that contract laboratories who perform the OECD tests on which regulation is often based, had to perform tests blind and therefore that there was in some way an effective ‘wall’ put between the industry representatives contracting and paying for the test, and the test laboratories.

⁴ The default value set in accordance with point (b) of Article 18(1) of Regulation (EC) No 396/2005 is 0.01 mg/kg food.

⁵ An extended one-generation reproductive toxicity study or an updated 2 generation reproductive study (which is not yet available). The 2001 update of the 2 gen repro study TG416 needs to be updated again because it does not include nipple retention, AGD at birth or measurement of thyroid hormones and TSH.

For the category 2a 'Suspected ED pesticides', Dk propose that approval would require further data from industry. For the category 2b 'Indicated ED pesticides', Dk propose to flag these for the generation of more data.

We consider that Denmark has provided some useful proposals. In particular, Section 4 of the Report on Criteria for Endocrine Disruptors by the Danish Centre on Endocrine Disruptors, provides some very useful and illuminating worked through examples of how their scheme would operate. However, we are very concerned indeed that the level of evidence required for their category 1 may hamper the necessary regulation that is urgently needed on the basis of precaution, for both industrial chemicals and pesticides. It needs to be recognised that definitive proof of an ED action may be elusive such that regulation of suspected EDCs is needed in many cases without requiring more testing. Moreover, neither REACH nor the Pesticide Regulation require absolute proof of adverse effects as regulation should progress if there are 'probable serious effects' or if the pesticide 'may cause adverse effects'.

Table 1: Denmark's Proposed Criteria for Endocrine Disruptors

	<p>Category 1- Confirmed ED</p> <p>Substances are placed in category 1 when they are known to have caused ED mediated adverse effects in humans or animal species living in the environment or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to cause adverse ED effects in humans or animals living in the environment.</p> <p>The animal studies shall provide clear evidence of ED effects in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effects should be considered not to be a secondary non-specific consequence of other toxic effects. However, when there is e.g. mechanistic information that raises doubt about the relevance of the effect for humans or the environment, category 2a may be more appropriate.</p> <p>Substances can be allocated to this category based on:</p> <ul style="list-style-type: none"> - Adverse <i>in vivo</i> effects where an ED mode of action is highly plausible - ED mode of action <i>in vivo</i> that is clearly linked to adverse effects <i>in vivo</i> (by eg. read-across).
<p>P O T E N T I A L</p>	<p>Category 2a - Suspected ED</p> <p>Substances are placed in category 2a when there is some evidence for ED effects from humans or experimental animals, and where the evidence is not sufficiently convincing to place the substance in category 1. If, for example, limitations in the study (or studies) make the quality of evidence less convincing, category 2a could be more appropriate. Such effects should be observed in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effect should be considered to be a secondary non-specific consequence of other toxic effects.</p> <p>Substances can be allocated to this category based on:</p> <ul style="list-style-type: none"> - Adverse effects <i>in vivo</i> where an ED mode of action is suspected - ED mode of action <i>in vivo</i> that is suspected to be linked to adverse effects <i>in vivo</i> - ED mode of action <i>in vitro</i> combined with toxicokinetic <i>in vivo</i> data (and relevant non test information such as read across, chemical categorisation and (Q)SAR predictions)
<p>E D</p>	<p>Category 2b - Substances with indication of ED properties (Indicated ED)</p> <p>Substances are placed in Category 2b when there is some <i>in vitro/in silico</i> evidence indicating a potential for endocrine disruption in intact organisms.</p> <p>The evidence could also be observed effects <i>in vivo</i> where there is general but not specific evidence relating those to ED (i.e. that may, or may not, be ED-mediated).</p>

iii) The German Federal Institute for Occupational Safety and Health (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin) (BAuA) proposals re human health criteria for endocrine disruption according to article 57(f) of the REACH Regulation (dated 20th October 2010)

Thresholds of regulation or potency cut-off values

The BAuA proposal relates to criteria to identify substances with ED properties under 57(f) of REACH. We consider this proposal is inappropriate particularly in its attempt to impose arbitrary ‘threshold of regulation’ or toxicity cut-off values to assist in the identification of SVHC with ED properties. The BAuA proposal suggests that such ‘threshold of regulation’ toxicity values are needed to show that a chemical has a certain level of potency that merits a comparable ‘equivalent level’ of concern as for CMR Cat 1 A or 1B (CLP). Thus, they consider that the aspect of equivalence should be ensured by consideration of the ‘potency’ of a substance, e.g. by assessing the dose-response relationship of endocrine disruption-related adverse effects. As a default assumption it is assumed that endocrine disruption-related adverse effects are only induced above a threshold dose/concentration.

Their argumentation highlights that it can be assumed that nearly every toxic effect might be accompanied by some endocrine-mediated effects or feedback responses at the cellular or molecular level, and therefore suggests the need to discriminate between substances with a low potency and those substances with a strong potency for ED-related adversity, which might be identified as SVHC. Therefore, BAuA consider that only substances, which demonstrate endocrine-mediated adverse effects at doses/concentrations at or below certain guidance values (‘cut-off values’) should be selected for SVHC nomination. BAuA consider it should be necessary that adverse effects are observed at dose levels below the cut-off values derived from upper limit of guidance values derived from STOT- RE category 1, and they therefore suggest that the oral cut-off value (rat) is 10mg/kg bw/day). However, it is not totally clear whether these thresholds are to be used as a guide or as a strict barrier. For example, there is some contradiction in that on page (6) BAuA suggest that “substances, which demonstrate endocrine-mediated adverse effects at doses/concentrations at or below certain guidance values ... should predominantly be selected for SVHC nomination”, where the word

'predominantly' suggests that there may be some selected that don't meet the guidance values; whereas on page (8) it states "conversely substances with ED-related adverse effects above the cut-off values are not considered to fulfil the criteria of Art 57(f). Nevertheless, whether these guidance cut-off values are to be strictly imposed or used just as guide values, we strongly disagree with them in any case, as we do not support a potency based approach for the reasons outlined below.

As a pragmatic approach BAuA have proposed to use the upper limit of the guidance values as defined for specific target organ toxicity (STOT) – repeated exposure (RE) Category 1 (Table 3.9.2, Annex I, CLP) and Category 2 carcinogens and Category 2 reproductive toxicants with ED action as a means of selecting chemicals which might be considered to have ED properties, but then only if the critical adverse effect related to the ED properties occurs at or below the cut-off values are these considered to fulfill the criteria as an ED substance according to Art.57(f). The BAuA proposal therefore considers, we feel misguidedly, that there will be chemicals with sufficient experimental data to allow for the conclusion that the alterations related to the endocrine system are not seriously impairing health, and therefore, compounds of low potency should not be designated as SVHC. We consider that the guidance cut off values they propose are far too high and anyway that potency triggers are simply not appropriate to be of use in the identification of chemicals with ED properties. However, we do not disagree that such substances may very well qualify for the candidate list, but rather that the candidate list should certainly not be limited to such chemicals.

As noted above under our critique of the De-UK PP, we consider that these STOT-RE 'cut-off' values are arbitrary and have no relevance to ED effects. EDC act on a system that is already biologically active, and it is therefore likely that there will not be a threshold for effects. Moreover, studies have clearly demonstrated that chemicals with endocrine disrupting properties can have 'additive' effects and exposure to mixtures of endocrine-active chemicals are an everyday reality. It would therefore be inappropriate to use thresholds while these cumulative effects are not taken into account.⁶

⁶ Kortenkamp A. *et al.* State of the art report on mixture toxicity. Final report dated 22 December 2009. Study Contract No. 070307/2007/485103/ETU/D.1 (Contractor: School of Pharmacy, University of London). The document is accessible on the DG Environment website at http://ec.europa.eu/environment/chemicals/pdf/report_Mixture%20toxicity.pdf

Equivalent concern

We consider that what is common to chemicals in REACH Article 57(a-e) is the potential for irreversible effects. For example, for the vPvB chemicals – it is not their toxicity or potency - that generates the concern, but the fact that if effects do come to light, it will be impossible to prevent harm from continuing due to the chemical's properties of persistence and bioaccumulation. Similarly, with chemicals with ED properties, it is their ability to cause delayed and irreversible effects which generate equivalent concern. For example, effects may manifest only at maturity from in-utero exposure. This means, for example, that if it was found that the majority of young men were infertile due to in-utero exposure to chemicals with ED properties, this dire situation could not be reversed, such that children growing up in the next 18 years or so would also suffer such a fate, because the causative exposure had already occurred.

Definition of 'endocrine disrupting properties'

We do not accept the BAuA proposal that possessing 'endocrine disrupting properties' should equate to meeting the WHO/IPCS definition of an EDC (see above – for explanation). Furthermore, we do not consider that there is a need for a different definition for human (mammalian) EDCs and non-mammalian organisms, even though the endocrine disrupting properties of some substances may be relevant for humans and for wildlife, whilst some may be only relevant for wildlife.

We consider that the WHO/IPCS (WHO/IPCS 2002) provides a useful scientific definition. However, it should be noted that fortunately this definition is not included in EU legislation but instead the EU legislation speaks of "chemicals with ED properties", which is preferable. The WHO/IPCS definition would require a too high a level of proof for a protective regulation. The difficulty here is to prove beyond doubt that the adverse effect is a *consequence* of endocrine disruption rather than the observed endocrine disruption being a secondary effect of some other mechanism of toxicity. Even if a weight-of-evidence analysis of all available information on the substance of question concluded that a chemical acted via an ED mode of action, if this requirement for proof that the adverse effect was a *consequence of ED* - was enshrined in legal text or guidance,

it could leave regulatory agencies vulnerable to laborious and difficult-to-defend legal challenges from industry, either at the outset, or as and when further information became available.

By using the term ‘endocrine disrupting properties’, a lower level of proof is required, which is needed for the regulatory setting in order to allow for timely action rather than regulation having to wait until damage has already occurred. It must be shown that the endocrine system is perturbed (to justify the term endocrine disrupting properties) but there is not a need to show that the adverse effects are a direct consequence of the perturbation of the endocrine system. The REACH legislation requires only that a chemical with ED properties must cause probable serious effects before it can be designated a SVHC, while the Pesticides Regulation requires evidence sufficient to determine that the chemical with ED properties may cause adverse effects. These requirements should not be made more burdensome during the actual implementation of the legislation.

It is clear that the use of the term ‘endocrine disrupting properties’, as used in REACH and the Pesticides Regulation, was not intended to only embrace chemicals which definitely ‘consequently cause adverse health effects’, otherwise the terms ‘probable serious effects’ or ‘may cause adverse effects’ would not have been included in REACH and the Pesticides Regulation, respectively. It is clear that the terms used in the EU legislation (probable and may) require a less definite adverse effect to be identified and moreover, do not require absolute certainty that the adverse effects are a consequence of the ED activity.

It should also be recognised that getting firm information about whether the adverse effects reported in an animal study were a consequence of endocrine disruption could require further animal testing – as not all mechanisms have been modelled in *in-vitro* test systems. We consider it would certainly be undesirable to continue testing on animals solely in order to clarify, beyond doubt, the mechanism of action. We therefore advocate a move towards an earlier decision point, as we consider it unacceptable to continue testing on animals solely in order to clarify, beyond doubt, the mechanism of action.

Interpretation of in vivo screens

BAuA consider that an ED *potential* may be indicated from *in vivo* tests screening for estrogenic activity (OECD 440 uterotrophic bioassay in rodents) or screening for (anti)androgenic activity (OECD 441 Hershberger bioassay in rats). They consider that at present, positive data from *in vivo* screening tests alone do not justify the conclusion that a substance is an endocrine disrupter in intact mammals. Therefore, they consider that data from such screening tests alone are not sufficient for SVHC identification. However, we consider that such screens provide clear evidence of endocrine disrupting properties, which might be predicted to lead to probable serious effects. This is especially because it is now known that oestrogens can act additively, as can anti-androgens and thyroid disruptors.

We certainly consider that if a chemical showed effects in, for example, the Hershberger assay (or the uterotrophic assay) using an intact immature animal, this should be considered to exhibit adverse effects and regulated accordingly. By extrapolation, not regulating such a chemical would leave immature boys vulnerable.

ED effects need not be the lead toxicity

We agree with BAuA that it should **not** be a pre-requisite that the ED-related adverse health effect is the most sensitive adverse effect that has been identified and/or that it should be the lead effect driving classification (e.g. the same substance might also be neurotoxic at a much lower dose, which is not (yet) specified as a criterion for SVHC identification) (p7/8).

Relevance of ED properties for human health

We agree with BAuA that as a default assumption, ED properties identified by a weight-of-evidence approach should be considered relevant for humans. Only in exceptional cases where non-relevance for humans can be clearly demonstrated beyond doubt and is accepted as scientifically plausible, would this default assumption not be valid.

For Substances drawn under authorisation because of CMR Properties, it should in addition, be noted if they are 57(f) chemicals with ED properties.

We agree with BAuA that substances that already fulfil Art. 57(a), (b) or (c) may additionally exert adverse health effects according to Art. 57(f). Therefore, we strongly

agree with BAuA that “consequently these substances should additionally be categorised as ED-SVHC according to Art. 57(f) for human health aspects” (p8). We consider this to be important particularly because in future there may be a change made to the REACH legislation such that ED substances may not be authorised on the basis of adequate control of the risks (see Art.138(7)).

iv) The Danish EPA’s Comments to BAuA proposal on human health criteria for endocrine disruption (ED) according to Art. 57 (f) of the REACH regulation (submitted by the Dk-EPA, 30th November 2010)

Endocrine disrupting properties and the term ‘consequently cause adverse effects’

The Danish EPA point out that the term endocrine disrupting properties is not defined in REACH nor in any REACH guidance. They suggest that it could refer to substances fulfilling the WHO/IPCS definition of an endocrine disruptor or a potential endocrine disruptor, or that is likely to do so. Or alternatively that it could be understood to relate to a substance that has the intrinsic potential to disrupt functions of the endocrine system in an organism. They furthermore note that such an interpretation would mean that there is no requirement that a substance having such an intrinsic potential would actually adversely affect the organism as a consequence of exposure to such a substance. Nevertheless as they had difficulties in seeing that a substance that is disrupting the endocrine system would not cause adverse effects, they did not favour such an interpretation. We concur that a substance which disrupts the endocrine system would very likely cause adverse effects, but we caution against requiring proof that the adverse effects seen are a direct consequence of the endocrine disruption, because of the difficulty of establishing beyond doubt such a causal mechanism of action.

Serious effects v adverse effects v probable serious effects (re Article 57f of REACH)

Article 57f of REACH requires that substances with ED properties must have “probable serious effects” rather than “adverse effects”. We agree with DK EPA that as known effects of endocrine disruptors are serious, it does not matter whether the term serious effects is equated to adverse effects or whether serious effects are considered to be more serious than adverse effects. However, we consider that it is clear that given the term ‘probable serious effects’ is used in REACH, there can be some degree of uncertainty in

the interpretation of whether they do or don't cause serious effects. This means that despite remaining uncertainty, chemicals can still be nominated as SVHC.

Thresholds for potency or a hazard based approach to identify ED properties of equivalent concern

We agree with Dk EPA that the general concerns of substances identified through REACH, Article 57(a)-(e) CMRs and PBTs are that they have the potential to cause severe long-term effects which may be irreversible and/or difficult to predict and/or reverse. The identification of a substance as a CMR is fully hazard driven and only the level of evidence for the presence of the properties is used in relation to the assignment to categories of CMR. Potency (e.g. expressed as a dose or concentration limit) of the substance is not considered. We therefore agree with Dk EPA that the identification of ED properties for the identification of substances for the candidate list should not be related to the potency of the substance.

Potential EDCs or Endocrine Modulators

In order to distinguish between endocrine active substances which are not (yet) considered to lead to adverse effects from endocrine disruption in an intact animal, from substances where such effects have been shown, the Dk EPA agree with a proposal made by the industry group, BIAC, to refer to the former as endocrine modulators or endocrine active substances or suspected endocrine disruptors. In contrast, we prefer the term chemical with endocrine disrupting properties or suspected endocrine disrupting chemical. Furthermore, like Dk EPA we consider that such chemicals can and should be identified through *in vitro* studies, read-across and QSARs in which various parts of the functioning of the endocrine system are studied.

v) The response of the French ANSES (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail) to the German BAuA's proposal re human health criteria for endocrine disruption according to article 57 of REACH (dated 10th January 2011)

We agree with ANSES that criteria for the Substances of Very High Concern identification will need to be revised regularly with increasing knowledge. We also agree that in

relation to identifying 57(f) substances with ED properties, there is no need to include a threshold to take into account potency as it does not exist for other SVHC criteria, and therefore that screening of ED substances eligible for article 57(f) should be performed based on the type of effects rather than the dose at which effects appear. Furthermore, we also agree that when dealing with prioritisation of substances for authorisation, knowing that effects covered under article 57(a) to (e) occur through an ED mode of action is also important.

Anses note that 2 parameters have to be clearly distinguished to achieve the task of identifying EDs as SVHC: the adversity of the substance and the ED mode of action related to the adverse effect considered.

In relation to the identification of the adversity of the effect, Anses suggest that the CLP regulation provides a comprehensive set of criteria to identify what are considered as adverse effects on health, as well as to identify which routes of exposure are relevant. Therefore, they support the use of classification as a basis for the identification of this parameter. They consider that STOT-RE, carcinogenicity and reproductive toxicity are the relevant human hazard classes for identifying ED human adverse effects and therefore that substances classified as STOT-RE's (category 1 and 2), C and R substances (category 1A, 1B or 2) and an ED mode of action should merit identification as a 57(f) chemical with ED properties. We agree that such substances should be judged to meet the 57(f) criteria, - but do not consider that only such substances should be included.

We consider that the term used in the REACH legislation implies that a degree of uncertainty may be present with respect to the adversity of the effects. Thus, "probable serious effects" means that serious effects are likely but not absolutely certain.

- vi) **The Proposal of the German Federal Environment Agency (UBA) entitled "Discussion paper on interpretation of Art. 57 (f) REACH with respect to substances having endocrine disrupting properties hazardous to the environment (26th May 2010)**

UBA prepared this discussion paper for the REACH competent authorities in order to start the debate on how to regulate chemicals with endocrine disrupting properties under REACH authorisation. The paper describes general thoughts on how to identify substances being of equivalent concern due to their ED properties for organisms in the environment. Article 57(f) of REACH provides for the option to identify endocrine disruptors as substances of very high concern, based on a case by case decision, when (i) there is scientific evidence of probable serious effects to human health or the environment and (ii) they give rise to an equivalent level of concern to those of PBT/vPvB and/or CMR substances. This means that even in the absence of officially agreed criteria, a chemical with ED properties can be proposed as a substance of very high concern under REACH authorisation, based on the scientific evidence presented on a case by case basis.

Considerations regarding the scientific evidence needed

We agree with UBA that information on all types of endocrine modes of action (eg. including influences on the moulting system) should be considered relevant for the assessment.

UBA suggest that *in vitro* tests are not considered to provide enough evidence of an endocrine mode of action and adverse effects in the environment, although these tests could provide valuable information on the mechanism and mode of action. Furthermore, UBA state that “substance specific data might not be sufficient to demonstrate a causal link between the endocrine mode of action and the adverse effects observed. Thus all available information (eg. general information providing evidence that observed adverse effects are consistent with the endocrine mode of action observed *in vitro*) is considered relevant in order to identify endocrine disruptors in a weight of evidence approach.” We agree that an adverse effect *in vivo*, coupled with an *in-vitro* study suggesting an endocrine mechanism should suffice in the identification of chemicals with ED properties. We would not consider it to be justifiable to require more *in vivo* experimentation when the adverse effects noted are generally consistent with *in-vitro* data suggesting an ED mechanism. Care needs to be taken when writing any guidance, to ensure that animal tests can be further minimised in future; there needs to be official acknowledgment of *in-vitro* test methods which are considered to be sufficiently predictive of adverse effects in a whole animal.

We concur that all available information (general information providing evidence that the observed adverse effects are consistent with the endocrine mode of action observed *in vitro*) are considered relevant in order to identify endocrine disruptors in a weight of evidence approach. However, as stated elsewhere in this document, we consider that the word 'consequently' should not be used in any regulatory setting due to the difficulty in getting proof that the observed adverse effects are definitely a consequence of the endocrine disruption seen.

Scientific evidence of probable serious effects to the environment

UBA suggest that the above term used in article 57(f) does not refer to adverse effects observed in laboratory studies only, but also should take into account the possible severity of the impact on the environment. Moreover, they suggest that it "includes analysis of impacts that might not be considered adverse in laboratory tests, but provide scientific evidence that there might be a severe impact to the environment". We agree that the full implications for the environment of the laboratory effects noted should be considered. However, we do not consider that potency or exposure considerations are required to designate a chemical as having ED properties, although the potency and exposure considerations could be considered when prioritising substances for authorisation.

Precautionary measures for chemicals of equivalent concern.

UBA note that as outlined by the Commission, the following 2 aspects (among others) might be used to justify precautionary measures. Namely i) potentially dangerous effects – where the scientific evaluation does not allow the risk to be determined with sufficient certainty and (ii) delayed effects which do not emerge until a long time after exposure. They note that although not all EDCs may have such properties, sex hormone disruptors are likely to fulfil these properties. (For example, the likelihood of changed courtship behaviour and its influence on population dynamics in the environment is difficult to predict from laboratory studies. However, if it influenced mating behaviour this would be inconsistent with protecting the population. Other effects may not be considered to be of direct relevance to the population level in the laboratory, but might have irreversible effects in future in the environment – for example, changes in secondary sex

characteristics might influence mating behaviour and thus the genetic pool of the population.) We concur with UBA that even what may appear to be subtle changes may have important future impacts and therefore the possible underestimation of both the severity of the effects and their possible future impact, should be taken into account when deciding whether a substance merits being subjected to authorisation.

The meaning of “adverse effects” definitively needs to be inclusive of increased susceptibility to naturally occurring stress factors in the environment. CHEM Trust would assume that most, if not all, ecotoxicological effects observed in the laboratory would also have an impact on the population level, provided population level effects could reasonably be predicted. This is certainly true for parameters such as survival and growth, but also for less obvious changes in metabolism following exposure to a chemical with endocrine disrupting properties. Also for example, if male fish with eggs in their testes were less fertile and fewer males were contributing to the next generation, in the short term this might not affect the population level, but over time this could result in the population being less adaptable due to a more limited genetic pool. Even for effects that are reversible in the adult, it cannot be assumed that this is harmless and of no consequence for the population. For example, perturbation of thyroid hormones, particularly during critical windows, might lead to altered programming of brain development in the next generation.

Further reflections on arguments for equivalent concern

In contrast to other chemicals, the focus on dose response for EDCs may lead to an underestimation of risk due to non linear dose response curves, including inverted U shaped curves, where larger effects or different effects may manifest at lower doses.

Furthermore, we suggest that the potential for EDCs to exert effects in combination plays an additional important role in the argumentation for equivalent concern, alongside the difficulty of getting an accurate assessment of the risk posed by the substance in isolation and the potential for delayed effects. Laboratory studies clearly show that additive effects may occur when animals are exposed to chemicals with anti-androgenic, estrogenic or thyroid disrupting properties. It will be very difficult to assess and deal with the risks from simultaneous exposure to several substances that are controlled under

various legislative instruments, which have been shown to have additive effects in laboratory tests. We therefore consider that the goal should be to substitute such chemicals with safer alternatives under REACH – in the same way that the substitution of PB(T) chemicals is required under REACH.

vii) The Proposal of the German Federal Environment Agency (UBA) entitled “Substances with endocrine disrupting properties in the environmental risk assessment under the new EU regulation on plant protection products (EC1107/2009) – A Proposal for a differentiated decision making” (Dr Tobias Frische) (dated 25th January 2010).

UBA prepared this handout for the ‘Expert Consultation on Endocrine Disruptors’ meeting of 26th January 2010 which related to the Pesticides Regulation criteria. In this handout, UBA noted the paradigm shift from decision making based on risk assessment to a hazard based approach. They noted that instead of a risk based decision, only the proven presence or assumed absence of endocrine disrupting properties are to be taken into account when making the decision as to whether or not the pesticide product should be approved for use. Whilst perhaps having some scientific reservations, UBA rightly accepted the political demand of a hazard-based, more precautionary-orientated decision-making as laid down in the new Pesticides Regulation, noting that such legislation would promote the use of safer alternatives and preclude possible serious effects in the environment.

However, UBA did have some concerns and suggested the need to differentiate various pesticides with endocrine disrupting properties. For example, they considered that if the endocrine disrupting properties were the basis of the pesticidal mechanism of action (only for invertebrates and plants) then if these pesticides were effectively banned it could be a retrograde step as many of them typically show a rather low toxic potential for vertebrates, and are therefore rather useful selectively acting pesticides. UBA accepted that there may be risks for closely related non-target invertebrates or plants, but nevertheless they considered that the loss of pesticides which have selective ED properties by design, would potentially have unfavourable environmental impacts. The Danish EPA have similarly agreed that when applying the definition in relation to

regulating the use of pesticides, biocides, medicine and veterinary medicine it should be considered whether to exclude certain types of non-vertebrate endocrine properties or mediated effects, such as plant and insect hormone disrupting properties. We understand the concerns expressed. However, there would need to be careful discussion on the implications of any such derogation, which ought to be limited to a case by case basis. Moreover, we suggest that the persistence of the pesticide in question ought to be very low before any such derogation might be considered.

In its paper of 2010, UBA also suggested that the cut-off criteria should also not apply to pesticides with endocrine disrupting properties when these properties are not decisive for the overall side-effects on non-target organisms. They suggested that these substances should still undergo the established risk-based assessment and risk management. UBA considered this was justifiable because effects other than endocrine mediated effects would drive the risk assessment and the respective risk-based decision making would be protective for the endocrine mediated effects. We strongly disagree with this suggestion. We do not consider that the endocrine disrupting properties of a pesticide need to be the 'lead effect' before such chemicals are judged to meet the cut-off criterion, for the reasons which we have already outlined above (see Section 1, point10). Neither do we consider that the potency of the endocrine disrupting properties should feature in the decision as to which chemicals are subject to the cut-off criterion for ED pesticides. We therefore totally disagree with the UBA proposal that substances which may cause relevant adverse effects to populations of non target organisms by rather non-specific and/or low potency ED properties should just undergo and be controlled by established risk-based assessment.

viii) The UK Chemicals Regulation Directorate (CRD's) proposal re 'Definition of an ecotoxicological endocrine disrupter for regulatory purposes' of April 2011.

This was developed with the Pesticides Regulation in mind and relates to ecotoxicological EDs only. It therefore supports the counterpart UK paper related to human health, which has been superseded by the joint De-UK PP.

Data evaluation – use all available information

We strongly disagree with point 24 of this proposal, which states that “all studies used in an assessment must have been conducted to an internationally recognised protocol.” We strongly maintain that all relevant information must be taken into account, including studies conducted in independent academic laboratories which may not use internationally recognised protocols, but nevertheless can be well conducted and reported.

This UK proposal notes that if a substance is considered to be an ED from a human health perspective, then it is unlikely to need consideration from an ecotoxicological perspective because regulation should ensue anyway. However, it is important to note that this will not always be the case, since under the Pesticides Regulation it is plausible that there may be non-negligible exposure of non-target pests whereas human exposure might be negligible. Also, information on the ecotoxicological ED effects will be needed to determine the risk management measures needed under REACH.

What effects should be considered adverse at the population level?

The UK document suggests that even though TG229 includes a measurement of fecundity it is considered that this study is not able to indicate adverse consequences for the population. We disagree. Egg production is recorded and quantitative fecundity is monitored daily throughout the test. Effects on egg production can and should be assumed to have a population level effect, without the need for a higher tier test such as the fish full life cycle study looking at hatchability and survival.

It needs to be recognised that although effects on egg production may not affect the population level in the laboratory, this may not hold true in the wild, where a small difference in egg production might well have an impact on reproductive performance. The distinctions that are made between findings that are likely to affect the population level, and those that are not, may be unrealistic and somewhat artificial, since there is no accepted way of reliably distinguishing between the two. Even traditional endpoints, such as egg hatchability, have no definite population effect, since survival to adulthood and breeding is density dependent. The distinction is deductive rather than scientific because there is no population dynamics component in the risk assessment process. Therefore,

we consider that if it is *reasonable to predict* that an effect could have implications for the population level in the wild, then that effect should be sufficient to justify that the chemical causes 'probable serious effects' or 'may cause adverse effects'. A precautionary approach is warranted because it would be very difficult, if not impossible, to prove the ecological relevance of all the effects recorded in the laboratory. Moreover, for all species threatened by extinction, the population level is less relevant and the goal should shift to protecting individual animals.

Level of evidence required re the mode of action

The UK's paper suggests in paragraph 29 that given the requirements that

- an ED needs to demonstrate the ability to produce an adverse effect in an intact organism,
 - the nature of the effect must pose a threat to the population: and
 - that there should be a reasonable and coherent line of evidence that the mode of action underlying the effects is endocrine disruption
- then it is really only possible to determine whether or not a substance is an ecotoxicological ED for mammals and fish.

We agree with the general principles, but are concerned that the requirement of the third bullet may be interpreted in an overly restrictive way. We suggest that although it would be ideal to have a coherent line of evidence to show that the mode of action underlying the effects seen is endocrine disruption, this presents too high a bar of proof for regulation. For example, we still do not know how DDT causes egg shell thinning, nor whether imposex (where a female grows a penis) in mollusc is mediated through endocrine disruption. Nevertheless, certainly in the latter case, it is clear that TBT exerts an endocrine disrupting effect. Therefore, with regard to any definition of EDCs we propose to drop the word consequently in any definition and moreover to accept that a chemical is an ED if disruption of an endocrine related organ is clearly evident. Such effects would include, for example, eggs in the testes or imposex in mollusc.

Furthermore, we consider that studies may be judged adequate to determine that a chemical is an ED in birds, amphibians or reptiles. For example, if a chemical caused

males to make VTG, or there were traces of intersex, coupled with effects likely to affect the population which were suggested to be linked to the endocrine disruption, then such chemicals could be judged to be EDs, even if the tests conducted were not OECD guideline studies.

The endocrine effect should not have to be the lead effect

The UK's document in paragraph 33 suggests that if the endocrine related endpoint from the fish full life cycle assay is some orders of magnitude greater than other key endpoints then the ED effect can be considered to be of limited regulator relevance. We disagree, as the ED effects may result in a tougher regulatory requirement (eg. effectively a ban under the Pesticides Regulation). Moreover, there is clearly a potential for additive effects from other chemicals which have common adverse outcomes and therefore effects at lower levels should not be ignored.

Therefore, we consider that the final overall conclusion of the UK document should be modified as follows. [Our inserts are shown in square parenthesis].

“Therefore overall, in relation to potential ecotoxicity concerns, it is proposed that a substance is regarded as an ecotoxicological ED for regulatory purposes when it satisfies the following definition and associated criteria:

- it should be an exogenous substance or mixture that alters function(s) of the endocrine system and ~~consequently~~ causes adverse effects in an intact organism, or its progeny, or (sub)populations.

And in doing so satisfies the following criteria:

- a) the nature of the effect must [be reasonably predicted to] pose a threat to population recruitment or stability: and
- b) there should be a [good] ~~reasonable and plausible coherent line of evidence from within the same taxonomic group~~ to suggest that the mode of action underlying the effect observed is endocrine disruption [or disruption of an endocrine related organ should be clearly evident]. [Effects noted in all vertebrate animal or cell line studies should be evaluated as the endocrine system has been highly conserved in evolution].
- ~~c) there should be a consideration of the concentration/dose causing adverse endocrine effects ... as described in paragraph 33.”~~

Abbreviations

BAuA	Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (German Federal Institute for Occupational Safety and Health)
BfR	Bundesinstitut für Risikobewertung (German Federal Institute for Risk Assessment)
CMR	Carcinogenic, Mutagenic or Reprotoxic
CRD	UK Chemicals Regulation Directorate
DK EPA	Danish Ministry of the Environment, Environmental Protection Agency
ED	Endocrine Disrupting
EDC	Endocrine Disrupting Chemical
EU	European Union
GHS	Globally Harmonised System
HPT	Hypothalamic-Pituitary-Thyroid
IPCS	International Programme on Chemical Safety
MoA	Mechanism or Mode of Action
MRL	Maximum Residue Levels
NGO	Non-Governmental Organisation
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative and Toxic
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
STOT	Specific Target Organ Toxicity
SVHC	Substance of Very High Concern
TG	Testing Guideline
TTC	Threshold of Toxicological Concern
WHO	World Health Organization

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Appendix 1: Other documents by CHEM Trust which relate specifically to the regulation of chemicals with ED properties]

1. A Joint Discussion Paper by CHEM Trust and WWF European Policy Office dated December 2010 (updating an initial WWF discussion paper of 2002). This Discussion Paper suggests a possible classification scheme for chemicals with ED properties, and is entitled,

“CHEM Trust and WWF-EPO proposals for the regulation of chemicals with endocrine disrupting properties under REACH (EC 1907/2006) and under the Plant Protection Products Regulation (EC No 1107/2009)”.

Available for free download at:

<http://www.chemtrust.org.uk/documents/CHEM%20Trust%20&%20WWF%20EDC%20Classification%20Paper%20Dec%202010.pdf>

2. Environment and Health NGOs', Consumer Organisations & Trade Union's Position Paper, April 2011 entitled “ Requirements for the proper regulation of chemicals with endocrine disrupting properties”. The following organisations are signatories to this Position Paper: CHEM Trust, Cancer Prevention & Education Society, WECF, Health Care Without Harm, Pesticide Action Network Europe, EEB, ChemSec, Health & Environment Alliance, Global 2000, Bund, BEUC and istas.

Available for free download at:

<http://www.chemtrust.org.uk/documents/NGOs%20requirements%20EDCs%20April%202011-FINAL.pdf>