CHEM Trust's critique of the European Food Safety Authority Scientific Committee (EFSA SC) opinion on EDCs[1] (March 2013)

Whilst there is much in the report that CHEM Trust can agree with, we disagree with the synthesis of the report which fails to conclude that current science highlights the need for urgent regulatory action and also fails to highlight that existing legislation (eg for pesticides) and the uncertainties in the risk assessment of EDCs mean that a hazard based approach should be adopted.

1) **We disagree with the EFSA SC on risk assessment**

The EFSA SC opinion states "to inform on risk and level of concern for the purpose of risk management decisions it is the opinion of the SC that risk assessment (taking into account hazard and exposure data/predictions) makes best use of available information. EDs can therefore be treated like most other substances of concern for human health and the environment, i.e. be subject to risk assessment and not only to hazard assessment."

CHEM Trust considers that risk management based on hazard identification rather than risk assessment is the correct approach. Risk assessment is not the way forward for EDCs as it is unlikely that EDCs have thresholds for effects, because they act on top of our own hormones, on a biochemical system that is already active and off the baseline. Moreover, it is well known that some EDCs can cause opposite effects at low doses as compared to high doses, such that it is impossible to be certain that so-called no observed effect levels derived for use in risk assessment are really correct, without an enormous amount of animal testing – covering a very wide spectrum of doses and endpoints, which is clearly unacceptable. The goal should therefore be elimination of exposure to EDCs.

The Pesticide legislation clearly mandates a hazard based approach and it is vital that the EU sticks to the letter of the law and is not deflected by those who want to pander to industry.

2) **We disagree with the EFSA SC that there is a sufficient lack of consensus about the existence of NMDRC to allow continued confidence in existing risk assessment methodologies**

[1] EFSA Scientific Committee; Scientific Opinion on the hazard assessment of endocrine disruptors: scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. EFSA Journal 2013; 11(3):3132. doi: 10.2903/j.efsa.2013.3132.
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EFSA says that there is "a lack of international consensus in the scientific community about the existence or relevance of low-dose effects and non-monotonic dose response curves (NMDRCs)". This is one of the principle areas of discordance between EFSA and its critics who maintain such effects are well established, at least for some endocrine disruptors. A joint conference organised by several EU member state Environment and Food agencies and the US National Institute of Environmental Health Sciences in Berlin 2012, generated a considerable measure of agreement on the existence of low dose effects amongst the participants. Most of the participants were in agreement that non-monotonic dose responses do occur and may be expected at some dose ranges for some substances, but the extent to which they might occur at so-called 'low doses' was considered to be a separate issue.

CHEM Trust considers that EFSA should not wait until there is scientific consensus on an issue before requiring action, but rather the question should be whether there is already reasonable scientific evidence. CT judges that there is reasonable scientific evidence for NMDRs as many independent scientists have published studies highlighting NMDRs.

As noted above, it will be impossible for animal welfare reasons to prove the presence or absence of NMDRs and/or low dose effects for each EDC (and for each end point). Moreover, as the EFSA SC noted, it "cannot conclude whether the current test methods are adequate to fully define dose response relationships". CHEM Trust would certainly argue that testing chemicals at just 3 or 4 doses is not sufficient to understand the dose response and accurately identify NOAELs. Moreover, even when it is acknowledged that statistically significant effects are occurring, the dose level causing those effects may not be taken forward as the NOAEL for risk assessment, as it can be argued by some that such effects are not predictive of an adverse effect/disease. At present, there is a lack of understanding about which effects are really predictive of disease. Therefore, CT considers that a hazard based approach which seeks to eliminate exposure is the correct way forward.

Nevertheless, we acknowledge that the SC has not totally dismissed the concern in that it "recommends as a follow up activity to clarify in a broader context the issues of biological thresholds and criteria for adversity, combined exposure to multiple substances and NMDRCs." Unfortunately, however, waiting for such follow up activity is not acceptable as it will stall the necessary legislative responses and furthermore, the outcome of any such a follow up activity will be in large part influenced by which scientists are involved.

3) **Linking the adverse effect to the endocrine MoA**

CT agrees with the EFSA SC conclusion that "demonstration of all the key events of an endocrine mode of action leading to the adverse outcome is not necessary, as this requires a very high burden of proof." We note that the EFSA SC considers that nevertheless there should be "logical and plausible reasoning to explain any

(potential) causal relationship between the observed endocrine activity and the endocrine-mediated adverse effects." We consider that having a high burden of proof that the adverse effects are caused by the endocrine activity of the chemical would not be warranted as it is notoriously difficult to prove the mechanism or mode of action of chemicals.

4) All toxicity data should be given due weight

CT agrees with the EFSA SC's conclusion that "a test does not necessarily need to be standardised in order to demonstrate either the endocrine activity or the adverse effect. Any data whose robustness has been demonstrated is acceptable for the hazard assessment. This assessment of the individual data for robustness needs to include a judgment on: 1) The validity of the method or model used (i.e. Is the method/model sufficiently predictive?); 2) The adequacy of the individual pieces of information, composed of the elements reliability (i.e. Was the method/model applied correctly?); and 3) Its relevance (i.e. Was the method/model appropriate for the intended purpose?)." However, we are concerned that consideration of these important scientific issues can be abused and bad judgements can be made, (perhaps because of a lack of sufficient expertise amongst regulatory scientists or advisory committees), whereby good data that raise concerns are not adequately taken into account.

5) Testing chemicals for ED properties

The EFSA report notes that "taken together, but bearing in mind the recommendations made in this opinion, a reasonably complete suite of standardised assays (for testing the effects of EASs) is (or will soon be) available for the oestrogen, androgen, thyroid, or steroidogenesis (EATS) modalities in mammals and fish, with fewer tests available for birds and amphibians." However, it fails to adequately stress that many of the available tests are currently not part of the legislative testing requirements in the EU. Furthermore, CHEM Trust also even doubts that it is actually true that a reasonably complete set of tests is available for EATs modalities, because they do not capture the range of endpoints that are known to be controlled by the different receptor isoforms for estrogen or thyroid hormone and in part because they don't adequately capture the range of developmental stages. A critical issue here is whether "any" endpoints of EAT can be appropriately used as a proxy for all endpoints.

The EFSA SC report also fails to put adequate focus on the need to develop new test methods to cover later life effects from in-utero exposures[2] and the modalities which are currently not covered.[3] CT is however, pleased that the EFSA SC report does highlight that in relation to mammals, there is currently not a single study involving exposure through the complete life cycle of a mammal, from conception to

[2] relevant for identifying chemicals implicated in human diseases such as early menopause, dementia or breast cancer related to in-utero exposures etc.

[3] Such as insulin or leptin disruption and the disruption of other hormones which may be involved in obesity and diabetes.

old age or a single study involving developmental exposure with follow-up into old age, as we consider the latter to be particularly important.

We also agree that a relevant weakness of current test methods is the limitation of some animal models in relation to certain human endocrine disorders in which EDs have been suggested to play a role, such as some mammary gland tumours and other hormonal cancers, endometriosis, metabolic syndrome and reproductive senescence . However, we feel that the conclusion of the SC on this does not sufficiently address the action that is needed within the EU in order to address these inadequacies. Thus, we feel it is not sufficient just to note that these limitations are discussed in the OECD DRP 178 (OECD, 2012b), and that their consideration is envisaged at the OECD level. Urgent action to address these shortcomings is needed in the EU, which can then play a useful role in taking these forward in OECD.

The EFSA SC also fails to clearly recommend urgent action to update the current testing required within the legislative frameworks (eg. REACH), to include both the in-vitro screens and the higher tier tests which are already available. However, we acknowledge that the SC does underline the need for the further development of testing strategies to generate adequate data for the identification and assessment of endocrine disrupting properties, even though it stops short of identifying the need to set down such testing strategies and to require these testing strategies to be mandated within existing legislation.

6) The mixture effects

The EFSA SC "recognises that combined exposure to multiple EASs could occur in such a way that combined toxicity could arise," but further notes that "the issue of combined toxicity resulting from combined exposure to multiple substances will be addressed by EFSA in a separate activity". However, it fails to highlight that cumulative exposures to EDCs is an issue which merits urgent and special treatment, because of the rise in endocrine related illnesses in the population at large, and because we are likely exposed to several EDCs with additive effects because the oestrogen and androgen receptors are rather 'promiscuous'.

7) The critical effect

We are pleased that the EFSA SC disagreed with ECETOC, who proposed (2011) to use the concept of 'critical effect' as a criterion for identifying a chemical as an ED for regulatory purposes, with the rationale that, if the endocrine-mediated adverse effects occurred at a dose level 10 times higher than the critical effect, the substance would not be considered to be an ED. The SC disagrees with the idea that a substance can be identified as an ED only when the endocrine-mediated adverse effects occur within a certain range of the critical effect. According to the IPCS/WHO definition for EDs, all substances with the ability to cause adverse effects consequent to an endocrine mode of action are to be regarded as EDs, independently from critical effect considerations.

8) **CT disagrees that regulation /risk management based on the critical effect would protect against ED effects**

CHEM Trust disagrees with the EFSA SC's opinion that health/ecotox based guidance values based on the critical effect would always be protective against any endocrine-mediated effect occurring at higher doses. We consider that this would not necessarily be the case, as such endocrine disruptors could still contribute to cumulative effects with other EDCs at levels below their NOAEL.

9) Potency should not be used alone

The EFSA SC notes that potency is usually considered in a context, e.g. in comparison of substances displaying the same effect. It further notes that potency for a particular endpoint *in vivo* may depend not only on the degree of exposure (the dose), but also on the duration and timing of exposure. Thus, for the establishment of potency values for EDs, critical periods of development (studies covering different life stages) and the duration of exposure should be taken into account. The SC is of the opinion that, to assess whether or not a (predefined) level of concern is reached for an ED, "potency should not be used alone" but should take account of actual or predicted exposure. We concur that it would be unscientific to use a potency consideration or 'cut off' in the identification of EDs to be regulated.

However, we disagree with the SC who therefore conclude that if regulation of identified EDs is to be based on a level of concern, whether or not this level of concern is reached, can only be determined by risk assessment, which needs to take account of actual or predicted exposure. A risk assessment based approach is, we feel, rightly not allowed in the Pesticide Regulation, which mandates a hazard based approach. Such a hazard based approach is the correct approach because of uncertainties in identifying the NOAELs and the potential for mixture effects coupled with additional concerns about EDs, due to the increase in endocrine-related diseases.

10)Human Relevance

The EFSA opinion concludes that "in relation to human health, the default assumption of any adverse effect seen in toxicity studies is that the effect is relevant to humans. This assumption can be rebutted with sound scientific data showing non-relevance. It is proposed that a structured framework, e.g. the WHO/IPCS human relevance framework (e.g. Boobis et al., 2008), is used to analyse the available evidence and biological plausibility to facilitate a robust and transparent conclusion." CHEM Trust agrees that human relevance should be the default assumption, but we feel that even a structured framework to examine whether this can be rebutted, can all too often be abused. Therefore, we would suggest that if data in mammalian animal studies raise concerns for an ED mode of action or an adverse effect, it must always be the assumption that this is relevant for humans. Due to small differences in the biology between species, it may be that the adverse effects seen in humans might vary somewhat as compared to those seen in the rodent test species, but we

feel that it would be prudent to accept relevance. Differences in metabolism should only be used to allow regulation of a substance active in humans but not shown to be active in the test animal, rather than to allow the non-regulation of a substance active in test animals, because the latter cases are difficult to resolve with absolute certainty, and such debate may serve to delay regulation of harmful chemicals.

11) **Terminology: Endocrine Active Substance vs. Endocrine Disruption**

We consider that the EFSA concept of an endocrine active substance (EAS)[4] is confusing and that it would be far better to stick to the WHO/IPCS and OECD nomenclature of an EDC[5] and possible[6] and potential[7] EDCs. These definitions provide greater clarity on the level of evidence for the concern. The terms 'endocrine active substance' and 'endocrine modulator' should be dropped.

CT considers that the introduction of the term EAS to cover all substances that in some way may interfere with the endocrine system, but not necessarily cause adverse effects, is not useful. This term was originally introduced in the 2010 EFSA technical report developed by a cross-EFSA task force, but we feel it had its origins in the erroneous industry concern that everything could be called an endocrine disruptor, even chocolate, because most chemicals interact in some way with the endocrine system, but the endocrine system copes with them and adverse effects are not seen.

EFSA notes that exposure to exogenous substances that exhibit endocrine activity (i.e. EASs) may stimulate modulation in feedback systems. If this modulation and its effects are temporary and within the homeostatic capacity of the endocrine system of the exposed organism, the effect of the substance might be considered endocrine modulation and hence non-adverse. However, CT considers that this term

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[4] EFSA defines an endocrine active substance (EAS) as:
"*Any chemical that can interact directly or indirectly with the endocrine system, and subsequently result in an effect on the endocrine system, target organs and tissues.*" (EFSA, 2010).

[5] *"An endocrine disrupter 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."* (WHO/IPCS, 2002).

[6] The OECD Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption (OECD, 2012a), provides an operational definition of a 'possible endocrine disruptor':
A possible endocrine disruptor 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."

[7] WHO/IPCS (WHO/IPCS, 2002) defines a 'potential endocrine disruptor' (which is typically based on in-vitro data) as follows:
"A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations."

‘endocrine modulation’ is also unnecessary, and again we feel it was derived from a misunderstanding of endocrine disruption. Chocolate is not, for example, an ED, because although it causes the secretion of insulin to reduce the chocolate induced high glucose levels, it does not perturb or interfere with the normal functioning of the insulin hormone.

CT concurs with the Endocrine Society, which has emphasized (Zoeller et al.,2012), that the ability of a chemical to interfere with hormone action (i.e. the hazard), is of itself a reliable predictor for adverse outcomes. The Endocrine Society published a statement of principles on endocrine disruptors (Zoeller et al., 2012) in which they proposed the following definition of an ED: *“An ED is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.”*
This definition gets to the essence of what should be considered an endocrine disruptor, namely something that interferes with some aspect of hormone action.

We therefore consider that it should be unnecessary to show adverse effects in animal tests (which would have to cover developmental periods) if a chemical has already been clearly shown to have hormone disrupting activity in vivo.

CHEM Trust also has reservations about the use of the IPCS/WHO definition of an EDC because it requires adverse effects to be shown and moreover there must be sufficient data to show these adverse effects are a consequence of the endocrine disrupting mode of action. The use of the IPCS/WHO definition is therefore problematic because (a) it requires adverse effects to be shown (b) it will be a driver for further testing on animals because it requires adverse effects in an intact animals and (c) it might be used to exclude chemicals as EDCs because it could be interpreted as requiring a high bar of proof that the adverse effects are a consequence of the endocrine disrupting mode of action.

The SC notes that the WHO and OECD definitions of possible/potential EDs overlaps with their definition of an EAS. This is very confusing, and we consider that the WHO/IPCS and OECD definitions are much clearer, in that they give a better indication of how the data are limited. We suggest that the terms EAS and endocrine modulation were brought in to pander to the concerns of industry that vast numbers of substances should not erroneously be considered to be endocrine disruptors.

We are particularly concerned about the terminology used in the EFSA SC opinion, because for example, page 16 seems to indicate that the committee suggest a substance is an endocrine modulator, until it reaches some threshold for effects, whereby it becomes an ED. We consider a substance to be an ED if it has the potential to cause adverse effects that are plausibly linked to its ED mode of action, and that this is an intrinsic property of the substance. This means that, unlike the EFSA proposal, the exposure or dose level required to elicit these effects are irrelevant to the terminology, such that the substance is termed an ED. We

therefore consider that the terms ‘EAS’ and ‘endocrine modulator’ should be dropped.

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