HSAC's CONTRIBUTION TO THE EUROPEAN COMMISSION PUBLIC CONSULTATION ON DEFINING CRITERIA FOR IDENTIFYING ENDOCRINE DISRUPTORS IN THE CONTEXT OF THE IMPLEMENTATION OF THE PLANT PROTECTION REGULATION AND BIOCIDAL PRODUCTS REGULATION

The Hazardous Substances Advisory Committee (HSAC) was asked by Defra to offer comments to help inform the UK Government response to the European Commission Public Consultation on Defining criteria for identifying endocrine disruptors in the context of the implementation of the plant protection regulation and biocidal products regulation. The Consultation closed on 16 January 2015. A link to the Consultation can be found below:

http://ec.europa.eu/dgs/health_food-safety/dgs_consultations/food/consultation_20150116_endocrine-disruptors_en.htm

The response below was provided to Defra and also submitted separately to the Commission by the HSAC Secretariat.

Responses by HSAC to the EU consultation on criteria for identifying endocrine disrupting chemicals (EDCs)

Section 2.1.4 – Option 1

Until agreed criteria have been adopted for identifying EDCs, the Plant Protection Products (PPP) Regulations specify the following interim criteria for the identification of PPP active substances, safeners or synergists which may be EDCs in mammals (and by extension, also other vertebrates):

> *Pending the adoption of [the] criteria, substances that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogenic category 2 and toxic for reproduction category 2, shall be considered to have endocrine disrupting properties. In addition, substances such as those that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 2 and which have toxic effects on the endocrine organs, may be considered to have such endocrine disrupting properties.*

Almost identical wording may be found in the Biocidal Products Regulations. Neither interim nor agreed regulatory criteria are required by REACH, but would nevertheless be helpful for identifying Substances of Very High Concern. A single set of criteria applied to most groups of chemicals would provide consistency and avoid a situation where a substance was banned under one piece of legislation but permitted for use under another. However, criteria based on the IPCS/WHO definition of an EDC (see section 2.2.4) could not be applicable to cosmetics as, under the 7th Amendment, these are not allowed to be subjected to animal testing.

It is clear that these interim criteria are entirely unsuitable for the identification of EDCs because they are not science-based, and simply rely on an unreliable association of endocrine disrupting properties with category 2 carcinogens and category 2 reproductive toxicants. Furthermore, it cannot be assumed that substances which have toxic effects on endocrine organs will automatically be EDCs. Finally, it is unclear how these interim criteria could be applied to industrial chemicals under REACH.

In consequence, Option 1 (which would simply retain the interim criteria indefinitely), is not considered acceptable.

Section 2.2.4 – Option 2

This option simply proposes to use the IPCS/WHO definition of an endocrine disrupter, as follows:

> *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.*
>
> *An adverse effects is a change in the morphology, physiology, growth, development, reproduction, or, life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.*

This definition is scientifically adequate in itself, although probably not sufficiently detailed for chemical regulatory purposes – *i.e*. regulators will need much more guidance about how to apply the definition in practice. However, when used within EU legislation covering plant protection products and biocides, it will lead to the withdrawal from the market, or prevention from entering the market, of many products which can probably be used safely subject to suitable risk assessment and management. The very weak evidence suggesting that the conduct of environmental risk assessments of most EDCs is unsafe (see Section 4 below) should therefore be re-considered. In the meanwhile, Option 2 appears to be an over-precautionary instrument if used to trigger bans of all PPPs and BPs with endocrine disrupting properties.

Section 2.3.4 – Option 3

This option also proposes to use the IPCS/WHO definition of an endocrine disrupter (see above), but would place substances in different categories depending on the weight of evidence against them. Thus, a Category 1 EDC would conform to the IPCS/WHO definition, while Cat. 2 would cover suspected EDCs where the evidence is insufficiently strong to place them in Cat. 1, and Cat. 3 would cover chemicals for which the evidence of EDC properties is insufficiently strong to place them in either categories 1 or 2. This option has the disadvantage of Option 2 (*i.e*. it will lead to the unjustifiable banning of many

substances that pose a very low environmental risk), but widens the net to include more chemicals on the basis of very vague descriptions of 'suspected' and 'insufficiently strong'. There is no guidance about how the weight of evidence assessment is to be conducted. This lack of clarity would lead to inconsistent decision-making on the part of regulators. More importantly, it would also place many chemicals with only weak evidence of endocrine disruption into a kind of limbo in which they would be tainted by association, and registrants might feel forced by public opinion to withdraw them on the basis of incomplete data. Option 3 is therefore even less justifiable than Option 2, although there would be some merit in allowing unrestricted use for all Cat. 2 and 3 substances subject to a range of specified environmental monitoring conditions.

Section 2.4.4 – Option 4

This option proposes to include considerations of potency as part of the hazard identification and characterisation of EDCs. The Commission roadmap gives no details of this process. However, one possibility is that if a substance is identified as an EDC according to the IPCS/WHO definition, but non-endocrine adverse effects are shown to occur at lower concentrations/doses, then the non-endocrine hazard would take precedence in subsequent regulatory action. For example, only substances whose endocrine disrupting effects are more potent than non-endocrine effects might be considered for banning or withdrawal from the market. Another possibility would allow risk assessment of EDCs whose potency falls below an arbitrary threshold.

While remaining over-precautionary, like the previous options, there is no doubt that consideration of potency would allow some endocrine disrupting substances with a negligible environmental risk to remain on, or enter, the market. In particular, risk management could be based on a concentration or dose which was expected to cause no adverse effects, endocrine or otherwise. Option 4 therefore appears to be the least inappropriate option of the four presented.

Section 4. - Other information

UK supports proportionate precaution when approving chemicals which may reach the environment, especially for EDCs for whom standardised toxicity testing methods have only recently become available and whose modes of action are not all well understood. Clearly great care should be taken in these circumstances. However, the weight of international scientific opinion favours risk assessment for EDCs in most circumstances which some major jurisdictions (USA, Canada and Japan) propose to do. It seems unjustified to simply halt the assessment process if a substance meets the IPCS/WHO EDC definition. Banning or withdrawing substances in this situation ignores the fact that many can be used safely with proper risk management e.g. azole fungicides, widely used for many years without any reported evidence of environmental or human damage relating to endocrine disruption.

It has been argued that risk assessment of EDCs is unsafe because of (i) the existence of non-monotonic dose-responses (NMDRs) prevent extrapolation of adverse effects from high doses to low doses, (ii) the possible absence of no-effect thresholds, and (iii) the inability of present toxicity tests to predict long-term effects. These concerns appear largely misplaced. A recent comprehensive review of NMDRs (USEPA, 2013) showed these phenomena are rare at low concentrations *in vivo* when adverse apical effects are considered. There is little evidence for the absence of EDC toxic thresholds and current theoretical understanding of endocrine systems implies they must operate using thresholds, or it would be impossible to distinguish hormonal signals from background 'noise' (Borgert *et al*., 2013). Safe levels of exposure for endocrine systems can therefore be estimated in practice. Some higher tier EDC-sensitive tests are indeed able to detect delayed long-term effects *e.g*. the Fish Sexual Development Test, TG 234. Further, critical periods of mammalian development (*e.g*. *in utero*) are covered by existing higher-tier tests which actually aim to identify developmental and reproductive toxicants, although most (except TG 443 – the Extended One-Generation Reproductive Toxicity Study) are limited in ability to demonstrate cause and effect (Testai *et al*., 2013). Existing mammalian tests do not cover some specific late onset endpoints, but work at OECD will correct this. A major point is that inter-individual variability in susceptibility can only be captured by risk assessment - hazard assessment will solely identify potential to do harm.There are circumstances in which risk assessment of EDCs is unsafe. For example, if exposure cannot be adequately modelled (*e.g*. for a very persistent and bioaccumulative substance), or if the dose/concentration response curve does not behave monotonically *in vivo* at low exposures, or if the possibility of delayed effects has not been properly investigated. However, there is no reason why these potential problems cannot be recognised by regulators.

Although the regulation of EDCs on the basis of hazard alone is now enshrined in EU legislation, this should not prevent a reappraisal of the evidence and, if justified, amendments to the law.

Borgert, C.J., Baker, S.P. and Matthews, J.C. (2013). Potency matters: thresholds govern endocrine activity. *Reg. Tox. Pharmacol*. **67**, 83-88.Testai, E. *et al*., (2013). A plea for risk assessment of endocrine disrupting chemicals. *Toxicology* **314**, 51-59.USEPA (2013). *State of the Science Evaluation: Nonmonotonic Dose Responses as They Apply to Estrogen, Androgen, and Thyroid Pathways and EPA Testing and Assessment Procedures*. United States Environmental Protection Agency. 178 pp.

Option C is preferred as it recognises that the societal worth of some substances outweighs their potential environmental risks. Of course, an unknown number of useful and potentially safe EDCs could still be removed from the market or prevented from entering it, so even Option C may have a significant socio-economic impact.