



## **CHEM Trust's comments on the UK's view on the issue of whether or not a threshold can be determined for endocrine disruptors identified as Substances of Very High Concern under REACH**

- The UK states that it is vitally important that EU regulatory positions are based on the best science available at the time. CHEM Trust concurs, but we suggest that it may be difficult to judge whose science is 'best'.
- The UK suggests that *"where there are different [scientific] viewpoints, regulatory positions should reflect where the balance of opinion lies across the relevant fields of expertise in the EU and worldwide."* However, we note that endocrinology is a fast developing area of study, and it is clear that many experts in the area take a different view of the science, than that enunciated by the UK. For example, the international Endocrine Society has outlined their concerns about non monotonic dose responses (NMDRs) from endocrine disruptors and has stated that effects may occur due to even infinitesimally low levels, if exposure occurs during a critical developmental window.<sup>1</sup>
- The UK maintains that the scientific advisory system that is in place in the EU should be used to determine where the true science lies and that *"to do otherwise is to negate the value of expertise and nullify the purpose of the EU's standing arrangements for the provision of advice"*. We consider that where different viewpoints are held by experts of the Member States of the EU, then the scientific uncertainty needs to be taken into account in a political decision of how to handle such uncertainty. The precautionary principle is embedded in EU legislation, and recourse to this principle may be triggered by lack of scientific certainty, that is, by an insufficient certainty in the risk assessment.
- Furthermore, CHEM Trust has concerns about the use of some selected scientific advisory systems. For example, in the working group of the scientific committee operated by EFSA, some Member States (the UK) seemed to be over-represented.<sup>2</sup> Although experts do

<sup>1</sup> Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, Woodruff TJ and Vom Saal FS (2012). Minireview: Endocrine-disrupting chemicals and public health protection: a statement of principles from the endocrine society. *Endocrinology* 153(9):1-14.

<sup>2</sup> EFSA Scientific Committee members: Jan Alexander, Diane Benford, Qasim Chaudhry, Anthony Hardy, Michael John Jeger, Robert Luttik, Ambroise Martin, Bernadette Ossendorp, Simon More, Alicja Mortensen, Birgit Noerrung, Joe Perry, Iona Pratt, John Sofos, Josef Schlatter, Kristen Sejrsen.

not serve on such working groups as representatives of their country of origin, there is a tendency for them to share the views of their compatriots in the regulatory agencies within their country. Therefore, in any scientific advisory group, the EU needs to ensure a good representation of experts from different Member States, so that the views of one particular Member State are not dominant. Moreover, it would be inappropriate to limit any consultation to just an expert group held under the jurisdiction of any one EU Directorate, such as SANCO, where again, certain views may predominate.

### **Thresholds**

- CHEM Trust agrees with the UK position that *“it is now well-accepted that the existence of thresholds cannot be proven by experimentation but can only be inferred from mechanisms of action and our understanding of biology.”* We further agree that *“science is not capable of determining the shape of the dose-response at very low doses”,* and that *“hypotheses regarding where on the dose-response curve the true threshold lies are beyond the ability of science to resolve.”*
- We disagree with the UK’s insistence that nevertheless thresholds do *“surely exist”* and that *“it is inconceivable that a single molecule of any substance can, of itself, produce significant detrimental consequences in an organism or (for ecotoxicological considerations) a population.”* We find the notion of discussing the effects of one molecule rather irrelevant, in that it is rather the exposure to very, very low doses or infinitesimally small doses that is relevant here. We find it entirely possible that exposure to very low doses of endocrine disruptors during foetal development may cause adverse effects due to a lack of homeostatic and other control mechanisms not being fully functional during early development.
- The UK maintains that *“several groups of experts have argued convincingly that the proposal for a non-threshold approach for non-cancer toxicity is at odds with decades of experience and repeatable observations in exposure-response relationships in pharmacology and toxicology and with the basic tenets of homeostasis (e.g. Rhomberg et al., 2011).”* We do not find this convincing, in that this is solely referenced to a review prepared with financial support provided by the industry group, the American Chemistry Council. In addition, the notion that this is at odds with decades of experience and repeatable

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The members of the working group on Endocrine Active Substances: Jan Alexander, Jacques Auger, Diane Benford, Susy Brescia, Gisela Degen, Anthony Hardy, Karen Ildico Hirsch-Ernst, Peter Hoet, Susanne Hougaard Bennekou, Robert Luttik, Peter Matthiessen, Wim Mennes, Peter Pärt, Daniel Pickford, Thomas Platzek, Josef Schlatter, Emanuela Testai and Theo Vermeire for the preparatory work on this scientific output; the representatives of the European Commission and EU Agencies: Gabriele Schoening, Niklas Andersson, Jean-Marc Vidal, Dorota Jarosinska, Sharon Munn, Daskaleros Panagiotis, Michael Walsh; the hearing experts: Susan Jobling, Trine Husøy and EFSA staff: Bernard Bottex, Miriam Jacobs, Djien Liem, Reinhilde Schoonjans and Sarah Trattng for the support provided to this scientific opinion.

observations is not borne out by observations noted in the report from Denmark,<sup>3</sup> one of the few EU countries where scientists in its regulatory agencies actually have direct and current experience of testing chemicals.

- We disagree with the UK's assertion that *"the presence of homeostatic and defence mechanisms, and the redundancy of cellular targets mean that a minimum degree of interaction of the chemical agent with the critical sites must be reached in order to elicit a toxicologically relevant effect"*. The UK continues this assertion by saying that *"below this critical level of interaction (threshold of adversity), homeostatic mechanisms would be able to counteract any perturbation produced by xenobiotic exposure, and no structural or functional changes would arise"* (EFSA, 2005). CHEM Trust disagrees because, as noted above, such homeostatic mechanisms are not necessarily fully functional in the foetus.
- The UK further maintains that *"other authors (Boobis et al., 2009) argue that additivity-to-background does not negate the existence of a threshold of adversity. One single molecule adding to a process already active (e.g. hormone receptor agonism) cannot change by itself (or on its own) the normal/physiological response of that process into an adverse response. They also dispute that the infinite sensitivity of the population argument is an abstract mathematical concept, which has no corroboration from empirical observations – there are limits to intraspecies variability."* However, whilst CHEM Trust would agree that the infinite sensitivity of a population is an abstract mathematical concept, we do not agree that this has no corroboration from empirical observations, in that recent epidemiological studies of very large populations (up to several 100,000), where thresholds were **not** observed, independent of whether cancer or non-cancer outcomes were analysed. Instead, risks increased linearly with dose in the low dose range. These observations have been made in studies investigating the effects of ozone, tobacco smoke, nitric oxide and sulphur dioxide, particulate matter and lead (see Kortenkamp et al, 2011, State of the art assessment of endocrine disrupters).
- The UK maintains that several studies which suggest that *"it cannot be assumed that there is a threshold for the effects of EDs (Welshon et al., 2003; Sheehan, 2006; Vandenberg et al., 2012; Zoeller et al., 2012; WHO/UNEP, 2013)"*... *"tend to portray endocrine disruption as a "special" form of toxicity and endocrinology as a "special" form of biology, almost some sort of magic/complex box, which generates something from nothing."* The UK maintains that *"these views do not reflect the balance of the available evidence and contrast with mainstream scientific thinking (Romberg and Goodman, 2012)"*. Again, CHEM Trust considers that it is very worrying that a review by scientists paid by the American Chemistry Council is considered mainstream, whilst the views of the Endocrine Society and experts

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<sup>3</sup> Danish Centre on Endocrine Disruptors, Input for the REACH-review in 2013 on endocrine disrupters, Final report 21 March 2013, MST- 621-00050.

writing on behalf of the World Health Organisation (WHO) are dismissed. The notion of something from nothing is related to the phenomenon, now widely accepted as proven beyond doubt, that mixtures of substances at dose levels below their 'no observed effect concentration' can add together to cause effects.

- The UK dismisses the concerns about NMDs, and the possibility that therefore the threshold level (apparent NOAEL) identified by conventional toxicity testing is incorrect. The UK maintains "*that there is no consensus in the scientific community on the existence and relevance in toxicology of these phenomena.*" The UK then suggests that "if and when they occur, they do not preclude the existence of a threshold". This is a very un-enlightened opinion, in that clearly NMDs do exist and for example, the NMD of tamoxifen has been known for many years.
- CHEM Trust is pleased to note that several MSs disagree with the UK's position and considers that there are greater uncertainties in assessment of EDCs as compared to other non-genotoxic forms of toxicity.

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