European Society of Endocrinology

The voice for endocrinology

31 January 2018

Re: Public consultation on the Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009

Response from the European Society of Endocrinology

1. The guidance needs to cover all endocrine pathways and a procedure to include further so far not covered but relevant non-EATS (Estrogen, androgen, thyroid, steroidogenic) pathways possibly affected by endocrine disrupting compounds (EDC): Currently, only the main classical endocrine axis have been addressed in these guidelines, OECD and other test procedures for EDC, while e.g. endocrine areas and targets related to health and disease issues like metabolism, obesity, polycystic ovary syndrome (PCOS), hypertension, osteoporosis, endocrine cancer, precocious puberty and menopause are not adequately addressed and covered. Furthermore, the guidance does not address issues of precaution for high risk populations, such as pregnant women or developing newborns.

2. The approach of the guidance document is strongly driven by classical toxicology paradigms (e.g. Klimisch criteria), while endocrine concepts, hormone-related approach, feedback and set-point oriented scientific models as well as developmental issues are not represented in this guidance document. Furthermore, the well-established and available systematic review methods of published scientific literature is not adequately considered and implemented.

3. The guidance document focusses on the mode of action (MOA) concept while EDC identification and labeling of such a compound should also occur in absence of MOA data if any component of the endocrine system is affected.

4. Any adverse effects related to / associated with /or controlled by the whole endocrine system (and not only for the classical EATS) should be considered relevant. Thus, EDC labeling must also include chemicals with activity outside of the OECD-EATS pathway interfering with other endocrine pathways (as listed above under 1.)

5. During the process all relevant data and information must be considered and not only data from GLP but also non-GLP (e.g. academic) data have to be included in collection and consideration of weight of evidence (WoE).

6. Systematic scientific review is a valid accepted approach to perform WoE determinations on the plausibility decision on EDC and might be superior to the toxicology-related adverse outcome pathway (AOP) process.

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7. The EDC guidance document for plant protection products (PPP) and biocide products (BP) needs to focus on hazard identification and risk characterization should not be the scope of the guidance document.

8. Studies on low-dose effects and approaches to address complex EDC mixture effects need to be included.

9. Concentration and dose-response data is not absolutely required for hazard identification.

10. The precautionary principle must be observed and must guide the complete approach.

11. The (relative) roles of systematic review, molecular initiating events (MIE), key events (KE), key event relationships (KER) and AOP concepts in evaluation of EDC activity should be included in the process as long as no comprehensive data sets are available.

12. EDC evaluation must be based on scientific data and organized as a transparent scientifically driven process.

13. The main concepts of EDC effects must be included and if data is available considered in the evaluation and labeling process: i) classical hormone receptor-mediated effects; ii) EDC interference with endogenous ligand delivery to the hormone receptor; iii) epigenetic effects related to chromatin modification and relevant for transgenerational impact of EDC.

14. If KE with endocrine action and plausibility have been observed this is sufficient for EDC characterization and no further AOP is required.

15. Various sources of peer-reviewed data (humans, animal experiments, in vitro and in silico) should be considered and thus quantitative differences of effects, dose-response, cross-talk etc. have to be taken into account with respect to their relevance to humans.

16. The guidance document and algorithms do not sufficiently describe what the action is if the data available for a substance evaluation is non-conclusive (more data needed? no authorization? no regulation?).

17. There is an imbalance in the guidance document for identification of false-positives vs. reducing of false-negative compounds.

18. Required high level of evidence (e.g. AOP, MIE, KER) may frequently lead to the situation that the available data is not sufficient to draw a final conclusion for EDC classification.

19. The proposed guidance approach may result in difficulties to clearly discriminate hormone, neuroendocrine and neurotransmitter signals and their downstream signaling and crosstalk.

20. Adverse effects of EDC through membrane receptors particularly in the developing brain need to be considered and implemented in the EDC identification and labeling strategies.

21. The guidance documents solely focus on mammalian data/human health. Clearly, available non-mammalian data should also be used for hazard identification and must be included to characterize and identify environmental hazards of EDC and their mixtures.

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