

## Consultation response

# 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



AmCham EU speaks for American companies committed to Europe on trade, investment and competitiveness issues. It aims to ensure a growth-orientated business and investment climate in Europe. AmCham EU facilitates the resolution of transatlantic issues that impact business and plays a role in creating better understanding of EU and US positions on business matters. Aggregate US investment in Europe totalled more than €2 trillion in 2016, directly supports more than 4.5 million jobs in Europe, and generates billions of euros annually in income, trade and research and development.

## Introduction

The American Chamber of Commerce to the European Union (AmCham EU) provides the input below into public consultation on the draft ECHA/EFSA Guidance Document for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009.

Given the critical importance of regulatory coherence, the draft guidance should be consistent with the ED Criteria for Biocides and Crop Protection Agents (latter are still being finalised). The draft guidance actually undermines the criteria, and effectively turns it upside down by proposing the proof of absence of ED effects, rather than requiring the demonstration of ED effects based on a robust weight of evidence assessment and consideration of all relevant data as is specified in the criteria. This lack of regulatory coherence is a major concern and AmChamEU would urge ECHA and EFSA to address this as a high priority.

## Specific concerns

**1. The draft guidance undermines the WHO definition of endocrine disruptors by introducing confusing references to oestrogen, androgen, thyroid and steroidogenesis activity of substances. This is contradictory to the ED Criteria themselves, which are based on the WHO definition.**

The term '(o)estrogen, androgen, thyroid, steroidogenic (EATS)-mediated' parameter as used in the draft is confused with

- (a) the identification of adversity and
- (b) the mistaken assumption that these parameters exclusively identify an endocrine mode-of-action (MoA).

This results in an unjustifiably low threshold for identification of endocrine disrupting properties. Preferably, the inaccurate distinction between EATS-mediated and 'sensitive to, but not diagnostic of EATS' (STBNDO-EATS) parameters should be abandoned, since none of the parameters indicated as EATS-mediated are exclusively 'diagnostic of EATS MoAs'. These parameters are nevertheless as critical in the weight-of-evidence (WoE) evaluation. In line with *the OECD guidance document (GD) 150 on standardised test guidelines for evaluating chemicals for endocrine disruption*, these parameters are mechanistically informative and will often provide the strongest support in the WoE. They also have the potential to change in response to other (non-endocrine) modes of toxicity. The draft should be modified to apply a WoE approach which is consistent with legal texts outlining the criteria to identify endocrine disruptors. This would mean evaluating the entirety of the substance-specific dataset to determine if any observed effect is mediated by an underlying endocrine mechanism. If it is considered useful to maintain the terminology 'EATS-mediated' and 'STBNDO-EATS', the strategy in the Guidance should be modified to reflect the same WoE approach for EATS-mediated effects as for STBNDO-EATS effects. A robust WoE evaluation should include parameters observed across multiple species, doses, and time points. It should not focus on isolated changes.

**2. The draft guidance reverses the burden of proof for demonstrating that a substance is not an endocrine disruptor. This stands in contradiction to the legal text of the endocrine disruptor criteria that require that the available data are used to determine if a substance is an endocrine disruptor.**

Together with the current concept of EATS-mediated parameters, the statements on data sufficiency) set a low threshold to identify a substance as having endocrine disrupting properties, whereas there is an almost unattainable threshold to disprove this.

### 3. Appendix A of the draft guidance singles-out concerns around thyroid toxicity and the role of liver enzyme activation without a clear rationale.

The consideration given to thyroid disruption in Appendix A is based on poorly supported, erroneous and contradictory assumptions on the complexity of Modes of Action of ‘thyroid disrupters’ and the relevance to humans. All hormone systems feature regulatory networks, synthesis dependent on precursors, factors affecting transport and target tissue availability and hepatic metabolism and clearance. These processes can be affected by environmental factors in relation to oestrogens and androgens (i.e. E and A) as much as for thyroid hormones (T). This is corroborated within the draft, on p. 56, in relation to the interpretation of results from Hershberger Assays:

‘With regard to serum hormone level, testosterone levels are useful to determine whether the test substance induces liver metabolism of testosterone, lowering serum levels, which could otherwise be misinterpreted as anti-androgenic effect.’ (lines 1344-1346). Consideration of specificity, as detailed in the legal text of the endocrine disruptor criteria under point 4 relating to identification (‘Adverse effects that are non-specific secondary consequences of other toxic effects shall not be considered for the identification of the substance as endocrine disruptor’) should be applied consistently throughout the guidance and to relevant potential Modes of Action (i.e. EATS).

The additional hazard characterisation, in particular relating to comparative hepatic enzyme activity, goes beyond the remit of the guidance as stated in the Scope (Section 2, lines 198-199): ‘The document does not provide guidance on how to further characterise the hazard potential of a substance or the risk to humans or non-target organisms.’

The approach to identifying thyroid disrupters proposed in Appendix A is not supported by the current state of science in this area. The statement that ‘it is presumed that substances that alter the circulating levels of T3 and/or T4 with concurrent histopathological findings in the thyroid would pose a hazard for human thyroid hormone insufficiency in adults...’ (Line 2660) is of significant concern, as a large number of registered plant protection products will cause some effect in the thyroid and in most cases, this is due to UDPGT mediated elimination of T4.

No reference is made to the well-established species differences in response to liver mediated elimination of thyroid hormones, and in fact, this statement stands in contradiction with the preceding paragraph (starting at line 2650): ‘There are notable differences in the systemic regulation of TH levels between commonly used experimental animal models and humans. Although the HPT axis and the basic physiological processes regulating TH synthesis are qualitatively similar across species, there are, however, quantitative species-specific differences (Janssen and Janssen 2017). All these aspects are making the relationship between changes in circulating THs, including the ones mediated by differences in metabolism and downstream adverse effects, very complex; therefore, species differences in the sensitivity of specific developmental outcomes as a result of substance-induced changes of circulating levels of THs cannot be ruled out at this time.’

No information on the conduct or interpretation of the assays is described on p. 96.

For the in vivo mechanistic studies, critical issues such as animal numbers, need to test both sexes, the dosing period, testing juveniles vs. adults are missing, as are the criteria for defining a positive response. As described in Appendix B, issues like these are critical for good hormone analysis. A conventional design for an assay assessing thyroid hormones in rats would be 15 animals/sex/group with a control, low, middle, and high dose

group, 120 animals/study. Assuming that 25% of the 500 registered PPPs require such a study this would amount to 15000 animals.

The in vitro comparative enzyme induction assay is based upon a flawed understanding of the species differences in response to liver enzyme inducers between rats and humans. The key issues of differences in thyroid binding hormone between species and the functional T4 reserve capacity in humans are omitted. No explanation of what would be required to establish a species difference in enzyme output is given.

**4. Questionable statements around the long-standing principles of the conduct and interpretation of (eco) toxicology studies have been included with no justification or consideration to the conflict with substance-specific legislation and requirements of the test guidelines.**

‘It is acknowledged that for some endocrine effects, due to the biology of the endocrine system, more complex dose responses (i.e. non-monotonic) may occur. Therefore, non-linear dose responses should not by default be dismissed as not supporting the assessment’ (p. 18, line 325).

The above statement does not adequately represent the absence of scientific consensus on this issue.

The omission of dose-concordance assessments may be appropriate when the understanding of the MoA indicates that non-monotonicity is likely, but should not be omitted by default.

‘Generally speaking, limit doses of 1,000 mg/kg/day are considered appropriate in all cases where indications of saturation of exposure or limited/no absorption are provided. If none of these criteria can be achieved, a dose of 2,000 mg/kg/day or the maximum feasible dose, whichever is lower, should be considered.’ (p. 12, line 117).

The statement above contradicts the consensus statement on scientific principles for the identification of endocrine disrupting chemicals that states on p. 104; para. 22: ‘However, there may be high doses (e.g. the oral toxicity limit dose of 1000 mg/kg bodyweight/day) above which identification as an endocrine disruptor would not be warranted.’ This position supports the view that effects only seen at higher doses than the current OECD upper limit dose (for repeated-dose toxicity studies: 1000 mg/kg bodyweight / day) are not relevant to the identification of endocrine disruptor hazards for humans. By all means, the respective guidance on the upper limit dose should be harmonised with the respective provisions in the relevant OECD test guidelines and the revised OECD GD 150.

Similarly, there are contradictions with limit levels and the need to seek a toxicological response in ecotoxicology studies (i.e. OECD TGs). This is exacerbated by the draft implying that there is established guidance or general agreement on concepts such as the Maximum Tolerable Concentration or Dose. This is not true, and in the absence of clear guidance in the draft, it is likely that studies will be performed that are not sufficient for the intended purposes. The final guidance document needs to address this and preferably initiate activities to resolve the inconsistencies (e.g. at the OECD level).

The draft gives the impression of introducing new data requirements. However, data requirements are set in the relevant substance-specific legislation, and it is beyond the remit of the guidance to alter legislation requirements. The type and amount of available information will vary considerably for different substances as directed by the different legislation, especially for non-active ones. The guidance document must be flexible enough to account for these situations. The legal texts outlining the criteria to identify EDs request to perform a WoE evaluation using the available data. These and other inconsistencies in the structure of the WoE concept (and in the definitions used in the draft) should be amended for consistency with the legal text of the EDs criteria.