CHEMTrust
Protecting humans and wildlife from harmful chemicals

Sent by email to *ENV-CARACAL@ec.europa.eu* and *GROW-CARACAL@ec.europa.eu* on 19.11.2020

Follow-up 3rd meeting of CASG-ED (19 October 2020)

Comments on document CASG-ED/2020/08: Proposals on a way forward to update the REACH Annexes in relation to endocrine disruption properties

General comments

CHEM Trust would like to thank the Commission for the document outlining ways for updating the REACH annexes with regard to endocrine disrupting properties. CHEM Trust welcomes that the discussion on updating the REACH annexes has finally started. Currently there is still a huge information gap on substances' ED properties and many ED assessments thus end up being inconclusive.[1] A proper protection for human health and the environment can only be achieved if information on ED properties is available to be able to identify those substances that are EDs.[2] Information requirements on endocrine disrupting properties have to be integrated in REACH in order to implement the principle of "no data, no market", which foresees that the burden of proof to ensure safe use stays with the REACH registrant. Given that these changes to the annexes are coming very late all registration requirements for chemicals currently on the market have already passed. This means the proposal for improving the identification of EDCs needs to be accompanied by a legal deadline which obliges companies to update their registration dossiers.

Moreover, EDs should be regarded as priority substances for which new toxicological and ecotoxicological information should be required between 1 and 10 tonnes. Given that the whole context for this exercise is the need to close knowledge gaps we were surprised that the Commission document puts a strong focus on potential false positive outcomes of *in vitro* tests, whereas no concern about potential false negative outcomes is mentioned. The latter is much more problematic from the perspective of enhancing protection for humans and wildlife and should be better addressed.

Support for Proposal 2

From the proposals presented we can only support the approach presented as **proposal 2** for three main reasons:

[1] https://echa.europa.eu/de/ed-assessment
[2] https://chemtrust.org/wp-content/uploads/CHEMTrust-newEDPolicy-July2020.pdf

1) It includes a follow-up on positive *in-vitro* tests included in Annex VII (i.e. for chemicals between 1-10 tpa). This follow-up is missing in proposal 1 which overemphasizes the occurrence of false positives outcomes instead of ensuring that indications for endocrine disrupting properties are further investigated. Given that the aim is to close knowledge gaps, a follow-up of positive alerts is always needed.
2) It includes a better integration of environment and human data, thus leading to a more holistic assessment of ED properties.
3) Is more in line with the approach in the OECD Guidance Document 150 and the ECHA/EFSA guidance document.

Specific comments and clarifications requests for Proposal 2

In CHEM Trust view the following points should be further clarified or amended in Proposal 2:

Annex VII

10.1. There is a need to emphasise the obligation to include a **comprehensive literature search** (incl. the EASIS-database) for ED properties by making a link to REACH Annex I. It would be good to specify details in the planned guidance document, i.e. that a predefined minimum search strategy should ensure that all published information needs to be included as a starting point. This should also include available evidence on non-EATS ED modalities.

In case valid (Q)SARs are not available, we propose there should be an obligation to do a (Q)SAR screening.

In case QSAR-screening or literature search show signs of ED properties, then this should always be followed up depending of the sort of evidence (e.g. by advancing the level of evidence according to OECD GD 150 or as proposed by the Danish Centre on Endocrine Disrupters).[3]

10.2. We support the follow-up with *in vivo* data in case one of the 5 *in vitro* tests is positive, as proposed. In the proposal there is no follow up foreseen in those cases when all 5 in vitro tests are negative but there are alerts from the literature review and potentially in silico data. We propose this should still be followed up depending of the type of concern as outlined above.

10.2.1 – 10.2.5 We support the inclusion of the *in vitro* tests. However, we would suggest to include more thyroid *in vitro* assays than just one, given the complexity of the thyroid endpoints and importance of thyroid hormones for brain development, metabolism, cardio-vascular function and other biological processes. Options would be a test battery that covers several MoAs, e.g. T-receptor binding, T-hormone transport, TPO inhibition, NIS inhibition, deiodinase inhibition.

[3] http://www.cend.dk/files/EDtestingstrategy.pdf

10.2.1 We cannot support and therefore propose to delete the waiver relating to the Toxcast data because it is questioned whether these have been properly validated and are convincing enough as stand-alone for regulatory purposes.

10.2.1 We cannot support and therefore propose to delete the waiver relating to the Uterotrophic bioassay. This assay is not very sensitive and therefore, there is a risk of false negative outcomes. Just to waive a TG 455 based on the existence of an Uterotrophic assay no matter of the outcome seems to be an unreliable approach to identify potentially estrogenic substances. If the waiver is kept, it should at minimum be specified that it should be an adequate and reliable study, including adequate dose levels.

10.2.2 We cannot support and therefore propose to delete the waiver to the Hershberger bioassay. It is not appropriate as a waiver for androgen receptor transactivation so that there is a risk of false negatives outcomes. It is also not a very sensitive assay. If the waiver is kept it should at minimum be specified that it should be an adequate and reliable study, including adequate dose levels.

Annex VIII

10.2.1 In line with our comment Annex VII, we suggest to delete the waiver re the ToxCast data.

10.2.1 and 10.2.2 For both tests it should be specified that it needs to be an adequate and reliable study, that includes adequate dose levels.

We would also welcome further discussions on which added value these two tests will provide, as their usefulness will depend on which *in vitro* tests are positive. The main outcome is that they would provide *in vivo* mechanistic information. However, it should be noted that the OECD guidance also mentions the options that an increase in uterine weight in the Uterotrophic assay as well as a significant change in absolute testis weight (increase or decrease) in the Hershberger assay may be regarded as adverse effects.

10.2.3. and 10.2.4. The proposed approach is supported.

Annex IX and X

Human health: Currently, the DNT/DIT and F2 cohorts in the EORGTS are only triggered, however, it is problematic that those effects that should be explored are those supposed to trigger the testing of the cohorts. Therefore, if an EOGTRS for ED properties is carried out it should always include the DNT/DIT cohorts. It should also be emphasized that even if a negative 2-generation study (OECD TG 416, latest update) is already available, this will not automatically replace the need for an EORGTS. Supplementary testing covering specific endpoints may be requested depending of the existing available data.

Environment: The suggestions in proposal 2 are supported.

Conclusion

We would like to emphasize that in all ED assessments the evidence for human health and the environment should be evaluated and considered together to make the testing strategy much more efficient and enables easier conclusions. Further, the aim of the standard information requirements should be to protect human health and the environment from serious effects caused by endocrine disruptors. Therefore, the focus should be on how to best detect and identify substances with ED properties instead of how to waive testing and follow-up on alerts.

It should be kept in mind that the European population is still exposed daily to thousands of chemicals that have not at all been tested or evaluated for their potential endocrine disrupting effects and that “no evidence of effect is not evidence of no effects”. Exposure to EDs during sensitive windows of development and the resulting hormonal imbalance may be detrimental even at low dose and may lead to serious and irreversible effects in current and future generations.