Response to public consultation on proposed update of the EDC information requirements in the biocides product regulation (BPR)

Preliminary comments submitted by the Health and Environment Alliance (HEAL)

March 2020

The Health and Environment Alliance (HEAL) welcomes the opportunity to comment on the proposed update of the EDC information requirements in the biocides products regulation (BPR).

In the context of this update, not only is it important to stress that thorough safety testing of biocidal active substances (AS) as well as co-formulants and products must take place before biocidal products are placed on the market, but also that it is critical for the protection objectives of the regulation to be met.

The entry into force of the ED identification criteria for biocides and the related implementation guidance (thereafter referred to as ECHA/EFSA guidance [1]) in 2018 makes the assessment of ED properties mandatory. The current delay in the biocides review programme should not be used as an excuse by applicants to evade EDC assessment for active substances, co-formulants (when ED concerns exist) and products. It should also not discourage evaluating authorities from requesting all the necessary information to perform thorough assessments ahead of the placing on the market or the granting of renewed authorisations. In cases when dossiers are incomplete in a way that prevents the clarification of ED concerns, authorities should either consider refusing to assess them or conclude that the EDC criteria are met by default.

COMMENTS ON THE PROPOSED DRAFT REGULATION

Whereas (2) – Whereas the mention that *'new testing strategies favouring in vitro tests against in vivo tests in order to reduce testing on vertebrate animals and a testing strategy and methods for the determination of endocrine disrupting properties of substances'* is a shared goal, it is important to stress that proper EDC identification is currently relying on the use and performing of animal testing. As long as no in vitro tests are validated to account for systemic toxicity and human health-relevant adverse endpoints for endocrine disruption, the use of animal tests remains a necessity and should be acknowledged.

Whereas (8) – We comment on the reference made to article 62 requiring testing on vertebrate animals as a 'last resort' option and the proposal that *'in setting data requirements for the approval of active substances and the authorisation of biocidal products, priority should be given to reliable in vitro methods as a substitute to in vivo methods requiring the use of vertebrate animals'*. Once again, all stakeholders agree on the ultimate goal to reduce animal testing. However, we must again stress that EDC identification is currently not possible when relying only on in vitro test methods. Such methods might be useful for preliminary screening of endocrine activity or substantiate/clarify a mode of action, but are in no way suitable to detect adverse effects relevant to humans. If the European Commission is serious about reducing the use of animal testing, then one way forward would be to more systematically rely on independent peer-reviewed literature during assessments and give it the same weight as guideline studies in a view to limit the repetition of animal studies.

We also question in how much this statement reflects point (6) according to which the adaptation of the information requirements is needed to *"allow for the identification of active substances generated in situ"*. It is indeed expected that to allow for the latter requires information on the metabolism. This needs to be taken into account when prioritizing heavy reliance on in vitro tests.

Whereas (9) – We welcome the acknowledgement that a negative UDS result does not prove that a substance does not induce gene mutation and therefore the proposed removal of its mention as well as proposed replacement by a reference to the an appropriate in vivo somatic cell genotoxicity study. We would also like to see a clarification here that negative results to an in vitro genotoxicity study alone is not sufficient to discard all concerns for genotoxicity.

Whereas (10) - We disagree with the proposed standard requirement of a two-generation reproductive toxicity study (TGRTS) in order to investigate the reproductive toxicity of a substance and would plead in favour of the extended one generation reproductive toxicity study (EOGRTS) as a standard requirement, with the inclusion of developmental neurotoxicity (DNT) and developmental immunotoxicity (DIT) cohorts. This is because of the EOGRTS higher sensitivity and its relevance in relation to endocrine disruption.

Whereas (11) - We welcome the Commission's intention to better address and assess neurotoxicity, which we believe has been an overlooked health endpoint so far. In order to

deliver, we believe that the text should clarify that independent peer-reviewed literature should be taken into account during the assessment, including a full review, and given the same weight as standard test guidelines during the assessment.

Whereas (13) - We also welcome the Commission's intention to evaluate the potential for unintended effects of substances on the immune system. First of all, we are of the opinion that performing an EOGRTS including a DIT cohort actually provides at least one validated test method to assess this endpoint. Second, the limitations of other OECD test guidelines are yet another strong argument in favour or clarifying in this section that independent peer-reviewed literature should be fully taken into account during the assessment.

Whereas (17) – Regarding non-active substances, we welcome the link made to information available under REACH, but would actually welcome a strengthening of the language about the provision of additional information, when deemed necessary by the assessing authority. The second sentence currently reads that *"applicants may need to provide additional information on substances of concern included in biocidal products in particular in order to prepare a data set that enables the identification of their endocrine disrupting properties".* We would welcome a clarification that applicants "should" provide such information whenever requested by the assessing authority and not already available under REACH. The only exception should be when there is already enough information on the health-relevant properties of the active substance to decide on the exclusion or substitution criteria.

COMMENTS ON THE PROPOSED DRAFT REGULATION

Proposed ANNEX I

Section 8.6 - In vivo genotoxicity study

We disagree with the proposed waiver for the required study in cases where *"the results are negative for the three in vitro tests listed in 8.5 [that is mutagenicity] and no other concern has been identified (e.g. metabolites of concern formed in mammals)".* We do no consider that the negative outcome to in vitro tests referred to in relation to the mutagenicity endpoint (point 8.5) is enough to discard concerns for adverse effects in humans. This is because mutagenicity is a very important health endpoint. Therefore, the proposed waiver in the right column which currently reads *"the results are negative for the three in vitro tests listed in 8.5 and no other concern has been identified (e.g. metabolites of concern formed in mammals)"* should be removed. Potential concerns should instead be investigated through in vivo tests.

Section 8.10 – Reproductive toxicity

While the proposed waiver for the test requirement makes sense in case the substance meets the criteria to be classified as a genotoxic carcinogen, we repeat the concern stated in relation to point 8.6 about the actual identification of such substances. Therefore, the proposed waiver only makes sense to us if the European Commission can guarantee to NOT use negative results of in vitro tests to discard adverse effects in humans. Failing to do so would create a dangerous loophole that would not only affect the identification of genotoxic substances, but also the addressing of reproductive toxicity concerns.

Section 8.10.1 - Prenatal development toxicity study (PNDT) on 2 species

We would welcome an addition here to clarify that existing information (from independent literature, open databases or in vitro tests) giving rise to concerns for potential adverse effects on fertility or development can be used by the assessing authority in order to trigger the request for a PNDT study.

Section 8.10.2 – EOGRTS

We are concerned at the proposed waiver for the requirement to perform an EOGRTS in the proposed case: *"A Two-Generation reproductive toxicity study conducted in accordance with OECD TG 416 (adopted 2001 or later) or equivalent information shall be considered appropriate to address this information requirement, if the study is available and was initiated before… (date of application of this amending Regulation)"* and we do not understand the rationale for it.

As the Commission is well aware, the EORGTS is much more suitable than the TG 416 in order to address ED endpoints and should be considered the very minimum level of requirement. The ECHA/EFSA guidance for the implementation of the identification criteria for endocrine disruptors in the BP regulation has been in force since June 2018; it refers to the OECD GD 150 and clarifies that *"The EOGRTS study (OECD TG 443) is preferable for detecting endocrine disruption because it provides an evaluation of a number of endocrine endpoints in the juvenile and adult F1, which are not included in the 2-generation study (OECD TG 416) adopted in 2001"* [2] .

Further, we question the added-value of *"the extension of cohort 1B to include F2 generation"* and would rather favour the mandatory inclusion of the DIT and DNT cohorts in the context of the performing of the EOGRTS.

In order to guarantee the condition mentioned in section 8.10 that *"the dataset is sufficiently comprehensive and informative"*, it is important that the update of the information requirements is used to:

- Stress that tests need to be performed at high enough doses allowing to see some toxicity so that the studies can be relevant for the assessment of substances and increase the efficiency of animal testing. Considering the limitations of currently validated tests, avoiding testing at too low doses is necessary.

- Clarify that independent peer-reviewed studies should be investigated and be given as much weight in the dataset as guideline studies – they provide an important basis to trigger in vivo tests to fully investigate concerns.

- Clarify that the burden of the proof is on the applicant. Therefore, the wording *"sufficiently comprehensive and informative"* should not be used at the discretion of the applicant's judgement but provide the assessing authority to request the data needed to fully investigate health concerns.

Section 8.11.2 – Carcinogenicity testing in a second species

We would appreciate a clarification of the scientific basis for the proposed waiver: *"The second carcinogenicity study does not need to be conducted if the applicant can justify **on the basis of scientific ground** that it is not necessary."* In order to clarify legal obligations and to avoid confusion, we would suggest a rewording to clarify that it is up to the assessing authority to decide if the scientific grounds to justify testing in a second species are met or not in the dossier. Any proposal for waiving a test requirement – especially on such an important endpoint as carcinogenicity – should be fully documented and transparent.

Finally, in most cases for compounds such as biocides, it is likely that one will only be able to judge whether tumours observed in two different species are relevant for humans AFTER the second study is being performed (when analysing the results).

Section 8.13.3 - Endocrine disruption

Left column:

- The current wording is unclear in terms of giving guidance on the test requirements, including whether it means that all of the mentioned studies or only specific ones from the package are to be provided. We would recommend at least clearly referring to the ECHA/EFSA guidance on the implementation of the EDC criteria, which itself refers to the conceptual framework of the OECD GD 150. This would lead to mentioning which study corresponds to each level and overall increase clarity of the entire section for the benefit of all stakeholders.

- When it comes to level 5 and point (v), we repeat that the OECD TG 443 should be the minimum standard requirement rather than the OECD TG 416.

- Overall, due to the known limitations of in vitro test methods as well as some of the level 3 and 4 test methods when it comes to endocrine disruption (eg high risks of false negatives with the Uterotrophic Assay), it should be clarified in the text that assessing authorities have the flexibility to request the EOGRTS based on their expert judgements of early indications of endocrine activity, and including from independent literature and databases. This would also contribute to limiting the repetition of animal studies.

- When it comes to point (vii) and the mention of a long-term repeated dose toxicity study (TG 451-3), we recall that the ECHA/EFSA guidance states that *"These tests **have not been designed to detect ED**, but do measure some 'EATS-mediated' parameters and some parameters' **sensitive to, but not diagnostic of, EATS' modalities**"* [3] - which leads us to question about the added-value of the study in the present context.

Right column:

We are concerned at the proposed wording:

*"Where sufficient weight of evidence to conclude on the presence or absence of a particular endocrine disrupting **mode of action** is available:*

- *Further testing on vertebrate animals for that effect shall be omitted for that mode of action;*

- *Further testing not involving vertebrate animals may be omitted for that mode of action.*

*In all cases, **adequate and reliable documentation** shall be provided."*

As we already commented in the context of the elaboration of the ECHA/EFSA guidance, the demonstration of a mode of action (MoA) is not a requirement of the EDC identification criteria themselves as adopted in the context of the pesticides (PPP) and biocide (BP) regulations. The criteria state that the adverse effect should be the consequence of an endocrine MoA. And this wording brings confusion. Therefore we suggest rephrasing the quoted paragraph in order to clarify that, as part of the weight of evidence approach, it is up to the expert judgement of the assessing authority to decide whether the sufficient information is available and whether further testing on

vertebrate or invertebrate animals is necessary or not.

This would also bring the text in line with the ECHA/EFSA guidance, which clarifies for instance that: *"The ED criteria state that a weight of evidence approach shall be applied for the assessment of the available scientific data"* [4] and that *"expert judgement will be necessary when considering the available lines of evidence, including the overall evaluation of the consistency of the data set as a whole"* [5].

In the context of this paragraph and the mention of the weight of evidence, we also recommend:

- Referencing EFSA's own guidance on the weight of evidence (introduced in 2017) [6].

- In relation to the wording *"adequate and reliable documentation shall be provided"*, we express the same concerns as above in section 8.10.2 about the *"sufficiently comprehensive and informative"* dataset mention.

Section 8.13.3.1 - Additional studies

We welcome the proposal for the authorities to request additional studies including the mammalian toxicity studies listed in 8.13.3(a).

However, when it comes to the (b) point on in vitro assays and in vivo screening assays providing data on endocrine mechanisms/pathways (OECD TG 455; OECD TG 458; OECD TG 456, the Aromastase assay, OECD TG 440, OECD TG 441, OPPTS), we are puzzled at the proposed sequencing of requests.

As is well documented, in vitro studies are useful for screening purposes mainly, while level 3 or level 4 in vivo studies are currently not all fit and sensitive enough in the context of EDC identification (for instance, the Uterotrophic assay/TG 440 can give rise to lots of false negatives). In this context, we wonder about the added-value of listing a number of them as "additional studies". Supposedly, such studies will not bring value 'in addition' to level 5 animal studies in the context of EDC identification, and rather have a value for early screening. Because of their limitations though, negative outcomes to in vitro screening studies and to in vivo level 3 and 4 studies should not allow for fully discarding potential adverse effects of a substance in humans. We would welcome a clarification about this part to guarantee that on the one hand, early indications of endocrine activity are fully investigated, and on the other hand that negative results to in vitro studies or level 3 and 4 studies are not used to waive further in vivo testing for adverse effects in humans. We would also welcome a reference to the ECHA/EFSA guidance, which refers itself to the OECD GD 150, provides a list of tests (as well as their respective values), and is meant to be updated regularly overtime.

Section 8.13.4 – Immunotoxicity and developmental immunotoxicity

We are concerned about the proposals regarding the investigation of immunotoxicity in this section. The text states *"If there is any evidence from repeat dose or reproductive toxicity studies that the active substance may have immunotoxic properties, then additional information or specific studies shall be required…".* To our knowledge, the DIT cohort in the EOGRTS is the only functional immunotoxic endpoint available in current test guidelines. We would therefore like to see a clarification about which immunotoxic endpoints (if any) the European Commission considers available in the repeated dose and reprotoxic studies that may lead to this triggering. This concern also adds further urgency to our request in point 8.10.2 to include the DIT cohorts in the EOGRTS.

Section 9.10.2 – Endocrine disruption in amphibians

We are concerned about the proposed condition to waive the study requirement: *"there is no indication for endocrine activity or endocrine related effects from a sufficient mammalian data set in accordance with 8.13.3 or from any other relevant information"*. This is because validated tests on amphibians that much better cover thyroid disruption than mammalian tests do already exist - including the recently validated Xenopus embryonic thyroid signaling assay (XETA, TG 248, level 3), the Amphibian Metamorphosis Assay (AMA, TG 231, level 3), the larval growth and development Assay (LAGDA, TG 241, level 4). All these tests are mentioned in the ECHA/EFSA guidance document and are increasingly referred to as relevant for hazard characterisation for mammalian endpoints in regulatory discussions. Therefore, a lack of indication of endocrine activity or endocrine related effects in mammalian data should not be used to waive the requirement to perform amphibian tests such as the XETA and the LAGDA tests in particular.

Proposed ANNEX I

Sections 8.7 and 9.1

We are concerned about the proposed language for waiving the test requirement on the product or mixture if, among other conditions *"synergistic effects between any of the components are not expected"*. It is currently unclear from the proposed wording how this will be demonstrated. Synergism is often the result of mixed mechanisms, which are pretty hard to predict. Therefore, we do not think that the proposed wording is adequate to orientate important decisions on testing requirements.

Notes:

1. ECHA/EFSA, "Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009", 7 June 2018, https://www.efsa.europa.eu/en/efsajournal/pub/5311
2. Ibid, p.50
3. Ibid, p.62
4. Ibid, p.7
5. Ibid, p.8
6. EFSA, "Guidance on the use of the weight of evidence approach in scientific assessments", 3 August 2017, https://www.efsa.europa.eu/en/efsajournal/pub/4971

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