EU Commissioner Mr Vytenis Andriukaitis 6 July 2016
European Commission Directorate General for Health and Food Safety
B – 1049
Brussels, Belgium

Open letter in response to the proposed criteria for identification and regulation of endocrine disrupting chemicals, under the PPP and Biocides Regulations

Dear Commissioner Andriukaitis,

We are writing to you as scientists conducting research into endocrine disrupting chemicals (EDCs) and systematic review methods for chemical risk assessment, in order to voice our concerns about the proposed criteria for identification and regulation of EDCs under the PPP and Biocides Regulations, and to contribute our perspective on the challenge of aggregating scientific evidence in the process of identifying EDCs (see Vandenberg et al. 2016*).

While we are encouraged that the proposal acknowledges the role which systematic review (SR) methods could play in identifying EDCs, and are satisfied with the use of the WHO/IPCS definition as a basis for the regulatory definition of EDC, we have two major concerns about the proposed criteria:

1. They place an under-defined, potentially unprecedentedly high, burden of proof on identifying problem compounds as having endocrine disrupting properties, with the result that the identification process will be either conducted inconsistently, or only a very small proportion of actual EDCs may be classified as such.

2. They present a confused set of processes for identifying, evaluating and integrating scientific evidence which unnecessarily privilege certain types of data, and cannot be adequately operationalised for regulatory identification of EDCs.

To resolve these issues, we recommend the following:

a. A clear, unambiguous definition of “known to cause adverse effects relevant for human health”.

b. Allowance for regulatory identification of a chemical substance as an EDC in the absence of “sufficient” evidence of harm from epidemiological studies.

c. The introduction of a hierarchy of categories for EDCs, with clear, unambiguous criteria distinguishing “known” from e.g. “probable”, “possible” or “not classifiable”.

d. The articulation of a systematic and coherent process for integrating evidence across the three components of the WHO/IPCS definition of EDC.

e. The definition of clear and unambiguous standards for strength of evidence within each of the three individual components of the EDC definition.

f. Ensuring all evidence is assessed on merit without prior privileging of certain study types.

Concern #1: Ambiguous and high burden of proof. The proposal states that a compound can only be classified as an EDC if it is "known to cause an adverse effect", but the evidence requirements for reaching this conclusion are left ambiguous. It is not therefore clear how the definition of "known" will be applied by different actors in interpreting evidence of endocrine disruption. As a consequence, the implementation of the regulation will be inconsistent and potential EDCs will not all be classified according to an equal standard.

We have particular concern that if the ambiguity in the proposal is resolved by following existing CLP Regulation, by requiring "sufficient" evidence of harm in humans in order to classify an EDC as "known to cause an adverse effect", then very few EDCs will be identified as such. As is the case for most health effects, it is extremely difficult to develop robust evidence of endocrine disruption from epidemiological studies; it also defeats the purpose of using animal studies to protect human health, if substances cannot be classified as EDCs until strong evidence has accumulated in humans.

Given that the strongest evidence for adverse health effects of chemicals often comes from animal studies, that animal studies may offer the only robust evidence available, and that evidence of health effects in animal studies is by default treated as predictive of health effects in humans, the criteria should either: (a) allow that evidence of harm in animal studies can be sufficient to describe an EDC as being "known to cause an adverse effect", even if there is a lower than "sufficient" level of evidence of harm from epidemiology studies; or (b) allow a compound to be classified as an EDC on the basis of it being "presumed" to cause an adverse effect in humans. We recommend (b) as a familiar, valid approach already used for classification of carcinogens, mutagens and reprotoxins (CMRs).

Concern #2: Confused processes. In the proposal, the list of factors to be considered in assessing the strength of scientific evidence, such as requiring that e.g. "positive and negative results shall be considered together", only partially capture the full set of procedures which need to be followed in identifying, evaluating and integrating scientific evidence relating to endocrine disruption. There is also an absence of coherent process describing how each component of the WHO/IPCS definition of EDC (i.e. evidence of adverse effect, endocrine mode of action, and effect as consequence of exposure) are to be combined into a final conclusion as to how a compound should be classified as an EDC.

Furthermore, while there is a welcome call to assess "all available relevant scientific evidence", the criteria must not privilege studies which are "performed according to internationally agreed study protocols" as the evidence on which regulatory identification as an EDC is to be "primarily" based. This is either unnecessary (because a systematic review will anyway privilege the best conducted studies based on empirical evidence of which methods produce the best results) or it introduces bias (by forcing reviewers to treat guideline studies as stronger than other studies when they may be weaker).

We suggest these shortcomings be addressed by the use of appropriate systematic review and evidence integration methods in the evidence review process. (While systematic review is mentioned in the proposed text, its use is restricted to analysing only "other relevant scientific information" in a process apparently either parallel or subservient to the current assessment methodology.)

Overall concerns: Overall, we are concerned that the proposed regulatory text creates an unprecedented and incoherent burden of proof for classifying a compound as an EDC. By unnecessarily privileging certain types of evidence, and implementing an opaque and ill-defined standard with a potentially very high burden of proof for identifying a compound as a "known" EDC, we believe there are serious questions as

to how the process for classifying compounds as an EDC will either be reliable (in that it can distinguish chemicals which require regulatory attention from those which do not) or credible (in that it will be trusted by stakeholders).

We would like to request a meeting so we can articulate our concerns in more detail, based on our experience of developing scientific guidance for the identification and classification of EDCs, and to discuss how they might be resolved through reformulation of the regulatory proposal.

We look forward to hearing your response.

Yours sincerely,

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Mr Paul Whaley. Lancaster Environment Centre, Lancaster University, Lancaster, UK.

Professor Tracey Woodruff. School of Medicine, Program on Reproductive Health and the Environment, University of California, San Francisco, Oakland, CA, USA. (added 7 July)

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***A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals** (2016, accepted). Laura N Vandenberg; Marlene Ågerstrand; Anna Beronius; Claire Beausoleil; Åke Bergman; Lisa A Bero; Carl-Gustaf Bornehag; C Scott Boyer; Glinda S Cooper; Ian Cotgreave; David Gee; Philippe Grandjean; Kathryn Z Guyton; Ulla Hass; Jerry J Heindel; Susan Jobling; Karen A Kidd; Andreas Kortenkamp; Malcolm R Macleod; Olwenn V Martin; Ulf Norinder; Martin Scheringer; Kristina A Thayer; Jorma Toppari; Paul Whaley; Tracey J Woodruff; Christina Ruden. *Environmental Health*