EUROPEAN
COMMISSION

Brussels, XXX
C(2016) 3752 projet

ANNEX 1

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ANNEX

to the

COMMISSION DELEGATED REGULATION (EU) …/...

setting out scientific criteria for the determination of endocrine-disrupting properties pursuant to Regulation (EU) No 528/2012

ANNEX

An active substance shall be considered as having endocrine disrupting properties with respect to humans or non-target organisms, where it meets the criteria set out in section A or section B.

Section A - Endocrine disrupting properties with respect to humans

1. An active substance shall be identified as having endocrine disrupting properties with respect to humans if it is a substance that meets all of the following criteria:

   (1) it is known to cause an adverse effect relevant for human health, which is a change in the morphology, physiology, growth, development, reproduction, or, life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences;

   (2) it has an endocrine mode of action;

   (3) the adverse effect relevant for human health is a consequence of the endocrine mode of action.

2. The identification of an active substance as having endocrine disrupting properties in accordance with point 1 shall be based on all of the following:

   (1) all available relevant scientific evidence:

      (a) primarily performed according to internationally agreed study protocols (in vivo studies or adequately validated alternative test systems predictive of adverse effects in humans or animals; as well as in vivo, in vitro and mechanistic studies informing about endocrine modes of action) and on Guidance on the implementation of Regulation (EU) No 528/2012, issued by the European Chemicals Agency.

      (b) applying a systematic review methodology to analyse other relevant scientific information.

   (2) a comparison of the weight of the scientific evidence on endocrine mediated adverse effects with the criteria set out in point 1, considering whether or not the effects are adverse, the mode of action, together with the biological plausibility of the causal link between the adverse effect and the endocrine mode of action.

   (3) In applying the weight of evidence determination referred in point 2, using expert judgement and internationally agreed guidelines, all of the following elements shall be considered:

      (a) the assessment of quality, reliability, reproducibility and consistency of the scientific evidence shall, in particular, consider all of the following factors:

         (i) Both positive and negative results shall be considered together in a single weight of evidence determination.

         (ii) The weight of evidence should consider the relevance of the study designs for the assessment of adverse effects and for the evaluation of mechanistic information. For the assessment of adverse effects, generally adequate reliable and representative data on humans shall

have precedence over other data; but positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience.

(iii) The biological plausibility of the link between the adverse effects and the endocrine mode of action.

(iv) The quality and consistency of the data shall be given appropriate weight, considering the pattern and coherence of the results within and between studies of a similar design and across different species.

(v) The route of exposure, toxicokinetic and metabolism studies are assumed to be relevant to humans, unless convincing evidence exists to explain the differences between test animals and humans.

(vi) The concept of the limit dose, and international guidelines on maximum recommended doses and for assessing confounding effects of excessive toxicity.

(b) adverse effects or endocrine modes of action that are non-specific secondary consequences of other toxic effects shall not be considered for the identification of the substance as endocrine disruptor.

(c) where there is information demonstrating that the adverse effects are clearly not relevant for humans the substance should not be considered a human endocrine disruptor.

Section B - Endocrine disrupting properties with respect to non-target organisms

1. An active substance shall be identified as having endocrine disrupting properties with respect to non-target organisms if it is a substance that meets all of following criteria:

(1) it is known to cause an adverse effect for non-target organisms, which is a change in the morphology, physiology, growth, development, reproduction, or, life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences, considered relevant at the population level;

(2) it has an endocrine mode of action;

(3) the adverse effect relevant for the non-target organism at the population level is a consequence of the endocrine mode of action.

2. The identification of an active substance as having endocrine disrupting properties in accordance with point 1 shall be based on all of the following:

(1) all available relevant scientific evidence:

(a) primarily performed according to internationally agreed study protocols (in vivo studies or adequately validated alternative test systems predictive of adverse effects in humans or animals; as well as in vivo, in vitro and mechanistic studies informing about endocrine modes of action) and on Guidance on the implementation of Regulation (EU) No 528/2012, issued by the European Chemicals Agency;

(b) applying a systematic review methodology to analyse other relevant scientific information.

(2) a comparison of the weight of the scientific evidence on endocrine mediated adverse effects with the criteria set out in point 1, considering whether or not the effects are adverse, the mode of action, together with the biological plausibility of the causal link between the adverse effect and the endocrine mode of action.

(3) in applying the weight of evidence determination referred in point 2(2), using expert judgement and internationally agreed guidelines, all of the following elements shall be considered:

(a) the assessment of quality, reliability, reproducibility and consistency of the scientific evidence shall consider all of the following factors:

(i) both positive and negative results shall be considered together in a single weight of evidence determination, discriminating between taxonomic groups (e.g. mammals, birds, fish) where relevant.

(ii) the weight of evidence should consider the relevance of the study designs for the relevance of the adverse effects at the population level and for the evaluation of mechanistic information. Generally, evidence from field studies shall have precedence over other data. Nevertheless positive results from well-conducted laboratory studies shall be considered even in the case lack of positive results in field studies.

(iii) the adverse consequences on reproduction and growth/development, as these are the effects most likely to impact on populations. Adequate, reliable and representative higher tier experimental studies and/or results from reliable population models shall be considered where available for assessing the relevance of the adverse effect at the population level.

(iv) the biological plausibility of the link between the adverse effects and the endocrine mode of action, and its relevance for populations of non-target organisms.

(v) the quality and consistency of the data shall be given appropriate weight, considering the pattern and coherence of the results at different doses or exposure levels within and between studies of a similar design and across different taxonomic groups.

(vi) the concept of the limit dose and international guidelines on maximum recommended doses and for assessing confounding effects of excessive toxicity.

(b) adverse effects or endocrine modes of action that are non-specific secondary consequences of other toxic effects shall not be considered for the identification of the substance as endocrine disruptor with respect to non-target organisms.

(c) where there is information demonstrating that the adverse effects are clearly not relevant at the population level for non-target organisms, the substance should not be considered a endocrine disruptor with respect to non-target organisms.