European Society of Endocrinology

Introduction to ESE and its activities on EDCs

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19 November 2018

Vision and Mission

It is our vision to **shape the future of endocrinology** to improve science, knowledge and health.

It is our mission to **advance endocrinology**.

We **unite**, **support** and **represent** our specialty, promoting collaboration and best practice, and enable our community to develop and share the best knowledge in endocrine science and medicine.

European Society of Endocrinology

Representing every part of the endocrine community

Formed in 2006, the European Society of Endocrinology is at the centre of Europe's endocrine community

- **Over 4100 individual members** and growing
- Representing **51 National Affiliated Societies** across Europe
- Collaborating with **12 Specialty Affiliated and 6 Associate Societies**

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Raising standards of clinical care and education in Europe

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The endocrinologists role in policy and advocacy

Through *interaction with policy makers and governing bodies*, endocrinologists can *influence the development of new guidelines, policies and regulations* to ensure a *better standard of life and of healthcare for patients*.

ESE, working with our collaborators, stands at the forefront of efforts to ensure greater *harmonisation of education, of clinical standards and of healthcare opportunities* across Europe and beyond.

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Alliance for Biomedical Research in Europe

Key issues and research in EDCs

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Identification of endocrine disruptors

- If an endocrine disruptor is defined as such in one life form, it should be considered so in all life forms unless proved otherwise; this is not the case at present.
- Currently you can still put into circulation an EDC for a specific purpose or in a product unless you show that there is an adverse effect in humans.
- EDCs need to be included in different legislations; the guidance document on EDC identification so far officially only applies to biocides and pesticides legislation.

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Example of EDC complexity

- Several pesticides and herbicides interfere with the endocrine system.
- Effects of pesticides and herbicides in various life forms and the metabolic pathways are currently unknown.
- Glyphosate illustrates how a compound claimed to be safe can interfere with a component of the endocrine system, ie, aromatase.
- This needs new immediate action and research, both on glyphosate alone and on glyphosate mixed with other compounds, ie co-formulants for its application.

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Example of EDC complexity

- EDC-MixRisk project within Horizon 2020 looks at the issue of mixtures with other compounds.
- This project has brought in certain information but more is needed.
- There is a reliance on experimental in-vitro models and animal experiments to extrapolate for human relevance, by combining with human epidemiology.

New research in this area: Co-Formulants in Glyphosate-Based Herbicides Disrupt Aromatase Activity in Human Cells below Toxic Levels

Nicolas Defarge, Eszter Takács, Verónica Laura Lozano, Robin Mesnage, Joël Spiroux de Vendômois, Gilles-Eric Séralini and András Székács

Int J Environ Res Public Health. 2016;13(3). pii: E264.

doi: 10.3390/ijerph13030264.

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New research within Europe

- 8 consortia being funded following the H2020 EDC call decided in August this year.
- Likely focus on developing and refining EDC testing methods.
- Scientists will cover endocrinology, toxicology, biology, environmental research, veterinary care.

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New research within Europe

- Four of the funded consortia will form an allied EDC structure with a kickoff meeting scheduled for end of January 2019.
- Example of research within these consortia is **‘A**ssays for identification of **t**hyroid **h**ormone axis-disrupting chemicals **e**laborating **n**ovel **a**ssessment’.
- The focus is on thyroid hormone and the brain.
- Cutting edge technology will be used to ‘short-list’ from 1,000s of compounds in-vitro those that should be tested in-vivo.
- Leader of this group is Andreas Kortenkamp (London).

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ESE Actions on EDCs

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EDC Working Group

Chair: Josef Köhrle, Charité – Universitätsmedizin Berlin

Members from: Spain, Italy, Denmark, France, the Netherlands, Finland & Greece

Core objectives:

- EU/European and national evidence based policies for EDCs.
- Additional research on (potential) harmful EDCs.

(EU) activities:

- Response to the EU public consultation on the guidance for the identification of EDCs.
- Supported MEP Poc in providing input to the PEST Committee report on the authorisation procedure for pesticides.

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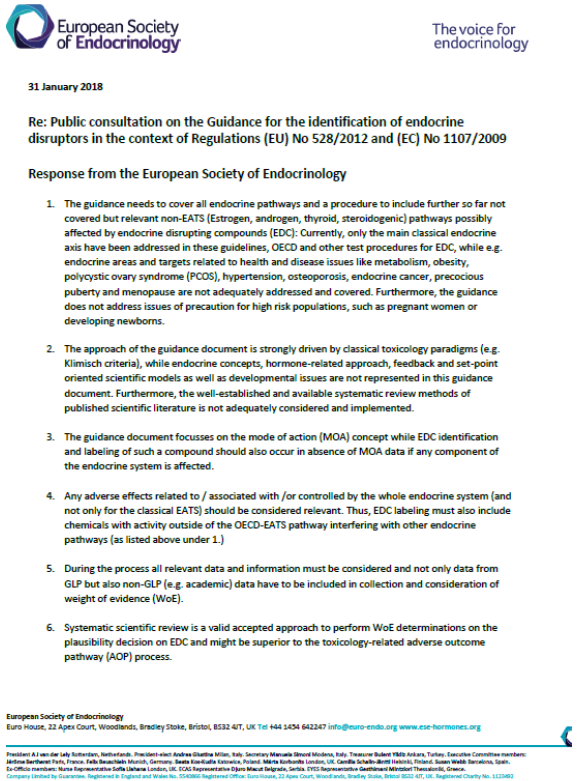
ESE Response to the EU Public Consultation

- Endocrine areas and targets related to health and disease issues like obesity, osteoporosis and metabolism have not been properly covered.
- Available systematic review methods of published scientific literature is not adequately considered and implemented.
- Studies on low-dose effects and approaches to address complex EDC mixture effects need to be included.



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The voice for endocrinology

31 January 2018

Re: 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

Response from the European Society of Endocrinology

1. The guidance needs to cover all endocrine pathways and a procedure to include further so far not covered but relevant non-EATS (Estrogen, androgen, thyroid, steroidogenic) pathways possibly affected by endocrine disrupting compounds (EDC): Currently, only the main classical endocrine axis have been addressed in these guidelines, OECD and other test procedures for EDC, while e.g. endocrine areas and targets related to health and disease issues like metabolism, obesity, polycystic ovary syndrome (PCOS), hypertension, osteoporosis, endocrine cancer, precocious puberty and menopause are not adequately addressed and covered. Furthermore, the guidance does not address issues of precaution for high risk populations, such as pregnant women or developing newborns.
2. The approach of the guidance document is strongly driven by classical toxicology paradigms (e.g. Klimisch criteria), while endocrine concepts, hormone-related approach, feedback and set-point oriented scientific models as well as developmental issues are not represented in this guidance document. Furthermore, the well-established and available systematic review methods of published scientific literature is not adequately considered and implemented.
3. The guidance document focusses on the mode of action (MOA) concept while EDC identification and labeling of such a compound should also occur in absence of MOA data if any component of the endocrine system is affected.
4. Any adverse effects related to / associated with /or controlled by the whole endocrine system (and not only for the classical EATS) should be considered relevant. Thus, EDC labeling must also include chemicals with activity outside of the OECD-EATS pathway interfering with other endocrine pathways (as listed above under 1.)
5. During the process all relevant data and information must be considered and not only data from GLP but also non-GLP (e.g. academic) data have to be included in collection and consideration of weight of evidence (WoE).
6. Systematic scientific review is a valid accepted approach to perform WoE determinations on the plausibility decision on EDC and might be superior to the toxicology-related adverse outcome pathway (AOP) process.

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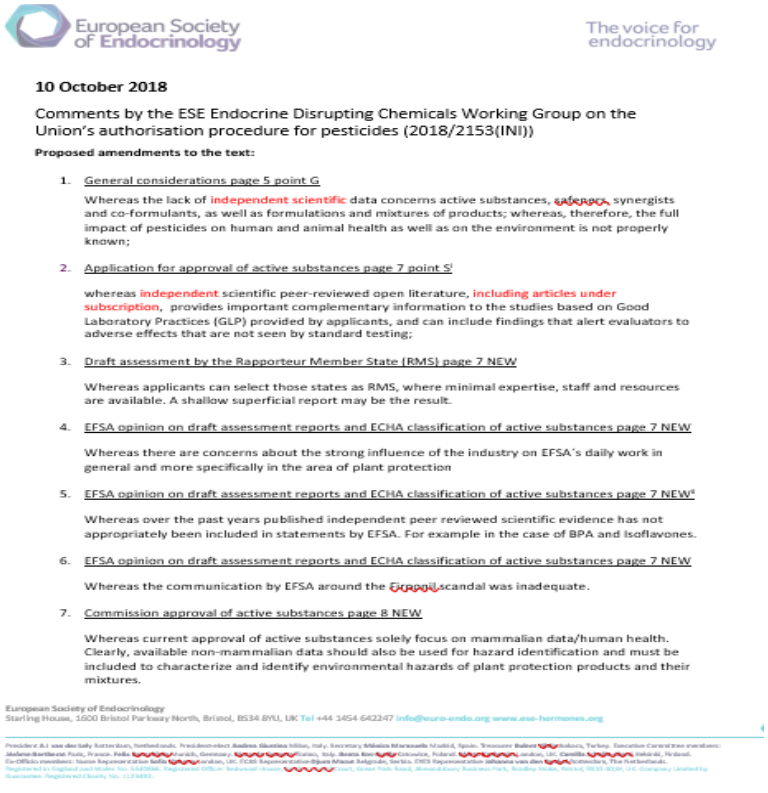
ESE input to PEST report MEP Pavel Poc:

- Raises concerns about the strong influence of the industry on EFSA´s daily work and more specifically in the area of plant protection.
- Calls on EFSA to acknowledge the latest cutting edge research available, including models and methods, during their assessment of new chemicals.
- Non-mammalian data should be included for hazard identification.



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The voice for endocrinology

10 October 2018

Comments by the ESE Endocrine Disrupting Chemicals Working Group on the Union's authorisation procedure for pesticides (2018/2153(INI))

Proposed amendments to the text:

1. General considerations page 5 point G

   Whereas the lack of independent scientific data concerns active substances, ~~adjuvants~~, synergists and co-formulants, as well as formulations and mixtures of products; whereas, therefore, the full impact of pesticides on human and animal health as well as on the environment is not properly known;

2. Application for approval of active substances page 7 point S[i]

   whereas independent scientific peer-reviewed open literature, including articles under subscription, provides important complementary information to the studies based on Good Laboratory Practices (GLP) provided by applicants, and can include findings that alert evaluators to adverse effects that are not seen by standard testing;

3. Draft assessment by the Rapporteur Member State (RMS) page 7 NEW

   Whereas applicants can select those states as RMS, where minimal expertise, staff and resources are available. A shallow superficial report may be the result.

4. EFSA opinion on draft assessment reports and ECHA classification of active substances page 7 NEW

   Whereas there are concerns about the strong influence of the industry on EFSA´s daily work in general and more specifically in the area of plant protection

5. EFSA opinion on draft assessment reports and ECHA classification of active substances page 7 NEW[ii]

   Whereas over the past years published independent peer reviewed scientific evidence has not appropriately been included in statements by EFSA. For example in the case of BPA and Isoflavones.

6. EFSA opinion on draft assessment reports and ECHA classification of active substances page 7 NEW

   Whereas the communication by EFSA around the ~~Glyphosate~~ scandal was inadequate.

7. Commission approval of active substances page 8 NEW

   Whereas current approval of active substances solely focus on mammalian data/human health. Clearly, available non-mammalian data should also be used for hazard identification and must be included to characterize and identify environmental hazards of plant protection products and their mixtures.

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ESE Statement on EC Communication

ESE welcomes:

- ✓ Broader focus on endocrine modalities beyond the classic EATS.
- ✓ Upscale of funding to tackle the many research gaps.
- ✓ Annual EDC forum to enable broader stakeholder input and transparency ***however*** **there are no clear measurable results and actions mentioned and these are essential**.

Remaining concerns:

- ➢ The tone of the communication lacks critical reflection on own past performance.
- ➢ The communication does not include proposals to speed up testing of new and old chemicals.
- ➢ No announcement of a new EU EDC strategy.
- ➢ The "Fitness Check" and references to knowledge gaps could imply further delay of concrete measures on the ground.
- ➢ Concern that the EDC forum will not really achieve measurable results and action.

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Summary and Conclusions

- We cannot expose another generation to EDC and endanger their development and health.
  - Several other areas and sources of EDC exposure are not regulated (daily use and personal care products, toys) - no clear timing and action plan is provided to address this.
  - The EDC mixture issue (“cocktail effect”) is not addressed.
  - No clear plan and agenda to stop further use of identified EDC.

- Precautionary principle of EU legislation is thus violated.

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