Statement by the European Society of Endocrinology, the Endocrine Society and the European Society for Paediatric Endocrinology

The European Society of Endocrinology (ESE), the Endocrine Society and the European Society for Paediatric Endocrinology, together representing the international and European endocrinology community submit our comments on the Commission's discussion papers presented at CARACAL 54 on the REACH revision. The comments focus on provisions most relevant for control of endocrine disrupting chemicals (EDCs):

- Generic risk management approach (GRA) and inclusion of both known and suspected EDCs
- Mixture Assessment Factor (MAF)
- Testing requirements for EDCs

We welcome the outline presented of the proposals, and in particular:

- Extension of the GRA
- Other actions to support substitution of safer alternatives
- Addressing combined exposure via MAF
- Earlier information on use, exposure and alternatives
- A 10 year limit for validity of registration.
- Updated testing proposals for complex endpoints
- CARACAL discussions on updated information requirements
- Promotion of data sharing to minimise animal testing

Regulatory approach should be based on prevention of exposure to harmful chemicals

The REACH regulation, implemented by the EU, has been a landmark in chemical safety. However, despite its progress in improving transparency and safety in chemical usage, it still leaves significant gaps in protection and widespread exposure to harmful chemicals, including EDCs, continues.

Scientific research has increasingly shown that even low-level (environmentally relevant), chronic exposure to EDCs such as bisphenol A[1] or some per- and polyfluoroalkyl substances (PFAS) can lead to significant developmentally programmed or acute health problems such as disrupted neurodevelopment in children, infertility, cancer, diabetes and obesity. Under current REACH restrictions hazardous substances, including those recognised as being of very high concern, are rarely banned from the EU market and if so, only after very lengthy periods. The process should consequently be revised such that restrictions become the default option for specific hazard categories and occur promptly.

Our Societies believe that a precautionary approach, enshrined in the EU Treaties, is essential to ensure faster and effective action to address health threats by reducing exposure to EDCs. While all populations are subject to harms from exposures, urgent action is needed to protect more sensitive populations such as children and pregnant women, and workers in high-exposure environments. Regulatory strategies, including identification and risk reduction, should be science-based, taking into account the health and economic benefits of restrictions, and should be applicable across all potential EDCs.

[1] https://www.efsa.europa.eu/en/topics/topic/bisphenol

Concrete steps towards improved restrictions

1. ***Extend Generic Risk Management Approach (GRA) to EDCs category 1 and 2***

The GRA should be extended to cover both known and suspected EDCs in categories 1 and 2, in line with the revised Regulation for Classification, Labelling and Packaging of substances and mixtures (CLP Regulation). The inclusion of category 2 here is essential to ensure that EDCs that pose a significant risk to health and the environment do not enter the EU market. This will increase levels of protection and speed up restrictions on the most harmful chemicals. The GRA is an important tool for preventing regrettable substitutions and addressing chemical mixtures, polymers, and low and medium tonnage substances.

2. ***Integrate a Mixture Assessment Factor (MAF) into REACH***

There is extensive scientific evidence that exposure to mixtures of chemicals at low but environmentally relevant levels can lead to more severe adverse impacts. Complex cumulative exposures during developmental windows such as foetal development, adolescence, and puberty, may alter disease and developmental trajectories in unalterable ways, even across generations.

The revised REACH needs to reflect the current science by applying a MAF to substances managed following a threshold concentration logic, which will allow chemical mixtures to be more effectively assessed and managed.

3. ***Testing chemicals for endocrine disrupting properties***

Improving the tests used under REACH information requirements is critical to safeguarding human health and the environment. The current data requirements for testing EDCs under REACH remain inadequate in both scope and sensitivity for effects on the endocrine system. While some relevant tests, such as those assessing reproductive toxicity or thyroid hormone system disruption, are in place, many are outdated, not sufficiently sensitive, highly variable, which limits their reliability and regulatory impact, or only required for high volume chemicals. Testing is often limited to individual substances and fails to factor in the "cocktail effect" of combined exposure to multiple EDCs. Furthermore, testing often fails to account for dose ranges or dose-response curves (i.e., non-monotonic dose response or NMDR) that are relevant for hormone biology but often much lower than for acute or chronic toxic effects observed using traditional models of toxicology.

Regulatory toxicology should incorporate relevant dose ranges and NMDR into testing and assessment strategies without further delay. Because of the presence of NMDR, it cannot be assumed that there are thresholds below which EDC exposures are safe.

We welcome the discussions in the CARACAL-subgroup on information requirements and expect proposals for up-to-date tests which can effectively identify EDCs.

4. ***New Approach Methodologies (NAMS)***

Our Societies appreciate and support the development and adoption NAMs, which show promise in achieving more high-throughput screening of chemicals. However, NAMs have not yet been sufficiently developed to comprehensively address biological complexity and evaluate all relevant endocrine endpoints. Moreover, NAMs need to be implemented in the context of a legislative and regulatory framework that allows prompt action following hazard identification results. We support

the application of NAMs for regulatory purposes when they demonstrably reflect biological understanding as well as or better than traditional methods. Currently, some NAMs may be appropriate for screening chemicals to identify hazards, but they should not be used to invalidate positive results from human or animal studies, nor should NAMs be evaluated in isolation to determine that a chemical is safe. Most NAMs have little evidence demonstrating the human relevance of their results. Furthermore, they remain unvalidated against the most sensitive in vivo assays and unable to assess sex as a biological variable, let alone endocrine tissue crosstalk, developmental stages, or genetic variability.

Our members support the 3R principle (Reduce, Refine, Replace) and strongly feel that animal testing should only be applied in case of scientific necessity where new approach methods are unable to obtain the same outcomes. Unfortunately, NAMs do not yet achieve this standard for the full assessment of EDCs.

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About ESE

The European Society of Endocrinology (ESE) provides a platform to develop and share leading research and best knowledge in endocrine science and medicine. Through the 50 National Societies involved with the ESE Council of Affiliated Societies (ECAS) and partnership with specialist endocrine societies, ESE and its partners jointly represent a community of over 20,000 European endocrinologists.

ESE and its partner societies work to promote knowledge and education in the field of endocrinology for healthcare professionals, researchers, patients and the public.

ESE informs policymakers on health decisions at the highest level through advocacy efforts across Europe. Find out more: www.ese-hormones.org.

About ESPE

The European Society for Paediatric Endocrinology (ESPE) is an international society registered in Europe that promotes the highest levels of clinical care for infants, children and adolescents with endocrine problems throughout the world, including in less advantaged areas. At the EU level, it works with the EU and partner organisations to create a healthier environment for children and adults.

To find out more about ESPE, please visit eurospe.org.

About the Endocrine Society

The Endocrine Society is the world's oldest and largest organization of scientists devoted to hormone research and physicians who care for people with hormone-related conditions.

The Society has more than 18,000 members, including scientists, physicians, educators, nurses and students in 122 countries. To learn more about the Society and the field of endocrinology, visit our site at www.endocrine.org. Follow us on X (formerly Twitter) @TheEndoSociety and @EndoMedia.