

## The 2013 Berlaymont Declaration on Endocrine Disrupters

In June 2012 the European Commission convened a conference of international scientists, representatives of interest groups, and European Union (EU) Member States in the Berlaymont complex in Brussels to discuss forthcoming policy initiatives for endocrine disrupters. The meeting was part of a wider consultation in preparation for regulatory activities for this group of chemicals. Several interest groups have already articulated their positions.

As scientists actively engaged in endocrine disrupter research we welcome the initiatives of the European Commission. European Union (EU)-funded research was instrumental in substantiating the plausibility that endocrine disrupters might lead to serious, irreversible human and wildlife health effects. As the first major economic area to target endocrine disrupters, the EU has the opportunity to put in place standards that will be exemplary for health and environmental protection policies in other regions of the world. We wish to express our views on this important topic and call on the European Commission to implement regulatory measures that are in line with the best available science.

1. We are concerned that the prevalence of endocrine-related diseases is higher than it has ever been. The disease burden continues to increase in the EU and globally.
2. Evidence is strengthening that environmental factors, including chemical exposures, play a role in these phenomena.
3. European wildlife is also affected and some effects are widespread.
4. Animal experiments and some human health studies have shown that exposure to endocrine disrupters during developmental periods can cause irreversible harm that becomes apparent long after these exposures took place.
5. Internationally agreed test methods currently capture only some of these effects and are inadequate for revealing the full range of the effects of EDCs.
6. Existing EU chemicals regulations are entirely inadequate for identifying EDCs, and internationally validated test methods that have been available for years have not been implemented.
7. Some proposals for regulating EDCs from EU Member States are not sufficiently protective, do not follow the best available science, and place commercial interests above the protection of human and wildlife health.
8. Certain EDCs have toxicological properties that preclude the definition of thresholds below which exposures can be deemed safe.
9. There is the plausibility that EDCs cause serious, irreversible harm, but more data are needed for better risk assessment. This tension can only be resolved by developing a targeted research strategy for endocrine disrupters as part of Horizon 2020 which should aim at better exposure assessment, assay development and human health studies.
10. We call on the European Commission to implement a regulatory regime for EDCs that is based on sound scientific principles.

Although uncertainties in risk assessment remain, European Commission-funded research has greatly contributed to substantiating the plausibility of serious, irreversible harm from endocrine disrupters. Scientific uncertainty should not delay regulatory action and commercial interests must not take precedent over concerns about risks associated with endocrine disrupters.

Our position is based on the following scientific observations and research findings which have been laid out in more detail in recent reports from the European Environment Agency, in a European Commission – funded report and an assessment conducted under the auspices of the World Health Organisation and the United Nations Environmental Programme<sup>1</sup>:

1. We are concerned that the prevalence of endocrine-related diseases continues to increase in the European Union and globally. This is not well recognised by the public and largely ignored by policy makers in EU Member States.
  - In some EU Member States large proportions of young men have semen quality so poor that it will seriously affect their chances of siring children. At the same time, congenital malformations such as hypospadias (malformations of the penis) and non-descending testes are increasing or levelling off at unfavourably high levels. Many Member States have not given attention to this issue and have not initiated relevant research studies.
  - There is a dramatic rise in breast cancer in Eastern and Southern European EU Member States. In West European countries, where breast cancer is more prevalent, incidences increase more slowly or are levelling off at rates much higher than 30 years ago.
  - With the exception of high prevalence countries such as The Netherlands and Austria, all EU countries are experiencing strong rises in prostate cancer. Similar trends exist for other hormonal cancers, including those of the testes, endometrium, ovaries and thyroid.
  - Neurobehavioural disorders, and thyroid diseases and disorders affecting brain development, represent a high and increasing pediatric disease burden in countries where these disease trends have been followed.
  - The prevalence of obesity and its comorbidity factors, type 2 diabetes and metabolic syndrome, have increased dramatically in almost all EU Member States.
  
2. We recognise that multiple causes underlie these trends, including nutrition or maternal and paternal age. However, because of the rapid pace with which these increases have occurred, explanations solely in terms of genetics, better diagnosis or life style lack plausibility. Evidence is strengthening that environmental factors, including chemical exposures, also play a role in these disease trends, but the chemicals involved are difficult to pinpoint. The full range of contributing chemical exposures is not known, but some associations have come to light:

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<sup>1</sup> European Environment Agency (2012) The impacts of endocrine disrupters on wildlife, people and their environment – the Weybridge +15 report. <http://www.eea.europa.eu/publications/the-impacts-of-endocrine-disrupters>

Kortenkamp A, Martin, O, Faust M, Evans R, McKinlay R, Orton F, Rosivatz E (2012) State of the art assessment of endocrine disrupters. DG Environment project contract number 070307/2009/550687/SER/D3. [http://ec.europa.eu/environment/endocrine/documents/4\\_SOTA%20EDC%20Final%20Report%20V3%206%20Feb%2012.pdf](http://ec.europa.eu/environment/endocrine/documents/4_SOTA%20EDC%20Final%20Report%20V3%206%20Feb%2012.pdf)

UNEP WHO (2013) State of the science of endocrine disrupting chemicals – 2012 (Editors: Bergman A, Heindel JJ, Jobling S, Kidd KA, Zoeller RT). <http://www.unep.org/hazardoussubstances/Portals/9/EDC/StateOfEDCScience.pdf>

- Testis maldescent in young boys has been linked with exposure to DES during pregnancy, certain polybrominated diphenyl ethers used as flame retardants, and occupational pesticide exposure.
  - High exposures to polychlorinated dioxins, certain polychlorinated biphenyls (PCBs) (in women who lack some detoxifying enzymes) and DDE (in early life) have been shown to be risk factors in breast cancer.
  - Prostate cancer risks were in some studies related to occupational exposures to pesticides (of an unidentified nature), to certain PCBs and to arsenic.
  - Developmental neurotoxicity with negative impacts on brain development has been linked with lead, methylmercury and PCBs.
3. There is a worldwide decline in biodiversity of wildlife species and it is plausible that chemical exposures are playing a role in this. Wildlife populations have been affected by endocrine disrupters, with adverse effects on growth and reproduction. Some of these effects are widespread.
- Seal colonies in heavily polluted areas of the Baltic and North Seas have been affected by female reproductive pathologies, bone damage and reproductive failure which correlate with exposure to persistent organic pollutants (POPs), especially PCBs. Concomitant with a decline in PCB exposures the populations are recovering.
  - Increased POP burdens in lesser black-backed gulls in Norway correlated with skewed sex ratios in favour of female chicks. When gulls are in poor condition they hatch more female chicks.
  - A large number of amphibians are highly threatened with extinction, and there are indications of an involvement of endocrine disrupters.
  - Especially in the UK, male fish have been widely affected by increased levels of the egg yolk protein vitellogenin and by intersex. This is attributed to exposure to sewage effluents which contain estrogenic and anti-androgenic chemicals.
  - The use of tributyltin and triphenyltin as anti-foulants on ship hulls have triggered the collapse of commercially important oyster populations and snail species. Reductions in exposure have led to a recovery of these populations.
4. Extensive laboratory studies and some human health studies have shown that interference with hormone action during critical periods of development can cause irreversible and delayed effects that do not become evident until later in life. These insights highlight the need to focus on exposures during windows of heightened sensitivity coupled with the evaluation of the full range of adverse effects later in life. There is the danger that important hazards are overlooked if testing is conducted outside these periods.
- In rodent experiments, certain dicarboximide, imidazole andazole pesticides can interfere with androgen action during fetal life, when male development is programmed. Some of the effects only become apparent in adult life and are irreversible; these include malformations of reproductive organs. Exposure to these chemicals in adult life does not induce such effects.
  - Epidemiological studies show that exposure to dioxin (TCDD) around the time of birth has a negative impact on semen quality. With exposure during puberty, the

opposite effect occurs, while exposure during adulthood has no influence on semen quality.

- Rodents exposed to estradiol and estrogenic chemicals around the time of birth suffer interferences with a brain signalling system that sets the timing of puberty. Exposure during other life stages does not produce this effect.
- The development of the female reproductive system is programmed in fetal life and can be disrupted at this stage by signalling from chemicals such as DES, with malformations being one consequence.
- The action of thyroid hormones during development in the womb is essential for many developmental landmarks, including the development of the brain and the neuro-endocrine system. Disruption of thyroid action by chemical exposures at this stage of development can have detrimental and irreversible effects.

5. Internationally agreed and validated test methods (OECD) for the identification of endocrine disrupters capture only a segment of the known range of endocrine disrupting effects, mainly focused on estrogenicity, (anti)androgenicity and thyroid disruption (“EAT”). Other aspects of the endocrine system(s) are not considered, although it is clear that the complexity of endocrine systems cannot be reduced to EAT. This introduces considerable uncertainties, and the likelihood of overlooking harmful effects in humans and wildlife is high.
  - For many endocrine disrupting effects, internationally agreed and validated test methods do not exist, although scientific tools and laboratory methods are available.
  - For a large range of human health effects, viable laboratory models are missing altogether. This seriously hampers progress with understanding the full extent of risks.
6. Important pieces of EU chemicals regulation are entirely inadequate for capturing endocrine disrupting effects. Even internationally validated and well established test systems that have been available for over a decade have not been implemented. Any measures aimed at protecting humans and wildlife from endocrine disrupters will be ineffective if testing requirements are not updated to incorporate endocrine disrupter testing.
  - The current testing and information requirements defined for industrial and commercial chemicals (REACH) and for plant protection products (PPPR) are not geared towards the identification of endocrine disrupting chemicals. The relevant regulations and directives (e.g. 544/2011 and 545/2011) require urgent updates to include the best available science.
  - Testing with the most sensitive and appropriate endpoints and with exposure regimens that cover periods of heightened sensitivity during development is currently not mandatory. As a result, many endocrine disrupting chemicals are not identified.
7. Proposals for the regulation of endocrine disrupting pesticides from certain EU Member States do not follow scientifically sound principles and are not sufficiently protective. By regulating as few endocrine disrupters as possible they place commercial interests above the protection of human and wildlife health.

- These proposals focus on the use of potency-based cut-off values as the basis for classifying pesticides as endocrine disrupters. We are concerned that these values set the bar too high, with the serious possibility that hardly any substance will be classified as an endocrine disrupter in the regulatory sense, thus effectively undermining the intention of the legislation.
  - Given the likelihood of mixture effects from exposures to numerous EDCs with similar effect profiles, even EDCs considered to be weakly potent are of concern because they may add to the combined effect.
8. We are concerned that the discussion about so-called low dose effects has paid too little attention to the possibility that many endocrine disrupters may act without thresholds because of pre-existing internal exposures to natural hormones and, in the case of background exposures, to substances with similar effect profiles.
- In such situations, endocrine disrupters entering a biological system will add to the internal load, without having to overcome a dose threshold. This is particularly relevant to estrogenic agents and to chemicals with effects similar to dioxins.
  - It is plausible that these types of endocrine disrupters will act independent of thresholds, as would be expected, e.g., for genotoxic carcinogens. This should be considered during the ongoing REACH revision.
9. In the foreseeable future, endocrine disrupter regulatory activities will have to cope with the tension between the plausibility of serious, irreversible damage and the delays in generating the data that are indispensable for comprehensive risk assessment. This tension can only be resolved by promoting further research into endocrine disrupters. We call on the European Commission to implement in Horizon 2020 a targeted endocrine disrupter research programme, with a focus on:
- *Exposure assessments and the identification of substances with endocrine disrupting properties:* There is a serious mismatch between substances that are well-researched and the vast numbers of chemicals in commercial use, for which endocrine disrupting properties have not been investigated very well, if at all. Despite years of endocrine disrupter research, the full spectrum of chemicals that might contribute to endocrine-related diseases and wildlife effects is unknown. This deadlock can only be broken by dedicated research strategies that harness the recent advances in unbiased chemical analytical technologies.
  - *Assay development:* Important aspects of endocrine disruption cannot be investigated, because suitable laboratory models and assessment criteria are missing altogether. This is especially relevant in the areas of hormonal carcinogenesis, female reproductive health, metabolic syndrome, obesity, and neuro-endocrine effects. Assays and assessment methodologies for many wildlife phyla and taxa are absent and fundamental research on the endocrinology of many invertebrate taxa is necessary. Concerted research and development efforts are urgently needed to fill these gaps.
  - *Research in support of better human health studies:* Due to the lack of relevant laboratory models for numerous health effects, endocrine disrupter research will have to depend on epidemiological studies in the foreseeable future. But human

epidemiology faces considerable difficulties in recognising the health risks that might stem from endocrine disruptors. Complications arise mainly from the time lag between disease causation and the diagnosis of health effects, the absence of methodologies for dealing with exposures to multiple chemicals, and the lack of information about the full spectrum of chemicals that might contribute to risks. The tissues collected in many existing cohorts are not geared towards ascertaining exposures to relevant endocrine disruptors, and towards dealing with exposures during critical life stages. This can only be resolved by allocating resources to set up new cohorts, with carefully planned chemical analytical strategies and clear hypotheses.

10. We call on the European Commission to implement a regulatory regime for endocrine disruptors that is based on sound scientific principles. Although uncertainties remain, European Commission-funded research has greatly contributed to substantiating the plausibility of serious, irreversible harm stemming from endocrine disruptors. Scientific uncertainty should therefore not delay regulatory action. Commercial interests must not take precedent over concerns about risks associated with endocrine disruptors. More specifically, we call on the European Commission to:

- Implement a regulatory regime that classifies endocrine disruptors by using weight-of-evidence approaches. Schemes based on cut-off values for potency are scientifically indefensible and are too formulaic to accommodate the subtleties needed for scientifically sound judgements.
- Update the testing requirements for chemical substances under REACH, PPPR and the Biocide Regulation to include effects of endocrine disruptors. Endocrine disruptor regulation will fail if these steps are not taken.
- Develop a targeted research strategy for endocrine disruptors as part of Horizon 2020. This strategy should aim to fill the gaps left by previous efforts, namely in terms of exposure assessment, assay development and better human health studies.

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