# Policy Perspective on Endocrine Disruptors
# September 2015


**Summary**

Endocrine disruption is an issue that continues to garner significant public, political and scientific interest. It can be technically complex, critical aspects are often confused and there remain diverging points of view amongst scientists and regulators worldwide. As an important stakeholder, the crop protection industry addresses in this paper key scientific issues related to endocrine disruption and crop protection products (pesticides).

Current regulation of crop protection products ensures high levels of protection for human health and the environment. Substances are only made available to farmers if they are proven safe for their intended use following extensive evaluation by regulatory authorities. This includes testing for endocrine-mediated effects of crop protection products, which are scientifically strong and sufficient to support regulatory decision-making.

The continued protection of human health and the environment results from science- and risk-based policymaking. Regulatory decisions should incorporate scientific information considering exposure, potency, (eco)toxicological testing and mode of action in a transparent risk assessment framework.

Using hazard-based decision-making fails to take into account all relevant scientific data and does not provide a rational basis for regulatory decision-making. Crop protection products therefore should not be characterized as endocrine disruptors based on hazard alone without factoring in realistic conditions of use and exposure through risk assessment. If inappropriate regulation on such products is adopted, there could be serious negative effects on food quality and security, farming, commodity trading and national economies without significantly improving the protection of human health and the environment.

Ultimately, the ability of farmers to produce abundant, high-quality food relies on science-based, predictable and relevant regulation in all countries around the world. The crop protection industry is committed to staying on top of the latest science and best testing methods to ensure the safety of its products.


## Many Endocrine Active Substances are not Endocrine Disruptors

The endocrine system is a set of glands that produce hormones (chemical messengers), which regulate processes such as growth, development, metabolism, reproduction and behavior. Hormones also maintain stability of the body's internal environment in response to changes in external conditions (homeostasis) as well as control changes at different stages throughout a lifetime (e.g., early development, onset of puberty).

Changes in the endocrine system can be caused by a variety of factors, including aging, certain diseases and conditions, stress, genetics and diet. Many substances, both natural and synthetic, can interact with the endocrine systems of humans and wildlife. Most **endocrine active substances (EASs)** will only produce biological changes within a living being's normal operating

range (homeostatic capacity) or be detoxified by metabolism and therefore, do not cause adverse effects. However, substances that upset homeostatic systems and cause adverse health effects are regarded as **endocrine disruptors (EDs)**. **Adverse effects** reduce a living being's functional capability that may result in a change in its shape, function, growth, development, reproduction or life span. (For technical definitions important to the regulation of EDs, see Box 1.)

EASs can be found in a variety of chemical classes, including natural products from plants and other living organisms, pharmaceuticals, crop protection products, and consumer and industrial manufacturing products. A large number of EASs of natural plant origin are consumed as food or feed, such as estrogenic compounds in soy (e.g., genistein and daidzein), mycotoxins (e.g. zearalenone) in cereals, and goitrogens in cabbage (glucosinates). Other common EASs are caffeine and sugar.

Such EASs do not cause harm at doses commonly consumed and there are wide margins of exposure between the dose consumed and the dose required to cause an adverse effect. Similarly, chemical products commonly regarded as potential EDs may actually be EASs under normal use conditions and therefore, do not cause adverse effects. Hence, risk assessment that includes exposure is important.

**Box 1: Technical Definitions Important to Regulation of Endocrine Disruptors**

The World Health Organization's International Programme on Chemical Safety (IPCS) defines an **endocrine disruptor** as *"an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations."*[1]

Under this widely accepted definition, for a substance to be regarded as an endocrine disruptor, it must cause an adverse effect in an intact organism or (sub)population by an endocrine mode of action. The IPCS defines a **mode of action** as: *"The biologically plausible sequence of key events, starting with the interaction of an agent with a cell, through functional and anatomical changes leading to an observed effect supported by robust experimental observations and mechanistic data."*[2]

Interaction with the endocrine system alone is therefore not sufficient to consider a substance an endocrine disruptor; the interaction must lead to an **adverse effect** (see definition below). For human health, adverse effects are typically taken from observations in laboratory animal studies and the reference to "intact organism" means the effects must occur within *in vivo* studies. For environmental species, evidence is taken from *in vivo* laboratory animal studies (e.g., mammals, birds, fish) and/or based on observations in populations in their natural environment.

The reference to "consequently" in the IPCS definition of an endocrine disruptor provides an additional requirement for the demonstration of a **biological plausible causal relationship** between the adverse effect and endocrine mode of action.

[1] Global assessment of the state-of-the-science of endocrine disruptors. 2002. Chapter 1: Executive summary. World Health Organization's International Programme on Chemical Safety. http://www.who.int/ipcs/publications/en/ch1.pdf.

[2] Boobis AR, Daston GP, Preston RJ, Olin SS. 2009. Application of key events, analysis to chemical carcinogens and noncarcinogens. *Crit Rev Food Sci Nutr*. 49(8):690-707.

It is important to note that endocrine disruption is not an adverse effect in itself; it is a mode of action leading to an adverse effect which manifests as carcinogenic, reproductive or developmental effects. These effects are observed in regulatory toxicological and ecotoxicological laboratory animal studies.

The IPCS defines an **adverse effect** as "*a change in the morphology, physiology, growth, development, reproduction or lifespan 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.*"[3]

This is a widely accepted *scientific* definition of an endocrine disruptor. However, further elements of hazard characterization, such as severity, (ir)reversibility, potency and lead toxicity, need to be considered in regulatory decision-making on crop protection products.

**Potency, Dose and Exposure Critical to Risk Assessment**

There is often confusion as to whether interaction of a substance with the endocrine system is in itself harmful or whether it could lead to harm under certain circumstances. Interaction with the endocrine system that leads to adverse effects in humans or wildlife (i.e., **endocrine disruption**) is dependent upon the potency of a substance, its level (**dose**), duration and timing of exposure.

**Potency** is a measure of a substance's strength to produce an adverse effect. A highly potent substance produces a large effect at low doses, while a substance of low potency leads to a small effect, even at higher doses. A potent substance may also cause an adverse effect after a short duration of exposure, whereas a less potent substance may require a longer period of exposure to have the same effect. The potency of a substance is important irrespective of whether exposure occurs during early developmental stages or in adulthood.[4]

**Exposure** describes to what extent an individual or population may come in contact with a substance (e.g., via food, water, inhalation or skin contact). The level, frequency and duration of exposure to a substance are all key determinants of whether or not, and to what extent, adverse health effects may occur. Adverse effects may be observed in laboratory animal studies at very high doses; however, these levels are significantly above those to which humans and/or animals living in the environment may ever be exposed. A further important consideration is the timing of exposure and whether exposure occurs during sensitive developmental stages (pregnancy, infancy, childhood and puberty) or in adulthood.

In regulatory decision-making, potency, dose and exposure must all be taken into consideration. In this context, it is important to remember that endocrine disruption is a mode of action, not an endpoint in itself. Chemical regulation is, and should continue to be, focused on adverse outcomes at environmentally relevant exposures rather than the mechanisms by which those effects occur. This is the approach used by the U.S., Canada, Japan and Australia, which is supported by the European Food Safety Authority (EFSA).

[3] Environmental health criteria 240: Principles and methods for the risk assessment of chemicals in food. 2009. Annex 1: Glossary of terms, A-3. World Health Organization's International Programme on Chemical Safety. http://www.who.int/foodsafety/publications/chemical-food/en/.

[4] Bogert, CJ, Baker, SP, Matthews, JC. 2013. Potency matters: thresholds govern endocrine activity. *Regul Toxicol Pharmacol.* 67(1):83-88.

## Regulatory Advancements Continue to Follow Technology

Significant regulatory developments have occurred in relation to endocrine disruption since the 1990s. As a result of the Food Quality Protection Act in 1996, the U.S. Environmental Protection Agency (EPA) established the Endocrine Disruptor Screening Program (EDSP).[5] The program provides a two-tiered process and series of tests for the screening and subsequent evaluation of chemicals with the potential to interact with the endocrine system.

In 1999, the European Commission established the European Union Community Strategy for EDs. [6] Specific legislative provisions relating to endocrine disruption have since been incorporated in the European Union (EU) regulations on Registration, Evaluation, Authorization and Restriction of Chemicals (REACH, 2007), Cosmetics (2009), Plant Protection Products (2009) and Biocidal Products (2011).

In parallel, significant work has also been undertaken by the Organisation for Economic Co-operation and Development (OECD) and EDSP to develop validated, internationally harmonized test guidelines and assessment procedures to evaluate chemicals for their potential to interact with the endocrine system. The OECD's Conceptual Framework for Testing and Assessment of Endocrine Disrupters[7] now contains more than 40 standardised *in vitro* and *in vivo* tests. This framework provides a toolbox that is used by regulatory authorities globally (see Box 2).

The crop protection industry has made significant contributions to basic research on endocrine disruption and applied research to develop standardized and validated tests for assessing substances. It continues to contribute to research through Long-Range Research Initiatives[8] and many of the tests integral to the OECD Conceptual Framework relied on the input of industry expertise.

## Regulatory Testing for Crop Protection Products Addresses Endocrine Activity

A principal objective of regulations governing the approval of crop protection products is to ensure a high level of protection for human health and the environment. These products are only approved by authorities and placed on the market if thorough testing and evaluation shows that they do not pose unacceptable risks. Extensive toxicological and ecotoxicological assessments are undertaken to evaluate a range of potential adverse effects, including those which may occur as a result of interactions with the endocrine disruption. These tests are sufficiently strong to support regulatory risk assessment.

The toxicological and ecotoxicological datasets developed for crop protection products are typically harmonized globally. Each active substance is tested in a battery of acute, sub-chronic and chronic tests according to internationally accepted regulatory test guidelines. Many of the tests are represented in the OECD's Conceptual Framework and specific studies may also be

[5] Endocrine Disruptor Screening Program, U.S. Environmental Protection Agency; [updated 2015 Jun 30]. http://www.epa.gov/endo/.

[6] European Commission: Environment. Endocrine Disruptors; [updated 2015 Sep 8]. http://ec.europa.eu/environment/endocrine/strategy/index_en.htm.

[7] Conceptual framework for testing and assessment of endocrine disrupters. Organisation for Economic Co-operation and Development. c2015. http://www.oecd.org/env/ehs/testing/oecdworkrelatedtoendocrinedisrupters.htm#CONCEPTUAL.

[8] Long-Range Research Initiative. American Chemistry Council. c2005-2015. http://lri.americanchemistry.com/.

generated under the EDSP. Box 2 below lists the tests available for the assessment of substances for their potential to interact with the endocrine system and cause adverse effects.

**Box 2: Tests for Tiered Assessment of Potential Endocrine Disrupters in OECD Conceptual Framework (as revised in 2012)**[7]

| **Mammalian and Non-Mammalian Toxicology** | |
|---|---|
| **Level 1** Existing data and non-test information | Physical and chemical properties (e.g., molecular weight, reactivity, volatility, biodegradability) |
| | All available (eco)toxicological data from standardized or non-standardized tests |
| | Read across, chemical categories, quantitative structure-activity relationships and other *in silico* predictions, and absorption, distribution, metabolism and excretion (ADME) model predictions |
| **Level 2** *In vitro* assays providing data about selected endocrine mechanism(s)/path way(s) with mammalian and non-mammalian methods | Estrogen or androgen receptor binding affinity (Office of Chemical Safety and Pollution Prevention (OCSPP) 890.1250 or 890.1150) |
| | Estrogen receptor transactivation (OECD testing guideline (TG) 455-457; OCSPP 890.1300) |
| | Androgen or thyroid transactivation (If/when TGs are available) |
| | Steroidogenesis *in vitro* (OECD TG 456; OCSPP 890.1550) |
| | MCF-7 cell proliferation assays (estrogen receptor ant/agonist) |
| | Other assays as appropriate |
| **Level 3** *In vivo* assays providing data about selected endocrine mechanism(s)/path way(s) | **Mammalian Toxicology** |
| | Uterotrophic assay (OECD TG 440; OCSPP 890.1600) |
| | Hershberger assay (OECD TG 441; OCSPP 890.1400) |
| | **Non-Mammalian Toxicology** |
| | *Xenopus* embryo thyroid signalling assay (when/if TG is available) |
| | Amphibian metamorphosis assay (OECD TG 231; OCSPP 890.1100) |
| | Fish reproductive screening assay (OECD TG 229; OCSPP 890.1350) |
| | Fish screening assay (OECD TG 230) |
| | Androgenized female stickleback screen (Guidance Document (GD) 140) |
| **Level 4** *In vivo* assays providing data on adverse effects on endocrine-relevant endpoints | **Mammalian Toxicology** |
| | Repeated dose 28-day study (OECD TG 407; OCSPP 870.3050) |
| | Repeated dose 90-day study (OECD TG 408; OCSPP 870.3100) |
| | One-generation reproduction toxicity study (OECD TG 415) |
| | Male pubertal assay (see GD 150, Chapter C4.3; OCSPP 890.1500) |
| | Female pubertal assay (see GD 150, Chapter C4.4; OCSPP 890.1450) |
| | Intact adult male endocrine screening assay (see GD 150, Chapter Annex 2.5) |
| | Prenatal developmental toxicity study (OECD TG 414; OCSPP 870.3700) |
| | Chronic toxicity and carcinogenicity studies (OECD TG 451, 452, 453; OCSPP 870.4100, 870.4200, 870.4300) |
| | Reproductive screening test (OECD TG 421 if enhanced; OCSPP 870.3550) |
| | Combined 28-day/reproductive screening assay (OECD TG 422 if enhanced; OCSPP 870.3650) |
| | Developmental neurotoxicity (OECD TG 426; OCSPP 870.6300) |
| | **Non-Mammalian Toxicology** |
| | Fish sexual development test (OECD TG 234) |

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|---|---|
| | Fish reproduction partial lifecycle test (when/if TG is available) |
| | Larval amphibian growth and development assay (OCSPP 890.2300)9 |
| | Avian reproduction assay (OECD TG 206; OCSPP 850.2300) |
| | Mollusc partial lifecycle assays (when TG is available) |
| | Chironomid toxicity test (TG 218-219) |
| | Daphnia reproduction test with male induction (OECD TG 211) |
| | Earthworm reproduction test (OECD TG 222) |
| | Enchytraeid reproduction test (OECD TG 220) |
| | Sediment water lumbriculus toxicity test using spiked sediment (OECD TG 225) |
| | Predatory mite reproduction test in soil (OECD TG 226) |
| | Collembolan reproduction test in soil (TG OECD 232) |
| **Level 5** *In vivo* assays providing more comprehensive data on adverse effects on endocrine-relevant endpoints over more extensive parts of lifecycle | **Mammalian Toxicology** |
| | Extended one-generation reproductive toxicity study (OECD TG 443; alternative to OCSPP 870.3800) |
| | Two-generation reproduction toxicity study (OECD TG 416 most recent update; OCSPP 870.3800) |
| | **Non-Mammalian Toxicology** |
| | Fish lifecycle toxicity test (OCSPP 850.1500 but no TG available) |
| | Medaka multi-generation test (when TG is available; OCSPP 890.2200 for Medaka extended one-generation reproduction test)[9] |
| | Avian two-generation reproductive toxicity assay (when TG is available; OCSPP 890.2100) |
| | Mysid lifecycle toxicity test (when TG is available) |
| | Copepod reproduction and development test (when TG is available) |
| | Sediment water chironomid lifecycle toxicity test (TG 233) |

For human health, the current toxicology test methods capable of detecting endocrine-mediated adverse effects in mammals include the following OECD and EPA Office of Chemical Safety and Pollution Prevention (OCSPP)[10] test guidelines:

- rodent and non-rodent repeat-dose toxicity studies
- rodent two-generation reproduction study
- rodent and rabbit developmental toxicity studies
- rodent (two species) chronic toxicity and carcinogenicity studies

These studies are able to identify adverse effects on the form and function of the test species resulting from multiple biological processes, including a wide spectrum of sensitive endpoints that are vulnerable to endocrine disruption. These tests are mandatory requirements in crop

[9] Endocrine Disruptor Screening Program, U.S. Environmental Protection Agency. Tier 2 Assay Validation Process; [updated 2015 Jun 30]. http://www.epa.gov/scipoly/oscpendo/index.htm.

[10] Series 890 – Endocrine disruptor screening program test guidelines. Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency [updated 26 Aug 2015]. http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series890.htm

protection product data packages and they represent the highest level of toxicological evaluation available, including the highest levels (4 and 5) of the OECD Conceptual Framework.

For the environment, a range of ecotoxicological tests are performed across various animal species (mammals, birds, fish, aquatic and terrestrial invertebrates), with some encompassing the lifecycle of the species, including reproduction. Specific endocrine testing in wildlife is typically triggered by an evaluation of the mechanistic data for vertebrates from the toxicology studies or by the crop protection product mode of action.

Current toxicological and ecotoxicological testing takes into account the potential for **sensitive windows of exposure** (conception, fetal growth and development during pregnancy; growth during neonatal and juvenile life stages; puberty; and adolescence) and **vulnerable populations** (pregnant or nursing women, the very young or very old).

- For human health, three of the studies mentioned above are designed to assess adverse effects that may occur as a result of exposure during the sensitive time periods: the rodent two-generation reproduction toxicology study and rodent and rabbit prenatal developmental toxicity studies.

- For environmental species, relevant ecotoxicological tests either address this directly by exposing all life stages (rat multi-generation reproduction studies or fish or invertebrate lifecycle studies) or operate by using known sensitive life stages that are predictive of effects on the whole lifecycle.

Test methods also allow for the determination of **thresholds for adverse effects** and for the establishment of regulatory reference values for use in risk assessment and regulatory decision-making. Biological and mechanistic considerations confirm that thresholds for adverse effects exist for crop protection products and are the rule, not the exception, for all endpoints, including those that may arise from endocrine disruption.[11] Therefore, the same principles should apply for endocrine disruption as for all other effects as there is nothing unique about endocrine disruption compared with other non-genotoxic forms of toxicity, which would justify adopting a non-threshold approach.

Moreover, the weight of available scientific evidence supports maintaining the current testing and risk assessment approaches and consequently, changes are not required in relation to **low-dose effects** and **non-monotonic dose-responses (NMDRs)**. Studies claiming low- dose effects or NMDRs often suffer from methodological shortcomings, have not been reproduced consistently between different laboratories, and have questionable results due to lack of toxicological significance. While NMDRs have been shown to exist, the current testing approaches for crop protection products can successfully establish No Observable Adverse Effect Levels in the low-dose range of exposure. Current data requirements include a sufficient range of dose levels and parameters to adequately characterize potential risk to human health and the environment and account for possible non-monotonicity in responses.

Existing risk assessment and risk management approaches also provide sufficient protection from combined exposures to trace levels of crop protection products that may be present in food

[11] Bogert, CJ, Baker, SP, Matthews, JC. 2013. Potency matters: thresholds govern endocrine activity. *Regul Toxicol Pharmacol.* 67(1):83-88.

or the environment (i.e., potential **mixture effects**). Humans and wildlife are continuously exposed to multiple chemicals – both natural and synthetic – from a variety of sources. Exposure to such chemicals does not mean they cause harm. Regulatory approval processes and safety factors used for crop protection products ensure high margins of safety, even in cases of potential combined exposure to substances with similar modes of action (affecting the same target organ or system).[12] Furthermore, exposure patterns (e.g., environmental fate, operator and consumers) for crop protection products are generally well understood as being an essential part of regulatory testing and approval.

## Holistic Approach Needed to Assess Endocrine-Related Diseases

Well-conducted epidemiological studies can provide the most direct and relevant information on risk factors for disease in humans. Crop protection products and health have been extensively examined in such studies, with most focusing on farmers and agricultural workers as the group typically most exposed.

The weight of this significant body of scientific literature does not show that crop protection products are associated with human disease, including endocrine-related cancers, as shown in an EFSA-supported publication.[13] In fact, the most consistent finding across the largest epidemiological studies on farmers and agricultural workers (including crop protection product applicators) is that this group is healthier than the general population.[14,15,16,17] Overall, these agricultural workers have lower mortality rates and incidences of most cancer types. Therefore, crop protection product exposure does not appear to be a cause of endocrine-related diseases.

For most of the endocrine-related human diseases frequently discussed, causes are simply not known. Several possible risk factors have been identified, including genetics, age and maternal age. For example, in the Institute of Medicine's 2012 review of the science regarding environmental risk factors for breast cancer, those with the clearest evidence include hormone therapy products, oral contraceptives, being overweight or obese, alcohol consumption and ionizing radiation; the evidence for exposure to chemicals was considered limited.[18]

A holistic approach is needed for assessment of endocrine-related diseases, including input from interdisciplinary expertise (e.g., epidemiologists, toxicologists, endocrinologists and medical professionals) to research all possible and the most plausible risk factors.

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[12] Endocrine Disruption: Regulatory Testing and Assessment of Crop Protection Products. 2014. CropLife International.

[13] Evangelia E Ntzani, Chondrogiorgi M, Ntritsos G, Evangelou E, Tzoulaki I. 2013. Literature review on epidemiological studies linking exposure to pesticides and health effects. European Food Safety Authority. http://www.efsa.europa.eu/en/supporting/doc/497e.pdf.

[14] Leveque-Morlais N, Tual S, Clin B, Adjemian A, Baldi I Lebailly P. 2014. The AGRIculture and CANcer (AGRICAN) cohort study: enrollment and causes of death for the 2005–2009 period. *Int Arch Occ Env Hea.* (2015) 88:61-73.

[15] Koutros S, Alavanja MC, Lubin JH, Sandler DP, Hoppin JA, Lynch CF, Knott C, Blair A, Freeman LE. 2010. An update of cancer incidence in the Agricultural Health Study. *J Occup Environ Med.* 52(11):1098-105.

[16] Waggoner JK, Kullman GJ, Henneberger PK, Umbach DM, Blair A, Alavanja MC, Kamel F, Lynch CF, Knott C, London SJ et al. 2011. Mortality in the Agricultural Health Study, 1993-2007. *Am J Epidemiol*. 173:71-83.

[17] Frost G, T. Brown T, Harding AH. 2011. Mortality and cancer incidence among British agricultural pesticide users. *Occup Med* (Lond). 61(5):303-10.

[18] Lamb JC, Boffetta P, Warren FG, Goodman JE, Hentz KL, Rhomberg LR, Staveley J, Swaen G, Van Der Kraak G, Williams AL. 2014. Critical Comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals - 2012. *Regul Toxicol Pharmacol.* 69(1):22-40.

## Risk Assessment and Management Protects Human and Environmental Health

Risk assessment forms the basis for regulatory decision-making and product approval, while risk management ensures the safe and effective use of crop protection products. Good stewardship supports and enhances risk management.

The crop protection industry protects people and the environment by following very stringent product development criteria, whereby thousands of chemicals are analysed and those with potential negative side effects are screened out from the very beginning. Products are then thoroughly tested according to local regulatory requirements and international standards. If they are safe for intended uses, they are delivered to the market responsibly. Following, the industry offers product support and stewardship training as well as promotes responsible handling practices. These necessary business operations ensure product sustainability and longevity as well as protect society.

All EASs and EDs need to be managed via science- and risk-based regulation[19] to ensure that useful substances remain available while ensuring the protection of human health and the environment. Crop protection products should not be characterized as EDs based on hazard alone without factoring in realistic conditions of use and exposure through risk assessment. These products are thoroughly evaluated for human and environmental risks via established regulatory frameworks and testing strategies prior to commercial release.

If inappropriate regulation on such products is adopted, there could be serious negative effects on food quality and security, farming, commodity trading and national economies (competitiveness of agriculture, employment, etc.) without significantly improving protection of human health and the environment. Crop protection products contribute to food safety and quality as well as increase crop yields and socio-economic well-being – benefits that outweigh hypothetical risks. On the other hand, products deemed EDs (see Box 1) by a full use assessment should be restricted or taken off the market to protect human health and the environment.

## Public Policy Must be Evidence-Based

Public policy-making should be based on a balanced, transparent and systematic assessment of relevant scientific evidence. Policy decisions should not be made on the basis of a single study or report. Rather, policymakers must look across all applicable evidence considering the strengths and weaknesses of each study, consistency (or absence of it) between findings, reproducibility and any outstanding areas of controversy. All of this information should be weighed before coming to an informed policy decision.

The IPCS 2002 “Global Assessment of the State-of-the-Science of Endocrine Disruptors” proposed a formal framework for assessing relationships between exposures to potential EDs and altered health outcomes. The framework was adapted from the Hill criteria (1965) and included five main elements for evaluating scientific evidence: 1) temporality, 2) strength of association, 3) consistency of observations, 4) biological plausibility and 5) evidence of recovery following diminution of the stressor. These criteria acknowledge scientific uncertainties, that a

[19] European Food Safety Authority Scientific Committee. 2013. Scientific opinion on the hazard assessment of endocrine disruptors. *EFSA Journal* 11(3):3132 [84 pp.].

degree of scientific judgment is involved, and that as additional data become available, this information can change the results of previous assessments.

The use of a formal and transparent weight-of-evidence framework to assess potential endocrine disruptors, such as that proposed by the IPCS in 2002, is essential to strengthen public policy. The 2012 World Health Organization and United Nations Environment Programme "Report on the State of Science of Endocrine Disrupting Chemicals" has moved away from this principle.

The crop protection industry supports the IPCS definition (Box 1), which is a widely accepted *scientific* definition of an ED. However, further elements of hazard characterization, such as severity, (ir) reversibility, potency and lead toxicity, need to be addressed in regulatory decision-making on crop protection products.

## Conclusions

The crop protection industry is advocating for a science- and risk-based approach to regulating endocrine active substances and endocrine disruptors to ensure farmers worldwide have access to useful crop protection products while protecting human health and the environment. To this end, the industry notes:

- Current crop protection product regulation ensures high levels of protection for human health and the environment. Substances are only placed on the market if they do not pose unacceptable risks following an extensive evaluation that involves independent review by regulatory authorities.

- The scope and nature of the current testing approaches for crop protection products are scientifically relevant and sufficient to:

  - address adverse effects mediated through endocrine mode(s) of action;
  - characterize those adverse effects in terms of a dose response; and
  - provide reference doses that can be used for human health and environmental risk assessment and regulatory decision-making.

- These approaches are rooted in the extensive core and tiered toxicological and ecotoxicological data packages of global crop protection product registrations. This testing specifically takes into account the potential for **sensitive windows of exposure** and **vulnerable populations** and allows for the determination of **thresholds of adversity** for the establishment of regulatory reference values.

- The weight of available scientific evidence supports maintaining the current testing and risk assessment approaches; changes to test guidelines are not required in relation to **low-dose effects** and **non-monotonic dose-responses**.

- The regulatory approval process for crop protection products ensures high margins of safety in cases of potential **mixture effects** from combined exposures to substances with similar modes of action (affecting the same target organ or system).

- The continued protection of human health and the environment should be founded on science- and risk-based policymaking. Regulatory decisions should incorporate all scientific information on exposure, (eco)toxicological testing and mode of action in a transparent risk assessment framework.

- Broader public policy on endocrine disruption should be based on a clear and comprehensive evaluation of all available scientific information. The crop protection industry supports the use of a structured, weight-of-evidence approach to integrate all scientific evidence considering the strengths and weaknesses of studies, consistency (or absence of it) between findings, reproducibility and any outstanding areas of controversy.

- In moving forward, an inclusive and collaborative approach should be taken to encompass the broad range of viewpoints with a genuine commitment to seek consensus and encourage further dialogue on outstanding issues of uncertainty or controversy. There should also be broad consensus on areas requiring further research or new requirements in testing methods.

- The crop protection industry will continue to invest in research on endocrine disruption, the development and safety evaluation of innovative products, and promotion of responsible stewardship practices. The industry will continue to engage openly and provide expertise in national and international developments regarding endocrine disruption (e.g., Strategic Approach to International Chemicals Management and International Conference on Chemicals Management).

In summary, the crop protection industry calls for a transparent process to set policy on endocrine active substances and endocrine disruptors, including employing best practices for data collection and evaluation, involving experts with recognized experience and varying perspectives, and ensuring that a clear weight-of-evidence framework is used to objectively determine cause and effect. There should also be broad consensus on critical areas requiring further research, including testing methods. The industry welcomes constructive dialogue to assess any gaps in scientific knowledge and to promote a better understanding of all scientific views on endocrine disruption.