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**Emerging policy issues and other issues of concern:  
report on progress on emerging policy issues:  
endocrine-disrupting chemicals**

**Crop protection industry comment by CropLife International  
on *State of the Science of Endocrine-Disrupting Chemicals–2012*,  
published by the World Health Organization and the  
United Nations Environment Programme, and the related  
summary for decision makers**

**Note by the secretariat**

The secretariat has the honour to circulate a crop protection industry comment by CropLife International on *State of the Science of Endocrine Disrupting Chemicals – 2012*, published by the World Health Organization and the United Nations Environment Programme, and the related summary for decision makers (see annex). The comment is reproduced as received, without formal editing.

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## Annex

### **Crop Protection Industry Comment on *WHO-UNEP State of the Science of Endocrine Disrupting Chemicals – 2012* and Related Summary for Decision-Makers**

#### **Introduction**

Endocrine active substances (EASs) and endocrine disruptors (EDs) are being discussed at governmental and intergovernmental levels. It is a very complex issue of significant public, political, and scientific interest and many aspects are still the subject of considerable scientific debate. In 2013, the World Health Organization (WHO) and United Nations Environment Programme (UNEP) jointly published a document titled the *State of the Science of Endocrine Disrupting Chemicals – 2012* as well as the accompanying *Summary for Decision-Makers*.

The crop protection industry and a number of independent scientists have significant concerns with the conclusions of the report and summary and the scientific basis on how these were developed.

This briefing paper explains why the two WHO-UNEP documents are not a true state of the science review and are misleading in their recommendations to policy makers. A more in-depth analysis and critique is provided by Lamb et al. (2014 *Critical Comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals – 2012, Regulatory Toxicology and Pharmacology* 69:22-40).

The purpose of this industry comment is to:

- provide an overview and key points on the shortcomings of the WHO-UNEP's so-called *State of the Science* and the Summary for Decision Makers;
- provide an explanation and easy to reference table of where and why the crop protection industry disagrees with the reports;
- provide definitions of 'endocrine active substances' and 'endocrine disruptors' and explain some of the terminology; and
- provide recommendations for policy makers regarding the utility of the 2012 WHO-UNEP documents and subsequent reviews in the future.

#### **WHO-UNEP Documents**

The *State of the Science of Endocrine Disrupting Chemicals – 2012* (WHO-UNEP 2012a) report claims to be an update to the 2002 report prepared by the WHO with the International Programme on Chemical Safety (IPCS) (WHO-IPCS 2002). However, the 2012 report falls well short of serving as a review and update of the state of the science of endocrine disrupting chemicals (EDCs) as it does not meet the needs of a current systematic assessment of endocrine disruption. Although the highly regarded 2002 report provided a framework for thoroughly reviewing the existing data on EDCs, the lack of a scientific approach in the 2012 report leads to a number of significant concerns about the conclusions contained in the report.

The companion document to the WHO-UNEP report, the Summary for Decision Makers (WHO-UNEP 2012b), is in fact not a representative summary of the main report, presenting evidence, mentioning diseases, and introducing conclusions not discussed in the main report. On further examination, this document is actually an entirely separate product of the WHO-UNEP process, which provides an inconsistent, fabricated assessment. To make matters worse, the Summary for Decision Makers is oversimplified to the point that it provides misleading statements and misrepresents the strength of the main report's data and conclusions. Finally, the Summary for Decision Makers is an advocacy document and cannot in any way be represented as a credible scientific document.

### **Endocrine System / Endocrine Active Substances (EASs) / Endocrine Disruptors (EDs)**

The endocrine system is made up of glands in our body that produce hormones, which are chemical messengers that collectively ensure the proper functioning of the body and enable growth and development.

EASs are able to interact with our endocrine system or even mimic our own hormones. At sufficiently high dose levels, typically much greater than those encountered under normal exposure conditions, some may have a negative impact on how the body functions<sup>1</sup>: they then may be called EDs.

We are surrounded on a daily basis by EASs. They can be natural or synthetic. Natural EASs can be found in vegetables, milk, coffee, soy,<sup>1</sup> etc. Synthetic examples are drugs such as paracetamol<sup>2</sup> (a common painkiller), ingredients in some cosmetics or plastics, and certain crop protection products.

Interaction of a substance with the endocrine system does not necessarily cause an adverse effect. The dose needed to cause a harmful effect and whether people, domesticated animals or wildlife will be exposed to this dose in real life situations is very important. Many compounds are harmful in large doses but benign under normal use conditions. Being able to identify substances that can cause harm and those that do not with typical exposure is an essential part of the regulatory and registration process of all substances, including crop protection products which undergo extensive testing and evaluation.

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<sup>1</sup> European Food Safety Authority, 2010. Scientific report on endocrine active substances.

<sup>2</sup> Albert, O. et al., 2013. Paracetamol, aspirin and indomethacin display endocrine disrupting properties in the adult human testis *in vitro*. *Human Reproduction*, Vol. 0, No. 0, p. 1–9.

While the distinction between EASs and EDs may often be wrongly communicated<sup>3</sup> – it is of paramount importance to clearly distinguish between them in the debate on how to regulate EDs and protect human health and the environment.

The World Health Organization (WHO) International Programme on Chemicals Safety defines an ED as a “substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in the intact organism, or its progeny, or (sub)-populations.” In applying this definition, the question is whether a substance “alters functions of the endocrine system” and if so, whether it “causes adverse effects in intact organisms.” While adversity and causation via interaction with the endocrine system are minimally required by this definition, it is also critical to consider if a substance has sufficient biological activity or potency to produce adverse effects at typical human or environmental exposure levels, and whether exposure occurs at particular sensitive periods in development.

### Critique of the WHO-UNEP reports

Endocrine disruption has been an environmental and human health issue of concern for well over two decades, with a great deal of research being funded and conducted globally. Therefore, the need for a current, comprehensive review of the state of the science of this research is significant and much anticipated. Unfortunately, the WHO-UNEP 2012 document fails to meet this need, and the global community is still waiting for a true review of the state of the science of endocrine disruption.

- The 2012 report **does not follow** the 2002 WHO-recommended weight-of-evidence approach and **ignores data quality**.
- The main report **implies rather than establishes** a causal relationship between chemical exposures and endocrine disruption.
- The main report discusses disease trends **without regard to known causes or risk factors**, even though disease trends **are not suitable** for showing that a chemical causes a particular disease.
- The main report **ignores real-world exposures** for most chemicals discussed.
- The main report presents **controversial topics** important to understanding endocrine disruption in a **one-sided manner**.
- The main report presents several, self-contradictory statements.

***Overall, the 2012 WHO-UNEP State of the Science report does not provide a balanced perspective, nor does it accurately reflect the state of the science on endocrine disruption.***

***The Summary for Decision Makers cannot be used for responsible decision-making based on the considerable number of weaknesses found in the main report and in the summary document itself.***

Refer to Table 1 on page 7 for examples of some of the misleading statements made in the Summary for Decision Makers that are not supported by data provided in the main report.

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<sup>3</sup> Foster, W.G. and Agzarian, J., 2008. Toward less confusing terminology in endocrine disruptor research. *Journal of Toxicology and Environmental Health Part B: Critical Reviews* 11, p. 152-161.

## Top 10 Reasons the WHO-UNEP 2012 Report Cannot Be Used to Support Evidence-Based Decisions

1. *It is **not objective**.* The 2012 report was produced by a limited set of authors who largely represent one portion of the spectrum of opinion on endocrine disruption rather than by the consensus of a large set of scientists spanning the entire range of views on the topic.
2. *It does not consider **all available evidence**.* The 2012 report displays a strong preference toward only citing studies that report an association with exposure; important studies providing contrary evidence were disregarded. The failure to identify studies with different results is potentially misleading, is contrary to best scientific practices, and does not facilitate sound policy decisions.
3. *It **ignores other known or possible risk factors that contribute to diseases**.* Many factors can affect disease trends, including changes in diagnostic criteria, screening and improved detection, intervention and treatment, lifestyle factors, and compilation of data from multiple sources. Such factors were not considered in the 2012 report.
4. *It does not consider **real-world conditions actually relevant to human health**.* The 2012 report does not consider dose, exposure, potency, or thresholds at which effects might not be seen—despite the fact that it is important to consider these factors when assessing the relevance of experimental animal data. Additionally, the limitations of low-dose studies were not addressed.
5. *It does not use **objective criteria in assessing whether chemicals cause disease**.* The 2012 report uses “best professional judgment” instead of a systemic process for assessing causation. The framework of objectivity used to create the 2002 report was abandoned in the 2012 report. As a result, causation was not demonstrated for a variety of conditions, including prostate cancer.
6. *It **poorly addresses controversial topics important to understanding endocrine disruption**.* Despite the number of scientific uncertainties and controversies that exist regarding endocrine disruption (e.g., bisphenol-A effects, thyroid effects from polychlorinated biphenyls, declining sperm counts), the 2012 report does not acknowledge these topics. Ignoring these topics implies a level of scientific agreement that does not exist.
7. *It **mischaracterizes primary study findings and ignores data quality and other important aspects of the scientific method**.* The 2012 report does not discuss the limitations of many of the studies, including low participation rates that raise concerns about the representativeness of the studies. As a result, the primary results are overstated.
8. *It does not use a **disciplined, unbiased approach to collect and review data**.* Not only does the 2012 report fail to describe the approach that the authors took to collect and review data, but because the report fails to include all available data and disregards data quality, it does not represent unbiased data collection and review. When interpreting data, the complete spectrum of findings must be considered.
9. *It does not use a **clear methodology to integrate and assess data**.* No systematic approach was applied to verify the consistency of study results, and the presence of bias and confounding in the original studies was inconsistently evaluated. Meaningful data integration and assessment must take into account these factors.
10. *It provides only a **cursory discussion of data gaps**.* Although identification of data gaps is an essential element of a state-of-the-science review, the 2012 report only describes data gaps in a broad manner and does not present them in its conclusions.

## Top 10 Reasons the WHO-UNEP Summary for Decision-Makers Cannot Be Used to Support Evidence-Based Decisions

1. *It is **not a representative summary of the main report**.* The Summary for Decision Makers is best characterized as “another product” of the WHO-UNEP process as it includes many assertions that do not reflect the analysis provided in the main report and draws conclusions on matters not mentioned in the main report (discussed below). The Summary for Decision Makers cannot be used as a basis for discussing the contents of the main report.
2. *It includes conclusions **not supported by and/or discussed in the main report**.* As an example, the only definitive information on specific health effects is presented in Figure 5 of the Summary for Decision Makers, which lists a range of disorders supposedly induced by EDC exposures. Data presented in the main report do not support these assertions.

3. *It discusses diseases **not mentioned in the main report**.* The Summary for Decision Makers asserts that Alzheimer and Parkinson's diseases are induced by exposure to EDCs. These diseases, however, are not discussed in the main report; no data are provided to support this conclusion.
4. *It presents evidence **not included in the main report**.* The Summary for Decision Makers presents human disease trends for autism and dyslexia as evidence for concern regarding endocrine disruption. The main report discusses autism and dyslexia in general terms and does not link either disease to EDC exposure.
5. *It **introduces inconsistencies** within itself and with the main report.* Although the Summary for Decision Makers definitively states that a wide variety of conditions are induced by developmental exposure to EDCs, in subsequent statements these diseases are described less definitively as "potential" diseases that could originate from early exposure to EDCs. It is inconsistent with the main report in that it identifies dyslexia and autism as being linked with EDC exposure despite the fact that the main report asserts no such relationship.
6. *It is **oversimplified**.* Although it is admirable to attempt to translate the information contained in the main report to the layperson, the Summary for Decision Makers ignores crucial analysis in this attempt. Because the Summary for Decision Makers fails to take into account data gaps and other critical information, the result is oversimplification of its conclusions.
7. *It provides **misleading overstatements** of evidence and strength of conclusion.* In an effort to simplify the information contained in the main report, the Summary for Decision Makers does not properly characterize data gaps. As a result, the strength of the main report's conclusions is overstated in the Summary for Decision Makers. For example, the title of Figure 5 (Diseases induced by exposure to EDCs during development in animal model and human studies) is misleading and suggests a confidence level in the relationship between EDCs and specific diseases that does not exist.
8. *It **implies more parallels between human and wildlife exposures than actually exist**.* Although the Summary for Decision Makers asserts that there are multiple parallels between human and wildlife EDC exposures, the main report only provides one example of such a parallel. This goes beyond the information provided in the main report by implying that multiple examples exist of similar observations in humans and wildlife, when this is not the case.
9. *It does not include **valid references** for many of its general statements.* Because many of the Summary for Decision Makers general statements do not cite particular sections of the main report or external references, it is difficult for the reader to find the basis for these statements. Scientific documents must be meticulous in citing the original source when stating conclusions.
10. *It is an **advocacy document** rather than a scientific report.* The discussions contained in the Summary for Decision Makers are advocacy-based, as evidenced by the lack of scientific citations, and do not report on the state of the science.

## Conclusions and Recommendations for Policy Makers

Creating a true review of the state of the science in any field is a considerable and complex task. The 2002 WHO-IPCS report admirably assessed the available scientific data on endocrine disruption and suggested how future research could answer outstanding questions. Unfortunately, the 2012 WHO-UNEP report did not live up to this ideal, therefore failing to provide a true state of the science review. More disappointing is the failure to build on the 2002 report and describe changes in the science since that time. The 2012 report and its companion document ultimately do not provide a suitable scientific basis for informed decision making about endocrine disruption and endocrine disruptors.

These shortcomings are significant enough that neither the 2012 WHO-UNEP report nor the Summary for Decision Makers should be used as the basis for further international action or policy development on endocrine disruptors. While endocrine disruption is an issue of significant public, political, and scientific interest, we strongly believe that chemicals policy should be based on a clear and comprehensive

evaluation of current science. We support the use of a structured weight-of-evidence approach<sup>4</sup> to integrate all available information on exposure, (eco) toxicological testing, mode of action, and epidemiology in a transparent and objective manner.

In the future, we urge WHO and UNEP to use a transparent process for selecting experts with recognized experience and varying perspectives, employ best practices for data collection and evaluation, and ensure that a clear weight of evidence framework is used for objectively integrating results for determining cause and effect. Adherence to these principles should ensure that state-of-the-science reports meet 21st century standards for comprehensive, systematic reviews of the literature when evaluating complex scientific issues.

The crop protection industry remains committed to an inclusive and collaborative approach on the issue of endocrine disruption, encompassing the broad range of viewpoints and with a genuine commitment to seek consensus and encourage further dialogue to address outstanding issues of uncertainty or controversy. There should also be broad consensus on critical areas requiring further research, including further developments in testing methods, where the Organization for Economic Co-operation and Development (OECD) is playing an important role. The crop protection industry has constructively contributed to these developments within OECD.

The crop protection industry welcomes further constructive dialogue to assess current gaps in scientific knowledge and promote a better understanding of the range of scientific perspectives on endocrine disruption. The goal here is not to undermine global efforts to understand and address issues related to endocrine disruption, but instead to strengthen them by ensuring that they are based on a comprehensive assessment of the current state of the science as a guide to risk-based decision making that ensures the protection of human health and the environment.

**Table 1: Misleading Statements in the Summary for Decision Makers**

Summary for Decision Makers Statement	Rebuttal
Endometriosis is induced by exposure to EDCs during development in animal model and human studies. <sup>1</sup>	<i>Unsupported.</i> The main report states that “it is now hypothesized [sic]” that developmental exposure can contribute to endometriosis risk (WHO-UNEP 2012a, p. 43). The hypothesis does not demonstrate that EDCs induce endometriosis.
Autoimmune disease is induced by exposure to EDCs during development in animal model and human studies. <sup>1</sup>	<i>Unsupported.</i> The main report states that “it is possible” that EDCs play a role in autoimmune disease development (WHO-UNEP 2012a, p. 167). The only specific chemical mentioned in the main report is bisphenol A, which is characterized as “could be a factor” (WHO-UNEP 2012a, p. 169) in autoimmune disease development.
Heart disease/hypertension are induced by exposure to EDCs during development in animal model and human studies. <sup>1</sup>	<i>Unsupported.</i> No data in the main report are presented to demonstrate that EDCs induce heart disease and hypertension.

<sup>4</sup> Weight of Evidence approach as outlined in the *WHO-IPCS 2002 Global Assessment of the State-of-the-Science of Endocrine Disruptors*, Chapter 7: Causal Criteria for Assessing Endocrine Disruptors—A Proposed Framework.

Alzheimer and Parkinson diseases are induced by exposure to EDCs during development in animal model and human studies. <sup>1</sup>	<b>Unsupported.</b> These diseases are not even mentioned in the main report. Furthermore, the Summary for Decision Makers contradicts itself on page 13, noting that these are “potential” diseases from early exposures to EDCs.
Exposure to EDCs has been linked with increased neurobehavioral disorder rates, including dyslexia and autism. <sup>2</sup>	<b>Unsupported.</b> Dyslexia is not mentioned in the main report in the context of endocrine disruption and only passively mentioned once as a public health trend in the initial overview (WHO-UNEP 2012a, p. 2). The main report does not present any data or link autism to exposure to EDCs.
There are important parallels between the increasing incidence of human disorders and those observed in wildlife. <sup>3</sup>	<b>Unsupported.</b> The main report provides one example of a disorder (failure of testes to descend) observed in humans and two deer species (WHO-UNEP 2012a, p. 2, p. 57). The Summary for Decision Makers misleadingly implies that multiple observations exist when this is not the case.
There are situations in which individually safe exposures of EDCs have reached a collectively harmful level or in which levels thought to be safe are not so. <sup>4</sup>	<b>Unsupported.</b> The main report does not present data showing that the combinations of EDCs that humans and wildlife are currently exposed to results in harm.

*Below are representative examples of some of the misleading statements made in the Summary for Decision Makers that are not supported by data provided in the main report.*

<sup>1</sup>WHO-UNEP 2012b, Figure 5, page 7

<sup>1</sup> WHO-UNEP 2012b, page 9

<sup>3</sup> WHO-UNEP 2012b, page 10

<sup>4</sup> WHO-UNEP 2012b, page 19

## Glossary of Terms

*Disease trend:* The general course of a disease over time as determined by surveillance and modern diagnostic technologies.

*Endocrine disrupting chemical (EDC):* An external substance that causes an adverse effect on an organism through changes to the endocrine system. Also referred to as an *endocrine disruptor*.

*Endocrine active substances (EAS):* Are able to interact with our endocrine system or even mimic our own hormones. Under normal use conditions, some may have a negative impact on how the body functions: they then may be called EDs.

*State-of-the-science review:* A review of scientific data/literature that has an objective scope and systematic approach to collecting, reviewing, integrating, and assessing all available data.

*Weight-of-evidence approach:* An approach used to evaluate data that gathers all relevant information, considers data quality and consistency, allows meaningful comparison of data no matter the source, and “weights” the information/data to draw conclusions.

## Critical References

Lamb JC, IV, Boffetta P, Foster WG, 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*. *Regulatory Toxicology and Pharmacology* 69:22-40.

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