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

Thought starter paper by CropLife International on endocrine-disrupting chemicals and the Strategic Approach to International Chemicals Management

Note by the secretariat

The secretariat has the honour to circulate a thought starter paper by CropLife International on endocrine-disrupting chemicals and the Strategic Approach to International Chemicals Management (see annex). The paper is reproduced as received by the secretariat, without formal editing.

* SAICM/OEWG.2/1.

Annex

CropLife International Thought Starter Paper on Endocrine Disruption Chemicals and the Strategic Approach to International Chemicals Management (SAICM)

October 2014

Executive Summary:

Concerns are increasingly being raised worldwide over possible links between exposure to synthetic chemicals, including pesticides, and their potential to have a harmful effect to humans or the environment through the disruption of endocrine systems.

Some non-governmental organizations paint an alarming picture of the current situation, with seemingly hundreds of toxic chemicals causing untold damage to our health and to the health of future generations. They argue that the science behind endocrine disrupters is not fully understood and therefore highly precautionary regulation is needed in order to manage the ”hidden risks” behind Endocrine Disrupting chemicals .

This thought starter sets out to present a more balanced view of the current situation, outlining some of the scientific facts behind the ED issue and highlighting the significant efforts already underway to understand and manage the few remaining uncertainties.

It is clear that regulatory systems around the world need to provide adequate protection from chemicals that may cause harm, and many substances (including pesticides) are already heavily regulated based on their potential to cause ED-related effects. Good regulatory systems use sound scientific principles to carefully weigh the risks and benefits in order to reach balanced and proportionate decisions on a case by case basis. The chemicals industry urges SAICM to endorse such approaches, rather than adopting overly precautionary and potentially damaging measures on the basis of unwarranted concerns supported by half-truths and unproven links between chemical exposures and human health.

To this end, this document sets out a number of suggestions which industry believes are essential under the SAICM umbrella in order to make useful and significant advances in understanding and managing the risks presented by ED substances.

Background – Facts behind the Concerns

In everyday life we are exposed to both natural (e.g. occurring in soybean, hops and carrots) and synthetic substances (e.g. human pharmaceuticals) which can interact with the endocrine system, i.e. are endocrine active substances. This interaction is not necessarily harmful. The endocrine system is naturally dynamic and responsive to various stimuli as part of its normal functioning. It is a necessary part of how our bodies interact with our environment (food, sunlight,) and in many cases this "disruption" is beneficial. The endocrine system also responds when we are ill or stressed, and this can often be confused with causing an illness as opposed to being a response to an illness. Therefore, it is extremely important to distinguish between an interaction resulting in a temporary adjustment and an interaction resulting in adverse effects in an intact organism. Only where there is clear evidence that substances cause adverse effects through an endocrine mode of action, should they be considered as endocrine disrupters.

- **WHO-UNEP Report**

Industry takes society´s concerns regarding endocrine disruption extremely seriously, as evidenced by the testing that already takes place on chemical compounds, but some concerns need to be put into context. The 2012 WHO/UNEP report on the State of Science of Endocrine Disrupting Chemicals suggests that several effects on human health are linked to environmental exposure to chemicals without proof of a causal relationship, ignoring the important role played by other factors such as lifestyle. In fact, the 2012 WHO/UNEP report interprets 'environmental exposure' as exposure to chemicals, when in the scientific literature, environmental exposure covers a multitude of characteristics in human populations including diet, exercise, lifestyle factors, infectious agents and even drug use; for wildlife these include factors relating to habitat, food supply, disease, predation and competition – factors which can be completely unrelated to chemical exposures.

To meet standards for sound scientific work, it is necessary to use consistent and objective criteria for evaluating studies and a transparent framework for evaluating the overall weight of the scientific evidence. Unfortunately, the 2012 WHO/UNEP report and especially the summary for policy makers fall short of this basic requirement. In addition, the literature cited in the 2012 report adds little to the WHO Report on Endocrine Disrupters published in 2002, which, by contrast, presents a transparent and balanced approach to evaluating the available literature, has a broader authorship, and presents a far more thorough analysis. Industry is committed to contributing to the development of meaningful scientific studies to assess, if there is any real evidence for a link between endocrine related health disorders and pesticides.

- **Low Dose Effects**

The idea of low-dose effects is a hypothesis which is not unique for endocrine disrupting chemicals, but which challenges the whole basis of modern chemical risk assessment. Since the 15th century toxicology has worked on the basis that the dose makes the poison, and this has withstood the rigorous scientific testing of the last six decades and still holds true. By contrast, the "low dose effects" is still a theory which lacks solid scientific evidence. To complicate matters, a definition of "low dose effect" is lacking and the low-dose effects described by some scientists are not adverse and hence not relevant for regulation. Nevertheless, in a recent EPA review of low dose effects (non-monotonic dose response NMDR, Ref 1) EPA concluded that "*there is currently no reproducible evidence that the early key events involved in the expression of NMDRs that are identified at low dose are predictive of adverse outcomes that may be seen in humans or wildlife populations for estrogen, androgen or thyroid endpoints and therefore, current testing strategies are unlikely to mischaracterize, as a consequence of NMDR, a chemical that has the potential for adverse perturbations. The conclusions affirm that the scientific evidence for non-monotonic low dose exposures leading to endocrine disruption and adverse effects is, at best, very weak.*"

- **Management of EDCs by Risk Assessment**

It is important to note that endocrine disrupting chemicals can be managed by the same principles as most other substances which cause potential harm to human health and the environment. Through state-of-the-art risk assessment, effects on the endocrine system can be assessed and appropriate risk management measures taken if necessary. A recent opinion of the European Food Safety Authority (EFSA, Ref 2) concluded that *"…risk assessment (taking into account hazard and exposure data/predictions) makes best use of available information*." Risk assessment couples hazard characterization with exposure. It takes account of vulnerable sub-populations while still allowing the benefits of the chemical to be realized. By contrast, hazard-based management does not take exposure into account. It is a blunt instrument, which is unjustified as an approach to protect human health and the environment. In addition, it does not meet the criteria for a sound scientifically based assessment (Ref 3).

The United States Environmental Protection Agency (USEPA) is currently developing its Endocrine Disrupter Screening Program (see below). The EDSP is a comprehensive, science based program which uses a risk assessment approach. It is built on the OECD conceptual framework (see below). This program enables compounds to be screened for endocrine activity, and if endocrine activity occurs, then tests to see if this activity is capable of causing an adverse effect over a range of doses and exposures. It augments existing test methodologies and is designed to identify toxicological effects which are truly a result of endocrine disruption, as opposed to other causes.

In order to prioritize endocrine disrupting chemicals and to focus on those substances which cause the highest concern, it is necessary to consider both the hazard **and** potential exposure. In order to identify those substances which are more likely to pose a risk, a full hazard characterization is necessary. According to the European Food Safety Authority (EFSA) this includes the consideration of the severity and (ir)reversibility of any critical effects. Furthermore, potency (e.g. the dose level at which the effect is observed, Ref 4) is a key element in determining whether a substance is of real concern. This has to be combined with data of potential exposure which is available for all registered pesticides in order to identify those substances which may pose an unacceptable risk. Industry supports this program approach because it is science based and enables rational decision making, rather than decision making based on hazard.

International Approaches to address potential ED concerns

- OECD

The OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters (as revised in 2012) (Ref 5) lists the OECD Test Guidelines and standardized test methods available, under development or proposed that can be used to evaluate chemicals for endocrine disruption. The Conceptual Framework is intended to provide a guide to the tests available which can provide information for endocrine disrupters' assessment but is not intended to be a testing strategy; it is not prescriptive and simply reflects the type of information the tests provide at the different levels, such as informing endocrine toxicity outcome pathways, moving from *in silico to in vitro and in vivo.* It should be noted that information on mechanisms/pathways is particularly important for assessing chemicals for endocrine disruption.

The description of the five levels of the draft Conceptual Framework are as follows:

Level 1. Existing data and non-test information
Level 2. In vitro assays providing data about selected endocrine mechanism(s)/pathway(s)
Level 3. In vivo assays providing data about selected endocrine mechanism(s)/pathway(s)
Level 4. In vivo assays providing data on adverse effects on endocrine relevant endpoints
Level 5. In vivo assays providing more comprehensive data on adverse effects on endocrine relevant endpoints over extensive parts of the life cycle of the organisms.

Information/tools from lower levels can be used to determine what specific higher level tests are needed for a specific chemical to increase evidence that it is/it is not an endocrine disrupter. This approach is illustrated in the Guidance Document on Standardized Test Guidelines for Evaluating Chemicals for Endocrine Disruption.

- US EPA ED Screening Program (Ref 6)

The 1996 Food Quality Protection Act, which amended the Federal Food, Drug, and Cosmetic Act directed EPA to develop an Endocrine Disrupter Screening Program, using appropriate validated test systems and other scientifically relevant information, to determine whether certain substances may have hormonal effects in humans, fish and wildlife. EPA continues to develop requirements for the screening and testing of pesticides, commercial chemicals, and environmental contaminants for their potential to disrupt the endocrine system. As part of the process, EPA has been developing and is refining a number of screening and ecotoxicological assays, and intends to use validated methods or assays to identify and characterize the endocrine activity of pesticides, commercial chemicals, and environmental contaminants, specifically in relation to estrogen, androgen, and thyroid hormones. EPA has started to use the assays in a two-tiered screening and testing process.

- Using Tier 1 screening assays, EPA identifies chemicals that have the potential to interact with the endocrine system. A Weight of Evidence approach will be used to assess the data from the testing battery, and determine whether or not the compound warrants further testing in Tier 2.

- Tier 2 comprises ecotoxicology tests which address a variety of species, dose levels and generations. These assays are in the process of being validated. EPA hopes to use these assays to determine whether adverse effects are a result of endocrine disruption, and whether or not endocrine disruption is responsible for impacting the apical endpoints of growth, reproduction and survival.

The endpoints generated from EDSP testing, coupled with existing test data, other scientifically relevant information and exposure data will be used by EPA as part of its risk assessment process to determine if and how these compounds are to be regulated for use, or not.

- European Commission

The European Commission (EC) is currently in the process of defining hazard based criteria for endocrine disrupting properties that will apply across all chemical sectors, including general chemicals, cosmetics, biocides and crop protection products (Ref 7). As the criteria for identifying the hazard are currently drafted, consideration of potency, lead toxic effect, severity and irreversibility are precluded. This hazard based approach would mean that once identified as an Endocrine Disrupter, a pesticide would be regulated without making a risk assessment, i.e. a new pesticide would not be registered or an existing one would be de-registered. For this hazard-based approach the EC has developed a number of options, on which a public consultation has been started at the end of September 2014. In addition, the likely impact of these options is being assessed.

It is worth noting for pesticides that already today all active substances that are legally sold in the EU have undergone rigorous and comprehensive testing to assess their potential impact on human health and the environment. The existing testing framework is designed to identify all adverse effects, including those that may occur via the endocrine system, at a wide range of dose levels as well as providing protection for vulnerable population groups, such as pregnant women, children and the elderly, as well as protecting consumers, operators and bystanders.

- Industry

The chemical and crop protection industries have always been committed to ensuring that their products can be used safely. Companies invest significant resources in testing and evaluating the safety of products, including assessing the potential risks originating from endocrine acting chemicals. The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) has proposed a scheme for risk assessment of endocrine disrupters which has been widely recognized and which was awarded the prize “best paper in advancing the science of risk assessment” by the Society of Toxicology (Ref 8). Industry has also continuously contributed to increasing the knowledge on endocrine disrupters, for example by the Cefic Long Range Research Initiative (LRI) project on combined low-dose exposure to anti-androgenic substances (Ref 9). Industry experts have also made a significant contribution to the development and validation of OECD Test Guidelines for endocrine disruptors (discussed above). In the United States, industry has participated in the public comments at the meetings of EPA’s Scientific Advisory Panels, which reviewed EDSP Tier 1 testing, and provided significant technical expertise and experience on the performance of the Tier 1 test battery.

Comment on Activities in the intercessional period between ICCM3 and ICCM4

It is important that key activities undertaken in the intercessional period help to promote a balanced and proportionate response to the alleged links between chemicals and ED-related effects for humans and the environment. This approach should

a) acknowledge the uncertainties in relation to the alleged links between chemical exposure and ED related illness,

b) follow internationally recognized science-based approaches to systematically assess the risks associated with potential endocrine disrupting chemicals, and

c) balance consequences of any subsequent regulatory actions against the significant social, economic and health benefits that the everyday use of synthetic chemicals can bring to the people of developing nations.

With regard to the ICCM 3 resolution to provide "*timely updates to the 2012 report on the state of the science of endocrine disrupting chemicals…with particular attention to the needs of developing countries and countries with economies in transition",* it is particularly important that ICCM activities are conducted in coherence with the OECD and other international agencies e.g. US-Environmental Protection Agency EPA, and the European Food Safety Agency (EFSA) to avoid diverging assessment approaches and the duplication of work. In particular, ICCM activities should support the efforts of the OECD Task Force on Endocrine Disrupter Testing and Assessment, which is engaged in developing and validating endocrine screens and tests, since these tests will provide a science-based foundation for identifying those endocrine disrupting substances of true concern.

It is also important that any updates to the 2012 report take into consideration the considerable shortcomings of the 2012 WHO/UNEP report, which did not follow well-established scientific and medical approaches for characterizing the strength and totality of scientific evidence, and therefore provides an unbalanced view about the actual risks of endocrine effects from exposures to chemicals. Specifically, it assumes causality from statistical associations which is not possible, and uses exposure as a proxy for hazard when there is no information on whether the exposure is sufficiently high to cause any effect. In its efforts to *"raise awareness and facilitate science-based information exchange"*, ICCM is strongly encouraged to look beyond the 2012 WHO/UNEP report and to make a balanced consideration of the ED threat based on the weight of evidence of all available scientific information.

Certain NGO's seek to identify pesticides as a specific ED concern, and call for the publication of "comprehensive lists of ED pesticides". However there is no clear scientific evidence justifying why pesticides as a group should be singled out for ED concern, especially since these are among the most extensively tested and highly regulated of any group of chemicals. Whilst internet searches easily identify "suspect lists" containing many chemicals, including pesticides, detailed examination of these lists reveals that the scientific evidence for ED concern is questionable and in many cases completely unsubstantiated by the available scientific data. Compiling and perpetuating such lists creates unnecessary concerns that can ultimately lead to restriction or withdrawal of substances that present no appreciable risk to health or the environment. Where such listed substances are essential tools for increasing food production or improving public health, and provide general economic benefit to developing nations, it is obvious that such lists are counterproductive and irresponsible in terms of an overall goal to improve world health.

Finally, regarding the ICCM3 resolution calling for *"…the development of case studies and advice on translation of research results into control actions",* it is critical that ICCM ensure that

1) the weight of all available scientific evidence demonstrates that any chemicals chosen for such case studies are of genuine ED concern, according to internationally accepted definitions and testing practices, and not simply "suspects" selected from questionable ED lists;

2) any exposure to such chemicals is accurately quantified using scientifically accepted methodology and

3) a clear causal link has been established between exposure to the chemical and the adverse health effects, ruling out other confounding factors.

Only in this way will case studies provide useful and effective means to address and manage the real ED-related health risks, and avoid unnecessary and potentially damaging over-regulation of many safe and beneficial chemicals.

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