European Crop Protection

POSITION PAPER
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ECPA position paper on the criteria *for the determination of endocrine disrupting properties* under Regulation 1107-2009

The European Commission is currently developing new criteria for the regulation of endocrine disruptors (EDs) that would apply to pesticides (plant protection products), biocides, and possibly to general chemicals (REACH) and cosmetics. The goal we all share is to safeguard human health and the environment and to ensure a high level of protection. The way these criteria are defined could have profound consequences for consumers, the agricultural sector, the food chain, and international trade. It is therefore essential that we strike the right balance and develop criteria that are proportionate, science based and which maintain the existing high levels of protection for human health and the environment.

This paper describes ECPA's views on the critical elements being considered in the development of these criteria.

Executive Summary

ECPA believes that endocrine disruptors can be treated like most other substances of potential concern, that is subject to ***risk assessment***, considering both ***hazard and exposure***.

ECPA is opposed to the establishment of regulatory categories for endocrine disruptors.

ECPA supports the development of a single set of scientific criteria for the determination of endocrine disrupting properties as required by Regulation 1107/2009. These criteria should use the WHO/IPCS definition as a basis and incorporate all the hazard characterisation elements (severity, (ir)reversibility, specificity, potency and lead toxicity). All relevant scientific information on a substance should be evaluated using a structured weight of evidence approach considering both the quality and consistency of data. This should provide a solid basis for regulatory decision making and ensure that the final ED criteria are sufficiently discriminative to separate out those substances that are of high regulatory concern from those that are not.

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Legislative background

Under Regulation 1107/2009[1] (plant protection products), *"endocrine disrupting properties"* has been introduced as a hazard based cut-off criterion and substances considered to have these properties will not be authorised (i.e. will be banned). No definition was included during the adoption of the regulation, however the European Commission was required to develop by 14 December 2013 a set of scientific criteria to determine what are endocrine disrupting properties.

In February 2013, the Directorate General of Environment of the European Commission (DG Environment) presented a draft proposal[2] for a set of horizontal criteria for the identification of endocrine disruptors (EDs) intended to be applied to pesticides and biocides, as well as to general chemicals (REACH) and cosmetics. In June 2014 the Commission published a roadmap document[3] with several different policy options for the criteria. At this time the Commission also initiated an impact assessment to evaluate the possible impacts of the different options. The Commission's proposal for the final criteria along with the impact assessment report are expected to be published in June 2016.

ECPA view on the criteria for the determination of endocrine disrupting properties

The WHO/IPCS[4] 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"*.

According to this definition, a substance should only be regarded as an endocrine disruptor if it causes an ***adverse effect*** in an ***intact organism*** or ***(sub) population***, by an ***endocrine mode of action***. Therefore, mere interaction with the endocrine system is not sufficient to consider a substance as an endocrine disruptor, the interaction must lead to an adverse effect[5]. The reference to "consequently" in the WHO/IPCS definition provides an additional requirement for the demonstration of a ***causal relationship*** between the adverse effect and the endocrine mode of action.

ECPA supports the WHO/IPCS definition as a ***scientific starting point*** and as ***a basis*** for the scientific criteria for the determination of endocrine disrupting properties. However, the definition by itself is not suitable to support regulatory decision making under Regulation 1107/2009. The incorporation of additional elements is essential to develop appropriate ***regulatory criteria*** suitable for regulatory purposes.

Critically the further "hazard characterisation" elements of ***severity*** of effect, ***(ir)reversibility*** of effect, ***specificity***, ***potency*** and ***lead toxicity*** must be included in the ED criteria (see Attachment 1 for a further explanation of these points). These aspects are essential to ensure that all relevant scientific information on

[1] Regulation 1107/2009, Annex II, point 3.6.5 and point 3.8.2
[2] DG Environment document: *Revised version of possible elements for criteria for identification of endocrine disruptors* (ED-AD-HOC-6/2013/02), 19 February 2013
[3] http://ec.europa.eu/smart-regulation/impact/planned_ia/docs/2014_env_009_endocrine_disruptors_en.pdf
[4] WHO/IPCS (2002) report: http://www.who.int/ipcs/publications/en/ch1.pdf
[5] WHO/IPCS defines an adverse effect as: *"A change in morphology, physiology, growth, reproduction, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences"* WHO/IPCS (2004), http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf

the hazard of a substance is considered in regulatory decisions within the hazard based cut-off included in Regulation 1107/2009. Taking full account of this information is a routine and normal part of chemicals evaluation and is critical to distinguish between those substances of high regulatory concern from those that are not.

Without these hazard characterisation elements, substances which pose little or no concern for human health or the environment will be considered to have endocrine disrupting properties and unnecessarily banned under Regulation 1107/2009. The resulting loss of essential plant protection products could significantly reduce the ability of European farmers to control crop pests and diseases without providing any demonstrated benefits to the protection of human health or the environment. Such a severe action would not represent proportionate regulation when considering the many natural substances we are exposed to on a daily basis (e.g. caffeine and certain phytoestrogens) which by their nature would also be regarded as having endocrine disrupting properties if using the WHO/IPCS definition alone.

In summary, ECPA supports the development of a single set of criteria for the determination of endocrine disrupting properties, which use the WHO/IPCS definition as a basis, but which also incorporate all the hazard characterisation elements (severity, (ir)reversibility, specificity, potency and lead toxicity). All relevant scientific information should be evaluated using a structured weight of evidence approach considering both the quality and consistency of data. This should provide a solid basis for regulatory decision making and ensure that the final ED criteria are sufficiently discriminative to separate out those substances that are of high regulatory concern from those that are not.

ECPA would also support the development of a technical guidance document to assist implementation of the final criteria (e.g. to provide further guidance on adversity). However, input from Member State regulatory authorities, as the principal end-users of such guidance, would be essential.

Categories for endocrine disruptors

In its paper presented in February 2013, DG Environment proposed the establishment of a set of categories of endocrine disruptors. These were intended to be analogous to the system of classification and labelling of substances which are regarded as carcinogenic, mutagenic and toxic for reproduction (CMR) under the CLP Regulation[6]. Under the proposal two categories would be established: (1) Category 1: *endocrine disruptors*, (2) Category 2: *suspected endocrine disruptors*. In the Commission roadmap document published in June 2014, an additional third category of *endocrine active substances*, was added.

ECPA opposes the concept of categories for EDs for the following reasons:

- It is not required under the Commission's legal obligations relating to endocrine disruption. Under Regulation 1107/2009, the Commission is required to present *"…specific scientific criteria for the determination of endocrine disrupting properties"*. This requires a single set of criteria to determine whether or not a substance has endocrine disrupting properties, it does ***not*** require a set of categories.

- Categorisation of EDs has no scientific basis. CMR adverse effects are well-defined toxicological outcomes which are suitable to categorisation. "Endocrine disruption" is not an adverse effect in itself, it is a mode of action. The term endocrine disruption artificially groups multiple modes of action leading to adverse effects of variable nature, severity and concern. These effects are manifested as carcinogenic,

[6] Regulation 1272/2008 on classification, labelling and packaging of substances and mixtures

reproductive, developmental or other effects which are already considered in regulatory decision making. What is and should be regulated are adverse effects themselves, not the underlying modes of action that cause them.

- Categorisation will inevitably lead to the creation of "black lists" that will be highly vulnerable to misinterpretation, misuse and unwarranted additional primary or secondary regulation, in Europe and globally. Substances which are not considered as endocrine disruptors under the proposed scheme by DG Environment will still be labelled as "suspected endocrine disruptors", despite the fact that they will have been fully evaluated for their human health and environmental safety and subsequently authorised for use under Regulation 1107/2009.

Potential impacts of the endocrine disruption criteria

ECPA is concerned that the ED criteria linked to the hazard based cut-offs in Regulation 1107/2009 could remove a significant number of active substances from the market without providing any demonstrated benefits to the protection of human health or the environment.

Several EU bodies have investigated the potential impacts of the cut-off criteria for endocrine disruption, including KEMI (Sweden) and the former UK Pesticide Safety Directorate (PSD, now the Chemicals Regulation Directorate, CRD).

In their assessment undertaken in 2009 PSD identified 13 active substances as *"most likely to be eliminated"* and a further 25 substances *"which may be eliminated"* by the ED cut-off criteria[7]. This provides a total of 38 substances[8] which may be removed from the market out of the 286 assessed (representing approximately 13% of currently approved substances in the EU).

However, numbers of substances potentially removed alone does not predict the true impact on European agriculture, the critical factor is which substances may be removed. Several bodies have therefore assessed the likely agronomic impacts of the removal of certain active substances or classes of substances. These include assessments by CRD, Teagasc (Ireland) and ECPA.

ECPA investigated the potential impact from losing the 38 substances identified by PSD in the analysis mentioned above. Key findings of the ECPA assessment are:

- The final impact on European agricultural output would be substantial. The yield impact on key crops such as wheat, potatoes, oilseed rape and vines are projected to be between 10-20% in an average year – with losses of up to 50% being possible in years of high disease pressure.

- Fungicides in particular are most vulnerable. Applying the PSD criteria, the 10 most important cereal fungicide plant protection products used in Germany in 2011 would be lost (in France, it would remove 7 of the top 10 products). The loss of the PSD identified active substances would lead to the removal of approximately 80% of fungicide products currently used across the EU (based on market value).

[7] Reference: http://www.pesticides.gov.uk/Resources/CRD/Migrated-Resources/ Documents/O/Outcomes_paper _-_summary_impact_assessment_(Jan_09).pdf

[8] Identified as eliminated by the endocrine disruption criteria alone (i.e. not eliminated by the hazard based cut-off in Regulation 1107/2009, e.g. CMT, POP/PBT).

- The market value of pesticide products identified as possibly being affected has been calculated at between €3-4 billion. While the 38 active substances represent 13% of the number of approved active substances currently on the EU market, they represent 35-45% of the current European market in terms of formulated plant protection product use.

It is clear that the ED criteria could have the potential to remove a significant number of substances from the market that have been approved as safe under a comprehensive EU authorisation process based on risk assessment. This could have a major impact on the ability of European farmers to control pests, manage resistance, maximise yields and to maintain farm profitability.

The criteria are also likely to significantly impact on innovation. On average, each new pesticide active substance requires at least 10 years of research and development with an investment of approximately €200 million. Companies can not justify such an investment when new active substances could potentially trigger the ED criteria. Investment in new substances being developed for the European market has already significantly reduced over the last 30 years[9].

The use of the ED criteria also has the potential for far reaching negative impacts on global commerce, and it has been estimated that approximately €65 billion of EU imports of raw and semi-processed agricultural products could be affected by this policy10. The focus on purely hazard based criteria is a barrier to trade and is not consistent with the WTO's Sanitary and Phytosanitary (SPS) Agreement.

Future: risk assessment for endocrine disruptors

There has been no demonstration of meaningful benefits to the protection of human health or the environment from hazard based cut-off criteria beyond those provided by the existing risk assessment process. Using cut-offs based simply on hazard fails to take into account all relevant scientific information and does not provide a suitable basis for regularly decision making.

The only sound alternative is to apply full risk assessment, taking into account all the available information of sufficiently good quality on the mode of action, hazard, exposure and adverse effects, using a structured weight of evidence approach. This is also the conclusion reached by EFSA[11] who have stated that "*endocrine disruptors can be treated like most other substances of potential concern for human health and the environment, that is subject to risk assessment, considering both the hazard and exposure"*.

[9] *R&D trends for chemical crop protection products and the position of the European Market*, consultancy study undertaken for ECPA by Phillips McDougall, September 2013
[10] *Potential Trade Effects on World Agricultural Exporters of European Union Regulations on Endocrine Disruptors*, report prepared by Kyd D. Brenner, February 2014
[11] EFSA Scientific Committee; *Scientific Opinion on the hazard assessment of endocrine disruptors: scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment*. EFSA Journal 2013;11(3):3132. [84 pp.] doi: 10.2903/j.efsa.2013.3132.

Attachment 1

What are the elements of hazard characterisation and why are they important for the final criteria for the determination of endocrine disrupting properties?

Under the WHO/IPCS definition[12] there are 3 requirements for a substance to be considered as an endocrine disruptor: (1) demonstration of an adverse effect in an intact organism or (sub)population, (2) an endocrine mode of action, and (3) a causal relationship between the endocrine activity (mode of action) and the adverse effect. The WHO/IPCS definition with these 3 elements provides a starting point for the final criteria for the determination of endocrine disrupting properties. However, the definition by itself is not suitable for regulatory purposes. The essential further "hazard characterisation" elements described below must be included to develop a set of final regulatory criteria suitable to support decision regulatory making under Regulation 1107/2009. These aspects are a routine and normal part of chemicals evaluation for all other areas of potential concern.

Severity of adverse effect
Severity describes the magnitude of an adverse effect and/or the qualitative nature of the adverse effect induced by a substance as observed in laboratory animal studies. Severe adverse effects would contribute to a greater overall level of concern.

(Ir)reversibility
Consideration of reversibility or irreversibility contributes to evaluation of severity. Reversibility implies that recovery of the individual or population (in laboratory animal studies) may occur after exposure to the substance in question has stopped. Reversible adverse effects would provide a lower overall level of concern.

Specificity
For a substance to be considered to have endocrine disrupting properties, the adverse effect should manifest as a direct consequence of a primary endocrine mode of action, and not indirectly as a result of secondary non-endocrine mediated systemic toxicity.

Potency
Potency is a factor of both the dose level at which adverse effects are induced and the duration required to cause those effects. A highly potent substance produces a large effect at low concentrations, while a substance of low potency leads to a small effect at even higher concentrations. Also, a potent substance may cause an adverse effect after a short exposure duration, whereas a less potent substance may require a longer exposure duration to elicit the same effect. Potency is therefore a measure of a substance's strength to produce an adverse effect. It is a routine part of the dose response considerations in the hazard characterisation of a substance and is an essential element to discriminate between substances of high regulatory concern (those of high potency) from those of lower concern (those of low potency).

Lead toxic effect
The lead toxic effect considers the dose response relationship of all effects observed in the toxicity dossier of a substance. It is considered to be the adverse effect that occurs at the lowest dose. The lead toxic effect describes the most sensitive toxicological endpoint (i.e. critical effect) and "drives" the risk assessment of a substance. Any risk management measures based on the lead toxic effect will be protective of all other adverse effects which occur at higher dose levels (including effects occurring via endocrine modes of action).

[12] WHO/IPCS (2002) report: http://www.who.int/ipcs/publications/en/ch1.pdf

In ECPA's view, a substance should only be considered of regulatory concern (i.e. considered to have endocrine disrupting properties), when the endocrine mediated adverse effect is the lead toxic effect and occurs at doses lower than those that cause other types of toxicity.

A further element considered important in relation to the development of the final criteria for the determination of endocrine disrupting properties is human/population relevance:

Human and population relevance
The endocrine mediated adverse effects observed in laboratory studies must be relevant to humans or non-target populations. For human health, relevance to humans is generally assumed by default in the absence of scientific data demonstrating non relevance. For environment, effects observed in studies must be relevant at the species population level.

All the above factors should be used to develop the final regulatory criteria for the determination of endocrine disrupting properties. In reaching regulatory decisions all relevant scientific information on these elements should be evaluated using a structured weight of evidence approach considering both the quality and consistency of data.