Endocrine Disruptors: Regulatory Landscape of the Pesticides, Biocides and Cosmetics sectors

Helena Eixarch, David Andrew and Amy Burrows of TSGE Consulting review the scientific and regulatory landscape of the endocrine disruptor identification process.

Introduction

The endocrine system is a complex network of glands, hormones and receptors. It provides the key communication and control link between the nervous system and bodily functions such as growth and development, immunity, metabolism, behaviour and the reproductive process.

The potential for chemicals to interfere with the normal functioning of the endocrine system has long been recognised, and there is increasing concern over the possible adverse effects in exposed populations.

According to the International Programme for Chemical Safety (IPCS, 2002), a joint programme of various UN Agencies including the World Health Organisation (WHO), endocrine disruptors are defined as "exogenous substances that alter function(s) of the endocrine system and consequently cause adverse health effects in an intact organism or its progeny, or (sub)populations (i.e. humans or wildlife)".

Identifying substances with endocrine-disrupting potential is a key priority, but remains a significant challenge.

Regulatory landscape

As awareness of endocrine disruptors grew, the European Commission (EC) responded with the 1999 'Strategy for Endocrine Disruptors'. This strategy set out a number of actions at European Union (EU) level, and identified short-term (research and international cooperation), mid-term (test methods) and long-term (regulatory) steps to take with the overall goal of minimizing exposure to endocrine disruptors.[1]

In the specific areas of Biocides and Plant Protection Products (PPP), legislation requires the Commission to specify scientific criteria for the determination of endocrine-disrupting properties. On 15th June 2016, the EC published two draft Acts[2,3] for the identification of endocrine disruptors. These Acts are currently being examined before final adoption (expected before the end of 2017). On the same date, the Commission adopted a Communication[4] presenting the science-based criteria (based on the WHO definition of endocrine disruptors) underlying these two draft measures.

EC draft scientific criteria for Biocides and PPP – Identification of endocrine disruptors

The standard approach to assessing the toxicity of chemical substances focusses on the identification of an adverse effect(s). For endocrine disruptors, the draft scientific criteria aim at including an additional element in legal form, i.e. the mode of action.

The mode of action is defined as "the inherent ability of a substance to interact or interfere with one or more components of an endocrine system". That is, how the chemical substance exerts its toxicity. Importantly, it is recognised that an endocrine mode of action does not represent a toxicological hazard per se, and does not necessarily lead to an adverse effect.

An adverse effect, as defined by the IPCS, is a "change in the morphology, physiology, growth, development, reproduction, or life span 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". To experimentally assess adverse effects at the molecular or cellular level, the EC is following the approach of the European Food Safety Authority (EFSA).[5] The EFSA states that transient, inconsistent and minor fluctuations at the biochemical and molecular level may be considered adaptive non-adverse changes; whereas sustained, consistent and permanent changes at the cell, organ or organism level, resulting in pathology or functional impairment *in vivo*, as well as altered timing of development, may be considered adverse. Expert judgement is required to assess the toxicological relevance of any effects on a case-by-case basis.

The next step after identifying the mode of action and adverse effects caused by a chemical is to establish a link between them – a causality. The EC considers that, in practice, it will be difficult to demonstrate causality; they therefore intend to follow the 'reasonable evidence' concept described by the EFSA.[5] Only a biologically plausible causal relationship between the endocrine mode of action and the observed adverse effect will be required; strict causality will not need to be conclusively demonstrated, thereby avoiding too rigid an approach.

The criteria for identifying endocrine disruptors are therefore fully in line with the WHO-IPCS definition: "Exogenous substances that alter function(s) of the endocrine system (MODE OF ACTION) and consequently (CAUSALITY) cause adverse health effects (ADVERSE EFFECTS)". All relevant scientific evidence should be used, applying a Weight of Evidence approach and a robust systematic review.

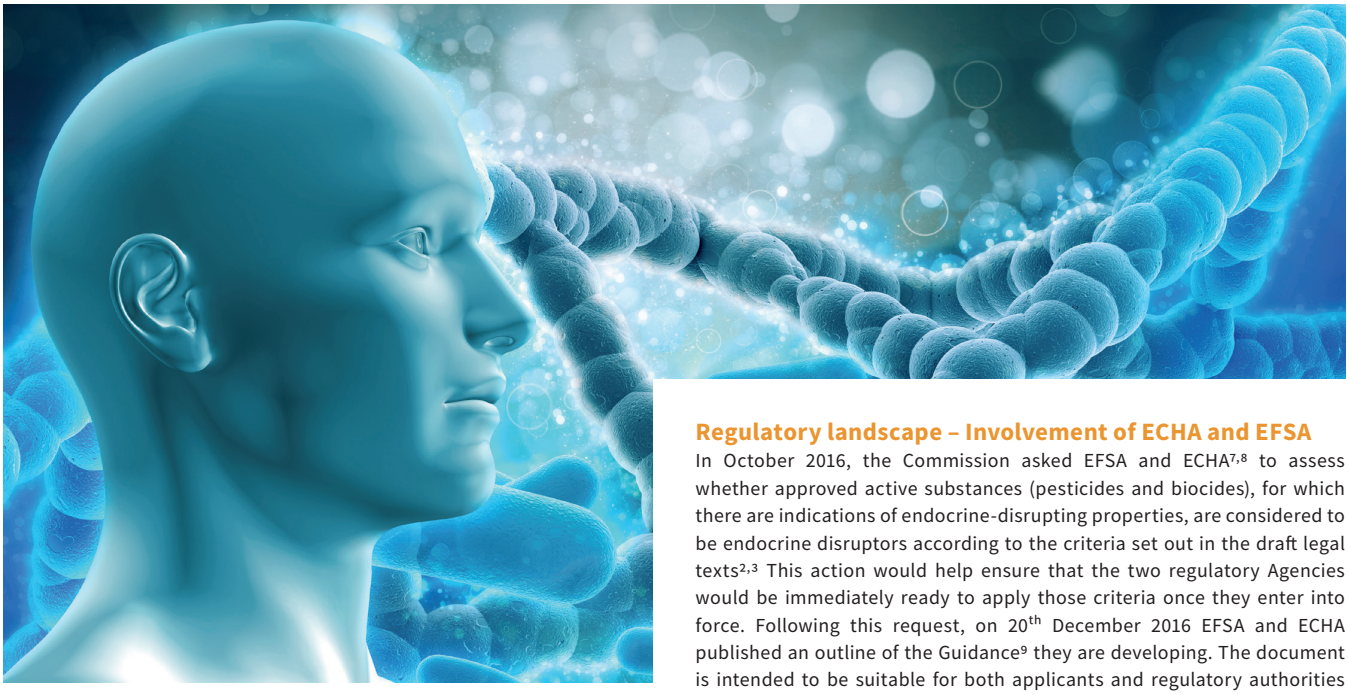
EC draft scientific criteria for Biocides and PPP – Regulatory consequences

PPP and Biocides legislation prohibit the approval of active substances having endocrine-disrupting properties on the basis of hazard, without undergoing a specific risk assessment considering the level of exposure. However, legislation allows exceptions based either on negligible risk and socio-economic considerations (Biocides) or based on negligible exposure (PPP). Scientific and technical knowledge has been evolving and suggests that endocrine disruptors in the PPP area could be assessed based on risk, like most other substances and therefore the negligible exposure concept should be updated to a negligible risk, in line with the Biocides legislation. The concept of hazard-based ban would nevertheless be maintained to ensure a high level of protection of health and the environment.

The question of whether an individual PPP or Biocide active substance is an endocrine disruptor will be assessed each time it is subject to an approval or renewal procedure. As approvals are only valid for a limited period of time and are routinely reviewed, the most recent scientific developments can be used to inform the approval decision, ensuring the application of appropriate scientific criteria, which is the Commission's intention.

Other regulatory areas – The Cosmetics sector

The draft measures described above only apply to the Biocides and PPP areas, with no legal consequence for chemicals regulated under other EU legislation.



However, the WHO-IPCS definition is also being applied to identify endocrine disruptors in other regulated areas:

- The European Chemicals Agency (ECHA) has included in their Candidate List, Substances of Very High Concern (SVHC) solely based on their endocrine-disrupting properties.
- The Commission has restricted the placing on the market of endocrine disruptors in the context of the REACH Regulation.
- The Commission has listed endocrine disruptors in the context of EU water quality legislation.

The Cosmetics Regulation (1223/2009) states, "when Community or internationally agreed criteria for identifying substances with endocrine-disrupting properties are available, or at the latest on 11th January 2015, the Commission shall review this Regulation with regard to substances with endocrine-disrupting properties".

It is evident the EC has incurred a delay in adopting their scientific criteria, with the draft legal acts for the PPP and Biocides sectors having been published in June 2016.[2,3]

Nevertheless, the EU cosmetics regulatory framework is already considering endocrine disruptors. The Scientific Committee on Consumer Safety (SCCS) endorses the WHO/IPCS definition of endocrine disruptor,[6] emphasizing the consideration of the three criteria: an adverse effect, a mode of action and a plausible causal relationship between the two. Examples of cosmetic ingredients with potential endocrine-disrupting properties evaluated by the SCCS include several parabens, triclosan or benzophenone.

Due to the ban on the animal testing of cosmetic ingredients, the SCCS recognises that full assessment of a potential endocrine-disrupting activity will remain a challenge until animal test methods are replaced by valid alternatives.

Regulatory landscape – Involvement of ECHA and EFSA

In October 2016, the Commission asked EFSA and ECHA[7,8] to assess whether approved active substances (pesticides and biocides), for which there are indications of endocrine-disrupting properties, are considered to be endocrine disruptors according to the criteria set out in the draft legal texts[2,3] This action would help ensure that the two regulatory Agencies would be immediately ready to apply those criteria once they enter into force. Following this request, on 20th December 2016 EFSA and ECHA published an outline of the Guidance[9] they are developing. The document is intended to be suitable for both applicants and regulatory authorities and could also be relevant for other chemical substances. Approval of the consolidated draft text is expected by the end of January 2018.

The Guidance will focus on the data and information needed for endocrine disruptor hazard identification: informative endpoints and test methods; chemical categories; read-across; available databases; (Q)SAR models; software tools and epidemiology data. The evaluation of this information will be performed in a Weight of Evidence-based approach.

The endocrine disruptors identification process will be described from two different starting points, as initially available information for substances may vary. One approach will start with data indicative of endocrine-mediated adverse effects and will set out how to evaluate the potential involvement of an endocrine mechanism. The second approach will start with data indicative of a mode of action and set out how to investigate whether this observed activity would result in adverse effects in intact organisms.

Due to the short timeline provided by the mandate, the already available relevant documents/guidance and developed tools in the context of endocrine disruptors will be used. The Guidance will only cover the oestrogen, androgen, thyroid and steroidogenesis hormonal pathways, which are the best characterized pathways, and only vertebrates (mammals, fish, birds, amphibians and reptiles) will be considered.

Concluding remarks

After adoption of the criteria to identify endocrine-disrupting substances, the legal obligations under the Biocides and PPP legislations will be fulfilled, and the EU's will be the first regulatory system worldwide to define scientific criteria for endocrine disruptor in legislation.

The Cosmetics sector will take advantage of these criteria, but assessment of potential endocrine-disrupting activities will remain a challenge unless animal test methods can be replaced with scientifically robust alternatives.

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CONTACT

Dr Helena Eixarch
Project manager – Cosmetics
TSGE Consulting
T: +34 673 612 721
E: helena.eixarch@tsgeconsulting.com