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European Union's strategy on endocrine disrupting chemicals and the current position of Slovenia

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In view of the European Union regulations 1107/2009 and 528/2012, which say that basic substances in plant protection and biocidal products marketed in the European Union (EU) should not have an inherent capacity to cause endocrine disruption, an initiative was started to define scientific criteria for the identification of endocrine disruptors (EDs). The objectives of the EU strategy on EDs are to protect human health and the environment, to assure the functioning of the market, and to provide clear and coherent criteria for the identification of EDs that could have broad application in the EU legislation. Policy issues were to be addressed by the *Ad-hoc group of Commission Services, EU Agencies and Member States* established in 2010, whereas the scientific issues were to be addressed by the *Endocrine Disruptors Expert Advisory Group* (ED EAG), established in 2011. The ED EAG adopted the 2002 World Health Organization (WHO) definition of endocrine disruptor and agreed that for its identification it is necessary to produce convincing evidence of a biologically plausible causal link between an adverse effect and endocrine disrupting mode of action. In 2014, the European Commission proposed four ED identification criteria options and three regulatory options, which are now being assessed for socio-economic, environmental, and health impact. Slovenia supports the establishing of identification criteria and favours option 4, according to which ED identification should be based on the WHO definition with the addition of potency as an element of hazard characterisation. As for regulatory options, Slovenia favours the risk-based rather than hazard-based regulation.

KEY WORDS: *endocrine disruptors; EU regulations; hazard identification criteria; risk assessment*

In 1998, the European Parliament adopted a resolution calling upon the European Commission (EC) to improve the regulatory framework for endocrine disruptors and to reinforce related research and communication to the public. In 1999, the EC proposed activities needed to respond to the public concern, which were based on the precautionary principle. It also proposed a research framework that would elucidate the causes and effects of identified endocrine disturbances. A number of research projects had been carried out since, and the EC had regularly reported on the developments in terms of substances prioritised for further investigation, new test methods, legislation, and further research (1).

Endocrine disruptors and the EU regulations

According to the widely accepted 2002 World Health Organization (WHO) definition,

An endocrine disruptor is 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. A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to adverse health effects in an intact organism, or its progeny, or (sub)populations (2).

The Glossary of Terms in the IPCS Environmental Health Criteria no. 240 define adverse effects as follows:

An adverse effect is a change in the morphology, 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).

EC regulations 1107/2009 (4) and 528/2012 (5) stipulate that basic substances, safeners, and synergists in plant protection products and basic substances in biocidal products, respectively, should not have endocrine-disrupting properties that may cause adverse effects if they are to be approved for marketing in the EU. The exceptions for plant protection products are if the exposure of non-target organisms is negligible or the "substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical method" (4). Similarly, the exceptions for the biocidal products are if the risks are negligible or the substance is "essential to prevent or control a serious danger to human health, animal health or the environment or not approving

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the substance would have "disproportionate negative impacts for society when compared with the risks…" (5).

However, neither regulation defines the criteria for the identification of ED. Until such criteria are adopted, the implementation of the regulations 1107/2009 and 528/2012 relies on the provisions of the classification, labelling and packaging regulation no. 1272/2008 (6) in the sense that substances classified as *carcinogenic* category 2 and *toxic for reproduction* category 2 in that regulation "shall be considered to have endocrine disrupting properties. In addition, substances, such as those classified, as toxic for reproduction category 2 and which have toxic effects on the endocrine organs, may be considered to have endocrine disrupting properties" (4). This interim approach, of course, is imprecise, as carcinogenicity, reproductive toxicity, or even endocrine organ toxicity may have little to do with endocrine disruption.

Many other EU regulations are in dire need for clear criteria for identifying EDs (1907/2006, 1223/2009, 93/42/EEC, 2007/47/EC, and 2000/60/EC) (7-11). Clear criteria will enable their universal application across the regulatory solutions in different settings. The initiative to further develop the EU strategy on EDs has the following objectives: to provide legally clear, predictable, and coherent criteria for the identification of EDs and to enable their universal application across the EU legislation with the ultimate objective of protecting human health and environment and of strengthening the internal EU market (12).

This article presents the latest developments concerning the efforts to come up with these universal, scientific criteria for the identification of EDs as well as the current position of the Republic of Slovenia on this issue.

Development of scientific criteria for the identification of endocrine disruptors

In 2010, the EC established an *Ad-hoc group of Commission Services, EU Agencies and Member States* for policy issues and a year later, a sub-group *Endocrine Disruptors Expert Advisory Group* (ED EAG) to address scientific issues relevant to endocrine disrupting substances not specific to any regulatory framework, including advice/orientation on scientific criteria for the identification of EDs. Both groups included representatives of Commission services, EU agencies, member states, industry associations, and non-governmental organisations (NGOs).

The ED EAG was not required to reach consensus and presented differing opinions and options for consideration by the Ad-hoc group (13). It adopted the WHO definition of EDs (2) by analysing each of the definition's elements. The starting point for discussion was the state-of-the-art assessment of endocrine disruptors by Kortenkamp et al. (14). The ED EAG agreed that the elements required for an endocrine disruptor to be identified were the evidence of an adverse effect and its relevance for humans at the individual and/or offspring level. To quote Kortenkamp, the evidence of an adverse effect requires "a biologically plausible causal link to an endocrine disrupting mode of action and for which disruption of the endocrine system was not a secondary consequence of other non endocrine-mediated systemic toxicity" (14). As for the relevance, it should be assumed unless non-relevance can be demonstrated. In relation to wildlife populations, data on all species at the population level are generally considered relevant (13).

Munn and Goumenou (13) give a detailed report about the scientific issues raised by the ED EAG in identifying and characterising EDs. Briefly, potency, severity, irreversibility, and lead toxicity were not considered elements of hazard identification but characterisation. Some experts suggested that these elements could come in handy in setting priorities and ranking the EDs, and/or differentiating EDs into classes or categories of lower or higher concern based on this information, but the suggestion received divided support. Those who opposed it believed that the information could only be used within a risk assessment context. There was no agreement, however, on how to consider these factors with respect to ED hazard characterisation outside the context of risk assessment (13). Discussing a basic scheme for considering evidence of endocrine disrupting properties of substances, the group singled out mode of action and adversity and favoured the weight-of-evidence approach that would include human epidemiology data, field data, animal experimental toxicology and ecotoxicology studies, *in vitro* data, and quantitative structure-activity relationship. Within given time, the group could not fully evaluate the adequacy of current assays for specific endocrine pathways but suggested that their development "should be informed by emerging human health issues or observed negative impacts on wildlife populations and hypothesised link to endocrine-related causes" (13). In a separate report, Munn and Goumenou (15) present issues, such as "effect-thresholds, the non-monotonous dose-response relationship, effects of mixtures, exposure during the critical windows of susceptibility, inadequacy of testing methods for the identification of outcomes at low doses and at the relevant developmental stages".

In the meantime, the EC also gave a mandate to the European Food Safety Authority (EFSA) Scientific Committee to give their opinion on ED hazard assessment. The Committee proposed a distinction between an endocrine active substance (EAS) and ED. EAS was defined as "any chemical that was able to interact directly or indirectly with the endocrine system resulting in effect on the endocrine system, target organs and tissues" (16). This interaction, however, does not necessarily result in an adverse effect. In contrast, an ED should be defined by three criteria: an adverse effect in an intact organism or a (sub) population; an endocrine activity; and a plausible causal relationship between the two. Similar to ED EAG, the

Committee considered critical effect, severity, (ir) reversibility, and potency as elements of ED hazard characterisation (16).

Criteria for identification

In June 2014, the EC published the Roadmap of the initiative to define criteria for identifying EDs, in which it proposes four options for identification and three for regulatory decision making (12), as follows:

Identification options

Option 1: No policy change. No criteria are specified. The interim criteria set in the plant protection and biocidal products regulations continue to apply.

Option 2: The identification of EDs is based on the WHO definition. This option lists the required evidence and step-by-step procedure for identification.

Option 3: As option 2, but includes categories based on the strength of evidence for fulfilling the WHO definition: Category I - endocrine disruptors; Category II - suspected endocrine disruptors; Category III - endocrine active substances.

Option 4: As option 2, but includes potency as an element of hazard characterisation.

Decision-making options

Option A: No policy change.

Option B: Addition of more risk assessment elements into sectorial legislation, so that marketing decisions are not mainly based on hazard identification.

Option C: Inclusion of socio-economic considerations as well as risk-benefit analysis into sectorial legislation to allow marketing endocrine-disrupting products that are "essential to prevent adverse socio-economic impacts" (12).

The Roadmap (12) also summarises the results of the preliminary impact assessment for each of the options of the two aspects.

In the second half of 2014, a public consultation on defining ED identifying criteria generated over 27,000 responses, most of which came from interest groups such as NGOs and farming sector rather than the general public. The respondents confirmed the need for the EU to establish definitive criteria for EDs (17). The EU strategy is due before the summer of 2016 (18).

Current position of Slovenia

Slovenia has actively been participating in the initiative to establish the ED-identifying criteria. Its current position is largely based on the scientific evidence presented in detail in the reports by Damstra et al. (2), Kortenkamp et al. (14), Munn and Goumenou (13, 15), EFSA (16, 19-20), EC Scientific Committees (21-22), Joint German-British position paper (23), and several other peer reviewed publications (24-61).

As for the identification criteria, Slovenia supports Option 4, which lists the required evidence and provides a step-by-step identification procedure, plus it includes potency to characterise the hazard. Potency here denotes relative toxicity of an agent in relation to a given or implied standard or reference (62); in other words, it is a measure of its strength in respect to other chemicals.

As for the decision-making options, Slovenia is in favour of Option B, which uses risk assessment as the basis for marketing approvals.

Concerning the effect thresholds and other uncertainties, the position of Slovenia is that these should be determined for each case separately, taking into account the weight of evidence for a particular chemical. Depending on the quantity and the quality of available data, either the threshold (42, 51, 54) or the non-threshold (36, 59) approach should be used. Slovenia also favours the use of semi-quantitative decision trees for regulatory purposes. In view of uncertainties and the complexity of the endocrine system, Slovenia opts for a higher safety (uncertainty) factor, depending on the quality and quantity of data. It still remains to clearly define which is the sufficient quantity and sufficient quality of data. Considering the trends to minimise the use of animals in toxicological experiments and the ban on animal testing in cosmetics (8), it is unlikely that sufficient data will be generated on the effects in intact organisms for a number of chemicals in everyday use. For those structurally related to "threshold EDs", it may be appropriate to reconsider using the Threshold of Toxicological Concern approach (63). Slovenia favours creating priority lists for regulation, based on potency, severity of effects, irreversibility, and lead toxicity, as well as the expected magnitude of exposure to a particular ED. Although these are the elements of hazard characterisation and risk assessment, Slovenia believes that ED regulation ought to be based on risk rather than hazard, provided there is sufficient information to assess the risk.

Instead of a conclusion

Until the identification criteria are set and EDs regulated across the EU legislation, we believe that it is important to continue raising awareness about EDs through media and events such as the recent conference organised by The Slovenian Society of Toxicology: Endocrine disrupting chemicals - from molecule to man (64).

In view of numerous controversies and uncertainties related to EDs, we believe that it is sensible to reduce exposure to natural and synthetic chemicals by changing our behaviour, regardless of current regulations. The following recommendations to reduce ED exposure are based on the national public health and chemical safety policies (65, 66) as well as common sense:

Maintain healthy lifestyle with balanced low-salt, low-sugar, low-fat diet, regular moderate physical activity, and sufficient rest to reduce the risk of illness (and therefore the

need to take medication). Also avoid alcohol, tobacco, and caffeine.

Closely observe manufacturer's instructions when using biocidal, chemical, medicinal, plant protection, and consumer products.

Use as few biocidal, chemical, medicinal, plant protection, and consumer products as possible.

Grow and prepare your own food.

Drink tap water.

Store food and water in clear glass containers and at appropriate temperature.

Wash hands before eating.

Minimise the number of consumer products at home and workplace, remove dust, and air rooms regularly.

Recycle and reuse products.

Produce as little waste as possible.

Reduce the use of electrical and electronic appliances.

Cut down on motorised travelling.

Reduce the use of cosmetics and personal hygiene products.

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Conflicts of interest

The authors have no conflict of interest to declare.

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Kemični povzročitelji hormonskih motenj - strategija Evropske unije in stališče Slovenije

Uredbi Evropske unije 1107/2009 in 528/2012 navajata, da osnovne snovi fitofarmacevtskih in biocidnih sredstev odobrene za uporabo v Evropski uniji (EU), same po sebi ne povzročajo hormonskih motenj. Zato je potrebno definirati znanstvene kriterije za identifikacijo kemičnih povzročiteljev hormonskih motenj (KPHM). Cilji strategije EU na področju KPHM so varovanje zdravja ljudi in okolja, zagotavljanje delovanja trga ter jasnih in skladnih kriterijev za identifikacijo KPHM, ki bodo omogočali široko uporabo teh kriterijev v zakonodaji. Za obravnavo politik je bila leta 2010 ustanovljena Ad-hoc skupina predstavnikov Evropske komisije, EU agencij in držav članic; leta 2011 pa še ekspertna svetovalna skupina (ESS), ki je obravnavala znanstvene vidike. ESS je privzela definicijo KPHM Svetovne zdravstvene organizacije (SZO) iz leta 2002. Člani ESS so soglašali, da so za identifikacijo KPHM potrebni prepričljivi dokazi biološko verjetne vzročne povezave med škodljivim učinkom in hormonskim načinom delovanja. Evropska komisija je 2014 predlagala 4 možnosti kriterijev za identifikacijo KPHM in 3 možnosti obravnave. Začela se je tudi poglobljena ocena socio-ekonomskih, okoljskih in zdravstvenih vplivov predlaganih možnosti. Slovenija podpira uvedbo 4. možnosti, v skladu s katero kriteriji za identifikacijo KPHM temeljijo na definiciji SZO ob upoštevanju moči kot elementa karakterizacije nevarnosti. Slovenija daje prednost nadzoru, ki temelji na oceni tveganja in ne zgolj na oceni nevarnosti.

KLJUČNE BESEDE: *EU zakonodaja; identifikacije nevarnosti; ocena tveganja*