

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

Lucija Perharič¹, Tanja Fatur¹, and Jernej Drofenik²

National Institute of Public Health¹, Administration of the Republic of Slovenia for Food Safety, Veterinary and Plant Protection², Ljubljana, Slovenia

[Received in October 2015; CrossChecked in October 2015; Accepted in June 2016]

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

Correspondence to: Lucija Perharič, National Institute of Public Health, Zaloška 29, Ljubljana, Slovenia, E-mail: lucija.perharic@nijz.si

The subject of this paper has partly been presented at the 2nd Congress of the Slovenian Society of Toxicology "Endocrine disrupting chemicals – from molecule to man" held in Ljubljana, Slovenia, from 23 to 24 April 2015.

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.

Acknowledgement

Lucija Perharič gratefully acknowledges the nomination to the *Ad-hoc group of Commission Services, EU Agencies and Member States* and the ED EAG by the Administration of the Republic of Slovenia for Food Safety, Veterinary and Plant Protection.

Conflicts of interest

The authors have no conflict of interest to declare.

REFERENCES

1. Commission of the European Communities (CEC). Commission staff working on the implementation of the "Community Strategy for Endocrine Disrupters" - a range of substances suspected of interfering with the hormone systems of humans and wildlife (COM (1999) 706), (COM (2001) 262) and (SEC (2004) 1372), Brussels 2007. [displayed 4 November 2010]. Available at http://ec.europa.eu/environment/chemicals/endocrine/pdf/sec_2007_1635.pdf
2. Damstra T, Barlow S, Bergman A, Kavlock R, Van Der Kraak G, editors. Global Assessment of the State-of-the-Science of Endocrine Disruptors. Geneva: World Health Organization, International Programme on Chemical Safety; 2002.
3. World Health Organization/International Programme on Chemical Safety (WHO/IPCS). Principles and methods for the risk assessment of chemicals in food. Environmental Health Criteria 240, Annex I, Glossary of terms. Geneva: WHO; 2009. [displayed 14 December 2010]. Available at <http://www.who.int/foodsafety/publications/chemical-food/en/>
4. Regulation (EC) No. 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009. p. 1-50.
5. Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products Text with EEA relevance. OJ L 167, 27.6.2012. p. 1-123.
6. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (Text with EEA relevance). OJ L 353, 31.12.2008. p. 1-1355.
7. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (Text with EEA relevance). OJ L 396, 30.12.2006, p.1-520.
8. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (Text with EEA relevance) OJ L 342, 22. 12 2009. p. 59-209.
9. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. OJ L 169, 12. 7. 1993. p. 1-43.
10. Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market. OJ L 247, 21.9.2007. p. 21-35.
11. Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy. OJ L 327, 22. 12. 2000. p.1-73.
12. European Commission (EC). Roadmap. Defining criteria for identifying Endocrine Disruptors in the context of the implementation of the Plant Protection Product Regulation and Biocidal Products Regulation. Brussels: European Commission; 2014 [displayed 30 November 2014]. Available at http://ec.europa.eu/smart-regulation/impact/planned_ia/docs/2014_env_009_endocrine_disruptors_en.pdf
13. Munn S, Goumenou M. Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances. Report of the Endocrine Disruptors Expert Advisory Group. European Commission. Joint Research Centre. Institute for Health and Consumer Protection. Ispra; 2013. [displayed 1 June 2013]. Available at <http://publications.jrc.ec.europa.eu/repository/bitstream/JRC79981/lbna25919enn.pdf>
14. Kortenkamp A, Martin O, Faust M, Evans R, McKinlay R, Orton F, Rosivatz E. State of the art assessment of endocrine disruptors, Final Report 2011 [displayed 1 March 2012]. Available at http://ec.europa.eu/environment/chemicals/endocrine/pdf/sota_edc_final_report.pdf
15. Munn S, Goumenou M. Thresholds for Endocrine Disruptors and Related Uncertainties Report of the Endocrine Disruptors. Expert Advisory Group. European Commission. Joint Research Centre. Institute for Health and Consumer Protection. Ispra; 2013. [displayed 10 December 2013].

- Available at <http://publications.jrc.ec.europa.eu/repository/bitstream/JRC83204/lb-na-26-068-en-n.pdf>
16. European food safety authority (EFSA) Scientific Committee. Scientific opinion on the hazard assessment of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. *EFSA J* 2013;11:3132. doi: 10.2903/j.efsa.2013.313
 17. European Commission (EC). Report on public consultation on defining criteria for identifying endocrine disruptors in the context of the implementation of the Plant Protection Product Regulation and Biocidal Products Regulation. Brussels: European Commission, Directorate general for health and food safety; 2015 [displayed 2 September 2015]. Available at http://ec.europa.eu/health/endocrine_disruptors/docs/2015_public_consultation_report_en.pdf
 18. European Commission (EC). EP Plenary - Commission statement - Commission action to comply with Judgement in case T-521/14: Sweden vs the Commission; 2016 [displayed 2 February 2016]. Available at https://ec.europa.eu/commission/2014-2019/andriukaitis/announcements/ep-plenary-commission-statement-commission-action-comply-judgement-case-t-52114-sweden-vs-commission_en
 19. European food safety authority (EFSA). Opinion of the Scientific panel on food additives, flavourings, processing aids and material in contact with food (AFC) on a request from the Commission related to Di-butylphtalate (DBP) for use in food contact materials. Question No EFSA-Q-2003-192. *The EFSA J* 2005;242:1-17.
 20. European Food safety authority (EFSA) Conclusion on the peer review of the pesticide risk assessment of the active substance prochloraz. *EFSA Journal* 2011; 9:2323.
 21. Scientific committee on toxicity, ecotoxicity and the environment (CSTEE). Opinion on the results of a second risk assessment of bis(2-ethylhexyl) phtalate (DEHP) Human health part. Adopted by the CSTEE during the 41st CSTEE plenary meeting, Brussels, 2004.
 22. SCHER (Scientific Committee on Health and Environmental Risks), SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks), SCCS (Scientific Committee on Consumer Safety). Toxicity and Assessment of Chemical Mixtures. European Commission. Directorate General for health and consumers: Brussels; 2012. [displayed 3 February 2013] Available at http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_155.pdf
 23. Bundesinstitut für Risikobewertung (BfR). Joint DE-UK Position Paper: Regulatory definition of an endocrine disrupter in relation to potential threat to human health. BfR, Berlin; 2011. [displayed 5 November 2011] Available at: http://www.bfr.bund.de/cm/343/regulatory_definition_of_an_endocrine_disrupter_in_relation_to_potential_threat_to_human_health.pdf
 24. Zorn B, Virant-Klun I, Verdenik I, Meden-Vrtovec H Semen quality changes among 2343 healthy Slovenian men included in an IVF-ET programme from 1983 to 1996. *Int J Androl* 1999; 22:178-83.
 25. Slob W. Thresholds in Toxicology and Risk Assessment. *Int J Toxicol* 1999;18:259-68. doi: 10.1080/109158199225413.
 26. Guo YL, Hsu PC, Hsu CC, Lambert GH. Semen quality after prenatal exposure to polychlorinated biphenyls and dibenzofurans. *Lancet* 2000; 356:1240-1.
 27. Jouannet P, Wang C, Eustache F, Kold-Jensen T, Auger J. Semen quality and male reproductive health: the controversy about human sperm decline. *APMIS* 2001; 109:333-44.
 28. National Toxicology Program (NTP). National Toxicology Program's report of the endocrine disruptors low dose peer review. Research Triangle Park, North Carolina: National Institute of Environmental Health Sciences. 2001.
 29. Walkowiak J, Wiener JA, Fastabend A, Heinzow B, Krämer U, Schmidt E, J Steingrube HJ, Wundram S, Winneke G. Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. *Lancet* 2001; 358:1602-7.
 30. Langer P, Tatjakova M, Kocan, Trnovec T, Sobokova E, Kliems I. From naturally occurring goitrogens to the effects of anthropogenic endocrine disruptors on the thyroid in Slovakia. *Bratisl Lek Listy* 2003; 104:101-7.
 31. Gill U, Chu I, Ryan JJ in Feely M. Polybrominated diphenyl ethers: human tissue levels and toxicology. *Rev Environ Contam Toxicol* 2004; 183:55-97.
 32. Pliškova M, Vondraček J, Fernandez Canton R, Nera J, Kočan A, Petrik J, Trnovec T, Sanderson T, van den Berg M, Machala M. Impact of Polychlorinated Biphenyl Contamination on Estrogenic Activity in Human Male Serum. *Environ Hlth Perspec* 2005; 113:1277-84.
 33. Seed J, Carney EW, Corley RA, Crofton KM, DeSesso JM, Foster PM, Kavlock R, Kimmel G, Klaunig J, Meek ME, Preston RJ, Slikker W Jr, Tabacova S, Williams GM, Wiltse J, Zoeller RT, Fenner-Crisp P, Patton DE. Overview: Using mode of action and life stage information to evaluate the human relevance of animal toxicity data. *Crit Rev Toxicol* 2005; 35:663-72.
 34. Hamers T, Kamstra JH, Sonneveld E, Murk AJ, Kester MHA, Andersson PL, Legler J, Brouwer A. In vitro profiling of the endocrine disrupting potency of brominated flame retardants. *Toxicol Sci* 2006; 92:157-73.
 35. Jan J, Sovcikova E, Kočan A, Wsolova L, Trnovec T. Developmental dental defects in children exposed to PCBs in eastern Slovakia. *Chemosphere* 2007; 67:S350-4. doi: 10.1016/j.chemosphere.2006.05.148.
 36. Sheenan DM. No-threshold dose-response curves for nongenotoxic chemicals: Findings and applications for risk assessment. *Environ Res* 2006;100:93-9.
 37. UNEP/ILO/WHO/IOPSMC (United Nations Environment Programme/International Labour Organization/World Health Organization/Inter-Organization Programme for the Sound Management of Chemicals). Principles for evaluating health risks in children associated with exposure to chemicals. Environmental Health Criteria Series 237. Geneva: World Health Organization; 2006.
 38. Harvey PW, Everett DJ, Springall CJ. Adverse effects of prolactin in rodents and humans: breast and prostate cancer. *J Psychopharmacol* 2008; 22:20-7. doi: 10.1177/0269881107082624
 39. Harvey PW, Everett DJ, Springall J. Adrenal toxicology: a strategy for assessment of functional toxicity to the adrenal cortex and steroidogenesis. *J Appl Toxicol* 2007;27:103-15.
 40. Meeker JD, Calafat AM, Hauser R. Di(2-ethylhexyl) phtalate metabolites may alter thyroid hormone levels in men. *Environ Hlth Perspec* 2007;115:1029-234.

41. Van der Ven LT, Van de Kuil T, Verhoef A, Verwer CM, Lilienthal H, Leonards PE, Schauer UM, Cantón RF, Litens S, De Jong FH, Visser TJ, Dekant W, Stern N, Håkansson H, Slob W, Van den Berg M, Vos JG, Piersma AH. Endocrine effects of tetrabromobisphenol-A (TBBPA) in Wistar rats as tested in a one-generation reproduction study and a subacute toxicity study. *Toxicol* 2007;245:76-89.
42. Slob W. What is a Practical Threshold? *Toxicol Pathol* 2007;35:848-9. doi: 10.1080/01926230701714844
43. Boobis AR, Ossendrop BC, Bansiak U, Hamy PY, Sebestyen I, Moetto A. Cumulative risk assessment of pesticide residues in food. *Toxicol Lett* 2008;180:137-150.
44. Calabrese EJ. Hormesis and medicine. *Br J Clin Pharmacol* 2008;66:594-617. doi: 10.1111/j.1365-2125.2008.03243.x
45. Leijts MM, Koppe JG, Olie K, van Aalderen WM, Voogt P, Vulsma T, Westra M, ten Tusscher GW. Delayed initiation of breast development in girls with higher prenatal dioxin exposure; a longitudinal cohort study. *Chemosphere* 2008;73:999-1004.
46. Sonneborn D, Park HY, Petrik J, Kocan A, Palkovicova L, Trnovec T, Nguyen D, Hertz-Picciotto I. Prenatal polychlorinated biphenyl exposures in eastern Slovakia modify effects of social factors on birthweight. *Paediatr Perinat Epidemiol* 2008;22:202-13.
47. Boobis AR, Datson GP, Preston RJ, Olin SS. Application of key events analysis to chemical carcinogens and noncarcinogens. *Crit Rev Food Sci Nutr* 2009;49: 690-707. doi: 10.1080/10408390903098673
48. Verhulst SL, Nelen V, Hond ED, Koppen G, Beunckens C, Vael C, Schoeters G, Desager K. Intrauterine exposure to environmental pollutants and body mass index during the first 3 years of life. *Environ Health Perspec* 2009;117:122-126.
49. White RH, Cote I, Zeise L, Fox M, Dominici F, Burke TA, White PD, Hattis DB, Samet JM. State-of-the-Science Workshop Report: Issues and Approaches in Low-Dose-Response Extrapolation for Environmental Health Risk Assessment. *Environ Health Perspec* 2009;117:283-287.
50. Boobis A, Budinsky R, Collie K, Crofton K, Embry M, Felter S, Hertzberg R, Kopp D, Mihlan G, Mumtaz M, Price P, Solomon K, Teuschler L, Yang R, Zaleski R. Critical analysis of the literature on low-dose synergy for use in screening chemical mixtures for risk assessment. *Crit Rev Toxicol* 2011;41:369-83.
51. Crump KS. Use of threshold and mode of action in risk assessment. *Crit Rev Toxicol* 2011;41: 637-650. doi: 10.3109/10408444.2011.566258.
52. Kristensen DM, Hass U, Laurianne L, Lottrup G, Jacobsen GR, P, Desdoits-Lethimonier C, Boberg J, Petersen JH, Toppari J, Kold Jensen J, Brunak S, Skakkebaek NE, Nellemann C, Main KM, Jégou BM, Leffers H. Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. *Hum Rep* 2011;26:235-44. doi: 10.1093/humrep/deq323.
53. Kristensen DM, Skalkam ML, Audouze K, Lesné L, Desdoits-Lethimonier C, Frederiksen H, Brunak S, Skakkebaek NE, Jégou B, Hansen JB, Junker S, Leffers H. Many Putative Endocrine Disruptors Inhibit Prostaglandin Synthesis. *Environ Health Perspec* 2011;119:534-41.
54. Rhomberg LR, Goodman JE, Haber LT, Dourson M, Andersen ME, Klaunig JE, Meek B, Price PS, McClellan RO, Cohen SM. Linear low-dose extrapolation for noncancer health effects is the exception, not the rule. *Crit Rev Toxicol* 2011;41:1-19. doi: 10.3109/10408444.2010.536524
55. Bars R, Fegert I, Gross M, Lewis D, Weltje L, Weyers A, Wheeler JR, Galay-Burgos M. Risk assessment of endocrine-active chemicals: identifying chemicals of regulatory concern. *Regul Toxicol Pharmacol* 2012;64:143-54.
56. Bergman Å, Heindel JJ, Jobling S, Kidd KA, Zoeller T, editors. State of the science of endocrine disrupting chemicals. Geneva: World Health Organization / United Nations Environment Programme; 2012 [displayed 1 February 2013]. Available at <http://www.who.int/ceh/publications/endocrine/en/>.
57. Rhomberg LR, Goodman JE. Low-dose effects and nonmonotonic dose-responses of endocrine disrupting chemicals: Has the case been made? *Regul Toxicol Pharmacol* 2012;64:130-33.
58. Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, Jr, Lee D-H, Shioda T, Soto AM, vom Saal FS, Welshons WV, Zoeller RT, Myers JP. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocr Rev* 2012;33:378-455. doi:10.1210/er.2011-1050
59. Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto, Woodruff TJ, F. S. Vom Saal FS. Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society. *Endocrinol* 2012;153:4097-110. doi: 10.1210/en.2012-1422
60. Nohynek GJ, Borgert CJ, Dietrich D, Rozman KK. Endocrine disruption: Fact or urban legend? *Toxicol Lett* 2013;223:295-305.
61. Tinwell H, Colombel S, Blanck O, Bars R. The screening of everyday life chemicals in validated assays targeting the pituitary-gonadal axis. *Regul Toxicol Pharmacol* 2013;66:184-96.
62. Environmental health and toxicology, U.S. Department of health and human Services. IUPAC Glossary of Terms Used in Toxicology 2016 [displayed 10 May 2016]. Available at <https://sis.nlm.nih.gov/enviro/iupacglossary/glossary.html>
63. Munro IC, A.G. Renwick AG, Danielewska-Nikiel D. The Threshold of Toxicological Concern (TTC) in risk assessment. *Tox Lett* 2008; 180:151-6.
64. Černe K, Kužner J, Perharič L, Sollner Dolenc M, Tišler T, editors. 2nd Congress of the Slovenian Society of Toxicology. Endocrine disrupting chemicals - from molecule to man. Book of abstracts. Ljubljana: Slovensko toksikološko društvo; 2015. [displayed 12 May 2015]. Available at http://www.tox.si/attachments/article/189/merged_document.pdf
65. Haines J, editor. An Integrated Approach to Sound Management of Chemicals and Waste. Initiation of Implementation of SAICM in Slovenia. Ljubljana: Intersectorial Committee for Chemical Safety; 2009.
66. Ministry of Health of the Republic of Slovenia (MoH). Areas of work and priorities [displayed 20 April 2015]. Available at http://www.mz.gov.si/en/areas_of_work_and_priorities/

Kemični povzročitelji hormonskih motenj - strategija Evropske unije in stališče Slovenije

Uredbi Evropske unije 1107/2009 in 528/2012 navajata, da osnovne snovi fitofarmaceutskih 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 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*