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IMPACT ASSESSMENT

Defining criteria for identifying endocrine disruptors in the context of the implementation of the plant protection products regulation and biocidal products regulation

Annex 9 out of 16

Accompanying the document

**COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN
PARLIAMENT AND THE COUNCIL**

on endocrine disruptors and the draft Commission acts setting out scientific criteria for their determination in the context of the EU legislation on plant protection products and biocidal products

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ANNEX 9

HUMAN HEALTH - HORMONE RELATED DISEASES

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This Annex focuses on the assessment of potential impacts, which build on the results of the screening study explained in Annexes 3 to 5. The results of the screening do not constitute evaluations of individual substances to be carried out under the respective chemical legislations [Regulation (EC) No 1107/2009 on plant protection products and Regulation (EU) No 528/2012 on biocidal products] and in no way prejudice future decisions on active substances to be taken pursuant to these two Regulations. It would thus be erroneous to consider that the substances listed in Annex 5 are considered as endocrine disruptors within the meaning of the EU legislation. The methods and results presented in this Annex are to be interpreted as an estimation of the potential impacts.

Annexes 8 to 15 describe the impacts expected when implementing the criteria to identify EDs (Options 1 to 4) under the current regulatory framework (Option A). In addition, it was assessed whether these expected impacts would remain the same or not under consideration of different regulatory implementations (Options B and C, only applicable to the PPP Regulation). The analyses of the impacts described in these Annexes translate into the "performance" of the options, which is one of the input parameters to the MCAs (Annex 6 and 7).

The MCAs results are not concluding on any preferred option for setting scientific criteria to identify endocrine disruptors, but aim at providing additional information to decision makers with regards to the potential impacts expected when implementing the criteria, after those would have been selected on the basis of science (two MCAs were performed: Options 1 to 4 under the current regulatory context, and Options A compared to Options B and C).

At a preliminary stage of the impact assessment it was anticipated that Option C should be discarded, nevertheless it was maintained for the analysis of the impacts for methodological reasons (see Section 4.2.3 of the main report and Annexes 6 and 7). Option C only applies to the PPP Regulation.

1. ENDOCRINE DISRUPTORS AND HORMONE RELATED DISEASES - EVIDENCE

The evidence on potential impacts on human health associated to different policy options for setting criteria to identify EDs is analysed in the following subsections with the aim to rank them.

Endocrine disruption is a relatively recent way of looking at the toxicity of chemicals, which aims at understanding the mode of action (MoA), i.e. how chemicals lead to the adverse effects observed. In 1991, a group of scientists concluded that a large number of man-made chemicals have the potential to disrupt the endocrine system of animals, including humans (Wingspread Statement¹), in particular because of the crucial role that hormones play in controlling the development of animals.

However, also natural substances are known to have endocrine disrupting properties. For instance, the soybean phytoestrogens (isoflavones) genistein and daidzein were reported to affect adversely thyroid function;^{2,3,4} bisphenol F formed during mustard production from a natural ingredient of mustard grains^{5,6} was reported to increase thyroxin levels of female rats⁷; caffeine was reported to exert embryo- and foeto-toxicity in rat and affect sperm quality in mice.^{8,9}

The possible association between incidence of certain human diseases and exposure to endocrine disruptors (EDs) has been raised in some international reports on the state of science on EDs which are mentioned below. However, evidence is scattered and its interpretation controversial, so that a causal link or even a possible association between ED exposure at environmental levels and the diseases mentioned in connection is not agreed among experts. A recent study carried out for the European Commission¹⁰ stresses that health outcomes are often the results of the synergies of multiple factors. For long latency diseases a

¹ Bern, H et al. 1992. Statement from the work session on chemically-induced alterations in sexual development: the wildlife/human connection. pp 1-8 in *Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection*. Eds. Colborn T. and Clement C., Princeton Scientific Publishing Co., NJ, U.S. Retrieved from: <http://www.ourstolenfuture.org/consensus/wingspread1.htm>

² Patisaul, H. B., and Jefferson, W. 2010. The pros and cons of phytoestrogens. *Frontiers in Neuroendocrinology*, 31(4), 400–419. <http://doi.org/10.1016/j.yfrne.2010.03.003>

³ Loutchanwoot, P., Srivilai, P., Jarry, H. 2013. Effects of the natural endocrine disruptor equol on the pituitary function in adult male rats. *Toxicology* Feb 8;304:69-75. doi: 10.1016/j.tox.2012.11.017.

⁴ Sosić-Jurjević B, et al. 2010. Suppressive effects of genistein and daidzein on pituitary-thyroid axis in orchidectomized middle-aged rats. *Exp Biol Med* (Maywood). May;235(5):590-8. doi: 10.1258/ebm.2009.009279.

⁵ Federal Department of Home Affairs FDHA. Federal Food Safety and Veterinary Office FSVO. Risk Assessment. Bisphenol F in mustard. Retrieved from: <http://www.efsa.europa.eu/sites/default/files/assets/af150611a-ax11.6.pdf>

⁶ Zoller, O. et al. 2016. Natural occurrence of bisphenol F in mustard, *Food Additives & Contaminants: Part A*, 33:1, 137-146, DOI: 10.1080/19440049.2015.1110623

⁷ Higashihara N, et al. 2007. Subacute oral toxicity study of bisphenol F based on the draft protocol for the "Enhanced OECD Test Guideline no. 407". *Arch Toxicol*. Dec;81(12):825-32. Epub 2007 Jul 13. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/17628788>

⁸ Bars, R. et al. 2012. Risk assessment of endocrine active chemicals: Identifying chemicals of regulatory concern. *Regulatory Toxicology and Pharmacology* 64 (1): 143-154. doi:10.1016/j.yrtph.2012.06.013

⁹ Tinwell, H., S. Colombel, O. Blanck, R. Bars. 2013. The screening of everyday life chemicals in validated assays targeting the pituitary–gonadal axis. *Regulatory Toxicology and Pharmacology* 66 (2): 184-196 doi:10.1016/j.yrtph.2013.04.002

¹⁰ Risk and Policy Analysts (RPA) et al. 2015. Study on the Calculation of the Benefits of Chemical Legislation on Human Health and the Environment, Final report for DG Environment, March 2016, Loddon, Norfolk, UK

number of assumptions are required which seriously limits the value of any indicator trying to measure the marginal contribution of chemicals legislation in lowering exposures.

The WHO-UNEP 2012 report “State of the science of Endocrine Disrupting Chemicals”¹¹ mentioned the following diseases in connection with ED exposure: prostate cancer and breast cancer, female and male reproductive health disorders, thyroid and metabolic disorders, neurodevelopment and immune disorders. The report highlighted the difficulties to prove an effective role of EDs exposure in the increasing incidence of these “*endocrine diseases and disorders*”. Scientific criticism to the general methodology used in the WHO-UNEP 2012 report was raised in 2014¹². This initiated a response¹³ by the authors of the WHO-UNEP 2012 report, triggering a further reply¹⁴ by the authors of the scientific comments on the methodology in 2015. These recent publications show that the controversy about the methodology used in the WHO-UNEP 2012 report seems not resolved.

Other scientists¹⁵ criticise the WHO-UNEP report 2012 (some of them ex-chair of European Commission Scientific Committees). They support the critics of Lamb et al. and further state: “the 2002 WHO/ICPS report demanded that a review of all data on endocrine disruption had to be appropriately performed according to the well-established principles of data evaluation. This was not adequately performed in the WHO/UNEP 2012 report and is also missing in the Zoeller et al.¹⁶ article”.

Finally, other critics^{17,18} to the WHO-UNEP 2012 report regarded more general scientific issues of debate, such as the existence and relevance of low-dose effects and non-monotonic dose-response curves for EDs (among these authors, some were members of European Agencies Scientific Committees).

¹¹ World Health Organization (WHO) 2012. State of the science of Endocrine Disrupting Chemicals 2012. Summary for Decision-Makers. Ed. Bergman Å., Heindel, J.J., Jobling S., Kidd, K.A., and Zoeller R.T. Retrieved from: http://www.unep.org/pdf/WHO_HSE_PHE_IHE_2013.1_eng.pdf

¹² Lamb J.C. et al. 2014. Critical comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals – 2012. *Regulatory Toxicology and Pharmacology* 69 (1) 22-40. doi:10.1016/j.yrtph.2014.02.002

¹³ Bergman, Å., et al. 2015. Manufacturing doubt about endocrine disrupter science – A rebuttal of industry-sponsored critical comments on the UNEP/WHO report “State of the Science of Endocrine Disrupting Chemicals 2012”, *Regulatory Toxicology and Pharmacology* 73 (3) 1007-1017, ISSN 0273-2300. Doi: 10.1016/j.yrtph.2015.07.026.

¹⁴ Lamb, et al. 2015. Comments on the opinions published by Bergman et al. (2015) on Critical Comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals, *Regulatory Toxicology and Pharmacology*. 73 (3) 754-757. ISSN 0273-2300, doi.org/10.1016/j.yrtph.2015.10.029

¹⁵ Autrup, H., Barileb, F. A., Blauboerc, B. J., Degend, G. H., Dekant, W., Dietrich, D., Domingog, J. L., Gorih G. B., Greim, H., Hengstlerd, J. G., Kacewj, S., Marquardtk, H., Pelkonenl, O., Savolainenm, K., and Vermeulenn, N. P. 2015. Principles of Pharmacology and Toxicology also Govern Effects of Chemicals on the Endocrine System. *Toxicol Sci*. 2015 Jul;146(1):11-5. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/26026993>

¹⁶ Zoeller, R. T., Bergman, A., Becher, G., Bjerregaard, P., Bornman, R., Brandt, I., Iguchi, T., Jobling, S., Kidd, K. A., Kortenkamp, A., et al. 2014. A path forward in the debate over health impacts of endocrine disrupting chemicals. *Environ. Health*, 14, 118

¹⁷ Testai, E., Galli, C.L., Dekant, W., Marinovich, M., Piersma, A.H., Sharpe, R.M., 2013. A plea for risk assessment of endocrine disrupting chemicals. *Toxicology*, <http://dx.doi.org/10.1016/j.tox.2013.07.018>

¹⁸ Borgert, C. J., Baker, S. P., and Matthews, J. C. 2013. Potency matters: thresholds govern endocrine activity. *Regul. Toxicol. Pharmacol.*, 67, 83–88.

In a recent external scientific report of EFSA ¹⁹ (2016) the evidence for the non-monotonic dose-response (NMDR) hypothesis was evaluated for substances in the area of food safety. The plausibility of NMDRs was assessed based on a systematic review methodology, which identified over 10'000 potentially relevant scientific studies. From these studies, 142 studies could be selected for the evaluation (49 in-vivo, 91 in-vitro, and 2 epidemiological studies). The report indicates that the empirical evidence for NMDR was limited or weak for most in vivo datasets that were selected for substances in the area of food safety. The report also indicates that *evaluation regarding the biological meaning (e.g. dose range studies, adversity of the effects, and toxicity at high doses leading to NMDR) and relevance for risk assessment were not part of this data analysis*, thus questioning the relevance of the evidence for the adverse effects.

In 2009 the Endocrine Society concluded that *“the evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong, and there is mounting evidence for effects on other endocrine systems, including thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis”*²⁰. In 2015, in a second statement, this is confirmed with further evidence from the past five years.^{21;22} Based on the current information it can be concluded that: certain reviews suggest a significant association between exposure to low doses of chemicals and diseases (WHO-UNEP 2012 report¹¹, Endocrine Society 2nd statement 2015²¹); other reviews suggest that this association is not supported by evidence;^{23;24} other publications criticise the methodology used by the reviews supporting the existence of such an association.^{13,14,25,26} In addition, it needs to be mentioned that the WHO and Endocrine Society reviews do not consider the regulatory context for PPP and BP in Europe, but base their reports on general available information without consideration of the different regulatory systems in place worldwide.

¹⁹ Beausoleil et al, 2016. Review of non-monotonic dose-responses of substances for human risk assessment. EFSA supporting publication 2016:EN-1027. 290pp.

²⁰ Diamanti-Kandarakis E. et al. 2009. Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. Endocrine Reviews 30(4):293-342, doi:10.1210/er.2009-0002. Retrieved from: <https://www.endocrine.org/endocrine-press/scientific-statements>

²¹ Gore, A.C., et al. 2015. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocrine Reviews 36 (6) doi.org/10.1210/er.2015-1010

²² Gore, A.C., et al. 2015. Executive Summary to EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocrine Reviews, 36(6):593–602. doi: 10.1210/er.2015-1093

²³ Ntzani EE, Chondrogiorgi M, Ntritsos G, Evangelou E, Tzoulaki I, 2013. Literature review on epidemiological studies linking exposure to pesticides and health effects. EFSA supporting publication 2013:EN-497, 159 pp. http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/497e.pdf

²⁴ Levêque-Morlais, N., et al. 2015. The AGRICulture and CANcer (AGRICAN) cohort study: enrollment and causes of death for the 2005–2009 period. International Archives of Occupational and Environmental Health. 88 (1): 61-73. DOI 10.1007/s00420-014-0933-x

²⁵ Gerhard J. Nohynek, Christopher J. Borgert, Daniel Dietrich, Karl K. Rozman. 2013. Endocrine disruption: Fact or urban legend? Toxicology Letters. 23 (6): 295-305, ISSN 0378-4274. DOI: <http://dx.doi.org/10.1016/j.toxlet.2013.10.022>

²⁶ Autrup, H., et al. 2015. Principles of Pharmacology and Toxicology Also Govern Effects of Chemicals on the Endocrine System. Toxicol. Sci. 146 (1): 11-15. doi: 10.1093/toxsci/kfv082

Since, the evidence regarding the causal link between ED exposure and some of the diseases seems to be still controversial among some experts, the following sections in this annex explore:

- 1) the evidence available at EU level on incidence of potentially hormone related diseases based on EUROSTAT and OECD data (section 1.1);
- 2) the epidemiological and laboratory evidence of a causal link between exposure to EDs and hormone related diseases (section 1.2);
- 3) the EU Regulation of active substances used in PPP and BP which are identified as EDs (section 1.3);
- 4) new methodological developments in addressing these issues (section 1.4).

1.1. Incidence of potentially hormone related diseases based on EUROSTAT and OECD data

Health statistic data available at EU28 or international level were analysed for the diseases mentioned in connection with EDs. A reference of the extent of a causal link with ED exposure mentioned in the source of the respective health statistic data was also given. In particular, data available via Eurostat and OECD were used for this analysis.

In general, it is difficult to conclude from health data available at EU and OECD level about the extent of a potential causal link between development of certain diseases and environmental exposure to endocrine disruptors. In fact, these health data are likely to be influenced by a better tracking of the diseases (e.g. cancer) resulting in higher scores of these diseases. Furthermore, many factors contribute to the development of these multifactorial diseases (e.g. obesity and diabetes are associated with various socio-economic factors). Below detailed information for cancer, obesity and diabetes is presented.

1.1.1. Causes of death - Annual standardised death rate (SDR) per 100 000 inhabitants (Eurostat, EU 28)

The following Eurostat data were selected for the analysis of diseases on the basis of the concerns raised by the international reports mentioned in Section 1.2 of this annex (Table 1).

Table 1. Eurostat data selected for the analysis

Malignant neoplasm of breast, total population
Malignant neoplasm of thyroid gland, total population
Diabetes mellitus, total population
Diseases of the circulatory system (I00-I99), total population
Malignant neoplasm of cervix uteri, female population
Malignant neoplasm of other parts of uterus, female population
Malignant neoplasm of ovary, female population
Malignant neoplasm of prostate, male population
Malignant neoplasm of testis, male population
Malignant neoplasms of cervix

Life expectancy has constantly increased at EU level over recent years (Figure 1). This is translated into decreasing standardised death rates²⁷ (SDR) for most causes of death.

This pattern applies to all diseases presented in Table 1 and Figure 1, making it difficult to assess the impact of EDs on these diseases, due to the generally decreasing - mortality rates. It is to note among these diseases that the SDR for thyroid cancer has very slightly increased at EU28 level from 0.6 in 2004 to 0.8 in 2012.

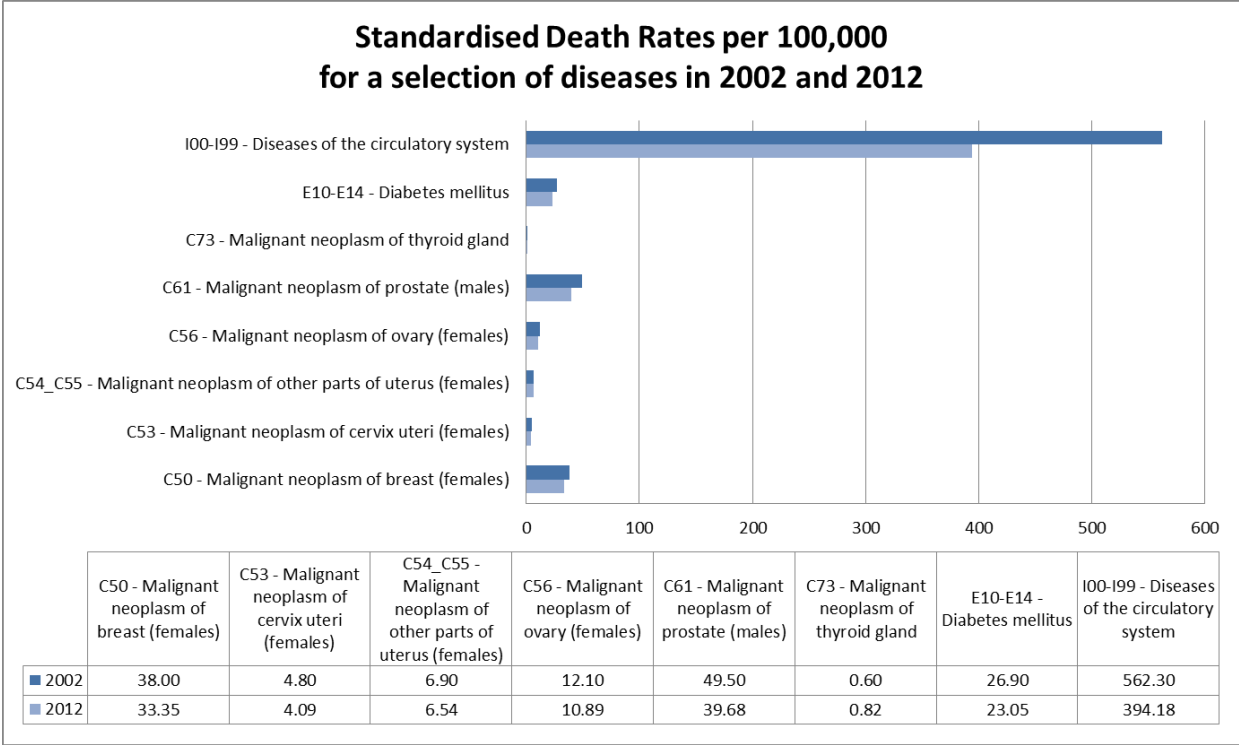


Figure 1. Standardised death Rates per 100,000 for a selection of diseases in 2002 and 2012.

1.1.2. Cancer morbidity, incidence per 100 000 females/males in some Member States (OECD data)

The following OECD data were selected for the analysis of diseases selected on the basis of the concerns raised by the international reports mentioned in Section 1.2 of this annex: malignant neoplasms of female breast, malignant neoplasms of cervix, and malignant neoplasms of prostate.

From 1998 to 2012, the incidence rate of female breast cancer has increased in most Member States (MS) except for Greece and Sweden (Figure 2). Over the same period, the incidence rate of prostate cancer has increased in most MS except for Greece (Figure 3). Decreasing or stable incidence rates of cervical cancer were observed during this period for most MS except for Ireland and Spain (Figure 4). However, as shown in Figure 1, the standardised death rate

²⁷ According to Eurostat; the standardised death rate, abbreviated as SDR, is the death rate of a population adjusted to a standard age distribution. It is calculated as a weighted average of the age-specific death rates of a given population; the weights are the age distribution of that population. Retrieved from: [http://ec.europa.eu/eurostat/statistics-explained/index.php/Glossary:Standardised_death_rate_\(SDR\)](http://ec.europa.eu/eurostat/statistics-explained/index.php/Glossary:Standardised_death_rate_(SDR))

for female breast cancer and prostate cancer decreased. The increase of the incidence of female breast cancer and prostate cancer may be due to better diagnosis tools and/or systems for these diseases over the recent years (which would be also confirmed by the decreased death rate) and not necessarily to exposure to EDs. Further, established known risk factors for breast cancer include: increasing age, family history, exposure to estrogen, genetic predisposition, some breast conditions and lifestyle related factors²⁸. This shows the challenge for establishing any causal link between exposure to EDs and this type of diseases.

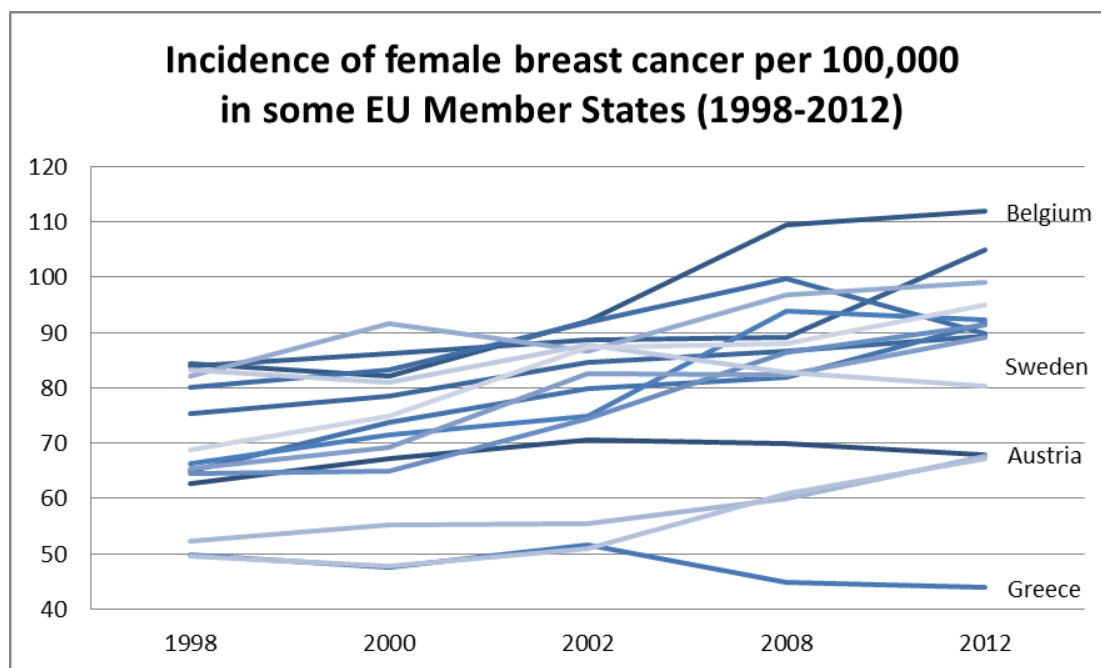


Figure 2. Incidence of female breast cancer per 100,000 in some EU MS (1998-2012)

²⁸ European Commission, JRC. European Network of Cancer Registries Factsheet 2014. Retrieved from: <http://www.enrc.eu/index.php/publications/factsheets>

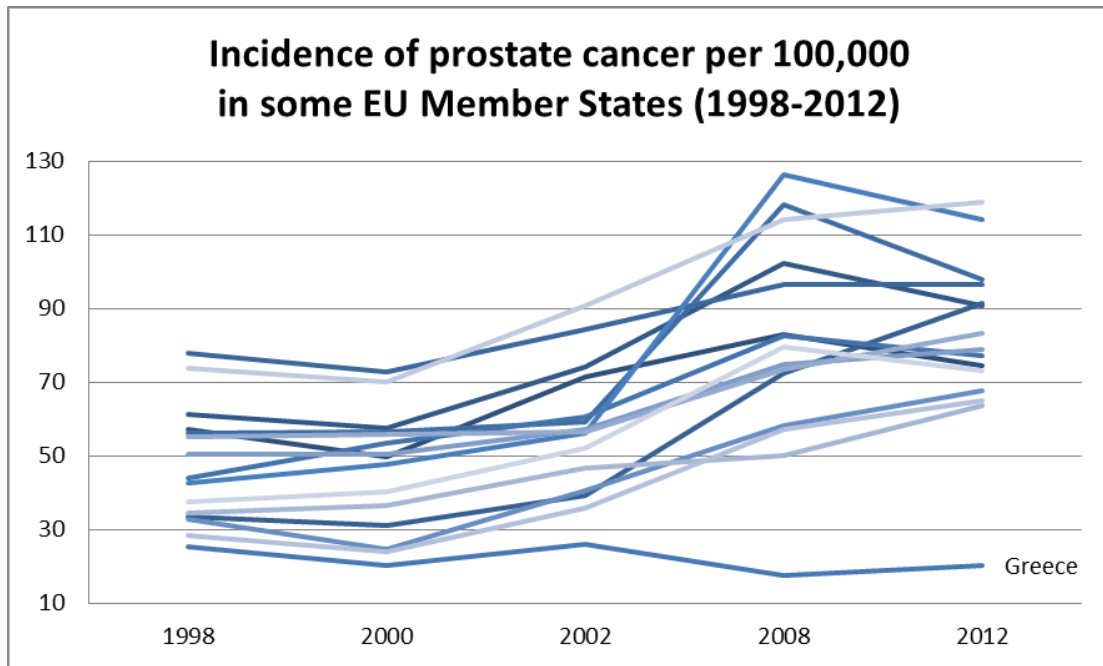


Figure 3. Incidence of prostate cancer per 100,000 in some EU MS (1998-2012)

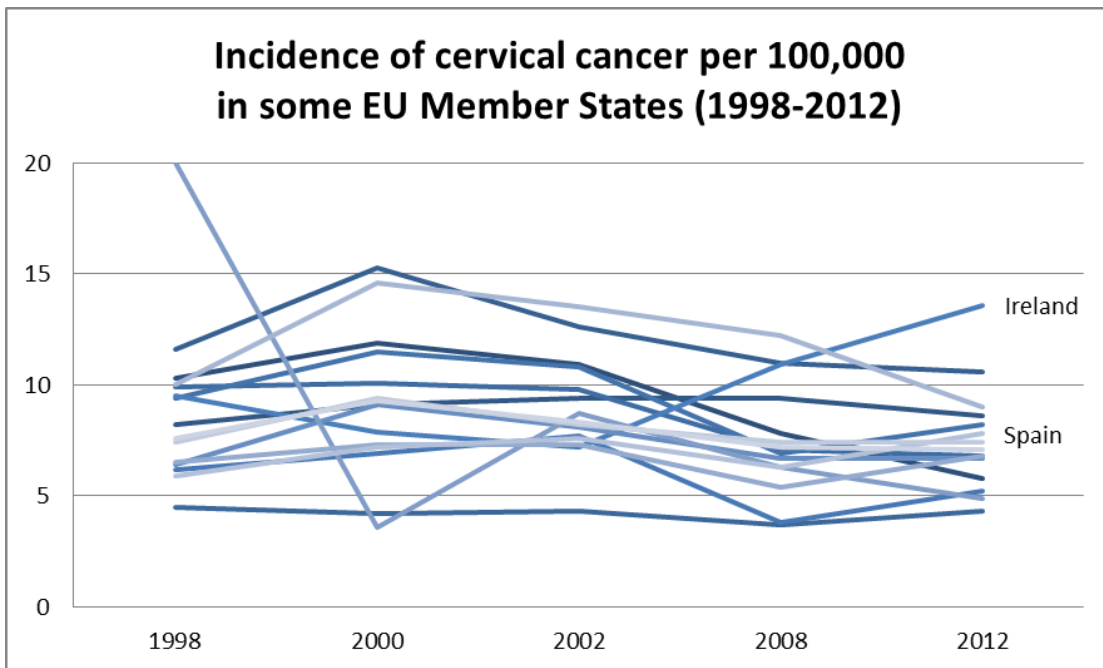


Figure 4. Incidence of cervical cancer per 100,000 in some EU Member States (1998-2012)

1.1.3. Obesity and Body Mass Index (BMI) (OECD data)

As a reference for obesity and BMI, section 2.5 of the OECD-report "Health at a Glance Europe 2014"²⁹ was analysed. It appears that the prevalence of obesity and overweight in

²⁹ OECD. 2014. Health at a Glance: Europe 2014, OECD Publishing. doi 10.1787/23056088

adults and children has increased in the EU over the last decade. The OECD³⁰, the WHO³¹ and MS³² have mainly pointed out socio-economic factors to explain the increase in obesity. For instance, the “Tackling Obesities: Future Choices – Project report”,³² produced by the UK Government’s Foresight Programme in 2007, analyses a multitude of causes of obesity and does not even mention once chemical exposure as a possible driver for obesity. In this report, the Section “Causes of obesity” starts with the chapter “biology” where the following is reported: *Numerous studies involving thousands of people worldwide have failed to find evidence to support the widely held belief that obese people must have slower metabolic rates, either burning energy more slowly than thin people, or being metabolically more efficient. In fact, the converse appears true. Energy expenditure while resting actually increases with body weight, reflecting the metabolic costs of maintaining a larger body size. After adjustment for differences in body size and composition, there is a remarkable similarity in energy expenditure between individuals.*

There is therefore no evidence in these general reports on obesity about a possible impact of exposure to EDs on the observed increased incidence of obesity.

1.1.4. Diabetes (WHO EURO-HFA data)

The prevalence of diabetes mellitus has increased in the EU over the last decade. However, it is not possible to conclude on the link with exposure to EDs as no epidemiological data are available linking exposure to EDs and the incidence of diabetes. Moreover, impact on this increase may be linked to several other factors including increased obesity prevalence and better diagnosis of diabetes

³⁰ OECD. 2014. Obesity Update June 2014. Retrieved from <http://www.oecd.org/health/obesity-update.htm>

³¹ World Health Organization (WHO). 2013. Country profiles on nutrition, physical activity and obesity in the 28 European Union Member States of the WHO European Region. Methodology and summary. Retrieved from <http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/country-work/country-profiles-on-nutrition,-physical-activity-and-obesity-in-the-28-european-union-member-states-of-the-who-european-region.-methodology-and-summary>.

³² Butland B., Jebb S., Kopelman P., et al. 2007. Foresight. Tackling obesity: future choices—project report, Government Office for Science, London. Retrieved from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/287937/07-1184x-tackling-obesity-future-choices-report.pdf.

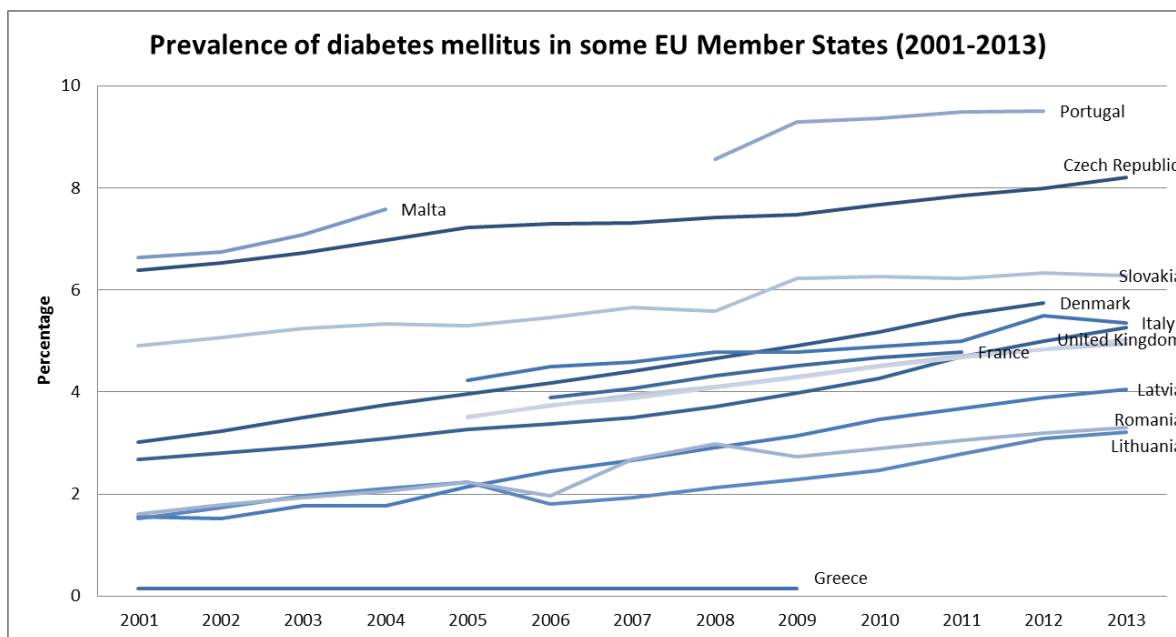


Figure 5. Prevalence of diabetes mellitus in some EU MS (2001-2013)

1.2. Epidemiological and laboratory data on a link between exposure to EDs and “hormone related diseases”

A group of scientists (mainly endocrinologists, most of them affiliated to the Endocrine Society) consider that the increased incidence of certain diseases in humans is at least partially linked to the exposure of environmental levels of EDs to which humans are daily exposed to.

Another group of scientists, mainly toxicologists/pharmacologists, including European Food Safety Authority (EFSA) and EU Scientific Committees, believe that reliable evidence of such possible associations is only available in case of high (occupational, accidental) exposure to certain chemicals.

This controversy is due to disagreement on:

- interpretation of epidemiological data;
- interpretation of laboratory data
- applicability of toxicological principles (e.g. potency of chemicals, shapes of dose-response curves, existence of safety thresholds);

These three topics are briefly explored below.

1.2.1. *Interpretation of epidemiological data*

The WHO-UNEP 2012 report suggests association between chemicals with endocrine disrupting properties and several diseases (e.g. some cancers, female and male reproductive health disorders, thyroid and metabolic disorders, neurodevelopment and immune disorders).

One of the rationales provided in the report for this association is that the increasing incidence of many of these diseases cannot be explained by genetic factors and therefore must be related to environmental factors because the observed increase in diseases incidence occurs in a relatively short timeframe. The report points out that humans and wildlife are daily exposed to some levels of chemicals and that *only a small fraction of these chemicals have been investigated in tests capable of identifying overt endocrine effects in intact organisms*.

The report also acknowledges the difficulties to prove the effective role of EDs exposure in the increasing incidence of what the report describes as “*endocrine diseases and disorders*”. It concludes that adopting primary preventive measures would certainly bring large benefits to human health. The underlying suggestion is that primary preventive measures for the several diseases with high prevalence mentioned in the report (cancers, reproductive disorders, diabetes, obesity, neurological disorders, etc.) means reducing exposure to EDs.

However, primary preventive measures and evidence on associations needs to be considered in a more general context. For instance the likelihood of several other potential environmental factors should be discussed on the basis of evidence.

In this regard, it should be noted that - despite the general difficulties of epidemiological studies in finding causal associations with chronic diseases - epidemiological evidence exists pointing at other factors as causal associations. For instance, the excess of calories in the diet³³, lack of exercise³⁴, or unhealthy diet (e.g. high saturated fat intake or low fruit and vegetable intake³⁵) are associated with chronic diseases including most of the cited *endocrine diseases and disorder*.^{36,37} As regards obesity, for instance, the “Tackling Obesities: Future Choices – Project report”³² analyses a multitude of causes of obesity and does not mention chemical exposure as a possible driver for obesity³⁸. It is worth mentioning that “*only 3.6 percent of Japanese have a body mass index (BMI) over 30, which is the international standard for obesity, whereas 32.0 percent of Americans do*”.^{39,40,41} Considering that low

³³ Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. 2008. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 371:569–578

³⁴ Bull FC, Armstrong TP, Dixon TD, Ham S, Neiman A, Pratt M. 2004. Physical inactivity. In: Ezzati M, Lopez A, Rodgers A, Murray CJL, eds. *Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors*. Geneva, World Health Organization.

³⁵ Boeing H, Dietrich T, Hoffmann K, Pischon T, Ferrari P, Lahmann PH et al. 2006. Intake of fruits and vegetables and risk of cancer of the upper aero-digestive tract: the prospective EPIC-study. *Cancer Causes and Control*. 17:957– 969.

³⁶ World Health Organization (WHO). 2009. *Global Health Risks: mortality and burden of disease attributable to selected major risks*. Retrieved from: http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf

³⁷ Lock K, Pomerleau J, Causer L, McKee M. 2004. Low fruit and vegetable consumption. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL, eds. *Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors*. Geneva, World Health Organization, 597–728.

³⁸ Prentice, A. 2007. Are Defects in Energy Expenditure Involved in the Causation of Obesity? *Short Science Review*. *Foresight Tackling Obesities: Future Choices*. *Obesity Reviews*, 8(s1):89–91. Retrieved from: <http://onlinelibrary.wiley.com/doi/10.1111/j.1467-789X.2007.00325.x/epdf>

³⁹ Senauer B., Gemma M. 2006. Paper presented at the meetings of the International Association of Agricultural Economists. Why Is the Obesity Rate So Low in Japan and High in the US?: Some Possible Economic Explanations. Gold Coast, Australia, 12–18 August. Retrieved from: <https://ideas.repec.org/p/ags/umrfwp/14321.html>

⁴⁰ Senauer B., Gemma M. 2006. Reducing Obesity: What Americans Can Learn from the Japanese. *Choices Magazine*. Retrieved from: <http://www.choicesmagazine.org/2006-4/grabbag/2006-4-12.htm>

levels of chemicals are found in consumer products, food and environment of any developed country, it seems unlikely that this factor has a significant influence on obesity trends, while other factors (e.g. excessive energy intake, decreased energy expenditure, differences in food prices, car ownership, television viewing, and other social factors⁴²) are recognised as main drivers for obesity in most reviews on the subject.³¹

Some epidemiological studies cited in the WHO-UNEP 2012 report refer to diseases associated with relatively high exposure to pesticides. These findings appear in contradiction with the systematic review “Literature review on epidemiological studies linking exposure to pesticides and health effects” published in 2013²³ and with the recent “Agrican cohort study”²⁴, both presented in more detail below.

The EFSA report “**Literature review on epidemiological studies linking exposure to pesticides and health effects**” was carried out applying a systematic review⁴³, which is a highly structured approach to reviewing and synthesising the scientific literature while limiting bias (see also section 1.4 below). A total of 603 epidemiological studies were considered to examine the association between pesticide exposure and a wide spectrum of health outcomes. Most studies pertained to cancer outcomes (N=164) and child health outcomes (N=84), but a large number also to neurological conditions and reproductive diseases. More than half of them examined occupational exposure to pesticides (N=329), i.e. exposure of farmers.

Despite the large volume of available data and the large number (more than 6000) of analyses available, firm conclusions could not be made for the majority of the health outcomes. The review acknowledges important methodological limitations in epidemiological studies, which in some cases are likely to overestimate associations. For instance, the review indicated that the overwhelming majority of evidence came from retrospective case-control analyses or cross-sectional analyses, rather than prospective cohort studies. Case-control and cross-sectional evidence are generally based on self-reported exposure and therefore prone to bias (“recall bias”) in exposure measurement. In retrospective studies misclassification is differential with higher exposures reported in participants with disease (recall bias). Moreover, self-reported exposure to pesticides was defined as “ever” versus “never” use, or as “regular” versus “non-regular” use, adding considerable uncertainty to any outcome. Acknowledging all these limitations and the potential of overestimating exposure to pesticides in participants with diseases (“recall bias”), the review found significant associations with pesticides exposure only for childhood leukaemia and Parkinson's disease. In addition, the review concludes that results should be regarded as *suggestive* of associations *only* and limitations especially regarding the heterogeneity of exposure should always been taken into consideration.

⁴¹ Food and agriculture organization of the United Nations (FAO). 2013. The State of Food and Agriculture 2013. ISSN 0081-4539 Retrieved from: <http://www.fao.org/docrep/018/i3300e/i3300e.pdf>

⁴² Nguyen, D. M., & El-Serag, H. B. 2010. The Epidemiology of Obesity. *Gastroenterology Clinics of North America*, 39(1), 1–7. doi.org/10.1016/j.gtc.2009.12.014

⁴³ European Food Safety Authority. 2010. Application of systematic review methodology to food and feed safety assessments to support decision making. *EFSA Journal* 8(6):1637. [90 pp.] doi:10.2903/j.efsa.2010.1637.

The "Agrican" cohort study²⁴ is a recent epidemiological study carried out in France, which follows since 2005 a cohort of 180.000 participants (88% farmers, 12% working in forestry, landscape gardeners, etc.). In November 2014, the first report was published.

France is the country in the EU with highest overall pesticide use. Cohort studies are the most informative (and most expensive) studies in epidemiology. Differently from other epidemiological studies (e.g. retrospective case-control studies), they allow studying different diseases at the same time. In the Agrican study 40 types of cancers and several other diseases were followed.

Cohort studies allow following groups of people particularly exposed to the risk factors under study (e.g. farmers exposed to certain pesticides). In addition, in cohort studies exposure levels can be measured much more precisely, since participants can be questioned several times on the evolution of their exposure to different substances, so that they have less sources of uncertainty (like e.g. recall bias).

The Scientific Council for this study was composed by members belonging to the International Centre of Research on Cancer (IARC), the French Institute INSERM, the League Against Cancer, the US National Cancer Institute, Paris University, Metz University and the Coordination for the study cohort Agricultural Health Study (AHS). Funding of this study was from French Public Institutes, Farmer Social Security, League Against Cancer, Centre for Fight Against Cancer and Universities.

The results of this study show that farmers have a higher life expectancy than the general population. The report mentions it is now widely accepted that agricultural populations present lower rates of mortality globally and for the main causes of death (cardiovascular diseases, cancer overall).^{44,45,46} This can be largely explained by specificities in farmers' life habits: their lower prevalence of smoking decreases the risk of contracting cardiovascular diseases and some cancers (lung, bladder, pancreas), as their level of physical activity reduces the risk of some other cancers (colon and rectum). Several causes of mortality were followed during the Agrican study, namely tumours, endocrine related diseases (e.g. diabetes), digestive diseases (e.g. cirrhosis), neurological diseases (e.g. Alzheimer, Parkinson), cardiovascular diseases, respiratory diseases, renal and genital diseases, dermatological diseases, bone diseases, infective diseases, accidents, suicides and others.

Considering all together the several causes of mortality followed during this study, mortality was lower compared to the general population of 29% for men and 28% for women, respectively. More in particular, as regards the diseases often referred to as possibly associated to exposure to EDs, mortality was lower among farmers than in the general population for tumours (M: - 30% and F: - 24%), for diabetes and other endocrine related diseases (M: - 33% and F: - 30%), for genital/urinary diseases (M: - 36% and F: - 43%), for neurological diseases (M: - 38% and F: - 39%).

⁴⁴ Blair A, Dosemeci M, Heineman EF . 1993. Cancer and other causes of death among male and female farmers from twenty-three states. *Am J Ind Med* 23:729–742

⁴⁵ Acquavella J, Olsen G, Cole P, Ireland B, Kaneene J, Schuman S et al. 1998. Cancer among farmers: a meta-analysis. *Ann Epidemiol* 8:64–74

⁴⁶ Blair A, Beane Freeman L. 2009. Epidemiologic studies of cancer in agricultural populations: observations and future directions. *J Agromed* 14:125–131

Since mortality depend on incidence and several other factors (e.g. appropriate treatment, early diagnosis, additional risk factors and protective factors), the "Agrican" study also analysed the incidence rates of several type of cancer (other diseases could not be analysed because of the absence of appropriate registers in France).

The review shows that incidence of cancer is higher in farmers than in the general population for following type of cancers: skin melanoma (+26%), myeloma multiple (+26%), lymphoma Hodgkin (F: +19%; M: +38%), lymphoma non-Hodgkin (F: +18%; M: +14%), lips cancer (M: +49%). On the other hand, incidence of cancer is lower in farmers than in the general population for following type of cancers: breast (F: -18%), pancreas (M: -17%), lungs (F: -36%; M: -46%), oral cavity/pharynx (F: -59%; M: -44%), oesophagus (M: -28%), larynx (M: -50%), liver (M: -24%), mesothelioma (M: -62%), colon (M: -13%), rectum (M: -20%), bladder (M: -38%).

Considering that farmers are generally exposed to higher levels of pesticides than the general population – including pesticides which may be identified as EDs - the results of the Agrican study suggest no link between exposure to EDs in the EU and onset of hormone related cancers (e.g. breast, prostate, testis cancer).

A large prospective cohort study, the Agricultural Health Study (AHS)⁴⁷ has been conducted in the USA since the beginning of the 1990s. It has enrolled around 90 000 individuals including more than 50 000 active farm owners using pesticides in two states where agriculture is mainly devoted to open field and livestock. This large prospective North American cohort is part of a newly established International Consortium for Agricultural Cohorts (AGRICOH) coordinated by the National Cancer Institute and the International Agency for Research on Cancer. The consortium now includes 26 prospective cohorts from 12 countries. The AGRICAN study is included in AGRICOH.

1.2.2. Interpretation of laboratory data

As regards interpretation of laboratory data, there is some disagreement among scientists on which evidence would be sufficient to identify a substance as an ED. The authors of the 2nd Endocrine Society Scientific Statement⁴⁸ endorse a definition of an ED which is not widely agreed, as it does not explicitly refer to an adverse effect (an ED is “*an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action*”).

Differently, the WHO/IPCS 2002 definition of an ED is widely agreed among toxicologists, pharmacologists and it was endorsed for instance by the EFSA Scientific Opinion 2013⁴⁹, the

⁴⁷ Alavanja MC, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF et al. 1996. Characteristics of pesticide use in a pesticide applicator cohort: the Agricultural Health Study. *Environ Health Perspect* 104: 362–369

⁴⁸ Gore A.C., Chappell V.A., Fenton S.E., Flaws J.A., Nadal A., Prins G.S., Toppari J., Zoeller R.T. 2015. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals, *Endocr Rev*. 36(6):E1-E150. DOI: 10.1210/er.2015-1010

⁴⁹ 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.

JRC report 2013⁵⁰, Kortenkamp report 2011⁵¹ (an ED 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*”).

The results of laboratory data are interpreted differently depending on whether or not an observed adverse effect is considered necessary to identify an ED. Even when agreeing on the WHO/IPCS 2002 definition of an ED, the interpretation of laboratory data can vary depending on what is considered an adverse effect, considering that the definition does not better specify it. In the EFSA Scientific opinion 2013 it is indicated that scientific criteria for assessment of adversity have not been generally defined. In this opinion it is concluded that it is difficult to propose ED-specific criteria for adversity and expert judgement in a weight-of-evidence approach is needed to assess substances for possible endocrine disrupting properties. Finally, an additional source for different views is the extrapolation from high doses, as typically used in laboratory animals, to the lower levels of exposure of humans in practice. As mentioned above, endocrinologists often refer to non-monotonic dose-response curves for EDs and therefore do not support the generally accepted principle of risk assessment where extrapolations are done to estimate exposures and effects from high to low doses.

1.2.3. Toxicological principles (e.g. existence of safety thresholds, potency of chemicals, shapes of dose-response curve, low dose effects)

The scientific debate on safety thresholds, non-monotonic dose-response curves, "window of vulnerability" and the impact of exposure to relatively low levels of EDs is on-going. As mentioned before, some scientists believe that the increased incidence of certain diseases in humans is at least partially linked to the low doses (low environmental levels) of EDs, while others believe that evidence of such possible associations is only available in case of high (occupational, accidental) exposure to certain chemicals.

This controversy is also reflected in ongoing discussions on some other issues: e.g. EDs to be treated differently from other chemicals, threshold/no threshold, windows of susceptibility, non-monotonic response curves. This issue was also addressed in the "meeting with the former Chief Scientific Advisor of the European Commission Ms Ann Glover⁵²", but has not yet been settled as shown in the conference "Endocrine disruptors: criteria for identification and related impacts" (1st June 2015, Brussels)⁵³ organised by the European Commission, where different scientific views were presented. Further, on the occasion of an expert conference organised by the German Federal Institute for Risk Assessment (BfR), held in

⁵⁰ Munn S., Goumenou M-P., 2013. Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances - Report of the Endocrine Disruptors Expert Advisory Group. JRC-IHCP [29pp.] DOI: 10.2788/8659 (online). Retrieved from: <http://publications.jrc.ec.europa.eu/repository/bitstream/JRC79981/lbna25919enn.pdf>

⁵¹ Kortenkamp, A., Martin, O., Faust, M., Evans, R., McKinlay, R., Orton, F., Rosivatz, E., 2011. State of the art assessment of endocrine disruptors. Final Report. Retrieved from: http://ec.europa.eu/environment/chemicals/endocrine/pdf/sota_edc_final_report.pdf

⁵² European Commission. 2013. Minutes of the expert meeting on endocrine disruptors. Retrieved from <http://sciences.blogs.liberation.fr/files/glover-u-s-perturbateurs-endocriniens.pdf>

⁵³ European Commission. 2015. Conference "Endocrine disruptors: criteria for identification and related impacts". Retrieved from: http://ec.europa.eu/health/endocrine_disruptors/events/ev_20150416_en.htm

Berlin in April 2016, a consensus statement on “Scientific principles for the identification of endocrine disrupting chemicals” was signed by the 23 internationally renowned scientists present at the conference. Among other things, the document produces lists the criteria for identifying the hazard potential of harmful endocrine substances. It also indicates that the assessment of the corresponding risks from endocrine disruptors on human health and wildlife would further require consideration of dose-response relationships, including potency, exposure assessment, and risk characterization, including susceptible sub-populations, severity and reversibility of effects.

Some key toxicological principles where there seems to be disagreement between toxicologists and endocrinologist are explained below. They are relevant to the assessment and regulation of EDs.

Are EDs different from other chemicals? Can safety thresholds be set?

Endocrinologists believe EDs should be treated differently from most other chemicals because of their MoA, and that in particular no safety threshold can be identified for them.

Toxicologists argue that EDs represent chemicals with different kind of effects (some of which already regulated by the legislation) and various endocrine-mediated modes of action, so that the entire class cannot be assimilated to a single one. They add further that when assessing and managing the risk posed by a chemical, it is the effective possibility that an adverse effect is produced that is ultimately important, and not the MoA through which an effect may eventually, possibly occur. Toxicologists generally contest that no safety threshold can be set. If this would be assumed, even the lowest/negligible exposure would imply a regulatory action, although no risk to human health and the environment could be identified.

Are windows of susceptibility, non-monotonic dose-response curves, mixture effects aspects specific to endocrine disruption?

The concept of windows of susceptibility (e.g. foetal exposure) is central to the “no threshold concept” for EDs. The “no threshold concept” is also related to the claimed presence of “non-monotonic dose-response curves” for EDs, meaning that effects may be higher at low doses than at higher doses of the chemical. Endocrinologists also often refer to the fact that mixtures of chemicals are not yet considered in the regulatory assessment and that this may underestimate risks, particularly for what concern EDs.

The “State of the Art Assessment of Endocrine Disrupters” report⁵⁴ commissioned through public procurement by the European Commission, considers critical windows of susceptibility a key issue for EDs. However, the European Food Safety Authority⁵⁵ and the Scientific

⁵⁴ Kortenkamp, A., Martin, O., Faust, M., Evans, R., McKinlay, R., Orton, F., Rosivatz, E., 2011. State of the art assessment of endocrine disrupters. Final Report. Retrieved from:

http://ec.europa.eu/environment/chemicals/endocrine/pdf/sota_edc_final_report.pdf

⁵⁵ 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

Committee for Consumer Safety⁵⁶ stated that mixtures, windows of susceptibility and non-monotonic dose-response curves are general issues applicable to all chemicals (and not specific to EDs) and that “*EDs can therefore be treated like most other substances of concern for human health and the environment, i.e. be subject to risk assessment and not only to hazard assessment*”.

Potential mixture effects are indeed not yet addressed in any legislation in the EU or elsewhere, although extensive research is growing on this topic, including also research projects funded by the European Commission, such as the four-year projects EDC-MixRisk⁵⁷ and EuroMix⁵⁸ financed through the Programme Horizon 2020. As regards regulatory action, the PPP sector is pioneering on this work, as EFSA is developing a methodology to consider cumulative risk of pesticide residues in food products.⁵⁹

It is however worth mentioning that in vivo evidence continues to accumulate that additional effects are absent at low doses/concentrations, which is consistent with pharmacological theory.^{60,61,62}

Low doses effects or thresholds of adversity for EDs like for other chemicals?

Toxicologists and pharmacologists generally agree that the statement from Paracelsus is still valid (*‘All compounds are poisons, it is the dose that makes the compound not a poison’*), implying that up to a threshold of adversity, the body can effectively neutralise hazards through homeostatic mechanisms.⁶³ This is reflected in the fact that it is generally agreed that no adversity in humans can be expected up to a certain threshold of exposure. It is also common practice for all chemicals to consider that threshold levels are different depending on the chemical and on the susceptibility of the individual or group of population exposed (depending on age, sex, physical status, medical treatment, etc.). A wealth of experience with thousands of chemicals evaluated in animal studies for reproductive hazard and risk

effects mediated by these substances on human health and the environment. EFSA Journal 2013;11(3):3132. doi: 10.2903/j.efsa.2013.3132.

⁵⁶ European Commission 2014. Scientific Committee on Consumer Safety. Memorandum on Endocrine Disruptors. Retrieved from:

http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_009.pdf

⁵⁷ EDC-MixRisk: safe chemicals for future generations. Information available on:

<http://edcmixrisk.ki.se/aboutedcmixrisk/>

⁵⁸ EuroMix: a tiered strategy for risk assessment of mixtures of multiple chemicals. Information available on:

<http://www.euromixproject.eu/>

⁵⁹ EFSA. 2016. Pesticides: breakthrough on cumulative risk assessment. Retrieved from:

<http://www.efsa.europa.eu/en/press/news/160127>

⁶⁰ Gerhard J. Nohynek, Christopher J. Borgert, Daniel Dietrich, Karl K. Rozman, 2013. Endocrine disruption: Fact or urban legend?, Toxicology Letters. 223 (3): 295-305, ISSN 0378-4274. doi.org/10.1016/j.toxlet.2013.10.022.

⁶¹ C.J. Borgert, E.V. Sargent, G. Casella, D.R. Dietrich, L.S. McCarty, R.J. Golden. 2011. The human relevant potency threshold: Reducing uncertainty by human calibration of cumulative risk assessments, Regulatory Toxicology and Pharmacology. 62 (2): 313-328, doi.org/10.1016/j.yrtph.2011.10.012.

⁶² Lorenz R. Rhomberg, Julie E. Goodman. 2012. Low-dose effects and nonmonotonic dose-responses of endocrine disrupting chemicals: Has the case been made?, Regulatory Toxicology and Pharmacology. 64(1): 130-133. doi.org/10.1016/j.yrtph.2012.06.015

⁶³ This is applicable for most substances. For few substances (mutagen and/or genotoxic substances) this is assumed not to be the case.

identification corroborates that threshold of adversity exists also for foetuses exposed to chemicals in utero. The threshold dose approach used so far in the risk assessment of reproductive toxicants⁶⁴ can be therefore considered as justified.

Most toxicologists consider that when low-dose adverse effects were observed in laboratory animals exposed to certain endocrine active agents, the findings could not be replicated. The validity and toxicological significance of many of these observations has therefore not yet been determined.⁶⁵

The Kortenkamp report discusses the fact that the existence of thresholds for EDs is highly debated and not yet solved, mainly due to issues relating to reproducibility. Confounding issues are also discussed as important, since *thresholds are obscured at population level by inter-individual variations in sensitivity and by background exposures*. The report concludes that as regards endocrine disruption, because of pre-existing internal exposures to hormones, even low doses of an ED would add to the effect of the internal background, with no threshold. This concept was however contested by one group of experts in the meeting with the European Commission Chief Scientific Advisor Anne Glover in October 2013 (see published minutes, p.2⁶⁶).

The EFSA Opinion 2013 indicated that safe doses/concentrations of EDs can be established if:

1. follow up of exposure at critical windows of susceptibility to later life stages is addressed; and
2. all available information is used in a weight of evidence approach.

Potency of chemicals and other elements of hazard characterisation (severity, specificity and irreversibility of effect, lead toxicity).

Endocrinologists generally refuse considering potency for identification of EDs. They believe that no prioritisation of EDs of higher concern can be set, since even low doses of a low potent ED may pose a danger to specific groups of population.

Toxicologists believe that risk assessment should consider potency together with exposure levels. Indeed, natural or synthetic (i.e. man-made) hormones (e.g. the oral contraceptive ethinylestradiol) are 10,000 to 1,000,000 fold more potent than other man-made chemicals used for other purposes which have an estrogenic activity. This needs to be taken into account when assessing the risk posed by chemicals. For instance (see Table 2): if the potency of daidzein (a natural chemical in soy-beans) is similar to the one of bisphenol A, but the daily intake of the latter is 1000 times lower, the risk posed by bisphenol A to humans is likely to be orders of magnitude lower than the one posed by daidzein. Similarly, if the potency of

⁶⁴ Piersma, A.H., et al. 2011. Reproductive toxicants have a threshold of adversity. Critical reviews in Toxicology 41(6) 545-554. doi: 10.3109/10408444.2011.554794

⁶⁵ Kroes, R., et al. 2004. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food and Chemical Toxicology 42: 65–83. doi:10.1016/j.fct.2003.08.006

⁶⁶ European Commission. 2013. Minutes of the expert meeting on endocrine disruptors. Retrieved from: <http://sciences.blogs.liberation.fr/files/glover-u-s-perturbateurs-endocriniens.pdf>

ethinyloestradiol is 100000 higher than the one of butylparaben, this needs to be considered when comparing the risks posed by the two chemicals.

Table 2. Calculations of Hygiene-Based Margins of Safety (HBMOS) for environmental oestrogens⁶⁷

SUBSTANCE	DAILY INTAKE	RELATIVE POTENCY	HBMOS ⁶⁸
Daidzein	1 mg/kg bw	1	1
Nonylphenol	2 µg/kg bw	2	250
Bisphenol A	1 µg/kg bw	1	1000
Ethinyloestradiol	0.5 µg/kg bw	40.000	0.05
Butylparaben	0.1 mg/kg bw	0.4	24

The Kortenkamp report considers that EDs should be identified according to the 2002 WHO-IPCS definition and using a weight of evidence approach which considers all the elements of hazard characterisation together, i.e. potency together with other factors such as severity, lead toxicity, specificity of effect and irreversibility. Rigid potency-based cut-off values as decisive decision criteria are not recommended. The EFSA Opinion on EDs 2013 indicated that to inform on a level of concern for EDs, severity, irreversibility and potency should be evaluated in relation to degree, timing and duration of exposure, i.e. using risk assessment.

In summary, the available relevant reports indicate that:

- There is consensus on the WHO/IPCS definition (2002) for identifying ED
- There are different endocrine modes of actions. Four modalities (pathways) are relatively well known and internationally agreed tests exist (the estrogen, androgen, thyroid and steroidogen modalities). There are other modalities which are not yet well known and for which no internationally agreed tests exist. For these modalities, still under discussion, science is under development and there is no consensus on the extent of evidence (e.g. diabetes) available.
- There is no consensus on the relevance of some scientific aspects for regulatory decision making (e.g. non-monotonic dose response curve, low dose effects and existence of safety thresholds for EDs), but a recent EU review on the empirical evidence and the BfR consensus statement mentioned above indicate that the evidence for this kind of curves is weak for most in vivo data.
- There is consensus that the assessment of potential risks from ED on human health and the environment would require consideration of dose-response relationships, exposure assessment, and risk characterisation (risk assessment).

⁶⁷ Bolt HM, Janning P, Michna H, Degen GH. 2001. Comparative assessment of endocrine modulators with oestrogenic activity: I. Definition of a hygiene-based margin of safety (HBMOS) for xeno-oestrogens against the background of European developments. Archives of Toxicology. 74: 649-662. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/11218041>

⁶⁸ HBMOS are defined as hygiene-based margin of safety in Bolt et al. 2001.

1.3. Regulation of active substances used in PPP and BP which are identified as EDs

The suggestion in the WHO-UNEP 2012 report that introducing primary preventive measures to reduce exposure to EDs contributes to a health effect is true in general terms. However, the statement is not considering the particular situation for the chemical active substances used in plant protection products (PPP) or biocidal products (BP) in the EU.

The PPP Regulation and BP Regulation are among the strictest chemicals regulations worldwide and they are underpinned by the precautionary principle as stated in recitals of these regulations.^{69;70} The EU authorisation system for PPP and BP is based on prior approval ("positive list") shifting responsibility for producing scientific evidence (burden of proof) to the business community. In other words, it is up to applicants asking for approval of a substance to produce studies and information demonstrating the substance can be safely used. The dossier will be then evaluated by Competent Authorities first at EU level and then also at national level. Only substances present on the positive list agreed at EU level can be used in PPP or BP placed on the EU market, provided they also pass the second step of national authorisation of the formulated products. The EU legislation in place implies that both PPP and BP are among the most "data rich" regulated product groups in the EU. Under both regulations, a detailed list of exhaustive data^{71;72} has to be submitted by the applicant before any approval of active substance or authorisation of a product containing the approved substances can be considered. These core data requirements include in vivo animal studies able to detect most adverse effects even in the second generation (offspring of treated animals).

It should be noted that in most cases where convincing evidence is presented in the WHO-UNEP 2012 for pesticides with endocrine disrupting properties, this is related to substances that are not anymore approved in the EU for use in PPP since years (e.g. DDT, vinclozolin, methoxychlor) (see Table 3). In particular, the report refers in total to 44 non-approved PPP and 14 approved PPP (among the 14 approved PPP, some are close to the renewal decision). The report also refers in total to three non-approved biocidal products (triphenyltin, tributyltin and triclosan), five approved (fenoxycarb, fipronil, permethrin, iodine, pyriproxyfen) and two under review (formaldehyde and linuron).

The WHO-UNEP 2012 report also refers to some epidemiological studies showing possible association between exposure to pesticides and rise in chronic diseases. Those studies in most cases refer to pesticides already banned in the EU: e.g. atrazine cited as associated to ovarian

⁶⁹ Article 1.4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309.

⁷⁰ Article 1.1 of Regulation (EU) No 528/2012 of the European Parliament and of the Council concerning the making available on the market and use of biocidal products. OJ L 167/1.

⁷¹ Regulations EU 283/2013 and EU 284/2013, setting data requirements for active substances and for PPP, respectively; Communications 2013/C 95/01 and 2013/C 95/02, detailing the list of test methods and guidance documents for active substances and for PPP, respectively.

⁷² 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. Official Journal of the European Union, L 167, 27 June 2012. doi:10.3000/19770677.L_2012.167.eng

cancer; dicofol cited as associated to higher incidence of early childhood leukaemia; phorate cited as associated to prostate cancer.

Table 3. Pesticides mentioned as EDs in the WHO-UNEP 2012 report but already removed from the EU market based on Directive 91/414/EC and Directive 79/117/EC⁷³

ACTIVE SUBSTANCE	BANNED SINCE	CLASS OR USE
methyl bromide	2011	fumigant pesticide
chlozolinate	2000	fungicide
hexachlorobenzene	2004/1979*	fungicide
procymidone	2006	fungicide
tributyltin (3AS)	2002	fungicide
trichlorophenate (derivative of 2,4,5-T)	1993**	fungicide
triphenyltin (fentin)	2002	fungicide
vinclozolin	2005	fungicide
2,4,5 T	2002	herbicide
acetochlor	2008	herbicide
alachlor	2006	herbicide
atrazine	2004	herbicide
bromacil	2002	herbicide
butylate	2002	herbicide
ethylene thiourea	1993**	herbicide
pentachloronitrobenzene (quintozene)	2000	herbicide
prodiamine (dithiopyr)	1993	herbicide
simazine	2004	herbicide
thiazopyr	2002	herbicide
pentachlorophenol	2002	herbicide, fungicide
carbaryl	2007	insecticide
coumpahos	1993	insecticide
permethrin	2000	insecticide
desethylatrazine	2004	metabolite atrazine ***
oxychlordane	2004	metabolite chlordane ***
heptachlor epoxide	2004/1979*	metabolite heptachlor***
2,4'-DDD	1993**	organochlorine insecticide
2,4'-DDT	1993**	organochlorine insecticide

⁷³ Council Directive 79/117/EEC of 21 December 1978 prohibiting the placing on the market and use of plant protection products containing certain active substances. OJ L 33, 8.2.1979, p. 36–40 (DA, DE, EN, FR, IT, NL). <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:31979L0117>

ACTIVE SUBSTANCE	BANNED SINCE	CLASS OR USE
4,4'-DDD	1993**	organochlorine insecticide
4,4'-DDE	1993**	organochlorine insecticide
4,4'-DDT	1993**	organochlorine insecticide
chlordane	2004/1979*	organochlorine insecticide
chlordecone (kepone)	2004	organochlorine insecticide
DDT	2004/1979*	organochlorine insecticide
dicofol	1979	organochlorine insecticide
dieldrin	2004/1979*	organochlorine insecticide
endosulfan	2005	organochlorine insecticide
endrin	2004/1979*	organochlorine insecticide
heptachlor	2004/1979*	organochlorine insecticide
lindane	2000	organochlorine insecticide
methoxychlor	2002	organochlorine insecticide
mirex	2004	organochlorine insecticide
nonachlor (trans and cis chlordane)	2004	organochlorine insecticide
toxaphene (campechlor)	1979	organochlorine insecticide
fenitrothion	2007	organophosphate insecticide
fonofos	2002	organophosphate insecticide
parathion	2001	organophosphate insecticide
phorate	2002	organophosphate insecticide
dibromochloropropane (DBCP)	1993**	pesticide/soil fumigant
* = banned in principle in 1979, with few exceptional uses left on the market		
** = not on the EU market since at least 1993: were never notified for assessment under the EU review program		
*** = date of ban equivalent of the one of the parent compound		

Also the 1st and 2nd Statements of the Endocrine Society (2009²⁰, 2015^{74,75}), which conclude that “*the evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong, and there is mounting evidence for effects on other endocrine systems, including thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis.*”, refer to pesticides where evidence for

⁷⁴ Gore, A.C., et al. 2015. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocrine Reviews* 36 (6) doi.org/10.1210/er.2015-1010

⁷⁵ Gore, A.C., et al. 2015. Executive Summary to EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocrine Reviews*, 36(6):593–602. doi: 10.1210/er.2015-1093

endocrine disrupting properties exists (e.g. atrazine, DDT) but which are already banned in the EU.

In addition, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) published in 2014 an Opinion⁷⁶ analysing the French National Institute for Health and Medical Research (INSERM) collective expert appraisal report “Pesticides. Health effects” on the health effects of pesticides, biocides and PPP. This Opinion points out that *the vast majority of substances identified by the INSERM report as having a presumed moderate or strong association with the occurrence of health effects concern substances that are now prohibited* in the EU. The Opinion concludes that among substances authorised for use in the EU, only for seven substances a presumed association with one or more health outcomes was observed.

It can be concluded that many of the active substances used in pesticides referred to in international studies and reports as EDs are not anymore approved in the EU. This shows that the past and current EU regulatory framework has been able to identify hazardous chemicals and ban them based on the risk of the occurrence of unacceptable adverse effects to human health, even if they were not specifically identified as EDs.

1.4. New methodological developments

1.4.1. Validated test methods and test guidelines

The “State of the Art Assessment of Endocrine Disrupters” report⁷⁷ commissioned through public procurement by the European Commission, maps ways of addressing EDs in EU chemicals legislation (e.g. PPP Regulation, BP Regulation, REACH). It stated that the data required in EU chemicals regulation did not capture the range of endocrine disrupting effects that can be measured with internationally agreed and validated test methods.

Methods are currently under development at OECD⁷⁸, both for in-vivo and in-vitro tests. Adverse outcome pathways (AOP)⁷⁹ are also under development and may provide a useful tool for understanding the endocrine MoA. An AOP is a structured representation of biological events leading to adverse effects. It links existing knowledge along one or more series of causally connected key events, connecting a molecular initiating event with an adverse outcome that occur at a level of biological organisation relevant to risk assessment. The linkage between the events is described by key event relationships that describe the causal relationships between the key events. AOPs increase the use of mechanistic

⁷⁶ ANSES Opinion. 2014. OPINION of the French Agency for Food, Environmental and Occupational Health & Safety on the INSERM collective expert appraisal report “Pesticides. Health effects”. Request No. 2013-SA-0116. Retrieved from <https://www.anses.fr/en/system/files/PHTO2013sa0116EN.pdf>

⁷⁷ Kortenkamp, A., Martin, O., Faust, M., Evans, R., McKinlay, R., Orton, F., Rosivatz, E., 2011. State of the art assessment of endocrine disrupters. Final Report. Retrieved from: http://ec.europa.eu/environment/chemicals/endocrine/pdf/sota_edc_final_report.pdf

⁷⁸ OECD. 2016. OECD Work Related to Endocrine Disrupters. Retrieved from: <http://www.oecd.org/env/ehs/testing/oecdworkrelatedtoendocrinedisrupters.htm>

⁷⁹ OECD. 2016. Adverse Outcome Pathways, Molecular Screening and Toxicogenomics. Retrieved from: <http://www.oecd.org/env/ehs/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm>

toxicological data for risk assessment and regulatory applications. EFSA and ECHA recognised the importance of these tools for risk assessment.^{80,81}

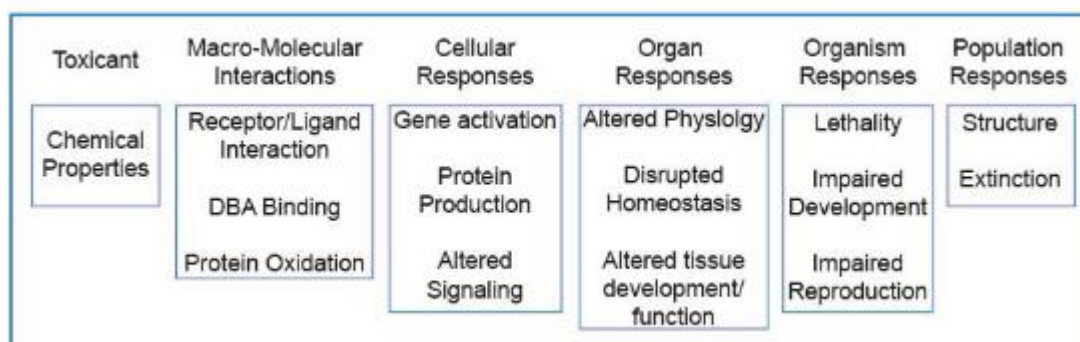


Figure 6. Schematic representation of the Adverse Outcome Pathway (AOP) illustrated with reference to a number of pathways.⁸²

These developments are followed by the European Commission closely and current data requirements are updated where needed. For instance, the PPP data requirements have been updated in 2013, including updated test guidelines which also consider ED (Regulations 283/2013 and 284/2013 and the respective Communications 2013/C 95/01 and 2013/C 95/02 listing relevant test methods and guidance documents), as for example the extended one-generation reproduction study (Test Guideline 443). This Test Guideline is able to detect serum thyroid hormone and thyroid-stimulating hormone levels following exposure during critical stages of development, as well as developmental neurotoxicity and immunotoxicity endpoints.

However, regarding the different "axes" or "modalities" of endocrine MoA for which methods are available, the EFSA Opinion 2013 highlights that a reasonably complete suite of standardised assays for testing the effects of EDs is currently available only for the estrogenic, androgenic, thyroid and steroidogenic (EATS) "modalities" of the endocrine system.

This is also reflected in the Kortenkamp report, which illustrates that the level of information differs among the different endocrine modalities. For instance, it considers that, for male reproductive health, there is a good coherent mechanistic evidence for explaining how ED may interfere with male reproductive development. The same is not true for female reproductive health, where an adequate mode for most female reproductive diseases is lacking, due to critical differences between rodents and humans. Overall, the current state of

⁸⁰ European Food Safety Authority, 2014. Modern methodologies and tools for human hazard assessment of chemicals. EFSA Journal 2014;12(4):3638, 87 pp. doi:10.2903/j.efsa.2014.3638

⁸¹ ECHA. New web platform available on adverse effects of chemicals. http://echa.europa.eu/view-article/-/journal_content/title/new-web-platform-available-on-adverse-effects-of-chemicals

⁸² OECD. 2016. Adverse outcome pathways, molecular screening and toxicogenomics. "What is an adverse outcome pathway". Retrieved from: <http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm>

knowledge prevents the establishment of a clear causal link between an endocrine MoA and an adverse effect for most endpoints in female reproductive health.

As regards "hormonal cancers", the Kortenkamp report refers that no suitable animal model is available for prostate, testis, or thyroid cancers. However, the Kortenkamp report supports the "plausibility" of a role for exposure to EDs in breast, prostate, testicular and to some extent thyroid cancers.

The Kortenkamp report also mentions that for metabolic disorders such as obesity, scientific interest is very novel and test methods are still unable to detect endpoints related to these disorders.

The EFSA Opinion on EDs points out that in principle, no single assay currently available or under development is likely to provide all the information needed to decide whether a substance is an ED (according to the WHO/IPCS definition endorsed by the EFSA Opinion). This is because of the need to provide both mechanistic information showing how the substance interacts with the endocrine system, and apical information⁸³ describing the adverse effects this interaction may cause.

1.4.2. Evidence-based toxicology (EBT) and systematic reviews

Further relevant methodological developments are **evidence-based toxicology (EBT)** and **systematic reviews** in general.

A systematic review is a highly structured approach to reviewing and synthesising the scientific literature while limiting bias. The method has been developed and is successfully applied since early '90s in evidence based medicine by associations like Cochrane⁸⁴. The steps to carrying out a systematic review include – before starting the review itself - framing the question to be addressed; appraising and deciding how relevant studies will be identified and retrieved; determining if any studies need to be excluded from the analysis; and deciding how the included studies will be appraised in terms of their quality and risk of bias. Ultimately the data will be synthesised across studies, often by a meta-analysis. A protocol of how the review will be conducted is prepared as first step and is often peer reviewed before the review starts.

⁸³ Definition of apical endpoint: *Traditional, directly measured whole-organism outcomes of exposure in in vivo tests, generally death, reproductive failure, or developmental dysfunction. Observable effects of exposure to a toxic chemical in a test animal. The effects reflect relatively gross changes in animals after substantial durations of exposure. An observable outcome in a whole organism, such as a clinical sign or pathologic state, that is indicative of a disease state that can result from exposure to a toxicant.* Definition available in: Appendix I. OECD Collection of Working Definitions 2012. Retrieved from: <http://www.oecd.org/chemicalsafety/testing/49963576.pdf>

⁸⁴ Cochrane is a global independent network of researchers, professionals, patients, carers, and people interested in health, Cochrane exists so that healthcare decisions get better. During the past 20 years, Cochrane has helped to transform the way health decisions are made, by gathering and summarising the best evidence from research to help you make informed choices about treatment. See Cochrane website: <http://www.cochrane.org>

EFSA has recently issued guidance in order to apply this methodology also in a food safety context and for PPP.^{85;86} Also the emerging discipline of evidence-based toxicology (EBT) is calling for this kind of reviews. Researchers using systematic reviews to address toxicological concerns include the non-profit Evidence-based Toxicology Collaboration (EBTC).⁸⁷

These developments are particularly important considering the need of a weight of evidence approach, suggested also by Kortenkamp. The Kortenkamp report considers that EDs should be identified according to the 2002 WHO-IPCS definition⁸⁸ and using a weight of evidence approach which considers all the elements of hazard characterisation together, i.e. potency together with other factors such as severity, lead toxicity, specificity of effect and irreversibility. This view to apply a weight-of-evidence approach was also advised in the EFSA 2013 report on EDs. The Scientific Committee concluded that all the available information on adversity and endocrine activity should be considered together, by adopting a weight-of-evidence approach.

2. ESTIMATION OF DISEASE COSTS RELATED TO EXPOSURE TO ENDOCRINE-DISRUPTING CHEMICALS

The analysis of the economic impact of ill-health, which can be considered distinct but complementary to the clinical or epidemiological approaches to disease burden, has been mainly carried out by using some variant of the Cost-of-Illness (COI) methodology, first formalised in the mid-1960s⁸⁹, though macroeconomic growth models have increasingly been used to better understand the dynamic and multifaceted nature of losses at the societal level⁹⁰.

The aim of COI studies is to assess the economic burden that a specific health problem (or groups of health conditions) imposes on a society, usually with respect to the utilisation of health care resources and productivity losses. This is done by identifying and measuring all the costs of a particular disease, including the direct, indirect, and intangible dimensions, and expressing the output in monetary terms.

COI studies can be described according to the following three dimensions:⁹¹

- a. the epidemiological data used: prevalence versus incidence approach;
- b. the methods chosen to estimate the economic costs: top down versus bottom-up;

⁸⁵ European Food Safety Authority; Application of systematic review methodology to food and feed safety assessments to support decision making. EFSA Journal 2010; 8(6):1637. doi:10.2903/j.efsa.2010.1637.

⁸⁶ European Food Safety Authority; Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092.

⁸⁷ See Evidence-based Toxicology Collaboration website <http://www.ebtox.com/>

⁸⁸ WHO/IPCS. 2002. Definition of an Endocrine Disruptor: *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.*

⁸⁹ Rice D.P. 1967. Estimating the Cost of Illness. Washington, DC: US Department of Health, Education, and Welfare, Public Health Services, 1966. Rice D.P. Estimating the cost of illness. Am J Public Health Nations Health 57(3):424-40. DOI <http://dx.doi.org/10.2105/AJPH.57.3.424>

⁹⁰ WHO. 2009. WHO guide to identifying the economic consequences of disease and injury, Geneva (App. C).

⁹¹ Tarricone R. 2006. Cost-of-illness analysis. What room in health economics? Health Policy 77(1):51-63. DOI <http://dx.doi.org/10.1016/j.healthpol.2005.07.016>

- c. the temporal relationship between the initiation of the study and the data collection: retrospective versus prospective studies.

Prevalence-based approaches estimate the direct and indirect economic burden to society incurred during a period of time (the base period, usually a year) as a result of the prevalence of the disease. This approach measures the value of resources used or lost during that specified period of time, irrespective of the time of disease onset. Prevalence-based studies estimate the number of cases of death and hospitalisations attributable to diseases in a given year, then, they estimate the costs that flow from those deaths or hospitalisations.

Incidence-based approaches represent the lifetime costs resulting from a disease or illness based on all cases with onset of diseases in a given base year; incidence-based studies estimate the number of new cases of death or hospitalisation in a given year and apply a lifetime cost estimate to these new cases⁹².

The incidence approach requires that the analysis be performed “from the bottom-up”, totalling the lifetime costs of illness. This, in turn, requires that input data be gathered at a level of detail much greater than that employed in the prevalence approach where, in general, the analysis is performed “from the top-down”, allocating portions of a known total expenditure to each of several broad disease category.

The difference in results between these two approaches is determined by several aspects, but assuming no changes in treatment regimens and constant incidence and prevalence patterns, the cost figures resulting from the two methods may be different for the different time horizons; it can be shown that in case of a disease with a short duration, the prevalence method leads to lower results, while in case of diseases with a long duration, it's the incidence method which leads to lower figures.⁹³

COI studies can also be performed prospectively or retrospectively, depending on the temporal relationship between the initiation of the study and the data collection. In retrospective COI studies, all the relevant events have already occurred when the study is initiated; this means that the process of data collection must refer to data already recorded. Conversely, in prospective COI studies, the relevant events have not already occurred when the study is initiated; this means that the process of data collection needs to be done by following-up the patients over time.

In COI studies, the cost of illness is estimated by identifying the cost-generating components and attributing a value to them. Costs are traditionally stratified into three categories: direct, indirect, and intangible costs, though COI studies have mainly focused on the first two cost categories, for the reasons explained in the following page.

Direct costs are those incurred by the health system, society, family and individual patient; they consist of healthcare and non-healthcare costs. The former include hospitalisation services, physician and nurse services, long-term care, prescription drugs, medical supplies and laboratory tests. The latter are related to the consumption of non-healthcare resources like

⁹² Rice D.P. 1994. Cost-of-illness studies: fact or fiction? *Lancet* 344 (8936): 1519-20.

⁹³ Ament A., Evers S. 1993. Cost of illness studies in health care: a comparison of two cases. *Health Policy* 26: 29-42

transportation, household expenditures, relocating, property losses, and informal cares of any kinds⁹⁴. Six steps are necessary to calculate them:⁹⁵

1. identify a cohort who has received the standard treatment for the disease;
2. determine the costs of each phase or component of treatment and the timing of these costs;
3. combine the cost estimates with probability data regarding the likelihood of receiving specific treatments and their timing. Incorporate survival data⁹⁶ in probability estimates based on the age of onset of the disease and life expectancy;
4. if total medical costs are used (rather than disease-specific cost elements), determine the background medical costs that would be incurred in the absence of the disease. Modify the disease-related costs as needed to obtain incremental costs;
5. discount the stream of treatment costs over time to estimate present value treatment costs;
6. aggregate the discounted stream to obtain an estimate of the total medical costs of the disease.

Indirect costs, in COI studies, occasionally refer to productivity losses due to morbidity and mortality, borne by the individual, family, society, or the employer. They are estimated through either one of the three following methods⁹⁷, though until recently little effort has been devoted to assess the validity or reliability of instruments for measuring productivity losses⁹⁸:

- a. Human Capital Approach (HCA)⁹⁹, which estimates the value of human capital as the present value of future earnings (estimated by examining the earnings of comparable individuals in a cross section of the population, adjusted by the probability of survival at each age and discounted to adjust for the difference in the value of benefits received

⁹⁴ On the economic valuation of informal care see, for instance, Van Den Berg B., Brouwer W.B.F, Koopmanschap M.A. 2004. Economic valuation of informal care: an overview of methods and applications. *Eur J Health Econ* 5(1):36-45. DOI <http://dx.doi.org/10.1007/s10198-003-0189-y>

⁹⁵ For a systematic review of methodologies used to calculate direct costs see, for instance, Clabaugh G., Ward M.M. 2008. Cost-of-illness studies in the United States: a systematic review of methodologies used for direct cost. *Value Health* 11(1):13-21. DOI <http://dx.doi.org/10.1111/j.1524-4733.2007.00210>

⁹⁶ In reality, data rarely exist regarding the probability of survival and direct costs for a specific disease for each age of diagnosis and sex. If there were such data, however, the estimated average direct costs would be calculated by weighting the direct costs for each age and sex by the percentage of incidence in each sex/age grouping.

⁹⁷ Jo C. 2014. Cost-of-illness studies: concepts, scopes, and methods. *Clin Mol Hepatol* 20(4):327-37. DOI <http://dx.doi.org/10.3350/cmh.2014.20.4.327>

⁹⁸ A systematic review of such instruments has been performed by Mattke S, Balakrishnan A, Bergamo G, et al. 2007. A review of methods to measure health-related productivity loss. *Am J Manag Care* 13(4):211-7. The authors, furthermore, point out how presenteeism (being present at work but working at a reduced capacity) may account for a larger proportion of losses than absenteeism (being absent from work). Retrieved from <http://www.ajmc.com/journals/issue/2007/2007-04-vol13-n4/apr07-2472p211-217/> On the issue of presenteeism, and the impact of health conditions to employers, a review of the literature has been carried out by Schultz A.B., Chen C.-Y., Edington D.W. 2009. The cost and impact of health conditions on presenteeism to employers: a review of the literature. *Pharmacoeconomics* 27(5):365-78. DOI <http://dx.doi.org/10.2165/00019053-200927050-00002> After reviewing the literature, they conclude that many health conditions are significantly associated with on-the-job productivity losses ("presenteeism"); what cannot be stated yet is the dollar value of those losses.

⁹⁹ The Human Capital Approach represents the simplest version of the Salary Conversion Methods, which attempt to estimate productivity losses based on self-reported lost time or decreased productivity.

today and in the future), under the assumption that future earnings are used as a proxy for future productivity¹⁰⁰. Depending on the available data sources, authors have used actual salaries of the respondents, mean salaries for the corporation, or national median wages;

- b. Friction Cost method, which estimates the value of human capital when the sick or impaired worker is taken over by another person (either through a reallocation of employees over jobs or by someone drawn from the ranks of the unemployed), who replaces the present value of a worker's future earnings until the sick or impaired worker returns or is eventually replaced¹⁰¹. This method is very demanding in terms of data requirements, as four questions need to be answered and corresponding data obtained¹⁰²: 1) When does a friction period occur? 2) How long does a friction period last? 3) What are the costs during the friction period? 4) How can the medium term economic consequences of illness that extends beyond the friction period be estimated?;
- c. Willingness-to-pay method, which measures, through various methods (e.g. surveys, examining the extra wages for highly risky jobs, examining the demand for products that leads to greater level of health or safety), the amount that an individual is eager to pay in order to reduce the probability of illness or mortality¹⁰³. In practice this method has been difficult to implement and its applications have been debated and have not produced generally accepted and validated figures, with empirical studies giving a broad range of results.¹⁰⁴ On the European Chemical Agency (ECHA) website willingness to pay values are available for health outcomes in relation to chemicals. Those values were specifically developed for socio-economic analysis in restriction proposals and applications for authorisation.¹⁰⁵

Intangible costs capture the psychological dimensions of the illness to the individual (and their family), i.e. the pain, anxiety and suffering; these costs are not usually monetised, because objective valuations of these impacts are rarely available or easily validated, due to

¹⁰⁰ On the empirical strengths of this method, see for instance, Glied S. 1996. Estimating the indirect cost of illness: an assessment of the forgone earnings approach. *Am J Public Health* 86 (12):1723-8.

¹⁰¹ Koopmanschap M.A., Rutten F.F.H, van Ineveld B.M., et al. 1995. The friction cost method for measuring indirect costs of disease. *J Health Econ* 14(2):171-89. DOI [http://dx.doi.org/10.1016/0167-6296\(94\)00044-5](http://dx.doi.org/10.1016/0167-6296(94)00044-5) These authors argue that the HCA overestimates the true absence-related productivity losses because short-term absences might be partially compensated with greater effort or unpaid overtime, whereas longer-term absences would lead to replacement of workers with new hires. They show that application of the HCA to calculate the indirect costs of disease in The Netherlands in 1988 resulted in these costs being 8.5 times higher than the indirect costs resulting from using the friction method.

¹⁰² Koopmanschap M.A., Rutten FFH. 1996. A practical guide for calculating indirect costs of disease. *Pharmacoeconomics* 10 (5): 460-6. Figure 2 on page 464 provides a schematic overview of the many estimations needed in order to calculate the indirect costs of diseases according to the friction method.

¹⁰³ Attempts to implement this approach using survey responses or revealed preferences estimates have produced values affected by statistical problems and measurement difficulties. On this issue see, for instance, Landefeld J.S., Seskin E.P. 1982. The economic value of life: linking theory to practice. *Am J Public Health* 72 (6): 555-66.

¹⁰⁴ Ament A., Evers S. 1993. Cost of illness studies in health care: a comparison of two cases. *Health Policy* 26: 29-42

¹⁰⁵ ECHA. 2016. Willingness to pay to avoid certain health impacts. Retrieved from: <http://echa.europa.eu/support/socio-economic-analysis-in-reach/willingness-to-pay-to-avoid-certain-health-impacts>

the measurement difficulties and related controversies.¹⁰⁶ These costs have therefore been expressed as non-monetary measures, such as DALYs (Disability Adjusted Life Years) or QALYs (Quality Adjusted Life Years); these are measures that combine and standardise health care costs and the 'lost economic or societal contribution' resulting from premature death or disability.

DALY measures the loss of one year of healthy life, therefore illustrating the negative impact of a condition, and they are commonly used to quantify the burden of disease at a population level;¹⁰⁷ QALYs are used to illustrate health benefits; they are life years adjusted by a quality weight, which is measured on a preference scale, where 'full health' equals a score of 1.0, being 'dead' a score of 0.0.¹⁰⁸

1.5. Cost of Illness (COI) studies related to Endocrine Disruptors

During the last couple of years a certain number of COI studies related to EDs were published; the main findings, and the underlying assumptions and simplifications involved, are summarised below.

The **Nordic Council of Ministers** published a report¹⁰⁹ estimating the costs for society related to negative effects on human male reproductive health suspected to be linked to exposure to EDs in Denmark, Finland, Iceland, Norway and Sweden. The figure below summarises the estimates of the direct, indirect and intangible costs (loss of life years and loss of quality of life) of effects on human male reproduction in the Nordic countries¹¹⁰.

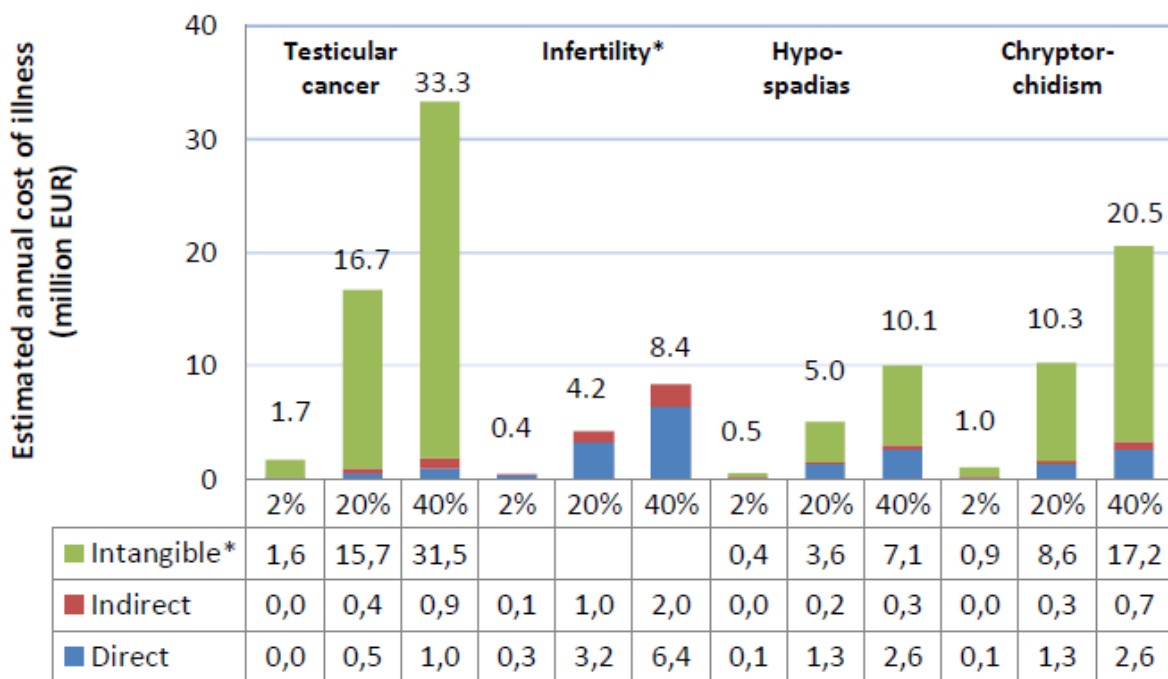
¹⁰⁶ Cooper BS, Rice DP. 1976. The economic cost of illness revisited. Soc Secur Bull 39(2):21-36, who conclude that estimates based on the human capital approach, reformulated using a willingness-to-pay criterion, produce the only clear, consistent, and objective values.

¹⁰⁷ A DALY comprises two other health gap indicators: YLL (Years of Life Lost), measuring the social burden of fatal health outcomes and YLD (Years Lost due to Disability), estimating non-fatal outcomes.

¹⁰⁸ The number of QALYs is calculated by weighting the time spent in health states with the preference-based scores associated with those states.

¹⁰⁹ Olsson, I-M, et al. 2014 The cost of inaction - A Socioeconomic analysis of costs linked to effects of endocrine disrupting substances on male reproductive health, Copenhagen: Nordisk Ministerråd, retrieved from: <http://norden.diva-portal.org/smash/get/diva2:763442/FULLTEXT04.pdf>

¹¹⁰ Direct and indirect costs were discounted by a rate of 4% per year, while the intangible costs were discounted by a pure time preference rate of 1.5% per year.



*Intangible costs of infertility are not quantified in this report.

Figure 7. Cost of effects on human male reproduction in the Nordic countries due to EDs at different levels of assumed etiologic fractions (millions of EUR per year of exposure)

Assuming an etiologic fraction¹¹¹ of 20%, the estimated cost of illness related to negative effects on male reproduction due to the present yearly exposure to EDs in the Nordic countries was estimated to be EUR 36 million per year of exposure.

Extrapolations to EU28 were made to estimate the equivalent costs in the EU assuming that the numbers of incidences of the different relevant health effects in the next 30 years would have been the same as today. Assuming etiologic fractions of 2%, 20%, and 40%, the discounted socio-economic costs for the EU-28 due to yearly exposure to EDs were estimated to be respectively EUR 59, EUR 592, and EUR 1,200 million per year of exposure, while the undiscounted costs were estimated to be equal to EUR 1,267 million per year of exposure to EDs at an etiologic fraction of 20%.

The following considerations need to be kept in mind, among others:

1. the basic assumption of the report was that exposure to EDs leads to the assessed negative health effects in human populations. However, the strength of the evidence for this causal link was not documented;

¹¹¹The Etiologic Fraction, in multifactorial diseases, is the fraction of all cases with a specific outcome (disease) that can be attributed to certain causing (etiological) factor (e.g. exposure to EDs, or lack of exercise, or other causing factors). In this respect, the EF is interpreted as a partitioning of causality; however, it could be interpreted also as proportion of preventable disease. These interpretations, although related, are not equivalent. See Levine B.J. 2007. What does population attributable fraction mean? *Prev Chronic Dis* 40(1): 1-5

2. to estimate the overall cost associated to an illness, etiologic fractions were estimated. However, an exact estimate of the etiological fraction is associated with large uncertainties, in particular for the health effects considered which are multifactorial. The report acknowledges that other factors which have been linked to the observed effects were dietary factors, obesity, smoking, degree of physical activity, and alcohol consumption. The chosen etiological fractions were based on expert advice and on current knowledge about the importance of genetic factors versus various environmental factors. However, establishing the etiological fraction attributed to exposure to EDs versus other environmental factors is always crucial, thus the selection of experts for this step played a key role in the final outcome of this study in particular considering that scientists still have different views on the evidence available on a causal link between exposure to EDs and health outcomes (Section 1.2 of this annex).
3. the incidence of the illnesses included in the report were different among the countries considered, and could depend on both genetic and environmental factors;
4. incidence rates for some of the conditions considered (e.g. hypospadias¹¹²) were not well covered, and no central source with information about incidence rates was available;
5. direct costs were derived from registry data from Swedish hospitals, but uncertainty was involved in extrapolating these estimates to the Nordic countries and to the EU;
6. intangible costs were evaluated by losses in Quality Adjusted Life Years (QALY). Bearing in mind that the validity of a QALY estimate might vary from country to country and greatly depends on how successful the treatment is, the extrapolation of QALY-measures from one country to another might give an uncertain measure.¹¹³

A series of articles were published in 2015 by authors affiliated to the **Endocrine Society**. The papers were all based on the same method and assessed different diseases associated with EDs.

Trasande et al.¹¹⁴ estimated the “Burden and Disease Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union”. This study focussed on those diseases for which evidence for causation by exposure to EDs was considered strongest, according to the experts consulted for this study. The ranges for etiological fractions of disease burden that could be attributed to EDs were then estimated.

¹¹² Hypospadias is a condition in which the opening of the urethra is any place along the underside of the penis, instead of at the tip of the penis. The meatus (hole) is most often found near the end of the penis ("distal" position), but it may also be found from the middle of the penile shaft to the base of the penis, or even within the scrotum ("proximal" positions). Sources: Urology care foundation, The official foundation of the American Urological association; Mayo Clinic.

¹¹³ For testicular cancer, e.g., there is an alternative QALY-loss estimate; this alternative estimate implies that 1.98 (rather than 1.09) QALYs are lost per case, and if this estimate was used, then the total discounted costs per year in the Nordic countries at an etiological fraction of 20% would have increased from EUR 36 to EUR 49 million.

¹¹⁴ Trasande, L., et al. 2015. Estimating Burden and Disease Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union, *Journal of Clinical Endocrinology and Metabolism* . 100(4):1245-1255. DOI <http://dx.doi.org/10.1210/jc.2014-4324>

Three general approaches on which to base attribution to EDs were used:

1. trends in incidence/prevalence over and above a baseline that would be difficult to attribute to genetics, accompanied by information on likely causal mechanisms by EDCs and/or increasing exposure;
2. data from genetic studies that allowed to quantify the remaining environmental contribution;
3. dose-response relationships between exposure to EDs and health outcomes, extrapolated by the epidemiological and toxicological literature and considered reliable by the experts consulted for this study.

For determining the probability of causation, the Intergovernmental Panel on Climate Change weight-of-evidence characterisation¹¹⁵ was adapted by a Steering Committee of scientists.

Starting from the WHO State of the Science of ED Chemicals (2012)¹¹⁶, which identified three distinct sets of health endpoints with the most substantial evidence for EDC attribution (obesity/diabetes, male reproductive health, and neurodevelopmental disability), the panel achieved consensus that “EDs causation was probable (> 20%)” for IQ loss and associated intellectual disability, autism, attention-deficit hyperactivity disorder, childhood obesity, adult obesity, adult diabetes, cryptorchidism, male infertility, and mortality associated with reduced testosterone.

The total costs of all conditions probably attributable to EDCs were EUR 191 billion, with sensitivity analyses suggesting costs ranging from EUR 81.3 to EUR 269 billion annually for the whole EU population.

Accounting for probability of causation, using the midpoint of each range for probability of causation produced costs ranging between EUR 2.5 and EUR 239 billion annually (median, EUR 157 billion); using the lowest end of the probability range produced a range of EUR 44 to EUR 235 billion (median, EUR 109 billion), while using the highest end of the probability ranges produced costs ranging from EUR 17.6 to EUR 246 billion (median, EUR 180 billion).

Even though the primary finding is that there is a substantial probability of very high disease costs across the life span associated with EDC exposure in the EU, the following elements should be considered:

1. an expert elicitation approach was used to estimate the probability that EDCs contribute to disease and disability. However, expert opinion is not a substitute for solid epidemiological evidence or for systematic toxicological documentation;
2. the assumption that a certain “attributable fraction” of health costs can be attributed to EDs is still very controversial among scientists.

¹¹⁵ Intergovernmental Panel on Climate Change. Guidance notes for lead authors of the IPCC Fourth Assessment Report on addressing uncertainties. WMO-UNEP, 2005. Retrieved from: <http://www.ipcc.ch/meetings/ar4-workshops-express-meetings/uncertainty-guidance-note.pdf>

¹¹⁶ Bergman Å, Heindel J, Jobling S, Kidd KA, Zoeller RT, 2012. eds. State of the science of endocrine disrupting chemicals, Geneva: United Nations Environment Programme and the World Health Organization, 2013, retrieved from: http://unep.org/pdf/9789241505031_eng.pdf

3. a recent scientific publication by Cartier et al. on organophosphorus pesticides (OPs) and neuro-development reported about the PELAGIE cohort (Brittany)¹¹⁷. The study from Cartier does not find any evidence for an association of pre-natal OP exposure and intelligence scores in the Brittany cohort. The authors speculate on what the reason(s) may be and discuss the US studies that underpin the study of Trasande et al.
4. The external report provided by the Ioannina School of Medicine to EFSA in 2013 may also provide additional information: they reviewed 32 publications in the area of pesticide exposure and mental and psychomotor development outcomes (including ADHD, autism, IQ loss)²³

Bellanger et al.¹¹⁸ applied the same approach for estimating "Neurobehavioral Deficits, Diseases, and Associated Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union". The expert panel focused on four exposure-outcome relationships that they considered having the greatest evidence for causation: PolyBrominated Diphenyl Ethers (PBDEs) exposure with reduced cognition, OrganoPhosphates (OP) exposure with reduced cognition, ED exposures (including phthalates) with Autism Spectrum Disorder (ASD), and ED exposures (including OP and PBDE) with Attention Deficit Hyperactivity Disorder (ADHD).

After evaluating the epidemiological and toxicological evidence, the experts consulted for this study concluded¹¹⁹:

1. assessment of a 70–100% probability that Organophosphates-associated IQ loss (and additional cases of intellectual disability) costs annually the EU EUR 146 billion (base-case scenario with a 5% estimate of AF (with 2% and 10% values as inputs for sensitivity analyses leading to EUR 46.8 billion and EUR 195 billion for a low and high case scenarios, respectively);
2. assessment of a 20-39% probability that EDC-associated Autism Spectrum Disorder costs annually the EU EUR 199 million (base-case scenario with a 5% estimate of AF, with 2%-10% as inputs for sensitivity analyses leading to EUR 79,7 million and EUR 399 million for a low and high case scenarios, respectively);
3. assessment of a 20-69% probability that EDC-associated Attention Deficit Hyperactivity Disorder costs annually the EU EUR 2,40 billion (base-case scenario with a 12,53% estimate of AF, with 10,76-17,28% as inputs for sensitivity analyses leading to EUR 1,21 billion and EUR 2,86 billion for a low and high case scenarios, respectively).

¹¹⁷ Cartier C., Warembourg C., Le Maner-Idrissi G., Lacroix A., Rouget F., Monfort C., Limon G., Durand G., Saint-Amour D., Cordier S., Chevrier C. 2015. Organophosphate Insecticide Metabolites in Prenatal and Childhood Urine Samples and Intelligence Scores at 6 Years of Age: Results from the Mother-Child PELAGIE Cohort (France). *Environ Health Perspect.* DOI: <http://dx.doi.org/10.1289/ehp.1409472>

¹¹⁸ Bellanger, M., Demeneix, B., Grandjean, P., Zoeller, R. T., and Trasande, L. 2015. Neurobehavioral Deficits, Diseases, and Associated Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union. *The Journal of Clinical Endocrinology & Metabolism* 100(4): 1256-1266. DOI <http://dx.doi.org/10.1210/jc.2014-4324>

¹¹⁹ Findings regarding the exposure to PolyBrominated Diphenyl Ethers (PBDEs) are not reported as this group of substances is not falling into the scope of the PPP or BP legislation, and therefore they cannot be considered relevant for the purpose of this IA.

These findings need to be considered in the light of the following:

1. estimates were limited due to uncertainties in the evidence (scarcity of European data on exposure-outcome relationships);
2. attributable fractions for the base-case scenario and for the sensitivity analysis were based on the expert panel's judgements;
3. some of the extrapolations were from subpopulations (e.g., Mexican American), and therefore the results rely on the generalisability of exposure-outcome relationships to European populations;
4. biomarker data were not available for all EU countries, and therefore judgment was used in extrapolating to the EU as a whole;
5. finally, none of the studies referred to data on PPP/BP exposure, except for the study on organophosphates as a whole class of pesticides. This class includes substances with very different toxicity and the study does not allow distinction of different substances within the class. In addition, the most toxic organophosphates have been removed from the EU market several years ago (e.g. diazinon, parathion, paraquat, fenitrothion, fonofos, phorate). Therefore, besides the fundamental methodological limitations of this study (in particular on the calculation of the etiological fraction attributed to ED exposure), the results of this study cannot be considered as directly relevant for this Impact Assessment (IA) which focusses on PPP and BP.

Hauser et al.¹²⁰ applied the same approach to estimating "Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union".

The expert panel focused on four exposure-outcome relationships: 1) phthalates and infertility; 2) polybrominated diphenyl ethers (PBDEs) and testicular cancer; 3) PBDEs and cryptorchidism; and 4) phthalates and reduced serum T, selected after assessing the availability of well-conducted human and animal studies to assess reproductive effects of these EDCs. None of these groups of substances is falling into the scope of the PPP or BP legislation, and therefore their findings cannot be considered directly relevant for the purpose of this IA.

Finally, **Legler et al.**¹²¹ followed the approach to estimate "Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union".

The expert panel focused on five exposure-outcome relationships: 1) prenatal DichloroDiphenyldichloroEthylene (DDE) exposure with obesity; 2) adult DDE exposure with diabetes; 3) adult phthalate exposure and obesity; 4) adult phthalate exposure and diabetes; 5) prenatal BPA exposure and obesity, selected after assessing the availability of well-conducted human and animal studies to assess reproductive effects of these EDCs.

¹²⁰ Hauser, R., et al. 2015. Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union. *The Journal of Clinical Endocrinology & Metabolism*. 100(4):1267-1277.

¹²¹ Legler, J., Fletcher, T., Govarts, E., Porta, M., Blumberg, B., Heindel, J. J., & Trasande, L. 2015. Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *The Journal of Clinical Endocrinology & Metabolism* . 100(4):1278-1288. DOI <http://dx.doi.org/10.1210/jc.2014-4325>

Also in this case, BPA is not falling into the scope of the PPP or BP legislation. In addition, DDE is not on the market in Europe as PPP or BP since at least 1993 (Table 3). Because of this, also in the case the findings of the study cannot be considered as relevant for the purpose of this IA.

The Health and Environment Alliance (**HEAL**) published a study¹²² estimating the health costs possibly associated to exposure to EDs in the EU, based on a paper by **L. Trasande**¹²³ (which estimated the contribution of exposure of a single EDC - Bisphenol A - to two different health conditions, childhood obesity and adult coronary heart disease, and this was equal to a 2-5% range).

The cost calculation, using the human capital approach, was performed for a list of diseases and conditions identified by HEAL as being associated with EDs exposure (on the basis of a review of the scientific literature): reproductive and fertility problems; abnormalities of the penis and testicles in baby boys; cancer of the breast, prostate, testes; children's behavioural disorders (such as autism and attention deficit hyperactivity disorder), obesity and diabetes¹²⁴.

Incidence rates and costs of treating the health effect considered were calculated, and for each health effect considered, total cost estimates for the EU28 countries were scaled up, on the basis of population size, from the estimates derived from the documented cost studies.

The estimates of total costs (direct and indirect) associated to EDs exposure, for those health conditions considered, amounted to EUR 636 billion per year in the EU; considering the assumption that EDs could contribute to 2-5% of the total health costs, HEAL concluded with a range comprised between EUR 13 and EUR 31 billion each year.

Even though the primary finding is that substantial costs for the EU health care systems could be attributable to EDs exposure, the following caveats should be carefully considered before any conclusion could be drawn:

1. the attributable fraction of 2-5% is based on just one study estimating the contribution of exposure of a single EDC, Bisphenol A, to two different health conditions; This chemical is not falling into the scope of the PPP or BP legislation, thus the findings cannot be considered as directly relevant for the purpose of this IA.
2. the country-disaggregated costs do not reflect differences in either prevalence or unit costs;
3. figures were not available for all the endocrine-related health problems selected for the analysis;

¹²² HEAL 2014. Health costs in the European Union. How much is related EDCs? Edited by G. K. Jensen.

Retrieved from: http://www.env-health.org/IMG/pdf/18062014_final_health_costs_in_the_european_union_how_much_is_realted_to_edcs.pdf

¹²³ Trasande. L. 2014. Further limiting Bisphenol A in food uses could provide health and economic benefits. Health Affairs. 33(2):316-323. DOI <http://dx.doi.org/10.1377/hlthaff.2013.0686>

¹²⁴ For each of these, the justification for the analysis was found in the Berlaymont declaration of 24 May 2013, when a group of the world's scientific experts on EDCs launched a plea calling on the European Commission "to implement regulatory measures that are in line with the best available science"

4. as acknowledged in the “Incidence and Costs” section of the report, even though many trends are upward, it is not always possible to distinguish between environmental factors, and specifically EDs, and improved diagnostics for the increases in incidence.

Further, **HEAL** published a technical briefing¹²⁵ on the economic evaluation of health impacts from EDCs, which builds on the previous report and on recent papers estimating costs attributable to EDC exposure, by broadening the previous approach, based on the human capital approach, and considering also the disutility costs of the health impacts (pain, suffering, discomfort and anxiety linked to the illness). HEAL's findings are summarised in Table 4.¹²⁶

The main conclusions reached by HEAL were the following:

1. the cost data given were judged to be defensible mid-range estimates, but given that the review was not comprehensive, these findings should have been considered as indicative;
2. however, with the evidence available, it was tentatively concluded that the disutility component might have been considered to be a non-trivial multiplier to the aggregate cost estimates that have been published in recent years, given that the inclusion of the disutility component seemed to double the estimates based on the two COI components of resources and opportunity costs.

Table 4. HEAL findings on the cost of health impacts.

Health Impact	Resource & Opportunity Costs	Disutility (WTP) Costs	COI:WTP ratio
Human Fertility	10,000	20,000	1:2
Cancer	15,000	75,000	1:5
Neurodevelopmental conditions	15,000	14,000	1:1
ADHD	12,000	N/A	
ASDs	1,500,000	N/A	
Diabetes	3000	16,000	1:5
Obesity	15,000	18,000	1:1.2

N/A = Not available

1.6. Relevance of the available COI studies in the context of PPP and BP

COI studies are considered to be an important measurement technique in health sciences. By measuring and comparing the economic burden of disease to society allows to improve the information in socio-economic analysis for regulatory decisions can be taken.

¹²⁵ HEAL, Towards Comprehensive Economic Valuation of Health Impacts from Endocrine Disrupting Chemicals. Retrieved from: http://env-health.org/IMG/pdf/2015.09.08_edcs_willingness_to_pay_heal_technical_briefing_final.pdf

¹²⁶ HEAL, Box 4, page 11 - figures per case expressed in EUR, at 2014 prices

The studies illustrated in the previous pages have provided estimates of the burden of disease associated to exposure to some endocrine-disrupting chemicals, showing that in the EU, EDCs may contribute substantially to:

- male reproductive health disorders and diseases, with up to EUR 1,2 billion of associated annual costs;¹²⁷
- male reproductive health disorders and diseases, with nearly EUR 15 billion of associated annual costs;¹²⁸
- obesity and diabetes, with more than EUR 18 billion of associated annual costs;¹²⁹
- neurobehavioral deficits and disease, with more than EUR 150 billion of associated annual costs;¹³⁰
- IQ loss and associated intellectual disability, autism, attention-deficit hyperactivity disorder, childhood obesity, adult obesity, adult diabetes, cryptorchidism, male infertility, and mortality associated with reduced testosterone, with a median value comprised between EUR 109 and EUR 180 billion of associated annual costs, depending on the probability of causation;¹³¹
- reproductive and fertility problems, abnormalities of the penis and testicles in baby boys; cancer of the breast, prostate, testes; children's behavioural disorders, obesity and diabetes, with between EUR 13 and EUR 31 billion of associated annual costs.¹³²

The indicated costs in the studies are substantial, and they could be underestimated as it is claimed that they are based on conservative assumptions and consider only those EDCs with the highest probability of causation.

These findings should be assessed in the light of the following considerations:

- the three distinct sets of health endpoints claimed to have the most substantial evidence for EDs attribution and considered in the analyses (obesity/diabetes, male reproductive health, and neurodevelopmental disability) have been based on the main

¹²⁷ Olsson, I-M., et al. 2014. The cost of inaction - A Socioeconomic analysis of costs linked to effects of endocrine disrupting substances on male reproductive health, Copenhagen: Nordisk Ministerråd. Retrieved from <http://norden.diva-portal.org/smash/get/diva2:763442/FULLTEXT04.pdf>

¹²⁸ Hauser, R., et al. 2015. Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union. *The Journal of Clinical Endocrinology & Metabolism*.100(4):1267-1277. DOI <http://dx.doi.org/10.1210/jc.2014-4325>

¹²⁹ Legler, J., et al.2015. Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *The Journal of Clinical Endocrinology & Metabolism*. 100(4):1278-1288. DOI <http://dx.doi.org/10.1210/jc.2014-4326>

¹³⁰ Bellanger, M., Demeneix, B., Grandjean, P., Zoeller, R. T., & Trasande, L. 2015. Neurobehavioral Deficits, Diseases, and Associated Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union. *The Journal of Clinical Endocrinology & Metabolism*. 100(4):1256-1266. DOI <http://dx.doi.org/10.1210/jc.2014-4324>

¹³¹ Trasande, L., et al. 2015. Estimating Burden and Disease Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union, *Journal of Clinical Endocrinology and Metabolism*. 100(4):1245-1255. DOI <http://dx.doi.org/10.1210/jc.2014-4324>

¹³² HEAL. 2014. Health costs in the European Union. How much is related EDCs? Edited by G. K. Jensen. Retrieved from: http://www.env-health.org/IMG/pdf/18062014_final_health_costs_in_the_european_union_how_much_is_realted_to_edcs.pdf

findings of the 2012 World Health Organization/United Nations Environment Programme State of the Science of Endocrine Disrupting Chemicals, whereas no consensus exists among scientists about the conclusions of this report;¹²

- assessment of the epidemiological and toxicological evidence available, as well as the probability that an ED contribute to disease and disability (etiologically fractions) have been established via expert elicitation by a selected group of few experts. Available guidance on this approach was not considered (e.g. the EFSA guidance on expert knowledge elicitation in food and feed safety risk assessment¹³³);
- no consideration has been given to available recent systematic reviews on pesticide exposure and associated health outcomes where results indicate that farmers have lower incidence of most cancers compared to the general population;²⁴
- judgment regarding reference levels, impact of covariates, and steepness of the dose-dependence of the outcomes was based on consensus among the authors or steering committees selected by the authors;
- whereas control for confounding was performed in many of the studies used, some of the extrapolations were from subpopulations (e.g., Mexican American), and therefore the results rely on the generalisability of exposure-outcome relationships to European populations;
- calculations could not take into account potential differences between exposure levels in the EU MS (e.g. biomarker data were not available for all EU countries, and therefore judgment was used in extrapolating to the EU as a whole);
- most of the EDs considered for the cost quantifications in these studies are outside the scope of the current IA, as they are not PPP or BP (for example Bisphenol A, PolyBrominated Diphenyl Ethers, OrganoPhosphates, Phthalates), or the PPP or BP have been banned in the EU years ago (DichloroDiphenyldichloroEthylene). Further, other conclusions were drawn referring to a whole class of pesticides (e.g. organophosphates), while this class includes substances of different toxicity. The most toxic substances of this class of pesticides have been banned in the EU already several years ago (Table 3).

In addition to the points highlighted before, it should always be kept in mind that performing a COI analysis is very challenging,¹³⁴ the choice of cost methodology (and their accuracy) for assessing both direct costs and losses in productivity, is largely driven by data availability, which varies among countries. This applies also to epidemiological data (i.e., disease prevalence, incidence, and associated mortality). COI studies imply also the assessment of the epidemiological and toxicological evidence which are available, as well as assumptions regarding, for instance, the discount rate chosen for reflecting the present value of future costs and health effects and the proportion of a disease that may be attributable to a substance's

¹³³ EFSA (European Food Safety Authority). Guidance on Expert Knowledge Elicitation in Food and Feed Safety Risk Assessment. EFSA Journal 2014; 12(6):3734. DOI <http://dx.doi.org/10.2903/j.efsa.2014.3734>

¹³⁴ Greenberg, D. et al. 2014. What Are the Challenges in Conducting Cost-of-Illness Studies? Value in Health Regional Issues. 4C:115-116. DOI <http://dx.doi.org/10.1016/j.vhri.2014.08.003>

exposure. As far as the population attributable fractions are concerned, errors in computations and interpretation may exist and, in some settings, the value of the estimates may be questionable;¹³⁵ also, conceptual problems in the definition and interpretation of attributable fractions exist.¹³⁶

One of the outcomes of these complexities is that reported estimates have been sometimes found inconsistent across studies, thereby raising concerns over the validity of these estimates and the methods used to calculate them.¹³⁷

Considering these limitations, the conclusions reached by the recent COI studies analysed should be taken with great caution, and viewed as suggestive about the costs of diseases related to exposure to EDs.

3. ASSESSMENT OF THE PERFORMANCE OF THE OPTIONS PRESENTED IN THIS IMPACT ASSESSMENT UNDER CONSIDERATION OF THE REGULATORY DECISION MAKING AND PROTECTION OF HUMAN HEALTH

In the previous sections the evidence related to endocrine mediated diseases and associated costs was discussed. The evidence shows that robust conclusions cannot be drawn on the link between exposure to environmental levels of EDs and increased incidence of endocrine mediated diseases and disorders. Nevertheless, protection of human health remains the highest priority, as it is a mayor objective in the PPP and BP Regulations, and thus guides this IA.

Protection of human health is therefore analysed under consideration of the current regulatory decision making under the PPP and BP Regulations, in particular evaluating if this regulatory framework is adequately protecting human health, as requested by those pieces of EU legislation and by the EU Treaty.

The precautionary principle underpins the EU legislation on placing on the market of PPP and BP, as stated in the corresponding recitals of these regulations.^{138,139} The EU authorisation system for PPP and BP is based on prior approval ("positive list") and shift the responsibility

¹³⁵ Rockhill B., Newman B., Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998; 88(1):15-9; Greenland S., Robins J.M. Conceptual problems in the definition and interpretation of attributable fractions. *Am J Epidemiol* 1988; 128(6):1185-97.

¹³⁶ Greenland S., Robins J.M. 1988. Conceptual problems in the definition and interpretation of attributable fractions. *Am J Epidemiol*. 128(6):1185-97. The authors argue that there is the need to distinguish three concepts of attributable fractions: the excess fraction, the etiologic fraction, and the incidence density fraction. These quantities do not necessarily approximate one another, and the etiologic fraction is not generally estimable without strong biologic assumptions. For this reasons, they conclude, care is needed in deciding which of the concepts is a appropriate for a particular situation.

¹³⁷ Akobundu E, Jing J, Blatt L, et al. 2006. Cost-of-illness studies: a review of current methods. *Pharmacoeconomics*. 24(9):869-90.

¹³⁸ Article 1.4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309.

¹³⁹ Article 1.1 of Regulation (EU) No 528/2012 of the European Parliament and of the Council concerning the making available on the market and use of biocidal products. OJ L 167/1.

for producing scientific evidence (burden of proof) to the industry.¹⁴⁰ In other words, the legislation requires that the substances be deemed hazardous until proven otherwise, and the burden of proof lies with the applicant requiring an authorisation to place the substance on the EU market to provide the scientific information needed to evaluate the possible risk. Also the preceding legislations put in place in the 90s (Directive 91/414/EC and Directive 98/8/EC, respectively) asked for a sound scientific risk assessment as a basis for regulatory decision making.

The Communication from the commission on the precautionary principle¹⁴¹ states that this principle is particularly relevant to the management of risk. It should be considered within a structured approach to the analysis of risk which comprises risk assessment, risk management, and risk communication. Further, the implementation of an approach based on the precautionary principle should start with a scientific evaluation, as complete as possible. Where action is deemed necessary, measures based on the precautionary principle should be, inter alia:

- proportional to the chosen level of protection,
- non-discriminatory in their application,
- consistent with similar measures already taken,
- based on an examination of the potential benefits and costs of action or lack of action (including, where appropriate and feasible, an economic cost/benefit analysis),
- subject to review, in the light of new scientific data, and
- capable of assigning responsibility for producing the scientific evidence necessary for a more comprehensive risk assessment.

In the EU, Plant Protection Products (PPP) and Biocidal Products (BP) are regulated products that need to be approved before they can be placed on the market. This pre-market approval system is considered as one of the strictest worldwide: any PPP or BP must be authorised – based on a sound scientific risk assessment¹⁴² - before it can be placed on the market and used. MS can only authorise PPP and BP which contain active substances placed on this "positive lists", and need to carry out additional evaluation of the specific product formulations and uses.

Both the PPP Regulation (EC) No 1107/2009 and the BP Regulation (EU) No 528/2012, as well as their corresponding preceding legislations, specify a detailed list of data requirements^{143,144} which have to be submitted by the applicant before any approval of active

¹⁴⁰ These are elements of the precautionary principle, see Communication from the Commission on the precautionary principle, COM(2000) 1 final. Retrieved from:

<http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52000DC0001>

¹⁴¹ European Commission, Communication from the Commission on the precautionary principle, COM(2000) 1 final. Retrieved from: <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52000DC0001>

¹⁴² Risk assessment considers the hazard of a substance and the exposure levels to which humans and the environment are exposed to. Comparing safety thresholds based on hazard data (hazard assessment) with exposure levels (exposure assessment), risk is calculated (risk assessment).

¹⁴³ Regulations EU 283/2013 and EU 284/2013, setting data requirements for active substances and for PPP, respectively; Communications 2013/C 95/01 and 2013/C 95/02, detailing the list of test methods and guidance documents for active substances and for PPP, respectively.

substance or authorisation of a product containing approved substances can be considered. This implies that both PPP and BP are among the most "data rich" regulated product groups in the EU.

As mentioned before in Section 1.3, several substances have been banned in the EU, sometimes since years, thanks to the EU on legislation on PPP and BP (Directive 91/414 and Directive 98/8/EC) which was based on risk assessment,¹⁴⁵ demonstrating the regulatory system in the EU worked efficiently in protecting human health.¹⁴⁶ Actually, Directive 98/8/EC already contained some hazard-based provisions for substances classified as toxic, very toxic, mutagens, carcinogens or toxic for reproduction for use by the general population. The rationale was that the general population may not be able to adequately control exposure and therefore hazard-based provisions would ensure highest safety.

The PPP Regulation introduced an additional step for all uses (no distinction of use by professionals or by the general population): for substance with particular hazard properties (e.g. endocrine disruption), the exposure is in principle not considered but the substance is banned, irrespectively of whether realistic levels of exposure to it would pose or not a real risk to human health (so called "cut-off criteria"). However, cut-off criteria may remove from the market substances which do not pose any risk to human health and the environment, due to the levels of exposure which are very far from the safety threshold established for those substances. In cases the foreseen derogations would be applied for, a "standard" risk assessment covering all areas would still be needed, as done also for any substance which is not identified as belonging to one of the particularly hazardous classes. As a consequence, even if a substance is not identified as an ED, it may still be non-approved if the adverse effects observed are considered to pose a risk to human health or the environment. The BP Regulation follows a similar rationale for the regulatory decision making, although differences in the derogations and their implementation exist with respect to the PPP Regulation. The regulatory decision process, including the approval of ED substances, for both PPP Regulation and BP Regulation is depicted in Figure 8.

¹⁴⁴ 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. Official Journal of the European Union, L 167, 27 June 2012. doi:10.3000/19770677.L_2012.167.eng

¹⁴⁵ Risk assessment considers the hazard of a substance and the exposure levels to which humans and the environment are exposed to. Comparing safety thresholds based on hazard data (hazard assessment) with exposure levels (exposure assessment), risk is calculated (risk assessment).

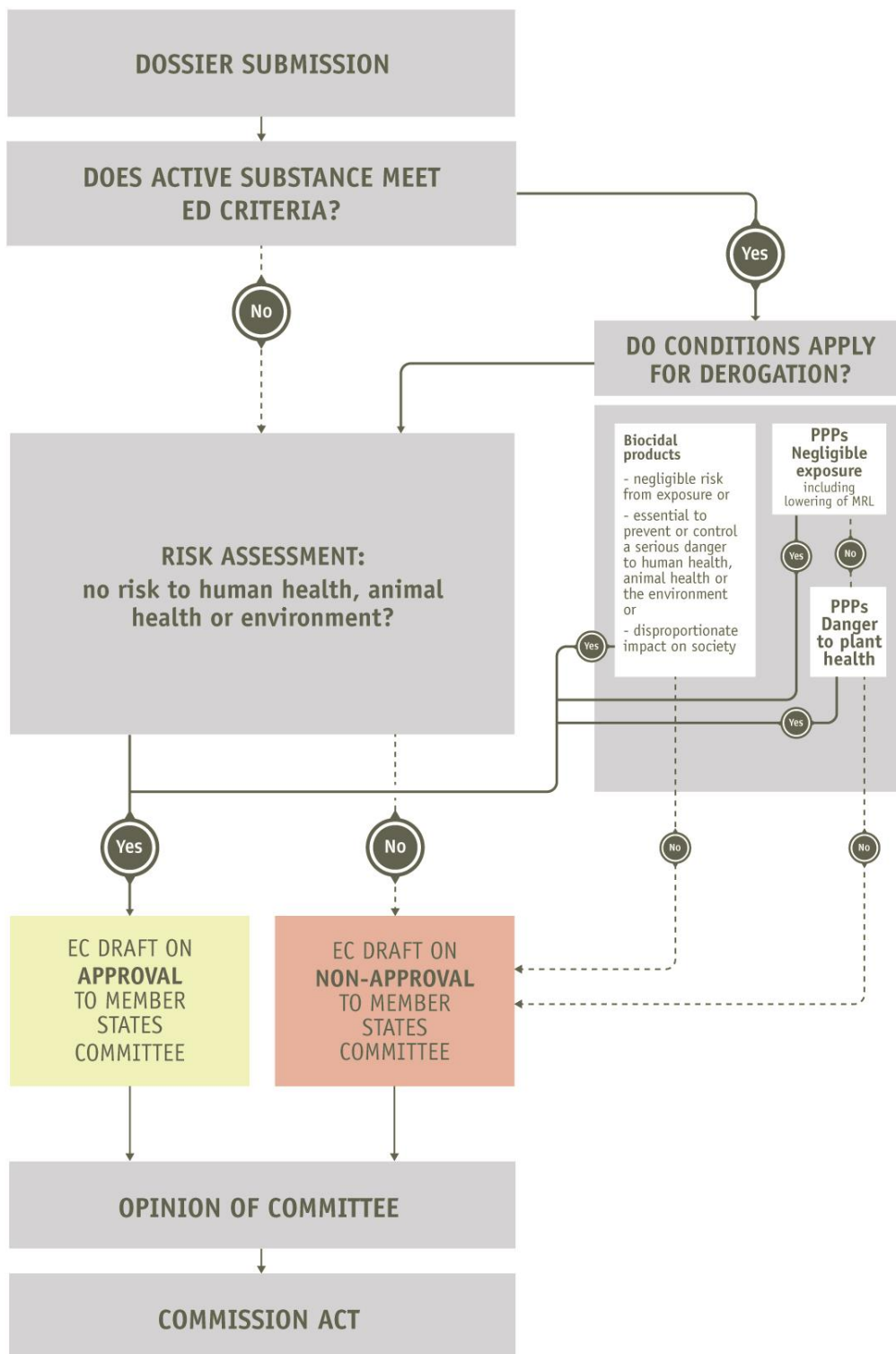


Figure 8. Regulatory decision making in the PPP and BP Regulations, under consideration of derogations for active substances identified as EDs

The EFSA opinion on EDs supports a case-by-case risk assessment approach to assess ED for decision making, which would be in line with the precautionary principle approach as defined in the Communication mentioned above. For instance, EFSA states that *"to inform on risk and level of concern for the purpose of risk management decisions risk assessment (taking into account hazard and exposure data/predictions) makes best use of available information. EDs can therefore be treated like most other substances of concern for human health and the environment, i.e. be subject to risk assessment and not only to hazard assessment"* (page 47).

Moreover, the EFSA opinion (page. 16) is *"in agreement with Kortenkamp et al. (2011) that, since points have not been defined where „threshold of adversity“ is crossed, it is difficult to propose specific criteria to differentiate between effects that represent an endocrine modulation and adverse effects on the endocrine system. Expert judgement will therefore be required to assess on a case-by-case basis the toxicological relevance of such changes. In general, transient, inconsistent and minor fluctuations at the biochemical and molecular level may be considered adaptive (i.e. non-adverse), whilst 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.*

The point at which endocrine modulation becomes an adverse effect cannot be determined on the basis of an absolute response value, but on the basis of a relative response (compared to the control/background response). The SC is therefore of the opinion that, as adversity is a prerequisite for identifying a substance as an ED, it is necessary to determine a biological threshold between endocrine modulation and adverse effect. For the time being, it is difficult to propose generic criteria to determine when this biological threshold is crossed. This is therefore likely to be done on a case-by-case basis through expert judgement."

Also the **Scientific Committee on Consumer Safety (SCCS)** supports the use of risk assessment to assess EDs for decision making.¹⁴⁷ In particular, the Memorandum states that *the SCCS supports the conclusions of EFSA that: "Critical effect, severity, (ir)reversibility and potency aspects are part of the hazard characterisation of EDs. To inform on risk and level of concern for the purpose of risk management decisions, risk assessment (taking into account hazard and exposure data/predictions) makes best use of available information. EDs can therefore be treated like most other substances of concern for human health and the environment, i.e. be subject to risk assessment and not only to hazard assessment."* [EFSA 2013]. The SCCS adds that *"due to the ban on animal testing for cosmetic ingredients effective since 2013, it will be extremely difficult in the future to differentiate between a potential ED and an ED, if the substance is registered solely for use in cosmetics products. The replacement of animal test methods by alternative methods in relation to complex toxicological endpoints (such as endocrine disruption) remains scientifically difficult, despite the additional efforts launched at various levels. With regard to substances with endocrine activity (potential endocrine disruptors), the assessment of their impact to human health without animal data remains a challenge."* (page 5)

¹⁴⁷ Scientific Committee on Consumer Safety (SCCS) Memorandum on Endocrine Disruptors. Retrieved from: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_009.pdf

Options 2/3 and 4 will identify a different number of EDs (see Annex 5 on screening results). Considering that no robust evidence is available to support a causal link between exposure to environmental levels of substances identified as EDs and certain human diseases (see section 1 and 2 of this annex), the impact on human health cannot be related to the number of substances identified as EDs. On the other hand, the current rules (**i.e. the risk assessment step following identification or non-identification of a substance as an ED**) ensure that authorised products do not have unacceptable effects on the health of humans. Therefore, it can be assumed that no differences on impacts on human health are expected between Option 2, Option 3, and Option 4 as human health will be equally protected. Differently, Option 1 is known to identify “false positives”, i.e. substances that appear to have no endocrine MoA. These substances may be removed from the market although they are not EDs according to the WHO/IPCS definition, as they do not act via an endocrine MoA. There is indeed a scientific consensus that interim criteria are not fit for correctly identifying EDs since they are unable to detect an ED mode of action. They detect many false positives because the interim criteria identify EDs even when no ED mode of action is present. They also detect many false negatives, as shown by the limited overlap between substances identified under option 1 (interim criteria) and option 2 (WHO definition). This overlap is visible in Fig 2 of the main report and in Table 1 of Annex A5. Therefore, the options rank 2/3/4 > 1 and this ranking of options has been considered for most of the MCA-scenarios, with exception of the MCA-scenarios "aim: exposure zero" for which the performance of the options is detailed further down.

It can be assumed that, based on recent scientific opinions from the EU Authority EFSA⁵⁵ and from the EU Scientific Committee SCCS⁵⁶, a risk assessment approach would protect human health from EDs in a similar way as a hazard approach followed by a risk assessment step. In fact, a product can be only placed on the market after a risk assessment has taken place (see Figure 7). Therefore it is ensured that no unacceptable effects will occur on the health of humans.¹⁴⁸ Supporting this conclusion are the recent WHO reports^{149,150} which recommend identifying risks from exposure to EDs. Furthermore, as a consequence of the PPP and BP EU legislation in place since the 90s, many active substances used in PPP and BP have been taken out from the EU market or restricted over the last decades based on regulatory decisions building on sound scientific risk assessments (see previous sections of this annex). This is due to the fact that some of the adverse effects which may be caused by EDs (e.g. carcinogenicity and reproductive effects) were studied and regulated before, without detailed knowledge of their potential endocrine MoA. In other words, as endocrine disruption is a new way of looking at the toxicity of chemicals (which considers¹⁵¹ adverse effect, MoA, and a causal

¹⁴⁸ It may even be argued that a risk assessment approach would ultimately protect human health better than a hazard approach followed by a risk assessment step. With an hazard preliminary step, we may ban substances posing no effective risk to human health and substitute them with less studied alternatives (which would pose more risk to human health because their assessment has more uncertainties)

¹⁴⁹ WHO 2014. Identification of risks from exposure to EDCs at the country level.

¹⁵⁰ WHO 2015 Identification of risks of EDCs: overview of existing practices and steps ahead. Report of a meeting in Bonn, Germany 7-8 July 2014

¹⁵¹ WHO/IPCS defines an ED 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*”

link between the two), irrespectively from the MoA, many of the adverse effects often associated to endocrine disruption were already detected in the context of the evidence provided for approval of chemicals. Where a risk was identified, those substances were removed from the market.

Option B Option B only applies to the PPP Regulation. The derogations to the non-approval of active substances, currently mainly hazard-based, would be updated in light of new scientific evidence (e.g. recent scientific opinions of EFSA , Scientific Committee SCHER , expert meeting in Berlin) to risk based derogations. While the general hazard approach for EDs would be maintained, the derogations would be based on a stronger risk component compared to the current situation. Amendments to the Annexes, via Regulatory Procedure with Scrutiny (RPS) are foreseen in Regulation (EC) No 1107/2009 taking into account current scientific and technological knowledge (cf. Article 78 of the PPP Regulation). This option is therefore feasible within the remit of the mandate of the Commission as it does not imply changes by ordinary legislative procedure to the basic act.

The inclusion of socio-economic considerations (Option C) may consider a risk/benefit analysis and protect human health to a less extent. This option would request a modification via ordinary legislative procedure of the current PPP Regulation.

As a consequence, the performance of options with respect to ED-related diseases and disorders is as follows: $A/B > C$. Also this ranking of options has been considered for most of the MCA-scenarios, with exception of the MCA-scenario "aim: exposure zero" for which the performance of the options is detailed further down.

In order to carry out a sensitivity analysis on the performance of the options, the MCA-scenario "aim: exposure zero" was developed. It assessed the performance of the options based on a different assumption which only aims at minimizing exposure: the higher the number of active substances identified as EDs, the better the performance of the option for human health with respect to exposure (without consideration of any risk assessment) . As a consequence, within this scenario, the options perform as follows: $2/3 > 4 > 1$ only based on exposure considerations. Regarding options A to C, the assessment was based on the number of correctly identified ED substances which will not be approved. As Option A would take from the market (non-approval) more substances identified as EDs than options B or C, it is assumed that it would perform the best with respect to exposure. Under this scenario, the options consequently perform as follows: $A > B > C$ only based on exposure considerations.