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COMMISSION STAFF WORKING DOCUMENT

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 11 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 11

ENVIRONMENT

Contents

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 prejudge 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. INTRODUCTION

The use of chemicals may cause environmental effects. That is why EU legislation concerning the placing on the market of plant protection products[1] (PPP) and biocidal products[2] (BP) provides that any PPP or BP may only be authorised for placing on the market and use when it is supported by a sound scientific risk assessment which includes consideration of environmental risk. Risk assessment considers the hazard of a substance and the exposure levels to which humans and the environment are exposed to. Risk is assessed by comparing safety thresholds based on hazard data (hazard assessment) with exposure levels (exposure assessment).

Endocrine disruption is a relatively recent way of looking at the toxicity of chemicals, which aims at understanding the mode of action, i.e. how chemicals lead to the adverse effects observed. Most of the adverse effects that may be produced by endocrine disruptors (ED) on the environment are however already considered by the EU legislation since several years and accordingly regulatory actions have been taken in the past. Concerns about the uncertainty regarding the extent of exposure to chemical pollutants in the environment, and the effects that they might have, were discussed at the Weybridge workshop on EDs in 1996[3]. One of the main conclusions reached at the meeting was that for wildlife, few cases within the EU were known where effects could be clearly ascribed to EDs. In 2001, an international workshop[3] on EDs was held in Aronsborg (Bålsta) Sweden and it concluded that further research on the topic was needed both for human health and wildlife, including development of test methods and testing strategies, besides up-to-date databases with information on EDs.

The impact on the environment of the different options setting criteria to identify EDs is analysed in the subsections below with the aim to rank the policy options proposed in this impact assessment. Some general considerations on endocrine disruption given in Annex 9 (Human Health – Hormone related diseases) are applicable also to this section. In addition, it needs to be considered that it is so far not possible to identify robust and reliable environmental impact indicators in relation to ecosystem services or species level effects, as concluded in a recent study carried out for the European Commission[4], which concluded that the indicators that could be developed for the environment were limited inter alia because of the lack of monitoring data.

[1] 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.
[2] 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.
[3] Workshop "The Impact of Endocrine Disruptors on Human Health and Wildlife", Weybridge UK, 2-4 December 1996. Retrieved on: http://ec.europa.eu/environment/chemicals/endocrine/documents/reports_en.htm
[4] 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

2. CHEMICAL QUALITY OF WATER

PPP are in general expected to enter the environment from diffuse routes by a variety of mechanisms. Contrarily, for biocidal products an important source for potential contamination of the environment is the effluent from sewage treatment plants.[5]

As mentioned above, both the PPP Regulation and the BP Regulation require a scientific environmental risk assessment, which includes the aquatic compartment, including both surface water and groundwater. For both cases, the predicted environmental concentrations derived from the use of a particular PPP or BP need to be calculated, based on the expected uses.

Concerning **groundwater,** particular conditions apply. Point 3(10) of Annex II to Regulation (EC) No 1107/2009 on PPP establishes that "*An active substance shall only be approved where it has been established for one or more representative uses that ... the predicted concentration of the active substance or of metabolites, degradation or reaction products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6)"*. Regulation (EC) No 1107/2009 further states in Article 4(3)(b) that *"a plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use, shall……have no immediate or delayed harmful effects on groundwater"*. In practice, this means that an active substance cannot be approved if its estimated concentration in groundwater exceeds the limit of 0.1µg/L (maximum permissible level in drinking water). This also applies to all the relevant metabolites and breakdown products that may be produced from degradation of the active substance. A metabolite is considered relevant when there is a reason to assume it has intrinsic properties comparable to the parent substance in terms of its biological target activity, or that it poses a higher or comparable risk to organisms than the parent substance or that it has certain toxicological properties that are considered unacceptable.[6,7]

As regards **drinking water,** Article 4(3)(b) of Regulation (EC) No 1107/2009 also mentions that *"a plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use, shall……have no immediate or delayed harmful effects on human health, including that of vulnerable groups, or animal health, directly or indirectly or through drinking water (taking into account substances resulting from water treatment)"*.

Considering this requirement for groundwater and drinking water, which does not depend on how criteria to identify EDs will look like, it is expected that the chemical quality of groundwater and drinking water will not be affected by the different options for criteria to

[5] Hecker, M. and Henner, H. 2011. Endocrine disruptor screening: regulatory perspectives and needs. Environmental Sciences Europe 23:15. doi:10.1186/2190-4715-23-15

[6] European Commission Guidance Document on the Assessment of the Relevance of Metabolites In Groundwater of Substances Regulated Under Council Directive 91/414/EEC. Retrieved on: http://ec.europa.eu/food/plant/pesticides/guidance_documents/docs/wrkdoc21_en.pdf

[7] Article 3(32) 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

identify EDs. In fact, it is expected that the current regulatory system based on risk assessment will ensure in any case that substances approved as PPP (and their relevant metabolites) will be present in groundwater and drinking water, at levels not exceeding 0.1µg/L if PPP are used correctly, taking into account any necessary restrictions to mitigate any possible risk of leaching to groundwater.

With respect to chemical quality of **surface water,** the PPP Regulation foresees that a risk assessment is carried out by comparing toxicity thresholds of key organisms with exposure values (PEC, predicted environmental concentration) according to relevant guidance documents[8]. As a consequence, low quantities of PPP may be acceptable in surface water, if it is demonstrated that these levels do not pose any risk to the relevant environmental species (e.g. aquatic organisms). This implies that the chemical quality of surface water may be affected only up to an extent which does not cause negative effects on aquatic organisms.

The approval of active substances and authorisation of BP under the BP Regulation is, like for PPP, based on a risk assessment. The main difference with PPP is the attention for the marine aquatic environment because of the use of wood preservatives and antifoulings. Applicants have to submit detailed information for active substances and BP concerning the environment (see in particular Points 9, 10 and 11 of Annex II and Annex III of the BP Regulation). Guidance is available regarding how to fulfil the information requirements and how to evaluate applications in order to protect the environment. The Guidance covers, inter alia, assessment of effects for the freshwater and marine aquatic compartments;[9] emission scenarios to estimate the potential release to the environment of active substances from BP or treated articles.[10]

For all kind of chemicals, including PPP and BP, the Water Framework Directive (Directive 2000/60/EC) allows to assess quality of water bodies via evaluation of:

1) "good chemical status" of water bodies (defined in terms of compliance with all the quality standards established for chemical substances at European level);

2) "good ecological status" of water bodies (defined in terms of quality of the biological community, the hydrological characteristics and the chemical characteristics).

As regards the "good chemical status" of water bodies, lists of "priority substances" and priority hazardous substances" are identified based on their toxicological profile and are periodically monitored in the EU water bodies. "Priority substances" include substances with ED properties. The values compiled are aimed at providing information which would inform regulatory decision makers on particular substances, and if applicable, take the necessary

[8] For instance: EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2013. Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013;11(7):3290, 268 pp. doi:10.2903/j.efsa.2013.3290.

[9] ECHA 2015. European Chemical Agency. Guidance on the Biocidal Products Regulation. Volume IV Environment – Part B Risk Assessment (active substances) Retrieved on: http://echa.europa.eu/documents/10162/15623299/bpr_guidance_ra_vol_iv_part_b_en.pdf

[10] ECHA 2016. Emission scenario documents. Retrieved from: http://echa.europa.eu/fr/guidance-documents/guidance-on-biocides-legislation/emission-scenario-documents

measures to remedy undesired levels of substances. In some cases, substances (or their metabolites) in the water can derive from different sources and it is not always easy to identify the most appropriate action to reduce substance levels in the environment.

Both for PPP and BP, if we compared the different options for criteria to identify EDs only considering the *chemical* quality of the groundwater, drinking water and surface water, the options would be ranked in terms of the number of substances identified, i.e. the higher the number of substances removed from the market the better the chemical status of the waters (option 1 > 2/3 > 4). This is an approach, which does not consider that some of these levels of chemicals would actually pose no risk to aquatic organisms.

Regarding options for regulatory decision making, Options A and B would rate equally assuming that both would lead to chemical qualities which would pose no risk to organisms, and both options would rate better than Option C. In other words, the options would perform A/B > C and this performance has been considered for all MCA-scenarios with exception of scenario 5 "aim: exposure zero" (see Annex 7).

This MCA-scenario "aim: exposure zero" was developed in order to perform a sensitivity analysis on the performance of the options. It assessed the performance of the options based on a different assumption: the higher the number of substances removed from the market, the better the performance of the options with respect only to exposure (no consideration of risk assessment) for the environment. Similarly, regarding options A to C, the assessment under this scenario 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 would perform the best with respect only to exposure (no consideration of risk assessment) for the environment. The options under this scenario consequently perform as A > B > C.

3. WILDLIFE VERTEBRATE POPULATIONS

3.1. Evidence on possible association between ED exposure and wildlife population declines

The possibility that the current decline in some wildlife populations may be at least partially due to exposure to EDs in the environment have been raised in international reports on the topic. The WHO-UNEP 2012 report "Science of Endocrine Disrupting Chemicals"[11] suggests an association between chemicals with ED properties and wildlife population declines.

The report indicates that the decline is due to a number of factors including overexploitation, loss of habitat, climate change and chemical contamination. However, the authors of the report state that, given their understanding of EDs and of their effects on the reproductive system, it is likely that declines in the numbers of some wildlife populations (raptors, seals and snails) have occurred because of the effects of chemicals (DDT, PCBs and tributyltin,

[11] 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

respectively) on these species. They stress that evidence for EDs as a cause of these population declines has increased in 2012 relative to 2002, because of the population recoveries following restrictions on the use of these chemicals. The report acknowledges that an endocrine mechanism for current wildlife declines is *probable*, but not proven. It also concludes that:

- EDs with mechanisms of action similar to the chemicals mentioned above are *suspected* to also be a factor contributing to declines seen in wildlife species today.
- Demonstrating a clear link between endocrine effects in individuals and population declines or other effects will always be challenging, because of the difficulty in isolating effects of chemicals from the effects of other stressors and ecological factors

The 2012 report of the European Environmental Agency[12] on EDs points out that there is evidence of reproductive and developmental harm linked to impairments in endocrine function in a number of wildlife species, particularly in environments that are contaminated by cocktails of chemicals that are in everyday use. Laboratory studies show that the reproductive systems of a broad range of vertebrate species (e.g. polar bears and fish) and some invertebrate species (e.g. snails, oysters and insects) are susceptible to ED chemicals, and that foetal/early exposure of animal models to these chemicals can reproduce the pathogenesis seen in some populations. According to the authors, in some fish species, the evidence linking exposure to chemicals with reproductive disorders and dysfunction is strong. According to the report it is clear that examples exist of male and female reproductive dysgenesis and of thyroid hormone disruption in some wildlife classes that can be linked, quite convincingly, to EDs exposure, although the report acknowledges that causation is difficult to prove.

Most if not all the evidence brought forward in the WHO-UNEP 2012 report refer to substances which are not anymore on the market (e.g. DDT, DDD, DDE, dicofol, atrazine, dibromochloropropane, lindane, tributyltin, hexachlorobenzene, carbaryl, vinclozolin, procymidone and fenitrothion, triphenyltin and triclosan) or they are not PPP or BP (e.g. PCBs, flame retardants, dioxins, mercury). A similar situation can be noted for the report of the EEA[12] as the report refers to PPP active substances that are not anymore allowed to be placed on the market (e.g. atrazin, diazinon, alachlor, vinclozolin, dieldrin, chlordane, dicofol, methoxychlor, nonylphenol ether, polyoxyethyleneglycol, nonylphenol ethoxylate, fenarimol and methoprene).

The conclusions of the WHO-UNEP 2012 report have been criticised in the public literature for misinterpreting the available evidence and for methodological issues.[13,14] According to Lamb et al., the WHO-UNEP 2012 report does not accurately reflect the original articles

[12] EEA Technical Report No 2/2012, The impacts of endocrine disrupters on wildlife, people and their environments – The Weybridge+15 (1996–2011) report. Retrieved on: www.eea.europa.eu/publications/the-impacts-of-endocrine-disrupters

[13] Lamb 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

[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 (Lamb et al. 2014). Regulatory toxicology and pharmacology 73(3): 754-757. doi:10.1016/j.yrtph.2015.10.029

which are cited as the two most prominent examples of evidence of ED in wildlife (link between DDT and bird population and between tributyltin and snail population): according to Lamb et al., the authors of the original works concluded that the lack of data on both exposure and effects in these organisms did not allow firm conclusions. E.g. according to Lamb et al. a review[15] on the possible link between tributyltin (TBT) and snail population decrease indicated inter alia the lack of agreement among researchers on the mechanism for induction of effects and the fact that female masculinisation by TBT or triphenyltin (TPT) has been confirmed in the laboratory in only a small fraction of species affected (7.5% or 20 species confirmed out of 268 total species examined). All these uncertainties were not indicated in the evidence reported on the topic in the WHO-UNEP 2012 report.

Lamb et al. do not agree with the conclusion of the WHO-UNEP 2012 report that *an endocrine mechanism for wildlife declines is probable but not conclusive.* They also state that it would be more appropriate to conclude that the evidence for an endocrine mechanism is hypothetical, rather than probable, particularly given the fact that for the two best known examples for wildlife declines, DDT and TBT, an endocrine mechanism, while possible, is only one of many potential factors that may be contributing to the observed population dynamics. Hecker and Henner[16] indicated that many studies have been conducted to describe potential EDs in wild and laboratory animals, but few studies have attempted to explore the ecological relevance of the exposure to endocrine active chemicals under field conditions.

Other scientists[17] criticise the WHO-UNEP 2012 report (some of them ex-chair of European Commission Scientific Committees). They support the critics of Lamb et al. 2014 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 report of 2012 and is also missing in the Zoeller et al.'s (2014) article.*

Finally, other critics[18,19] to the WHO-UNEP 2012 report regarded more general methodological issues, 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).

[15] Titley-O'Neal, C.P., Munkittrick, K.R., and MacDonald, B.A., 2011. The effects of organotin on female gastropods. Journal of Environmental Monitoring. 13: 2360-2388. DOI: 10.1039/C1EM10011D

[16] Hecker, M. and Henner, H. 2011. Endocrine disruptor screening: regulatory perspectives and needs. Environmental Sciences Europe 23:15

[17] Autrup, H., Barileb, F. A., Blaauboerc, 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.

[18] 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

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

The Kortenkamp report[20] provides an overview on the ED effects in different animal species. In fish, effects of EDs on reproductive endpoints are well documented both in the field and the laboratory; in amphibians, EDs have been shown to affect reproductive and thyroid endpoints; in marine mammals, ED has not been studied in great detail, but there are strong indications that endocrine related endpoints have been affected by persistent organic pollutants (POPs) in wild populations; in birds, abnormalities of the reproductive tract, thyroid function and hormonally sensitive behavioural endpoints have been reported in the wild and can be induced in the laboratory with model EDs and hormones; in reptiles, ED remains a largely unexplored area of research and is not covered by the assays currently validated; in invertebrates, knowledge of endocrinology and how it is affected by EDs is largely confined to arthropods and molluscs.

Similarly to the WHO-UNEP 2012 report, also in the Kortenkamp report, the evidence reported in favour of a link between exposure to EDs and adverse effect in the environment is limited to substances which are not PPP or BP. In the rare cases, where the effect in a wild species is linked to a specific PPP or BP, these substances happen to be not anymore on the EU market since years (Table 1).

Table 1. 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/EC[21]

ACTIVE SUBSTANCE	NON-APPROVED SINCE	CLASS OR USE
hexachlorobenzene	2004/1979*	fungicide
tributylin (3AS)	2002	fungicide
atrazine	2004	herbicide
terbufos	2002	insecticide
trichlorfon	2007	insecticide
mirex	2004	insecticide
coumpahos	1993	insecticide
permethrin	2000	insecticide
heptachlor epoxide	2004/1979*	metabolite heptachlor***
chlordane	2004/1979*	organochlorine insecticide
4,4'-DDE	1993**	organochlorine insecticide
DDT	2004/1979*	organochlorine insecticide
dicofol	1979	organochlorine insecticide
dieldrin	2004/1979*	organochlorine insecticide
endosulfan	2005	organochlorine insecticide
heptachlor	2004/1979*	organochlorine insecticide
lindane	2000	organochlorine insecticide
methoxychlor	2002	organochlorine insecticide
nonachlor (trans and cis chlordane)	2004	organochlorine insecticide
toxaphene (campechlor)	1979	organochlorine insecticide
fonofos	2002	organophosphate insecticide
phorate	2002	organophosphate insecticide

[20] 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

[21] 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). Available on: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:31979L0117

phorate	2002	organophosphate insecticide
oxychlordane	2004	metabolite chlordane ***
*= non-approved 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 non-approval equivalent of the one of the parent compound		

3.2. Consideration of vertebrate and invertebrate populations

A reasonably complete suite of standardised assays for testing the effects of EDs is available for the oestrogenic, androgenic, thyroid and steroidogenic modalities in mammals and fish, with fewer tests for birds and amphibians.[8] For invertebrates, standardised mechanistic assays are not yet available as OECD testing guidelines, mainly due to poor current understanding of endocrinology in most invertebrates understanding, which differs from the one of vertebrates., and the lack of screening endpoints specifically related to ED.

Therefore, the screening of chemicals performed as a supportive study for this IA focused on vertebrate wildlife species.

As a consequence, considering the current state of knowledge, the evidence compiled in this IA focusses on impacts related to potential associations between exposure to EDs and adverse effects limited to human health and wild vertebrate species. However, effects on invertebrates are also assessed, including effects on reproduction, before approval or authorisation of PPP and BP (see next section).

3.3. Environmental risk assessment in the context of approval of active substances used in PPP and BP and rating of the options for identifying ED criteria

As mentioned in Section 1 of this Annex, it needs to be considered that it is so far not possible to identify robust and reliable environmental impact indicators in relation to ecosystem services or species level effects,[4] which implies that robust conclusions are difficult to extract. Nevertheless, protection of the environment remains a priority, as it is a mayor objective in the PPP and BP Regulations, and thus guides this impact assessment. Protection of the environment is therefore analysed under consideration of the current regulatory decision making under the PPP and BP Regulations.

As mentioned already in other sections of this IA report, PPP and BP are among the strictest regulated chemicals worldwide.[22;23] 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.[24] Only substances present on the positive list can be used

[22] 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.

[23] 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.

[24] 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

in PPP or BP placed on the EU market, if applicable with restrictions in use, provided they also pass the second step of national authorisation of the formulated products.

The EU legislation in place also 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 data requirements[25;26] is specified and has to be submitted by the applicant before any approval of the active substance or authorisation of a product containing the approved substances can be considered. These core data requirements, in particular under the PPP regulation, include testing of several non-target species which cover several ecological compartments (earthworms, algae, fish, aquatic and terrestrial arthropods including bees, birds, mammals, terrestrial plants). These tests cover, in most of the cases, reproductive effects, and may include also early-life studies, full-life-cycle, multi-generation tests or more complex semi-field studies if so required. It could be thus concluded that effects on wildlife species, in terms of potential reproductive effects which may be potentially relevant for population effects, are already covered by the PPP Regulation. In addition, tests which would cover ED endpoints have been added recently to the data requirements. For BP the studies should also, if appropriate, address the potential effects on sensitive taxa or species in the marine environment that contains key taxa that are not present in freshwater environment (e.g. Echinodermata).

Further, recent trends in environmental risk assessment may be considered, as for instance the application of the ecosystem service concept[27], The Economics of Ecosystems and Biodiversity (TEEB)[28], which would also cover effects on biodiversity. The European Food Safety Authority concluded that in general environmental risk assessment should be based on effects on populations rather than for individuals.[29]

Confirming this trend it should be mentioned that also under REACH[30] it was recognised that the information on selected species may still be a poor predictor of impacts at the ecosystem level.

Confirming the fact that the current EU regulatory system already addresses EDs, is the fact that most of the evidence presented in the WHO-UNEP 2012 report for pesticides with ED

[25] 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.

[26] 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

[27] EFSA Panel on Plant Protection Products and their Residues (PPR); Scientific Opinion on the development of specific protection goal options for environmental risk assessment of pesticides, in particular in relation to the revision of the Guidance Documents on Aquatic and Terrestrial Ecotoxicology (SANCO/3268/2001 and SANCO/10329/2002). EFSA Journal 2010;8(10):1821. [55 pp.] doi:10.2903/j.efsa.2010.1821. Available online: www.efsa.europa.eu/efsajournal.htm

[28] See The economics of ecosystems and biodiversity (TEEB) website: http://www.teebweb.org/

[29] 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.

[30] Assessing the health and environmental impacts in the context of socio-economic analysis under REACH. Final Report- Part 1: Literature review and recommendations. March 2011. Prepared for the European Commission, Directorate-General for Environment. Available at: http://echa.europa.eu/documents/10162/13580/reach_sea_part1_en.pdf.

properties related wildlife effects, is concerning substances that are not anymore approved in the EU as PPP or BP for many years (e.g. DDT, vinclozolin, methoxychlor, terbutyltin) (see Table 1).

Regarding biocides, for instance, ***triclosan***, a disinfectant identified as a substance with ED properties in the 2012 WHO/UNEP report, is not approved in the EU as an active substance to be used in BP (product-types 1, 2, 7 and 9) since 2014 and 2016, respectively.[31]

Triclosan is an antibacterial active ingredient for use in disinfectants and preservatives. It may also have virucidal and fungicidal activity. In the WHO-UNEP 2012 report, it is mentioned that triclosan disrupts steroidogogenic enzymes involved in the production of testosterone and estrogen, which could lead to reduced reproductive success in both males and females. The 2012 WHO/UNEP report indicated that there is growing number of studies from the open literature showing potential problems with triclosan concerning ED. It is pointed out to postpone the assessment on ED properties until the currently on-going evaluation under REACH has been finalised[32].

Regarding biocides, the situation may be more complex due to the possibility to consider socio economic factors. An interesting example is ***creosote,*** a wood preservative identified as biocidal substance with potential ED properties under option 1. Creosote is a distillate of coal tars and it is a complex mixture of hundreds of distinct compounds, including bi- and polycyclic aromatic hydrocarbons. It is used for biocidal treatment of timber as wood preservative by vacuum-pressure impregnation (product type 8). Creosote was approved in 2013[33]: it contains PBT constituents and it is classified as carcinogenic category 2, thus fulfilling the exclusion criteria under the BP Regulation. However, it was approved based on the assessment report which concluded that there are no realistic alternatives. Also the results of the public consultation on this active substance indicated that there would be severe economic and practical consequences if creosote treated wood cannot be used in infrastructure built for telephone communications and railway connections. The approval specifies that BP containing creosote may only be authorised for uses where no appropriate alternatives are available.

As illustrated in the previous paragraphs, several substances have been non-approved in the EU, sometimes since years, or approved subject to strict conditions in recent years, demonstrating the regulatory system in the EU succeeds in protecting the environment.

As a consequence, it can be assumed, based on available scientific evidence from EU agencies and scientific committees,[34;35] that a regulatory decision making based on a risk assessment would protect environment in a similar way as a hazard approach.

[31] Commission Implementing Decision of 24 April 2014 (2014/227/EU) and of 27 January 2016 (2016/110/EU)
[32] For further information see the decision on substance evaluation for Triclosan. Retrieved from: http://echa.europa.eu/documents/10162/13628/corap_sev1_222-182-2_dec_final_public_2710_en.pdf
[33] Commission Directive 2011/71/EU
[34] 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.

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 the environment to a less extent. This option would request a modification via ordinary legislative procedure of the current PPP Regulation.

Option 1 is not able to identify EDs relevant for the environment. 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.

As a consequence, the performance of options would be 2/3/4 > 1 and A/B > C, respectively. These performances of the options have been considered for all MCA-scenarios with exception of the MCA-scenarios "aim: exposure zero".

In order to perform a sensitivity analysis on the performance of the options, the MCA-scenario "aim: exposure zero" was developed. It assessed the performance of the options considering a different assumption only based on exposure considerations: the higher the number of active substances identified as EDs, the better the performance of the option with respect to exposure (without consideration of any risk assessment) for the environment.. As a consequence, within this scenario, the options performed as follows: 2/3 > 4 > 1. 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.

4. ANIMAL WELFARE

Animal testing is required on a standard basis to assess the safety of active substances and PPP and BP, to both humans and the environment. Also the potential of chemicals to disrupt

[35] 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

endocrine functions relies on a large number of *in vivo* tests, i.e. tests using live animals[36]. With increasing testing demands and requirements the number of rats, mice, fish and frogs needed for generating the relevant data will grow[37].

The EU legislation in place tries to reduce as much as possible the use of animals for scientific purposes (see Sections below). In addition, the European Commission, trade associations and companies are cooperating via the European Partnership for Alternative Approaches to Animal Testing (EPAA) to accelerate the development, validation and acceptance of alternative approaches to animal use in regulatory testing. The overall aim is the replacement, reduction and refinement (3Rs) of animal use in regulatory testing[38]. However, for the purpose of identifying EDs, it is likely that *in vivo* animal testing cannot be avoided completely, as in accordance with the WHO/IPCS definition (2002), an ED is defined 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*".

It is thus expected that the four options may thus have an effect on animal testing. Therefore they will be assessed on the basis of the number of animal tests they would trigger: for the purpose of the multi-criteria analysis, it was assumed that the more animal tests an option implies, the worst performing it is.

Further, in the public consultation (See Annex 2) it was also indicated that evidence coming from *in vivo* testing is required in order to identify an ED. This is applicable for all options; however, for Option 3, additional animal tests would be needed to clarify the status of the active substances found in the Categories II and III. This would imply the use of more animals to generate data.

It was also pointed out that the ED criteria would involve large numbers of test animals to provide data which would not add any additional understanding to the toxicological behaviour of the chemicals that already have extensive data packages. Further, for some areas it would be difficult in the future to differentiate between a potential ED and an ED, for instance for substances registered solely for use in cosmetic products due to the ban on animal testing for cosmetic ingredients (effective since 2013).

Despite the on-going additional efforts launched at various levels, the replacement of animal test methods by alternative *in vitro* or *in silico* methods in relation to complex toxicological endpoints is considered to be scientifically challenging. However, another respondent to the public consultation stressed that the definition of EDs should be flexible enough to allow for use of alternative methods to *in vivo* tests. Limiting the definition to evidence only provided by animal testing would preclude adoption of approaches that could minimise or eliminate the use of animals.

[36] Only in vivo can absorption, distribution, metabolism and excretion of a chemical be accounted for. The impacts of ED on wildlife, people and their environments – The Weybridge+15 (1996–2011) report: europa.eu/publications/the-impacts-of-endocrine-disrupters.

[37] Hecker, M. and Henner, H. 2011. Endocrine disruptor screening: regulatory perspectives and needs. Environmental Sciences Europe 23:15

[38] EPAA. 2016. European Partnership for Alternative Approaches to Animal Testing website. Retrieved from: http://ec.europa.eu/growth/sectors/chemicals/epaa/index_en.htm

It was also pointed out that the protection of humans and wildlife from the effects of EDs should not lead to the addition of new tests to what is already an exhaustive testing strategy. Non-animal test methods should be promoted in order to produce safety data relevant to humans and to replace animal studies currently in use. Tests on vertebrates should be undertaken as a last resort.

4.1. Provisions in relation to Animal Testing in EU legislation

4.1.1. General provisions

The protection and welfare of animals is an area covered by a wide range of EU legislation.

Article 13 of the Treaty on the Functioning of the European Union states that "*In formulating and implementing the Union's agriculture, fisheries, transport, internal market, research and technological development and space policies, the Union and the Member States shall, since animals are sentient beings, pay full regard to the welfare requirements of animals, while respecting the legislative or administrative provisions and customs of the Member States relating in particular to religious rites, cultural traditions and regional heritage*."

The use of animals for scientific purposes has been covered by EU legislation since 1986. Directive 2010/63/EU[39] on the protection of animals used for scientific purposes (replacing Directive 86/609/EEC) entered in effect on the January 1, 2013. The directive strengthens the legislation and improves the welfare of those animals which still need to be used. The principle of the 'Three Rs' (to Replace, Reduce and Refine the use of animals) is clearly stated.

This Directive widens the scope of animal testing and includes foetuses of mammalian species in their last trimester of development and cephalopods, as well as animals used for the purposes of basic research, higher education and training. It lays down minimum standards for housing and care, regulates the use of animals through a systematic project evaluation requiring inter alia assessment of pain, suffering distress and lasting harm caused to the animals. It requires regular risk-based inspections and improves transparency through measures such as publication of non-technical project summaries and retrospective assessment. The development, validation and implementation of alternative methods is promoted through measures such as establishment of a EU reference laboratory for the validation of alternative methods supported by laboratories within Member States and requiring Member States to promote alternative methods at national level.

[39] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, OJ L 276, 20.10.2010

4.1.2. Plant Protection Products Regulation

The PPP Regulation[40], which regulates the placing on the market of PPP, aims to reduce animal testing to the maximum.

Animals are used in the assessment of the safety of active substances and PPP, to both humans and the environment, as required by the Regulation. Although alternative test methods have reduced the reliance on animal testing and the number of animals involved, computer simulation and *in vitro* methods cannot yet replicate the complexity or reaction of a living creature.

Article 62 (1) of the Regulation states that: "*Testing on vertebrate animals for the purposes of this Regulation shall be undertaken only where no other methods are available. Duplication of tests and studies on vertebrates undertaken for the purposes of this Regulation shall be avoided in accordance with paragraphs 2 to 6*."

Animal testing on vertebrate animals should therefore be minimised (cf. also Article 7 (d) and Article 33 (3) (c); but also Regulation EU 283/2013 setting data requirements for active substances[41]) and undertaken only as a last resort. There should not be duplication of tests and data sharing is promoted: "*The prospective applicant and the holder or holders of the relevant authorisations shall make every effort to ensure that they share tests and studies involving vertebrate animals. The costs of sharing the test and study reports shall be determined in a fair, transparent and non-discriminatory way. The prospective applicant is only required to share in the costs of information he is required to submit to meet the authorisation requirements.*" (Article 62 (3) of the PPP Regulation).

The PPP Regulation also includes several recitals and articles that refer to the development and promotion of alternative methods and the importance of replacing animal studies. For instance, Recital 11 of the Regulation states that "*The development of non-animal test methods should be promoted in order to produce safety data relevant to humans and to replace animal studies currently in use*."

In addition, the PPP Regulation stipulates the standard data requirements[35] which have to be submitted in all cases.

4.1.3. Biocidal Products Regulation

The BP Regulation[42], which regulates the placing on the market and the use of BP, aims at minimising animal testing as far as possible.

One aim of the regulation is to avoid unnecessary testing on animals (cf. article 62 of the BP Regulation: "*In order to avoid animal testing, testing on vertebrates for the purposes of this*

[40] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC, OJ L309,24.11.2009

[41] Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, OLJ L93, 3.4.2013

[42] 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, OJ L167,27.6.2012

Regulation shall be undertaken only as a last resort. Testing on vertebrates shall not be repeated for the purposes of this Regulation"). Therefore, before carrying out any tests on animals, companies need to send an inquiry to the European Chemicals Agency (ECHA) to find out whether the same test or study has already been conducted and submitted under EU biocides legislation. If such information exists, companies are required to share the data. The owner of the data and the applicant seeking to rely on this data for a purpose under the BP Regulation must negotiate and come to a mutually acceptable arrangement. In absence of an agreement on sharing of vertebrate animal studies between the data owner and the prospective applicant, the Agency may allow the use of the studies by the prospective applicant without prejudice to the decision on the compensation made by national courts.

Annex II of the BP Regulation (information requirements for active substances) also refers to Directive 86/609/EEC on the protection of animals used for scientific purposes as it requires that "*Tests performed should comply with the relevant requirements of protection of laboratory animals, set out in Directive 2010/63/EU of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes (2) and in the case of ecotoxicological and toxicological tests, good laboratory practice, set out in Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their application for tests on chemical substances (3) or other international standards recognised as being equivalent by the Commission or the Agency. Tests on physico-chemical properties and safety-relevant substance data should be performed at least according to international standards."*[42]

In addition, the BP Regulation requires information to be submitted as part of the application for the approval of an active substance (Article 6 of the BP Regulation) or for the authorisation of a BP (Article 20 of the BP Regulation).

4.2. Expected impacts on animal testing by the options presented in this impact assessment

While recognising that animal testing is still needed to ensure the protection of human health and the environment, EU legislation sets very high animal welfare standards for such testing and requires that whenever possible this testing is replaced, reduced and refined.

None of the options for criteria to identify EDs will succeed in avoiding animal testing. On the contrary, some options may actually trigger further animal testing, which is a reason of concern for several respondents to the public consultation who specifically called for the development and use of methods that do not rely on animal testing in order to produce safety data.

Option 1 (interim criteria) is based on Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (CLP Regulation): in order for an applicant to prove that an active substance is not carcinogenic category 2, toxic for

reproduction category 2, and does not have toxic effects on the endocrine organs, studies, mostly based on animal tests, will need to be provided.

Options 2, 3 and 4 are all based on the WHO/IPCS definition which implies the need for evidence from experimental *in-vivo* animal studies to support the claim that a substance has/has not the capacity to cause endocrine-mediated adverse effects in humans or wildlife populations. These options make it difficult to identify an ED based only on *in vitro* testing.

Furthermore, Option 3 (WHO/IPCS definition + additional categories) would potentially trigger even more animal testing. If an active substance would be categorised as a suspected ED or an endocrine active substance (Categories II and III of Option 3), the applicant may need to provide additional studies (most probably based on animal testing) to prove that the substance should not be categorised. Applicant would be requested to do so by authorities for clarification or, alternatively, they may provide the data in order to demonstrate that the substance should not be considered a suspected ED or an endocrine active substance to avoid "negative flagging" (substances placed in Categories II and III could be subject to misinterpretation).

Looking at the animal tests which may be triggered by the different options, Option 3 is considered as performing worse that the Options 1, 2, and 4. The latter are based on standard data requirements under the PPP and BP legislation, while Category III may trigger additional animal testing without direct regulatory consequences. The options are thus performing 1/2/4>3.

With regards to Options A to C, no difference in terms of animal tests required is expected because the data requirements under the PPP Regulation and BP Regulation are set. The fact that the decision on the approval of a substance is taken mainly based on hazard or based on risk, or that socio economic elements can be taken into consideration, is not expected to affect the data requirements for a dossier. Therefore, in terms of animal welfare, all options are performing the same: A/B/C.