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COMMISSION STAFF WORKING PAPER

4th Report on the implementation of the "Community Strategy for Endocrine Disrupters" a range of substances suspected of interfering with the hormone systems of humans and wildlife (COM (1999) 706)

Summary

The present document is the 4th report on the implementation of the Community strategy on endocrine disrupters.

Results from numerous research projects are increasing our knowledge and understanding of the functioning of the endocrine system and its susceptibility and sensitivity to exogenous substances. While it is apparent that many substances may cause changes in the body's hormonal signalling mechanism it is considerably more challenging to identify when such changes will result in adverse effects on health.

In recognition of the need to address the problem of endocrine disrupters, many pieces of EU chemicals' legislation contain specific provisions on this issue. Currently the main focus, both within the EU and internationally, is to agree on approaches for the identification and assessment of endocrine disrupters.

EU legislation currently offers relatively limited opportunities for an integrated assessment of the cumulative effects of different substances having adverse effects on the endocrine system. While the assessment of such cumulative effects are being undertaken in relation to certain product types (e.g. plant protection products) or for substances which are part of the same substance class (e.g.selected phthalates in the context of REACH), there is no mechanism for assessing the cumulative impact of the range of endocrine disruptors to which human beings and the environment are exposed.

Given the increasing concerns in relation to the potential impact of endocrine disrupting substances, particularly in relation to human fertility, the Commission has contracted a major study to be carried out on the basis of which it will review the existing Community strategy.

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1. INTRODUCTION

In December 1999, the Commission adopted a Communication to the Council and European Parliament on a Community Strategy for Endocrine Disrupters[1]. The strategy addresses the key requirements of further research; international co-operation; communication to the public and appropriate policy action. Recommendations are made for short-, medium- and long-term actions. On 26 October 2000, the European Parliament adopted a Resolution on endocrine disrupters, emphasising the application of the precautionary principle and calling on the Commission to identify substances for immediate action.

On 30 March 2000 the Environment Council adopted Conclusions on the Commission Communication in which it stressed the precautionary principle, the need to develop quick and effective risk management strategies and the need for consistency with the overall chemicals policy. The Council invited the Commission to report back on the progress of the work at regular intervals, and for the first time in early 2001.

To date the Commission has produced three reports on the implementation of the Community strategy[2,3,4]. The present document is the 4th report in the series. In November 2010 the European Food safety Authority published a scientific report of its Endocrine Active Substances Task Force. The report provides an overview of existing knowledge and of the challenges for risk assessment in relation to food and feed as well as a summary of current initiatives at national, EU and international levels.[5]

In the Council conclusions of 22nd December 2009 on the "Combination Effects of Chemicals" the Commission was invited to include in the present document, recommendations as to how exposure to multiple endocrine disruptors should be further addressed within relevant existing Community legislation[6].

2. PROGRESS ON SHORT-TERM ACTIONS

2.1. Establishment of a List of Priority Substances

As described in the 3rd report, the Commission services developed a priority list of substances to be investigated further on the basis of their possible endocrine disrupting properties. A database containing the information that was used to establish this priority list, was made available through DG ENV's Endocrine Disruptor Website[7]. The database has proven useful in providing regulators and researchers with a considerable amount of information on

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1 Communication from the Commission to the Council and the Euro[ean Parliament-Community Strategy for Endocrine Disrupters. COM (1999) 706 final

2 Communication from the Commission to the Council and the European Parliament on the implementation of the Community Strategy for Endocrine Disrupters. COM (2001) 262 final

3 Commission staff working document on implementation of the Community Strategy for Endocrine Disrupters. SEC (2004) 1372.

4 Commission staff working document on the implementation of the Community strategy for endocrine disrupters. SEC(2007) 1635.

5 EFSA. Scientific Report on EAS. EFSA Journal; 8(11): 1932.

6 Council of the European Union 17820/09

7 http://ec.europa.eu/environment/endocrine/strategy/short_en.htm

potential endocrine disruptors at one address and has been used by a number of stakeholders for prioritisation.

The Commission services are currently examining the possibility of setting-up a web-based IT platform on Endocrine Active Substances. The platform would incorporate the existing data base and would provide an interactive, user-friendly source of scientific and technical information that could be used by the scientific and regulatory community as well as civil society and industry. At an international workshop organised in October 2010 by the European Commission's Joint Research Centre (DG JRC) it was recommended that the platform should be developed in an incremental manner with priority being given initially to EU funded research projects.

2.2. Communication to the Public

DG Research and Development (RTD) maintains a dedicated website[8] on endocrine disruptor research in the EU, funded by the European Commission, which is updated regularly as regards ongoing and past projects in this area. Many of the funded projects also maintain their own dedicated websites.

DG RTD has organised four international workshops to discuss testing strategies in relation to endocrine disruptors (2005, 2006, Brussels, 2006 Helsinki, 2008 Prague). DG ENV maintains a dedicated website[9] on the general information on endocrine disruptors and the activities of the Commission under the Community Strategy for Endocrine Disrupters.

DG JRC has recently launched a dedicated website[10] on their activities on Endocrine Disruptors.

2.3. Monitoring Programmes

At the level of the EU, there are no coordinated or combined monitoring programmes specifically dedicated to endocrine disruptors. However, there are many individual programmes carried out at national, European and global level which include such substances within their scope. Such individual programmes are frequently undertaken to ensure that standards (e.g. emission standards, residue limits or environmental/health quality standards) established under national or EU legislation are complied with. Member States, the European Commission and EU Agencies also generate and report the results of surveillance monitoring designed to assess the concentrations of chemicals to which human populations and biota are actually exposed and carried out in fulfilment of obligations deriving from international agreement (e.g. Stockholm Convention, OSPAR Convention (OSPAR), Convention on the Protection of the Marine Environment of the Baltic Sea Area (HELCOM), Arctic Monitoring and Assessment Programme (AMAP), Co-operative Programme for Monitoring and Evaluation of the Long-range Transmission of Air Pollutants in Europe (EMEP)) or international organisations (e.g. World Health Organisation (WHO), United Nations Environment Programme (UNEP).

Significant amounts of monitoring data are also generated by the scientific community in the framework of the research projects supported via national and EU research programmes. DG

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8 http://ec.europa.eu/research/endocrine/index_en.html

9 http://ec.europa.eu/environment/endocrine/index_en.htm

10 http://ihcp.jrc.ec.europa.eu/our_activities/cons-prod-nutrition/endocrine_disrupters

RTD has launched a coordination action called COPHES[11], which is working towards an EU Human Biomonitoring framework. This will be accompanied by a feasibility study called DEMOCOPHES, funded by DG ENV, which began in autumn 2010. A minimum of 120 (60 for Cyprus and Luxemburg) sample pairs per country (i.e. 240 samples) will be investigated. A minimum of four biomarkers will be measured: total mercury in scalp hair, cadmium, cotinine and phthalates in urine. Member States will also have the opportunity, in the scope of the pilot study, to carry out measurements of further biomarkers which may include additional substances with endocrine disrupting effects.

There is little if any co-ordination regarding the way that data are collected, managed, assessed and reported across the different monitoring programmes. Consequently, a resource that could potentially play a very significant role in shaping and informing policies, including policy on endocrine disruptors (EDs), is not used effectively. To address this issue the Commission is undertaking a feasibility study to examine how the quite abundant substances' monitoring data could be used in a more systematic way.

3. MEDIUM-TERM ACTIONS

3.1. Identification and assessment of endocrine disruptors

Considerable efforts have been made at national, EU and international level to identify and assess endocrine disruptors. There has been considerable activity within the EU to develop criteria and testing strategies for identification of endocrine disruptors as a consequence of severe restrictions on substances identified as endocrine disruptors imposed by several pieces of legislation (see section 4). The Commission and several Member States have initiated work on possible criteria for identification of endocrine disruptors. There has been considerable activity also under OECD as regards development of guidelines for testing potential endocrine disruptors. Seven test methods designed for testing endocrine disrupting properties have been agreed and adopted (TG 229 Fish Short Term Reproduction Assay, TG 230 The 21-day Fish Assay: A short-term screening for endocrine or reproductive activity, TG 231 The Amphibian Metamorphosis Assay, TG 407 Repeated Dose 28-Day Oral Toxicity Study in Rodents, TG 440 Uterotrophic Bioassay in Rodents: A short-term screening test for oestrogenic properties, TG 441 The Hershberger Bioassay in rats: a short term test for (anti)androgenic properties, TG 455 The Stably Transfected Human Estrogen Receptor-α Transcriptional Activation Assay for Detection of Estrogenic Agonist-Activity of Chemicals) and several others are in the pipeline for the coming period. In addition, the Endocrine Disruptor Testing and Assessment Advisory Group has initiated work on a guidance document for the assessment of chemicals for endocrine disruption and on a detailed review paper on additional endocrine effects related endpoints.

3.2. Research

3.2.1. The EU Framework Programmes (see previous reports for details of some of the projects completed under earlier framework programmes)

The **CREDO cluster** (Cluster of Research into Endocrine Disruption in Europe) [12]. was launched in April 2003 as a direct response to the need for further research identified in the

[11] European coordination action on human biomonitoring - http://www.eu-hbm.info/

[12] http://ec.europa.eu/research/endocrine/projects_clusters_en.html

Community strategy on Endocrine Disrupters and lasted until 2008. Four projects with a total budget of approximately €20 million were part of the cluster encompassing 63 laboratories across Europe. One of the results of the cluster was to demonstrate that the conventional approach for estimating no-observed-effect-levels for chemicals is inadequate when it comes to capturing some low dose effects of substances with endocrine disrupting effects. The determinants of additive combination effects of several of such substances with a common mode of action are now well understood. Such substances with a relatively low potency and at low exposure levels can still work together to produce significant combination effects when they are present in sufficient numbers. Furthermore, a wide variety of endocrine disrupting substances has been found together in human tissue specimens, and in specimens of wild fish. Existing mode-of-action-screens that focus on estrogenic, anti-androgenic and thyroid disrupting properties of substances do not take account of recent knowledge about hormone signalling. The reproductive and developmental effects of certain endocrine disruptors are comparable across phyla, from invertebrates to mammals.

The integrated project REPROTECT[13] was undertaken as part of the **Sixth Research Framework Programme** (FP6, 2002-2006) It involved 32 participating European groups including the Joint research Centre. The project, began in July 2004 with an EC contribution of €9.1 million, and a total budget of €13.2 million over 5 years. The aim was to develop *in vitro* methods reflecting relevant toxicological targets of reproductive toxicants with the aim to combine successfully optimised tests in a battery approach. Adverse effects on the mammalian reproductive cycle were predicted by more than 20 different tests reflecting various toxicological endpoints of the reproductive cycle. Effects on Leydig and Sertoli cells, folliculogenesis, germ cell maturation, sperm cells, steroidogenesis, the endocrine system, fertilization and on the pre-implantation embryo are assayed by the various test systems. The development/optimization of each test has been performed according to the European Centre for the Validation of Alternative Methods(ECVAM) modular approach[14]. An independent statistical evaluation has been performed for the majority of the tests in order to define their reproducibility. The project also carried out a feasibility study, in which 10 substances, selected by an independent expert group but the identity of which was unknown to the participating laboratories, were analyzed in a test battery approach. The outcome of the study indicated that the known *in vivo* (in the animal) effects of the 10 test substances could be mostly - even though not in all cases - correctly predicted. The results of the feasibility study were published in August of 2010 in a special issue of "Reproductive Toxicology" along with 19 other papers from ReProTect partners.[15]

The CASCADE[16] network of excellence started in 2004 with an EC contribution of €14.4 million over six years. CASCADE brought 24 research groups from nine EU Member States together in a network for durable coordination and integration of research on chemical residues in food, especially substances with endocrine disrupting effects. The main focus of CASCADE has been to reshape the research environment in Europe. This has been done by introducing new ways of conducting and relating to research both within and beyond the research community. By mobilizing several hundred European scientists and enabling knowledge sharing and exchange of human capital, CASCADE has opened doors for collaboration and cooperation. The project ended in 2010 and became the CASCADE

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13 http://www.reprotect.eu/

14 A modular approach to the ECVAM principles on test validity. ATLA 32, 467-472, 2004

15 Reproductive Toxicology 2010, Volume 30, Issue 1, Pages 1-218

16 http://www.cascadenet.org/

Association for Collaboration in Endocrine Research and Training, a network which will continue to offer training, risk assessment and collaborative partnership.

In addition, the following ongoing large-scale projects are of relevance to the field of endocrine disruption and food: NEWGENERIS[17] focusing on the role of exposure to genotoxic substances (including endocrine disruptors) in the development of childhood cancer and immune disorders, PHIME[18] focusing on public health impact of long-term, low level mixed element exposure in susceptible population strata and BIOCOP[19] working on new technologies to screen multiple contaminants in food.

Moreover, eight "Specific Targeted Research Projects" with EC contributions between €1-5 million and lasting up to four years, as well as a number of Coordination Actions/Specific Support Actions were financed. These are listed on the dedicated website[20] on endocrine disrupter research in the EU. They looked at issues such as toxicity and hazard of non-dioxin-like PCBs present in food[21] or the use of (Q)SAR models for the prediction of the toxicity of chemical substances[22].

Funding of research on endocrine disruptors has continued in the **Seventh Research Framework Programme** (FP7, 2007–2013) mainly from the Themes 'Environment' and 'Food, Agriculture and Fisheries, and Biotechnology'. This provides evidence for continued interest from policy-makers and other stakeholders, and persisting scientific uncertainties. 18 projects have already been launched from the first three calls for proposals with relevance to endocrine disruption (listed on the EDC website).

In 2008 the NECTAR cluster[23] (Network for Environment Chemical Toxicants Affecting Reproduction) comprising 4 projects and receiving over €10M from the EU, was launched within the frame of the Environment theme. The focus of these projects is on the impact of early life exposures to endocrine disrupting substances on foetal testes development and male reproductive disorders in newborns and young adults (DEER), the impact of fetal exposures to mixtures of endocrine disrupting substances on human reproductive health (CONTAMED), and the impact of such substances on female reproductive tissue and consequent effects on conception, maintenance of pregnancy, and hormonal processes that regulate reproduction (REEF). According to the external mid-term review of the cluster, carried out in 2010, the mechanistic information produced in these projects should add significant support to biologically based health risk assessments of such substances.

In 2009 the 'Food, Agriculture and Fisheries, and Biotechnology' theme launched the project OBELIX[24] (2009- 2013) which is investigating whether prenatal exposure to endocrine disrupting compounds in food plays a role in the development of obesity and related disorders later in life. To achieve this, the project uses a multidisciplinary approach that combines epidemiology, neonatology, endocrinology, toxicology, analytical chemistry and risk assessment.

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17 http://www.newgeneris.org/
18 http://www.phime.org/
19 http://www.biocop.org/
20 http://ec.europa.eu/research/endocrine/index_en.html
21 http://www.cascadenet.org/~athon
22 http://www.caesar-project.eu/
23 http://www.nectarcluster.eu/
24 http://www.theobelixproject.org/

The PERFOOD[25] project (2009-2012) focuses on the development of robust and reliable analytical tools, including reference materials for the determination of perfluorinated compounds (PFCs) in food items. The aim is to qualify and quantify PFCs in our diet, understand how PFCs are transferred from the environment into dietary items, and quantify the possible contribution of food/beverage contact materials and food and water processing to the overall PFC levels in our diet. PERFOOD brings together a number of renowned research institutes in Europe with experts in food consumption and drinking water quality as well as food processing and packaging.

3.2.2. Additional Research Activities at DG JRC

Endocrine disruption is also an important aspect for environmental risk assessment (ERA) of chemicals, plant protection products/biocides and pharmaceuticals. In 2008, the JRC carried out a study to examine the potential use of the Threshold of Toxicological Concern (TTC) concept when applied to the assessment of endocrine active substances in aquatic ecosystems[26]. In 2008, the JRC held a workshop- "Thresholds of Toxicological Concern for Endocrine Active Substances in the Aquatic Environment" with the participation of the OECD, industry, the Commission and academia (Gross *et al.,* 2009).

4. LONG-TERM ACTIONS

4.1. Legislative actions - implementation of existing legislation

4.1.1. REACH

In accordance with Article 57 of the Regulation[27], substances:

- having endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health or to the environment which give rise to a level of concern equivalent to that of CMR substances categories 1A or 1B, or to PBT or vPvB substances,

- and that have been identified on a case-by case basis in accordance with the procedure set out in Article 59 of the Regulation,

may be included in Annex XIV (List of Substances Subject to Authorisation) in accordance with the procedure laid down in Article 58 of the Regulation.

Chapter 2 of Title VII of the Regulation (Articles 60 to 64) sets down the provisions for granting authorisations.

For substances that are included in Annex XIV, authorisations can be granted on condition that risks arising from the use of the substance are adequately controlled (article 60.2). However, for substances in Annex XIV that were identified:

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25 http://www.perfood.eu/

26 Gross et al. "Thresholds of toxicological Concern fo Endocrine Active Substances in the Aquatic Environment", Integrated Environmental Assessment and Management 6(1), pp.2-11 (2009)

27 Regulation (EC) No 1907/2006 of the European Parliament and the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). OJ l 396, Vol 49. 30.12.2006, p1

- as CMR (Carcinogenic, Mutagenic or Toxic for Reproduction) categories 1A or 1B or as substances of equivalent concern, and for which it is not possible to determine a threshold,

- or that were identified as PBT (Persistent, Bioaccumulative and Toxic) or vPvB (very Persistent and very Bioaccumulative), or as substances of equivalent concern,

authorisations can only be granted if it is shown that the socio-economic benefits outweigh the risks arising from the use of the substance and if there are no suitable alternative substances or technologies (Art 60.4).

On 17 February 2011, the European Commission decided to place six substances on Annex XIV of the Regulation of which three, bis(2-ethylexyl) phthalate (DEHP), benzyl butyl phthalate (BBP) and di-butyl phthalate (DBP) are known to have negative impacts on sexual development associated with negative impacts on the endocrine system.

Germany has announced its intention to prepare an Annex XV dossier in accordance with Article 59 of the Regulation for the possible inclusion of 4-(1,1,3,3-tetramethylbutyl)phenol on Annex XIV. This substance, also known as 4-tert-octylphenol, is suspected of having negative effects on the endocrine system. Similarly, Denmark has proposed to prepare Annex XV dossiers on 1,2-benzenedicarboxylic acid, di C7-C11 branched and linear alkyl esters based in part on concerns relating to endocrine disrupting properties.

Under Article 138.7 of the Regulation the Commission is required, by 1 June 2013, to carry out a review to assess whether substances subject to authorisation with regard to their endocrine disrupting properties should be included in Article 60.3 and consequently, only possible to be authorised via the procedure laid down in Article 60.4 (if socio-economic benefits outweigh risks and if there is no alternative).

Annex XVII of REACH lists the existing restrictions on the manufacture, placing on the market and use of certain dangerous substances, preparations and articles. Entry 51 of this Annex, which concerns three phthalates (DEHP, DBP and BBP) that are classified as toxic for reproduction and which act on the endocrine system, stipulates that these chemicals shall not be used as substances or as constituents of preparations, at concentrations higher than 0.1% by mass of the plasticised material, in toys and childcare articles. Entry 52 in Annex XVII concerns a further three phthalates (DINP, DIDP and DNOP). However, these substances are not classified and the associated restrictions are accordingly less stringent.. Entry 52 stipulates that these chemicals shall not be used as substances or as constituents of preparations, at concentrations higher than 0.1% by mass of plasticised material in toys and childcare articles which can be placed in the mouth by children. At the request of the Commission, ECHA carried out a review of the new available information on these phthalates. It concluded that the new available information on these substances was not of a nature to bring a new perspective to the assessments which were carried out in the past, and did not indicate the need for an urgent re-examination of the existing restrictions. However, ECHA recognised the need for further in-depth assessment of certain pieces of new available information in order to evaluate their reliability and relevance, among other issues with regard to endocrine disrupting effects (ECHA's review reports are available at: http://echa.europa.eu/reach/restriction/existing_restriction_en.asp).

4.1.2. Plant Protection Products Regulation (PPPR)

Substances identified as having ED properties that may cause adverse effects in humans cannot be authorized under the new PPPR[28]. By December 2013 the Commission is required to present (to the Standing Committee on Food Chain and Animal Health) a draft of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties (in relation to human health impacts) to be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 79(4). With regard to the ecological impacts, substances having endocrine disrupting properties that may have adverse effects on non-target organisms, can also not be authorized under the PPPR. However, in contrast to the situation with human health impacts, there is no obligation upon the Commission to present criteria for the determination of ED properties in relation to non-target organisms.

Pending the adoption of the scientific criteria for the identification of endocrine disruptors referred to in the preceding paragraph, the PPPR requires that substances that are, or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as Carcinogenic (Category 2) and Toxic for Reproduction (Category 2) shall be considered as having ED properties and accordingly shall not be authorized. In addition, substances, such as those that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 2 and which have toxic effects on the endocrine organs, may be considered to have such endocrine disrupting properties.

If on the basis of the assessment of EU or internationally agreed test guidelines or other available data and information, reviewed by the Authority, an active substance is considered to have endocrine disrupting properties that may cause adverse effect in humans, it shall be approved as a candidate for substitution in accordance with Article 24 of the PPPR.

Finally, if a substance is deemed to be an endocrine disruptor, it shall not be considered a substance of low risk.

EFSA's Scientific Panel on Plant Protection Products and their Residues (PPR) has recently published opinions on cumulative and synergistic risks from pesticides.[29,30] The PPR Panel is currently working on the development of probabilistic methodologies to assess the cumulative exposure and risk to pesticide residues in food, and, will also identify by the end of 2011 "cumulative assessment groups" of pesticides. These are substances that can be grouped together for risk assessment based on the identification of similar mode/mechanism of toxicological action. Although to date no formally agreed testing strategies for the identification and characterisation of endocrine disrupting substances are available, substances that have or that are suspected to have, such features are already given particular consideration in the on-going work on the establishment of cumulative assessment groups.

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[28] Regulation (EC) No 1107/2009 of the European Parliament and the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ l 309, Vol 52, 24.11.2009, p1

[29] Opinion of the Scientific Panel on Plant Protection Products and their Residues to evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) 396/2005. EFSA Journal (2008) 704, pp 1-84.

[30] Scientific opinion on Risk Assessment for a Selected Group of Pesticides from the Triazole Group to Test Possible Methodologies to Assess Cumulative Effects from Exposure through Food from these Pesticides on Human Health. EFSA Journal 2009; 7 (9); 1167 [187pp]

4.1.3. Biocides

At the technical meetings of the Biocidal Products Directive (BPD) 98/8/EC[31], coordinated by the JRC, approximately 400 substances are under review for their PBT (Persistent, Bioaccumulative or Toxic), or CMR (carcinogen, mutagen or toxic for reproduction) or potential endocrine disruptive properties. This review is being carried out in order to identify as early as possible those active substances that may not satisfy the criteria for inclusion in Annex I according to the future Biocidal Products Regulation which will adapt the current provisions of the BPD in a very similar way as under the PPPR described above .

4.1.4. Regulation on Cosmetics

Although substances with endocrine disrupting effects are currently not restricted under Regulation (EC) 1223/2009[32] on cosmetic products, Article 15(4) calls upon the Commission to review this Regulation with regard to substances with endocrine-disrupting properties, when EU, or internationally, agreed criteria for identifying substances with endocrine-disrupting properties are available, or at the latest by 11 January 2015. In 2010, the Commission appointed a panel of experts to report on the current status and future prospects on alternative (non-animal) methods for cosmetics testing, and to provide realistic estimates of the time required for the development of alternative methods where not already existing. Among the evaluated tests, alternative methods aiming to detect endocrine active compounds have been considered as part of reproductive toxicity testing[33].

4.1.5. Legislation on Food Contact Materials

EFSA's Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) published its latest opinion on Bisphenol A in September 2010[34] covering the latest scientific evidence. Based on this opinion and applying the precautionary principle the Commission has banned its use in infant feeding bottles while maintaining the authorisation in other plastic food contact materials with a specific migration limit of 0.6 milligram per kilogram food[35].

In 2010, the JRC's European Reference Laboratory on Food Contact Materials (EURL-FCM), jointly with the Network of National Reference Laboratories in the EU Member States, developed and validated a new analytical method for the quantitative determination of Bisphenol A in milk food simulant.

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31 Directive 98/8/EC of the European Parliament and the Council of 16 February 1998 concerning the placing on the pacing of biocidal products on the market. OJ L123, Vol 41, 24.4.1998. p1.

32 Regulation 1223/2009 of the European Parliament and of the Council of 30th November 2009 on cosmetic products. OJ L 342. 22.12.2009. p59

33 Adler et al. Arch Toxicol (2011) 85:367–485

34 Scientific Opinion on Bisphenol A: evaluation of a study investigating its neurodevelopmental toxicity, review of recent scientific literature on its toxicity and advice on the Danish risk assessment of Bisphenol A. EFSA Journal 2010; 8(9): 1829 {116pp}

35 Commission Directive 2011/8/EU of 28 January 2011 amending Directive 2002/72/EC as regards the restriction of use of Bisphenol A in plastic infant feeding bottles.

4.1.6. The Water Framework Directive[36] and the associated Directive on Environmental Quality Standards (for Priority Substances)[37]

These existing directives address the control of chemical substances (priority substances) that pose a risk to the aquatic environment and/or to human health via the aquatic environment; these may include endocrine disrupting substances. Substances identified as PBT (Persistent, Bioaccumulative and Toxic) or as being of equivalent level of concern in the context of the directives, may be designated as priority hazardous substances. Consistent with Article 57 of REACH, the equivalent level of concern can include substances having endocrine disrupting properties, e.g. nonylphenol.

As required by Article 8 of the EQS Directive, the Commission has been conducting its first review of the priority substances list. This has included applying the prioritisation principles outlined in Artile 16 of the Water Framework Directive to identify possible new priority and priority hazardous substances. The forthcoming Commission proposal is expected in early autumn 2011.

4.1.7. Food Additives

EFSA´s Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) has decided to consider endocrine effects for the preparation of guidance on submissions for food additive evaluations that will replace the current available guidance on submissions for food additive evaluations by the SCF (EC, 2001b).

4.1.8. Occupational Safety and Health

As far as the EU Occupational Safety and Health *acquis* is concerned, EDs have not been tackled as a separate grouping of substances. However, where EDs may present a risk to the health and safety of workers, the relevant regulatory requirements will apply, in particular Directive 98/24/EC on chemical agents[38].

In accordance with Directive 98/24/EC, the Commission shall, in order to protect workers from chemical risks, propose Indicative Occupational Exposure Limit Values (IOELVs)[39] to be set at EU level. In carrying out this task, the Commission is assisted by the Scientific Committee for Occupational Exposure Limits to Chemical Agents (SCOEL). Following the recommendation of SCOEL, the Commission has adopted an indicative occupational exposure limit value of 10 mg/m^3 for Bisphenol-A from inhalable dust.

A contractor is currently studying the health, socioeconomic and environmental impacts related to the possible extension of the scope of Directive 2004/37/EC1 of the European

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36 Directive 2000/60 of the European Parliament and the Council of 23 October 2000 establishing a framework for Community action in the field of water policy. OJ L327 22.12.2000. pp 1-73

37 Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy OJ l 348 24.12.2008 pp 84-97.

38 OJ L 158 5.5.1998 pp 11-23

39 IOELVs are health-based, non-binding values, derived from the most recent scientific data available and taking into account the availability of measurement techniques. They set threshold levels of exposure below which, in general, no detrimental effects are expected for any given substance after short-term or daily exposure over a working life time. The national occupational exposure limit values which the Member States will establish taking the EU indicative occupational exposure limit value into account will apply in all work environments across the EU

Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work[40], to include category 1 and 2 reprotoxic substances. Given that the mode of action of many reprotoxic substances is through the endocrine system, the conclusions of this study and the follow-up action to be taken by the Commission will also be highly relevant to the regulation of such substances in the work-place.

4.2. Legislative Actions-New Legislation

4.2.1. Biocides

On 12 June 2009, the European Commission adopted a proposal for a Regulation concerning the placing on the market and use of biocidal products (COM(2009)267). The proposed Regulation will repeal and replace the current Directive 98/8/EC concerning the placing of biocidal products on the market. Under Article 5 (exclusion criteria), the proposed regulation imposes specific conditions for the authorisation of active substances which have been classified carcinogen, mutagen or toxic for reproduction in accordance with Regulation (EC) No 1272/2008, **or identified as having endocrine disrupting properties.**

4.2.2. Toys

The new Toy Safety Directive[41] substantially amends the old Directive across virtually all safety aspects. It improves the existing rules for the marketing of toys that are produced in and imported into the EU with a view to reducing toy-related accidents and achieving long-term health benefits.

This new Directive came into force on 20 July 2009 and the Member States must begin applying the new measures from 20 of July 2011, except for Annex II part III on substance requirements, which must be applicable from 20 July 2013. The new Directive brings, in particular, more references on substances by limiting the amounts of certain chemicals that may be contained in materials used for toys.

The Directive requires the Commission to systematically and regularly evaluate the occurrence of hazardous substances or materials in toys. The Directive gives the Commission the possibility to adopt specific limit values for subsatnces used in toys intended for use by children under 36 months, or in other toys intended to be placed in the mouth, and this provision can be applied to endocrine disruptors on a substance by substance basis.

A group of experts has been established to advise the Commission in the preparation of legislative proposals and policy initiatives with regards to chemical substances which may be used in toys. The Expert subgroup will focus among others issues on limit values for chemicals in toys and the Commission intends to make available to this group the outcomes of the study on State of the art of the assessment of endocrine disruptors (see Section 7 below).

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40 OJ L 158, 30.04.2004 pp 50-76

41 Directive 2009/48/EC of the European Parliament and of the Council of 18 June 2009 on the safety of toys. OJ L 170, 30.06.2009. pp 1-37

5. INTERNATIONAL INITIATIVES

The OECD in the context of its chemicals' programme has a major programme dedicated to endocrine disruption. The programme has given rise to a number of additional test guidelines as well as a conceptual framework including a tiered approach to the identification of potential endocrine disruptors. The European Commission as well as EFSA and ECHA are contributing actively to this programme. For more details see Section 3.

IPCS/WHO/UNEP are in the process of updating the major review and global reference document on endocrine disrupting effects first published in 2002[42]. There are regular contacts between the Commission services and these international organisations to co-ordinate activities.

6. EXPOSURE TO MULTIPLE ENDOCRINE DISRUPTORS.

In response to the request from the Council (see Introduction) the Commission has examined the way that exposure to multiple endocrine disruptors is currently addressed in EU legislation.

Existing EU legislation already offers some possibilities for assessing the cumulative impacts of several substances with regard to their impact on the endocrine system. One Member State has proposed that a group of substances from the phthalate family be collectively considered as candidates for restrictive measures at the level of the EU under REACH based on concerns regarding their impact on the endocrine system (see section 4). Within the framework of EU legislation relating to plant protection products, methodologies are being evaluated for assessing the cumulative impact of active substances, and these methodologies, once validated/endorsed, will also be applicable to active substances that have impacts on the endocrine system.

Where EU legislation allows the possibility of assessing cumulative effects, the scope of such assessments is generally rather narrow. In the case of plant protection products, for example, the possibility exists to assess the cumulative impacts of the residues of different active substances remaining in food and feed. In the proposed revision to the Biocidal Products Directive, it will be possible to assess the cumulative effect of the same active substance used in different products. However, current EU legislation does not provide for a comprehensive, integrated assessment of cumulative effects taking into account different routes of exposure and different product types. Thus the recent study carried out in Denmark highlighting the concerns associated with the exposure of toddlers to different endocrine disruptors in food, in water, in plastic bottles, plastic shoes, toys and medicines[43] could not trigger a similarly comprehensive assessment and possible response within the context of current EU legislation. Any response would, by virtue of the design and scope of current legislation, be partial and not integrated.

The preceding paragraphs serve to underline that the challenge of how to deal with exposure to multiple endocrine disruptors is closely linked to the challenge of assessing the cumulative effects of chemicals. What is required is a framework that provides both for the assessment of the endocrine disrupting potential of individual chemicals as well as the possibility to assess,

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42 WHO/IPCS review from 2002.

43 www.65000.dk

when appropriate, the cumulative impact of identified combinations of substances on the endocrine system (see section 7).

7. FUTURE DEVELOPMENTS

The challenge posed by endocrine disrupting substances is attracting increasing interest both within the EU and internationally. As the number of research projects and regulatory initiatives continues to expand there is an increasing need for co-ordination in order to ensure a coherent and consistent approach. The relevant Commission services and agencies have established an ad-hoc group for the exchange of information related to endocrine disruptors. The Commission has also invited Member States, relevant Agencies, stakeholders and international organisations to attend meetings of an ad-hoc contact group to exchange information on endocrine disruptors and to assist the Commission in shaping future policy in this area. EFSA has also established an internal Task Force and there is also a joint initiative between EFSA and ECHA on endocrine disruptors.

In order to respond to the regulatory requirements and in particular REACH and the PPPR, the Commission intends to develop a systematic approach for the identification and assessment of endocrine disruptors which can be applied across the different pieces of legislation. The detailed application of a general framework will necessarily need to be adapted to the specific requirements of each piece of legislation. However, the general concept should be consistent and should ensure that endocrine disruptors are dealt with in a consistent and co-ordinated manner. The Commission's future work will take into account the ongoing international initiatives and in particular the work of the OECD and WHO/IPCS/UNEP.

Given the increasing importance of the endocrine disruptor issue, our rapidly expanding knowledge and the large number of ongoing research projects and regulatory initiatives, the Commission has indicated in its work programme for 2011 that it will review the present EU strategy and if appropriate propose a revision. In order to provide input to this review process the Commission services intend in 2012 to organise a major conference on endocrine disruptors.

In order to provide a solid scientific and technical foundation for its future work, the Commission services have also launched a major study on state of the art of the assessment of endocrine disruptors that will be completed by August 2011. The objective of the study is to analyze and summarize results of regulatory relevance to the scientific debate in the field of endocrine disrupting properties of substances (industrial chemicals, plant protection products, biocides, synthetic and natural hormones, pharmaceuticals, veterinary drugs) taking into account the Community Strategy for Endocrine Disrupters and the Commission Communication and Staff Working Documents on the implementation of the Strategy. The study will review the scientific knowledge published in the literature over the last 10 years and in the reports of more than 80 FP funded projects and will review the approaches for assessment of endocrine disruptors used in selected Member States, in major competing economies outside the EU and in international bodies. Based on these reviews, the study will draw conclusions and answer policy relevant questions.

Finally, the 2008 Communication from the Commission on Safe Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector[44], contains the following objective (objective #12):

"*Measures to reduce the potentially harmful impacts of pharmaceuticals on the European environment and public health should be proposed"*

Given that a number of the substances originating from pharmaceutical products and which have been identified as posing a potential risk to public health and the environment, are known, or suspected, endocrine disruptors, actions taken in relation to objective #12 from the 2008 Communication are likely to deliver benefits in terms of a reduced exposure to endocrine disruptors. The Commission services are planning to launch a study in 2011 to examine the impact on human health and the environment of pharmaceutical residues present in environmental media.

[44] COM(2008) 666 final Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions -Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector