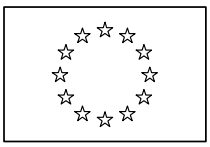

COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 30.11.2007
SEC(2007) 1635

COMMISSION STAFF WORKING DOCUMENT

on the implementation of the "Community Strategy for Endocrine Disrupters" - a range of substances suspected of interfering with the hormone systems of humans and wildlife (COM (1999) 706), (COM (2001) 262) and (SEC (2004) 1372)

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SUMMARY

Following the adoption by the Commission of a Communication to the Council and European Parliament on a "Community Strategy for Endocrine Disrupters" in December 1999 (COM (1999)706), the Council invited the Commission to report regularly on the progress of the work. The first progress report was adopted in June 2001. A second progress report summarising the implementation of the Strategy during the period 2001-2003 was adopted in October 2004 (SEC (2004)1372). This is the third progress report on the implementation of the Strategy during the period 2004–2006. It describes the developments that have been made in terms of activities on prioritising substances for further investigation, stimulating research, agreeing test methods or adapting legislation.

The "Community Strategy for Endocrine Disrupters" contains activities in the short, medium and long term. The short and medium term actions focus on gathering scientific data on "candidate substances" with a view to prioritising testing, guide research and monitoring efforts and to identify specific cases of consumer use and ecosystem exposure. The long-term actions focus on review and possible adaptation of policy and Community legislation.

Considering that the "endocrine disruption" is not a toxicological endpoint per se, but it is a class of many mechanisms of action that may lead in different species to various types of effects which may result in adverse consequences on humans and ecosystems, the key short-term action is the establishment of a priority list of substances for further evaluation of their endocrine disrupting effects. This prioritisation work started in the year 2000. A number of some 600 chemical substances ("candidates") have been screened, evaluated and a preliminary priority list was established. This work was completed at the end of 2006.

The preliminary priority list of substances for further evaluation is not a negative list of substances but it is meant to provide a basis for gathering further data on endocrine disrupting effects of those substances and for their subsequent evaluation. The list was elaborated in a stepwise approach. Between 2000 and 2006 the Commission has contracted three studies on identification and evaluation of substances.

In total 575 substances were investigated over the past six years as to their endocrine disrupting (ED) effects. In terms of prioritisation, it was found that, out of this number, 320 substances showed evidence or potential evidence for ED effects, while in total, 109 substances were not retained in the priority list, either due to insufficient data on ED effects or insufficient scientific evidence. 147 substances have been excluded from the evaluation during the process as they were identified as double entries, mixtures or of doubtful relevance.

An assessment of the legal status of the substances with evidence or potential evidence of endocrine disrupting effects showed, that the majority of them are already subject to a ban or restriction or are addressed under existing Community legislation, although for reasons not necessarily related to endocrine disruption.

As regards medium-term actions, the Commission and Member States continue to participate in the OECD - Endocrine Disrupter Testing and Assessment Task Force (EDTA), which was set up in 1998 with the goal of developing agreed test methods for endocrine disrupters. The latest estimates are that agreed test methods for some environmental and human health effects will be finalised in 2007. Furthermore, addressing the medium term research and development objectives, endocrine disrupters were addressed under the 5th (FP5 – 1998-2001) and 6th (FP6 – 2002-2006) EU Research Framework Programmes and will also be addressed under the 7th Framework Programme of the European Community for Research, Technological Development and Demonstration Activities (FP7 - 2007–2013).

Regarding long term actions, relevant developments since 2004 were the adoption of the regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), formally adopted on 18 December 2006, the proposal for a directive setting environmental quality standards for priority substances under the water framework directive (2006) or the proposal for a regulation revising directive 91/414/EC on plant protection products (2006).

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1. CONTEXT

Endocrine Disrupters are a group of chemicals (natural, synthetic, industrial chemicals or by-products) present in the environment and suspected to alter the functions of the endocrine system and, consequently, causing adverse health effects in an intact organism, or its offspring, or (sub) population.

In wildlife, endocrine disrupters have clearly been shown to cause abnormalities and impaired reproductive performance in some species, and to be associated with changes in immunity, behaviour and skeletal deformities. In humans, endocrine disrupters have been suggested as being responsible for apparent changes seen in human health patterns over recent decades. These include declining sperm counts in some geographical regions, increased incidences in numbers of male children born with genital malformations and increased incidences of certain types of cancer that are known to be sensitive to hormones. More controversially, links have been suggested with impairment in neural development and sexual behaviour.

In order to address the potential environmental and health impacts of endocrine disruption the Commission adopted a Communication to the Council and European Parliament on a "Community Strategy for Endocrine Disrupters" in December 1999. This Strategy sets out a number of actions relating to, *inter alia*, identification of substances, monitoring, research, international co-ordination and communication to the public.

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.

2. PROGRESS ON SHORT-TERM ACTIONS

As it is emphasized in the Opinion of the Scientific Committee on Health and Environmental Risks (SCHER) adopted in November 2005[1], "endocrine disruption is not a toxicological endpoint per se, but is one class of the many mechanisms of action that may lead to various types of effects in different species, which may result in adverse consequences on humans and ecosystems".

The short-term actions have therefore focused on the need to gather up-to-date scientific information on endocrine disrupting effects and on the extent to which it is affecting people and wildlife. The work on identification and prioritisation of

[1] SCHER Opinion on "Endocrine Disrupting Chemicals: a Non-animal Testing Approach" (BUAV report–2004)

substances for further evaluation of their endocrine disrupting effects has continued and a preliminary priority list of the substances was established.

2.1. Establishment of a priority list of substances for further evaluation of their endocrine disrupting effects (see Annex 1, Fig 1)

2.1.1. Background

Between the years 2000 and 2006 the Commission has contracted three studies on identification and evaluation of substances as to their endocrine disrupting effects. In June 2000, the study towards the establishment of a priority list of substances for further evaluation of their endocrine disrupting effects – preparation of a "candidate list" of substances as a basis for priority setting[2] (BKH-study), established a list of 553 candidate substances. Stakeholders, Member States and the Commission Scientific Committee on Toxicology, Ecotoxicity and the Environment (CSTEE) were consulted on the approach and gave their input. Furthermore, a first list of 118 substances showing endocrine disrupting effects or potential endocrine disrupting effects was established. Out of these 118 substances indicating evidence or potential evidence of endocrine disrupting effects, 109 were already addressed under existing community legislation.

In 2002, a follow up study "on gathering information on 435 substances with insufficient data"[3] (RPS-BKH-study) was carried out. It aimed on refinement of the evaluation-methodology and on the investigation of the remaining 435 substances from the "candidate list" and also focused on candidate substances identified as High Production Volume Chemicals (HPVC), persistent in the environment and to which human- or wildlife-exposure could be expected. 204 substances were identified according to these criteria and their endocrine disrupting effects were evaluated. 147 of them were identified, showing either a clear evidence of endocrine disrupting effects or potential endocrine disrupting effects.

For the substances that showed a clear evidence of endocrine disrupting effects, it was investigated if there is exposure concern for humans or wildlife. 84 of them showed high exposure concern, 5 showed medium and 4 substances showed low exposure concern.

Out of 147 substances indicating evidence or potential evidence of endocrine disrupting effects, 129 were already addressed under existing community legislation.

In the 2002 study, 172 candidate substances were reported as not yet evaluated, as they were supposed to be mainly Low Production Volume Chemicals (LPVC).

[2] Study "towards the establishment of a priority list of substances for further evaluation of their role in endocrine disruption – preparation of a candidate list of substances as a basis for priority setting" BKH, 2000

[3] Study on "gathering information on 435 substances with insufficient data", RPS-BHK, November 2002.

2.1.2 "Study on enhancing the endocrine disrupter's priority list with a focus on low production volume chemicals" (DHI –Study)

In November 2005 the Commission, DG Environment, contracted "DHI Water and Environment" to carry out a further study[4], focusing on the remaining Low Production Volume Chemicals (LPVC). Commissioning this study, the Commission also took into account the recommendation from the former Scientific Committee on Toxicity, Ecotoxicity and Environment (CSTEE)[5], where the committee stated that LPVC with high release in the environment or with high potency were not sufficiently covered in the previous work on the priority setting.

Starting work, it turned out that 173 substances were left from the previous study and 22 substances were newly identified as candidates by stakeholders, therefore, in total 195 substances were identified for evaluation. After a first close look at the substances, it became obvious that many of them were neither LPVC nor HPVC, but they were produced in quantities lower then 10t/year. Furthermore, it turned out that 88 substances were of doubtful relevance as they were not listed in the existing chemicals database "ESIS"[6], an indication that they are not in use anymore, or not identified clearly by a single CAS N°. It was decided to exclude these 88, and thus, 107 substances remained for evaluation.

As in the previous study, the evaluation of endocrine disrupting effects in humans or wildlife was based on the following screening criteria: persistency, production data, consumption/use patterns, environmental concentrations (range), evaluation of endocrine disrupting effects taking into consideration the relevance of the effects parameter, test reliability, dose-response relationship, endocrine disruption potency, endocrine disruption structure-activity relationships, comparison with systemic toxicity and evaluation of exposure concern to human and wildlife.

The results of the evaluation were: out of 107 substances, 34 were showing a clear evidence of endocrine disrupting effects in at least one intact organism (Category 1), 21 were showing some evidence, suggesting endocrine disrupting potential (Category 2) and 52 substances showed insufficient data to decide on endocrine disrupting (ED) effects or there was no scientific basis for their inclusion in the priority list (Category 3a or 3b). For results, see Annex 2, Grouping of substances, Tables 1 – 5.

Furthermore, for the 34 substances showing a clear evidence of endocrine disrupting effects, exposure concern to human or wildlife (Category 1) was evaluated. As only very few monitoring data sets were available for these substances, it was decided to base exposure evaluations on EUSES[7] calculations. EUSES is designed to be a decision support system for the evaluation of exposure of chemicals to man and the environment. Out of 34 substances, 12 substances showed high exposure concern, 16 substances showed medium and 6 substances showed low exposure concern.

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[4] Study on" enhancing the endocrine disrupter priority list with a focus on low production volume chemicals", DHI Water and Environment 2006

[5] Opinion of the CSTEE on "two study reports for endocrine disrupters by WRc-NSF and BKH Consulting Engineers", November 2003

[6] ESIS: European chemical Substances Information System, DG JRC, European Chemicals Bureau

[7] EUSES: European Union System for the Evaluation of Substances

An assessment of the legal status of the DHI- evaluated substances with an evidence or potential evidence of endocrine disrupting effects showed, that 29 are already subject to a ban or restriction or are addressed under existing Community legislation, whereas 27 are not (see Annex 2, Grouping of substances, Tables 1 – 3).

During the DHI study, stakeholders, experts and Member States were involved at the very beginning, when input in terms of recent scientific data on the candidate substances in question as well as identification of further candidate substances was requested. Later on, they were involved again when the draft final report was subject to internet consultation during November 2006. Then, mainly experts replied, providing input on single substances evaluation as well as on the presentation of the report. Industry expressed its concern that the results of the evaluation of the substances could be misunderstood as full risk assessments. Moreover, industry expressed the concern that the priority list could be seen as a definitive list of substances and not as a list of substances for further evaluation of their endocrine disrupting effects. Industry also provided scientific data on some of the evaluated substances. All received comments were taken into account as far as possible.

The final report of the DHI study is available on DG ENV's Endocrine Disrupters Website[8].

2.1.3. Preliminary priority list of substances for further evaluation of their endocrine disrupting effects

The substances on the priority list are mainly man-made chemicals used in industry, agriculture and consumer products. Substances with a clear evidence of endocrine disrupting effects belong to many different groups of chemicals, e.g., alkylphenols and its derivatives, benzoates, chlorinated paraffines, phthalates, dioxins/furans, triazines or PCBs.

The preliminary priority list of substances for further evaluation is not a negative list of substances but it is meant to provide a basis for gathering further data on endocrine disrupting effects of those substances and for their subsequent evaluation. The list now comprises in total 428 substances. Out of them, 194 showed a clear evidence of endocrine disrupting effects (Category 1), 125 showed a potential evidence of endocrine disrupting effects (Category 2), whereas 109 showed either no scientific basis for inclusion in the list or insufficient data to decide about (Category 3a or 3b).

A database comprising all scientific information underlying the priority setting was established. It presents in a transparent manner the scientific data and references on human health, wildlife effects gathered in the three studies, as well as the categories in terms of priority concluded on that scientific basis. Compiling the database was one of the deliveries of the DHI - Study. The database is available on DG ENV's Endocrine Disrupters Website[9].

For the future, it is planned to work on the database further by developing a methodology that makes the list iterative, meaning that substances can be included or

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

released from it. The methodology to be developed needs to be broadly discussed with experts, Member States and stakeholders. The database will then serve as a "dynamic working list", ensuring that substances, where necessary, can continuously be fed into relevant legislation in order to manage risks properly.

The assessment of the legal status of priority substances (Category 1 and Category 2) resulted in total in 269 substances that are already subject to a ban or restriction or addressed under existing Community legislation and 51 substances that are neither restricted nor being addressed.

3. PROGRESS ON MEDIUM-TERM ACTIONS

As part of the medium-term actions, the Commission is supporting the development and validation of test methods by working closely with Member States to coordinate the European Union input to OECD. The medium-term actions also include research and development.

3.1. Identification and assessment of endocrine disrupters

The availability of agreed test strategies/methods to identify and assess endocrine disrupting chemicals is a basic requirement for comprehensive legislative action aimed at protecting people and the environment from the potential dangers posed by these chemicals.

The Commission participates in the OECD - Endocrine Disrupters Testing and Assessment Task Force (EDTA), which was set up in 1998 under the authority of the National Co-ordinators for the Test Guidelines Programme. The aim of the Task Force is to develop an internationally harmonised testing strategy as well as coordinating and overseeing the work of different sub-groups charged with developing new or revising existing test guidelines to assess the potential endocrine disrupting properties of chemicals. The Task Force met for the tenth time in spring 2007.

The latest estimates are that agreed test methods for human health effects will be finalised in 2007. In particular, an in vivo test guideline for screening for estrogenic effects, uterotrophic assay, will be most probably available by the end of 2007. Other draft in vivo test guidelines like the Hershberger assay or revised test guideline 407 are under development and might be available from 2008 onwards. Test methods for environmental effects include fish screening assay, amphibian metamorphosis assay and some invertebrate tests (e.g. copepod test). The first agreed test guidelines are estimated to be available by 2008. Alternative non animal test methods for ED screening are also progressing under the auspices of the OECD. In particular, a draft OECD test guideline for agonist estrogenic assessment using an in vitro estrogen receptor (ER) transcriptional activation assay has been submitted by Japan and was peer reviewed earlier this year. The EC/JRC is collaborating with the US and Japan on the validation of (ER) binding assays, androgen receptor (AR) binding assays and steroidogenesis assays.

An overview of the ED test methods that are currently in (pre)validation under the auspices of the OECD is set out in Annex 3.

3.2. Research and development

Under the Fifth Framework Programme (FP5, 1999–2001), over 60 million euros were spent on 23 projects dealing with endocrine disrupters. The final reports of most of these projects are available[10]. As a direct response to the call to enhance research efforts by the European Commission's Strategy on endocrine disrupters, the CREDO cluster (Cluster of Research into Endocrine Disruption in Europe) was established[11]. It was launched in April 2003 and will last until 2007. Four projects with a total budget of approximately 20 million EUR participated in the cluster encompassing 63 laboratories in Europe. The cluster was co-ordinated by the EDEN project[12]. CREDO has until now already greatly contributed to improving the knowledge about endocrine disruption.

The projects funded under FP5 focused on a number of issues such as hazard and risk characterisation of various groups of endocrine disrupters; epidemiological approaches to exposure assessment including the use of biomarkers and birth cohorts; development of new methods and tests for analysis of toxicity; the role of genetic susceptibility in disease development; and investigation of mechanisms of disease development in various organs in 'real life' exposure situations (i.e., with low doses and multiple exposures). Endocrine-related reproductive effects were also widely studied, showing correlations especially between exposure to various chemicals and reproductive parameters in a variety of animal models and also in human studies.

Furthermore, the projects observed neurobehavioural effects of some chemicals. In particular, elevated polychlorinated biphenyl (PCB) serum concentration was correlated with poor sensomotor function in children. Finally, work on multiple effects of endocrine disrupters gave contradictory results with some research demonstrating no morphological effects, while others found effects, elaborated mechanisms and proposed risk assessment for non-reproductive organs in humans.

The Sixth Research Framework Programme (FP6, 2002-2006), addressed different topics related to endocrine disruption. By the end of FP6, 10 projects with at least some relevance to the area of endocrine disrupters were funded, with EC contributions of around 50 million EUR in total. The adoption of the European Environment and Health Action Plan in 2004 has served as a stimulus for research, as one of the goals of this Action Plan is to understand health impacts of endocrine disrupters[13] in view of co-ordinating risk reduction measures, which is one of the recommendations of this Action Plan. The recently published mid-term review[14] of the Action Plan has acknowledged significant progress in better identification of the mechanisms for co-ordinating risk reduction measures. It is, however, recognised that "more work needs to be done in linking research on priority diseases to appropriate policy processes and information systems".

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[10] http://ec.europa.eu/research/quality-of-life/ka4/ka4_reports_en.html
[11] http://www.credocluster.info/
[12] http://www.edenresearch.info/
[13] http://ec.europa.eu/environment/health/index_en.htm
[14] http://eur-lex.europa.eu/LexUriServ/site/en/com/2007/com2007_0314en01.pdf

The projects supported under FP6 focus on the studies of health outcomes after exposure to chemicals with potential neuroimmune or endocrine mediated effects or develop test methods for their detection. Some projects have also addressed the issue in a context of integrated environment and health risk assessments.

The integrated project REPROTECT[15], led by the Joint Research Centre (JRC) with 32 participating European groups, began in July 2004 with an EC contribution of 9.1 million EUR, and a total budget of 13.2 million EUR over 5 years. The aim is to validate a conceptual framework in the area of reproductive toxicity and to develop a substantial number of alternative test methods making use of advanced technologies. Within this project, six tests for assessing (anti)estrogenic and (anti)androgenic compounds have been optimised and are now being analysed for predictive power. Two of these tests are continuing validation under the auspices of the OECD. These in vitro tests could contribute to substantially reduce the number of animals that are currently required in reproductive toxicity testing. Furthermore, such methods have discrete advantages that go beyond reduced speed, cost and animal use, such as the possibility to use human cells and receptors.

The CASCADE project has started in 2004 with an EC contribution of 14.4 million EUR during five years[16]. CASCADE brings 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 chemicals with endocrine disrupting properties.

In addition, the following projects are of relevance to the field of endocrine disruption: NEWGENERIS[17] focusing on the role of exposure to genotoxic chemicals (including endocrine disrupters) 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, BIOCOP[19] working on new technologies to screen multiple chemical contaminants in food and NOMIRACLE[20] developing novel methods and tools to better evaluate chemical risks. INTARESE[21] aims at producing a new integrated risk assessment framework, based on the full chain approach (causal chain spanning sources of pollution, releases into various media, dispersion and transport, exposure medium inhalation/dermal contact/ingestion, intake, uptake, dose, health effects and impacts). It includes household chemicals. Another two integrated projects, HEIMTSA and 2-FUN, which started in 2007, aim at further enhancing the full chain methodology and extending it to cover monetary valuation of health impacts from environmental stressors, including endocrine disrupting chemicals, and the health impacts of combined exposure to them and other stressors. These projects are expected to develop computational tools for assessing the health impacts of Community policies linked to chemicals such as endocrine disrupters. Moreover, eight "Specific Targeted Research Projects" with EC contributions between 1-5 million EUR and a duration of up to

[15] http://www.reprotect.eu
[16] www.cascadenet.org
[17] www.newgeneris.org
[18] www.phime.org
[19] www.biocop.org
[20] http://nomiracle.jrc.it/default.aspx
[21] www.intarese.org

four years, as well as a few Coordination Actions/Specific Support Actions were financed.

The projects funded by FP6 related to endocrine disrupters are listed in the annex of the mid-term review report of the Environment and Health Action Plan published in June 2007[22].

Funding of research on endocrine disrupters will continue in the Seventh Research Framework Programme (FP7, 2007–2013). Theme 6 'Environment' as an example, will include an "Environment and Health" activity which will fund, among others, research related to health impacts of chemicals including endocrine disrupters. In addition, the JRC has been developing toxicogenomic capabilities for studying the biological basis underlying endocrine disruption in the context of its work on human exposure to environmental stressors and health effects. The JRC also held an expert workshop on molecular modelling approaches for human hazard assessment of chemicals (2006) using endocrine disruption and metabolism as case studies (report in preparation). This workshop identified promising in silico approaches for ED hazard assessment testing batteries which are now being followed up in the JRC led validation programme.

A webpage on endocrine disrupter-related research was created by DG Research[23] and the JRC[24] will soon host the database on endocrine disrupting chemicals developed under the DG ENV's contracted studies (part 2.1.3. above).

4. PROGRESS ON LONG-TERM ACTIONS

The long-term actions include the review and adaptation of existing legislation, governing testing, assessment and use of chemicals and substances within the EU.

4.1. Legislative actions

4.1.1. Regulation (EC) N° 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

The Regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)[25] was formally adopted on 18 December 2006 by the Council of Environment Ministers following the vote in second reading of the European Parliament on 13 December 2006. REACH has entered into force on 1 June 2007.

One of the key elements of REACH is an authorisation procedure for substances of very high concern. Substances of very high concern include those that are carcinogenic, mutagenic or toxic to reproduction (CMRs), categories 1 and 2.

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[22] http://eur-lex.europa.eu/LexUriServ/site/en/com/2007/com2007_0314en01.pdf
[23] http://ec.europa.eu/research/endocrine/index_en.html
[24] http://ecb.jrc.it
[25] Regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals, establishing a European Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) N° 793/93 and Commission Regulation (EC) N°1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEX, 93/67/EEC and 2000/21/EC

Furthermore, substances meeting the regulation's criteria for being persistent, bioaccumulative and toxic (PBTs) or very persistent and very bioaccumulative (vPvBs) are also of very high concern. In addition, substances that are not covered by the CMR-, PBT- or vPvB- criteria can be identified on a case-by-case basis when they are causing serious and irreversible effects to humans or the environment, which are equivalent to those of the CMRs, PBTs and vPvBs. These substances are then considered to be "of equivalent concern" and can also be subject to authorisation as far as they are proposed to be put on the "candidate list" for inclusion in Annex XIV of REACH and prioritised for authorisation. Substances of "equivalent concern" include those having endocrine disrupting properties. The identification of the substances of very high concern starts on the initiative of the Commission or Member States and leads to the establishment of the candidate list. The "endocrine disrupter priority list" could be used as a reference material for this process. A guidance document on how Member States should choose and justify their proposals for substances of equivalent concern is currently being prepared by the European Chemicals Bureau[26].

The authorisation procedure requires the Commission to give specific permission before a substance subject to authorisation could be used for a particular purpose, marketed as such or as a component of a product. Given that many of the serious human health effects which have so far been associated with endocrine disrupting chemicals are testicular cancer, breast cancer, prostate cancer, decrease in sperm quality, cryptorchidism and hypospadia, it is likely that many substances will fall under this authorisation procedure directly as a CMR substance. Furthermore, adverse effects on the endocrine system of wildlife species have been causally linked to certain persistent, bioaccumulative and toxic substances. Such substances would be subject to authorisation as a result of their PBT-properties. It should be noted that many of the priority substances are pesticides and by-products formed, for example, during combustion, and therefore they are not within the scope of REACH. The number of substances out of the endocrine disrupter priority list that could be expected to be identified, on a case-by-case basis, as substances of "equivalent concern" as defined in REACH, might potentially be a few dozen.

4.1.2. Directive 2000/60/EC establishing a framework for Community action in the field of water policy (Water Framework Directive) and Directive 2006/118/EC on the protection of groundwater against pollution and deterioration

The **Water Framework Directive** (WFD) sets environmental objectives of good chemical status for surface waters and for the prevention of pollution of groundwater.

For **surface waters**, the Directive provides for a two-tiered approach to control chemical pollution, which includes actions at national level and EU wide action.

At the ***national level***, Member States are required to identify chemical pollutants of significance for each of the water bodies (an indicative list of the main pollutants is included in the Annex VIII of the Directive), to set quality standards for the water, to establish emission control measures and to achieve these standards by 2015. A specific category includes those *"substances and preparations, or the breakdown*

[26] RIP-4.3: Guidance document on Inclusion of Substances in Annex XIV

products of such, which have proved to possess carcinogenic or mutagenic properties which may affect steroidgenic, thyroid, reproduction or other endocrine-related functions in or via the aquatic environment" (Annex VIII – Group 4). This means that there is an obligation for Member States to take action to prevent human exposure of endocrine disrupting substances via the aquatic environment. This action shall be coordinated in river basins, and a programme of measures shall be in place in 2009 and become operational in 2012.

At the ***Community level***, the WFD sets out a strategy against pollution of surface waters by chemical pollutants (Article 16). This strategy includes the identification of substances of particular concern at Community level, and the adoption of environmental quality standards and emission controls for such substances. The first list of 33 substances was adopted in 2001 (Decision 2455/2001/EC), and the Commission adopted a proposed Directive (COM (2006)397) setting environmental quality standards for these substances in 2006, as well as a related Communication (COM (2006)398). It should be noted that, out of these 33 substances, 21 are candidate endocrine disruptor substances for which an evidence or potential evidence of endocrine disrupting effects was found during the priority setting process in the years 2000–2003.

The list of substances is to be reviewed every four years, and as further knowledge regarding endocrine disrupting properties is gathered, this information could be taken into account in the future prioritisation of substances for action at Community level.

From the first priority list, certain substances can also be classified as "priority hazardous" and should be subject to complete phase-out of all emissions, losses and discharges during a 20-year timeframe. Endocrine disrupting effects could become an important factor for sorting substances or groups of substances into this group.

Regarding groundwater, the new **Groundwater Directive** (developed under Article 17 of the WFD) was adopted on 12 December 2006 (Directive 2006/118/EC). It requests Member States to establish threshold values (groundwater standards for defining the groundwater good chemical status) for all pollutants representing a risk to groundwater, taking a minimum list of pollutants (Annex III of the directive) into consideration. Although endocrine disrupters are not explicitly listed, in principle, they could be covered by this clause if Member States identified them and considered that they could represent a risk for the pollution of groundwater. This proposal also includes the requirement to identify and reverse a significant increasing trend in pollutant concentrations, which would implicitly cover endocrine disrupters if they have been identified as representing a pollution risk.

Regarding prevention, direct and indirect inputs of pollutants are regulated both by the Water Framework Directive and the Groundwater Directive proposal (Article 6 of the proposal), thus ensuring a continuity of the protection regime of Directive 80/68/EEC which will be repealed in 2013. Along this principle, inputs of hazardous substances have to be prevented, while inputs of non-hazardous pollutants have to be limited to avoid groundwater pollution.

4.1.3. Directive 91/414/EEC concerning the placing of plant protection products on the market

Directive 91/414/EEC sets out a Community harmonised framework for authorisation, use and control of plant protection products.

In 1992, the European Commission started a Community-wide review process for all active ingredients used in plant protection products within the European Union. The review should make sure that active substances can be used safely regarding human health, the environment, ecotoxicology and residues in the food chain. It will be completed in 2008.

The issue of possible endocrine disrupting properties of active substances used in plant protection products is not yet fully incorporated in the risk assessment procedures because of lack of harmonised and internationally-agreed test protocols. But the competent authorities in the EU have identified this gap and have highlighted the need for a test procedure which could confirm whether or not "identified candidates" are real endocrine disrupting substances. Work on this matter is ongoing at the OECD and it is foreseen that as soon as agreed test methodologies are endorsed, these would be integrated into the assessment procedures applied in the Community risk assessment. In the meantime, where substances are currently being evaluated and where there is a suspicion of endocrine disrupting potential of a substance, additional testing has been requested and performed, and the results assessed. Several substances have so far been tested according to a specific protocol called "fish full life cycle test". The results of these tests have allowed competent authorities to resolve doubts about those substances.

Apart from technical aspects that are expected to be solved in the near future, consideration of endocrine disrupting properties of active substances would receive greater priority in decision-making. The new proposal for a regulation revising Directive 91/414/EEC, which was adopted by the Commission in July 2006, includes provisions that prohibit the use of active substances that have been identified as endocrine disruptors, unless the exposure of humans to the active substance in a plant protection product, under realistic proposed conditions of use, is negligible.

4.1.4. Directive 98/8/EC concerning the placing of biocidal products on the market

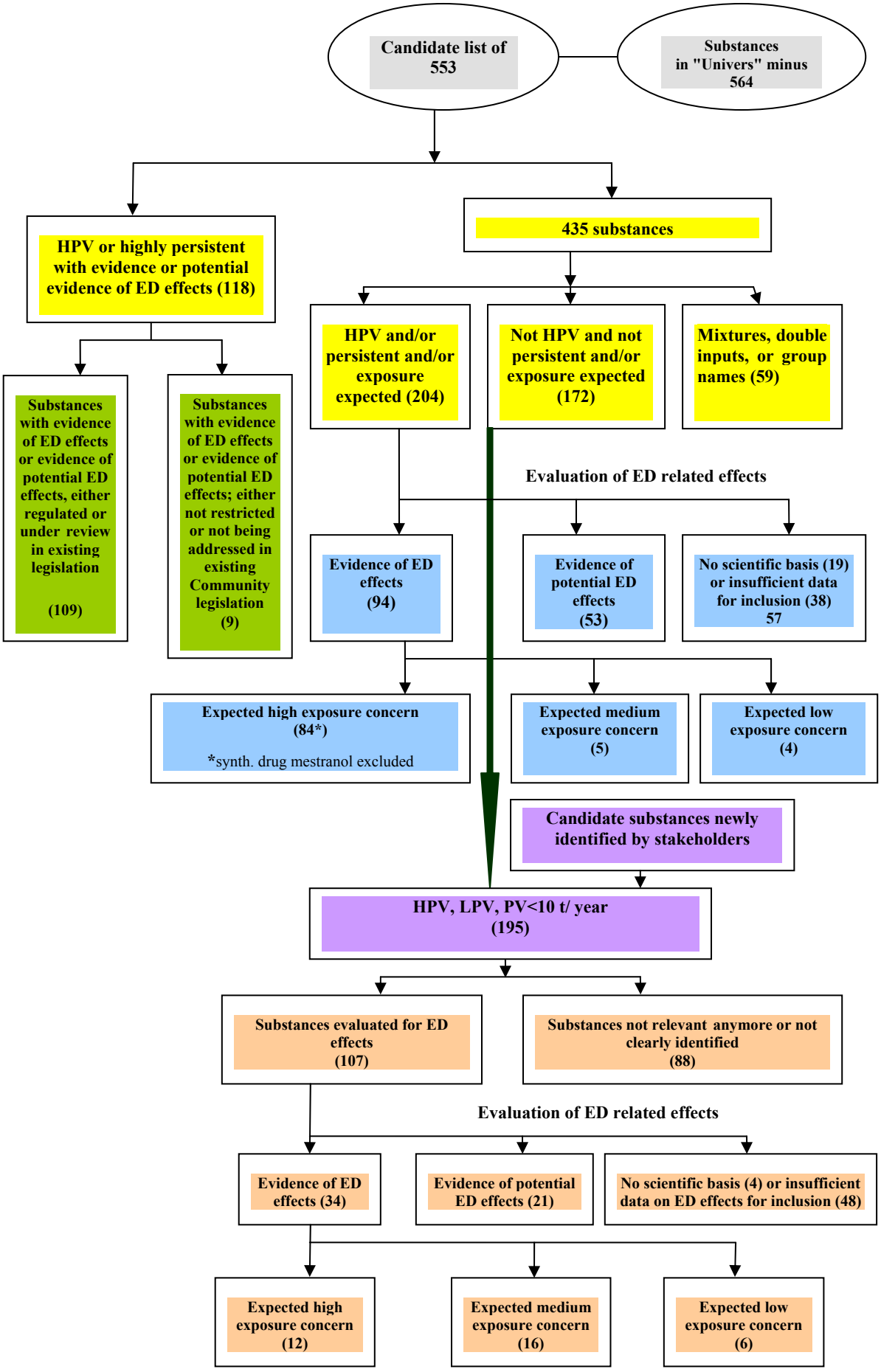
Within this Directive, active substances are being evaluated and authorised for biocidal applications after the risk for man and environment has been assessed. This assessment also takes into consideration the potential adverse effects that rise from exposure to endocrine disrupting chemicals. Although a specific evaluation strategy for the assessment of endocrine disrupting effects is not explicitly described within this Directive, these adverse effects are taken into account when assessing risks associated with the use of the substances. These aspects are also taken into account in the specific "PBT Working Group" assessing the persistence, bioaccumulative and toxic properties of biocides. Like all other legislative actions, also Directive 98/8/EC will benefit from the final acceptance of the standardized testing methods at the OECD level.

4.1.5. Directive 96/22/EC concerning the prohibition on the use in stock-farming of certain substances having a hormonal or thyrostatic action and beta-agonists

The use of substances having an oestrogenic, gestagenic or androgenic effect is restricted under Directive 96/22/EC concerning the prohibition on the use in stock-farming of certain substances having a hormonal or thyrostatic action and beta-agonists, as amended by Directive 2003/74/EC. The Directive prohibits the use of substances having a hormonal action for growth promotion in farm animals and identifies precise circumstances under which they may be administered to food producing animals for other purposes. After 14 October 2006, i.e., the date of expiry of the transitional period established in Article 5a, oestradiol 17β or its ester-like derivatives may no longer be used for oestrus induction in cattle, horses, sheep or goats.

ANNEX 1: Establishment of the priority list

Figure 1: Establishment of the priority list of substances for further evaluation of their endocrine disrupting (ED) effects


Candidate list of 553
Substances in "Univers" minus 564
HPV or highly persistent with evidence or potential evidence of ED effects (118)
435 substances
Substances with evidence of ED effects or evidence of potential ED effects, either regulated or under review in existing legislation (109)
Substances with evidence of ED effects or evidence of potential ED effects; either not restricted or not being addressed in existing Community legislation (9)
HPV and/or persistent and/or exposure expected (204)
Not HPV and not persistent and/or exposure expected (172)
Mixtures, double inputs, or group names (59)
Evaluation of ED related effects
Evidence of ED effects (94)
Evidence of potential ED effects (53)
No scientific basis (19) or insufficient data for inclusion (38) 57
Expected high exposure concern (84*)
*synth. drug mestranol excluded
Expected medium exposure concern (5)
Expected low exposure concern (4)
Candidate substances newly identified by stakeholders
HPV, LPV, PV<10 t/ year (195)
Substances evaluated for ED effects (107)
Substances not relevant anymore or not clearly identified (88)
Evaluation of ED related effects
Evidence of ED effects (34)
Evidence of potential ED effects (21)
No scientific basis (4) or insufficient data on ED effects for inclusion (48)
Expected high exposure concern (12)
Expected medium exposure concern (16)
Expected low exposure concern (6)

ANNEX 2: Grouping of substances evaluated during DHI – Study 2005/2006

Table 1: Substances with evidence or potential evidence of ED effects which are neither restricted nor currently being addressed under existing Community legislation (**27 substances**)[27]

Group name	CAS Number	Substance	Status under Dir 76/769/EEC[28] or adaptations to technical progress	Status under Reg 793/93/EEC[29]	Status of review under Dir 91/414/EEC[30]	Other Risk Assessment Instruments	Other Risk Management Instruments	Other Hazard Identification Instruments
Alkylphenols and derivatives	99-71-8	4-sec-Butylphenol = 4-(1-Methylpropyl)phenol						
	1131-60-8	4-Cyclohexylphenol						
	3115-49-9	4-Nonylphenoxyaceticacid						
	27193-28-8	Phenol(1,1,3,3-tetramethylbutyl) octylphenol[31]						
Benzophenones	131-55-5	Benzophenone-2,(Bp-2), 2,2',4,4'-tetrahydroxybenzo-phenone						

[27] These substances have not been specifically evaluated in the past because they were considered as having a low priority due to their low production volumes and the fact that, at that point in time, there was no toxicological knowledge on their possible endocrine disrupting effects available.

[28] Directive 76/769/EEC relating to restrictions on marketing and use of certain dangerous substances and preparations, or adaptations to technical progress (ATP) of Dir 76/769/EEC

[29] Regulation (EEC) No.793/93 on the evaluation and control of the risks of existing substances

[30] Directive 91/414/EEC concerning the placing of plant protection products on the market

[31] Despite the fact that this substance is not a priority substance under Reg. 793/93/EC, UK has put this substances on its national priority list because of its similarity to nonylphenol

Group name	CAS Number	Substance	Status under Dir 76/769/EEC[28] or adaptations to technical progress	Status under Reg 793/93/EEC[29]	Status of review under Dir 91/414/EEC[30]	Other Risk Assessment Instruments	Other Risk Management Instruments	Other Hazard Identification Instruments
	131-54-4	2,2'-Dihydroxy-4,4'-dimethoxybenzophenon						
Bisphenols	77-40-7	2,2-Bis(4-hydroxyphenyl)-n-butan = Bisphenol B						
	92-69-3	4-Hydroxybiphenyl = 4-Phenylphenol						
	1806-29-7	2,2'-Dihydroxybiphenyl = 2,2'-Biphenol						
Camphor derivatives	15087-24-8	3-Benzylidene camphor (3-BC)						
	36861-47-9	3-(4-Methylbenzylidene)-camphor						
Coumaric acid and derivatives	7400-08-0	p-Coumaric acid (PCA)						
	5466-77-3	2-ethyl-hexyl-4-methoxycinnamate						
DDT derivatives and metabolites	83-05-6	p,p'-DDA						
Flavonoids	491-80-5	Biochanin A						
	84-69-5	Diisobutylphthalate						

Group name	CAS Number	Substance	Status under Dir 76/769/EEC[28] or adaptations to technical progress	Status under Reg 793/93/EEC[29]	Status of review under Dir 91/414/EEC[30]	Other Risk Assessment Instruments	Other Risk Management Instruments	Other Hazard Identification Instruments
	4376-20-9	Mono 2 ethyl hexylphthalate (MEHP)						
	131-70-4	Mono-n-butylphthalate						
	131-16-8	Di-n-propylphthalate (DprP) = Dipropylphthalate						
	84-75-3	Di-n-hexylphthalate (DnHP) = Dihexylphthalate (DHP)						
Siloxans	33204-76-1	2,6-cis-Diphenylhexamethyl-cyclotetrasiloxane - 2,6-cis-[(PhMeSiO)2(Me2SiO)2]						
Other substances	77-09-8	3,3'-Bis(4-hydroxyphenyl)-phthalid = Phenolphthaleine						
	81-92-5	2-[Bis(4-hydroxyphenyl)-methyl]-benzylalkohol = Phenolphthalol						
	14007-30-8	2,2-Bis(4-hydroxyphenyl)-n-hexane						
	2581-34-2	3-methyl-4-nitrophenol						
	50-18-0	Cyclophosphamide						

Group name	CAS Number	Substance	Status under Dir 76/769/EEC[28] or adaptations to technical progress	Status under Reg 793/93/EEC[29]	Status of review under Dir 91/414/EEC[30]	Other Risk Assessment Instruments	Other Risk Management Instruments	Other Hazard Identification Instruments
	96-12-8	Dibromochloro-propane (DBCP)						

Table 2: Substances with evidence of ED effects (Category 1), which are already regulated or being addressed under existing legislation (20 substances)

Group name	CAS Number	Substance	Exposure concern	Status under Dir 76/769/EEC or adaptations to technical progress	Status under Reg 793/93/EEC	Status of review under Dir 91/414/EEC	Other Risk Assessment Instruments	Other Risk Management Instruments	Other Hazard Identification Instruments
Alkylphenols and derivatives	104-40-5	4-Nonylphenol (4-NP)	Medium	Dir 2003/53/EC 26th ATP. Dir 76/769/EEC (Restriction)					
Alkylphenol ethoxylates	20427-84-3	4-Nonylphenoldiethoxylate (NP2EO)		Dir 2003/53/EC 26th ATP. Dir 76/769/EEC (Restriction)					
Benzenic acid and derivatives	94-26-8	n-Butyl p-hydroxybenzoate	Medium					Com Dec 1999/217/EC[32]	
	94-13-3	n-Propyl-p-hydroxybenzoate	Medium					Dir 2002/72/EC[33]	
	99-76-3	Methyl p-hydroxybenzoate	Medium					Dir 2002/72/EC; Dir 95/2/EC	

[32] Commission Decision 1999/217/EC adopting a register of flavouring substances used in or on foodstuffs drawn up in application of Regulation (EC) No 2232/96.

[33] Directive 2002/72/EC relating to plastic materials and articles intended to come into contact with foodstuffs

Group name	CAS Number	Substance	Exposure concern	Status under Dir 76/769/EEC or adaptations to technical progress	Status under Reg 793/93/EEC	Status of review under Dir 91/414/EEC	Other Risk Assessment Instruments	Other Risk Management Instruments	Other Hazard Identification Instruments
	120-47-8	Ethyl-4-hydroxy-benzoate	Medium					Dir 2002/72/EC; Com Dec 1999/217/EC	
	99-96-7	p-Hydroxybenzoic acid	Medium					Dir 2002/72/EC	
Benzo-phenones	131-56-6	2,4-Dihydroxy-benzophenon = Resbenzophenone	High					Dir 2002/72/EC	
	611-99-4	4,4'-Dihydroxybenzo-phenon	Medium					Dir 2002/72/EC	
Biphenol	92-88-6	4,4'-Dihydroxy-biphenyl = 4,4'-Biphenol	High					Dir 2002/72/EC	
Organo-phosphor pesticides	1113-02-6	Omethoate	Low			Phased out in 2003 (Regulation (EC) 2076/2002)	Omethoate is a metabolite of dimethoate. Risk for consumer assessed when setting pesticide residues MRLs		
Organothio-phosphor pesticides	13593-03-8	Quinalphos = Chinalphos	Medium			Phased out in 2003 (Regulation (EC) 2076/2002)			

Group name	CAS Number	Substance	Exposure concern	Status under Dir 76/769/EEC or adaptations to technical progress	Status under Reg 793/93/EEC	Status of review under Dir 91/414/EEC	Other Risk Assessment Instruments	Other Risk Management Instruments	Other Hazard Identification Instruments
Phthalates	131-18-0	Di-n-pentylphthalate (DPP) = Dipentylphthalate	Medium						Dir 67/548/EEC, Annex I
Siloxans	556-67-2	Cyclotetrasiloxane	High						Dir 67/548/EEC, Annex I
Other substances	25013-16-5	tert.-Butylhydroxy-anisole (BHA)	High					Dir 2002/72/EC; Dir 95/2/EC[34]	
	1634-04-4	Methyl-tert-butyl ether (MTBE)	Medium		Priority substance covered by Reg. (EC) 143/97				
	10043-35-3	Boric Acid	Medium		Priority substance covered by Reg. (EC) 2364/2000	Covered by Dir 91/414; phased out in 2004 by Decision 129/2004		Dir 2002/72/EC; Dir 95/2/EC	
Other pesticides	6164-98-3	Chlordimeform	Low						PIC substance

[34] Directive 95/2/EC of the European Parliament and of the Council of 20 February 1995 on food additives other than colours and sweeteners

Group name	CAS Number	Substance	Exposure concern	Status under Dir 76/769/EEC or adaptations to technical progress	Status under Reg 793/93/EEC	Status of review under Dir 91/414/EEC	Other Risk Assessment Instruments	Other Risk Management Instruments	Other Hazard Identification Instruments
	1582-09-8	Trifluralin	High			SCFCAH voted in March 2007 in favour of COM proposal not to authorise the substance; publication of decision is pending			
	96-45-7	Ethylene Thiourea (ETU)	Low				ETU is a metabolite of some dithio-carbamates. Risk for consumer assessed when setting pesticide residues MRLs		

Table 3: Substances with potential evidence of ED effects (Category 2), which are already regulated or being addressed under existing legislation (9 substances)

Group name	CAS Number	Substance	Status under Dir 76/769/EEC or adaptations to technical progress	Status under Reg 793/93/EEC	Status of review under Dir 91/414/EEC	Other Risk Assessment Instruments	Other Risk Management Instruments	Hazard Identification Instruments
Alkylphenols and derivatives	106-44-5	p-cresol					Dir 2002/72/EC Com Dec 1999/217/EC	Dir 67/548/EEC, Annex I
Bisphenols	6807-17-6	2,2-Bis(4-hydroxyphenyl)-4-methyl-n-pentane						Dir 67/548/EEC, Annex I
Benzophenons	131-57-7	2-hydroxy-4-methoxy-benzophenone					Dir 2002/72/EC	
Nitrophenols	100-02-7	4-nitrophenol						Dir 67/548/EEC, Annex I
Organo-phosphor pesticides	2597-03-7'	Elsan = Dimephenthoate						Dir 67/548/EEC, Annex I
PCBs	2051-60-7	PCB 1 (2-Chlorobiphenyl)					Reg 850/2004/EEC[35]	
	2051-61-8	PCB 2 (3-Chlorobiphenyl)					Reg 850/2004/EEC	

[35] Regulation (EC) N° 850/2004/EEC of the European Parliament and of the Council of 29 April 2004 on persistent organic pollutants and amending Directive 79/117/EEC

Group name	CAS Number	Substance	Status under Dir 76/769/EEC or adaptations to technical progress	Status under Reg 793/93/EEC	Status of review under Dir 91/414/EEC	Other Risk Assessment Instruments	Other Risk Management Instruments	Hazard Identification Instruments
	2051-62-9	PCB 3 (4-Chlorobiphenyl)					Reg 850/2004/EEC	
Pyrethrins	121-29-9	Pyrethrin			covered by Dir 91/414; notified in list 4C, decision pending			Dir 67/548/EEC, Annex I

Table 4: Substances with no or insufficient data on ED effects gathered (Category 3a and 3b), for which there is currently no support for their inclusion in the priority list (48 substances)

Group name	CAS Number	Substance
Alkylphenols and derivatives	87-26-3	2-sec-Pentylphenol = 2-(1-Methylbutyl)phenol
	27214-47-7	Phenol, 4-sec-octyl-
	26401-75-2	Phenol, 2-sec-octyl-
	18626-98-7	Phenol, 2-(1-methylheptyl)-
	1818-08-2	Phenol, 4-(1-methylheptyl)-
	17404-44-3	Phenol, 2-(1-ethylhexyl)-
	37631-10-0	Phenol, 2-(1-propylpentyl)-
	3307-01-5	Phenol, 4-(1-propylpentyl)-
	949-13-3	Phenol, 2-octyl-
	27985-70-2	Phenol, (1-methylheptyl)-
	3884-95-5	Phenol, 2-(1,1,3,3-tetramethylbutyl)-
	3307-00-4	Phenol, 4-(1-ethylhexyl)-
	1322-97-0	Ethanol, 2-(octylphenoxy)- = Octylphenolethoxylate
	27986-36-3	Ethanol, 2-(nonylphenoxy)-
	1009-11-6	4-Hydroxy-n-butyrophenone

Group name	CAS Number	Substance
	70-70-2	4-Hydroxypropiophenone
	7786-61-0	4-vinylguaiacol (4-VG)
	2628-17-3	4-vinylphenol (4-VP)
Phenylhydroxy-phenylmethanes	28994-41-4	Phenyl-2-hydroxyphenylmethane = 2-Benzylphenol = o-Benzylphenol
Chlorphenole	25167-81-1	Dichlorophenol
Hexachlorocyclo-hexane and isomers	13171-00-1	4-Acetyl-1,1-dimethyl-6-tert.-butylindane
Naphthalene and derivatives	530-91-6	Tetrahydronaphthol-2
	15231-91-1	6-Bromo-2-naphthol
	1125-78-6	5,6,7,8-Tetrahydro-2-naphthol = 6-Hydroxytetralin
	90-15-3	1-Naphthol(*)
Bisphenols	3373-03-3	1,1-Bis(4-hydroxyphenyl)-n-heptane
	24362-98-9	1,1-Bis(4-hydroxyphenyl)-n-hexane
	620-92-8	Bis(4-hydroxyphenyl)methane
	52479-85-3	2,3,4,3',4',5'-Hexahydroxybenzophenon
Siloxanes	56-33-7	Diphenyltetramethyldisiloxane PhMe2-SiOSiMe2Ph

Group name	CAS Number	Substance
	10448-09-6	Phenylheptamethylcyclotetrasiloxane [(PhMeSiO)(Me2SiO)3]
Polycyclic Aromatic Hydrocarbons	53-96-3	n-2-Fluorenylacetamide
Methoxychlor and derivatives	14868-03-2	Bis-OH-MDDE
Organophosphor pesticides	682-80-4	Demefion
	2540-82-1	Formothion
	70393-85-0	Glufosinate-ammonium
Polychlorinated Biphenyls and biphenylethers	2050-68-2	PCB 15 (4,4'-Dichlorobiphenyl)(*)
Other substances	303-38-8	2,3-dihydroxybenzoicacid (2,3-DHBA)
	490-79-9	2,5-dihydroxybenzoicacid (2,5-DHBA)
	533-73-3	Hydroxyhydroquinone
	1222-05-5	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta(g)-2-benzopyrane(*)
	33704-61-9	6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)indanone
	114369-43-6	Fenbuconazole
	118-56-9	3,3,5-trimethyl-cyclohexyl salicylate

Group name	CAS Number	Substance
	25550-58-7	Dinitrophenol(*)
	463-56-9	Thiocyanate(*)
	21245-02-3	2-ethyl-hexyl-4-dimethyl-aminobenzoate
	79-44-7	Dimethylcarbamylchloride(*)

(*) Some information and legislative coverage for these substances is already achieved, but there is no data available in relation to endocrine disrupting effects that would support their inclusion into the priority list

Table 5: Substances which are deemed not to be endocrine disrupters, on the basis of available information (4 substances)

Group name	CAS Number	Substance
Alkylbenzenes and Styrenes	104-51-8	n-Butylbenzene
Pyrimidines and Pyridines	314-40-9	Bromacil
Other substances	537-98-4	Ferulic acid (FA)
	545-55-1	TEPA

ANNEX 3: Overview of the ED test methods currently in (pre)validation under the auspices of the OECD.

Receptor Binding Assays				
hrERα	The FWA assay protocol utilizes the Pan Vera hrERα full length ER, and the CERI protocol utilizes the CERI-ERα, which contains the ligand binding domain of hrERα.	binding	Validation starting in February 2007 in 5 labs.	US lead international collaboration study
hrAR	Human recombinant AR assay. Ligand binding domain expressed in E. coli.	binding	Under development. Approximately 900 chemicals have been tested.	METI Japan
hrAR	Human recombinant AR assay.	binding	Prevalidation starting now (initially as part of ReProTect.)	EC:ECVAM Bayer Lead international collaboration study
hrTR	Human recombinant TR assay. Full-length expressed in E. coli. TRs α1 and β1 binding assays.	binding	Under development. Approximately 60 chemicals have been tested using both receptors.	METI Japan
Transcriptional Activation Assays				
ERα	HeLa-9903 cells with plasmids containing hERα cDNA driven by SV40 promotor and luciferase reporter plasmid.	Stable, ag/antag	The agonist assay was peer reviewed in March-07. International validation of the antagonist assay is planned for 2007.	CERI/MHLW Japan
	HeLa-9903 cells: hERα/pcDNA3.1 receptor expressing plasmid and ERE-AUG-Luc+ reporter	Transient, ag	Pre-validated and Validated under domestic multi-lab. validation using same test chemicals as hERa-HeLa-9903 cell line. Should be	CERI/MHLW Japan

	plasmid		considered for (preliminary) Peer review.	
	MELN. MCF-7 cells with endogenous ERα + luciferase stably transfected	ag/antag	Validation in 2007. Report in late 2007 or early 2008.	EC/ECVAM
	ER-CALUX. T47 D (human breast cancer) cells with endogenous ERα + luciferase stably transfected	ag/antag	Going through optimisation. Validation planned for 2008.	EC/ECVAM
	LUMI cell, BG1 cells with endogenous ERα + luciferase stably transfected (XDS Inc)	ag/antag	Validation will be initiated in late 2007, done by late 2008. In delay.	US lead (ICCVAM) international collaboration study with ECVAM and JaCVAM
ERβ	HeLa, hERß/pcDNA3.1, ERE-AUG-Luc+	Transient, ag	Completed data collection for 250 compounds	CERI/MHLW Japan
AR	CV-1 cells hAR/pcDNA3.1 receptor expressing plasmid and ARE-AUG-Luc+ reporter plasmid	Transient, ag/antag	Pre-validated and validated in Japan in 4 labs, with 5 chemicals. Should be considered for (preliminary) Peer review.	CERI/MHLW Japan
	AR-Ecoscreen™ stable CHO clone	Stable, ag/antag	Pre-validated and validated in Japan in 4 labs, with 5 chemicals. Should be considered for (preliminary) Peer review.	CERI/MHLW Japan
	PALM. PC-3 (prostate adenocarcinoma) cells stably transfected with hAR and luciferase reporter gene	ag/antag	Validation in 2007	EC/ECVAM

	CALUX. U2-OS (bone cell) cells stably transfected with hAR and luciferase reporter construct	ag/antag	Validation in 2007	EC/ECVAM
TRβ	RXR co-transfected CHO cells are used	Transient, ag/antag	Under development, 150 chemicals tested so far.	MHLW Japan
Aromatase & Steroidogenesis Assays				
	Aromatase, KGN cells		Prevalidated.	
	Steroidogenesis, H295R		Validation starts March 2007.	US lead international collaboration study