List of Endocrine Disrupting Chemicals

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DANISH CENTRE ON ENDOCRINE DISRUPTERS

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Abbreviations

AR	Androgen Receptor
BP	Biocidal products
CAS	Chemical Abstracts Service
CeHoS	Centre on Endocrine Disrupters
CoRAP	Community Rolling Action Plan
D4	Octamethylcyclotetrasiloxane
Danish EPA	Danish Environmental Protection Agency
DCHP	Dichlohexyl phthalate
DHP	Dihexyl phthalate
DK	Denmark
DPP	Di-n-penthylphthalate
DTU	Technical University of Denmark
ECHA	European Chemicals Agency
ED	Endocrine disrupter
EDC	Endocrine disrupting chemical
Env.Exp.	Environmental exposure
EU	European Union
GD	Gestation day
hERalpha	human Estrogen Receptor alpha
hThRa	Thyroid hormone Receptor alpha
hThRb	Thyroid hormone Receptor beta
Hum.Exp.	Human exposure
ID	Identification
IPCP	International Panel on Chemical Pollution
IUCLID	International Uniform Chemical Information Database
MoA	mode of action
MTBE	Methyl tertiary butyl ether
NCBI	National Center for Biotechnology information
NGO	Non-governmental organisation
NO	Norway
OECD GD	Organisation for Economic Co-operation and Development Guidance Document
OMC	Ethylhexyl methoxycinnamate
PAH	polycyclic aromatic hydrocarbon
PCP	Pentachlorophenol
PPP	Plant protection products
PubMed	Public Medline
PXR	Pregnane X Receptor
QSAR	Quantitative Structure-Activity Relationships
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RoU	Range of use
SE	Sweden
SIN	Substitute it now!
SPIN	Substances in Preparations in the Nordic Countries
SVHC	Substances of Very High Concern
SQL	Structured Query Language
TEDX	The Endocrine Disruption Exchange
ToxCast	Toxicity Forecaster
UI	Use Index

US EPA	United States Environmental Protection Agency
UVCB	substance of unknown or variable composition
WHO	World Health Organization
WoE	Weight of evidence

Contents

1. Terms of reference and scope

This report has been prepared by the Danish Centre on Endocrine Disrupters (CeHoS) as a project contracted by the Danish Environmental Protection Agency (EPA). CeHoS is an interdisciplinary scientific network without walls. The main purpose of the CeHoS is to build and gather new knowledge on endocrine disrupting chemicals (EDCs) with the focus on providing information requested for the preventive work of the regulatory authorities. CeHoS is financed by the Ministry of the Environment and the scientific work programme is followed by an international scientific advisory board.

The overall scope of this project is to provide a science based consolidated list of EDCs and suspected EDCs which can be used by the authorities as,

1. Basis for input to EU regulation
2. Basis for the eco-label criteria
3. Clear communication to consumers

The project was carried out by a project team: Ulla Hass (project leader), Mille Dahl Andersen, Sofie Christiansen, Sine Abildgaard Rosenberg, Karen Mandrup Egebjerg, Sidsel Brandt, Eva B. Wedebye and Nikolai G. Nikolov at the Technical University of Denmark (DTU) and Henrik Holbech and Jane Ebsen Morthorst at University of Southern Denmark (SDU).

2. Background and aim

After many years of knowledge building on EDCs, there is now a political consensus on the need to minimize the exposure of humans and the environment for those substances. The first step in this regard is to identify the substances that are EDs and to decide how to handle these under the various jurisdictions. There are already a number of lists of suspected and potential EDs established by authorities and non-governmental organisations (NGO’s). These lists were used in the present project for establishing a basis list with all of these substances.

The project included the following activities:
1. Preparation of background lists of suspected EDs
2. Development of a prioritised basis list based on the existing lists of suspected EDs
3. Assessment of whether the prioritised substances meet the World Health Organizations (WHO's) definition as EDs
4. Reporting and proposals for following up on this new list of EDs

The project was divided into two phases. The separate deliveries for Phase 1 were:

1. Collection and preparation of background lists of suspected EDs
2. Development of a prioritized basis list
3. Literature screening of 12 of the prioritized substances to evaluate whether they may be EDCs according to the WHO definition
4. Assessment of two substances from the prioritized basis list
5 Evaluation of 17 substances previously assessed to be EDCs in reports from CeHoS (Hass et al. 2012a, Hass et al. 2012b)

The separate deliveries for Phase 2 were:

1. Hazard screening of 40-50 of the prioritized substances to evaluate whether they may be EDC according to the WHO definition and selection of 12-16 highly prioritized substances

2. Evaluate whether the selected 12-16 substances fulfil the WHO definition of an endocrine disrupter

3. Reporting of both phase 1 and 2

3. The basis list

Methodology overview

The planned first step was to identify and assemble already existing and publically available lists of possible EDCs (background lists) into one list containing relevant information from the different lists, exposure data and mode of action (MoA) data from Quantitative Structure-Activity Relationships (QSAR) predictions obtained from an earlier project (Wedebye 2014). Subsequently the list should be prioritized according to MoA and exposure data, founding a prioritized basis list.

Early in the process the Danish EPA informed the project group of the European Chemicals Agency's (ECHA's) master list (unpublished) and recommended this to be included in the project, because this list can contribute with further potential EDs as well as various relevant hazard and non-hazard scenario codes. The ECHA's master list was provided by the Danish EPA on October 7, 2016.

Inclusion of the master list in the project increased the workload in the project, but lead also to more comprehensive number of substances suspected to be EDCs.

It soon turned up that ECHA's master list included a substantial amount of information that was not included in the background lists. Thus, it was necessary to handle the ECHA master list differently compared to the other lists available. Hence, the prioritising work on the master list and the background lists was done in parallel resulting in 1) a list based on the ECHAs master list, called basis list-M and 2) another list (basis list-S) based on the remaining substances listed only in the other background lists. Figure 1 shows an overview of this work.

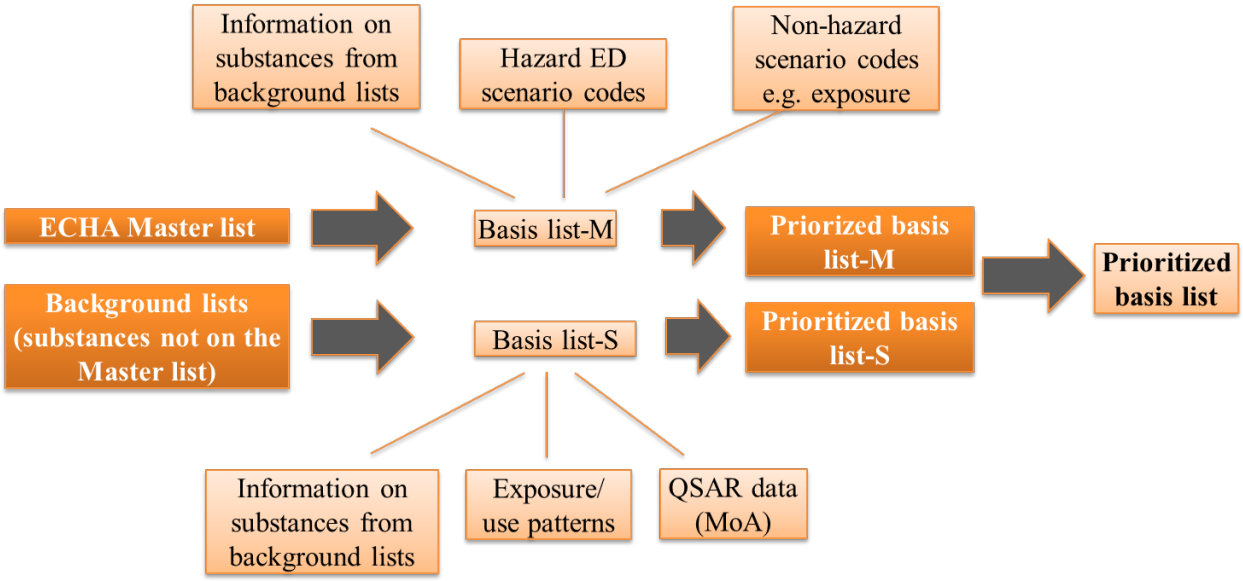

Figure 1 The ECHA Master list provided the basis for constructing the basis list-M. For the substances included, information from any of the background lists was added. The substances on the basis list-M were prioritized according to selected ED scenario codes and exposure codes. The supplementary list, called basis list-S, was generated by assembling the remaining substances listed on other background lists, but not on the basis list-M. As with the basis list-M, relevant information on substances from background lists were added to the basis list-S together with any corresponding exposure and QSAR data. The substances on basis list-S were prioritized according to MoA information from QSAR data and exposure data.

Background lists

Background lists of suspected/potential endocrine disrupting chemicals (EDCs) were generated based on various already existing lists when the project was initiated September 1, 2016, i.e.:

- Assessment of Danish Criteria for Identification of Endocrine Disruptors (CeHoS reports) (Hass et al. 2012a, 2012b),
- The Priority List of Chemicals (European Commission, 2016a),
- The DK Consumer Council list (DK Consumer Council, 2016),
- The Substitute it now! (SIN) list (ChemSec, 2016),
- Trade Union Priority List for Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Authorisation (European Trade Union Confederation, 2010).
- The List of potential Endocrine Disruptors (TEDX, 2016),
- State of the science of Endocrine Disrupting Chemicals 2012 (WHO, 2012)

These lists were partly identified in a draft overview report from 2016 prepared by The International Panel on Chemical Pollution (draft report, IPCP, 2016) (where 24 lists and databases were identified) while some of the lists were already known to the project group members. Background lists were generated by extracting data specifically on EDCs from the different lists.

Table 1 gives an overview of the background lists, including information on the number of substances and unique Chemical Abstracts Service (CAS) numbers on these lists and whether the lists are from governmental or non- governmental organizations. Note that in some of the background lists some substances have been listed with more than one unique CAS number.

Table 1 An overview of the identified background lists as well as information on the number of substances on each list, the number of unique CAS numbers and whether the lists are established by governmental or non-governmental organizations.

Background lists	**No. of substances**	**Unique CAS no.**
By governmental organizations		
CeHoS evaluations[1]	26	26
EU Com Prio list[2]	408	408
By non-governmental organizations		
DK Consumer Council list[3]	32	34
SIN list[4]	94	97
Trade Union list[5]	71	115
TEDX list[6]	1038	1052
WHO list[7]	176	181

1) Assessment of Danish Criteria for Identification of Endocrine Disruptors (CeHoS 22+4 project) (Hass *et* al. 2012a, 2012b)
2) Priority List of Chemicals (European Commission, 2016a)
3) 32 Endocrine Disrupting Chemicals (Consumer Council, 2016)
4) Substitute it now! (SIN) list (ChemSec, 2016)
5) Trade Union Priority List for REACH Authorization (European Trade Union Confederation, 2010)
6) List of potential Endocrine Disruptors (TEDX, 2016)
7) State of the science of Endocrine Disrupting Chemicals 2012 (WHO, 2012)

The ECHA master list and basis list-M

The ECHA master list includes confidential information and is therefore not included here. However, a description of the ECHAs screening work[1], the screening definitions (including various ED scenario codes) [2] and some information related to substance IDs for registered substances[3] are publicly available on the ECHA homepage.

[1] https://echa.europa.eu/documents/10162/19126370/common_screening_approach_en.pdf/b195b928-25ce-4a1c-9eec-8f58ca724f58
[2] https://echa.europa.eu/documents/10162/19126370/screening_definition_document_en.pdf/e588a9f8-c55e-4412-a760-49ddbf7ac687
[3] https://echa.europa.eu/information-on-chemicals/registered-substances

The master list contained some information from several of the lists that had already been generated background lists from, i.e.: the Priority List of Chemicals (European Commission, 2016a), the SIN list (ChemSec, 2016), the List of potential Endocrine Disruptors (TEDX, 2016) and Endocrine Disrupting Chemicals 2012 (WHO, 2012). However, the master list did not include all the substances from the background lists, i.e. the other existing lists of potential EDCs. The reason for this is, that the version of the master list provided from ECHA via Danish EPA mainly includes registered substances, which are substances that are imported or manufactured in EU at a tonnage of 100 tons/year or higher. However, it should be noted that ECHA's screening collect data for all substances, including those not registered, and these data are available in ECHAs internal systems.

From the master list, a list called the basis list-M was generated, containing CAS numbers of all substances on the master list, substance name, as well as other relevant information. The CAS numbers from the background lists that did not match any of the CAS numbers in the master list were assembled in a supplementary list, which was kept as an independent list called basis list-S (see figure 1). This was done because the sorting of the two lists could not be executed in the same way, as the basis list-M contains hazard and non-hazard scenario codes obtained from the ECHA master list, which were not possible to generate for the supplementary list.

Methods for developing the basis list-M

The following steps were taken to develop the basis list-M:

1) Extraction of substances with unique CAS numbers from the Master list leading to 7,203 substances.
2) Selection of substances with ED scenario codes and excluding substances, where the term "similar to" is used in the various ED scenario codes for effects. This lead to 3,562 substances.
3) Supplementation with information on substances from other background lists. This was generally done in the following way:
   - If the CAS number on the other background list(s) was already included, any relevant new information from the other list(s) was added
   - If the CAS number on the other background list(s) was not included, the substance along with relevant information was added to basis list-S (see later for details).

The basis list-M was further developed to contain all exposure data as well as information on which substances that are on the REACH Candidate list of Substances of Very High Concern (SVHC) (European Chemicals Agency 2016b) and/or on the Community Rolling Action Plan (CoRAP) list (European Chemicals Agency 2016c). This was done, because the information was to be used when selecting substances on the basis list-M for evaluation of ED properties.

The downloaded and processed background lists that were included the ECHA master list were checked with regard to updated versions of some of the background lists. As a result of this, the information with regards to the SIN list and the TEDX list was revised. A keyword search on the SIN list was conducted by ECHA using the keyword "endocrine" to extract the substances with ED

effects. However, this search did not appear to identify all the presumed ED substances in the SIN list. Therefore, an updated SIN list database with substances in the ED category was downloaded. This list was matched up by CAS number within the in basis list-M to ensure that substances with ED concern on the SIN list were correct.

The TEDX list has been updated since ECHA included it in the master list. In the newer version of the TEDX list, downloaded September 26 2016, some substances have been excluded from the list, and some new substances have been added. Furthermore, the CAS numbers for some of the substances also seemed to have been corrected; former CAS numbers existed in slightly modified versions for the same substance name and with the same literature references. These issues were updated within the basis list-M. Furthermore, 78 substances on the TEDX list had no CAS numbers making it impossible with certainty to identify these substances on the basis list-M, and they were therefore not included in the subsequent work.

An overview of the number of unique CAS numbers for substances from the different background lists and regulatory lists within the basis list-M and the basis list-S is shown in table 2.

Table 2 Overview of the number of unique CAS numbers for substances from the different background lists and regulatory lists within the basis list-M and the basis list-S.

Background lists	**Basis list-M**	**Basis list-S**
Danish CeHoS list*	14	12
SIN list	42	55
EU Com Prio list	64	344
Trade union list	84	31
TEDX list	178	796
WHO list	50	131
DK Consumer Council list	24	10
Regulatory lists	**Basis list**	**Supplementary list**
CoRAP list	65	0
REACH Candidate list	5	21

* Referring to Hass et al. 2012a and Hass et al. 2012b, CeHoS reports

Methods for developing the basis list-S

The supplementary list, i.e. basis list-S was constructed using Excel and primarily the conditional formatting tool, which makes it possible to identify duplicate values, in this case CAS numbers. Furthermore, the search (and replace) function was also used in some cases. Some of the background lists contained substances identified by more than one CAS number. In these cases, these were split into individual CAS numbers (this was already done in the master list and basis list-M) to avoid overlooking relevant data attached to an ‘alternative’ CAS number.

The basis list-S has a total of 995 substances with unique CAS numbers.

Besides information about which background list the different substances appeared on, exposure information from the Substances in Preparations in Nordic Countries (SPIN) database as well as MoA information from QSAR predictions were added to the supplementary list.

Integrating SPIN data

SPIN is a database on the use of Substances in Preparations in the Nordic Countries (www.spin2000.net). The database is based on data from the Product Registries of Norway, Sweden, Denmark, and Finland. The SPIN data were downloaded from the online SPIN database (www.spin2000.net). This was done by first downloading the complete list of CAS numbers on all substances with SPIN data (in total 27,603 substances). This list was matched with the CAS numbers on the basis list-S, and SPIN data were downloaded for the matched CAS numbers.

Of the 995 unique CAS numbers on the basis list-S, 190 had SPIN data. Substance data extracted from the SPIN database is presented in table 3, which is an example for the substance Polyvinylchloride (CAS number 9002-86-2). Consumer and occupational exposure data from SPIN were merged into one category, called human exposure (Hum. Exp.). Similarly, exposure data for surface water, air, soil, and waste water were merged into one category, called environmental exposure (Env. Exp.). Range of use (RoU) was given its own category. The scores 1-5 given in the different categories are according to the SPIN database scores, see the descriptions in table 4. In agreement with the Danish EPA it was decided to merge the scores 4 and 5 (in the use index) into one category called probable to very probable exposure (this has also been done in the Master list). Also for RoU, the scores with the symbols 4 and 5 were merged into one category called wide to very wide range of applications and the score with the symbol 1 were not included. As can be seen in table 3, the scores may vary between countries and between the different sub-categories. It was decided, together with the Danish EPA, that the highest score for a substance in one or more countries or in one or more sub-categories was determining the category both in terms of exposure and RoU.

Table 3 Example on how data from the SPIN database is displayed. Here with Polyvinylchloride (CAS number 9002-86-2) as an example

Country	**Latest year**	**Use Index (UI)**						**Range of Use (RoU)**
		Surface water	Air	Soil	Waste water	Consumer	Occupational	
		Max 5	Max 5	Max 5	Max 5	Max 5	Max 5	Max 5
DK	2014	3	4	3	4	4	5	4
NO	2014	3	4	4	3	5	5	3
SE	2014	3	3	4	4	5	5	4

Table 4 Overview and explanations of the categorisations and rankings from the SPIN database

Parameter	Score	Value	Explanation
	Blank		The substance is not registered in the country, or no data calculated
Use Index	0, 1 or 2	0-2	The registered use does not indicate direct exposure*
	3	3	One or several uses indicate a potential exposure
	4	4	One or several uses indicate a probable exposure
	5	5	One or several uses indicate a very probable exposure
Range of Use	1	1-3	Very narrow range of applications
	2	4-10	Narrow range of applications
	3	11-32	Intermediate range of applications
	4	33-100	Wide range of applications
	5	>100	Very wide range of applications

* Note that the registered use categories do not include all potential uses of the substance, and the potential for direct exposure can therefore not be excluded.

Integrating QSAR data on endocrine activity

QSAR data related to endocrine activity were available from a previous report (Wedebye 2014) to the Danish EPA. The list of substances from this report contained a total of 9,374 unique CAS numbers, which were matched with the CAS numbers on the supplementary list. Of the 995 unique CAS numbers on the supplementary list, 381 had associated QSAR data, and of these 297 had a positive QSAR prediction in one or more of the QSAR endpoints listed below:

- Battery: Androgen Receptor (AR) antagonism (human vector); 2,297 POS_IN
- Battery: Binding to the human Estrogen Receptor alpha (hERalpha) Balanced; 3,579 POS_IN
- Battery: Binding to the human Estrogen Receptor alpha (hERalpha); ALL, 1,621POS_IN
- Battery: Activation of the human Estrogen Receptor alpha (hERalpha); 1,592 POS_IN
- Single: Mammalian Estrogen Receptor agonism (US EPA CERAPP project); 4,192 POS_IN
- Battery: Binding to human Thyroid hormone Receptor alpha (hThRa); 201 POS_IN
- Battery: Binding to human Thyroid hormone Receptor beta (hThRb); 689 POS_IN

Predictions from an additional QSAR model were included in the previous QSAR report (Wedebye 2014) as supporting information:
- Binding to the human pregnane X receptor (PXR) in vitro, 3,281 POS_IN out of the 9,236

The predictions from this model were included with the equal weight as predictions from the other seven models in the MoA data in the supplementary list.

4. Prioritizing of the substances on the basis list

Prioritizing of the substances on the basis list-M

The basis list with a total number of 7,203 substances was derived from ECHA Master list. Of these 7,203 substances, 3,573 are positive in one or more ED scenario codes. Exclusion of ED scenario codes containing “similar to” lead to 3,562 substances, i.e. 11 substances were excluded. An

overview and detailed descriptions of the scenario codes can be found on ECHAs homepage[4]. The 3.573 substances were then prioritized; first by ED scenario codes "toxicity to endocrine organs"; then by MoA ED scenario codes in QSAR and/or ToxCast; and lastly by exposure level in SPIN.

When prioritizing the 3,573 substances according to hazard scenarios, two hazard scenarios were chosen: "toxicity to endocrine organs – related to oestrogen, androgen or thyroid hormone systems" and "toxicity to endocrine organs – **not** related to oestrogen, androgen or thyroid hormone systems". A total of 1,231 substances had at least one of these two hazard scenarios. The 1,231 substances were then further prioritized according to MoA resulting in 126 substances that were positive also in one or more of the MoA ED scenario codes. Finally, these 126 substances were prioritized according to the risk for exposure. For this two approaches were chosen: 1) either human **or** environmental exposure had a probable to very probable risk, and 2) a more restrictive approach where both human **and** environmental exposure had a probable to very probable risk (see table 5). Thus from the 126 substances, 110 had a probable to very probable risk of exposure to either human **or** environment, and of these 11 are on the CoRAP list and 2 are on the REACH candidate list of SVHC. Correspondingly, of the 126 substances 84 had a probable to very probable risk of exposure to both human **and** environment, and of these 9 are on the CoRAP list and 2 are on the REACH candidate list of SVHC (see table 5).

It should be noted that for some of the ED scenario codes there was no positive scores on any of the 7,203 substances. Furthermore, ED scenario codes concerning constituents, impurities and additives were excluded to limit the number of substances.

The high number of substances with ED scenario codes, i.e. 3,562, may give the impression that a large percentage of substances may be EDs. However, screening scenario results do not provide the full truth as they may pick findings of low or no importance. Thus, such results are to be used in combination and confirmed with manual assessments.

Table 5 Results from the prioritization of the basis list-M with regards to hazard scenarios, MoA and the risk for exposure.

Total number of substances with unique CAS numbers on ECHA master list and basis list-M	7,203	
Substances with ED scenario codes (excluding "similar to")	3,562	
Substances with ED scenario code (Toxicity to endocrine organs)	1,231	
Substances with MoA ED scenario code (in QSAR and/or ToxCast)	126	
Substances reported in SPIN to pose probable to very probable risk of exposure	Hum. OR Env.	Hum. AND Env.
	110* (97)	**84**(73)**

*Of the 110 chemicals 11 are on the CoRAP list and 2 are on REACH candidate list of SVHC. The number in the parentheses represents the number of substances excluding those on the CoRAP or the REACH candidate list.
**Of the 84 chemicals 9 are on the CoRAP list and 2 are on REACH candidate list of SVHC. The number in the parentheses is the number of substances that are not included either on the CoRAP or the REACH candidate list.

[4] https://echa.europa.eu/documents/10162/19126370/screening_definition_document_en.pdf/e588a9f8-c55e-4412-a760-49ddbf7ac687

Prioritizing of the substances on the basis list-S

The basis list-S of 995 substances was sorted in Excel, first by QSAR predictions of ED MoA and then by risk of exposure as reported in SPIN. When sorting by MoA in QSAR, substances that were predicted to have ED MoA in one or more of the QSAR endpoints were prioritized. Out of the 995 substances, 298 had a positive prediction in one or more of the QSAR endpoints (See table 6). These substances were then further prioritized according to exposure data in SPIN. For 83 of the 298 substances exposure data was reported in SPIN. Like for the basis list-M, two approaches were chosen;1) either human **OR** environmental exposure had a probable to very probable risk, and 2) a more restrictive approach where both human **AND** environmental exposure had a probable to very probable risk (See table 6). From this, 79 out of the 298 substances had a probable to very probable risk of exposure to either human **OR** environment, out of which five substances are on the REACH candidate list of SVHC. Correspondingly, 49 of the 298 substances posed probable to very probable risk for exposure of both humans **AND** environment, out of which four are on the REACH candidate list of SVHC (see table 6).

The prioritisation of substances in the S-list could also have been based on ToxCast positive results and not only QSARs. This would increase the number of prioritised substances. However, inclusion of these data for the substances on basis list-S was not possible within the time frame for the project.

Table 6 Results from the prioritization of the basis list-S with regards to MoA and probable to very probable risk of exposure.

Total number of substances with unique CAS numbers	995	
Substances with ED MoA (in QSAR)	298	
Substances with SPIN data	83*	
Substances reported in SPIN to pose probable to very probable risk of exposure	Hum. OR Env.	Hum. AND Env.
	79(74)*	**49(45)****

* The number (74) represents the number of substances excluding 5 substances that are on the REACH candidate list.
** The number (45) represents the number of substances excluding 4 substances that are on the REACH candidate list.

Prioritized basis list of suspected/potential EDs

The number of prioritized suspected/potential EDs from the prioritization of substances on the basis list-M (table 5) and the basis list-S (table 6) are merged in table 7.

Table 7 Number of prioritized substances on the basis list. Merged results from the prioritization of the basis list-M and the basis list-S with regards to hazard scenarios, MoAs and exposure level. The number in the parentheses represents the number of substances excluding the substances that are included on the CoRAP or the REACH candidate list.

Total number of substances with unique CAS numbers	8,198
Substances reported in SPIN to pose a probable to very probable risk of human OR environmental exposure	**189 (171)**
Substances reported in SPIN to pose probable to very probable risk of human AND environmental exposure in SPIN	**133 (118)**

5. Evaluations of substances for endocrine disrupting properties

Evaluation of previous CeHoS evaluations of substances

Two previous CeHoS reports have evaluated a total of 26 substances according to a Danish proposal on criteria for endocrine disrupters (Hass et al. 2012a, Hass et al. 2012b). The Danish EPA has in the current project requested a re-evaluation based on experiences during the recent years with regards to hazard identification of EDC's in EU. It was decided to focus on the 17 substances considered EDs, i.e. those in category 1 in the previous evaluations, since these substances are considered most relevant with regards to the purposes of the present project.

The re- evaluation has been done based on the data sheets for each of the substances allocated into category 1. The lead to a subdivision into subcategory 1.1 and 1.2, where:

- Sub-category 1.1: Substances, where we evaluate that the data show that these are EDs in category 1, i.e. the data is evaluated to fulfil the WHO definition of an ED
- Sub-category 1.2: Substances where the data show that these are likely to be EDs in category 1, but where there are some limitations with regards to the data. These limitations have been indicated as keywords in the table below (see table 8). Thus, for these substances the data is evaluated as likely to fulfil the WHO definition of an ED, but there are some uncertainties.

As can be seen in table 8, this re-evaluation confirmed that for 10 of the 17 substances we still evaluate that the data show that these substances are EDs in category 1 (i.e., in sub-category 1.1). The remaining 7 substances were allocated to sub-category 1.2, i.e. are evaluated as likely to be EDs in category 1. However, various limitations in the data for these substances may make it more difficult to obtain international agreement for these seven substances compared to the 10 substances in category 1.1.

The prioritized basis list-M and prioritized basis list-S have been updated with respect to this re-evaluation.

Table 8 Overview of the result of the re-evaluations of the category 1 substances in Hass et al. 2012a and 2012b incl. subdivision into sub-category 1.1 or 1.2

Chemical	Sub-category	Limitations (keywords)
3-benzylidene camphor	1.2	Small group size and only studies from one laboratory
4-methylbenzylidene camphor	1.1	
Benzophenone-2	1.2	Only one study showing hypospadias on GD18
Butylparaben	1.1	
Dicyclohexyl phthalate (DCHP)	1.1	
Dihexyl phthalate (DHP)	1.1	
Ethylhexyl methoxycinnamate (OMC)	1.1	
Metam natrium	1.1	
Methyl tertiary butyl ether (MTBE)	1.2	Conflicting data
Pentachlorophenol (PCP)	1.2	General toxicity may have influences the results
Quadrosilan	1.1	
Resorcinol	1.2	Conflicting data
Tert-butylhydroxyanisole	1.1	
Thiram	1.2	Adverse effect seen after i.p. dosing
Zineb	1.2	A bit unclear data
Tebuconazole	1.1	
Triclosan	1.1	

Evaluation of the substances on the prioritized basis list

The selection of substances for ED assessment was conducted in collaboration with the Danish EPA. During the work, it soon became clear that both the basis list-M and the basis list-S mainly contain substances suspected to be EDCs. As a consequence finding enough literature suited for a thorough assessment for ED effects for some randomly picked substances could be challenging or even not possible. Therefore, two literature screening phases were included in the project.

The focus for the first literature screening phase including 12 substances was selection of substances of relevance for ED in humans, whereas the focus for the second literature screening

phase (40 substances) was both ED effects in humans and the environment. In both phases, substances on the CoRAP list or REACH candidate list due to ED effects as well as substances previously evaluated by CeHoS (Hass et al. 2012a and Hass et al. 2012b) were excluded from the selection process. An overview of the work is shown in figure 2.

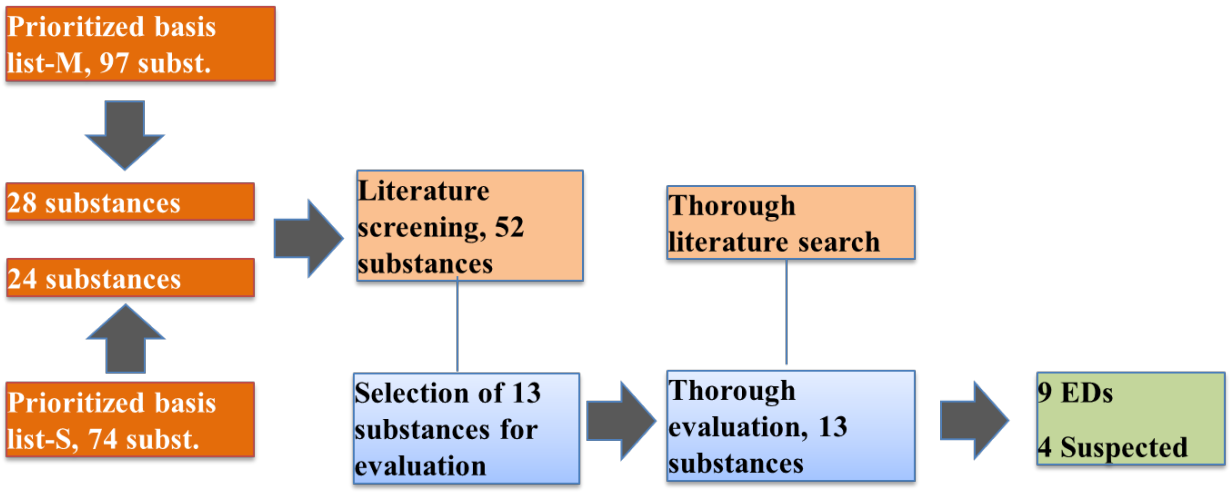

Figure 2 Overview of literature screening, selection of substances for evaluation and results of the evaluations (see text for details)

Literature screening and selection of substances for ED assessment

In the first literature screening phase, 12 substances were selected among the top prioritized substances, 8 from the basis list-M and 4 from the basis list-S, see table 9. The substances were selected partly based on expert judgements and partly by looking at other hazard and non-hazard information provided in the lists. Furthermore, it was aimed to select substances from different use categories (table 9).

Table 9 Suspected ED substances selected for the first literature screening for ED effects.

CAS no.	Name	Alternative name(s)	Use
Basis list-S			
52918-63-5	Deltamethrin		Pesticide, insecticide
52645-53-1	Permethrin	3-Phenoxybenzyl (1RS)-cis,trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate	Pesticide, insecticide
67747-09-5	Procloraz	N-Propyl-N-[2-(2,4,6-trichlorophenoxy)ethyl]-1H-imidazole-1-carboxamide	Pesticide, fungicide
35554-44-0	Imazalil		Pesticide, fungicide
Basis list-M			
101-20-2	Triclocarban	3-(4-Chlorophenyl)-1-(3,4-dichlorophenyl)urea	Antimicrobial agent
556-67-2	Octamethylcyclotetrasiloxane	Cyclotetrasiloxane; D4	Organosilicon compound
1330-78-5	Tris(methylphenyl) phosphate	Tricresyl phosphate	Flame retardant, plasticizer
25637-99-4	Hexabromocyclododecane	1,2,5,6,9,10-Hexabromocyclododecane	Flame retardant
13674-87-8	Tris[2-chloro-1-(chloromethyl)ethyl] phosphate	tris (1,3-dichloro-2-propyl) phosphate	Flame retardant
111-76-2	2-butoxyethanol	ethylene glycol monobutyl ether	Surfactant
1948-33-0	2-tert-butylhydroquinone		Antioxidant
118-56-9	Homosalate	3,3,5-trimethyl-cyclohexyl salicylate	UV-filter

For the 12 substances selected for the first literature screening, a quick search was performed on PubMed (NCBI, 2016) to get an overview on the amount and type of public available literature on the individual substances. Based on this screening a qualified choice on the case studies was made, and also it was evaluated whether some substances could be excluded. Furthermore, robust study summaries in IUCLID were retrieved to get an overview of the confidential data on the substances. For the PubMed literature search the following keywords were used:

(endocrine) AND substance name
(endocrine) AND CAS number

For some of the substances no literature could be found regarding ED in PubMed. In these cases a subsequent literature search was made using only the substance name or CAS number to retrieve all literature on these substances and not only literature including ‘endocrine’ as a keyword. In cases where only a limited amount of data (e.g. only *in vitro* data) could be found, searches were made by using alternative names and/or abbreviations for the substance and by searching for references within the available articles.

Out of the 12 substances, 6 substances (1 from the basis list-S and 5 from the basis list-M) were excluded from further assessment due to lack of relevant data (e.g. no data related to ED effects), too limited data (e.g. only *in vitro* data) or because the substance is a substance of unknown or variable composition (UVCB), see table 10. This was only based on the PubMed search results.

Table 10 Substances excluded for further assessment and reason for exclusion based on PubMed search results in the first literature screening

CAS no.	Name	Reason for exclusion
Basis list-S		
35554-44-0	Imazalil	Only *in vitro* and *in ovo* data
Basis list-M		
1330-78-5	tris(methylphenyl) phosphate	UVCB
13674-87-8	tris[2-chloro-1-(chloromethyl)ethyl] phosphate	Only *in vitro*/*in ovo* data, and environmental relevant literature
111-76-2	2-butoxyethanol	No relevant literature with regard to ED
1948-33-0	2-tert-butylhydroquinone	No relevant literature with regard to ED
118-56-9	Homosalate	Only *in vitro* data, environmental relevant literature, and two negative *in vivo* studies

Based on the literature screening Triclocarban (CAS number: 101-20-2) and Deltamethrin (CAS number: 52918-63-5) were selected for further assessment as there appeared to be available data allowing a thorough assessment for ED effects on humans. A more thorough literature search was conducted on these substances using the following keywords:

(androgen) AND substance name
(oestrogen) AND substance name
(thyroid) AND substance name
(reproduction) AND substance name

As for substances with no or only very limited available literature, new searches using alternative names, abbreviations of chemical name and/or searches including solely substance name or CAS number were performed. Furthermore, relevant literature was found by searching for relevant references within the already identified articles and/or reviews.

In the second literature screening, the 20 first substances from each of the 2 prioritized lists were selected excluding substances selected in the first literature screening.

For these 40 substances, literature screenings were performed in PubMed to provide an overview of the amount and type of public available literature on the individual substances.

The PubMed Searches were performed as follows:

Search round 1: search queries using the keyword: (endocrine) AND substance name / CAS number

Search round 2: for substances with no relevant results in search round 1, the following 3 search queries were made:

1. Alternative name(s) / substance name / CAS number

2. For substances with >20 search results in search round 1, the following search queries were made in order to narrow down the results: (androgen / oestrogen / thyroid / steroidogenesis) AND substance name

3. For substances without data on *in vivo* adverse effect results in the previous searches (based on reading the abstracts), the following search was made: Substance name AND toxicity. If this search gave > 20 results, then 'AND developmental' was added to the search query: Substance name AND toxicity AND developmental.

Besides the PubMed search, a search for more ED information for each substance was made in Google as well as in PubChem by searching for the CAS number or substance name.

Based on the screening results an overview table with relevant ED information for each of the 40 substances was made by reading the titles and abstracts from the PubMed searches. Any additional information from REACH dossiers for substances that are registered was also noted. Based on this an initial overview of the relevance of the substance was made (Table 11). Among these substances as well as those included in the first literature screen, 13 substances were finally selected for further ED assessment at a meeting with DK EPA in August 23 2017 (Table 12).

Table 11 Suspected ED substances selected for the second literature screening for ED effects (see text for details)

CAS no.	**Substance name**	**Priority and comments**
Basis list-M		
95-38-5	2-(2-heptadec-8-enyl-2-imidazolin-1-yl)ethanol	Excluded, lack of ED data
110-25-8	(Z)-N-methyl-N-(1-oxo-9-octadecenyl)glycine	Excluded, lack of ED MoA data
123-30-8	4-aminophenol	Excluded, lack of ED MoA data
683-18-1	Dibutyltin dichloride	Relevant?
85586-07-8	Sulfuric acid, mono-C12-14-alkyl esters, sodium salts	Excluded, lack of data
121158-58-5	Phenol, dodecyl-, branched	Relevant?
59-50-7	Chlorocresol	Relevant?
80-54-6	2-(4-tert-butylbenzyl)propionaldehyde	Selected, Hum
97-78-9	N-lauroylsarcosine	Excluded, lack of ED MoA data
115-95-7	linalyl acetate	Excluded, lack of ED data
1067-33-0	dibutyltin di(acetate)	Excluded, lack of ED data
6846-50-0	1-isopropyl-2,2-dimethyltrimethylene diisobutyrate	Excluded, lack of ED data
56-18-8	3,3'-iminodi(propylamine)	Excluded, lack of ED data
68-11-1	mercaptoacetic acid	Relevant?
69-72-7	salicylic acid	Selected, Hum
79-06-1	Acrylamide	Relevant?
79-77-6	(E)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one	Excluded, lack of ED MoA data
80-26-2	p-menth-1-en-8-yl acetate	Excluded, lack of ED MoA data
95-63-6	1,2,4-trimethylbenzene	Excluded, lack of ED MoA data
97-53-0	Eugenol	Relevant? Ecotox?

CAS no.	Substance name	Priority and comments
Basis list-S		
26761-40-0	Di-isodecyl phthalate	Selected, hum
56-55-3	Benzo(a)anthracene	Excluded (PAH)
122-14-5	Fenitrothion	Selected, hum
50-32-8	Benzo(a)pyrene	Excluded (PAH)
80844-07-1	Ethofenprox	Relevant, Ecotox?
82657-04-3	Bifenthrin	Selected, Ecotox
131-18-0	Di-n-pentylphthalate (DPP)	Selected, Hum
26002-80-2	Sumithrin	Excluded, lack of ED effects
76674-21-0	Flutriafol	Excluded, lack of ED data
1478-61-1	Bisphenol AF	Selected, hum and ecotox
117-39-5	Quercetin	Relevant?
6386-73-8	3 , 3' , 5-tribromobisphenol A	Excluded, lack of adverse effect data
4247-02-3	Isobutyl paraben	Selected, hum
520-33-2	Hesperetin	Excluded, lack of adverse effect data
97-23-4	Dichlorophen	Excluded, lack of ED data
70-30-4	Hexachlorophene	Selected, hum
189-55-9	Dibenzo[a, i]pyrene	Excluded (PAH)
205-82-3	Benzo[j]fluoranthene	Excluded (PAH)
205-99-2	Benzo[b]fluoranthene	Excluded (PAH)
207-08-9	Benzo[k]fluoranthene	Excluded (PAH)

Table 12 Suspected ED substances selected for evaluation of ED effects, human and/or environment

Literature screening	CAS	Substance name	Human ED eval.	Eco ED eval
Basislist-M				
First	101-20-2	Triclocarban	Yes	
First	556-67-2	Octamethylcyclotetrasiloxane (D4)	Yes	
First	1330-78-5	Tris(methylphenyl) phosphate	Yes	
Second	80-54-6	2-(4-tert-butylbenzyl)propionaldehyde	Yes	
Second	69-72-7	Salicylic acid	Yes	
Basis list-S				
First	52918-63-5	Deltamethrin	Yes	
First	67747-09-5	Procloraz	Yes	Yes
Second	122-14-5	Fenitrothion	Yes	
Second	82657-04-3	Bifenthrin		Yes
Second	131-18-0	Di-n-pentylphthalate (DPP)	Yes	
Second	1478-61-1	Bisphenol AF	Yes	Yes
Second	4247-02-3	Isobutyl paraben	Yes	
Second	70-30-4	Hexachlorophene	Yes	

Template for ED assessment

As suggested by the Danish EPA, selected headlines from ECHA's Annex XV report: "Proposal for identification of a substance of very high concern on the basis of the criteria set out in REACH article 57" (European Chemicals Agency, 2016a) were used as a template for the hazard assessment. The decision of using ECHA's Annex XV report as a template was made in order to reduce excessive work, in case the Danish-EPA decide to propose one or more of the substances to be identified as an SVHC in accordance with the requirements set out in Annex XV to REACH (European Chemicals Agency 2016a).

Criteria for ED evaluation

The selected substances were assessed according to WHOs definition of an EDC and a potential EDC:

"An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations." (World Health Organization, 2002)

"A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations." (World Health Organization, 2002).

According to the recent Draft for public consultation Guidance for the identification of endocrine disruptors [5] a substance shall be considered as having endocrine disrupting properties if it meets all of the following criteria:

a) it shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;

b) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;

c) the adverse effect is a consequence of the endocrine mode of action.

Also, it is stated that point (c) above should be understood as (differences from above in italics): the adverse effect is a consequence of the endocrine *activity, i.e. the substance has an endocrine mode of action – there is a biologically plausible link between the endocrine activity and the adverse effect.*

Based on the above, the term plausible link has been used in the evaluations here.

If the evaluation of a substance showed that the data did not fulfil the above criteria for identification of an ED, it was evaluated whether the data fulfil the WHO definition of a potential ED. If so, the proposed Danish criteria (Hass et al. 2011) was used to evaluate whether the substance is a suspected ED or a substance with indications of ED properties (Figure 3).

[5] Draft for public consultation Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009, December 7, 2017

Figure 3 Proposed Danish criteria for suspected and indicated EDs (further details in Hass et al. 2011)

Group 2a - Suspected ED

Substances are placed in Group 2a when there is some evidence from humans or experimental animals, and where the evidence is not sufficiently convincing to place the substance in Group 1. If for example limitations in the study (or studies) make the quality of evidence less convincing, Group 2a could be more appropriate. Such effects should be observed in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effect should be considered not to be a secondary non-specific consequence of other toxic effects.

Substances can be allocated to this group based on:

- Adverse effects *in vivo* where an ED mode of action is suspected
- ED mode of action *in vivo* that is suspected to be linked to adverse effects *in vivo*
- ED mode of action *in vitro* combined with toxicokinetic *in vivo* data (and relevant non test information such as read across, chemical categorisation and QSAR predictions)

Group 2b – Substances with indications of ED properties (indicated ED)

Substances are placed in Group 2b when there is *in vitro*/in silico evidence indicating potential for endocrine disruption in intact organisms. Evidence could also be observed effects *in vivo* that could be ED-mediated.

Assessment of the evidence

The papers found for each of the substances were evaluated with regards to the quality of the study and the type and level of evidence provided by each paper.

The quality of the studies was evaluated as low, medium or high. The evaluation considered both strengths and limitations of the study and included parameters such as; identification of the substance by CAS no, information on purity of the substance, the number of doses tested, the group size for *in vivo* studies etc.

The evidence in each paper was evaluated as weak, moderate or strong. This evaluation considered the consistency and magnitude of the results, the relevance of the effects studied etc. Also, it was considered whether the effects observed could be secondary non-specific consequence of other toxic effects such as cytotoxicity (*in vitro* studies) or general toxicity (animal studies).

The overall level of evidence for *in vitro* ED MoA, *in vivo* ED MoA, endocrine related adverse effects and plausible link was evaluated using the terms weak, moderate or strong. This was based on weight of evidence (WOE) considering all of the findings, both positive and negative, in each area and especially for the plausible link also the general knowledge (ref to OECD GD 150).

The evaluation of each substance was done using a WOE approach. To fulfil the WHO definition of an EDC, it was considered that the level of evidence should be at least moderate for both ED MoA (*in vitro* or *in vivo*) and endocrine-related adverse effect as well as for the plausible link.

Human relevance was also considered when evaluating the substance for ED with regards to humans. In accordance to current praxis and also the scientific criteria for determining ED properties applicable to the BP (Biocidal products) and PPP (Plant protection products) Regulations, relevance to humans was assumed by default in the absence of appropriate scientific data demonstrating non-relevance. In cases where relevant scientific data questioning the relevance to humans was found, this is reflected in the evaluation of the substance. If no such data was found, relevance to humans is assumed and not mentioned in the evaluations.

Results of the evaluations

The detailed evaluations of the selected substances can be found in Appendix 1.

An overview is shown in table 13.

Table 13 Overview of the results of the evaluations of the13 substances from the prioritized basis list (see text and Appendix 1 for details). Evaluations with regards to ED effects in humans or the environment are marked with H or E (respectively) in column 1.

Substance (CAS), H or E	***In vitro* MoA**	***In vivo* MoA**	**Adverse effects**	**Plausible link**	**Eval.**
Deltamethrin (52918-63-5), H	Strong; AR antagonistic	Weak; AR antagonistic	Moderate; male reproductive organs	Moderate	Suspected
Prochloraz (67747-09-5), H	Strong: aromatase inhibition, anti-estrogenic and anti-androgenic	Strong: anti-androgenic	Strong; Anti-androgenic, nipple retention	Strong	ED
Prochloraz (67747-09-5), E	See above	Strong: aromatase inhibition in fish	Strong; Skewed phenotypic sex ratio in fish and amphibians	Strong	ED
Triclocarban (101-20-2), H	Moderate; Amplification of androgen- and estrogen-mediated activity	Strong; Androgenic	Moderate; Increased weight of all accessory sex organs	Strong	ED
Octamethylcyclo-tetrasiloxane (D4) (556-67-2), H	Strong; Estrogenic	Strong; Estrogenic	Strong; Reduced fertility, disturbed oestrous cycles, reduced ovulations, increased uterus weights with endometrial hyperplasia, vaginal mucification and ovarian atrophy	Strong	ED

Substance (CAS), H or E	***In vitro* MoA**	***In vivo* MoA**	**Adverse effects**	**Plausible link**	**Eval.**
Tris(methylphenyl) phosphate (1330-78-5), H	Strong; Effects on steroidogenesis leading to increased oestrogen levels	None-weak	Strong; Adverse reproductive toxicity effects in adult males	Moderate	ED
2-(4-tert-butylbenzyl)-propionaldehyde (80-54-6), H	Strong; estrogenic Weak; anti-androgenic	No data	Weak to moderate; atrophy of testes	Moderate	Suspected
Salicylic acid (69-72-7), H	Moderate; Reduced testosterone	Moderate; Anti-androgen, reduced testosterone;	Moderate; Effect on spermatogenesis	Strong	ED
Fenitrothion (122-14-5), H	Moderate; Anti-androgenic and androgenic	Strong; Anti-androgenic	Strong; Decreased AGD and increased NR in male pups, effects on testis histology, sperm parameters, weight of reproductive organs and testosterone levels in adult rats.	Strong	ED
Bifenthrin (82657-04-3), E	Strong: Estrogenic for 1S-Cis BF enantiomer. Not for technical BF	Moderate-strong: Metabolite 4-OH BF estrogenic and 1S-Cis enantiomer estrogenic. Several negative studies with technical BF	Low-moderate: Adverse ED specific endpoint not tested with 1S-Cis BF or the metabolite 4-OH BF. Fecundity affected in fish at low ng/l but not ED specific endpoint	Moderate	Suspected
Di-n-pentylphthalate (131-18-0), H	Strong; Decreased steroid synthesis, Anti-androgenic	Strong; Anti-androgenic	Strong; Decreased AGD and increased nipple retention in male offspring, effects on sperm count, malformations of male reproductive organs and decreased weight of male reproductive organs	Strong	ED

Substance (CAS), H or E	*In vitro* MoA	*In vivo* MoA	Adverse effects	Plausible link	Eval.
Bisphenol AF (1478-61-1), H	Strong; Estrogenic	Strong; Estrogenic	Strong; Delay in male puberty, advancement in female puberty and clear effects on fertility	Strong	ED
Bisphenol AF (1478-61-1), E	Strong; Estrogenic	Strong; Estrogenic	Strong; mammalian population relevant effects on fertility, lack of non-mammalian population relevant data	Strong	ED
Isobutyl paraben (4247-02-3), H	Strong; Estrogenic	Strong; estrogenic	Moderate; Adverse effects on sperm motility and sperm numbers in male pups and effects on sexual dimorphic behaviour	Moderate	ED
Hexachlorophene (70-30-4), H	Moderate; Anti-oestrogenic	No relevant data	Weak to moderate; Adverse effects on testis histology manifested as seminiferous toxicity	Weak	Suspected

6. Discussion

Limitations as regards risk for exposure data, MoA data and adverse effect data

When prioritizing the lists (basis list-M and basis list-S) according to exposure in SPIN and to MoA, it became clear that only some substances are registered in the SPIN database, QSAR and the US EPA's Toxicity Forecaster (ToxCast) (as included in the ECHA master list). Thus some substances on the lists may be high exposure substances or may have one or more ED MoA, but they are not prioritized due to lack of information. Furthermore, risk for exposure data from the SPIN database only contains data from one or more of the Nordic countries: Sweden, Norway, Finland and Denmark. This data was obtained from registrations recorded from 2008–2014 and can therefore vary between different countries and years. To our knowledge databases similar to the SPIN database do not exist for other EU countries or other countries around the world. Thus, it was not possible to extract data that indicate the risk for exposure in other EU countries.

The literature screening of the 52 substances showed that there was a lack of relevant MoA data and/or adverse effect data for around 40-50% of the substances (Figure 3). The overview of the second literature screening (table 11) indicated that in most cases there was a lack of ED MoA data,

but also in several cases there was a lack of relevant adverse effect data. Whether the lack of data is similar for the non-screened substances on the prioritised basis list (i.e. 171-52 = 119 substances) has not been investigated. However, several of the substances in especially the first literature screening was chosen based on knowledge in the project group and Danish EPA pointing towards a high likelihood for the presence of relevant ED data. Thus is appears plausible that the lack of data for the non-screened substances may be at least of similar magnitude as for the screened substances.

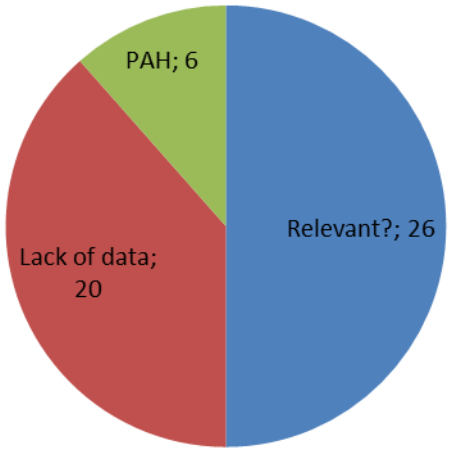

Figure 3. Overview of the results of both the first and second literature screening of 52 substances, from the prioritized basis list of suspected EDs with risk for exposure. “Lack of data”: lack of ED MoA data, relevant adverse effect data or both; “Relevant?”: Screening of the ED MoA data and adverse effect data indicate that the substances are relevant with regards to ED assessment; PAH (polyaromatic hydrocarbon): these substances were excluded from the selection and it is unknown whether there are relevant data.

7. Conclusions and recommendations for further work

- The background lists and the master list include several thousands of substances suspected to be EDCs.

- The amount of data for the substances being listed as suspected EDCs on various lists vary considerably from no data found in published literature, over e.g. some MoA data (*in vitro*, QSAR) to comprehensive *in vivo* and MoA data.

- A prioritization with regards to hazard scenarios, mode of action and risk for exposure lead to around 180 substances on the prioritized basis list.

- A "literature ED hazard screening" step was needed to select those suspected substances of highest relevance for ED assessment.

- A literature screening of 52 of the prioritized substances showed that there was a lack of relevant MoA data and/or adverse effect data for around 40-50% of the substances.

- The time needed for ED assessment of individual suspected EDs varies substantially depending mainly on the amount of data available (e.g. from a few to many studies).

- The thorough evaluations of 13 of the prioritized suspected EDs selected based on the "literature ED hazard screening" step, concludes that 9 fulfil the WHO definition of an EDC, whereas 4 are suspected EDCs.

- A re-evaluation of 17 substances previously evaluated as EDCs (Hass et al. 2012a, Hass et al. 2012b) confirmed that for 10 substances it is evaluated that the data show that these substances fulfil the WHO-definition of an EDC. The remaining 7 substances are evaluated as likely to fulfil the WHO-definition of an EDC, however various limitations in the data indicate that it may be more difficult to obtain international agreement that these 7 substances are EDs, compared to the 10 substances.

Recommendations

It is recommended to consider further evaluations of the substances on the prioritized basis list from this project with focus on

- Thorough evaluation of the rest of the potentially relevant substances found in the literature screening in this project, i.e. 13 substances
- Literature screening of the non-screened prioritized substances (119 substances) and thorough evaluation of the potentially relevant substances

Generally, it is recommended to initiate studies to address data gaps with regards to both ED MoA and ED relevant adverse effects for many substances suspected to be EDCs. Also, more data on risk for exposure are recommended as many of the suspected EDs were not prioritized due to lack of such data.

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