b k h consulting engineers
member of the rps group plc
environmental, civil and sanitary engineering

M0355008/1786Q/10/11/00

EUROPEAN COMMISSION DG ENV

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*

FINAL REPORT
(Incorporating corrigenda to final report dated 21 June 2000)

BKH Consulting Engineers, Delft, The Netherlands
in association with
TNO Nutrition and Food Research, Zeist, The Netherlands

Delft, 10 November 2000

Head Office
P.O. Box 5094, 2600 GB Delft
The Netherlands
Tel. :+31(0)15 262 52 99
Fax: +31(0)15 261 93 26
E-mail bkh-office@bkh.nl
Visiting address: Poortweg 10, Delft

Offices in:
Bangladesh
Chile, Colombia
Kenya
India, Sri Lanka

COLOPHON

client	:	European Commission DG ENV
project	:	Endocrine disrupting substances (man-made chemicals)
project number:		M0355008
report	:	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.* Final report (incorporating corrigenda to final report dated 21 June 2000)
report volume	:	29 pages (exclusive Annexes)
authors	:	Ch. Groshart, P.C. Okkerman (Okk@BKH.NL)
team leader	:	I. van der Putte
date of submission:		10 November 2000
authorisation:		(I. van der Putte, team leader)

Contents Page

PREFACE ..... **III**

ABBREVIATIONS ..... **IV**

EXECUTIVE SUMMARY **1**

1 INTRODUCTION **5**

1.1 BACKGROUND 5
1.2 OBJECTIVES AND SCOPE OF THE CURRENT PROJECT 6

2 PROJECT APPROACH **7**

2.1 STEP 1: REVIEW OF EXISTING LISTS AND OTHER SOURCES OF INFORMATION 9
2.1.1 Inventory of lists and literature *9*
2.1.2 Development of a database on endocrine disruption *9*
2.2 STEP 2: SELECTION OF HIGHLY PERSISTENT AND/OR HPV SUBSTANCES 10
2.3 STEP 3: PRELIMINARY EVALUATION OF SCIENTIFIC EVIDENCE OF ED-RELATED EFFECTS 11
2.4 STEP 4: PRELIMINARY EVALUATION OF EXPOSURE TO HUMANS AND WILDLIFE 12
2.4.1 Literature research and processing of data *13*

3 RESULTS **14**

3.1 WORKING LIST OF SUBSTANCES 14
3.2 FIRST SELECTION: HIGH PRODUCTION VOLUME CHEMICALS AND PERSISTENT CHEMICALS 15
3.3 SECOND SELECTION: EVIDENCE OF ENDOCRINE DISRUPTION 15
3.4 THIRD SELECTION: HIGH MEDIUM OR LOW EXPOSURE CONCERN 17

4. CONCLUSIONS AND RECOMMENDATIONS **25**

4.1 CONCLUSIONS 25
4.2 RECOMMENDATIONS 28

5 REFERENCES **29**

CONTENTS OF ANNEXES

Annex 1 Candidate list of 553 substances

Annex 2 Background documents

Annex 3 Contacted organisations

Annex 4 Framework of the database

Annex 5 Effect parameters included in the database

Annex 6 List of 146 substances evaluated in the Expert meeting

Annex 7 Human health and wildlife relevant data on endocrine disruption included in the database on the 146 substances evaluated in the Expert meeting

Annex 8 Human health and wildlife relevant data on endocrine disruption included in the database on the remaining substances.

Annex 9 Working list of 564 chemicals with their literature source

Annex 10 List of 564 substances with their selection criteria

Annex 11 References of studies and reports on endocrine disruption incorporated in the database

Annex 12 Scientific evidence used in the Expert meeting for the evaluation of the 146 selected substances

Annex 13 List of 146 substances with endocrine disruption categorisations prepared in the Expert meeting

Annex 14 Summary profiles of chemicals with information on use, production, emission, monitoring and legal status

Annex 15 List of 66 substances with categorisation high, medium or low exposure concern

PREFACE

BKH Consulting Engineers (Delft, the Netherlands) has been commissioned by the European Commission by letter of 1 February 1999 to conduct a study on endocrine disruption focusing on man-made chemicals. This is a first step towards the establishment, by the Commission, of a priority list of substances for further evaluation of their role in endocrine disruption. Project co-ordinators for the EC are Mrs K. Tierney, Dr H. Nover and Mr D. Klein. The project was carried out in association with TNO Nutrition and Food Research Institute (Zeist, the Netherlands). The project team included Mrs C.P. Groshart, Mr P.C. Okkerman, Mrs G.J. Folkers-Gerritsen, Mr W.B.A. Wassenberg (BKH), Dr R.F. Witkamp, Dr E.M. de Groene, and Dr C.J.M. Arts (TNO). Project co-ordinator for BKH is Dr I. van der Putte. A stakeholder meeting with representatives from government, NGO's and industry, was held on the 27th May 1999. A meeting with experts in the field of endocrine disruption was held on 27th and 28th September 1999.
It should be noted that the results of this study will be used as a basis for consultation by the Commission. This consultation process constitutes the second step in the establishment of a priority list of substances for further evaluation of their role in endocrine disruption, as outlined in the Commission Communication to Council and European Parliament on a Community Strategy for Endocrine Disrupters (COM (1999)706).

ABBREVIATIONS

AHH	Aryl Hydrocarbon Hydroxylase
BUA	Bundes Umwelt Amt (Germany)
CAS	Chemical Abstract Service
CEFIC	European Chemical Industry Council
ED	Endocrine disrupting
EPA	Environmental Protection Agency
HPV	High Production Volume
IUCLID	International Uniform Chemical Information Database
NGO	Non-Governmental Organisation
QSAR	Quantitative Structure Activity Relationship
RIVM	National Institute of Public Health and the Environment, The Netherlands
RIZA/RIKZ	Institute for Inland Water- and Wastewater management / Institute for Coastal and Marine Management, The Netherlands
SMILES	Simplified Molecular Input Line Entry System (a code for the Structure of the Chemical)
WHO	World Health Organisation
DES	Diethylstilbestrol

EXECUTIVE SUMMARY

In recent years effects have been reported in animal species and human beings that are attributed to the influence of certain substances on hormonal systems.
As announced in the Communication from the Commission to the Council and the European Parliament on a Community Strategy for Endocrine Disrupters (COM(1999)706 final), a priority list of substances is to be established to further evaluate their role in endocrine disruption. The objective of the present study is to prepare a candidate list of substances, on the basis of available information for specific selection criteria, which can be used in this priority-setting exercise.

The following steps have been taken in the study:

STEP	*DESCRIPTION*	*RESULTS*
1.	Review of existing lists and other sources of information	564 substances
2.	Selection of highly persistent and/or HPV substances	146 substances
3.	Preliminary evaluation of scientific evidence of ED-related effects	66 substances (35 clustered substances)
4.	Preliminary evaluation of exposure to humans and wildlife	60 substances (29 clustered substances)

In Figure I the project approach and its outcome are presented schematically.

The starting point of the study is a working list, compiled from the lists of suspected endocrine disrupting chemicals drawn up by various organisations as well as from an up-to-date literature search. The working list was presented and discussed at a stakeholder meeting with representatives of government, industry and NGOs.
For the working list consisting of 564 substances scientific evidence on endocrine disruption was gathered. A further analysis was made for a number of 146 High Production Volume chemicals and/or highly persistent substances.
A panel of experts in the field of endocrine disrupting effects of substances on human health and wildlife categorised these 146 substances on the basis of the available evidence into three categories:

Category 1. At least one study providing evidence of endocrine disruption in an intact organism. Not a formal weight of evidence approach.

Category 2. Potential for endocrine disruption. In vitro data indicating potential for endocrine disruption in intact organisms. Also includes effects in-vivo that may, or may not, be ED-mediated. May include structural analyses and metabolic considerations

Category 3. No scientific basis for inclusion in list or no data[1]

[1] Category 3 also consisted of substances with insufficient data.

The outcome of the expert meeting was that on the basis on available data on endocrine disruption, 66 substances are to be categorised into category 1, 51 substances into category 2 and 29 in category 3. The category 3 substances included 18 substances with no or insufficient data and 11 substances that had scientific evidence for exclusion from the working list of 564 chemicals.

For a further categorisation of category 1 into substances having high, medium and low exposure-concern summary profiles were prepared with physico chemical properties, production, emissions, use, exposure and monitoring data. Special attention was given to possible exposure of vulnerable groups.

The following guidelines were used:

High exposure concern	Human exposure is expected, due to environmental concentrations and those in food or consumer products, also taking into consideration exposure of vulnerable groups *And/Or* Wildlife exposure is expected, due to use and emission patterns, and the chemical is persistent and bioaccumulative
Medium exposure concern	Human exposure is not expected *And* Wildlife exposure is expected, due to use and emission patterns, but the chemical is readily biodegradable and not bioaccumulative
Low exposure concern	No human exposure *And* No wildlife exposure

After a detailed evaluation 60 (29 chemical groups) of the 66 chemicals (35 chemical groups) in category 1 are considered as substances having high exposure concern and evidence on endocrine disruption. This group of 60 substances includes substances such as DDT, PCBs, organo-tins and dioxins as well as chemicals such as styrene, phthalates and some pesticides.

A number of 11 substances have been excluded from the initial working list of 564 substances because there was no scientific basis for inclusion in the list. The candidate list consists therefore of 553 substances sorted into three groups, as shown in Table I.

The list is also open to change. As new information becomes available, chemicals may either be removed from or added to the list.

.

Figure I Schematic overview of the project steps and the results

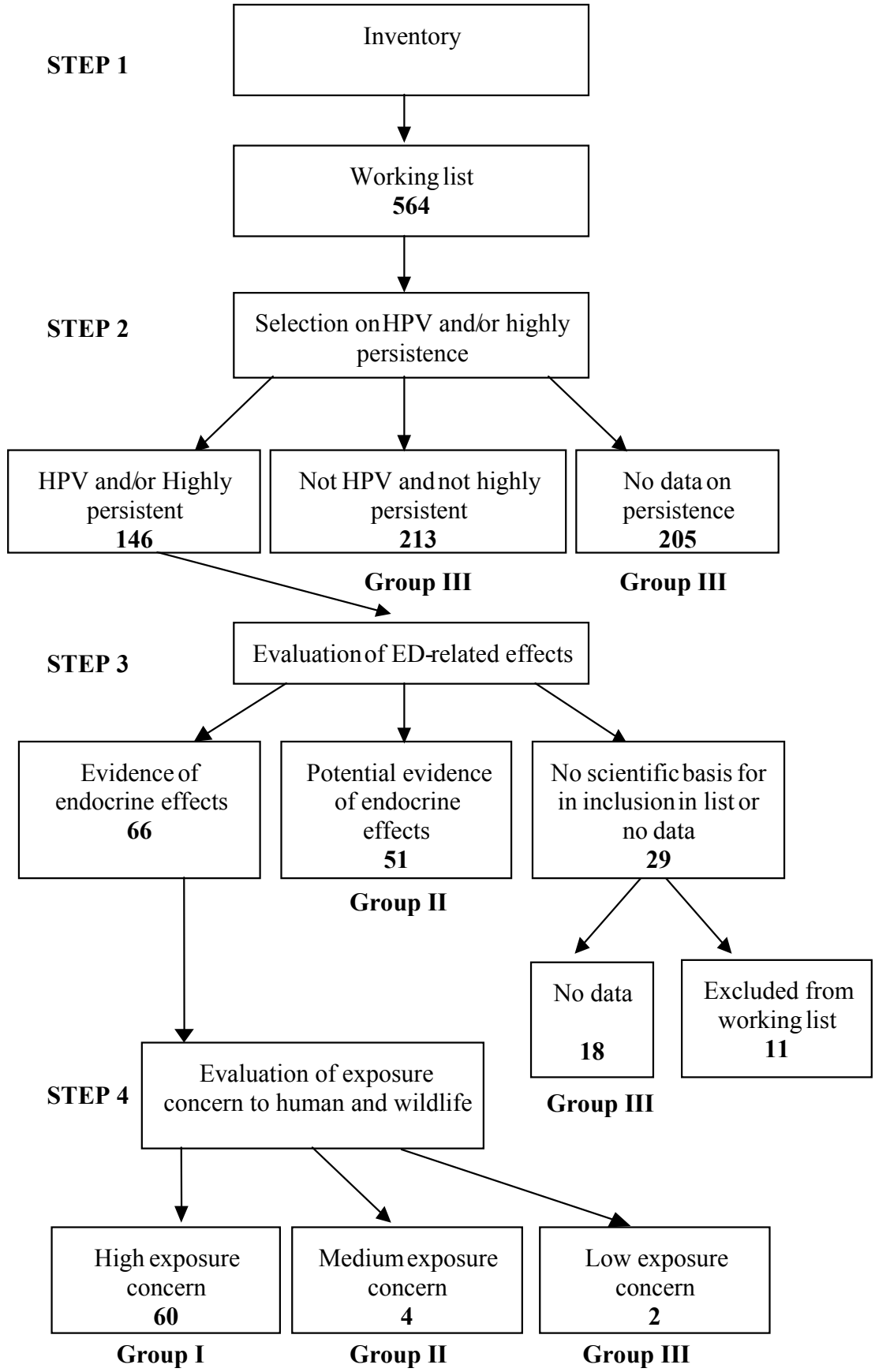


Table I. List of candidate substances – summary of work to date

GROUP I

Selection criteria			*Number of substances*	*Listing*
Highly persistent And/or HPV	At least one study showing endocrine disruption in an intact organism (Category 1)	High concern in terms of human and wildlife exposure	60 (29 chemical groups)	See Annex 1.

GROUP II

Selection criteria			*Number of substances*	*Listing*
Highly persistent And/or HPV	At least one study showing endocrine disruption in an intact organism (Category 1)	Medium concern in terms of human and wildlife exposure	4	See Annex 1.
	Potential for endocrine disruption (Category 2)		51	

GROUP III

Selection criteria			*Number of substances*	*Listing*
Highly persistent And/or HPV	At least one study showing endocrine disruption in an intact organism (Category 1)	Low concern in terms of human and wildlife exposure	2	See Annex 1.
	No sufficient data (Category 3)		18*	
Not HPV and not highly persistent			213	
Not HPV and no data on persistence			205**	

* Excluding 11 Substances that have been excluded from the candidate list because of data giving no basis for inclusion in the list (Category 3)

** No Smiles notations were readily available for QSAR estimations on persistence.

1 INTRODUCTION

1.1 Background

Since the outcome of the book “Our stolen future” (Colborn, et al, 1996) and the BBC documentary “Assault on the Male” (Deboray Cadbury) the health effects of many man-made chemicals are again in the centre of interest. There is growing public concern about a range of man-made chemicals, which are suspected of interfering with the endocrine systems of both humans and wildlife, so-called endocrine disrupters. Possible adverse effects of endocrine disrupters include cancers, behavioural changes and reproductive abnormalities. The effects of endocrine disrupters are the greatest during foetal development and in juveniles. Effects on reproduction and the immune system have been reported for fish, alligators, seals and birds.

The threat of impairment of human reproductive function and the impact on health and reproduction of wildlife as a result of exposure to endocrine-active substances in the diet and in the environment is a topic receiving increasing attention. During the last years, numerous studies have been performed, reviewing the health impact of "endocrine" disrupters. There is conclusive evidence for effects on wildlife, but the evidence for effects on humans are varying and sometimes contradictory. It is still unclear whether the presence of environmental pollutants could lead to actual exposure of the human population to such an extent that human reproductive function could be adversely affected. To address the concern of the public, in December (2-4) 1996 a European workshop on Endocrine-disrupters was held by the European commission (DG XII), the European Environmental Agency, the European Centre for Environment and Health and the World Health Organisation with scientists and policy-makers from all over the world. The result of this workshop was that there is a call for action to reduce uncertainties and risks concerning reproductive health due to endocrine disrupters.

Various organisations have published lists of suspected endocrine-disrupters. It was decided to conduct a more in depth investigation into such lists in order to ascertain and assess the reliability of the selection criteria used to establish the lists and to include information on the sources, uses of such chemicals and the pathways in human and wildlife exposure. In December 1999 a Communication from the Commission to the Council and the European Parliament on a Community Strategy for Endocrine Disrupters (COM(1999)706 final) was published. As announced in the Communication this study serves as a first step in establishing a priority list of substances for further evaluation of their role in endocrine disruption.

The priority list will be used, inter-alia,

- to identify substances for ‘priority’ testing once agreed test methods become available,
- to identify substances which can be, or are already being addressed, under existing Community legislation covering hazard identification, risk assessment and risk management,
- to identify gaps in knowledge on aspects such as dose/response relationships, sources/pathways of exposure and epidemiological studies of cause/effect relationships which will help guide further research and/or monitoring efforts, and
- to identify specific cases of consumer use, for example, the case of potentially more vulnerable groups of consumers such as children, for special consideration from a consumer policy point of view.

1.2 Objectives and scope of the current project

The objectives of the study are:
1 to identify selection criteria and produce a working list of substances associated with endocrine disruption;
2 to quantify the production volumes and to identify the sources/uses and pathways of human and wildlife exposure for these chemicals;
3 to prepare a candidate list grouped according to available information on selection criteria.

The following *working* definitions of endocrine disrupters or suspected endocrine disrupters served as a basis for the project:
- An endocrine disrupter 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 (IPCS);

- A potential endocrine disrupter 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 (IPCS).

Two classes of endocrine disrupters can be distinguished:
1 *'Natural' hormones* which include oestrogen, progesterone and testosterone found naturally in the body of humans and animals, and phytoestrogens, substances contained in some plants such as alfalfa sprouts and Soya beans which display oestrogen-like activity when ingested by the body;
2 Man-made substances which include

- *Synthetically-produced hormones*, including those hormones which are identical to natural hormones, such as oral contraceptives, hormone replacement treatment and some animal feed additives, which have been designed intentionally to interfere with and modulate the endocrine system; and
- *Man-made chemicals* designed for uses in industry such as in some industrial cleaning agents, in agriculture such as in some pesticides, and in consumer goods such as in some plastic additives. It also includes chemicals produced as a by-product of industrial processes such as dioxins, which are suspected of interfering with the endocrine systems of humans and wildlife.

The present project is focused on man-made chemicals.

2 PROJECT APPROACH

The project was carried out in four steps as shown in Table 2.1.
The first step in the project was the creation of a working list of substances associated with endocrine disruption. This working list was compiled from lists of suspected endocrine disrupters from different organisations and countries as well as from an up-to-date literature search. Three further steps were followed applying different selection criteria and expert evaluations.

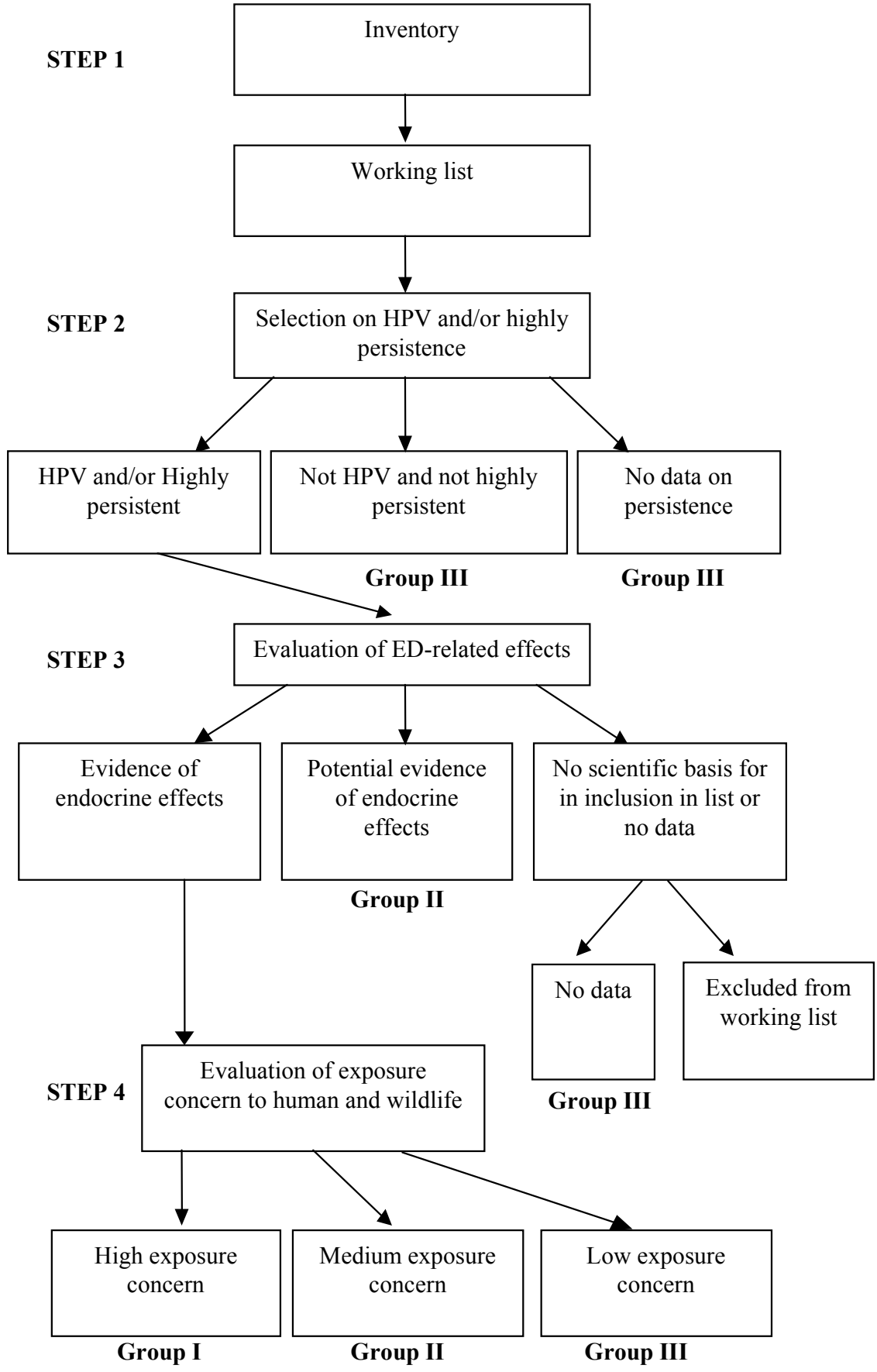
- A first selection was made after consultation of stakeholders applying criteria on production volume and persistence.
- A second selection was made after consultation of experts in the field of endocrine disruption. Substances were selected on the basis of scientific evidence.
- The third and last selection was based on criteria related to exposure of vulnerable groups, environmental behaviour and monitoring data.

Table 2.1 Project steps

STEP	***DESCRIPTION***
1.	Review of existing lists and other sources of information
2.	Selection of highly persistent and/or HPV substances
3.	Preliminary evaluation of scientific evidence of ED-related effects
4.	Preliminary evaluation of exposure to humans and wildlife

In Figure 2.1 the project steps are presented schematically.

Figure 2.1 Schematic overview of the project steps



2.1 Step 1: Review of existing lists and other sources of information

This step included the following activities:
- Inventory of lists and literature;
- Development of a database on endocrine disruption.;

2.1.1 Inventory of lists and literature

The inventory was carried out as follows:

a) An inventory of available lists of potential endocrine disrupters and suspected endocrine disrupters from various organisations was made to prepare a working list. For this purpose background documents on which these lists were based, were collected (Annex 2). In these background documents, drawn up by governmental and non-governmental organisations, the problem was brought to the attention of the public and the lists of suspected endocrine disrupters were given.
   Additionally substances that could potentially be associated with endocrine disruption from the primary literature and in reviews, and that were not yet on the working list, were added.

b) The collection of literature from key experts, review documents and a literature search to include the most recent references not covered by the review documents. In review documents (such as WHO- EHC reports) all literature on certain chemicals is collected and in most cases also evaluated.
   Key experts from national focal points, branch organisations and non-governmental organisations were contacted for information by email and fax. Some were contacted directly by personal interviews. In Annex 3, an overview is given of the contacted organisations.
   Background documents were used for backtracking and retrieving primary literature sources. Review documents from WHO: Environmental Health Criteria and EU risk assessments were collected. Furthermore databases like IUCLID, ISIS and AQUATOX were used as sources of information.
   A literature search to retrieve references, not yet covered by the review documents was carried out for almost all chemicals in on-line databases like DIMDI-TOXCAS, TOXLINE, TOXBIO, IPA and in Environmental ROUTENET (Internet: www.csa.com). The search was based on the CAS number or, if not available, on the chemical name. Only chemicals such as DDT and PCB, which were assessed in many studies, were not included in the literature search. References retrieved from the literature search were selected on their title and the publication years 1997 and 1998.
   Primarily the data are based on the review documents, but data from original sources have also been added and if original sources became available for the data from the review documents, these data have been checked.

2.1.2 Development of a database on endocrine disruption

A database was developed including all substances from the working list with the available data on endocrine disruption. The database only includes information on experiments from primary publications or from background and review documents with sufficient experimental information (like the background documents UBA98, SEPA98 and WHO Environmental Health Criteria). In Annex 4, the framework of the database is given.

It should be noted that chemicals have been added to the working list on the basis of data on endocrine disruption according to the evaluated literature. Furthermore the database contains positive as well as negative test results: data on experiments that show evidence of endocrine disruption related effects (positive) and data on experiments showing no evidence of endocrine related effects (negative).

The database contains references and background information on experiments with a wide range of effects that are in some way linked to endocrine disruption. Information on human health relevant and wildlife relevant endocrine disrupting effects were collected. Human health relevant endocrine disrupting effects were mainly in vivo experiments with rats, mice, and monkeys, in vitro experiments with human cancer cells and a restricted number of epidemiological studies. Wildlife experiments were mainly in vivo laboratory and field experiments with fish, birds, amphibians, insects, crustaceans and molluscs. The main effects included are effects on reproduction, reproductive organs, hormone levels and fertility cycles. Additionally information was included on experiments testing effect parameters like thyroid and pituitary hormone levels, effects on hatching and development of offspring and the influence of Ca-metabolism on eggshell thinning. In Annex 5, an overview is given of the identified endocrine disruption related effect parameters, included in the database.

It should be emphasised that descriptions of the working mechanisms of these effects are, in most cases, not available. Furthermore, there is a clear difference in the extent and the seriousness of the effect, which, in most cases, can only be made evident by relating it to a substance like DES or estradiol, for which the seriousness of the effects are more clear. Moreover, there is a variety of testing methods applied to test and evaluate the chemicals. These are not yet based on internationally accepted methods, which are still under development.

In addition to the database, a summary was prepared with the rationale of the different organisations for the selection of substances on lists. The information not only includes the evidence on endocrine disruption given by these organisations but also information on bioaccumulation, persistence and legal status. This information is available as a background document at the European Commission.

2.2 Step 2: Selection of highly persistent and/or HPV substances

A stakeholder meeting with representatives of governments, industry and NGO's was held at 27th May 1999. At the stakeholder meeting it was decided to narrow down the number of chemicals to be evaluated and to install an expert panel in order to evaluate the available data.
The first selection of chemicals was based on "high production volume" (HPV) and/or persistence. Both parameters were chosen as an indicator of exposure probability. This is explained by the assumption that human and environmental exposure to a chemical is more likely when this chemical is produced in high quantities or in case this chemical is persistent in the environment. The metals were all selected because these elements persist in the environment.

The selection of "high production volume" chemicals was based on the HPV list from Regulation (EEC) No. 793/93 on chemicals with a production volume of more than 1000 tonnes per year. For selection of persistent chemicals, Quantitative Structural Analysis Relations (QSAR) based on the Syracuse Biodegradation programme is used as a first indication of the persistence of a substance. Two models were used: the linear regression method and the ultimate degradation method (Syracuse program, 1997). These models used the CAS number and the SMILES notation (structure of the chemical) as data entry. The linear regression method leads to the definition of classes of biodegradation probability. Substances with a biodegradation probability of >0.5 are expected to biodegrade rapidly. Substances with a probability of <0.1 are expected to biodegrade slowly.
The ultimate degradation model predicts the time for ultimate degradation (complete mineralisation) of a substance. This model is based on the results of a survey of 17 biodegradation experts that were asked to evaluate 200 chemicals in terms of the time required to achieve ultimate biodegradation. The substances were rated to time units: 5 = hours; 4 = days; 3 = weeks; 2 = months; 1 = more than months. The results were averaged per substance and

formulated to 36 fragments and molecular weight parameter like the probability estimation on linear regression. Substances that take more than months (level 1) to biodegrade, combined with a biodegradation probability of <0.1 are considered highly persistent. Substances not fulfilling both criteria are not considered to be highly persistent.
In Annex 6 the list of chemicals selected on basis of HPV and persistence is presented.

2.3 Step 3: Preliminary evaluation of scientific evidence of ED-related effects

At the expert meeting a panel of experts (organisations listed in Annex 3) on endocrine disruption with respect to human health and wildlife were asked to evaluate all available information to categorise the selected group of substances. The information, that was available to the experts, consisted of experimental data taken up in the database, including the publications and reports from which the data in the database were derived, plus information from industry (A summary of all data on endocrine disruption in the database is presented in Annex 7 and 8). For the evaluation the experts took a precautionary approach: All data were evaluated, but more weight was given to positive data. The following criteria were used to categorise the selected chemicals:

Category 1.	At least one study providing evidence of endocrine disruption in an intact organism. Not a formal weight of evidence approach.
Category 2.	Potential for endocrine disruption. In vitro data indicating potential for endocrine disruption in intact organisms. Also includes effects in-vivo that may, or may not, be ED-mediated. May include structural analyses and metabolic considerations
Category 3.	No scientific basis for inclusion in list or no data

The lists of chemicals were distributed among groups of experts according to their specialisation in Human health and Wildlife, respectively. Each group prepared categorisation proposals based on the available background information and presented the results in the panel meeting in which a final categorisation was determined.

The experts used the following guidelines and criteria:
- All experimental data were taken into consideration (both positive and negative test results);
- In case reliable in-vivo evidence for endocrine disruption was available, the respective substance was categorised into category 1;
- In case less reliable in-vivo evidence for endocrine disruption was available (for example in case of contradictory test results), the respective substance was categorised into category 2;
- In case only in-vitro evidence for endocrine disruption was available with positive test results, the respective substance was categorised as category 2;
- Substances with no data but closely related to substances categorised as category 1 were categorised into category 2
- Substances with no data but closely related to substances categorised as category 2 were categorised into category 2
- Substances with no evidence for endocrine disruption or no data and not related to category 1 or 2 substances were categorised into category 3.

It should be emphasised that category 3 contains two groups of substances:
- Substances with sufficient data for evaluation, which are not considered to be endocrine disrupters;
- Substances with no or insufficient data available.

At the expert meeting it was decided to combine both groups of substances in one category.

2.4 Step 4: Preliminary evaluation of exposure to humans and wildlife

In this Step the category 1 chemicals were further evaluated to identify their "concern for exposure". Categorisation into high, medium and low concern was based on qualitative criteria, because in this stage it was not possible to derive representative exposure concentrations nor approved (No) observed endocrine disrupting effect concentrations.

Exposure concern is especially referring to the exposure of vulnerable groups such as (breastfeeding) infants and medical patients, but also to the exposure of wildlife such as sediment living organisms and top predators.

The following guidelines were used:

High concern	Human exposure is expected, due to environmental concentrations and those in food or consumer products, also taking in consideration exposure of vulnerable groups *And/Or* Wildlife exposure is expected, due to use and emission patterns, and the chemical is persistent and bioaccumulative
Medium concern	Human exposure is not expected *And* Wildlife exposure is expected, due to use and emission patterns, but the chemical is readily biodegradable and not bioaccumulative
Low concern	No human exposure *And* No wildlife exposure

For the different levels of exposure concern the following chemical properties are identified:

Chemicals with high exposure concern are:
- Chemicals intentionally or unintentionally applied in food products or cosmetics;
- Chemicals applied in residential areas (e.g. herbicides for weed control on pavements);
- Chemicals in consumer products causing direct or indirect exposure (such as additives in food packaging materials or toys for children);
- Chemicals emitted in the environment and considered being persistent;
- High production volume chemicals emitted in the environment and considered being bioaccumulative;

Chemicals with medium exposure concern are:
- High production volume chemicals with no human exposure, emitted in the environment and although not considered as persistent or bioaccumulative, but observed in environmental compartments;

Chemicals with low exposure concern are:
- Chemicals not causing human exposure nor wildlife exposure.

2.4.1 Literature research and processing of data

The literature research already performed for Step 1 was also used for the evaluation in Step 4. Furthermore for most of the selected chemicals, review documents were used, like:
- Environmental Health Criteria of the WHO/IPCS,
- the IUCLID database,
- Swedish EPA report (Olsen, 1998),
- two German BUA reports (Gulden, 1998) and Bruhn, 1998),
- CEFIC information, received at the expert meeting,
- Fraunhofer report on monitoring data (Fraunhofer, 1999),
- TemaNord report (TemaNord, 1996)
- EU risk assessments (e.g. on phthalates and PBDEs),
- Dutch RIVM criteria documents,
- Dutch RIZA/RIKZ water system surveys.

Use was made of reports and documents sent to BKH by experts and handbooks, including the Pesticides Manual (Worthing, 1987) and the Merck index (1999).

Based on the gathered information a summary profile was made. In this profile the reason for selection is presented per chemical or group of related chemicals. Furthermore data on the chemical characteristics (including bioaccumulation and biodegradation), use, production volumes, exposure and emissions, vulnerable use/groups and environmental concentrations are included.

3 RESULTS

3.1 Working list of substances

The working list is a compilation of 12 existing lists, including a number of sub-lists derived from national authorities and non-governmental organisations. This information and an overview of the selection criteria as applied by the various organisations to obtain the 12 lists used to draw up the working list, are presented in a background document (BKH, 2000). The list was supplemented with substances with literature evidence on endocrine disruption, leading to a working list of 564 substances. The list includes 175 analogues and metabolites of DDT, PCB, bisphenols, dioxins and furans, which are handled as individual substances. The complete working list is given in Annex 9. In the database all retrieved data on endocrine disrupting activity of substances on the working list are included. Note that natural and synthetically-produced chemicals are excluded from the working list as these substances are not within the scope of this study.

The individual chemicals on the working list have been clustered into 18 groups of pesticides, 18 groups of industrial chemicals, 1 group of metals and other substances, respectively. The 38 groups are presented in Table 3.1.

Table 3.1. Groups of chemicals and number of substances per group

No	Groups	Number of substances per group
	Pesticides	
1	Benzamidazoles	2
2	Carbamates	6
3	Chlorinated cyclodienes and camphenes	17
4	Chlorophenoxy compounds	5
5	DDT, derivatives and metabolites	28
6	Dicarboximides	5
7	Dinitroanilides	3
8	Dithiocarbamates	9
9	Hexachlorocyclohexane and Isomers	4
10	Hydroxybenzonitrils	2
11	Linuron, diuron and derivatives - metabolites	6
12	Methoxychlor and derivatives	9
13	Organo phosphorpesticides	28
14	Pyrethrins	1
15	Pyrethroids	12
16	Pyrimidines and pyridines	3
17	Triazines and triazoles	21
18	Other pesticides	27
	Industrial chemicals	
19	Alkylbenzenes and styrenes	5
20	Chlorophenols and benzenes	7
21	Alkylphenols and derivatives	71
22	Chlorinated paraffins (CPs)	3
23	Phthalates	19
24	Phenylsiloxanes	10
25	Phenylhydroxyphenylmethanes	2
26	Bisphenols	46
27	Triphenylmethane-derivatives	10
28	Diphenylpropane-derivatives	5
29	Biphenyls	5
30	Polychlorinated biphenyls (PCB)	63
31	Brominated and polybrominated biphenyls and biphenyl ethers (PBBs and PBDEs)	5
32	Polychlorinated terphenyls (PCT)	2
33	Naphthalenes and derivatives	8
34	Polycyclic Aromatic Hydrocarbons (PAH)	16

No	Groups	Number of substances per group
35	Dioxins	16
36	Furans	22
	Metals	
37	Metals	29
38	Other substances	32
	Total	564

3.2 First selection: High production volume chemicals and persistent chemicals

At the stakeholder meeting it was decided to prepare a first selection of substances from the working list to be evaluated by experts. As selection criteria were recommended to use production volume and/or persistence. It should be noted that biodegradation QSAR calculations were not used for metals, therefore all metals on the working list were included. More details on the selection are given in Annex 6. The results of the selections are summarised in Table 3.2.

Table 3.2: The number of substances that are selected and evaluated

Filter criteria:	Number of substances	
A: HPV	74	(incl. 6 metals and 1 persistent)
B: Highly persistent	51	(incl. 1 HPV)
C: Metals	29	(incl. 6 HPV)
First selection (A+B+C)	146	
Remaining substances	418	
All listed man made chemicals	564	

The database contains 1657 records on Human health relevant endocrine disrupting effects and 448 records on Wildlife endocrine disrupting effects, for 359 and 106 substances, respectively. The database includes both positive and negative test results.

146 substances were evaluated at the expert meeting. The list of substances is presented in Annex 6 with per substance the number of positive and negative test results in the database and information on production volumes and persistence.

A substantial group of substances (205) were not included in the first selection of 146 substances, because a smiles notation was not readily available and no QSAR calculation on persistence could be made. In Annex 10 all chemicals are listed with their selection criteria.

3.3 Second selection: Evidence of endocrine disruption

The experts evaluated information from the database plus the available primary sources plus the information presented by CEFIC.
A summary of all endocrine disruption effects data (included in the database) on substances evaluated by the experts, is presented in Annex 7. A summary of all endocrine disruption data (included in the database) of the remaining substances is presented in Annex 8. A complete reference list of all publications and reports in the database is given in Annex 11.

In Annex 12 and 13 the results of the discussions at the expert meeting are presented. The scientific evidence used by the experts for the evaluation of the selected substances is presented in Annex 12. In Annex 13 the results of the categorisation per chemical are given. In Table 3.3 these results are summarised. Based on the human health data 42 substances were categorised as category 1, 70 as category 2 and 35 as category 3. Based on wildlife data 29 substances were

categorised as category 1, 22 as category 2 and 64 as category 3[1]. Data on wildlife were available in a minor extent. This may account for the higher number of substances categorised as category 3. For the final categorisation of the substance the category of both human health and/or wildlife giving the strongest evidence for endocrine disruption, was used. Finally 66 of the 146 evaluated chemicals were categorised as category 1, 51 as category 2 and 29 as category 3 of which 18 had insufficient data to exclude them from the list and 11 were excluded from the list. These substances are excluded: aluminium, cadmium, copper oxychlor, copper sulfate, lead, mercury, methylmercury, phenol, fenthion, DIDP (a phthalate) and ethylene glycol.

Table 3.3 The summarised results of the expert meeting: number of substances in category 1, 2 or 3.

Categorisation based on	Category 1	Category 2	Category 3
Human data	42	69	35
Wildlife data	29	22	64
All data	66	51	29*

* 18 chemicals with no or insufficient data

The 66 category 1 substances consist of 8 groups of tributyltins, tetrabutyltins, tripropyltins, triphenyltins, chlordanes, DDTs, dioxins/furans and PCBs, respectively and 27 individual chemicals, total 35 category 1 chemical groups.
The list contains substances, like chlordane, kepone, mirex, toxaphene, DDT, hexachlorobenzene, organo tins, PCBs, polychlorinated dibenzodioxins and –furans, as well as substances like styrene, resorcinol, phthalates and pesticides like maneb, metam natrium, thiram and zineb.

It should be noted that no in vivo experiments were available for 1,2,3,7,8-Pentabromo-dibenzofuran. For 1,2,3,7,8-Pentachloro-dibenzodioxin only effects on the induction of hepatic AHH are available. Nevertheless these substances were categorised as category 1 substances by the experts, based on the similarity with 2,3,7,8-Tetrachlorinated dibenzodioxin.

The experts selected the category 1 substances on a wide range of endocrine disrupting effects as presented in Table 3.4. The main effects were effects on uterus-, testes-, prostate weight or other sex organ weights, effects on sperm development, vaginal opening, imposex, effects on thyroid hormone levels or synthesis, and neuroendocrine pituitary effects.

For some substances epidemiological studies have been used as evidence:

Kepone	Disturbances in sperm in workers at a pesticides factory;
Resorcinol	Changes in goitrogenic activity in workers;
PBB	Hypothyroidism among PBB workers;
Styrene	Elevation of prolactin levels and enhanced TRH stimulated prolactin secretion in Female styrene-exposed workers at a styrene factory.

[1] Wildlife effects on 32 chemicals (PCBs, dioxins/furans and PBBs) were not evaluated due to lack of resources.

Table 3.4 Endocrine Disrupting effects observed in category 1 substances (↑: Increase; ↓: Decrease)

Name	Effects
Chlordanes (2)*	Testicular toxicity
Kepone (Chlordecone)	Sperm development ↓
Mirex	Testis descent ↓
Toxaphene	Thyroid tumours ↑
DDTs (3)*	Oestrus cycle ↑; Ovulation ↓ Eggshell thickness ↓; Uterus weight ↑
Vinclozolin	Testis weight ↓; Testosterone levels ↓; Sexual potency ↓; Sex organs malformation. ↑
Maneb	Thyroid hormone synthesis ↓
Metam Natrium	Neuroendocrine Pituitary effects
Thiram	Thyroid hormone synthesis ↓
Zineb	Thyroid hormone synthesis ↓
Gamma-HCH Lindane	Testis weight ↓; Vaginal opening ↓; Uterus weight ↓
Linuron	Sex organs weight ↓
Amitrol	Thyroid hormone synthesis ↓
Atrazine	Pseudopregnancies ↑; Estrous cycle irregular; Androgen receptors ↓
Acetochlor	Thyroid hormone levels ↓
Alachlor	Thyroid hormone levels ↓
Nitrofen	Thyroid effects
Hexachlorobenzene	Testicular effects; Ovarian effects; Testosterone levels
Tributyltin compounds (18)*	Imposex
Triphenyltin (2)*	Imposex
Tri-n-propyltin (TPrT)	Imposex
Tetrabutyltin (TTBT)	Imposex**
4-tert-Octylphenol	Vaginal opening ↑; Uterus weight ↑
Phenol, nonyl-	Uterus weight ↑; Testis weight ↓; Vitellogenin level ↑
Butylbenzylphthalate (BBP)	Testes weight ↓; Sperm production ↓; Testosterone levels ↓
Di-(2-ethylhexyl) phthalate (DEHP)	Testes weight ↓; Sex organs weight ↓; Sperm production ↓; Testosterone levels ↓; Ovarian weight ↓
Di-n-butylphthalate (DBP)	Testicular atrophy; Prostate atrophy
Bisphenol A	Skewed sex ratio; Prostate size ↑; Prolactin secretion ↑; Persistent vaginal cornification; Vaginal opening ↑
PCBs (9)*	Thyroid effects; Uterus weight ↑; Endometriosis; Progesterone receptors ↑; Uterus weight ↓; Uterus weight ↑; T4 plasma levels ↓; Estrous cycle length ↑
PBBs = Brominated Biphenyls	Thyroid hormone levels ↓; Sex hormone levels ↓
Dioxins/Furans (3)*	Hepatic AHH induction ; Uterus weight ↓; Sperm number ↓; Thyroid effects; Neoplasms ***
3,4-Dichloroaniline	Androgen synthesis
4-Nitrotoluene	Uterus weight
Styrene	Prolactin secretion ↑; Pituitary effects
Resorcinol	T4/T3 metabolism ↓; Thyroid effects

* In between brackets the number of individual substances of the group, is given.

** Tetrabutyltin is debutylated to TBT in both vertebrates and invertebrates. Therefore same effects as TBT

*** Due to structural analogy all 2,3,7,8-substituted congeners have been categorised in category 1

3.4 Third selection: High medium or low exposure concern

The category 1 chemical groups (35) with evidence for endocrine disrupting effects were evaluated in greater detail concerning exposure. Substances that were closely related were handled together in one summary profile. The summary profiles gives an overview of the physical and chemical properties, bioaccumulating potential and degradation in the environment, as well as an overview of the use, production volumes, emissions and monitoring data on the substances. Based on this information a conclusion is drawn about the concern this chemical group presents. The summary documents are given in Annex 14.

In Annex 15 the results of the detailed evaluation per chemical group are summarised. In Table 3.5 the results of the detailed evaluation is summarised.

Table 3.5 Number of substances with high, medium or low exposure concern

	High concern	Medium concern	Low concern
Number of chemicals/ chemical groups	29	4	2

Of the 29 chemical groups that have been categorised as high concern for exposure chemical groups such as DDT, PCBs, dioxins, and organo-tins are included. Other chemical groups included are the phthalates (BBP, DBP and DEHP), the pesticides chlordane, chlordecone, HCB, lindane, linuron, mirex and toxaphene and the industrial chemicals bisphenol A and PBBs. Other pesticides that are categorised as having high concern for exposure are acetochlor, alachlor, maneb, thiram, metam natrium, zineb, vinclozolin and atrazine. In addition styrene, 3,4-dichloroaniline and resorcinol are included. However it should be noted that the information on which the categorisation of styrene is based is fairly old and exposure conditions may have changed. The information on resorcinol is also limited. In table 3.6 the information on which the chemical groups are categorised as having high, medium and low concern for exposure, is summarised.

Table 3.6 Information on chemical groups with high, medium and low concern for exposure.

Substance	Concern	HPV	Concerned use	Human exposure	Wildlife exposure	Soluble	Persistent	Bioaccumulation	Mea-Sured	Observed in environment	Remark
Acetochlor	High	Yes	Herbicide also on food crops	Food, workers		Moderately	Not persistent	Not bioaccumulated (slightly)	No	No	Exposure should be checked
Alachlor	High	Yes	Herbicide also on food crops	Food, workers		Moderately	Not persistent	Not bioaccumulated (slightly)	Yes	Yes	Exposure should be checked
Atrazine	High	Yes	Herbicide on food crops and alongside roads and uncultured land	Food, workers, soil alongside roads: children		Moderately	Persistent	Not bioaccumulated	Yes, water and food	Yes	
BBP	High	Yes	Softener and plasticizer in toys, packaging material, vinyl floor tiles, vinyl foams and carpet backing, in cosmetic industry	Toys: children; cosmetics, carpet, wall paper, paint		moderately	Not persistent	Bioaccumulates based on log Kow but metabolised and excreted	Yes	Yes, water	
Bisphenol A	High	Yes	Resin in plastic dental fillings, teeth coating especially of children; packaging as coating in food cans	Food; teeth children; production workers		moderately	Persistent	Not bioaccumulative	Yes	Yes	
Chlordane	High	No	Insecticide mostly on non-food crops; forbidden in EU and US	Found in mother milk		poorly	Persistent	Bioaccumulation observed	Yes	Yes in mother milk	Should be checked if chlordane is still found in mother milk and what the source is.
Chordecone	High	No	Fungicide, insecticide on some food crops and in insect traps (ants)	Insect traps, human milk: children; food and production workers		Poorly	Persistent	Bioaccumulation observed	Yes	Yes in food, biota and mother milk	Relatively old information, should be checked if uses are still there and if still measured in mother milk and food

Substance	Concern	HPV	Concerned use	Human exposure	Wildlife exposure	Soluble	Persistent	Bioaccumulation	Mea-Sured	Observed in environment	Remark
DBP	High	Yes	Plasticizer and softener in toys; carpet backing; also in hair spray, nail polish, glue, coatings on cellophane, cosmetics and as a solvent in polysulfide dental impression materials, perfumes and as textile lubricating agent	Numerous exposure possibilities: food (through packaging), toys, cosmetics, dental fillings, glue, textiles for all groups and production workers		poorly	Low to medium persistent	Bioaccumulated only at low trophic levels	Yes	Yes, water and biota	
DDT	High	Yes	Insecticide against sickness forbidden in EU, USA and Japan but still used in some countries	Widespread persistence in environment, biota, mother milk and food	Widespread persistence in environment and biota	poorly	Persistent	Bioaccumulated	Yes	Yes	
DEHP	High	Yes	Plasticizer in toys and in tubes and bags used for blood transfusion and other medical equipment	Children through shewing on toys and patients		poorly	Persistent	Bioaccumulation observed	Yes	Yes	
Dichloroaniline (3,4-)	High	Yes	Intermediate (closed system); also metabolite of linuron	Indirectly through linuron and diuron which are used on food.	Through industrial wastewater and as metabolite of linuron	Good	Not readily biodegradable	Not bioaccumulated	Yes	Yes	
HCB	High	Yes	Fungicide on seeds and food crops; Severely restricted in the EU but still used in some parts of the world Long range transport	Found in humans, fish and cow's milk	Found in environment and biota; exposure through production at industrial wastewater	Poorly	Persistent	Bioaccumulation observed	Yes	Yes in cow's milk and fish	
Lindane	High	Yes	Insecticide on seed and soil before food crops are planted	Long range transport seen; found in fish (food)	Through wastewater at production and through application on soil and seeds	Poorly	Inherently biodegradable	Bioaccumulation observed	Yes	Yes, biota (fish), water systems	

Substance	Concern	HPV	Concerned use	Human exposure	Wildlife exposure	Soluble	Persistent	Bioaccumulation	Mea-Sured	Observed in environment	Remark
Linuron	High	Yes	Herbicide on food crops	Food	At production (wastewater) and application	medium	Inherently biodegradable; metabolite 3,4-DCA	Not bioaccumulated	Yes	Hardly observed and if observed around detectielimit; however 3,4-DCA is measured	
Maneb	High	Yes	Fungicide on fruit and food crops	Food	At production (wastewater) and application	Poorly	Degraded to metabolites whereunder ETU	Not bioaccumulated	No	No, but the metabolites ETU has been found	
Metam-natrium	High	Yes	Fungicide on soil before culturing, nematicide, herbicide	Food	At production (wastewater) and application	Very good	Expected to degrade quickly, MITC also	Not bioaccumulated	No	No, but metabolite MITC has been found	
Mirex	High	No	Insecticide (ants), as a polymer and as a flame retardant. Limited use for agricultural purposes	Food (fish, meat) and found in human mother milk	At production (wastewater) and application	poorly	Persistent	Highly bioaccumulated	Yes	Yes found in humans, meat, fish, food crops and mother milk	Information on uses in EU are very limited
PBB	High	No	Flame retardants	Exposure through workers at production site	At production (wastewater) and at the waste stage.	Poorly to medium	Persistent	Most are bioaccumulated and biomagnified	Yes	Yes in biota	
PCBs	High	No	In past used in electrical equipment, heath-transfer systems, hydraulic systems, in plastics, coats, glues, paints etc.; PCB are severely restricted and banned; still available through existing products	Exposure indirectly through food (fish), and mother milk by emission through the waste stage	Emission at production and at the waste stage	poorly	Persistent	Bioaccumulation observed	Yes	Yes in biota, humans and mother milk	

Substance	Concern	HPV	Concerned use	Human exposure	Wildlife exposure	Soluble	Persistent	Bioaccumulation	Mea-Sured	Observed in environment	Remark
Dioxins/ Furans	High	No	Forming during combustion (municipal waste incineration), metal production, paper and pulp production, chlorophenols and herbicides	Exposure through emission at production and at waste stage (incineration); in food and mother milk	Exposure through emission at production and at waste stage (incineration)	poorly	Persistent	Highly accumulating	Yes	Yes in food (fish, meat, dairy products) and mother milk	
Resorcinol	High	Yes	Used in the manufacture of adhesives, dyes, in pharmaceutical preparations (for skin) tanning, dyes, cosmetics, as topical antipruric and antiseptic	Exposure through skin, Exposure through emission at production and at waste stage; inhalation of wood and cigarette smoke	Exposure through emission at production and at waste stage	Very good	Readily biodegradation	Not bioaccumulated	Yes	Yes, but only in effluents and wastewater, cigarette smoke and wood smoke.	Little information available
Styrene	High	Yes	Used in closed systems; used in chemical industry, paints, lacquers, varnishes, paper, pulp and board and in polymers: polystyrene, styrene-butadiene, rubber (latex); also a flavoring agent for ice cream and candy; use of styrene in hobbies, crafts and toys; use of polystyrene containers as package for food	Food (flavoring agent; packaging); toys; Exposure through emissions from production and use; emitted in automobile exhaust;	Exposure through emission at production and at waste stage	moderately	Readily biodegradable	Not bioaccumulated	Yes	Yes in food, air and water (partly old data)	Based on old information; not clear in how far the uses are still the same.
Thiram	High	Yes	Leaf-fungicide on fruit and vegetables; also used in domestic area as antifungicide and antibacterial paint.	Food, workers	At production (wastewater) and application	Poorly	Degraded to metabolites whereunder ETU	Not bioaccumulated	No	No, but the metabolites MITC?? has been found	

Substance	Concern	HPV	Concerned use	Human exposure	Wildlife exposure	Soluble	Persistent	Bioaccumulation	Mea-Sured	Observed in environment	Remark
Toxaphene	High	No	Insecticide on grain, fruit, vegetables, nuts; as a piscicide and as veterinary for ticks and mites in livestock; in EU forbidden as plant protection product	Food and workers at production plant and at application; long boundary transport; found in mother milk	At production, waste stage and application; long boundary transport	Poorly	Persistent	Highly accumulative	Yes	Yes in biota and mother milk	
Tributyltin	High	Yes	Used as molluscicides, antifouling paints, wood preservatives, disinfectants and biocides for cooling systems	Workers at production and indirectly in food through use as pesticide (fish)	At production, waste stage and application	poorly	Persistent	Highly bioaccumulative	Yes	Yes, in water, sediment and biota	Little information available
Tri-n-propyltin	High	Metal	No info	No info	No info	Moderately	Readily biodegradable	No bioaccumulation	No	No	Little information available
Triphenyltin	High	Metal	Fungicide on food crops and molluscicide on food crops	Food (vegetables and indirectly via fish)	At production, waste stage and application	poorly	Persistent	Highly bioaccumulative	Yes	Yes in biota (fish), water and sediment	
Vinclozolin	High	Yes	Fungicide on fruit, vegetables and ornamental plants	Food, workers at production and application	At production, waste stage and application	poorly	Inherently biodegradable to metabolites m1 and m2 which are also inherently biodegradable	No bioaccumulation	yes	Yes, in water	
Zineb	High	Yes	Leaf fungicide on fruit and vegetable crops	Food, workers at production and application	At production, waste stage and application	poorly	Degraded to metabolites whereunder ETU	Not bioaccumulated	no	No, but the metabolites ETU has been found	
Amitrole	Medium	Yes	Herbicide, not directly on food crops, alongside roads	Soil alongside roads children, workers		Very good	Rapidly degraded to metabolites	Not bioaccumulated	Yes, water	yes	
Nitrofen	Medium	Yes	Herbicide on vegetables, Restricted in the EU: not to be used as plant protection product	Food (not likely because it is forbidden) and exposure of workers at production and application	At production (wastewater) and application	poorly	Inherently biodegradable	Bioaccumulation observed	no	No	

Substance	Concern	HPV	Concerned use	Human exposure	Wildlife exposure	Soluble	Persistent	Bioaccumulation	Mea-Sured	Observed in environment	Remark
Nonylphenol	Medium	Yes	Used as raw materials for detergents, emulsifiers, wetting and dispersion agents in paints, anti-oxidants, pesticide and in PVC; also used as spermicides in contraceptive foams; biodegradation products of APEOs	Exposure through release from polystyrene and PVC (nonylphenol) e.g. in baby bottles	At production (wastewater) and at the waste stage.	poorly	Inherently biodegradable	Expected to bioaccumulate	yes	Yes in water and biota	
4 tert. Octylphenol	Medium	Yes	Used as raw materials for detergents, emulsifiers, wetting and dispersion agents in paints, anti-oxidants, pesticide and in PVC; also used as spermicides in contraceptive foams; biodegradation products of APEOs	Exposure through release from polystyrene and PVC (nonylphenol) e.g. in baby bottles	At production (wastewater) and at the waste stage.	poorly	Inherently biodegradable	Expected to bioaccumulate	yes	Yes in water and biota	
4-nitro-toluene	Low	Yes	Intermediate (closed system) in varnish industry, pharmaceuticals and fragrants	Only exposure through workers at production site	At production (wastewater)	poorly	Inherently biodegradable	Not bioaccumulated	hardly	Hardly	Very little information available
Tetrabutyltin	Low	Yes	Intermediate for production of other organotins	Workers at production plant	At production and waste stage	poorly	Persistent	-	no	no	Check if there are only limited applications for TetraBT

4. CONCLUSIONS AND RECOMMENDATIONS

4.1 Conclusions

In this study, a working list of 564 substances has been drawn up for which information on endocrine disrupting effects has been gathered.
This study is carried out in four Steps, used to group the substances according to available information on selected criteria.

STEP	*DESCRIPTION*	*RESULTS*
1.	Review of existing lists and other sources of information	564 substances
2.	Selection of highly persistent and/or HPV substances	146 substances
3.	Preliminary evaluation of scientific evidence of ED-related effects	66 substances (35 chemical groups)
4.	Preliminary evaluation of exposure to humans and wildlife	60 substances (29 chemical groups)

In Annex 10 an overview of all selection criteria on the substances is given. In Figure 4.1 an overview is given of the results of all steps of the project and in table 4.1 the grouping of the chemicals is given.

146 HPV and persistent chemicals are evaluated of which 66 (35 chemical groups) are to be considered as category 1 chemicals (evidence for endocrine disruption in a living organism).

After a detailed evaluation, 60 substances (29 chemical groups) in category 1 are to be considered as having high exposure concern. This group of 60 chemicals contains the chemicals DDT, PCBs, organotins and dioxins as well as styrene, phthalates and some pesticides. A number of 11 category 3 chemicals (no scientific basis for inclusion in list) have been excluded from the list of which 553 substances remain. The candidate list contains therefore 553 substances of which 60 substances are in Group I, 55 substances are in Group II and 448 substances are in Group III.

The candidate list of 553 must not be considered as final. Based on new data other chemicals may be added to the list in future. In other instances clear evidence may become available that a substance on the list should be removed. The list should therefore be open to change: additions and removals.

Figure 4.1 Schematic overview of the project steps and the results

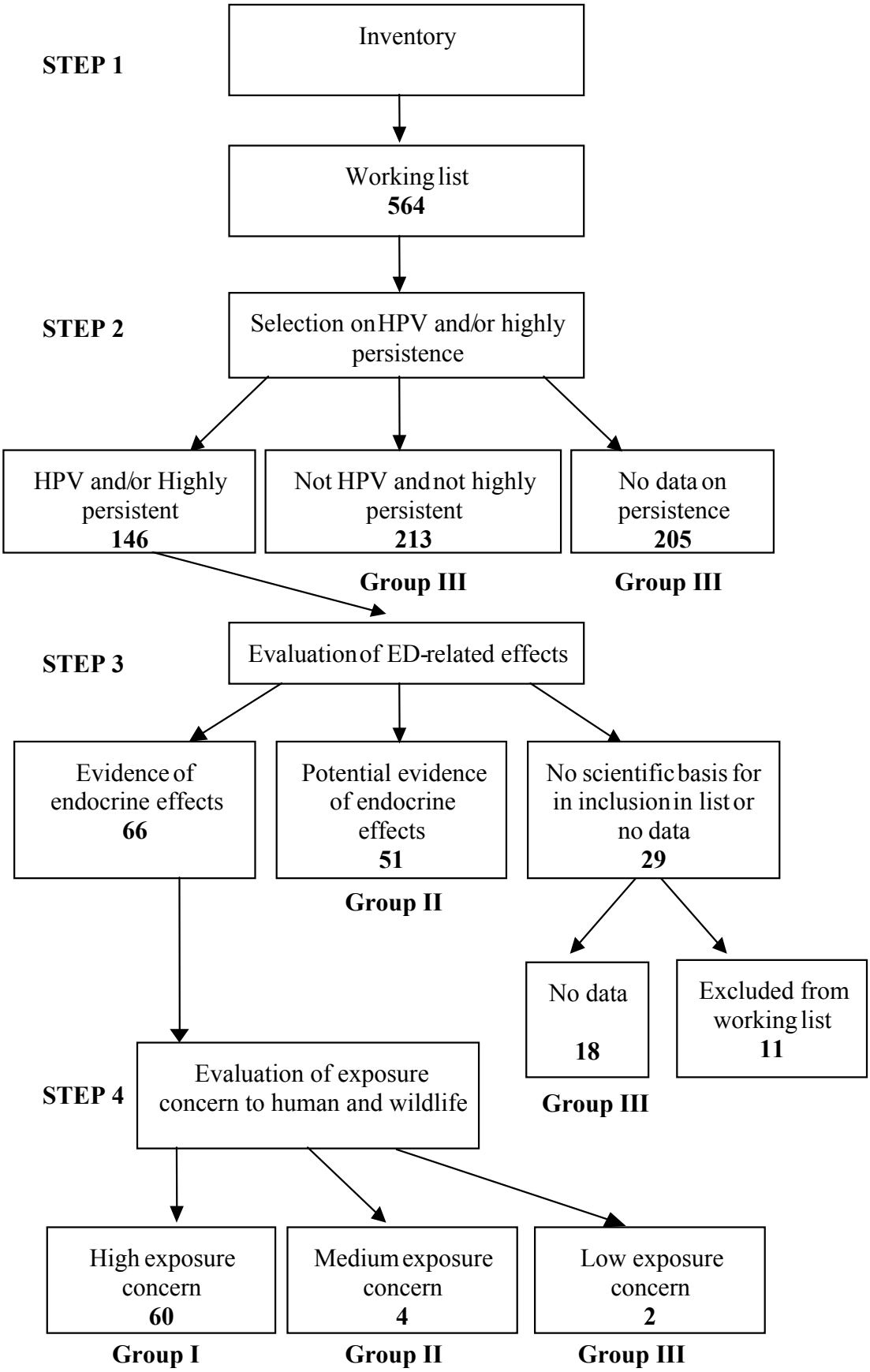


Table 4.1. List of candidate substances – summary of work to date

GROUP I

Selection criteria			*Number of substances*	*Listing*
Highly persistent And/or HPV	At least one study showing endocrine disruption in an intact organism (Category 1)	High concern in terms of human and wildlife exposure	60 (29 chemical groups)	See Annex 1.

GROUP II

Selection criteria			*Number of substances*	*Listing*
Highly persistent And/or	At least one study showing endocrine disruption in an intact organism (Category 1)	Medium concern in terms of human and wildlife exposure	4	See Annex 1
HPV	Potential for endocrine disruption (Category 2)		51	

GROUP III

Selection criteria			*Number of substances*	*Listing*
Highly persistent And/or HPV	At least one study showing endocrine disruption in an intact organism (Category 1)	Low concern in terms of human and wildlife exposure	2	See Annex 1
	No sufficient data (Category 3)		18*	
Not HPV and not highly persistent			213	
Not HPV and no data on persistence			205**	

* Excluding 11 Substances that have been excluded from the candidate list because of data giving no basis for inclusion in the list (Category 3)

** No Smiles notations were readily available for QSAR estimations on persistence.

4.2 Recommendations

This project is a first step into the overview of data and evaluation of substances associated with endocrine disruption. Although an approach has been used that 146 selected chemicals (HPV, persistent) are probably also the chemicals inherently related to high risk of exposure, some notes have to be made to this approach. A substantial group of chemicals was not selected in the group of 146, because no QSAR estimation on persistence could be made. For these chemicals persistence is unknown. Another consideration must be made towards the HPV criterion (>1000 tonnes/year). Substances that are produced in quantities smaller than 1000 tonnes per year with a moderate persistence might also present a high risk of exposure.

Recommendation 1: A follow-up has to be made to further evaluate the substances on the candidate list of 553 chemicals.

A considerable number of 205 chemicals were not included in first selection, because Smiles notations were not readily available. To complete the process for these substances Smiles notations should be prepared and in a number of cases additional information, if necessary by testing, should be provided.

At present there is no consensus yet on the methodology to assess endocrine disrupting effects.

Recommendation 2: It is important that an agreement is reached on the effect parameters indicating endocrine disruption

Recommendation 3: Standard tests have to be developed to identify endocrine disrupters

Recommendation 4: These tests should be applied with priority to category 1 substances with evidence of endocrine disrupting activity. Risk assessments will also need to be reconsidered when agreed test methods become available.

Recommendation 5: The database must be expanded with additional information on endocrine disrupting activity.

There is a need to increase the reliability and significance of the data.

Recommendation 6: For the evaluation of endocrine disruption effects a comparison should be made with the concentrations at which toxic effects (reproduction, mortality) occur.

Recommendation 7: Information is needed on the effects of endocrine disruption at a population level

In the selected group of 146 HPV and persistent chemicals, 51 have been categorised as category 2 chemicals due to a lack of sufficient information on endocrine disruption (e.g. in vivo tests).

Recommendation 8: For category 2 substances information should be supplemented with additional endocrine disruption data to reach a final categorisation (1 or 3).

Recommendation 9: The chemicals categorised as category 3 should be supplemented with additional endocrine disruption data; with the option to exclude them from the list or upgrade them to a category 2 or 1.

5 REFERENCES

BKH (2000), Background document on the project "Identification of chemicals related to endocrine disruption", Delft, The Netherlands.

COM (1999) 706 final, Communication from the Commission to the Council and the European parliament, Community strategy for Endocrine Disrupters, a range of substances suspected of interfering with the hormone systems of humans and wildlife.

Merck (1999), Merck index through online host.

Syracuse program, 1997. BIOWWIN Biodegradation Probability program version 3.6.

Worthing (1987) The Pesticide Manual, The British Crop Protection Council.