This project is funded by
the Horizon 2020 Framework
Programme of the European Union

EuroMix

European Test and Risk Assessment Strategies for Mixtures

Project number 633172

Collaborative project
H2020-SFS-2014-2

Deliverable D2.1 – Report

Report describing cumulative assessment groups for a broad range of chemicals, based on information extracted from (literature) databases

WP 2 – **QSAR and TTC approaches for setting test priorities**

Due month of deliverable: M18 (October 2016)
Actual submission month: M18 (October 2016)

Deliverable leader: BPI

Document status: version draft 3 Creation date: 2/11/2016

Project co-funded by the European Commission within the H2020 Programme		
Dissemination Level		
PU	Public	x
PP	Restricted to other programme participants (including the Commission)	
RE	Restricted to a group specified by the consortium (including the Commission)	
CO	Confidential, only for members of the consortium (including the Commission)	

Deliverable D2.1

Report describing cumulative assessment groups for a broad range of chemicals, based on information extracted from (literature) databases

October, 2016

Deliverable D2.1

Name of Deliverable:

Report describing cumulative assessment groups for a broad range of chemicals, based on information extracted from (literature) databases

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1 Introduction

The aim of this task is to identify chemical substances relevant for the EuroMix Project; that is pesticide and non-pesticide chemicals which can be grouped into cumulative assessment groups (CAGs). The European Food Safety Authority (EFSA) has previously published an Opinion describing the approach to be followed for grouping pesticides into CAGs based on their toxicological profile (EFSA, 2014). The present report takes into consideration the EFSA Opinion for pesticides and introduces a similar strategy to be considered for grouping of non-pesticide chemicals into CAGs.

A broad range of pesticide and non-pesticide chemicals were considered to generate a Chemical Inventory (CI) of substances of potential relevance for dietary cumulative risk assessment (CRA). The chemicals considered belong to several chemical categories including pesticides (plant protection and biocidal products), environmental pollutants (e.g. dioxins, PAHs), food contaminants (e.g. mycotoxins), chemical migrants from food package materials (Non-Intentionally Added Substances, NIAS) and bioactive alkaloids (e.g. pyrrolizidine alkaloids). In addition, several other chemicals and pharmaceuticals were compiled. The selection of the compounds to be included in the CI was based on the principle that the CI should be as broad as possible including substances of known toxicological profile, representative of different chemical categories that could be of relevance for dietary CRA. This list was used as a starting-point for the collection of relevant toxicity data. Moreover, it is used as basis for the Q(S)AR and molecular docking analyses performed in Work Package 2 (WP2).

For most of the substances included in the CI list, data were collected with regard to specific toxicological effects on the liver (liver toxicity), the developing foetus (developmental toxicity), endocrine effects and to a minor extent also to effects on the immune system (immunotoxicity). With regard to data collection for grouping plant protection product active substances in CAGs for toxic effects on the liver, the developing embryo/foetus and the endocrine system, the endpoints (parameters) as described in the EFSA External Scientific Report have been considered (Vv.Aa. *et al*, 2013). This report was produced by the National Institute for Public Health and the Environment (RIVM), the International Centre for Pesticides and Health Risk Prevention (ICPS) and the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) in the context of their contract with EFSA. Other source documents considered for plant protection and biocide active substances data collection included the Draft/Renewal Assessment Reports (DARs/RARs) prepared in the context of Regulation (EC) No. 1107/2009, the Competent Authority Reports (CARs) prepared in the context of Regulation (EC) No. 528/2012, the Toxicity Reference Database (ToxRefDB) and The Endocrine Disruption Exchange (TEDX) database for chemicals with the potential to affect the endocrine system.

Toxicological data collected for each substance were populated in a database specifically designed for this purpose, also referred to as EuroMix Toxicity Database (ETDB). This database was then used as one of the source documents to collect data for the grouping of pesticides and non-pesticides into three cumulative assessment groups using the categories and subcategories as described in a previous External Scientific Report submitted to EFSA by the Danish Technical University (DTU, 2012). In this latter report it has been proposed to allocate pesticides according to 4 CAG levels, i.e:

- CAG level 1: toxicological target (organ/tissue)

- CAG level 2: common phenomenological effect (on the toxicological target)
- CAG level 3: common mode of action
- CAG level 4: common mechanism of action.

In the EuroMix project the grouping of the pesticides and non-pesticides has been initially performed at level 1 and level 2 of the following CAGs:

- Liver toxicity (CAG level 1) – Steatosis (fatty changes; CAG level 2)
- Developmental toxicity (CAG level 1) – Malformations (skeletal malformations and cleft palate; CAG level 2)
- Reproductive toxicity (endocrine effects; CAG level 1) – Decreased anogenital distance; CAG level 2)

Since the DTU report (2012) did not recommend any CAGs for toxicity to the immune system, no attempt was made to group compounds for immunotoxicity.

A list of grouped compounds was generated and provided to WP5 to allow exposure-driven mixture selection (see Deliverable 5.1). The list will also be used by WP2-Task 2 and WP3 within EuroMix for the further refinement of the defined CAGs (CAG levels 3 and 4) using *in silico* and *in vitro* methodologies, respectively.

2 Categories of Compounds considered in the EuroMix Project

The rationale behind the selection of the chemical categories to be considered in the Euromix Project was to include both pesticides and non-pesticide chemicals of potential relevance for dietary CRA. Pesticides include plant protection and biocidal active ingredients as defined in point 10 of Article 3 to Directive 2009/128/EC of the European Parliament and of the Council establishing a framework for Community action to achieve the sustainable use of pesticides. The non-pesticide chemicals considered as representative for dietary CRA were the chemical migrants from food package materials (NIAS), food contact materials (FCM), environmental pollutants (e.g. dioxins, PAHs, PFAS, PBBs, PBDE, metals), food contaminants (e.g. mycotoxins), and bioactive alkaloids (e.g. pyrrolizidine alkaloids).

3 Chemical Inventory List

3.1 Purpose and structure of the Chemical Inventory

The Chemical Inventory (CI) is a broad list of chemical substances specifically developed to serve as a 'pool' of substances potentially relevant for consideration in the frames of the EuroMix Project. Several versions of the CI have been generated in time (Chemical Iventory_15-10-2015, Chemical Inventory_19-07-2016, placed on EuroMix Share) eventually resulting in a final CI referred to as Chemical Inventory_final (see APPENDIX A, also placed on EuroMix Share). The CI was used as a starting point to create a database of substances for which there is reliable toxicological data available (refer to Section 4) and from which CAGs may be identified (refer to Section 5). The final CI list is organised as an excel file consisting of different spreadsheets, each referring to a specific chemical category of interest as previously described in Section 2. The chemical categories and the number of substances included in each category are summarised in Table 3.1-1.

Table 3.1-1 Summary of the CI list

Chemical Category		**No. of Chemical Substances**
Pesticides	**Plant Protection a.i.**	501
	Biocidal a.i.	34
Non-pesticides	**NIAS & FCM migrants**	66
	Mycotoxins	20
	Alkaloids	40
	Environmental pollutants	308
Other chemicals		224

For each chemical substance, information was provided regarding its identity i.e. the substance chemical common name (or structural name in case of environmental pollutants), the chemical

category (for plant protection products only), the chemical class, the product type (for NIAS and FCM migrants only) and the CAS number.

3.2 Criteria for the Selection of Compounds included in the Chemical Inventory

The selection of the compounds to be included in the CI was based on the principle that the CI should be as broad as possible including substances of known toxicological profile, representative of different chemical categories that could be of relevance for dietary CRA. In that respect, the compounds included in each category of the CI were selected considering three main parameters:

- *chemical variability*, in order to ensure that a wide range of chemicals has been considered and,
- *food safety relevance (e.g under discussion at EFSA), and/or*
- *toxicological data availability*, since for each of the substances in the CI specific toxicological parameters have to be collected for the development of a hazard-based database (refer to Section 4).

Plant protection product active substances

Plant protection product active substances are defined as *"substances, including micro-organisms having general or specific action against harmful organisms or on plants, parts of plants or plant products"* as described in point 2 (2) of Article 2 to Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market. Micro-organisms are currently out of the scope of the EuroMix Project and are therefore not considered in the CI population. A summary of the chemical categories and numbers of plant protection product active substances included in the CI is presented in Table 3.2-1.

Table 3.2-1 Summary of plant protection product active substances included in the CI

Chemical Category	No. of Chemical Substances
Acaricide	12
Acaricide/Fungicide	1
Acaricide/Fungicide/Nematicide	1
Acaricide/Insecticide	20
Acaricide/Insecticide/Nematicide	5
Acaricide/Insecticide/Plant Growth Regulator	1
Algicide	1
Algicide/Fungicide	2
Antifeedant	1
Antifouling/microbicide	1
Avicide/Insecticide	1
Bactericide	6

Chemical Category	No. of Chemical Substances
Biocide (disinfectant)	1
Fungicide	120
Fungicide/Acaricide	1
Fungicide/Bactericide	1
Fungicide/Herbicide	1
Fungicide/Herbicide/Insecticide/Molluscicide/Plant Growth Regulator	1
Fungicide/Herbicide/Nematicide	3
Fungicide/Molluscicide	1
Fungicide/Plant Growth Regulator	2
Herbicide	167
Herbicide Safener	3
Herbicide/Plant Growth Regulator	12
Insect attractant	1
Insect repellent	1
Insecticide	64
Insecticide/Acaricide	11
Insecticide/Acaricide/Molluscicide	1
Insecticide/Acaricide/Nematicide	2
Insecticide/Molluscicide	1
Insecticide/Nematicide	4
Microbiocide	6
Microbiocide/Nematicide	1
Miscellaneous (used to generate phosphine)	2
Molluscicide	2
Nematicide	1
Other Pesticide	8
Plant activator	1
Plant growth regulator	23
Plant Growth Stimulator	3
Rodenticide	4
TOTAL PLANT PROTECTION PRODUCT ACTIVE SUBSTANCES	**501**

In addition to the wide range of chemical categories of plant protection product active substances the selection of the individual chemicals was based on the availability of reliable toxicological data.

For an active substance to be included in the CI it should meet one or more of the following conditions:

- EU approved under Regulation (EC) No. 1107/2009 as indicated in the "EU – Pesticides Database" of the European Commission (Url: http://ec.europa.eu/food/plant/pesticides/index_en.htm);
- Peer reviewed by EFSA;
- Included in the Commission Implementing Regulation (EU) 2015/595 concerning pesticides to be monitored in/on products of plant and animal origin;
- Included in the list of priority substances in the field of water policy as published by the European Commission (EC, 2012).
- Included in the EFSA External Scientific Report (Vv.Aa. *et al*, 2013) or Nielsen *et al.* 2014 (DTU report).

Biocide products active substances

A biocide product 'active substance' is defined as *"*a substance or a micro-organism that has an action on or against harmful organisms*"* as described in the Regulation (EC) No 528/2012 concerning the making available on the market and use of biocidal products. A summary of the number of biocide active substances included in the CI and the product types containing these substances is presented in Table 3.2-2. Almost all biocides included in the CI were also PPPs active substances.

Table 3.2-2 Summary of biocide active substances included in the CI

Group of product types	Product Type	No. of Chemical Substances
Disinfectans	**PT 2:** Disinfectants and algaecides not intended for direct application to humans or animals	2
	PT 4: Food and feed area	1
Preservatives	**PT 6 :** Preservatives for products during storage	4
	PT 7: Film preservatives	4
	PT 8: Wood preservatives	13
	PT 9: Fibre, leather, rubber and polymerised materials preservatives	4
	PT 10: Construction material preservatives	3
	PT 11: Preservatives for liquid-cooling and processing systems	1
	PT 12: Slimicides	2
	PT 13: Working or cuttting fluid preservatives	1
Pest control	**PT14:** Rodenticides	3
	PT18: Insecticides, acaricides and	16

Group of product types	Product Type	No. of Chemical Substances
	products to control other arthropods	
	PT20: Control of other vertebrates	1
Other biocidal products	**PT21:** Antifouling products	1
TOTAL NUMBER OF PRODUCT TYPES	**14**	

In total 34 biocide active substances have been included in the CI, some of them are contained in more than one product type. For an active substance to be included in the CI it should meet one or more of the following criteria:

- Active substances representative of different product types
- EU approved active substance under Regulation (EC) No 528/2012
- Substances for which a dossier has been submitted and accepted or validated by a Member State (Article 95 Reg. 528/2012, List of substances, 2 Sep 2015)
- Further selection based on existing ECHA & EFSA evaluation in order to ensure availability of reliable toxicological data.

Non-Intentionally Added Substances (NIAS) & Food Contact Materials migrants (FCM) migrants

Materials and articles intended to come into contact directly or indirectly with food (Food Contact materials, FCM) are regulated by the Regulations (EC) No 1935/2004 and (EU) No 10/2011 aiming to ensure the good manufacturing practice and that the release of substances from food contact materials and articles will not lead to unacceptable changes in the composition of the food. Substances used in the manufacture of plastic materials or articles may contain impurities originating from their manufacturing or extraction process and which are non-intentionally added together with the substance in the manufacture of the plastic material. During the manufacture and use of plastic materials and articles, reaction and degradation products can be formed. These reactions and the respective products are non-intentionally present in the plastic materials.

The above non-intentionally added substances to the final consumer products (Non Intentionally Added Substances, NIAS) are defined 'non-intentionally added substance' means an impurity in the substances used or a reaction intermediate substance, formed during the production process or a decomposition or reaction product (Regulation (EU) No 10/2011).
Materials with a complex composition may contain a large number of NIAS and the identification of all of them is not easy and in many cases is not possible.
The selection of the FCM migrants and NIAS to be included in the CI was made taking into account their toxicity, the provisions of the Regulation EU Reg 10/2011 and the possibility to be formed and migrate to the consumer products. The availability of analytical and exposure data was also taken into account.

A summary of the FCM migrants and NIAS included in the CI is presented in Table 3.2-3.

Table 3.2-3 Summary of FCM and NIAS included in the CI

Chemical Category	No. of Chemical Substances
NIAS	12
Plasticizer in FCM	7
Solvents-plasticizers-monomers-chemical Intermediates	36
Plasticizer	6
Solvents	5
TOTAL FCM migrants and NIAS	**66**

Mycotoxins

Mycotoxins are the toxic secondary metabolites produced by several species of fungi under specific temperature and humidity conditions. A mold species may produce many different mycotoxins, while several species may produce the same mycotoxin. Their toxicity varies widely and depends on the organism infected and its susceptibility, metabolism, and defence mechanisms.
The selection of 20 mycotoxins in total to be included in the CI (Table 3.2-4) was made taking in to account their toxicity and the availability of analytical and exposure data.
The selection was based on one of the following criteria:

- Regulated by the Regulation (EC) 1881/2006 and Recommendation 165/2013.
- EFSA scientific reports and opinions regarding their toxicological data.
- EU discussions for new regulated mycotoxins.

Table 3.2-4 Mycotoxins included in the CI

Chemical Category	No. of Chemical Substances
Mycotoxins	20

Alkaloids

Regarding the group of alkaloid chemicals, the focus was on pyrrolizidine alkaloids (PAs). Information was obtained mainly from two documents, i.e. the Scientific Opinion on PAs in food and feed by the EFSA Panel on Contaminants in the Food Chain (EFSA-CONTAM 2011) and the EFSA supporting publication on the occurrence of PAs in food (Mulder *et al.,* 2015).

Environmental pollutants

A chemicals inventory list was developed including different categories of environmental pollutants i.e. all chemically possible individual PCB-congeners, polycyclic aromatic hydrocarbons (PAHs), polybrominated diphenyl ethers (PBDE), per- and polyfluoroalkyl Substances (PFAS), polybrominated biphenyls (PBBs), dioxins, chemical elements (e.g. metals) and other chemicals that could be considered to be potential environmental pollutants (Table 3.2-5). This CI list includes also CAS-numbers for the individual compounds.

Table 3.2-5 Environmental pollutants included in the CI

Chemical Category	No. of Chemical Substances
Polychlorinated biphenyls (PCBs)	209
Polycyclic aromatic hydrocarbons (PAHs)	23
Polybrominated diphenyl ethers (PBDEs)	16
Per- and Polyfluoroalkyl Substances (PFAS)	11
Polybrominated biphenyls (PBBs)	3
Dioxins	18
Chemical elements / metals	18
Other	10
TOTAL environmental pollutants	**308**

Other chemicals

As indicated above and presented in Table 3.1-1, besides the pesticides and non-pesticides, one additional spreadsheet containing other chemicals was included in the CI. The substances included in this category are mainly pharmaceuticals, substances included in the Endocrine Active Substances Information System (EASIS) and miscellaneous chemicals. Most of these compounds were rather difficult to assign into one of the previous categories. It is noted that a large number of EASIS compounds that fall into other categories of CI have been included in the relevant spreadsheets.

The whole EASIS dataset was tested *in silico* for endocrine activity through 3D molecular docking, because of its potential interest for *in vitro* and *in vivo* subsequent activities (WP3 and WP4).

3.3 Completed Chemical Inventory List

The complete final CI list of substances is presented in a separate excel file attached as APPENDIX A to this report. This list is used as the starting-point for the collection of relevant data for the EuroMix Toxicity Database (ETDB, see Section 4). Moreover, it is used as a basis for the QSAR and molecular docking analyses performed in WP2 (see Deliverable 2.2).

3.4 Conclusion

The Chemical Inventory (CI) is a broad list of chemical substances that has been developed in the frames of Work Package 2 (Task 2.1) of the EuroMix project. The selection of the compounds to be included in the CI was based on the principle that the CI should be as broad as possible including substances from several chemical categories. Therefore, in this extensive list of chemicals approximately one thousand substances have been included representing different chemical categories i.e. pesticides (plant protection products and biocides), environmental pollutants (e.g. dioxins, PAHs, PCBs, PBDE, PFAS, PBBs), food contaminants (e.g. mycotoxins), chemical migrants from food package materials (NIAS) and bioactive alkaloids (e.g. pyrrolizidine alkaloids), metals,

pharmaceuticals and miscellaneous chemicals. This list was used as a starting-point for the collection of relevant toxicity data (Section 4) to be used for the allocation of the substances in CAGs (Section 5). Moreover, it is used as basis for the Q(S)AR and molecular docking analyses performed in Work Package 2 (WP2).

4 Toxicity Database

4.1 Structure of Database

Toxicological data collected for each substance were populated in a database specifically designed for this purpose on the basis of the format previously developed by ANSES and ICPS (Vv.Aa*. et al*, 2013).

The database was an Excel file structured in a way to facilitate the storage of relevant information extracted from the source documents (open literature studies, regulatory documents, etc). The Excel database was organized in separate worksheets, one for each chemical category included in the CI list i.e. PPPs & Biocides, Mycotoxins, NIAS & Phthalate esters Alkaloids and Environmental pollutants. The database structure (template) is presented in Table 4.1-1. Exceptionally, for environmental pollutants, the database structure was modified to fit the nature of the input data available (Table 4.1-1b).

Each worksheet was designed to include the following data:

- Specific data for each substance i.e. chemical name, CAS number, chemical class, intended use chemical class, MoA on target organism.
- Specific data for each study used for data collection i.e. reference, type of study, source, year of publication.
- Specific data for the study protocol used in each study i.e. animal species and strain, route and type of administration, duration or the study.
- Specific data for the toxicological endpoints derived by each study, i.e. measured endpoint, specific LOAEL and NOEAL values for the measured endpoint, study NOAEL (and the respective units and data regarding the mode or mechanism of action if available).
- Exposure data (only for environmental pollutants), including average exposure levels, details on exposure groups and relevant references.

Table 4.1-1 Database structure *

Organ / target system	Chemical Name	CAS Number	Chemical Class	Intended Use	MoA on target organism	Study	Species	Strain	Route of administration	Type of administration	Measured endpoint indicative of a possible common effect	Details on measured endpoint	Specific LOAEL	Specific NOAEL	Study NOAEL	Dose unit	Remarks	Mode/ mechanism of action (known/ Unknown/ Presumed)	Details on mode/mechanism of action	Source	Reference	Year of evaluation (publication of conclusion/ review report)

** considered for pesticides (plant protection products and biocides), mycotoxins, NIAS & Phthalate esters and bioactive alkaloids*

Table 4.1-1b Modified Database structure for environmental pollutants*

Substance	Endpoint	species	NOAEL/LOAEL	NOAEL/LOAEL comment	NOAEL reference	Average exposure level	Exposure comment	Exposure reference	Comment

** NOAELs and LOAELS are effect-specific*

The description of the fields included in the Database is presented in more details in Table 4.1-2

Table 4.1-2 Description of database fields (IDs)

Titles of database fields (IDs)	Description of database fields (IDs)
Organ / target system	Indicates the target organ or system (i.e. liver toxicity, developmental toxicity, endocrine effects, immunotoxicity)
Chemical name	Records the name of the chemical
CAS number	Records CAS number of the chemical
Chemical Class	Indicates the chemical class of each chemical (e.g. pesticide-triazine, environmental pollutant - dioxin, food contaminant - mycotoxins)
Intended use	Records the intended use of each substance (e.g. pesticide / herbicide, biocide /insecticide).
MoA on target organism	Indicates the mode of action of each substance in the target organism e.g. pesticidal MoA / Absorbed by roots, synthetic auxin, etc
Study	Records the type of study / protocol (e.g. extended one-generation study, 28-days study)
Species	Records the species used for each toxicity study (e.g. rat, dog)
Strain	Records the specific strain used for the toxicity study, when applicable.
Route of administration	Indicates the route of exposure that is used for exposing the animals (e.g. oral, inhalation, dermal, direct)
Type of administration	Records the method that is used to exposure the animal to the test compound (e.g. feed, gavage, whole-body, water, topical, subcutaneous, intravenous)
Measured endpoint indicative of a possible common effect [#]	Records the measured endpoint of interest e.g. liver histopathology, anogenital distance, etc.
Details on measured endpoint [#]	Indicates a more detailed description of what is actually observed, if applicable.
Specific LOAEL	Records the actual specific dose at which the effect (measured endpoint) is observed.
Specific NOAEL	Records the actual specific no-effect dose level for the specific effect (measured endpoint).
Study NOAEL	Records the actual no-adverse effect dose level for the study.
Dose unit	Records the units of NO(A)EL and LO(A)EL values (e.g. mg/kg bw day).
Remarks	Records any additional remarks about the study and the results that cannot be given under any of the other columns.
Mode/mechanism of action known/Unknown/Presumed	Records any information regarding the mode or mechanisms of action if available.
Additional remarks about the mode/mechanisms of action	Records any additional comments as regards the mode/mechanism of action

Titles of database fields (IDs)	Description of database fields (IDs)
Source	Indicates the source used for the toxicity data (e.g. DAR, open literature study).
Reference	Records the reference given within the Source (e.g. the study ID if available, name of the authors)
Year of evaluation (publication of conclusion/review report)	Records the reporting date of the study when available. If the reference is a scientific paper (open literature study), this can be the date of publishing.
Average exposure level	Records the daily population exposure levels to environmental pollutants, when available. The exposure levels observed are not linked to the toxicological endpoint observed.
Exposure comment	Provides details on the exposure data provided for environmental contaminants (e.g. details on the survey performed to obtain the data, data only on children).
Exposure reference	Indicates the source used for the exposure data provided for environmental contaminants (e.g. EFSA, Scientific opinion) providing the relevant *URL* when available.
Comment	Records any additional remarks about the study and the results that cannot be given under any of the other columns.

In the environmental pollutant worksheet of the database, information under "Measured endpoint indicative of a possible common effect" and "Details on measured endpoint", are merged into one column under the heading "Endpoint".

4.2 Source Documents used for Database Population

Plant protection product (PPPs) active substances

With regard to data collection for the purpose of grouping plant protection product active substances in CAGs for endocrine effects, the main source of information was the regulatory assessment report available at EU level. For each PPP substance first the EU Pesticide Database (http://ec.europa.eu/sanco_pesticides/) was visited in order to check the exact approval status of the substance. In cases where the "Risk Assessment" had been performed by the Commission, the Draft Assessment Report (DAR) - i.e. the EU evaluation of the substance - is not publically available in the EFSA website but it was obtained from the confidential area of CIRCABC for PPPs. In case where the "Risk Assessment" had been performed by EFSA, then the EFSA website (http://www.efsa.europa.eu/) was visited and a specific search was performed in order to retrieve the EFSA Conclusion, containing the final List of EndPoints (LoEPs), the DAR/RAR (Draft/Renewal Assessment Report) and the Final Addendum for the substance, to serve as source documents.

In addition to the regulatory documents, the following list/databases have been considered for relevant data:

- Substitute It Now (SIN) list: substances that have been identified by the NGO ChemSec as being substances of concern. Endocrine disrupting activity is included as an effect of concern.
- The Endocrine Disruption Exchange (TEDX) list: open literature data for potential Endocrine Disruptors, developed by the US Organisation TEDX.

- Endocrine Active Substances Information System (EASIS): JRC Database of study reports on substances related to endocrine activity.
- Open literature data (other than TEDX).

With regard to data collection for grouping plant protection product active substances in CAGs for effects on liver and development, the EFSA External Scientific Report has been considered (Vv. Aa. *et al*, 2013). This report was produced by the National Institute for Public Health and the Environment (RIVM), the International Centre for Pesticides and Health Risk Prevention (ICPS) and the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) in the context of their contract with EFSA. The relevant databases developed by ANSES and ICPS were used in the frame of the EuroMix project following personal communication and agreement between EuroMix Coordinator and EFSA.

Furthermore, previous work performed by the Danish Technical University (DTU) (Nielsen et al 2014) has also been considered.

The data included in DTU report and in ANSES and ICPS databases have not been copied in the EuroMix Toxicity database, but they have been considered for the allocation of the substances in CAGS (refer to Section 5).

Biocide products (BP) active substances

With regard to data collection for the purpose of grouping biocide products active substances in CAGs for endocrine effects, the main source of information was the regulatory assessment report available at EU level. For each BP substance, first the ECHA "Biocidal Active Substances" website (http://echa.europa.eu/web/guest/information-on-chemicals/biocidal-active-substances) was visited in order to check the exact approval status of the substance and the retrieval of the appropriate data, i.e. Assessment Report including the Final List of Endpoints and the Doc IIIA of the Final Competent Assessment Report (CAR), where the detailed evaluation of each study is reported.

Almost all biocides included in the CI were also PPP active substances, therefore, relevant data from DAR/RAR, and EFSA conclusion have also been screened for these substances. Other source documents considered for the population of database were the aforementioned lists/databases i.e. TEDX, open literature data, EASIS and the SIN list.

With regard to data collection for grouping biocides in CAGs for effects on liver and development, the EFSA External Scientific Report (Vv.Aa. *et al*, 2013) and the Danish Technical University (DTU) (Nielsen *et al.*, 2014) have been considered as previously described for PPP active substances.

Non-Intentionally Added Substances (NIAS) & Food Contact Materials (FCM)

For the collection of the toxicological data and grouping of FCM migrants and NIAS in CAGs the following scientific data reports were taken into consideration:

- EFSA Scientific Reports
- ECHA Risk Assessment reports

- OECD reports
- NTP technical reports of US Department of Health and Human Services
- Risk assessment reports of Federal Institute for Occupational Safety and Health (BAuA)
- Open literature studies

Mycotoxins

With regard to data collection for grouping mycotoxins in CAGs the EFSA External Scientific Reports (2006, 2011, 2013) and open literature studies have been considered.

Alkaloids

Toxicological information on pyrrolizidine alkaloids was obtained from the Scientific Opinion on PAs in food and feed by the EFSA Panel on Contaminants in the Food Chain (EFSA-CONTAM 2011).

Environmental pollutants

Information on toxicity (NOAELs/LOAELs) relevant to liver toxicity, developmental toxicity and endocrine endpoints for the compounds listed under environmental pollutants was primarily identified from studies reviewed and referenced in relevant EFSA Opinions and reports from the Joint FAO/WHO Expert Committee on Food Additives (JECFA). References and data for the dioxin-like PCBs were identified from an earlier opinion from the Scientific Committee on Food (SCF 2000).

4.3 Methodology for Database Population

For the substances included in the EuroMix CI, all relevant data were gathered for the respective source documents. During the first months of the project implementation period it was decided to focus on specific endpoints relevant for liver toxicity, developmental toxicity, endocrine disruption and immunotoxicity. These specific effects are listed in Table 4.3-1 below:

Table 4.3-1 Effects/endpoints that have been considered for the population of EuroMix toxicity database

Liver Toxicity	
Hepatocellular necrosis	
Hepatocellular degeneration	
Liver hypertrophy	
Steatosis (Fatty liver)	
Cholestasis	
Developmental toxicity	
Measured endpoints	**Details on measured endpoints (examples)**
Prenatal body weight changes	Foetus/litter
Delayed prenatal development	Reduced, delayed or non-ossification

Post-implantation losses / decreased number of live foetuses	Early/late resorption/dead foetus/ abortions
Runts	
Malformations/Anomalies	When no further details available
External malformations	Facial (cleft palate),
Visceral malformations	Brain (hydrocephaly, excencephaly…), eye (anophtalmia/microphtalmia…)…
Skeletal malformations	Scull, Vertebrae, forelimb flexures
External variations	Increased / decreased anogenital distance
Visceral variations	Kidney (dilated renal pelvis), urinary tract…
Skeletal variations	Vertebrae, supernumerary ribs…
Mechanistic study endpoints	
Postnatal body weight changes	Body weight gain or body weight loss (At Birth, At PN4, lactation, weaning)
Delayed postnatal development	Eye opening, sexual maturation, neurotoxicity…
Postnatal death / decreased survival of offspring	Birth, PN4, lactation, weaning
Reduced litter size	
Increased anogenital distance of male offspring	
Decreased anogenital distance of male offspring	
Increased anogenital distance of female offspring	
Decreased anogenital distance of female offspring	
Nipples retention in male offspring	
Nipples retention in female offspring	
Preputial separation of offspring	
Delayed vaginal opening of offspring	
Clinical signs in offspring	
Increased weight of male offspring reproductive organs	Testes (absolute and/or relative weight), epididymides, seminal vesicles, prostate
Decreased weight of male offspring reproductive organs	Testes (absolute and/or relative weight), epididymides, seminal vesicles, prostate
Increased weight of female offspring reproductive organs	Ovaries, uterus, vagina, mammary gland
Decreased weight of female offspring reproductive organs	Ovaries, uterus, vagina, mammary gland
Increased weight of offspring endocrine organs	
Decreased weight of offspring endocrine organs	
Increased weight of offspring other organs	
Decreased weight of offspring other organs	
Pathological changes of female offspring reproductive organs	Ovaries, uterus, vagina, mammary gland

Pathological changes of offspring endocrine organs	
Pathological changes of male offspring reproductive organs	Testes (leydig cell hyperplasia…), epididymides, seminal vesicles, prostate
Pathological changes of offspring other organs	
Altered sperm in male offspring	Number, mobility, morphology
Impaired fertility of male offspring	Sex hormone, fertility index…
Impaired fertility of female offspring	Fertility index, oestrus cycle, sex hormone…
Developmental neurotoxicity	Behavioural ontogeny, motor activity, learning memory, neuropathology
Endocrine effects	
Effects on endocrine organs	
Organ	**Effect**
adrenals	Organ weight or histopathological changes
testis	Organ weight or histopathological changes
epididymides	Organ weight or histopathological changes
penis	Organ weight or histopathological changes
accessory sex glands (e.g. Cowper's gland, seminal vesicles, prostate gland, bulbourethral glands, Glans penis)	Organ weight or histopathological changes
ovaries	Organ weight or histopathological changes
placenta	Organ weight or histopathological changes
cervix	Organ weight or histopathological changes
uterus (endometrium)	Organ weight or histopathological changes
vagina	Organ weight or histopathological changes
hypothalamus	Organ weight or histopathological changes
pituitary	Organ weight or histopathological changes
mammary gland	Organ weight or histopathological changes
Hormone levels	
estradiol	
testosterone	
aromatase	
Reproductive or developmental effects that could be relevant for endocrine disruption	
Nipple retention	
Genital abnormalities	
Changes of anogenital distance in female pup	
Changes of anogenital distance in male pup	
Changes in sperm numbers	
Changes in sperm motility	

Changes in sperm morphology	
Changes in oestrus cyclicity	
Age at Vaginal opening	
Age at preputial separation	
Immunotoxicity	
Haematological parameters / clinical biochemistry	
Measured endpoints	**Details on measured endpoints (examples)**
Number of white blood cells (WBC)	Changes in the relative of absolute number of lymphocytes, eosinophils, neutrophils, etc
Cytokines levels	Changes in cytokines levels
Immunoglobulin levels	Changes in serum immunoglobulin levels (IgM, IgG or IgE)
Albumin and globulin levels	Albumin to globulin ratio
Autoantibodies	Increased levels of autoantibodies
Organ / tissue effects	
Spleen	Organ weight and histopathological changes
Thymus	Organ weight and histopathological changes
Lymph nodes	Organ weight and histopathological changes
Lung	Respiratory sensitization
Human epidemiological data	
Increases incidence of infections	Effects indicative of immunosuppression
Response to vaccination	Effects indicative of immunosuppression
Delayed-type hypersensitivity (DTH)	Delayed-type hypersensitivity (DTH) to naturally occurring antigens is an effect indicative of immunosuppression
Abnormal elevation of cellular or humoral immune function	Effects indicative of immunostimulation and autoimmunity
Increased incidence of autoimmune diseases	Effects indicative of immunostimulation and autoimmunity
Allergy	Increased incidence of allergies is an effects indicative of immunostimulation

Later on during the project implementation period it was decided to focus on the following specific phenomenological effects: liver steatosis, skeletal malformations and cleft palate and decreased anogenital distance. All data that had been collected and captured in EuroMix toxicity database up to that moment were kept since they could be used for other purposes during the project

implementation. Therefore, for certain substances more detailed toxicological data have been presented in the EuroMix toxicity database than for others.

For PPP and BP active substances included in the EuroMix CI, all relevant data were gathered for the respective source documents. The population of each cell of the database excel file was conducted in accordance with the description presented in the Table 4.1-2 (Description of database fields IDs). For substances that fall into more than one regulatory category (i.e. pesticides and biocides) the information from all relevant regulatory documents and databases was captured. As regards the data collection for endocrine effects, the following studies have not been screened and included in the EuroMix toxicity database:

- studies that have been evaluated in the regulatory documents and considered to be not acceptable;
- range-finding studies;
- acute studies since they are not considered to be relevant to detect adverse effects on the endocrine system.

As regards the data collection for liver and developmental toxicity, as stated before, the data included in DTU report (Nielsen et al 2014) and in ANSES and ICPS databases (Vv.Aa. *et al*, 2013) have not been copied in the EuroMix Toxicity database, but they have been considered for the allocation of the substances in CAGs (refer to Section 5). In some cases liver and developmental toxicity effects found in the screened documents have been captured in the EuroMix toxicity database.

The relevant toxicological data for NIAS, FCM migrants and mycotoxins derived by the source documents listed in Section 4.2 were populated in the EuroMix Toxicity Database. The general rules for database population have been followed in order to capture all necessary data in the appropriate fields of the database as presented in Table 4.1-2.

To obtain toxicity data for alkaloids the Scientific Opinion on PAs in food and feed by the EFSA Panel on Contaminants in the Food Chain (EFSA-CONTAM 2011) was consulted. The population of each cell of the database excel file was conducted in accordance with the description presented in the Table 4.1-2 (Description of database fields IDs).

Toxicity studies reviewed in available EFSA opinions and relevant to liver toxicity, developmental toxicity and endocrine endpoints provided the information on NOAELs/LOAELs for the compounds listed under environmental pollutants. The strategy was to include information on endpoints related to these three areas of toxicity without being too restrictive. Consequently, toxicity data were summarised for many specific endpoints beyond hepatic steatosis, craniofacial malformations and decreased AGD. When relevant endpoints and toxicity studies had been identified from the EFSA opinions, the lowest NOAELs (or LOAELs if NOAELs could not be identified) were included in the data base for each endpoint. If toxicological information was lacking for any relevant endpoint this was noted in the database.

4.4 Completed Database

The complete database for substances, the EuroMix Toxicity Database (ETDB) is presented in a separate excel file called EuroMix Toxicity Database (ETDB)_28-08-2016 or EuroMix Toxicity Database (ETDB)_final and is attached as APPENDIX B to this report (also placed on the EuroMix Share).

4.5 Conclusion

For certain substances included in the CI list, data were collected with regard to specific toxicological effects on the liver (liver toxicity), the developing foetus and embryos (developmental toxicity) and the endocrine system. The toxicological data were gathered from the respective source documents for each compound category and were populated in a database specifically designed for this purpose. For some substances a more detailed screening for the relevant effects has been conducted, while for the rest of compounds less data have been captured in the toxicity database, since during the project implementation period it was decided to focus only on more specific phenomenological effects i.e. liver steatosis, skeletal malformations and cleft palate and decreased anogenital distance. The developed EuroMix toxicity database has been used for the allocation of different substances in CAGs as described in Section 5 of this report.

5 Cumulative Assessment Groups (CAGs)

5.1 Identification of CAGs

The starting point for grouping pesticide and non-pesticide chemicals in the frames of the EuroMix Project was the criteria described in the EFSA Scientific Opinion on the Identification of Pesticides to be Included in Cumulative Assessment Groups on the Basis of their Toxicological Profile (EFSA, 2014). This Opinion was drafted based also on previous work carried out by the EFSA Panel on Plant Protection Products and their Residues in 2008 (EFSA, 2008) as followed further in the Identification of Cumulative Assessment Groups of Pesticides External Scientific Report submitted to EFSA by the Danish Technical University (DTU, 2012).

Consequently, in line with the EFSA Opinion (2014) substances were grouped together based on the *"occurrence of toxicologically relevant and unambiguously defined effects on the target organ i.e. on specific effects, even if the underlying initial biochemical events causing these effects have not (yet) been demonstrated experimentally"*. This methodology identifies CAGs at several levels, i.e. CAG level 1 at organ/organ system level; CAG level 2 based on specific phenomenological effects; and potentially further refinement based on information about the specific mode (level 3) or mechanism (level 4) of action. During the course of data collection and population for inclusion of substances in CAGs it was recognized, that there was often little or no data available on mode or mechanism of action. Thus, the grouping methodology was based on phenomenological effects of the substances.

The following approach was applied:

- CAG level 1: Toxicological target organ
- CAG level 2: Common specific phenomenological effect

The initial screening of the chemicals included in the CI list (see Section 3) for toxic effect(s) on target organ/organ systems resulted in the allocation of active substances into CAGs at level 1. The following organ systems were suggested for CRA: Liver, Developing foetus, Endocrine system. Substances that showed effects on several organ/organ systems were allocated into more than one CAGs. Substances that exerted a specific phenomenological effect on the target organ/organ system in question without any consideration of mode or mechanism of action were included in CAG level 2. The phenomenological effects identified were: Steatosis (liver), Malformations including skeletal malformations and cleft palate (developing foetus) and decreased AGD in male offspring (endocrine effect).

A summary of the CAG level 1 and level 2 parameters considered are presented in Table 5.1-1:

Table 5.1-1 CAG level 1 and level 2 parameters considered

Organ / Organ system	Phenomenological effect
Liver	Steatosis
Developing foetus	Malformations • skeletal malformations

Organ / Organ system	Phenomenological effect
	• cleft palate
Endocrine system	Decreased AGD

The compounds used for the grouping exercise and corresponding toxicological data were obtained from:

- The EuroMix Toxicity Database (ETDB as described in Section 4). Regarding pesticide chemicals, it was decided together with WP5 (Task 5.3) to mainly use those pesticides that were assigned to the specific CAGs (level 2) by the Danish Technical University (DTU, 2012). These were complemented with some relevant pesticides from the ETDB, e.g. cyproconazole in the case of steatosis and developmental malformations. For the non-pesticide compounds, the toxicological data in the database were searched for the specific phenomenological effect parameters. Since relatively few non-pesticide compounds affecting these parameters could be identified, two other data sources were accessed: papers by Al-Eryani *et al.* (2015) and Christiansen (2012) and the ToxRefDB (October 2014 version).

- Paper by Al-Eryani *et al.* (2015). The authors have identified environmental chemicals associated with the development of fatty liver disease in rodents by searching (in 2013) two databases of rodent toxicology studies, i.e. the ToxRefDB[1] (EPA) and the CEBS[2] (NTP) for liver endpoints, such as ''fatty change'', ''lipid deposition'' and ''steatosis,''. The list of compounds resulting from the search in CEBS was further examined for usefulness in the EuroMix project by considering food relevance and consulting the original NTP studies (http://ntpsearch.niehs.nih.gov/texis/search/?pr=ntp_web_entire_site_all&mu=Testing+Status). The outcome of the ToxRefDB search was not used for EuroMix, but instead a similar search was performed with a more recent version of ToxRefDB (see below).

- Publication by Christiansen *et al* (2012). This paper describes the selection of 13 endocrine disrupting compounds for mixture experiments in rats. A number of these compounds have been previously reported to decrease AGD in male rodents [see Table 1 in Christiansen *et al* (2012)] and therefore were considered also to be relevant for the EuroMix project.

-ToxRefDB. The contents of the October 2014, ToxRefDB data release was used to identify compounds that affect the phenomenological effect parameters (CAG level 2) defined in the EuroMix project. The data were downloaded in April 2016 from the EPA website (https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data) and queried for the CAG level 2 effect parameters (steatosis, skeletal malformations/cleft palate, and decreased AGD in male offspring).

Collection and population for the toxicological parameters included in Table 5.1-1, resulted in the identification of the following CAGs:

Table 5.1-2 Description of CAGs identified

[1] ToxRefDB: Toxicity Reference Database
[2] CEBS: Chemical Effects in Biological Systems

Description of CAGs		No. of Pesticides *	No. of Non-pesticides **
Level 1	**Level 2**		
Liver effects	**Steatosis**	94	32
Developmental effects	**Total** [#]	68	17
	Skeletal malformations	62	15
	Cleft palate	21	8
Endocrine effects	**Decreased AGD in male offspring**	10	9

* pesticides: plant protection product and biocide active substances;

** non-pesticides: environmental pollutants (PCBs), food contaminants (mycotoxins), chemical migrants from food package materials (NIAS and phthalate esters) and bioactive alkaloids (pyrrolizidine alkaloids);

[#] skeletal malformations and cleft palate – note that the same chemical may exhibit both cleft palate and skeletal malformations; AGD: Ano-genital distance

Substances that caused toxic effects on different target organ/organ systems were allocated into more than one CAG of the same level. For instance, a substance causing both liver steatosis and malformations is included in both groups.

In many cases, a substance was found to lead to several specific phenomenological effects in a given target organ/organ system. For instance, a substance linked to malformations could have both skeletal malformations and cleft palate. In this case, it is counted once in the total malformation phenomenological effect, and it is included both in the skeletal malformation and cleft palate groups. A possible explanation to this finding is that the proposed different specific effects could be considered as representing a continuum of pathological findings for a given target organ/organ system (EFSA, 2014).

Detailed information on the lists of substances included in each group as described in Table 5.1-2 is presented in a separate database file called List of compounds for MCRA_final (see APPENDIX C, also placed on EuroMix Share) created by extracting the relevant information from the ETDB (described in Section 4 of this report) as well as the above mentioned sources. The CAGs, liver steatosis, developmental malformations and decreased AGD in male offspring, are described in three separate spreadsheets. Each spreadsheet, contains the list of the pesticide and non-pesticide substances including details on the identification of the substance (e.g. chemical name, CAS number) and the specific NO(A)EL/LO(A)EL of the toxic effect, when available.

Since many substances appear in many groups, the data entries for performing CRA are of considerable magnitude and should be further refined. However, as previously described, due to lack of or inconclusive data on mode/mechanism of action, the groups identified and described in Table 5.1-2, could not be further refined into CAGs at level 3 and 4. Instead, the proposed groups are based on phenomenological effects, i.e. CAG level 2. In order for these CAGs to be considered in CRA, reduction in the size of each group is desirable.

The database included in APPENDIX C of this report is used as a starting point for the exposure-based identification of relevant mixtures in WP5 (Milestone MS8 related to Task 5.3) and also used for further refinement of the hazard-based CAGs in WP2-Task 2.2 (in silico: QSAR and molecular docking analysis) and WP3 (*in vitro* studies).

In order to allow exposure-based identification of relevant mixtures (WP5), first Relative Potency Factors (RPFs) were calculated as follows:

- Take specific NOAEL if known (if more NOAELs are available, select the lowest value)
- If NOAEL is not known, take "surrogate" value: read-across NOAEL,
- If no suitable read-across NOAEL is available, take the TTC x 100
    - TTC values of Cramer classes:

	TTC in ug/person/day	TTC (EuroMix) in ug/ kg bw/day
genotoxic	0.15	0.002
organophosphate/carbamate	18	0.24
Cramer class III	90	1.2
Cramer class II	540	7.2
Cramer class I	1800	24

(TTC (µg/p/d) = 5th% NOEL(µg/kg/d) x 60 (kg/p) x 1/100)

- Choose a reference substance = the compound in a CAG with lowest NOAEL
- Calculate RPF by dividing NOAEL of reference compound by the selected (surrogate) NOAEL

5.2 Conclusion

The identification of chemicals that may be grouped together and subjected to joint risk assessment is a prerequisite for CRA. The proposed groups are based on toxic effects on different target organ/organ systems (CAG level 1) and phenomenological effects (CAG level 2). The hazard-based data entries are of considerable magnitude and will be further refined considering exposure data prior to consideration in CRA (refer to WP5).

6 Conclusions and Future Perspectives

The scope of Task 2.1 is to identify chemical substances which can be grouped into cumulative assessment groups (CAGs) for consideration in cumulative risk assessment (CRA). For this purpose, a broad list of chemical substances was compiled into a Chemical Inventory (CI). So far, the CI contains approximately 1000 substances of different chemical categories, i.e. pesticides (plant protection products and biocides), environmental pollutants (e.g. dioxins, PAHs, PCBs, PBDE, PFAS, PBBs), food contaminants (e.g. mycotoxins), chemical migrants from food package materials (NIAS), bioactive alkaloids (e.g. pyrrolizidine alkaloids), metals and miscellaneous chemicals, for which experimental toxicological data could be retrieved. The intention is to consider this CI as a dynamic list of chemicals that may be complemented during the course of the EuroMix project with even more chemical substances from the same or additional chemical categories for which potential CAGs may be identified. The broader the CI list the more likely it is to identify CAGs.

The CI list was used as the basis for the identification of chemicals to be included in CAGs based on phenomenological effects, in line with the methodology described in the EFSA Scientific Opinion on the Identification of Pesticides to be Included in Cumulative Assessment Groups on the Basis of their Toxicological Profile (EFSA, 2014). In order to provide CAGs for liver, developmental and endocrine effects, toxicological data on these organs/systems were collected and populated in a database

specifically designed for this purpose, the EuroMix Toxicity Database (ETDB). Additionally, relevant databases developed by ANSES and ICPS for liver and developmental effects of plant protection product active substances were considered following personal communication and agreement between the EuroMix Coordinator and EFSA.

A diagrammatic representation of the CAGs identified is presented in Figure 6-1.

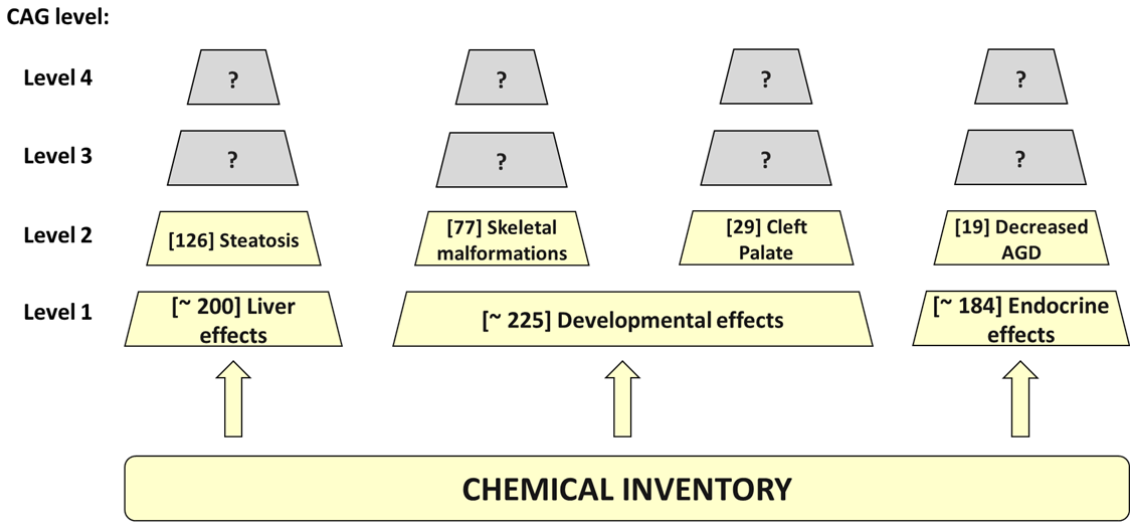

Figure 6-1 CAGs identified from the Chemical Inventory list

(The number in [brackets] is the number of substances identified in each group. The question mark (?) indicates that no substances could be placed in CAG levels 3 and 4 of the EFSA Guidance (2014). AGD: Anogenital distance in male offspring).

As indicated in Figure 6-1, four CAGs are identified on the selected organs/systems (level 1) based on phenomenological effects (level 2), i.e. liver steatosis, skeletal malformations in developing foetus, cleft palate in developing foetus and decreased anogenital distance as endocrine effect. Due to lack of or inconclusive data on mode (level 3) and mechanism (level 4) of action, the CAG groups identified could not be further refined into CAGs at levels 3 and 4. As a consequence, the CAGs identified are quite large and therefore it would be highly demanding with respect to resources (e.g. exposure data, mathematical models) to proceed with CRA. It is recognised that before these CAGs are considered in CRA, reduction in the size of each group is required. This may be achieved by predicting levels 3 and 4 using *in silico* approaches (Task 2.2) or by further investigating the mode/mechanism of action through appropriate *in vitro* studies (WP3). In parallel, the hazard-based CAGs may be further refined considering exposure data prior to consideration in CRA (refer to WP5).

The aim of WP2 of the EuroMix project is not only to provide a list of chemicals that serve as a basis for the specific tasks in this project, such as the selection of compounds and mixtures to be studied in WP3 and WP4, but also, more generally, to set up a (tiered) strategy for the integrated use of in silico approaches to prioritise chemicals for further risk assessment in the context of mixtures (Task 2.4, Deliverable 2.4). Not only QSAR and TTC but also the Hazard Index (HI) approach is foreseen to be parts of such a strategy. The HI is the sum of Hazard Quotients (HQs), i.e. ratio between exposure

and the reference value for the common toxic effect of each component in a mixture (Bopp et al 2016). To determine whether the toxicity of the mixture is driven by one substance, the Maximum Cumulative Ratio (MCR) can be calculated. The MCR is the ratio of the cumulative risk posed by a combined exposure to multiple chemicals (so the HI) under the assumption of dose addition divided by the risk of the most toxic chemical (Valloton and Price 2016). If the majority of the risk is driven by one compound, it might be decided not to prioritise that mixture for further assessment (or to limit the risk assessment to that one compound, if not already performed). This prioritisation approach would be benefited not only by the availability of toxicological data (Points of Departure, such as NOAELs, and "surrogate" values, such as TTC values) but also of exposure data. For that reason it would be helpful to populate the EuroMix Toxicity Database with more exposure data (e.g. average exposure values).

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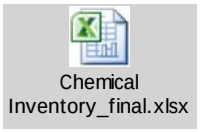
List of Abbreviations

AGD	AnoGenital Distance
ANSES	Environmental and Occupational Health & Safety
BPA	Bisphenol A
CAG	Cumulative Assessment Group
CAR	Competent Authority Report
CAS	CAS registry number
CEBS	Chemical Effects in Biological Systems
CI	Chemical Inventory
CRA	Cumulative Risk Assessment
DAR	Draft Assessment Report
DTU	Danish Technical University
EASIS	Endocrine Active Substances Information System
EC	European Union
ECHA	European Chemical Industry Council
EFSA	European Food Safety Authority
ETDB	EuroMix Toxicity Database
EU	European Union
FCM	Food Contact Materials
ICPS	International Centre for Pesticides and Health Risk Prevention
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LO(A)EL	Lowest Observed (Adverse) Effect Level
LoEPs	List of Endpoints
MoA	Mode of Action
NIAS	Non-Intentionally Added Substances
NO(A)EL	No Observed (Adverse) Effect Level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PAHs	Polycyclic Aromatic Hydrocarbons
PBBs	Polybrominated Biphenyls
PBDE	Polybrominated Diphenyl Ethers
PCBs	Polychlorinated biphenyls
PFAS	Per- and Polyfluoroalkyl Substances

QSAR	Quantitative structure–activity relationship
RAR	Renewal Assessment Report
RIVM	National Institute for Public Health and the Environment
RPFs	Relative Potency Factors
SIN	Substitute It Now list
TEDX	The Endocrine Disruption Exchange
ToxRefDB	Toxicity Reference animal Database
WP	Work Package

Appendices

A. Chemical Inventory



B. Database

C. Cumulative Assessment Groups