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Prioritised list of known emerging chemicals

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WP 16 - Emerging Substances

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2 Introduction

The emerging chemicals issue clearly appears as a major current concern for both the scientific community, societal actors, and public authorities. However, this issue still remains imperfectly defined and may recover different aspects both from a conceptual and methodological point of view. Basically, “Emerging contaminants” may be considered as compounds recently appeared in the environment, for instance newly developed substitutes of substances currently under regulation or which have been banned. They can be also considered as “contaminants of emerging concerns”, *i.e.* compounds present for a while in the environment-food-human continuum but for which the concern has increased recently. In the scope of the “European Human Biomonitoring Initiative“ (HBM4EU) and its related WP16, emerging chemicals should be understood as chemicals of emerging concern (see deliverable 4.2 – Scoping documents for 2018).

Consequently, the number of possible concerned substances is extremely high, encompassing compounds of very diverse nature (substance group and use), properties (chemistry) and origin (sources of exposure). Various initiatives and/or sources of information are available that have proposed some lists of emerging compounds in various contexts, mainly in the field of environment (e.g. Norman network) but also through toxicological databases. These sources appear in some extend overlapping, and at the same time complementary. But at the present time there is no global - if not aggregated - view about this inventory issue. In that context, one goal of the HBM4EU Work Package 16 (WP16) was to provide such global picture about the existing lists or databases related to emerging chemicals at international level.

Beside the descriptive aspect of this work, this inventory is also of interest for guiding further developments foreseen within the HBM4EU WP16. Indeed, the data processing step associated to suspect and in some extent untargeted screening approaches consists to use a reference library to compare and match each detected signal in the analysed sample to a list of already known and referenced compounds. Nowadays, the creation of such reference libraries is commonly driven by each laboratory’s field of activity without much exchange, so that no global and integrated library is yet available and a need of mutualisation and harmonisation clearly appears to reach more efficient use of these libraries. Moreover, the definition and implementation of improved QA/QC criteria for ensuring higher confidence level in terms of identification of the considered markers also appears as an important work to be carried out. In the frame of the HBM4EU project WP16, several partners have already developed such MS reference libraries for annotation of suspect and untargeted screening profiles, and/or are involved in the definition and implementation of appropriate QA/QC dispositions to consolidate this data processing aspect.

One goal of WP16 is then to aggregate these existing capabilities for finally proposing an extended and qualitatively consolidated MS reference library to be used for suspect and untargeted screenings of emerging chemicals. In that context, the present inventory of existing lists or databases related to emerging chemicals at international level represents a useful tool to orientate the selection of compounds to be characterised as reference standard and indexed in a global MS reference library.

3 Prioritised list of known emerging chemicals

3.1 Purpose of the exercise

The purpose of this task was to establish a "list of known chemicals (parent compounds and/or metabolites) to be considered as biomarkers of exposure for chemicals emerging concern". The outcome of task 16.1 is to provide a suitable starting point for the practical high resolution screening exercises that will be conducted in WP16. The goal of task 16.1 has been more precisely defined as: "to create an all-inclusive list of emerging compounds relevant for biomonitoring based on existing inventories of emerging compounds within the EU, to be addressed through suspect screening strategies with increasing coverage from now to the end of the HBM4EU program". In that context, several considerations were taken into account:

- The list will include information provided by the contributing inventories, but at a minimum: name, accurate monoisotopic mass, chemical structure (simplified molecular-input line-entry specification (SMILES) and International Chemical Identifier (InChI) key), elemental composition.
- Related exposure data/information will be used as primary criteria for inclusion
- No selection will be made on toxicological properties other than selections made by the organisations that collated the contributing inventories.
- The NORMAN list will be considered as one main source of information, but considering that exposure markers in human matrices may differ from the exposure markers in environmental/aquatic compartments
- Information collected from WP16 partners will be incorporated (emerging compounds suggested in the HBM4EU questionnaire).
- Compounds for which a validated 'standard' quantitative biomonitoring approach is already available will be possibly excluded from the list.

The list will be used as a guiding rail for the suspect screening related activities for partners involved in WP16 (task 16.2). Indeed, the long-term goal of WP16 in terms of screening capabilities (i.e. availability of appropriate large scale screening methods with corresponding necessary MS libraries for annotation) would be to cover a maximal part of this list as defined within this deliverable. As a first step, existing analytical capabilities will be assessed in the scope of characterising their ability to detect one sub-part (x %, x to be experimentally determined) of this global list from human urine and blood samples. For a subset of compounds for which several labs will have simultaneously demonstrated they are present with high detection rate, further information such as exposure data, toxicological data, QSAR will be collated. The 'end-goal' of this work within WP16 is to be able to suggest a number of emerging compounds/biomarkers to HBM4EU that should be considered for inclusion into the regular biomonitoring programs.

3.1.1 Metabolites of chemical compounds

The list described in this deliverable is (primarily) based on chemical compounds that are present in the external environment. However, many of these compounds will undergo biotransformation reactions (metabolism) once present in the human body. As suspect screening activities within WP16 will be conducted in biological matrices, for many of the compounds on the list one or more metabolites might be detected in the sample and consequently should appear in the feature table reporting the relevant exposure markers to be considered. Consequently, a crucial next step based on the work described here involves generating a resource that includes (possible) metabolites based on the parent compounds currently included in the list. Such a resource can be populated using several tools including *in silico* methods, analytical techniques, bioreactors, field studies, and/or existing databases. Based on the experience of the partners in this WP, the database

including metabolites is expected to be several times larger than the existing list and therefore data management procedures need to be developed. Though of critical importance, this work falls outside the scope of the current deliverable and will be further pursued by WP16 in years 2-5.

3.2 Methodology

3.2.1 Identification and combination of data sources containing emerging chemicals

The following data sources were used to compile the list of emerging compounds constituting this deliverable:

1. The databases that were incorporated in an exercise conducted by UBA and described in the International Journal of Hygiene and Environmental Health 220 (2017) 103–112. The original inventory from 2009 was updated in 2017.
2. Databases containing emerging compounds suggested by HBM4EU members in the 2017 questionnaire.

Eleven lists of potentially emerging compounds of relevance for HBM4EU (see Table 1) were combined in a single database. Information extracted from the individual lists was: “CAS number”, “monoisotopic mass”, and “simplified molecular-input line-entry specification” (SMILES)”. All individual lists reported CAS numbers (though not available for all entries in the respective databases), the other two variables were inconsistently included in some databases. Databases were merged on CAS number. For entries for which either the monoisotopic mass or SMILES were missing, information was retrieved from Chemical Identifier Resolver (CIR) [https://cactus.nci.nih.gov/chemical/structure_documentation], using the “Webchem“ package, developed for the R Project for Statistical Computing[1]. Manual checking indicated that information was not available for all CAS numbers. For the entries that contained information on SMILES, but no information on monoisotopic mass, this information was added using the same methodology.

3. Databases included in the US Environmental Protection Agency’s Chemistry Dashboard (https://comptox.epa.gov/dashboard/).

The Chemistry Dashboard is a part of a suite of databases and web applications developed by the US Environmental Protection Agency's Chemical Safety for Sustainability Research Program. These databases and apps support EPA's computational toxicology research efforts to develop innovative methods to change how chemicals are currently evaluated for potential health risks. The information is combined by the US EPA to help prioritise chemicals based on potential health risks.

The data in the dashboard are of varying quality with the highest quality data being assembled by the DSSTox Program. The majority of the chemical structures within the database has been compiled from public sources, such as PubChem, and have varying levels of reliability and accuracy. Links to over twenty external resources are provided. These include other dashboard apps developed by EPA and other agency, interagency, and public databases containing data of interest to environmental chemists. It also integrates chemistry linkages across other EPA dashboards and chemistry resources such as ACToR, ToxCast, EDSP21 and CPCat. Expansion, curation, and validation of the content is ongoing.

Description Chemistry Dashboard from https://comptox.epa.gov/dashboard/.

3.2.2 Data curation and preparation of list for HRMS screening

Considering the large number of databases contributing to the list of emerging chemicals, and the varying degree of details that was provided for each chemical in these databases, data curation was considered as an important and mandatory step to make the leap from conducting a data

inventory to generating a list that is ready to use for HRMS screening. The following steps were conducted as part of data curation:

1. Using WebChem[2] package for R[1], SMILES and monoisotopic mass were generated for each entry for which this information was missing, based on the reported CAS number .
2. All compounds included in the list for which SMILES were not available were removed.
3. All inorganic compounds were removed from the list. Although some inorganic compounds might be detected depending on the LC-HRMS method used, these require special treatment and should be considered separately. For the current database a choice was made to focus on organic and organometallic compounds only.
4. Using the JChem Structure Checker tool[3], erroneous SMILES (valence errors) were removed from the list. Valence errors also occurred for metal complexes of organic ligands, which showed "too many" covalent bonds in the SMILES notation.
5. Using the JChem Standardier tool[4], fragments (i.e., small molecules from multi-molecule compounds such as water, and counter ions of ionized acids or bases) were removed and charged molecules were neutralised.
6. Using the OpenBabel chemical toolbox[5] CANONICAL SMILES were retrieved, including conversion of dative bonds (i.e. nitro groups or N oxides are written with 5-valent nitrogen) and aromatisation.
7. Using the OpenBabel chemical toolbox[5] InChIKeys were retrieved based on the CANONICAL SMILES

The list resulting from steps 1-7 was then collapsed on two levels, resulting in two “MS ready” databases:

A. A database containing one line per unique InChIKey. Each line represents a unique compound in terms of both structural and stereochemistry.
B. A database containing one line per unique InChIKey main layer. Each line represents a unique compound in terms of structural chemistry only.

In each database unique compounds can be traced back to the original database from which the compound was retrieved and the information that was provided in this database.

3.3 Results

3.3.1 Identification and combination of data sources containing emerging chemicals

The resulting database includes a total of 145,284 entries, containing 107655 unique CAS numbers, and 109237 unique smiles. 51 databases contributed to the database (Tables 1 and 2).

Table 1: Lists included from UBA exercise and HBM4EU inventory (10/23/2017)

List Name	Number of Chemicals	List Description
NORMAN merged suspects list dated 24/05/2017	14633	http://www.norman-network.com/?q=node/236
EFSA FoodToxDB	5812	https://www.efsa.europa.eu/en/data/chemical-hazards-data
ECHA Candidate list	203	https://echa.europa.eu/nl/candidate-list-table
COSING (cosmetic ingredient database)	25267	https://ec.europa.eu/growth/sectors/cosmetics/cosing_nl
REACH ANNEX III	64900	https://echa.europa.eu/nl/information-on-chemicals/annex-iii-inventory
List of PBT/vPvB-substancesc (67/548/EECd and 793/93/EECe as from May 2008)	128	https://echa.europa.eu/nl/information-on-chemicals/pbt-vpvb-assessments-under-the-previous-eu-chemicals-legislation
T3DB	3674	http://www.t3db.ca/
US EPA CPCAT database (includes SPIN 2000)	43600	https://www.epa.gov/chemical-research/chemical-and-product-categories-cpcat
OECD HPV 2007	4645	http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2009)40&doclanguage=en
EC EDS list	433	(http://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm)
TEDX list	1409	(https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/about-the-tedx-list)

Table 2: Lists included from US EPA chemistry dashboard (11/03/2017)

List Name	Number of Chemicals	List Description
Algal Toxins	54	A set of algal toxins of interest
ATSDR Toxic Substances Portal Chemical List	200	The Agency for Toxic Substances and Disease Registry (ATSDR)is a federal public health agency of the U.S. Department of Health and Human Services.
Bisphenol Compounds	52	This list represents a collection of Bisphenol Compounds
California Office of Environmental Health Haard Assessment	972	The OEHHA Chemical Database is a compilation of health hazard information including reference exposure levels, California public health goals, child-specific reference doses, Propos. 65 safe harbor numbers, soil-screening levels, and fish advisories
Confirmed list of chemicals in the NIST SRM2585 reference material	221	This is a confirmed list of chemicals contained in the NIST SRM2585 dust sample.
DNT Screening Library	1476	DNTSCREEN is a list of chemicals that is being used in medium- and high-throughput in vitro and zebrafish assays.
Drinking Water Suspects, KWR Water, Netherlands	136	KWRSJERPS is a list of prioritised suspects relevant for human health in drinking water from KWR Water in Nieuwegein, The Netherlands. The methods are detailed in[6]

List Name	Number of Chemicals	List Description
EPA Integrated Risk Information System (IRIS)	510	EPA's IRIS Program identifies and characterises the health hazards of chemicals found in the environment. Each IRIS assessment can cover a chemical, a group of related chemicals, or a complex mixture.
EPA Toxcast Screening Library	4736	TOXCAST includes all EPA-provided chemicals for which screening data have been generated in the ToxCast research program since 2007.
EU Cosmetic Ingredients Inventory (Combined 2000/2006)	2878	EUCOSMETICS contains the Combined Inventory of Ingredients Employed in Cosmetic Products (2000, SCCNFP/0389/00 Final) and Revised Inventory (2006, Decision 2006/257/EC), prepared for NORMAN by P. von der Ohe (UBA) and R. Aalizadeh (Uni. Athens).
French Monitoring List	1171	FRENCHLIST contains substances for prospective monitoring activities in France, developed in cooperation with the NORMAN Network Working Group 1 on Prioritization. Provided by Valeria Dulio, INERIS, France. Further information available on http://www.norman-network.net/
Hazardous Air Pollutants	180	These air toxics, also called Hazardous Air Pollutants, are subject to regulation under Title III of the Clean Air Act
HERO: Health and Environmental Research Online	495	The Health and Environmental Research Online (HERO) database provides an easy way to access and influence the scientific literature behind EPA science assessments.
ITN ANTIBIOTIC LIST	464	ITNANTIBIOTIC is a list of antibiotics compiled by Nikiforos Alygizakis (Environmental Institute/University of Athens) as part of the Marie Skłodowska-Curie Actions (MSCA) Innovative Training Network (ITN) ANSWER (EU H2020 Grant 675530).
KEMI List of Substances on the Market	30418	The KEMI Market List contains chemicals expected to be on the market. Complied by Stellan Fischer, KEMI (Swedish Chemicals Agency) from various regulatory databases, including hazard and exposure scores to support the identification of unknowns.
List of Swiss Pesticides and Transformation Products	183	SWISSPEST is a list of registered insecticides and fungicides in Switzerland along with their major transformation products. This list was used for a suspect screening approach described in Moschet et al 2013[7]
MassBank Reference Spectra Collection	1224	This MassBank list contains chemicals associated with the full MassBank collection of reference standard spectra available on MassBank.EU, MassBank.JP and MassBank of North America as well as the Open Data collection, curated by Williams/Schymanski.
MassBank.EU Collection: Special Cases	263	The MassBank.EU list contains curated chemicals (Schymanski/Williams) associated with the literature/tentative/unknown/SI spectra available on MassBank.EU that are not available as part of the full MassBank collection of reference standard spectra.
mzCloud database	3310	mzCloud is a state of the art mass spectral database that assists analysts in identifying compounds in areas such as life sciences, metabolomics, pharmaceutical research, toxicology, forensic investigations and environmental analysis.
National Environmental Methods Index	1455	The National Environment Methods Index (NEMI) is a searchable database of environmental methods, protocols, statistical and analytical methods.
NIOSH IDLH Values	372	The immediately dangerous to life or health (IDLH) values are used by the National Institute for Occupational Safety and Health (NIOSH) as respirator selection criteria.
NIOSH International Chemical Safety Cards	1609	The International Chemical Safety Cards (ICSC) summarises essential health and safety information on chemicals.
NIOSH Pocket Guide to Chemical Hazards	615	The NIOSH Pocket Guide to Chemical Hazards (NPG) informs workers, employers, and occupational health professionals about workplace chemicals and their hazards.
NIOSH Skin Notation Profiles	57	The NIOSH skin notations relies on multiple skin notations to provide users a warning on the direct, systemic, and sensitising effects of exposures of the skin to chemicals.

List Name	Number of Chemicals	List Description
NORMAN Collaborative Trial 2015 Targets and Suspects	732	NORMANCT15 is a compilation of all target and suspect substances reported by participants in the NORMAN Collaborative Trial on Non-target Screening, run by the NORMAN Network and described in Schymanski et al 2015[8]
Norman Network PFAS (KEMI Report)	2257	Perfluorinated substances from a Swedish Chemicals Agency Report (provided by Stellan Fischer) on the occurrence and use of highly fluorinated substances.
NORMAN Network Priority List	922	NORMANPRI contains the list of priority substances determined by the NORMAN Network Working Group 1 on Prioritization, provided by Valeria Dulio, INERIS, France. Further details available on http://www.norman-network.net/
NormaNEWS: Norman Early Warning System	131	The NORMAN Early Warning System (NormaNEWS) is a collaborative activity run by the NORMAN Network to investigate newly identified contaminants of emerging concern via retrospective screening on HRMS data.
PFAS list provided by X.Trier et al	597	PFASTRIER is a compilation of PFAS kindly provided by Xenia Trier, David Lunderberg, Graham Peaslee, Zhanyun Wang and colleagues. Structural curation by the Dashboard team. Original details on the NORMAN Suspect List Exchange. Further information available on http://www.norman-network.net/
Pharmaceutical List with EU, Swiss and US Consumption Data	953	SWISSPHARMA is a list of pharmaceuticals with consumption data from Switzerland, France, Germany and the USA, used for a suspect screening/exposure modelling approach described in Singer et al 2016[9]
Provisional Peer Reviewed Toxicity Values	403	The Provisional Peer-Reviewed Toxicity Values (PPRTVs) currently represent the second tier of human health toxicity values for the EPA Superfund and Resource Conservation and Recovery Act (RCRA) hazardous waste programs.
Stockholm Convention on Organic Pollutants	38	Stockholm Convention on Persistent Organic Pollutants is an international environmental treaty.
STOFF-IDENT Database of Water-Relevant Substances	7953	STOFF-IDENT is a database of water relevant substances collated from various sources within the STOFF-IDENT and FOR-IDENT projects, hosted by LfU, HSWT and TUM. The database at https://www.lfu.bayern.de/stoffident/#!home has additional functionality
Superfund Chemical Data Matrix	220	The Superfund Chemical Data Matrix (SCDM) generates a list of the corresponding Hazard Ranking System (HRS) factor values, benchmarks, and data elements for a particular chemical.
Surfactant List Screened in Swiss Wastewater (2014)	122	EAWAGSURF is a list of surfactants screened in Swiss wastewater effluents as part of a 2014 study. Structures/mixtures are being progressively curated and linked (Schymanski/Williams). Further details in Schymanski et al 2014[10]
TOX21SL: Tox21 Screening Library	8947	TOX21SL is list of unique substances in Tox21 multi-federal agency screening library, contributed by the EPA, National Toxicology Program (NTP), and National Center for Advances in Translational Science (NCATS).
Toxics Release Inventory	589	In general chemicals covered by the TRI Program are those that cause one or more of the following: 1) Cancer or other chronic human health effects; 2) Significant adverse acute human health effects; 3) Significant adverse environmental effects
TSCA Surfactant List (subset)	100	TSCASURF contains information on surfactants compiled by James Little (while at Eastman Chemical) from the TSCA Database. This is being progressively curated and extended.
University Jaume I Target Substances	508	UJIBADE is a list of target substances from University Jaume I, Castellon, Spain used for retention time prediction in Bade et al 2015[11]

List Name	Number of Chemicals	List Description
University of Athens Surfactant and Suspect List	60	ATHENSSUS is a compilation of suspects, predicted transformation products and surfactants screened in wastewater by University of Athens, as described in Gago-Ferrero et al 2015[12]

As expected, several CAS numbers were included in more than one databases (Table 3).

Table 3: Overlap between databases

Included in 1 list	Included in 2 lists	Included in 3 lists	Included in 4 lists	Included in 5 lists	Included in 6 lists
4	15397	3933	469	90	12

3.3.2 Data curation and preparation of list for HRMS screening

Results from data curation and preparation of list for HRMS screening are shown in Figure 1. 30,740 entries had to be removed because SMILES were not reported and could not be generated. Furthermore 3227 entries were removed because SMILES represented inorganic compounds. The remaining 111,317 represented 70,583 unique compounds. When not considering stereochemistry the list of unique compounds in the database is further reduced to 66,015.

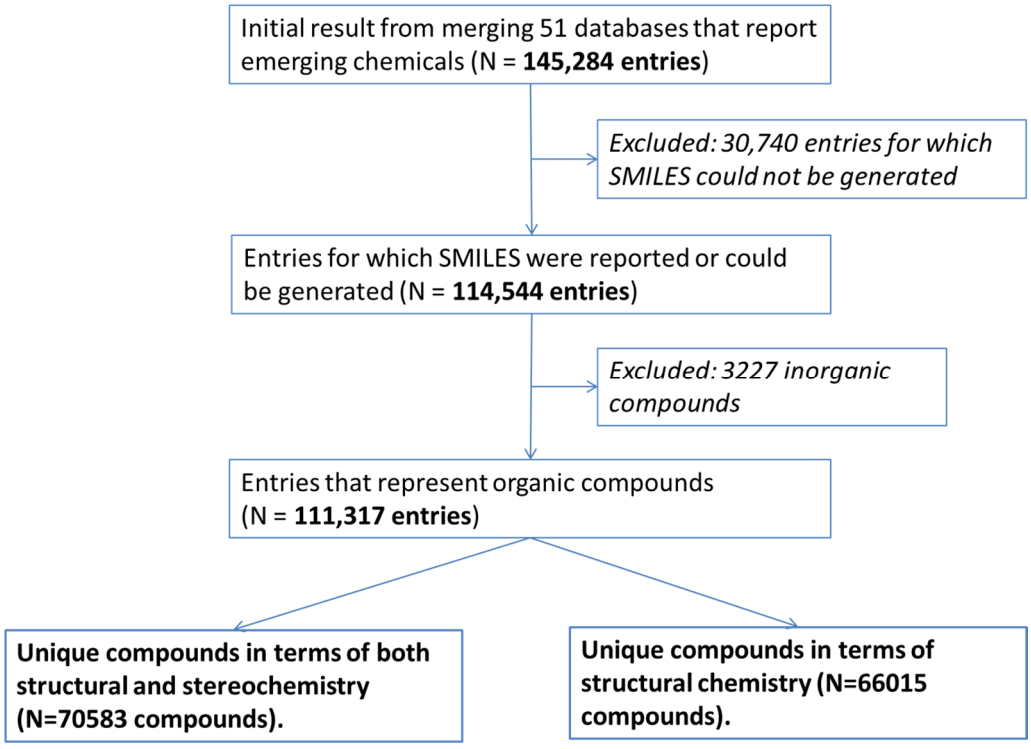

Figure 1: Flow diagram representing results from data curation and preparation of list for HRMS screening.

The complete database is available on request from Jelle Vlaanderen (Utrecht University): J.J.Vlaanderen@uu.nl

4 Conclusion

In the state, the elaborated inventory of already identified emerging compounds aggregates for the first time the main different sources of information related to this topic that are available at international level. Moreover, the intensive curation work that has been performed permitted to deal with the overlapping and redundancy of these various existing lists and databases, while improving the qualitative aspect of the inventory. In the context of the HBM4EU WP16, the further prioritisation within this inventory of exposure markers does not appear as a necessity or objective.

Indeed, the purpose of WP16 is now to develop and/or improve appropriate screening methods and related MS reference libraries permitting to detect a maximal number of these listed features, then to apply these approaches to a set of human urine and blood samples for documenting the real presence of these markers in human. The eventual prioritisation, or need for developing full quantitative and targeted methods for some of these markers, will be a matter of another work outside WP16 that will be possibly envisaged on the basis of the exploratory exposure data generated from the present work.

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