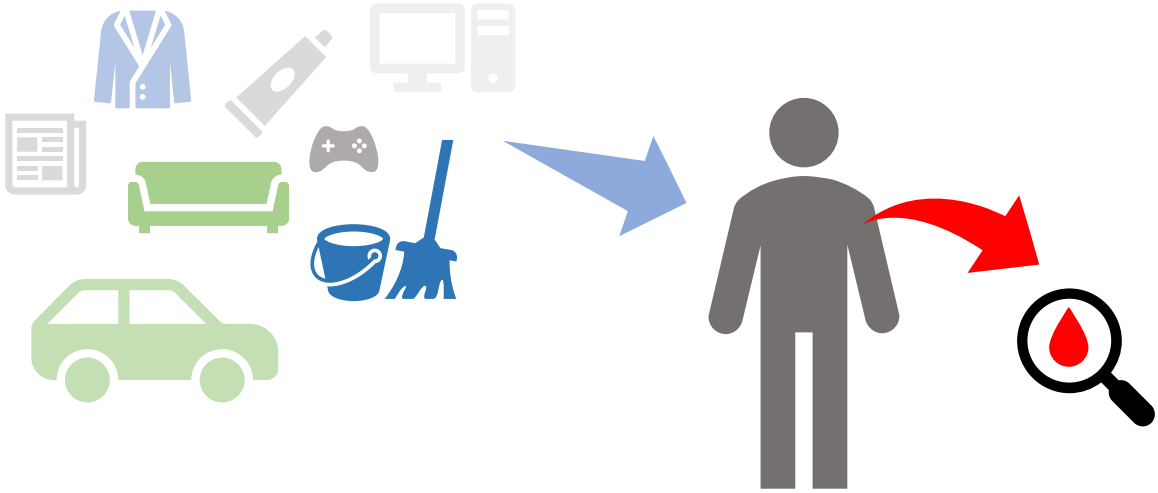
Identification of new and emerging risk chemicals and validation of the exposure index with a focus on humans

Jana Weiss[1], Josefin Engelhardt[1], Stellan Fischer[2] and Carl-Henrik Eriksson[2]



[1]Dept. Environmental Science, Stockholm University

[2]The Swedish Chemicals Agency, Sundbyberg

Rapport till Naturvårdsverket

Överenskommelse N2 21-20-010

Stockholm 2022-06-01

Rapportförfattare Jana Weiss, ACES Josefin Engelhardt, ACES Stellan Fischer, KEMI Carl-Henrik Eriksson, KEMI	**Utgivare** Institutionen för Miljövetenskap (ACES) Stockholms universitet **Postadress** Svante Arrheniusv. 8 SE-11418 Stockholm **Telefon** 08-672212
Rapporttitel och undertitel Identifiering av nya riskkemikalier och validering av exponerings index med fokus på människa	**Beställare** Naturvårdsverket 106 48 Stockholm **Finansiering** Hälsorelaterad miljöövervakning (HÄMI)
Nyckelord för plats	
Nyckelord för ämne NERCs, riskkemikalier, prioriteringsstrategi, Svenska produktregistret, antioxidanter	
Tidpunkt för insamling av underlagsdata 2020-01-01 – 2021-12-31	

Sammanfattning

Syftet med denna studie var att finna strategier för att identifiera nya riskkemikalier som vi människor kan bli exponerade för, baserat på den information som finns i Svenska produktregistret (SE-PR). En kombination av information om den registrerade användningen av kemikalier, och modellerade egenskaper som kan förutspå persistens och huruvida kemikalierna är benägna att bioackumuleras i mänskligt blod och urin användes. Med denna strategi kunde olika listor av prioriterade kemikalier som kunde potentiellt vara riskkemikalier i blod och urin hos människa presenteras.

Kort summerat: Kemikalier som är lätt biologiskt nedbrytbara bör övervakas i urin och icke biologiskt nedbrytbara bör analyseras i blod. Kemikalier med hög fördelningskoefficient för oktanol-luft (log K_{OA}> 8) bör prioriteras för analys både i blod och urin. Fördelningskoefficienten för oktanol-vatten delar upp de prioriterade kemikalierna i tre grupper; opolära (log K_{OW}> 6) och polära (log K_{OW} 3,5-6) kemikalier för analys i blod, och polära (log K_{OW} <4) kemikalier för analys i urin.

Med denna strategi prioriterades syntetiska antioxidanter som potentiella riskkemikalier både i blod. Med riktad kemisk analys kunde sex antioxidanter detekteras i en pool av blodprover från människor som bor i Stockholmsregionen.

Table of Contents

Summary

The overarching aim of this study was to investigate strategies to identify new and emerging risk chemicals (NERCs) of human concern. Comparing chemicals analysed in human blood, as reviewed in the human blood database (HBDB), with chemicals currently used and registered in the Swedish product register (SE-PR), a mismatch can be seen as typically already regulated chemicals are being monitored.

To identify NERCs of human concern, a combination of data has been used. For chemicals in SE-PR, an exposure index (EI) has been calculated based on use pattern, expressing the likelihood that the chemical will reach the recipient, here consumers and occupationally-exposed humans. For chemicals in HBDB, typical structural properties were derived representing chemicals that are persistent and prone to bioaccumulate in human blood. Similarly, structural properties for chemicals typically analysed in human urine were reviewed to be able to recommend target matrix for future monitoring. To achieve an as complete dataset as possible, OPERA *in silico* prediction models were used, available in CompTox (US EPA). Several models were investigated and the quality of the data generated were discussed.

The prioritization strategy was applied to chemicals with high $EI_{consumers}$ in SE-PR. The result suggests that chemicals that are readily biodegradable should be monitored in urine and chemicals not prone to biodegrade to be analysed in blood. Chemicals with a high octanol-air partition coefficient (log K_{OA} >8) are prioritized both in blood and urine. The octanol-water partition coefficient is dividing the prioritized chemicals into three groups; non-polar (log K_{OW}>6) and polar (log K_{OW} 3.5-6) chemicals for analysis in blood, and polar (log K_{OW} <4) chemicals for analysis in urine. With this strategy, synthetic phenolic antioxidants (SPAs) were top-prioritized as potential NERCs in blood. Six SPAs could be detected using target chemical analysis in a representative blood sample pool from humans living in Stockholm region.

Further, by using the list BLOODEXPOSOME, containing chemicals linked to blood derived from a text mining and database fusion approach, the exposure index for consumers ($EI_{consumers}$) were compared to the exposure index for occupationally ($EI_{occupational}$) exposed. The majority of the chemicals with a high $EI_{occupational}$ in SE-PR were also present in the BLOODEXPOSOME list, whereas only a fraction of the chemicals with a high $EI_{consumers}$ were included in the list. A possible explanation could be that occupational exposure is more investigated and reported in literature, and hence more data is available for the data harvested in the blood exposome project.

The prioritization strategy, as described for $EI_{consumers}$ was also applied to chemicals in SE-PR with high $EI_{occupational}$. Prioritized chemicals for blood analysis (non-polar, log K_{OW}>6) constituted mainly of SPAs, but also some brominated flame retardants with low value of the $EI_{consumers}$. As the $EI_{consumers}$ is not taking emission from products into consideration, many chemicals are assumed to only be of occupational concern. Several studies reporting exposure via e.g. dust demonstrates the opposite and thus, many more chemicals from products are potentially exposing consumers than predicted.

This study addresses the need to find strategies to identify NERCs and demonstrates how information in the SE-PR can be combined with easily accessible modelled properties to prioritize chemicals of human concern. Finally, identified shortcomings of the study are discussed, and recommended further research in the topic are listed.

Sammanfattning (Swedish summary)

Det finns en diskrepans mellan de kemikalier som analyserats i humant blod (sammanställt i en databas för humanblod, HBDB) och de kemikalier som för närvarande används (registrerade i det svenska produktregistret, SE-PR). Detta främst då det är de redan reglerade kemikalier som övervakas. Syftet med denna studie var därför att finna strategier för att identifiera nya riskkemikalier som vi människor kan bli exponerade för, baserat på den information som finns i SE-PR.

Data från olika källor sammanställdes och kombinerades för att kunna prioritera potentiella riskkemikalier. För kemikalier i SE-PR har exponeringsindex (EI) beräknats baserat på den registrerade användningen. EI uttrycker sannolikheten för att kemikalierna når mottagaren, i detta fall konsumenter och yrkesexponerade människor. Baserat på de kemikalier som finns i HBDB härleddes typiska strukturella egenskaper som kan användas för att förutspå persistens och huruvida kemikalierna är benägna att bioackumuleras i mänskligt blod. På liknande sätt granskades strukturella egenskaper för kemikalier som typiskt analyseras i mänsklig urin för att kunna rekommendera målmatris för framtida övervakning. För att uppnå en så komplett datauppsättning som möjligt användes OPERA *in silico* prediktionsmodeller som finns tillgängliga i CompTox (US EPA). Flera modeller undersöktes och kvaliteten på den data som genererades diskuterades för att skapa en prioriteringsstrategi.

Prioriteringsstrategin användes sedan för kemikalier med högt $EI_{konsument}$ i SE-PR. Resultatet tyder på att kemikalier som är lätt biologiskt nedbrytbara bör övervakas i urin och kemikalier som inte är benägna att bli biologiskt nedbrytbara bör analyseras i blod. Kemikalier med hög fördelningskoefficient för oktanol-luft (log K_{OA}> 8) bör prioriteras för analys både i blod och urin. Fördelningskoefficienten för oktanol-vatten delar upp de prioriterade kemikalierna i tre grupper; opolära (log K_{OW}> 6) och polära (log K_{OW} 3,5-6) kemikalier för analys i blod, och polära (log K_{OW} <4) kemikalier för analys i urin. Med denna strategi prioriterades syntetiska antioxidanter som potentiella riskkemikalier i blod. Med riktad kemisk analys kunde sex antioxidanter detekteras i en pool av blodprover från människor som bor i Stockholmsregionen.

Dessutom, för att jämföra exponeringsindexet för konsumenter ($EI_{konsument}$) med exponeringsindex för yrkesmässigt exponerade ($EI_{yrkesmässig}$) användes en lista som fanns tillgänglig i CompTox, BLOODEXPOSOME, som är resultatet från en automatisk textutvinning där alla kemikalier kopplade till blod har sammanställts. Det visade sig att majoriteten av kemikalierna med en hög $EI_{yrkesmässig}$ i SE-PR också fanns i BLOODEXPOSOME-listan, medan endast en bråkdel av kemikalierna med en hög $EI_{konsument}$ fanns med i listan. Detta indikerar att $EI_{yrkesmässig}$ bättre beskriver potentiell exponering till människa än vad $EI_{konsument}$ gör. En förklaringen kan vara att yrkesexponering är mer undersökt och rapporterad, vilket reflekteras i att mer data finns tillgänglig listan.

Prioriteringsstrategin, som beskrivs för $EI_{konsument}$ användes även för kemikalier i SE-PR med hög $EI_{yrkesmässig}$. Resultatet visade att prioriterade kemikalier för blodanalys (opolära, log K_{OW}> 6) hos yrkesmässigt exponerade huvudsakligen bestod av antioxidanter, men även några bromerade flamskyddsmedel fanns med i prioriteringslistan, vilka hade lågt $EI_{konsument}$. Eftersom $EI_{konsument}$ inte tar hänsyn till utsläpp från produkter, antas många kemikalier endast vara av yrkesmässig betydelse i beräkningen av EI. Flera studier som rapporterar exponering via t.ex. damm visar motsatsen och därför kan många fler kemikalier från produkter potentiellt exponera konsumenterna än vad som förutspåtts.

Denna studie tar upp behovet av att hitta strategier för att identifiera nya riskkemikalier, och visar hur informationen i SE-PR kan användas i kombination med information från tillgängliga modeller för att prioritera kemikalier som vi potentiellt kan vara exponerade för. Slutligen, brister som identifierats i studien diskuteras och en lista presenteras med rekommenderad fortsatt forskning.

1. Introduction

As the Technosphere is becoming more and more complex with chemicals prone to constitute a risk for human and environmental health, there is a need to identify new and emerging risk chemicals (NERCs). Most prioritization approaches to identify organic pollutants in the environment have been based on modelling the exposure and the effect (Burns et al. 2017; EEA 2011; Guillén et al. 2012), whereas others use data-driven approaches and suspect screening (Gago-Ferrero et al. 2018; Sjerps et al. 2016). The US Environmental Protection Agency's (EPA) ToxCast program aims to address these concerns by screening and prioritizing chemicals for potential human toxicity using *in vitro assays* and *in silico* approaches, e.g. for pesticides (Judson Richard et al. 2010). ExpoCast, initiated by US EPA, develop tools for rapid chemical evaluation based on potential for exposure (among others) and have demonstrated that information on use is a good factor for the prediction of new chemicals of concern relevant to human exposure (Mitchell et al. 2013; Wambaugh et al. 2013).

The Swedish Product Register (SE-PR), hosted by the Swedish Chemicals Agency (KEMI) contains information on more than 130 000 chemical products (substances or preparations) that are professionally produced in or imported into Sweden. The registry contains the chemical composition of chemical products, the use category and branch category for products, quantities, consumer availability and label symbol. To the chemicals in SE-PR, an exposure index (EI) has been calculated, expressing the likelihood that the chemical will reach the recipient/target matrix. This index can be used as the first selection criteria for prioritization.

There are few studies that have attempted to validate the EI, mainly towards water and sewage. Data on measured concentrations of organic chemicals in sewage treatment plants were compiled from the literature, and the correlation between predicted emission levels and observed concentrations was assessed by linear regression analysis (Undeman et al. 2011). The adequacy of the parameters employed in the EI was further explored by calibration of the model to measured concentrations. The EI for sewage treatment plant was found to be of limited use for ranking contaminant levels in STPs. There were several explanations to that, such as small dataset, high uncertainties in the chemical levels, and that chemical property data could be improved. Another approach used focused on the identities, more than the levels of the chemicals in wastewater (Gago-Ferrero et al. 2018). They used advanced liquid chromatography coupled to high resolution mass spectrometry (LC-HRMS) to screen for chemicals with high exposure index in the SE-PR. A total of 160 chemicals were prioritized for the suspect screening, mainly consisting of scarcely investigated chemicals, which resulted in successfully identification of 23 chemicals.

The RiskMix project is focusing on risk assessment of complex chemical mixtures. As a first step a review of all organic contaminants (OCs) that have been identified in human blood was made and a human blood database (HBDB) created (Engelhardt et al. Submitted to Exposure & Health 2022). In this study, the chemicals in HBDB have been used to characterize the typical properties of OCs ending up in human blood, and applied to the chemicals in SE-PR with a high $EI_{Consumer}$ for prioritization of potential NERCs of human concern.

1.1 Aim of the project

The project is divided into four tasks:

1. Compare the human biomonitoring data compiled within RiskMix with the corresponding exposure index to humans (EI consumers and occupational) in the Swedish product register (SE-PR) to validate the EI as a tool of relevance to identify NERCs
2. Extract and prioritise organic chemicals with a high EI in SE-PR hosted by KemI for further evaluation in real samples
3. Expand the EI to predict the distribution in humans, i.e. to identify the most suitable matrix for biomonitoring programs
4. Perform target chemical analysis of selected prioritised chemicals using the large pools of human blood sample acquired from different population in the RiskMix project to further validate the EI as a tool of relevance to identify NERCs

Together, these tasks will help understanding how the chemicals registered in SE-PR can be used in the search for NERCs of human concern. The method and results sections describe and present the databases used and prioritization strategies, whereas in the conclusions the specific tasks are specifically addressed again. Finally, several lists of prioritized potential NERCs are provided. Although, the main purpose of this study is to identify properties to be used for prioritization purposes, which could be implemented on a regular basis on databases such as the SE-PR.

2. Method

2.1 Databases

Three databases have been used for this study (Table 1); a newly established database on anthropogenic organic chemicals reported in human blood (the human blood database, HBDB); the database of registered chemicals in the Swedish product register (SE-PR); and, a first review of anthropogenic organic chemicals analysed in human urine. Details about the first two databases are provided below.

Table 1. Overview of databases used for the project.

Database	Description	Chemicals	Reference
SE-PR	Currently used chemicals on the Swedish market with an assigned high EI	922	www.kemi.se
HBDB	Anthropogenic OCs reported in human blood	394	(Engelhardt et al. Submitted to Exposure & Health 2022)
Urine	Anthropogenic OCs reported in urine	97	www.cdc.gov/nchs/nhanes/

For the purpose of Task 3, a characterization of properties typically found for chemicals analysed in urine was reviewed. Data was gathered from two sources, i.e. chemicals reported in the National report on Human Exposure to Environmental Chemicals (NHANES) from United States Centers for Disease Control and Prevention (CDC), and chemicals reported in Swedish EPA's Health-related environmental monitoring (HÄMI) database. In total, 149 chemicals were listed, of which 113 chemicals have been reported above detection limit.

2.1.1 SE-PR

The Swedish Products Register (SE-PR) is a database including information about chemical products manufactured in, transferred within or imported into Sweden. The SE-PR contains information regarding usage, composition of the chemical products and volumes and the register consists of more than 200,000 chemical products. Today, nearly 3 000 companies have to provide data on their chemical products to the SE-PR when the annual volume of the chemical product reaches 0.1 tonnes or if the

chemical product's customs tariff number is listed in the Swedish Customs list Annex 1 of the Chemical Products and Biotechnical Organisms Ordinance. In addition, since February 2020, all chemical products (regardless of annual volume) containing intentionally added per- and polyfluoroalkyl substances (PFASs) needs to be reported into the SE-PR if the company's annual turnover is above 5 million SEK. The SE-PR contains chemicals on the Swedish market, but the information on potential exposure can only be estimated. Another limitation is that articles imported to Sweden are not included.

To the chemicals in SE-PR, an exposure index (EI) has been calculated by first defining a use index describing the general potential of a chemical to be released from a specific type of use (Fischer et al. 2006; Undeman et al. 2011). This is done for each specific quantity of a chemical in the product concerned. Use index values are then added together for the substance concerned to give a substance-specific use index. Then, quantitative data for a substance are used to calculate the EI. This methodology calculates index values for six different recipients representing surface water, soil, air, sewage treatment plant and human consumer and occupational. The EI only describes the potential of a recipients to be exposed to the chemical. It does not take into consideration any of the inherent properties of the chemical, which can for example be essential for the bioavailability, stability etc. As proposed in this project, by using a combination of information on use pattern, production volumes, physicochemical properties and *in silico* modelling the most problematic chemicals regarding exposure can be prioritized for further investigation.

2.1.2 Human blood database

The human blood database (HBDB) was created for the RiskMix project to gather the anthropogenic organic chemical profile that has been analysed in human blood (Engelhardt et al. Submitted to Exposure & Health 2022). That database is, up to date, the most comprehensive list of anthropogenic organic chemicals analysed for in human blood there is, although it does not claim to be all-inclusive as only a limited literature review was performed.

In short, chemicals reported as analysed for in human blood in the scientific literature (including the peer-reviewed extended abstracts of the Dioxin conference) and chemicals reported in international biomonitoring programs, such as the ones coordinated by CDC (NHANES) and SE-EPA (HÄMI), were collected. In total 559 organic contaminants have been analysed for, out of which 440 OCs were also reported above limit of detection. The majority of the chemicals (54%) in HBDB are so-called persistent organic pollutants (POPs) regulated by the Stockholm Convention (http://www.pops.int/), and another 9% are metabolites thereof.

2.2 Chemical property collection

CompTox Chemicals Dashboard was released in August 2016 to provide public access to chemical data (Williams et al. 2017). It 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. Today, more than 900,000 chemicals are in the database (https://comptox.epa.gov/dashboard). The main purpose of CompTox is to support EPA's computational toxicology research efforts to develop innovative methods for environmental and health risk assessments.

Easily accessible information about the chemicals investigated in this study were collected from CompTox. Experimental data is generally the priority information to be used over modelled data. Although, experimental data is often lacking for many chemicals, thus, QSAR modelled data in OPERA was used for the prioritization purpose in this study to be able to collect an as comprehensive dataset as possible. OPERA is a tool available in CompTox providing a suite of property predictions from the National Center for Computational Toxicology at the US Environmental Protection Agency (Mansouri

et al. 2018). It is a free and open-source suite of QSAR models providing predictions on physicochemical properties, environmental fate and toxicity endpoints. The OPERA predicted properties are derived from carefully curated data (Mansouri et al. 2016). By using the offline version of OPERA (available for download here: https://github.com/NIEHS/OPERA) more detailed data is provided, such as the prediction range and applicability domain. In this study, the focus has been to identify properties typical for chemicals which can become human blood contaminants, hence properties describing persistence and bioaccumulation. The investigated models are described in Table 2, together with the number of chemicals in the training set for the models. Table 2 also contain the percentage of chemicals in the three dataset that are within the applicability domain of the model. For bioaccumulation the octanol-water (K_{OW}) and octanol-air (K_{OA}) partition coefficients and the bioconcentration factor (BCF) were investigated. For persistence, the biodegradation half-life (BioHL), ready biodegradability (Ready Biod), whole-body primary biotransformation rate (KM) and the atmospheric hydroxylation rate (AOH) were investigated.

In CompTox it is possible to use a batch search function (max 10,000 entries) where basic information on chemicals (molecular weight, monoisotopic mass, chemical formula etc.), *in silico* modelled properties as well as information whether or not the chemical is present in over 300 lists can be extracted. These lists are associated with a project, publication, source database, or other collections addressing toxicity, exposure, substances of concern and much more. Here we have used the list BLOODEXPOSOME containing 20,483 chemicals which have been linked to blood by using text mining and database fusion approach (Barupal and Fiehn 2019). The purpose was to get a first indication if the prioritized chemicals already have been analysed in blood and reported in literature. The chemicals in BLOODEXPOSOME list were also compared to the EI to humans (consumer and occupational) to see if a the EI was reflected by the chemical's presence in the list.

2.3 Chemical prioritization strategy

The aim of Task 2 was to find a prioritization strategy to identify potential NERCs in SE-PR targeting human exposure. As a first step, chemicals in SE-PR with a high EI to consumers were investigated. Secondly, also chemicals in SE-PR with a high occupational EI were investigated. In addition, in Task 3 the aim was to expand the strategy to identify the most suitable matrix for the prioritized NERCs. Here we have investigated the difference in chemical properties targeting blood and urine. The properties of chemicals analysed in human blood and urine were collected and used to define typical chemical properties in the two matrices. The prioritization was made based on the most prominent properties in each matrix and the goal was to extract lists of chemicals targeting either blood or urine. Further, for confirmation of the strategy a selection of prioritized chemicals was further investigated with chemical target analysis of human blood.

2.4 Target analysis of prioritized chemicals for confirmation

The aim of Task 4 was to perform target analysis in human blood of prioritized chemicals in SE-PR for confirmation of the strategy. Chemicals from top-priority list, Prio 1 (Table 4) were selected for exposure confirmation by chemical target analysis in human blood. The two chemicals were 2,4,6-Tris(tert-butyl)phenol (2,4,6-TtBP) and 4,4'-Methylenebis(2,6-di-t-butylphenol) (4,4-MBP), which are synthetic phenolic antioxidants (SPAs). Structurally resembling antioxidants (phenols with tert-butyl substituents) from SE-PR (high $EI_{consumer}$) were also included in the analysis (Table 5).

A rigorous method development was performed to identify sources of background contamination and optimization of method parameters and is published elsewhere (Arvstrand 2021) The method is based on two previous studies that have analysed SPAs in human blood (serum and plasma) (Du et al. 2019; Liu and Mabury 2018). In summary, the following method was used on human serum samples: 2 mL

serum was added to a 15 mL centrifuge tube together with 3 mL isohexane (iHX) and with 5 ng surrogate internal standard (BHT-D21). Before gentle rocking (20 min) on the test tube tilt shaker (SWELAB 440), aluminum foil was used to cover the tube to minimize contamination identified from the caps. The test tube was centrifuged at 3000 rpm for 5 min. The supernatant was transferred to another 15 mL tube, and the sample was extracted two more times with 3 mL iHX. The pooled extract was evaporated under a stream of nitrogen, lead through metal tips to avoid contamination from rubber tubes, to roughly 1 mL. The sample was loaded onto a pre-washed (5 mL iHX:DCM 1:1) 0.5 g 5% H2O silica gel column, packed in a Pasteur pipette. The sample was eluted with 5 mL iHX:DCM 1:1 and the sample eluent evaporated under a gentle stream of nitrogen gas to ca 0.2 mL. The extract was transferred to a vial with 5 ng of a volumetric internal standard (CB189) and end volume was 300 µL.

The chemical analysis was performed on a GC-MS system (Agilent 7890A GC, 5975C inert EI/CI MSD Triple-Axis Detector and 7693 Autosampler US). An electron ionization (EI) method was used, with a DB-5MS (30 m, 0.25 mm x 0.25 µm, Agilent J&W U.S) column using helium as carrier gas at constant flow of 1.25 mL/min, with initial temp 50°C, hold for 2.2 min, then 25°C/min to 180°C and hold for 3 min. Then 25°C/min to 310°C and hold for 12 min. Injection of 1 µL was done in splitless mode with 255°C injection temperature. The transfer line held at 310°C, MS quad 150°C MS source 230°C.

The method limit of detection (MDL) and quantification (MQL) were determined by the detected or quantifiable levels in the serum and based on the background contamination determined in sampling and method blank samples. Lowest MDL was achieved for the target SPA 2,4,6-TtBP (0.002 ng/mL) and highest MDL for 2,2'-MBP (0.6 ng/mL).

The target analysis was performed on a pooled human serum sample, constituted of 100 individuals donating blood at Blodcentralen in Odenplan, Stockholm in February 2020 (Ethic approval Dnr 2022-00032-01). The average age was 47 years old (19-75 years) and 63% were male. The final method was applied on the sample pool, which were analysed in triplicates.

3. Results

3.1 HBDB and SE-PR comparison

The purpose of Task 1 was to investigate whether the chemicals that are currently being used also are being monitored. For that purpose, CAS-numbers were used to search for the HBDB chemicals in the SE-PR (not restricted to chemicals with high EI to humans). Information on the volumes (tonnes) and years in the SE-PR database (1995-2019) were also collected.

In total, 69 of 394 chemicals monitored in HBDB were also registered in SE-PR. As the majority of the chemicals in HBDB are POPs which are regulated under Stockholm Convention, many of them were already phased out in 1992 when the SE-PR started the registration, such as the PCBs. Thus, we did not expect to find these chemicals in SE-PR. Still, 8 POPs were found in SE-PR, i.e. TCDD, BDE209, g-HCH, PCB, PCP, HCB, PFOS and PFOA. In addition, 13 PAHs could also be found in SE-PR and HBDB. It was not possible to extract information about the use of these chemicals from SE-PR.

The chemicals in HBDB with largest yearly volumes reported in SE-PR correspond to industrial solvents (n=17). These industrial chemicals are only analysed by the US CDC's National Biomonitoring Program (US-CDC 2019) and many of the reported levels in human blood are below quantification levels (Engelhardt et al. Submitted to Exposure & Health 2022).

Chemical groups with data on quantities registered in SE-PR between 1992-2019 are presented in Appendix 1, i.e. alkylphenols, bisphenols, chlorinated paraffins, flame retardants, parabens, chemicals in personal care products, phthalates and UV-filters. Decreasing time trends for the quantities in SE-

PR could be seen for 4-nonylphenol, TBBPA, short- and medium-chain chlorinated paraffins, BDE209, triclosan, several phthalates (BBzP, DEHP, DBP, DEP, DNOP), benzophenone-1 and oxybenzone. Increasing time trends could be seen for the unregulated bisphenol AF, ethylparaben, and galaxolide.

3.2 Molar weight distribution of the chemicals in the three databases

The distribution of the molar weight of the chemicals in the three datasets are presented in Figure 1. The OCs in HBDB are generally heavier than the OCs in urine, peaking around 300-400 g/mol. Characteristic for POPs are that they are aromatic and halogenated, which increase the molar weight compared to the smaller and hydrophilic OCs found in urine. The chemicals currently being used and registered in SE-PR are generally lighter, peaking at 200 g/mol, although 14% (n=126) of the chemicals have a molar weight between 300-400 g/mol.

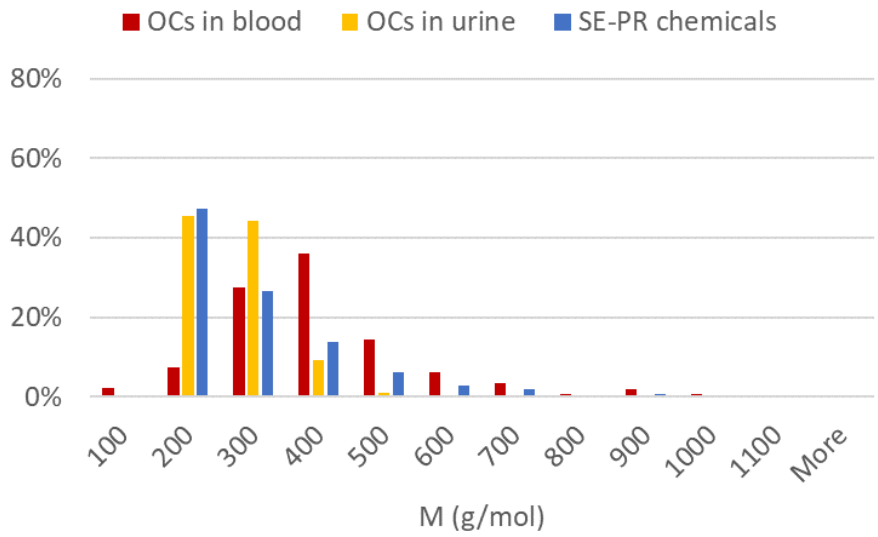


Figure 1. The distribution of molar weight (M) for chemicals in HBDB, in urine database and SE-PR

3.3 OPERA prediction models for prioritization of NERCs

In Table 2 the OPERA prediction models are investigated regarding the coverage of the applicability domain of the chemicals in the three datasets. The purpose is to use the applicability domain as an indication of qualitative prediction, i.e. the chemical structure spaces in which the model makes predictions with a given reliability. Thus, the probability of an erroneous prediction of a chemical structure not covered by the model is larger and results should therefore be interpreted with care.

3.3.1 Persistence

With a focus on the chemicals in HBDB, the chemical structure space coverage was >80% for all models except for one, the biodegradation half-life (Table 2). This model is based on the smallest dataset of experimentally tested chemicals (Mansouri et al. 2018). Consequently, only 20% of the chemicals in the SE-PR are within the applicability domain of the biodegradation half-life (Table 2), reflecting that degradation half-lives still have not been measured for most chemicals in commerce. Thus, the model is not suitable for predicting and identifying potential NERCs in this set of chemicals.

The ready biodegradation test is an uncomplicated and less expensive screening and results are available for many more chemicals. Several test guidelines for evaluating the ultimate biodegradation, i.e. the complete mineralization of chemicals, have been provided by the Organization for Economic Co-operation and Development (OECD) and is used by REACH for screening for PBT chemicals (ECHA 2017). Almost 1200 chemicals are in the training dataset for ready biodegradability of organic

chemicals and >90% of the chemicals in SE-PR are within the applicability domain. The experimental data for the model is tested according to OECD ready-biodegradability 301 which measures the biochemical oxygen demand (BOD) in aerobic aqueous medium for 28 days. Chemicals with a BOD value higher than 60% are considered as readily-biodegradable while those with a BOD lower than 60% are regarded as non-readily biodegradable.

The biotransformation rate constant in fish is based on a study that describes the biotransformation pathways as a function of structural and electronic descriptors, conducted on a set of amide-containing compounds (Helbling et al. 2010). In OPERA that model covers 12 descriptors for organic chemicals in fish and 548 chemicals are in the training set. Almost 90% of the chemicals in HBDB are within the applicability domain and 74% of the chemicals in SE-PR. Slightly less chemicals are covered for the atmospheric hydroxylation rate (84% in HBDB and 65% in SE-PR). Chemicals prone to hydroxylate before reaching the recipient, here humans, are less likely to persistent and bioaccumulate. Therefore, it was of interest to see if chemicals typically found in human blood would be less reactive.

Table 2. OPERA models investigated, abbreviation and details on the models training set (Mansouri et al. 2018). The coverage of the applicability domain of the three databases are given in percentage.

Opera model	Short name	Chemicals in training dataset	Chemicals within the applicability domain		
			HBDB (n=394)	Urine (n=97)	SE-PR (n=922)
Biodegradation half-life (days) for compounds containing only carbon and hydrogen	BioHL	151	59%	10%	20%
Ready biodegradability of organic chemicals	Ready Biod	1196	87%	99%	92%
The whole-body primary biotransformation rate constant for organic chemicals in fish	KM	548	89%	85%	74%
Hydroxylation rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals	AOH	818	84%	58%	65%
The octanol-water partition coefficient	K_{OW}	14 544	95%	98%	89%
The octanol-air partition coefficient	K_{OA}	277	93%	64%	70%
Fish bioconcentration factor	BCF	618	92%	91%	75%

3.3.2 Bioaccumulation

Previous studies have shown that high octanol-water (K_{OW}) and high octanol-air (K_{OA}) partition coefficients are typical properties of chemicals that are found in humans and biota (Czub and McLachlan 2004; Kelly et al. 2007). In addition, Kelly and co-workers described that chemicals with a low K_{OW} can to a high degree enter the food web containing air-breathing organisms (including humans) if they also have a high K_{OA}, leading to a low rate of respiratory elimination to air (Kelly et al. 2007). Bioconcentration refers to direct transfers of the chemical from the surrounding environmental medium into the animal, i.e. for a fish, bioconcentration of a substance in the water includes direct uptake from water through its gills. Bioconcentration models for humans are more complex due to the many exposure pathways. Thus the bioconcentration factor (BCF) determined in fish is commonly used to illustrate general bioaccumulation.

The chemical regulation of EU REACH sets a K_{OW} >4.5 and Log K_{OA} >5 and BCF>2000 as chemicals that are prone to bioaccumulate (ECHA 2017). According to US-EPA, BCFs greater than 1000 are of concern, and beyond 5000 indicate chemicals that are of high risk concern (US-EPA 2015). More than 90% of the chemicals in HBDB are within the applicability domain of these three models, as well as more than 70% of the chemicals in SE-PR.

3.4 Selection of properties for prioritization of potential NERCs in human blood and urine

Based on the typical modelled properties listed in Table 2, found for OCs in human blood and urine the priority criteria are set for potential NERCs in SE-PR.

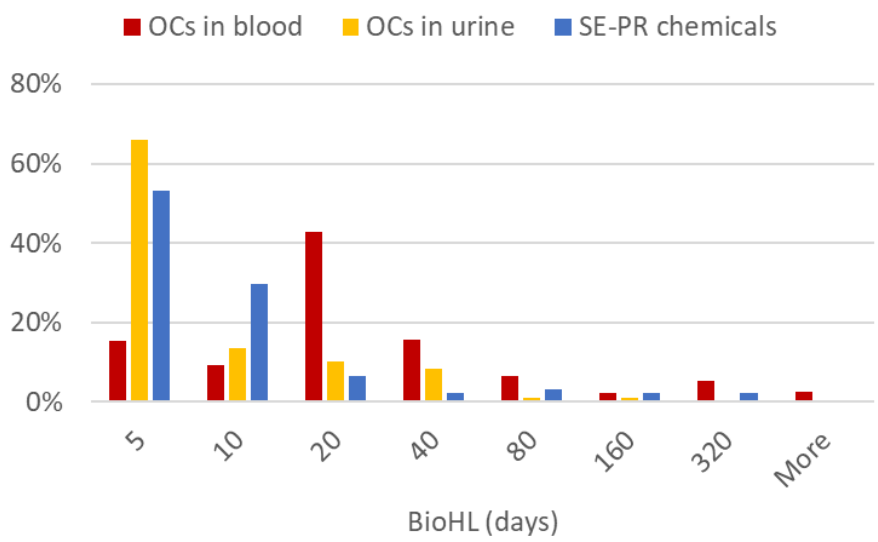


Figure 2. The distribution of biodegradation half-life (BioHL) for chemicals in HBDB, in urine database and SE-PR

The biodegradation half-life is generally longer for the chemicals found in human blood than in urine, which is expected (Figure 2). Despite that, as only few chemicals in all three datasets are within the applicability domain of this model the prediction is not considered robust for prioritization and will not be used. The ready biodegradable test on the other hand showed promising robustness. Only 8% of the chemicals in HBDB are biodegradable, whereas as much as 85% of the chemicals in urine are predicted to be biodegradable, as expected since this is an indication of excretion (Table 3). Thus, as a first step in the prioritization strategy, chemicals in SE-PR that are biodegradable are potential urine NERCs and those that are not are potential blood NERCs (Figure 8).

Table 3. The percentage of chemicals modelled from the three datasets that are predicted ready biodegradable.

Dataset	Number of chemicals modelled	Ready biodegradable
Human blood database	394	8%
Urine analysis	97	85%
SE-PR with a high $EI_{consumer}$	922	61%

The biotransformation rate (KM) clearly separates the chemicals found in human blood and urine (Figure 3). The majority of the chemicals in blood have a log KM between 2-3 days. This criterion is not suitable for the prioritization of potential NERCs in human blood as almost all chemicals in SE-PR have a log KM <2. Thus, this model is not used in the prioritization strategy as the whole range of KM values are interesting for blood analysis.

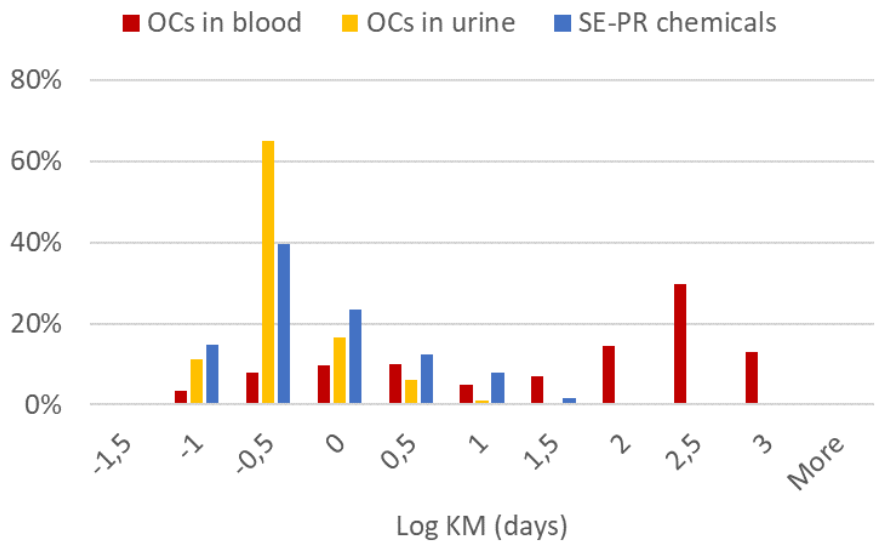


Figure 3. The distribution of log biotransformation rate (log KM) for organic chemicals in fish for chemicals in HBDB, in urine database and SE-PR

Similar pattern is observed for the atmospheric hydroxylation rate (AOH). The majority of the blood related OCs in HBDB have log AOH of -12 cm^3/mol sec (Figure 4). Only very few chemicals in SE-PR have that low hydroxylation rate. In addition, in urine only 58% of the chemicals were within the applicability domain for the AOH prediction. This together makes this model unsuitable for the prediction of NERCs in humans and is not included in the prioritization strategy.

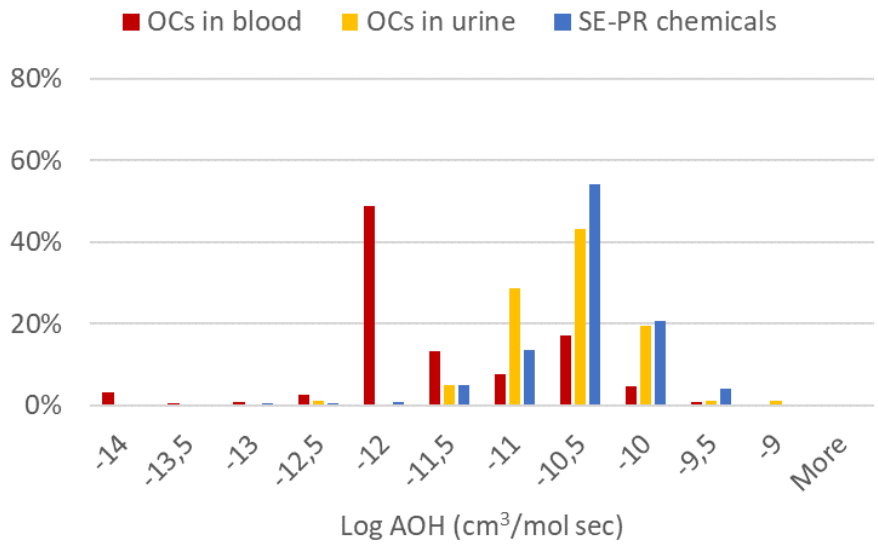


Figure 4. The distribution of logarithmic atmospheric hydroxylation rate (log AOH) for chemicals in HBDB, in urine database and SE-PR

A high octanol-air partitioning (log K_{OA} >6) is essential for chemicals to bioaccumulate in air-breathing organisms such as humans (Czub and McLachlan 2004; Kelly et al. 2007). This is clearly visual in Figure 5, where the majority of OCs in both blood and urine have a log K_{OA} >8. In NHANES, an ongoing exposure of the more volatile solvents are monitored which are the group of chemicals with a log K_{OA} 3-5 (CDC 2019). In addition, the per- and polyfluoroalkyl carboxylic and sulfonic acids also have a predicted log K_{OA} <6. For the prioritization process, chemicals with a log K_{OA} >8 are considered potential blood NERCs, and chemicals with a log K_{OA} 8-10 are considered potential urine NERCs (Figure 8).

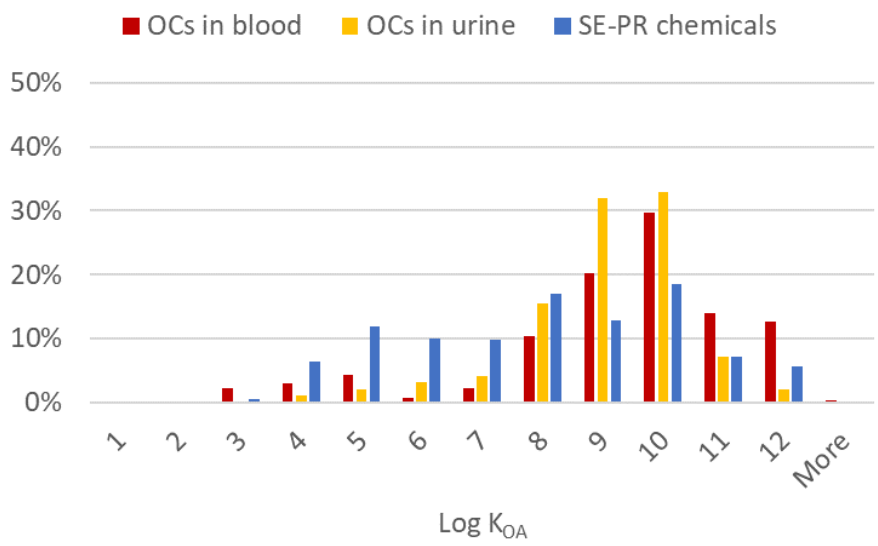


Figure 5. The distribution of logarithmic octanol-air partition coefficient (log K_{OA}) for chemicals in HBDB, in urine database and SE-PR

The distribution of chemicals spanning over the K_{OW} range is clearly separating the blood related OCs (log K_{OW} >5) and urine related OCs (log K_{OW} <6). By setting a cut-off criteria of log K_{OW} >6 the chemicals will be prioritized for NERCs in blood (Figure 8). There is another group of chemicals with lower hydrophobicity (log K_{OW} 3.5-6) in HBDB which are metabolites of POPs and phenolic chemicals. These

chemicals are gaining increasing attention due to their potential health effects, such as on the endocrine system (WHO/UNEP 2013). Therefore, a separate group for chemicals fulfilling this criterion is created for prioritization for blood analysis (Figure 8). The majority of the chemicals in urine have a log K_{OW} <4, which is used for prioritization for urine analysis (Figure 8).

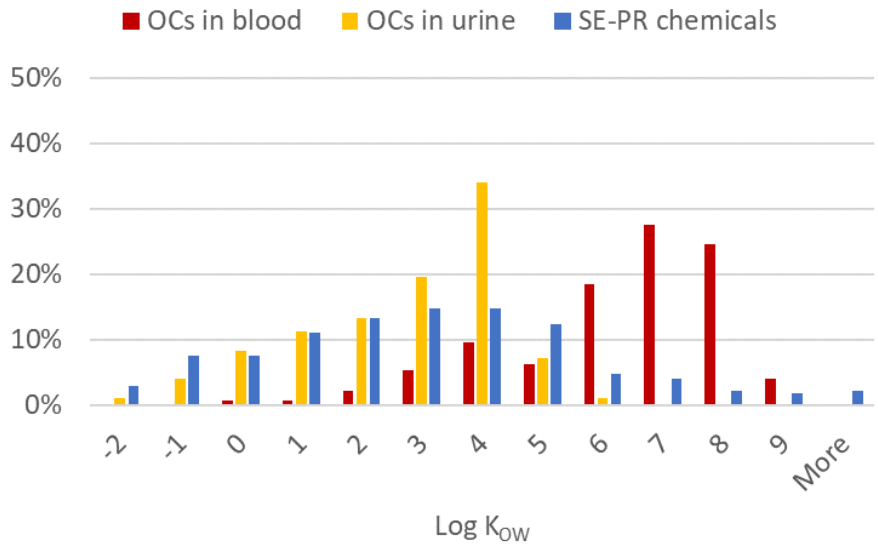


Figure 6. The distribution of logarithmic octanol-water partition coefficient (log K_{OW}) for chemicals in HBDB, in urine database and SE-PR

Around 52% of the OCs in HBDB have a high (>10 000) BCF, whereas in urine the BCFs are <1000. For prioritization, a cut-off of 2000 L/kg is used for chemicals of risk of bioaccumulation according to REACH. Here we could see that 48% of the chemicals in HBDB have an evenly distributed BCF indicating the BCF is not a measurement for bioaccumulation in humans but for fish. In addition, all chemicals in HBDB that are not biodegradable, with log K_{OA}>8 and log K_{OW}>6 have a BCF>100 L/kg. Therefore, Prio 1-3 in human blood all have a predicted BCF>100 (Figure 8). For urine analysis, chemicals with a BCF <1000 are all selected for prioritization.

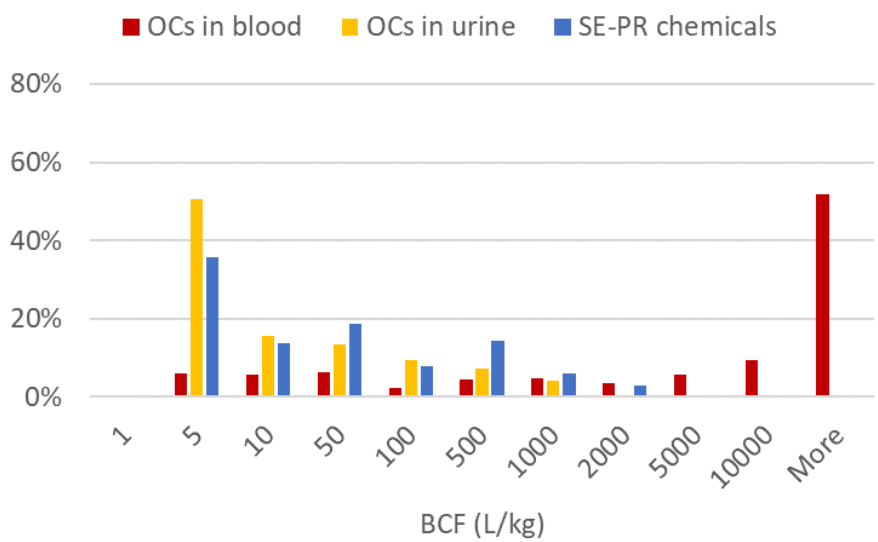


Figure 7. The distribution of bioconcentration factor (BCF) for chemicals in HBDB, in urine database and SE-PR

3.5 Prioritization of potential NERCs in human blood and urine

The chemicals in the SE-PR database used here all have a high probability of exposure to humans according the $EI_{Consumer}$. The chemicals are further prioritized for monitoring in human blood or urine according the prioritization scheme presented in Figure 8. Three groups are identified: For blood analysis, typical POPs which are lipophilic and persistent (Prio 1-2, n=16, Table 4), less lipophilic chemicals, e.g. pesticide metabolites and phenolic chemicals (Prio 3, n=50, Appendix 2), and finally the biodegradable chemicals to be monitored in urine (Prio 1 in urine, n=123, Appendix 3). In comparison, 52% of the chemicals in HBDB fulfil the criteria for Prio 1, 56% for Prio 2 and 13% of for Prio 3. Chemicals in HBDB that do not fulfil the Prio 1-3 criteria are e.g. the parabens and phthalates (as they are ready biodegradable), the PFAAs and PFSAs (log K_{OA}<6) and UV-filters (BCF <100). These chemicals are representing another group of chemicals of concern which need to be identified with other complementary strategies.

As expected, not all chemicals in SE-PR are well known and covered for in the models training/validation sets. This was considered by indicating whether or not the chemical is within the applicability domain for the model in the list of the prioritized chemicals. These values should be read with care and need experimental confirmation. As experimental values are rare, the models would benefit from performing experiments on structurally complementing chemicals to expand the applicability domain. This would lead to more reliable models which could be implemented already in the design of the chemicals before being released on the market.

Only 4 chemicals were modelled to have the properties typical for POPs, and high probability to be found in human blood. Two of them are tert-butyl phenols (2,4,6-TtBP and 2,2'-MBP) used as synthetic phenolic antioxidants (SPAs), and were selected for further confirmation of the strategy by target analysis of human blood.

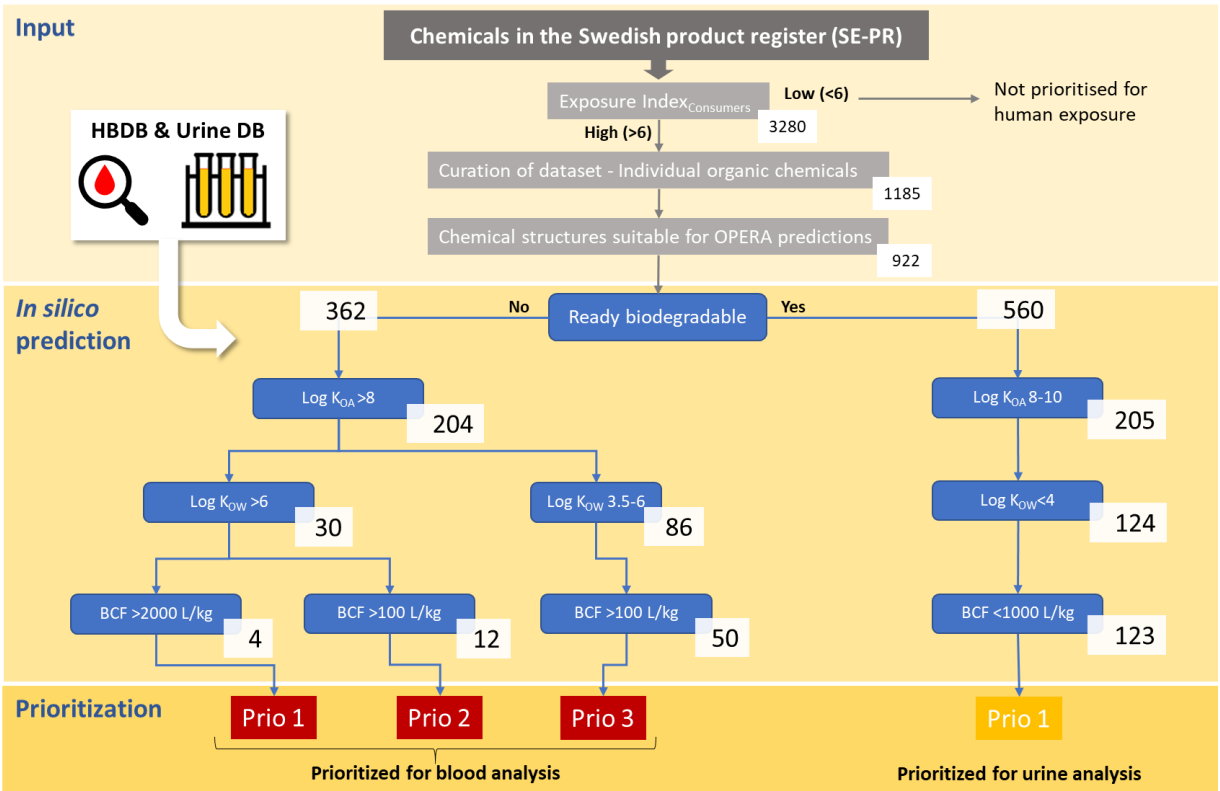


Figure 8. Prioritization scheme for potential new or emerging risk chemicals to be searched for in human blood or urine.

Table 4. Chemicals with Prio 1 and 2 predicted as potential new or emerging risk chemicals to be monitored in human blood are listed with the CAS identifier, preferred chemical name (according CompTox) and molar mass (M). The OPERA modelled predictions for octanol-air (KOA) and octanol -water (KOW) partition coefficients, bioconcentration factor (BCF), atmospheric hydroxylation rate and biotransformation rate constant (KM) are reported, and values with an Asterix (*) indicates that the chemical structures are outside the applicability domain. Chemicals already reported in human blood exposome according to Barupal and Fiehn (Barupal and Fiehn 2019) are indicated with a yes (Y).

CAS no	Chemical name	M (g/mol)	Log K_{OA}	Log K_{OW}	BCF (L/kg)	Log AOH (cm3/mol sec)	Log KM (days)	Blood exposome
Prio 1 for blood analysis								
732-26-3	2,4,6-Tris(tert-butyl)phenol	262.4	9.7	6.1	13804	-10.78	1.81	Y
1745-89-7	4,4'-Isopropylidenebis(2-allylphenol)	308.4	9.3*	6.0	2455	-10.02*	0.26	-
15721-78-5	N,N-Bis(4-tert-octylphenyl)amine	393.7	10.3*	9.9*	6166*	-10.54*	0.72*	-
118-82-1	4,4'-Methylenebis(2,6-di-t-butylphenol)	424.7	9.6*	8.3*	2884*	-10.55*	-0.25*	Y
Prio 2 for blood analysis								
52315-07-8	Cypermethrin	416.3	11.7	6.6	339	-10.47*	0.7	Y
52918-63-5	Deltamethrin	505.2	11.7	6.2	324	-10.47*	0.51	-
301-02-0	(9Z)-Octadec-9-enamide	281.5	11.1	7.2	933	-10.30*	-0.04	-
50-32-8	Benzo(a)pyrene	252.3	9.6	6.1	1096	-10.11*	0.05	Y
24448-20-2	(1-Methylethylidene)bis(4,1-phenyleneoxy-2,1-ethanediyl) bismethacrylate	452.5	11.7	6.4	112	-9.94*	0.87*	-
50530-43-3	5-(Dodecyldithio)-1,3,4-thiadiazole-2(3H)-thione	350.6	10.8	6.2*	490	-10.77*	0.54	-
119-47-1	2,2'-Methylenebis(4-methyl-6-tert-butylphenol)	340.5	9.4*	6.3	550	-10.64*	0.03	Y
80584-90-3	2-Ethyl-N-(2-ethylhexyl)-N-[(4-methyl-1H-benzotriazol-1-yl)methyl]hexan-1-amine	386.6	11.7	6.1*	219	-10.55*	0.8*	-
6535-46-2	C.I. Pigment Red 112	484.8	9.7*	6.1	407	-10.69*	-0.75*	-
7695-91-2	Acetic acid alpha-tocopherol	472.8	11.7	9.2*	1479*	-10.61*	0.54*	Y
89347-09-1	1,3,4-Thiadiazole, 2,5-bis(tert-nonyldithio)-	466.8	11.7*	8.6*	417*	-10.63*	1.03	-
10191-41-0	alpha-Tocopherol	430.7	10.3*	9.4*	1698*	-10.63*	-0.02*	Y

3.6 Comparing $EI_{consumer}$ and $EI_{occupational}$ using the BLOODEXPOSOME list

The BLOODEXPOSOME list, which was included in the batch search in CompTox and added to the list of prioritized chemicals for human blood analysis in Table 4, is from a "Blood exposome project" (Barupal and Fiehn 2019). They used an automated text mining and database fusion approach to extract all chemicals being associated to blood (Barupal and Fiehn 2019). The immense amount of data gathered in BLOODEXPOSOME has not been manually curated and errors or missing blood data can occur. The erroneous links could be irrelevant due to studies investigating distribution after administration, chemicals listed for analysis but not detected, or lacking data as sufficient chemical identification was missing. The quality of the data provided by the BLOODEXPOSOME list has not been evaluated in this project, although the list has been used as indication of blood exposure.

In the Prio 1-3 lists for blood analysis, 25 chemicals (38%) are indicated to have been reported in association to blood in the BLOODEXPOSOME list. In total, 350 chemicals (38%) in SE-PR with a high $EI_{consumers}$ are indicated in the BLOODEXPOSOME list. To further evaluate the use of the list to identify NERCs, chemicals in SE-PR register were searched for in BLOODEXPOSOME list and the EI to humans compared, i.e. answering if there is a correlation between high EI to humans and presence on the BLOODEXPOSOME list. Both the EI for consumers and occupational exposure was compared.

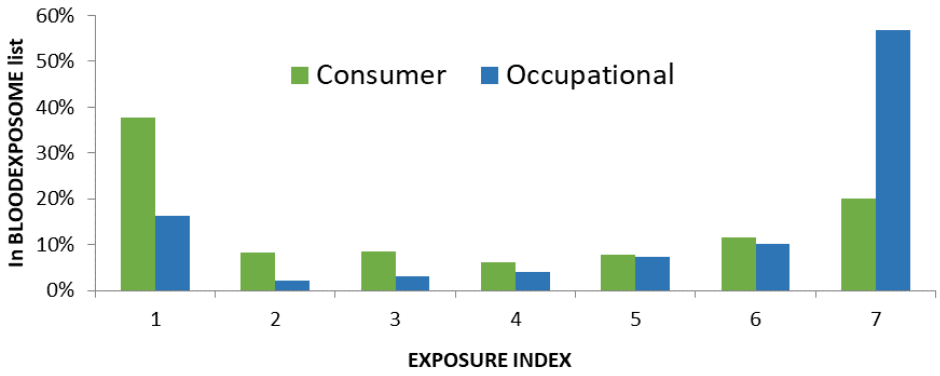


Figure 9. Chemicals present in the BLOODEXPOSOME list compared to the exposure index (1-7) allocated for consumer and occupational exposure predicted in SE-PR.

Of the organic chemicals in SE-PR listed 2018 and with an EI calculated, 1475 individual chemicals could be found in the BLOODEXPOSOME list. The majority of the $EI_{consumer}$ was only 1, whereas the majority of $EI_{occupational}$ was 7 (Figure 9). A possible explanation could be that the emissions of chemicals in products are not included in the calculations of the EIs, and therefore it is erroneously assumed that only people working with the production (occupational) are exposed. Another explanation could be that occupational exposure is more investigated and reported, and hence more data is available for the data harvested in the blood exposome project.

The strategy presented for prioritization of NERCs based on high $EI_{consumer}$ was performed on the list of chemicals with high $EI_{occupational}$. On the Prio 1 list for blood analysis, based on the EI to occupationally exposed humans 21 chemicals could be found; half of them are antioxidants (Appendix 6). All four Prio 1 chemicals from the $EI_{consumer}$ based predictions are present. Interestingly, the $EI_{consumer}$ is only 1 for most of the Prio 1 chemicals with high $EI_{occupational}$. Four novel brominated flame retardants are on the Prio 1 list for occupational exposure, chemicals found in for example household dust (Zuiderveen et al. 2020). Two of them are reported in the BLOODEXPOSOME list. This illustrates that the exposure to many of the chemicals in products is not limited to occupational exposure. The exposure index to

consumers is not taking emission from products into consideration. Thus, many more chemicals from products are potentially exposing consumers than predicted.

3.7 Target analysis of SPA in human serum

The results from the target analysis of the SPAs in Prio 1 list; 2,4,6-TtBP and 4,4'-MBP together with 4 additional SPAs are reported in Table 5. On Prio 2 list the 2,2'-MBP can be found, and 2,4-DtBP and BHT are on the Prio 3 list and OPP is not prioritized due to a predicted BCF <100. Four of the SPAs have previously been reported in plasma from China (Du et al. 2019), and 3 SPAs have been analysed for in serum from the US (Liu and Mabury 2018). 2,4-DtBP and BHT were found within the same range as previously reported, although the BHT in the reference sample was quite high. Low, but quantifiable levels of 2,4,6-TtBP were found in the pooled serum sample.

Levels above the max concentration of the calibration curve were indicated for the 2,2'-MBP in the pooled serum sample analysed in triplicate. Due to time constraints this analysis was not repeated. The SPAs are included in future analysis of serum samples and the levels will then be confirmed. 4,4'-MBP and OPP were detected in the pooled serum sample, but below quantification level.

Table 5. Target analysis of selected prioritized antioxidants; the method quantification limit (MQL) and levels (ng/mL) found in human serum samples in this study, and compared to literature data.

				This study- Sweden		*US (Liu and Mabury 2018)*	*China (Du et al. 2019)*
CAS	**Chemical name**	**Short**	**MQL**	**Pooled serum**	**Reference serum**	**Serum**	**Plasma**
96-76-4	2,4-Di-tert-butylphenol	2,4-DtBP	0.16	2.6±0.5	4.1±0.6	3.7-15	0.35-4.0
128-37-0	Butylated hydroxytoluene	BHT	0.67	3.6±0.5	84±4.2	2.6-22	0.36-64
732-26-3	2,4,6-Tris(tert-butyl)phenol	2,4,6-TtBP	0.006	0.08±0.02	<LOD	<LOD	<LOD-0.14
119-47-1	2,2'-Methylenebis(4-methyl-6-tert-butylphenol)	2,2'-MBP	2.0	>2000*	<LOD	n.a.	0.05-81
118-82-1	4,4'-Methylenebis(2,6-di-t-butylphenol)	4,4'-MBP	0.17	<LOQ	<LOD	n.a.	n.a.
2082-79-3	Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate	OPP	1.1	<LOQ	<LOD	n.a.	n.a.

*Outside calibration curve and need to be confirmed not to be a background contamination. n.a. not analysed

The SPAs selected for target analysis all had a high $EI_{consumer}$. The tonnage for the SPAs reported in SE-PR are shown in Figure 10 and the number of products is presented in Appendix 4. Highest tonnage can be seen for BHT and OPP. High BHT levels in human blood could reflect that, whereas the low BCF value of OPP could be the reason for not finding it in high levels in blood. Low tonnage is registered in SE-PR for 2,4-DtBP, but in REACH it is considered a high production volume chemical (>1000 tonnes), just as BHT, 2,2'-MBP and OPP (>10 000 tonnes).

Both in the US and in EU the 2,4,6-TtBP was recently considered a PBT (ECHA 2018; US-EPA 2021). According to the information in SE-PR, the 2,4,6-TtBP tonnage decreased to almost zero in 2019, and the number of products is also very low (Figure 10 and Appendix 4). In REACH, the tonnage registered in EU is 100-1000 tonnes and the substance is described to be used by professional workers, not

consumers. The $EI_{occupational}$ value is also 7. The exposure can also come from products where 2,4,6-TtBP has been used and where emission is not foreseen.

Similar conclusion can be drawn for 4,4'-MBP. It is currently under evaluation for PBT and the tonnage registered in REACH is between 100-1000 tonne annually. All SPAs except the 2,4,6-TtBP are, according REACH, being used by consumers, in articles and by professional workers (widespread uses). Thus, a high $EI_{consumer}$ is more likely for these SPAs. More detailed information on products and industry from SE-PR, as well as functional use from CompTox, can be found in Appendix 5.

Figure 10. Tonnage registered in SE-PR for the target analytes.

4. Discussion

To further develop the input parameters of the exposure index applied to the chemicals in SE-PR was not the scope of this project, but it is a suggestion to do that. There are indications in this study that a refinement is necessary to ensure robust exposure prediction. The goal in this study was to validate whether or not the chemicals with a high exposure index to consumers constitute a risk for human exposure. To do that, we have applied a prioritization strategy to identify potential NERCs and then searched for those chemicals in human serum. We could detect the two top prioritized SPAs 2,4,6-TtBP (>LOQ) and 4,4'-MBP (>LOD) in the human blood pooled sample representing the general population of Stockholm 2020. In addition, four more SPAs with high probability to be exposed to consumers were

confirmed to be present in blood (>LOD). Analysis of individual samples is planned to determine the general spread in the population.

Although not applicable to the six SPAs selected for further investigation here, the tonnage registered in SE-PR could potentially be used as an early warning for potential NERCs. Chemicals not regulated, e.g. the bisphenol A analogue BPAF is increasing on the market and should be monitored to ensure that the population, and especially sensitive subgroups are not exposed. The majority of the regulated OCs in HBDB have a clear decreasing trend in the registered tonnage in SE-PR, illustrating the reaction from the market after regulation. The information gathered in SE-PR is valuable and could be used to monitor for new and upcoming chemicals and trends based on volumes or products. The information is not comprehensive though, as a large volume of chemicals in articles being imported to Sweden are not covered in the registry. Therefore, the strategy presented here is a tool to find problematic chemicals in a limited dataset, and should be complemented with other databases, such as the collaboration between the Nordic countries via the SPIN database (http://spin2000.net/).

For convenience, CompTox provides an executive summary of three physicochemical properties considered safe; green area log K_{OW} 2-7; log BCF <5; log VP <-1 (Figure 11). These are not in accordance with the properties of the chemicals found in the HBDB. To illustrate, we have used the physicochemical properties of DDT in Figure 11, which is considered safe for the environment according to CompTox.

We have shown that log K_{OW} <6 is of relevance for human exposure (Figure 6), especially considering the currently used chemicals that we know less of (than the well characterized POPs). The BCF is a measurement of bioconcentration capacity in fish and is less appropriate for predicting human bioaccumulation. Even so, it is an indicator of bioavailability. In the HBDB, chemicals with BCF from 5 and upwards are present, although the majority of the chemicals have a BCF >10 000 (log BCF 4), of which 142 chemicals have a BCF >100 000 (Figure 7). As suggested by US EPA, the cut off value for "safe" chemicals is <100 000 (log BCF 5), and up to 10 000 000 000 (log BCF 10) "acceptable" (yellow). ECHA consider chemicals prone for bioaccumulation at a BCF >2000 (Annex XIII, section 1.1.2).

A high vapour pressure (VP) results in that chemicals are distributed to the air and could be transferred to remote areas. It could also increase the risk for humans and animals to inhale it. This is most probably the reason for CompTox to define that chemicals with a log VP >0.1 mmHg to be problematic (red). A high K_{OA} is the result of low partition to air and high partition to the octanol phase, i.e. it is dependent on the K_{OW} and VP. In accordance with the results here, log K_{OA} >6 has been demonstrated to increase the probability for chemicals to biomagnify both in air-breathing and water respiring organisms (Kelly et al. 2007). We therefore question the choice to project vapour pressures below 0.1 mmHg as safe by CompTox.

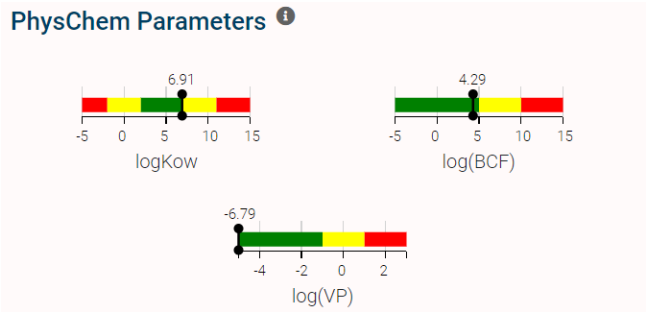


Figure 11. From Executive Summary for DDT in CompTox. Information text: "These PhysChem Parameters are those of primary concern for the distribution and bioavailability of chemicals in the environment: logP, Bioconcentration Factor and Vapor Pressure. The color coding illustrates the acceptable ranges."

5. Conclusion

The major conclusions are here presented divided into the four project tasks:

1. Compare the human biomonitoring data compiled within RiskMix with the corresponding exposure index to humans (EI consumers and occupational) in the Swedish product register (SE-PR) to validate the EI as a tool of relevance to identify NERCs

Results in section 3.1. Most of the chemicals that have been analysed in blood are regulated chemicals with an already historical use. This illustrates the need to update the monitoring programs to identify NERCs that are currently used and to which humans are exposed.

2. Extract and prioritise organic chemicals with a high EI to humans (consumers and occupational) in SE-PR hosted by KemI for further evaluation in real samples

Results in section 3.3-3.6. In this project a first attempt was made to identify chemical properties that could be used to predict if a chemical would potentially become a NERC. The strategy was to investigate a series of *in silico* prediction models available from OPERA and apply them to databases of analysed chemicals in two matrices, blood and urine. The prioritization strategy was applied to chemicals with high $EI_{consumers}$ in SE-PR. Three priority lists targeting two different groups of potential NERCs, for non-polar (Prio 1-2) and polar chemicals (Prio 3) were created for human blood analysis. In addition, one list of prioritized chemicals for human urine was also created. On the Prio 1 list for human blood analysis synthetic phenolic antioxidants (SPAs) could be found. This group of chemicals could also be found when applying the strategy on chemicals with high $EI_{occupational}$. Generally, chemicals reported in blood from the blood exposome project have a higher $EI_{occupational}$ than $EI_{consumer}$, which could be a result from that emissions from products are not considered in the calculation of the EI.

3. Expand the EI to predict the distribution in humans, i.e. to identify the most suitable matrix for biomonitoring programs

Results in section 3.3-3.6. In this project a first attempt was made to predict whether a chemical would be found in human blood or urine based on their chemical properties. The strategy was to use structural information from analysed chemicals in the two matrices, and to identify differences that could be used for prediction of the distribution. Most evident was that a high log K_{OW} and high BCF value indicated chemicals prone to be distributed in blood, whereas chemicals prone to undergo transformation is more suitable to analyse in urine. Although sufficient as guidance, these general observations could be biased based on that more persistent and lipophilic chemicals have been reported in blood, and that generally, less persistent and more polar chemicals are analysed for in urine. There are indications that the latter are also distributed to blood, and thus, also blood could be a suitable matrix for the monitoring of less persistent, more polar chemicals. To better investigate this, the distribution should be measured after administration in controlled experiments, and also include metabolites, to be able to identify suitable matrices.

4. Perform target chemical analysis of selected prioritised chemicals using the large pools of human blood sample acquired from different people in the RiskMix project to further validate the $EI_{consumers}$ as a tool of relevance to identify NERCs

Results in section 3.7. Based on the chemicals on the Prio 1 list, an analytical method was tested and validated for the analysis of 6 SPAs in human blood. All 6 chemicals were detected in a human blood pool representing the average of 100 individuals in Stockholm 2019. The analysis method need further optimization, which is currently ongoing. It can be concluded that chemicals prioritised as potential NERCs in SE-PR could be found in human blood. The correlation of the magnitude of the exposure vs

the exposure index was not the scope here. A number of individual samples will be analysed to investigate the variance in levels and the detection frequency.

6. Identified shortcomings and recommended further research

- The exposure index is a rough estimation of the probability of a chemical to be within the close vicinity of the recipient. Properties of the product, such as use category, volume, number of products and for $EI_{consumer}$ also the consumer availability are being used for the calculation. The index does not take the chemical product composition into account, i.e. whether or not it is probable that a chemical migrates out of the product. The chemical properties such as volatility, and emission rates are also not considered, which would strongly influence the exposure probability to the consumers. These values are not commonly available from the producers. Further refining of the exposure index taking emissions from products into account is recommended, when possible.
- The applicability domain of many *in silico* models needs to be expanded to cover the large universe of chemicals being used on the market. As experimental data on physicochemical properties of many of the chemicals are lacking, there is an urgent need to predict the properties by using robust *in silico* models to ensure that "safe" (sustainable) chemicals are being used on the market. We recommend to expand the applicability domain, which could be done by identifying a set of representative chemical structures being used on the market (nationally/internationally) to be tested in appropriate experimental settings.
- No transformation (biotic and abiotic) products have been considered in this first-tier prioritization strategy. This is an important mechanism that should be included to a) refine the characterization of the chemical and its fate, b) identify problematic transformation products, and c) to better identify the targeted matrix to monitor. Several *in silico* prediction tools are available and could easily be added to the strategy. The data generated need to be evaluated and confirmative chemical analysis performed.
- To confirm the exposure route, chemical lists, such as for the blood exposome (Barupal and Fiehn 2019), which are directly available for database matches in CompTox are valuable. We suggest to use text mining to regularly update the list for blood exposome. Also, a similar list for urine associated chemicals should be created, which can be used for curation. In addition, with curation of the data the anthropogenic, organic contaminants could be extracted to be used to further improve the prediction of NERCs in urine.
- The strategy presented here could be extended to predict NERCs in other human matrices such as breast milk and cord blood to identify chemical exposure to a vulnerable sub-population, or to environmental matrices such as waste water and sludge to validate the exposure index for those matrices. For that purpose, comprehensive reviews of chemicals found in recipients could provide the information on property values that could be used in the prioritization strategy.
- Just as in this study, final confirmation based on qualitative chemical analysis should be performed on prioritized chemicals and those structurally resembling. The exposure levels, variation in the population and identification of sources will together enable proper chemical management and form the basis for the decision to further implement the chemical in monitoring programs. For that proper analytical methods are needed, preferably including the analysis of the transformation products/metabolites.
- The information registered in SE-PR could be used to flag chemicals that shows an increasing trend in use or changes in use pattern. By automatically applying the additional *in silico* models to the chemical identifiers an early warning system would be implemented. This would facilitate the analysis of trends in chemical structures, functions and production volumes, just to mention some.

References

Arvstrand L (2021) Target analysis of synthetic phenolic antioxidants inhuman serum, prioritized by using an exposure index applied to the Swedish Products Register. Stockholm university

Barupal DK, Fiehn O (2019) Generating the Blood Exposome Database Using a Comprehensive Text Mining and Database Fusion Approach Environmental Health Perspectives 127:097008 doi:doi:10.1289/EHP4713

Burns EE, Thomas-Oates J, Kolpin DW, Furlong ET, Boxall ABA (2017) Are exposure predictions used for the prioritization of pharmaceuticals in the environment fit for purpose? Environ Toxicol Chem 36:2823-2832

CDC (2019) Fourth National Report on Human Exposure to Environmental Chemicals.

Czub G, McLachlan MS (2004) Bioaccumulation Potential of Persistent Organic Chemicals in Humans Environmental Science & Technology 38:2406-2412 doi:10.1021/es034871v

Du B et al. (2019) Prevalence, Biotransformation, and Maternal Transfer of Synthetic Phenolic Antioxidants in Pregnant Women from South China Environmental Science & Technology 53:13959-13969 doi:10.1021/acs.est.9b04709

ECHA (2017) Guidance on Information Requirements and Chemical Safety Assessment. Part C: PBT/vPvB assessment. European Chemicals Agency,

ECHA (2018) Substance Evaluation Conclusion as required by REACH Article 48 and Evaluation Report for 2,4,6-tri-tert-butylphenol vol EC No 211-989-5. Belgian Federal Public Service Health,

EEA (2011) A modelling approach for the prioritisation of chemicals under the water framework directive. Luxembourg: Office for Official Publications of the European Communities. doi:10.2788/76427

Engelhardt JE, Norström K, Weiss JM (Submitted to Exposure & Health 2022) Anthropogenic organic contaminants analysed in human blood and cumulative risk

Fischer S, Almkvist Å, Karlsson E, Åkerblom M (2006) Final report on the project: Preparation of a Product Register based ExposureIndex. Stockholm, Sweden

Gago-Ferrero P, Krettek A, Fisher SW, Wiberg K, Ahrens L (2018) Suspect screening and regulatory databases: A powerful combination to identify emerging micropollutants Environmental Science & Technology 52:6881-6894

Guillén D, Ginebreda A, Farré M, Darbra RM, Petrovic M, Gros M, Barcelo D (2012) Prioritization of chemicals in the aquatic environment based on risk assessment: Analytical modeling and regulatory perspective. Science of The Total Environment 440:236-252

Helbling DE, Hollender J, Kohler H-PE, Fenner K (2010) Structure-Based Interpretation of Biotransformation Pathways of Amide-Containing Compounds in Sludge-Seeded Bioreactors Environmental Science & Technology 44:6628-6635 doi:10.1021/es101035b

Judson Richard S et al. (2010) In Vitro Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project Environmental Health Perspectives 118:485-492 doi:10.1289/ehp.0901392

Kelly BC, Ikonomou MG, Blair JD, Morin AE, Gobas FAPC (2007) Food web-specific biomagnification of persistent organic pollutants Science 317:236-239

Liu R, Mabury SA (2018) Synthetic Phenolic Antioxidants and Transformation Products in Human Sera from United States Donors Environmental Science & Technology Letters 5:419-423 doi:10.1021/acs.estlett.8b00223

Mansouri K, Grulke C, Judson R, Williams A (2018) OPERA: A free and open source QSAR tool for predicting physicochemical properties and environmental fate endpoints

Mansouri K, Grulke CM, Richard AM, Judson RS, Williams AJ (2016) An automated curation procedure for addressing chemical errors and inconsistencies in public datasets used in QSAR modelling SAR and QSAR in Environmental Research 27:911-937 doi:10.1080/1062936X.2016.1253611

Mitchell J, Pabon N, Collier ZA, Egeghy PP, Cohen-Hubal E, Linkov I, Vallero DA (2013) A decision analytic approach to exposure-based chemical prioritization PloS one 8:e70911-e70911 doi:10.1371/journal.pone.0070911

Sjerps RMA, Vughs D, van Leerdam JA, ter Laak TL, van Wezel AP (2016) Data-driven prioritization of chemicals for various water types using suspect screening LC-HRMS Water Research 93:254-264

Undeman E, Fisher S, McLachlan MS (2011) Evaluation of a novel high throughput screening tool for relative emissions of industrial chemicals used in chemical products Chemosphere 82:996-1001

US-EPA (2015) Estimating Persistence, Bioaccumulation, and Toxicity Using the PBT Profiler - In: Sustainable Futures / P2 Framework Manual 2012 EPA-748-B12-001.

US-EPA (2021) 2,4,6-tris(tert-butyl)phenol (2,4,6-TTBP); Regulation of Persistent, Bioaccumulative, and Toxic Chemicals Under TSCA Section 6(h). Federal Register - The Daily Journal of the United States Government

Wambaugh JF et al. (2013) High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project Environmental Science & Technology 47:8479-8488 doi:10.1021/es400482g

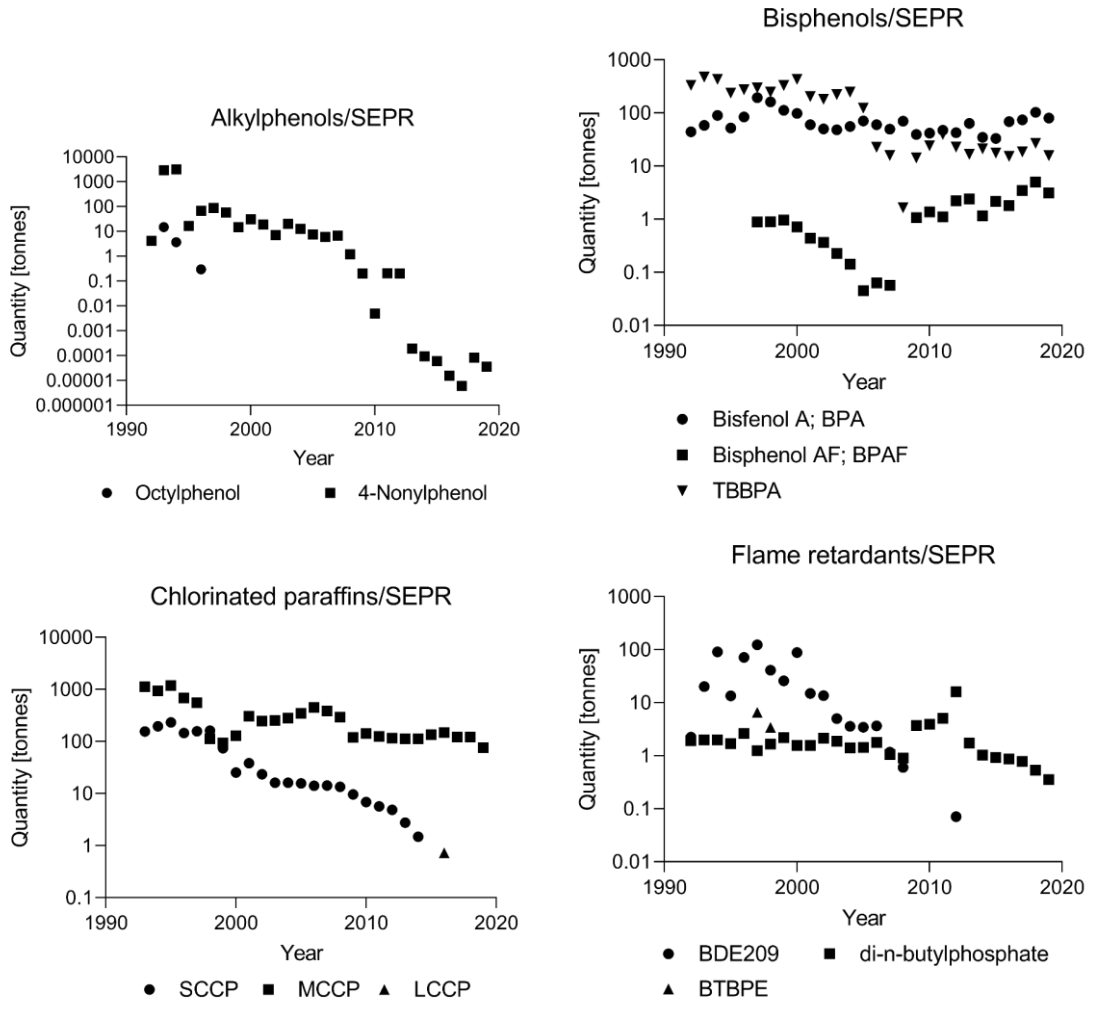
WHO/UNEP (2013) State of the science of endocrine disrupting chemicals - 2012. Geneva, Switzerland

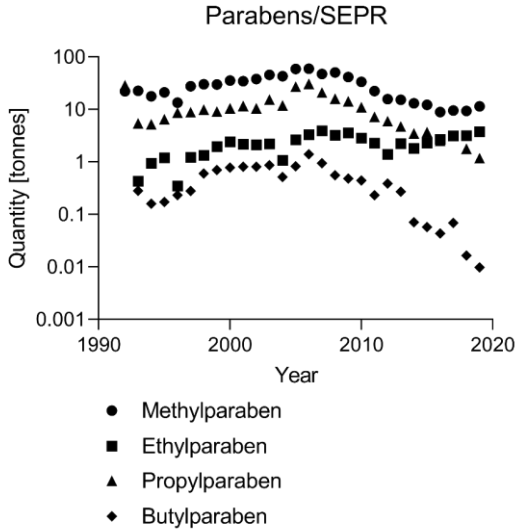
Williams AJ et al. (2017) The CompTox Chemistry Dashboard: a community data resource for environmental chemistry Journal of Cheminformatics 9:61 doi:10.1186/s13321-017-0247-6

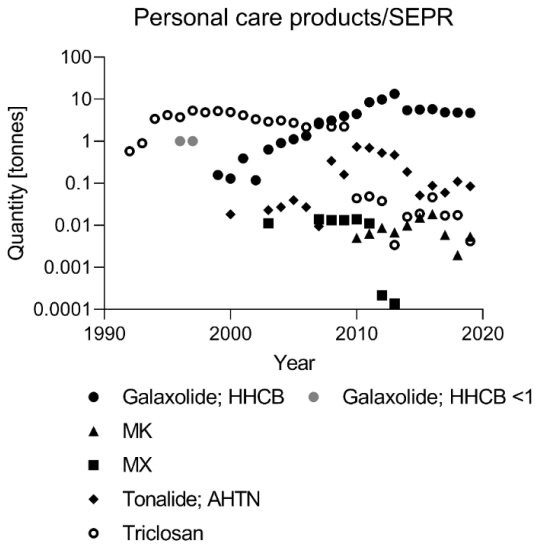
Zuiderveen EAR, Slootweg JC, de Boer J (2020) Novel brominated flame retardants - A review of their occurrence in indoor air, dust, consumer goods and food Chemosphere 255:126816 doi:https://doi.org/10.1016/j.chemosphere.2020.126816

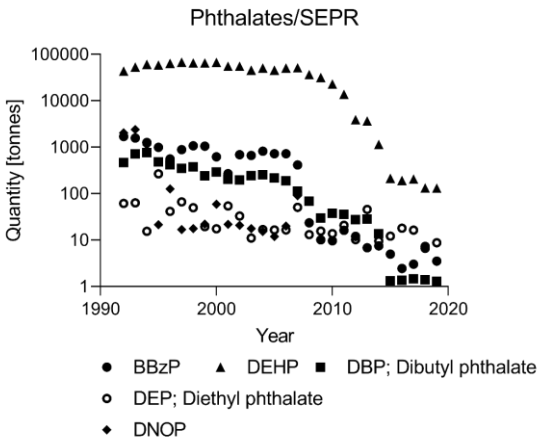
APPENDICES

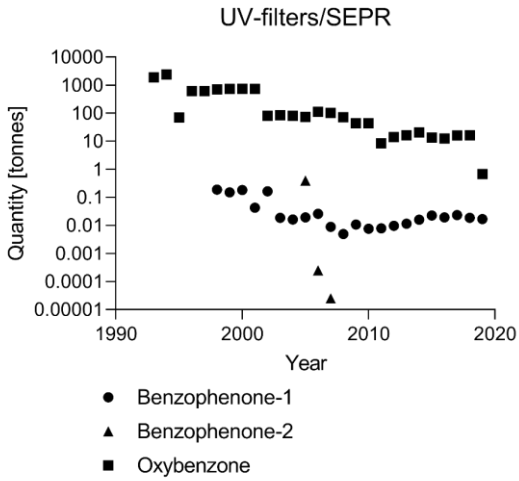
Appendix 1. Quantity (tonnes) registered in SE-PR between 1992-2019 of a selection of chemicals present in HBDB.




Parabens/SEPR
Quantity [tonnes]
100
10
1
0.1
0.01
0.001
1990
2000
2010
2020
Year
Methylparaben
Ethylparaben
Propylparaben
Butylparaben


Personal care products/SEPR
Quantity [tonnes]
100
10
1
0.1
0.01
0.001
0.0001
1990
2000
2010
2020
Year
Galaxolide; HHCB
Galaxolide; HHCB <1
MK
MX
Tonalide; AHTN
Triclosan


Phthalates/SEPR
Quantity [tonnes]
100000
10000
1000
100
10
1
1990
2000
2010
2020
Year
BBzP
DEHP
DBP; Dibutyl phthalate
DEP; Diethyl phthalate
DNOP


UV-filters/SEPR
Quantity [tonnes]
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
1990
2000
2010
2020
Year
Benzophenone-1
Benzophenone-2
Oxybenzone

Appendix 2. Chemicals with Prio 3 predicted as potential new or emerging risk chemicals to be monitored in human blood are listed with the CAS identifier, preferred chemical name (according CompTox) and molar mass (M). The OPERA modelled predictions for octanol-air (KOA) and octanol -water (KOW) partition coefficients, bioconcentration factor (BCF), atmospheric hydroxylation rate and biotransformation rate constant (KM) are reported, and values with a red font indicates that the chemical structures are outside the applicability domain. Chemicals already reported in human blood exposome according to Barupal and Fiehn (Barupal and Fiehn 2019) are indicated with a yes (Y).

CAS no	Chemical name	M (g/mol)	Log K_{OA}	Log K_{OW}	BCF (L/kg)	Log AOH (cm3/mol sec)	Log KM (days)	Blood exposome
597-82-0	Phosphorothioic acid, O,O,O-triphenyl ester	342.4	11.7	4.3	1380	-10.74	0.19	-
90-30-2	N-Phenyl-1-naphthylamine	219.3	11.0	4.2	1698	-10.93	-0.18	Y
101-02-0	Triphenyl phosphite	310.3	10.8	4.1	490	-10.28	0.25	Y
92-84-2	Phenothiazine	199.3	10.3	4.2	355	-10.73	0.04	Y
603-35-0	Triphenylphosphine	262.3	9.9	5.7	741	-10.86	0.56	Y
1809-14-9	Dioctyl phosphonate	306.4	9.8	4.8	457	-10.74	0.05	-
128-37-0	Butylated hydroxytoluene	220.4	9.3	5.1	1072	-10.84	0.32	Y
70788-30-6	Cyclohexanepropanol, 2,2,6-trimethyl-.alpha.-propyl-	226.4	9.3	3.9	251	-10.62	0.47	-
28219-61-6	2-Ethyl-4-(2',2',3-trimethylcyclopent-3'-enyl)but-2-enol	208.3	9.2	4.3	155	-9.78	-0.27	-
139504-68-0	2-Butanol, 1-[[2-(1,1-dimethylethyl)cyclohexyl]oxy]-	228.4	9.2	4.3	102	-10.72	-0.19	-
140-66-9	4-(1,1,3,3-Tetramethylbutyl)phenol	206.3	8.7	4.9	288	-10.78	-0.04	Y
128-39-2	2,6-Di-tert-butylphenol	206.3	8.7	4.9	427	-10.83	-0.05	-
96-76-4	2,4-Di-tert-butylphenol	206.3	8.7	5.2	251	-10.83	-0.37	Y
5875-45-6	Phenol, 2,5-bis(1,1-dimethylethyl)-	206.3	8.7	4.9	251	-10.83	-0.09	-
80-43-3	Dicumyl peroxide	270.4	8.6	5.5	417	-10.78	-0.01	Y
55066-48-3	3-Methyl-5-phenylpentan-1-ol	178.3	8.5	4.0	269	-10.68	-0.55	-
66068-84-6	Cyclohexanol, 4-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)-	236.4	8.5	4.2	372	-10.63	0.19	-
32388-55-9	Acetylcedrene	246.4	8.4	4.1	891	-10.05	1.38	-
2481-94-9	C.I. Solvent Yellow 56	253.3	8.3	3.7	145	-10.72	0.43	-

1222-05-5	Cyclopenta[g]-2-benzopyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-	258.4	8.2	5.9	794	-10.75	0.44	Y
6197-30-4	2-Ethylhexyl-2-cyano-3,3-diphenylacrylate	361.5	11.7	5.9	550	-10.86	0.02	Y
75980-60-8	Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide	348.4	11.7	5.5	178	-10.86	-0.2	Y
3147-75-9	Octrizole	323.4	10.8	4.0	245	-10.78	0.57	-
6386-38-5	Methyl 3,5-bis(tert-butyl)-4-hydroxyhydrocinnamate	292.4	10.5	5.0	417	-10.71	0.47	-
34432-92-3	N-Ethyl-N-(2-(1-(2-methylpropoxy)ethoxy)ethyl)-4-(phenylazo)aniline	369.5	9.9	4.3	151	-10.63	0.54	-
82919-37-7	Methyl 1,2,2,6,6-pentamethyl-4-piperidyl sebacate	369.5	9.8	3.8	204	-10.68	0.45	-
91273-04-0	1H-1,2,4-Triazole-1-methanamine, N,N-bis(2-ethylhexyl)-	322.5	9.6	5.1	275	-10.63	0.89	-
38083-17-9	Climbazole	292.8	9.5	3.5	110	-10.72	-0.84	-
7212-44-4	Nerolidol	222.4	9.3	4.9	115	-9.76	-0.27	Y
84-74-2	Dibutyl phthalate	278.3	8.8	4.6	166	-10.84	-0.4	Y
81-14-1	Musk ketone	294.3	8.6	4.3	631	-10.74	-0.24	Y
34562-31-7	3,5-Diethyl-1-phenyl-2-propyl-1,2-dihydropyridine	255.4	8.5	4.3	501	-9.93	0.79	-
81-15-2	2,4,6-Trinitro-1,3-dimethyl-5-tert-butylbenzene	297.3	8.4	3.9	4074	-10.77	-0.03	Y
51-03-6	Piperonyl butoxide	338.4	10.9	4.8	126	-10.78	0.62	Y
25973-55-1	2-(2-Hydroxy-3,5-di-tert-pentylphenyl)benzotriazole	351.5	10.5	5.0	891	-10.64	0.77	Y
74336-59-7	Pyrazolo[5,1-b]quinazolin-9(1H)-one, 3-[2-(4-chloro-2-nitrophenyl)diazenyl]-2-methyl-	382.8	9.8	3.8	102	-10.66	0.33	-
17354-14-2	1,4-Bis(butylamino)anthracene-9,10-dione	350.5	9.6	3.9	191	-10.7	-0.59	-

4378-61-4	C.I. Vat Orange 3	464.1	11.7	4.3	954993	-10.91	-0.2	-
162881-26-7	(Phenylphosphoryl)bis[(2,4,6-trimethylphenyl)methanone]	418.5	11.7	4.1	1995	-10.64	0.37	-
10254-57-6	4,4'-Methylene bis(dibutyldithiocarbamate)	422.8	11.7	5.4	288	-10.53	0.63	-
13393-93-6	1-Phenanthrenemethanol, tetradecahydro-1,4a-dimethyl-7-(1-methylethyl)-, (1R,4aR,4bS,10aR)-	292.5	10.6	5.3	525	-10.78	0.88	-
23328-53-2	2-(2H-Benzotriazol-2-yl)-6-dodecyl-4-methylphenol	393.6	10.3	5.6	170	-10.63	0.46	-
128-80-3	D & C Green No. 6	418.5	9.7	5.9	224	-10.7	-0.49	-
3089-17-6	2,9-Dichloro-5,12-dihydroquino[2,3-b]acridine-7,14-dione	381.2	9.7	4.4	117	-10.81	-0.49	-
3010-23-9	2-Heptadecyl-4,5-dihydro-1H-imidazole-1-ethanamine	351.6	10.6	4.8	363	-10.53	0.03	-
88949-33-1	Pigment Red 264	440.5	10.2	5.0	347	-10.75	0.19	-
125-20-2	3,3-Bis(4-hydroxy-5-isopropyl-o-tolyl)phthalide	430.5	9.6	5.3	1905	-10.1	-0.06	Y
2372-82-9	N-(3-Aminopropyl)-N-dodecylpropane-1,3-diamine	299.5	9.2	5.1	759	-11.04	-0.42	-
30125-47-4	C.I. Pigment Yellow 138	693.9	11.7	5.5	501187	-10.75	0.69	-
5590-18-1	3,3'-(1,4-Phenylenediimino)bis(4,5,6,7-tetrachloro-1H-isoindol-1-one)	641.9	9.7	4.9	199526	-10.89	0.63	-

Appendix 3. Chemicals with Prio 1 predicted as potential new or emerging risk chemicals to be monitored in human urine are listed with the CAS identifier, preferred chemical name (according CompTox) and molar mass (M). The OPERA modelled predictions for octanol-air (KOA) and octanol -water (KOW) partition coefficients, bioconcentration factor (BCF), atmospheric hydroxylation rate and biotransformation rate constant (KM) are reported, and values with a red font indicates that the chemical structures are outside the applicability domain. Chemicals already reported in human blood exposome according to Barupal and Fiehn (Barupal and Fiehn 2019) are indicated with a yes (Y).

CAS no	Chemical name	M (g/mol)	Log K_{OA}	Log K_{OW}	BCF (L/kg)	Log AOH (cm3/mol sec)	Log KM (days)	Blood exposome
31906-04-4	4-(4-Hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde	210.3	9.3	3.1	15	-10.04	-0.38	-
118-58-1	Benzyl salicylate	228.2	9.3	3.1	25	-10.84	-0.89	-
119515-38-7	Icaridin	229.3	9.3	2.5	4	-10.74	-0.28	Y
65405-77-8	(3Z)-Hex-3-en-1-yl salicylate	220.3	9.2	2.8	17	-10.47	-0.83	-
25961-89-1	Ethanol, 2-[2-[2-(hexyloxy)ethoxy]ethoxy]-	234.3	9.0	1.9	15	-10.61	-0.14	Y
91-44-1	7-Diethylamino-4-methylcoumarin	231.3	9.0	2.9	20	-10.56	-0.17	-
25485-88-5	Cyclohexyl 2-hydroxybenzoate	220.3	8.9	3.2	10	-10.76	-0.87	-
1559-34-8	3,6,9,12-Tetraoxahexadecan-1-ol	250.3	8.8	0.1	4	-10.62	-0.14	-
2050-08-0	Pentyl 2-hydroxybenzoate	208.3	8.8	3.2	28	-10.76	-0.83	-
5650-20-4	Tetraethylene glycol monoethyl ether	222.3	8.7	-0.1	3	-10.43	-0.06	-
629-25-4	Sodium dodecanoate	222.3	8.7	1.3	251	-10.89	-0.43	-
94-26-8	Butylparaben	194.2	8.6	3.6	9	-10.76	-0.98	Y
87-20-7	Isoamyl salicylate	208.3	8.6	3.1	17	-10.77	-0.95	-
99-76-3	Methylparaben	152.1	8.6	2.0	7	-10.95	-0.83	Y
5026-62-0	Methylparaben sodium	174.1	8.6	-1.6	7	-10.95	-0.83	-
143-22-6	2-[2-(2-Butoxyethoxy)ethoxy]ethanol	206.3	8.5	0.8	4	-10.44	-0.59	-
4247-02-3	Isobutylparaben	194.2	8.5	3.0	13	-10.76	-0.99	Y
101-83-7	Dicyclohexylamine	181.3	8.5	3.8	5	-10.92	-0.5	Y
15763-76-5	Sodium 4-isopropylbenzenesulfonate	222.2	8.5	-1.8	6	-10.92	-0.77	-
142-31-4	Sodium octyl sulfate	232.3	8.5	0.2	6	-11.02	-0.5	-
94-13-3	Propylparaben	180.2	8.4	3.0	7	-10.73	-0.98	Y
126-92-1	Sodium ethasulfate	232.3	8.4	0.2	6	-11.12	-0.42	-

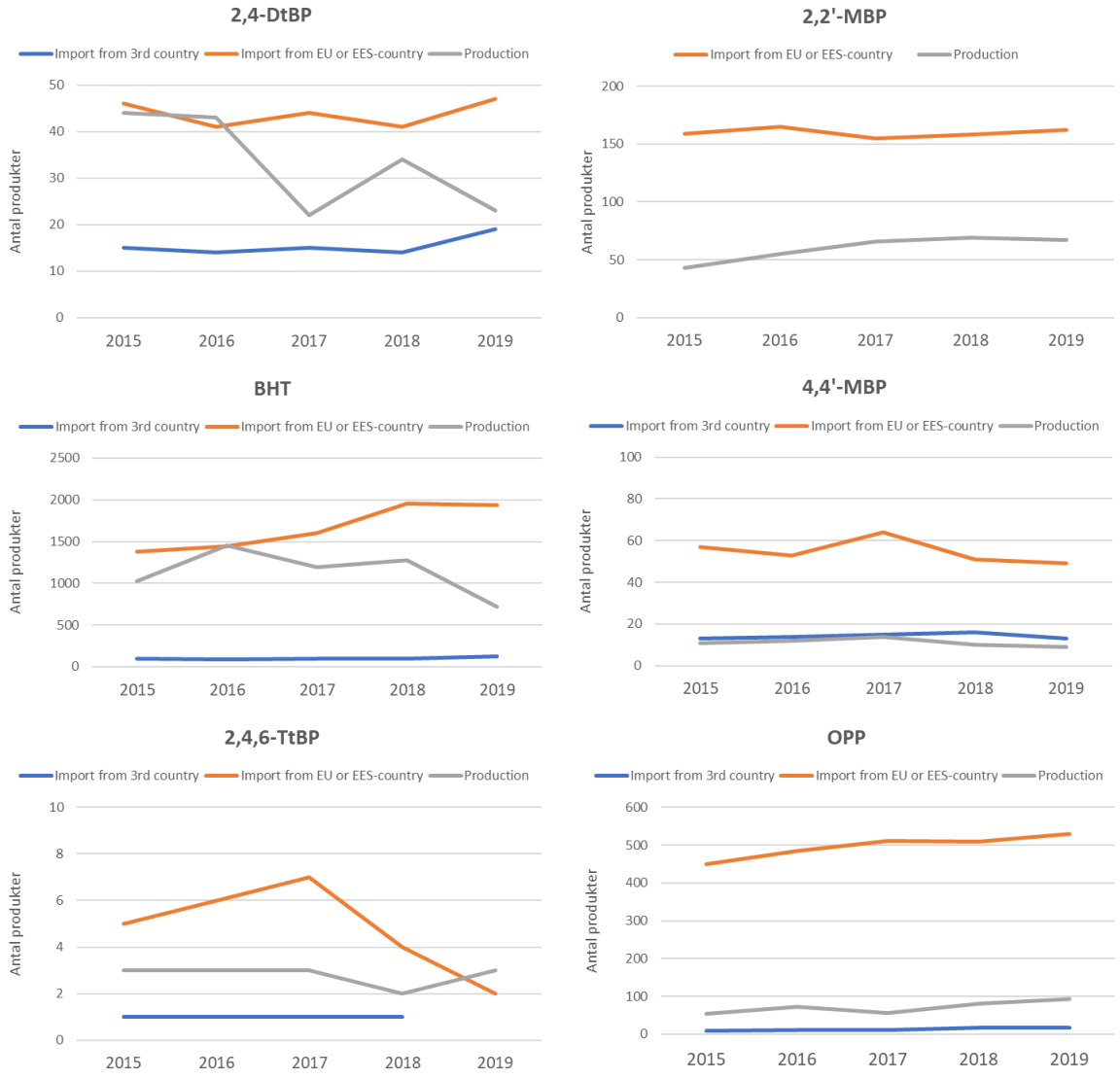
112-59-4	2-[2-(Hexyloxy)ethoxy]ethanol	190.3	8.4	1.7	4	-10.43	-0.62	Y
135-19-3	2-Naphthalenol	144.2	8.4	2.7	112	-9.77	-0.99	Y
102-20-5	2-Phenylethyl phenylacetate	240.3	8.2	3.6	295	-10.84	-0.19	-
2752-95-6	Butyl diphenyl phosphate	306.3	9.8	3.6	35	-10.79	-0.77	-
2235-54-3	Ammonium dodecyl sulfate	283.4	9.7	2.1	6	-10.73	-0.3	-
151-21-3	Sodium dodecyl sulfate	288.4	9.7	1.6	6	-10.73	-0.3	-
54982-83-1	1,4-Dioxacyclohexadecane-5,16-dione	256.3	9.5	3.4	6	-11.12	-0.29	-
105-95-3	1,4-Dioxacycloheptadecane-5,17-dione	270.4	9.3	3.7	14	-11.11	-0.26	Y
6259-76-3	Hexyl salicylate	222.3	9.1	3.2	28	-10.77	-0.67	Y
142-78-9	Laurylethanolamide	243.4	9.0	3.2	17	-10.82	-0.15	-
51580-86-0	Sodium dichloro-s-triazinetrione dihydrate	256.0	8.8	0.4	2	-12.41	-0.64	-
23778-52-1	3,6,9,12,15-Pentaoxahexadecanol	252.3	8.6	-0.3	3	-10.56	-0.14	-
23783-42-8	2,5,8,11-Tetraoxatridecan-13-ol	208.3	8.5	-0.4	2	-10.35	-0.4	-
42978-66-5	Tripropylene glycol diacrylate	300.4	8.4	2.2	13	-10.56	-0.12	-
6440-58-0	1,3-Dimethylol-5,5-dimethylhydantoin	188.2	8.2	-0.7	1	-10.94	-1.06	-
116-25-6	1-(Hydroxymethyl)-5,5-dimethylhydantoin	158.2	8.1	0.0	2	-10.93	-1.05	-
18760-44-6	Thiophene, 3-(decyloxy)tetrahydro-, 1,1-dioxide	276.4	8.0	3.5	9	-10.73	-0.2	-
4314-14-1	C.I.Solvent Yellow 16	278.3	8.0	3.8	26	-10.64	-0.57	-
3055-94-5	Triethylene glycol monododecyl ether	318.5	11.5	3.2	66	-10.79	-0.02	-
4292-10-8	N-Laurylamidopropyl-N,N-dimethylbetaine	342.5	10.9	3.0	37	-10.92	-0.16	-
73772-45-9	Capramidopropyl betaine	314.5	10.8	2.1	34	-10.92	-0.19	-
593-29-3	Potassium stearate	322.6	10.6	0.8	513	-10.78	0.05	-
61792-31-2	Lauramidopropylamine oxide	300.5	10.6	3.9	209	-10.76	0.05	-
137-16-6	Sodium [dodecanoyl(methyl)amino]acetate	293.4	10.6	1.3	120	-10.93	-0.13	-
1786-94-3	3,6,9,12,15-Pentaoxanonadecan-1-ol	294.4	10.3	0.3	4	-10.73	-0.23	-
27138-31-4	Di(propylene glycol) dibenzoate	342.4	10.2	3.4	56	-10.86	-0.08	-
120-55-8	Diethylene glycol dibenzoate	314.3	10.2	2.7	33	-10.84	-0.41	-
112-03-8	N,N,N-Trimethyloctadecan-1-aminium chloride	348.1	9.8	1.8	437	-11.19	0.91	-

120-40-1	N,N-Bis(2-hydroxyethyl)dodecanamide	287.4	9.2	3.6	55	-10.76	-0.12	Y
109-17-1	Tetraethyleneglycol dimethacrylate	330.4	8.8	1.5	5	-10.08	0.61	Y
54549-24-5	D-Glucopyranoside, hexyl	264.3	8.6	0.2	1	-10.79	-0.87	-
496-46-8	Glycoluril	142.1	8.4	-1.3	3	-11.51	-0.96	Y
31387-97-0	Butyl D-glucoside	236.3	8.4	-1.0	1	-10.73	-0.93	-
16485-10-2	Panthenol	205.3	8.4	-1.2	1	-10.82	-1.09	Y
81-13-0	Dexpanthenol	205.3	8.4	-1.2	1	-10.82	-1.09	-
66057-30-5	Dipotassium 2-(3-methylphenoxy)ethyl phosphate	308.4	8.4	-2.2	5	-10.78	-0.41	-
57-33-0	Pentobarbital sodium	248.3	8.4	0.2	2	-11.21	-0.32	-
149-91-7	Gallic acid	170.1	8.2	0.7	5	-11.44	-0.96	Y
14246-53-8	Glycine, N-(1-oxooctyl)-	201.3	8.1	0.7	3	-11.23	-0.65	Y
50-81-7	L-Ascorbic acid	176.1	8.1	-1.9	2	-11.09	-1.04	Y
6381-77-7	Sodium erythorbate	198.1	8.1	-2.2	2	-11.09	-1.04	-
67806-10-4	Tetradecanamide, N-[3-(dimethyloxidoamino)propyl]-	328.5	11.1	3.6	708	-10.76	-0.14	-
4403-12-7	Triethylene glycol monotridecyl ether	332.5	10.9	3.4	263	-10.78	-0.26	-
3088-31-1	Diethylene glycol monolauryl ether sulfate sodium salt	376.5	10.9	0.9	8	-10.75	-0.55	-
143-18-0	Potassium oleate	320.6	10.6	0.9	93	-10.31	-0.04	-
120-56-9	Ethylenebis(oxyethylene) dibenzoate	358.4	10.5	2.8	35	-10.86	1	-
577-11-7	Docusate sodium	444.6	10.5	2.2	9	-10.92	0.19	-
7491-09-0	Potassium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate	460.7	10.5	1.1	9	-10.92	0.19	-
23601-40-3	2,5,8,11,14,17-Hexaoxanonadecan-19-ol	296.4	10.2	-0.3	3	-10.63	-0.24	-
126-58-9	Dipentaerythritol	254.3	9.5	-2.3	2	-10.65	-0.93	-
56863-02-6	Linoleic diethanolamide	367.6	9.5	3.6	372	-9.94	-0.73	-
27836-64-2	Dodecyl D-glucopyranoside	348.5	9.4	2.4	30	-10.78	-0.56	-
98283-67-1	Undecyl glucoside	334.5	9.4	2.1	24	-10.78	-0.53	-
29781-81-5	Decyl alpha-D-Glucopyranoside	320.4	9.4	1.4	10	-10.78	-0.52	-

54549-25-6	Decyl D-glucopyranoside	320.4	9.4	1.4	10	-10.78	-0.52	-
58846-77-8	Decyl beta-D-glucopyranoside	320.4	9.4	1.4	10	-10.78	-0.52	-
67968-63-2	Dipotassium 9-sulfonatooctadecanoate	440.7	9.4	1.1	14	-10.73	-0.71	-
3655-00-3	Disodium lauriminodipropionate	373.4	9.3	1.5	29	-10.92	-0.7	-
14960-06-6	beta-Alanine, N-(2-carboxyethyl)-N-dodecyl-, monosodium salt	351.5	9.3	1.5	29	-10.92	-0.7	-
60177-36-8	1,4-Anhydro-5-O-octanoylhexitol	290.4	9.2	1.0	1	-10.82	-0.51	-
50-70-4	D-Glucitol	182.2	8.5	-2.4	2	-10.41	-1.09	Y
69-65-8	D-Mannitol	182.2	8.5	-2.4	2	-10.41	-1.09	Y
52663-87-3	N-(2-Carboxyethyl)-N-octyl-beta-alanine	273.4	8.4	3.8	6	-10.93	-0.17	-
94441-92-6	.beta.-Alanine, N-(2-carboxyethyl)-N-(2-ethylhexyl)-, sodium salt (1:1)	295.4	8.4	1.2	3	-10.92	0.02	-
84962-98-1	Sodium 3-(trihydroxysilyl)propyl methylphosphonate	238.2	8.4	-1.4	3	-10.74	-0.21	-
527-07-1	Sodium D-gluconate	218.1	8.2	-2.4	4	-11.09	-0.93	-
526-95-4	D-Gluconic acid	196.2	8.2	-2.5	4	-11.09	-0.93	-
50-99-7	D-Glucose	180.2	8.2	-2.8	2	-10.89	-0.97	-
54163-66-5	Butanedioic acid, 2-(octen-1-yl)-, sodium salt (1:2)	272.3	8.1	-0.5	3	-10.65	-0.48	-
24599-21-1	2-(Methacryloyloxy)ethyl dihydrogen phosphate	210.1	8.1	0.4	4	-10.46	-0.72	-
13150-00-0	Sodium lauryltrioxyethylene sulfate	420.5	10.5	1.9	8	-10.75	0.21	-
25446-78-0	Ethanol, 2-[2-[2-(tridecyloxy)ethoxy]ethoxy]-, hydrogen sulfate, sodium salt	434.6	10.4	3.2	7	-10.75	0.45	-
9051-57-4	2-(2-{2-[2-(4-Nonylphenoxy)ethoxy]ethoxy}ethoxy)ethyl hydrogen sulfate--ammonia (1/1)	493.7	10.3	3.9	7	-10.53	0.56	-
57-50-1	Sucrose	342.3	9.6	-3.7	2	-10.78	-0.84	Y
6419-19-8	Aminotrimethylene phosphonic acid	299.0	9.5	-3.5	3	-10.92	-0.93	Y
178949-82-1	N,N'-Ethylenedi-(L-aspartic acid) trisodium salt	358.2	9.5	-2.2	4	-10.97	-0.8	-
140-01-2	Diethylenetriaminepentaacetic acid pentasodium salt	503.3	9.5	-1.6	4	-10.93	-0.53	-
37971-36-1	2-Phosphono-1,2,4-butanetricarboxylic acid	270.1	9.5	0.0	3	-11.06	-0.5	-

66669-53-2	Tetrasodium hydrogen 2-phosphonatobutane-1,2,4-tricarboxylate	358.1	9.5	-0.7	3	-11.06	-0.5	-
2809-21-4	Etidronic acid	206.0	9.5	-0.4	3	-10.49	-1.04	Y
3794-83-0	Tetrasodium etidronate	294.0	9.5	-0.9	3	-10.49	-1.04	-
7414-83-7	Etidronate disodium	250.0	9.5	-0.9	3	-10.49	-1.04	-
554-62-1	Phytosphingosine	317.5	9.4	3.3	85	-10.78	-0.6	-
64-02-8	Ethylenediaminetetraacetic acid tetrasodium salt	380.2	9.4	-1.5	4	-11.01	-0.51	-
6381-92-6	Disodium ethylenediaminetetraacetate dihydrate	372.2	9.4	-1.5	4	-11.01	-0.51	-
139-33-3	Ethylenediaminetetraacetic acid, disodium salt	336.2	9.4	-1.5	4	-11.01	-0.51	-
60-00-4	Ethylenediaminetetraacetic acid	292.2	9.4	-1.5	4	-11.01	-0.51	Y
64972-19-6	Sodium N-(2-carboxyethyl)-N-(3-(decyloxy)propyl)-beta-alaninate	381.5	9.4	1.5	7	-10.92	-0.74	-
68298-18-0	Glycine, N-[2-(carboxymethoxy)ethyl]-N-[2-[(1-oxooctyl)amino]ethyl]-, disodium salt	390.4	9.3	0.1	3	-10.77	-0.72	-
29923-31-7	L-Glutamic acid, N-(1-oxododecyl)-, sodium salt (1:1)	351.4	9.3	0.6	7	-11.11	-0.71	-
31138-65-5	Monosodium D-glucoheptonate	248.2	8.5	-2.4	3	-11.07	-0.93	-
144538-83-0	Tetrasodium iminidisuccinate	337.1	8.4	-2.7	4	-11.02	-0.51	-
51981-21-6	Tetrasodium glutamate diacetate	351.1	8.4	-1.4	4	-11.02	-0.88	-
570-22-9	1H-Imidazole-4,5-dicarboxylic acid	156.1	8.1	-1.4	5	-11.48	-0.97	Y
164462-16-2	Alanine, N,N-bis(carboxymethyl)-, trisodium salt	271.1	8.1	-1.7	4	-11.08	-1.08	-
129050-62-0	.beta.-Alanine, N,N-bis(carboxymethyl)-, sodium salt (1:3)	271.1	8.1	-1.7	4	-11.08	-0.18	-
3055-99-0	Polyoxyethylene (9) lauryl ether	582.8	10.2	2.6	37	-10.75	0.46	Y
15827-60-8	Phosphonic acid, [[(phosphonomethyl)imino]bis[2,1-ethanediylnitrilobis(methylene)]]tetrakis-	573.2	9.6	-3.5	3	-10.68	-0.49	Y
39236-46-9	Imidazolidinyl urea	388.3	9.6	-0.9	3	-10.77	-0.85	Y
2235-43-0	Pentasodium nitrilotris(methylenephosphonate)	409.0	9.5	-2.6	3	-10.92	-0.93	-
5995-42-6	(((2-Hydroxyethyl)imino)bis(methylene))bisphosphonic acid	249.1	9.5	-1.8	3	-10.5	-1.09	-

Appendix 4. The number of products registered in SE-PR of prioritized target analytes.



Appendix 5. Information on the target analytes extracted from the SE-PR (in Swedish) and CompTox.

	Information från SE-PR 2018 (in Swedish)				**Information from CompTox**	
Abbr. (CAS)	**Funktion (top 2)**	**Kvantitet ämne (S)**	**Antal produkter**	**Bransch (top 3)**	**Collected Data on Functional Use[a]**	**Predicted Probability of Associated Functional Use (top 3)[b]**
2,4-DtBP (96-76-4)	Hydraulvätskor, färg och lack	0,12	86	Exportinriktad verksamhet, Handel samt reparation av motorfordon och motorcyklar, Tillverkning av trä och varor av trä, kork och rotting o.d. utom möbler	Antioxidant	Antioxidant, uv_absorber, heat_stabilizer
BHT (128-37-0)	Färg och lack, tryckfärg	443	3356	Exportinriktad verksamhet, Tillverkning av möbler, Tillverkning av trä och varor av trä, kork och rotting o.d. utom möbler	Antimicrobial	Antioxidant, uv_absorber, heat_stabilizer
2,4,6-TtBP (732-26-3)	Bil och båtvårdsprodukter, bränsletillsatser	0,08	7	Handel samt reparation av motorfordon och motorcyklar, Partihandel med kemiska produkter, Tillverkning av stenkolsprodukter och raffinerade petroleumprodukter	Antioxidant	Antioxidant, uv_absorber, heat_stabilizer
2,2'-MBP (119-47-1)	Färgämne, råvara och mellanprodukt	17	226	Grafisk produktion och reproduktion av inspelningar, Tillverkning av gummivaror, Exportinriktad verksamhet	Antioxidant	Antioxidant, uv_absorber, heat_stabilizer
4,4'-MBP (118-82-1)	Hydraul vätska, smörjmedel	4,3	70	Tillverkning av övriga maskiner, Tillverkning av motorfordon, släpfordon och påhängsvagnar and Handel samt reparation av motorfordon och motorcyklar	Antioxidant	Antioxidant, uv_absorber, heat_stabilizer
OPP (2082-79-3)	Råvara och mellanprodukt, lim	232	612	Plastvarutillverkning, Exportinriktad verksamhet, Tillverkning av gummivaror	Antioxidant	Heat_stabilizer, antioxidant, lubricating_agent

[a]*The following papers are recommended reading in regards to the Collected Data on Functional Use table:* K Isaacs et al, 2016, Toxicology Reports and K Phillips et al 2017, Green Chemistry.

[b]*The following paper is recommended reading in regards to the Predicted Probability of Associated Functional Use Table:* K Phillips et al 2017, Green Chemistry.

Appendix 6. Chemicals with Prio 1 predicted as potential new or emerging risk chemicals to be monitored in human blood are listed with the CAS identifier (four chemicals that are also in Prio 1 list for consumers are indicated in bold), preferred chemical name (according CompTox) and molar mass (M). The OPERA modelled predictions for octanol-air (KOA) and octanol -water (KOW) partition coefficients, bioconcentration factor (BCF), and values with a red font indicates that the chemical structures are outside the applicability domain. Chemicals already reported in human blood exposome according to Barupal and Fiehn (Barupal and Fiehn 2019) are indicated with a yes (Y). The exposure index for consumers and occupational exposure is given with a range 1-7, and the function as reported in CompTox.

CAS no	Chemical name	M (g/mol)	Log K_{OA}	Log K_{OW}	BCF (L/kg)	Blood exposome	$EI_{consumer}$	$EI_{occupational}$	Function[a]
37853-59-1	1,2-Bis(2,4,6-tribromophenoxy)ethane (BTBPE)	687.6	12	7.6	1548817	Y	1	7	BFR
32588-76-4	1,2-Bis(tetrabromophthalimido)ethane (EBTEBPI)	951.5	12	6.7	389045	-	1	7	BFR
84852-53-9	1,1'-Ethane-1,2-diylbis(pentabromobenzene) (DBDPE)	971.2	12	7.5	288403	Y	1	7	BFR
21850-44-2	Tetrabromobisphenol A-bis(2,3-dibromopropyl ether) (TBBPA-BDBPE)	943.6	12	9.0	14791	-	1	7	BFR
732-26-3	2,4,6-Tris(tert-butyl)phenol	262.4	9.7	6.1	13804	Y	7	7	Antioxidant
78-33-1	Tris(4-tert-butylphenyl) phosphate	494.6	12	8.6	7079	Y	5	7	Plasticizer
145650-60-8	Bis(2,4-di-tert-butyl-6-methylphenyl)ethyl phosphite	514.7	12	10	6761	-	1	7	Processing aid
31565-23-8	di(tert-dodecyl) pentasulphide	499.0	12	8.3	6607	-	1	6	No information
15721-78-5	N,N-Bis(4-tert-octylphenyl)amine	393.7	10	9.9	6166	-	6	7	*Antioxidant
82657-04-3	Bifenthrin	422.9	10	6.2	5012	-	1	6	*Antimicrobial
80693-00-1	3,9-Bis(2,6-di-tert-butyl-4-methylphenoxy)-1,5,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane	632.8	12	9.5	4898	-	1	7	Antioxidant
13280-61-0	Benzene, 1,4-bis[2-(2-methylphenyl)ethenyl]-	310.4	10	7.2	4074	-	1	7	*Whitener
10081-67-1	4-(2-Phenylpropan-2-yl)-N-[4-(2-phenylpropan-2-yl)phenyl]aniline	405.6	10	9.3	3890	-	1	7	Antioxidant

17540-75-9	4-(Butan-2-yl)-2,6-di-tert-butylphenol	262.4	9.8	6.9	3090	-	1	7	Antioxidant
7128-64-5	2,2'-(2,5-Thiophenediyl)bis[5-(1,1-dimethylethyl)benzoxazole]	430.6	12	6.8	3020	-	5	7	Whitener
118-82-1	4,4'-Methylenebis(2,6-di-t-butylphenol)	424.7	9.6	8.3	2884	Y	7	7	Antioxidant
1843-03-4	Phenol, 4,4',4''-(1-methyl-1-propanyl-3-ylidene)tris 2-(1,1-dimethylethyl)-5-methyl-	544.8	9.5	10	2818	-	1	7	Antioxidant
85-60-9	4,4'-Butane-1,1-diylbis(2-tert-butyl-5-methylphenol)	382.6	9.5	8.0	2399	Y	3	7	Antioxidant
4306-88-1	Phenol, 2,6-bis(1,1-dimethylethyl)-4-nonyl-	332.6	11	8.9	2291	-	4	7	No information
61167-58-6	2-tert-Butyl-6-(3-tert-butyl-2-hydroxy-5-methylbenzyl)-4-methylphenyl prop-2-enoate	394.6	10	6.6	2239	-	3	6	Antioxidant
1745-89-7	4,4'-Isopropylidenebis(2-allylphenol)	308.4	9.3	6.0	2455	-	7	7	Antioxidant

[a]Reported functional use (*predicted) information from CompTox