PRIORITIZATION STRATEGY FOR THE IDENTIFICATION OF NEW AND EMERGING RISK CHEMICALS ON THE SWEDISH MARKET

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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 [1-3], whereas others use data-driven approaches and suspect screening [4,5]. 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, as for example pesticides [6]. Another project (ExpoCast), initiated by US EPA to develop tools for rapid chemical evaluation based on potential for exposure, among others, have demonstrated that information on use is a good factor for the prediction of new chemicals of concern relevant to human exposure [7,8].

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, *e.g.* 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 by first defining a use index describing the general potential of a chemical to be released from a specific type of use [9,10]. 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 five different recipients representing surface water, soil, air, sewage treatment plant and human (consumer and occupational). The EI only describes the potential of a chemical to be exposed to the recipients. 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.

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. In this study we aimed to investigate the use of the EI to consumers ($EI_{consumer}$), applied to the database of chemicals in the SE-PR to prioritize NERCs for further investigation. Different prioritization strategies have been applied to the set of chemicals with a high $EI_{consumer}$. For the selection and the discussion, we compare the properties of chemicals which typically are found in human blood. Focus in this study has been towards the classical chemical pollutants, *i.e.* the persistent and bioaccumulative, although the dataset can be further investigated to identify others, such as the polar and mobile NERCs.

Materials and methods

The strategy for prioritization of potential NERCs was to combine a high EI with easily accessible data on chemical properties. Typically, chemicals being persistent and bioaccumulative are of concern according to Stockholm Convention on persistent organic pollutants (POPs). The criteria for a bioaccumulative chemical is set to a bioconcentration factor (BCF) >2000 within the REACH framework (EC/Annex XIII). In REACH, persistence is measured by half-lives in different matrices, and the shortest half-life for a persistent chemical is 40 days in fresh- or estuarine water. Those criteria for bioaccumulation and persistence was used to prioritize chemicals for further investigation. Neither environmental conditions, nor the biotransformation is considered. Thus, it should not be interpreted that the chemicals are persistent *per se*. Previous studies have shown that low water solubility (S_W), 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 [11,12]. In addition, Kelly and coworkers 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 [12].

The properties for chemicals prone to end up in humans have been extracted from the recently established human blood database (HBDB) containing 508 organic contaminants (see abstract Engelhardt et al. 2021, OHC). KEMI provided a list of 3280 chemicals in SE-PR with high $EIc_{onsumers}$ (>6). After removal of inorganics, polymers and mixtures a total of 937 unique chemicals were listed for further evaluation. To get as comprehensive material as possible, it was decided to use modelled data on the two datasets, even though experimental data is to prefer. OPERA is an open source quantitative structure activity-relationship tool box, maintained by the National Center

for Computational Toxicology at the US EPA [13]. In total, 437 chemicals in HBDB and 922 chemicals in SE-PR could be modelled in OPERA.

The OPERA modelled properties used for prioritization were BCF, biodegradation half-life, S_W, K_{OW} and K_{OA}. The cut-off values are specified in Table 1.

Results and discussion

Typically, high K_{OW} and high K_{OA} can be seen in the majority of the chemicals in the HBDB (>73%, Figure 1), as well as low S_W which is closely related to a high K_{OW} (Table 1). Two thirds of the chemicals found in human serum also have a high BCF, which is an indicator for bioaccumulative chemicals. Biodegradation half-lives on the other hand do not describe the chemicals found in human serum, even though a conservative 40-days cut off-value was set. In OPERA, the model was based on only 150 chemicals for the biodegradation test, in comparison to 14 050 for Log K_{OW}. Thus, the half-life values are poor indicators for persistence and other values should be searched for.

Table 1. Comparison between properties of the chemicals in the human blood database (HBDB) and the SE-PR chemicals with a high exposure index to consumers ($EI_{consumer}$) and the numbers of chemical prioritized for further investigation based on different strategies.

OPERA modelled properties	**HBDB (n=437)**	**SE-PR $EI_{consumer}$ >6 (n=922)**
Bioconcentration factor (BCF) >2000	66%	1%
Biodegredation half life (days) >40	9%	4%
Octanol-air partition coefficient Log K_{OA} >6	87%	72%
Octanol-water partition coefficient Log K_{OW} >5	73%	15%
Water solubility < $1E^{-5}$ mol/L	79%	28%
Chemicals with the properties in the HBDB and prioritized in SE-PR		
P and B criteria REACH - BCF >2000, Bio>40 days	58 (13%)	4 (0.4%)
Czub and McLachlan 2004 - Log K_{OW} 2-11, Log K_{OA} 6-12	385 (88%)	402 (44%)
Kelly et al 2007 - air-breathing -Log K_{OW} <5, Log K_{OA} >6	76 (17%)	525 (57%)
- water-respiring and air-breathing - Log K_{OW} >5, Log K_{OA} >6	317 (73%)	133 (14%)
BCF >2000, Log K_{OA} >6, Log K_{OW} >5, S_W<$1E^{-5}$ mol/L	269 (61%)	3 (0.3%)

The majority of the chemicals (99%) in the SE-PR with a high $EI_{consumer}$ could be considered non-problematic when looking at the P and B criteria set by REACH, based on the BCF only (Table 1). The chemicals in HBDB is best described by the chemical properties described in Czub and McLachlan, which would correspond to that 402 chemicals in SE-PR should be prioritized for further investigation. To ensure reliable analytical exposure data, target analysis is preferred. Setting up analytical methods for 402 chemicals is not feasible and therefore, further prioritization was evaluated. The goal was to have an approach with a high coverage on the HBDB and few chemicals for prioritization in the SE-PR (described in Table 1 as "ratio"). By using the cut of values for the four properties BCF >2000, log K_{OA} >6, log K_{OW} <5 and S_W <$1E^{-5}$ mol/L we received the best result (ratio 90).

Three chemicals were prioritized with that extended strategy; a musk substance, a pigment and an antioxidant. The exposure to musk substance (AHTN) has been confirmed in for example human breast milk from US [14], and in human serum from China [15]. For the pigment (C.I. Yellow 138) no information on exposure was available. The pigment had been confirmed to be in tattoo ink in a previous study [16]. It was not possible to obtain analytical standards, only bulk volumes of pigments in technical mixtures could be found. Pure analytical standards are needed to optimize the analytical method needed for the confirmation of the exposure.

The antioxidant was 4,4′-methylenebis(2,6-di-tert-butylphenol) (4,4′-MBP). In China, 4,4'-MBP has been reported up to 18 ng/mL in municipal sewage sludge [17] and as non-detect in household dust [18]. It has never been searched for in human samples. Analytical standards are available and thus, this chemical has been prioritized for further investigation.

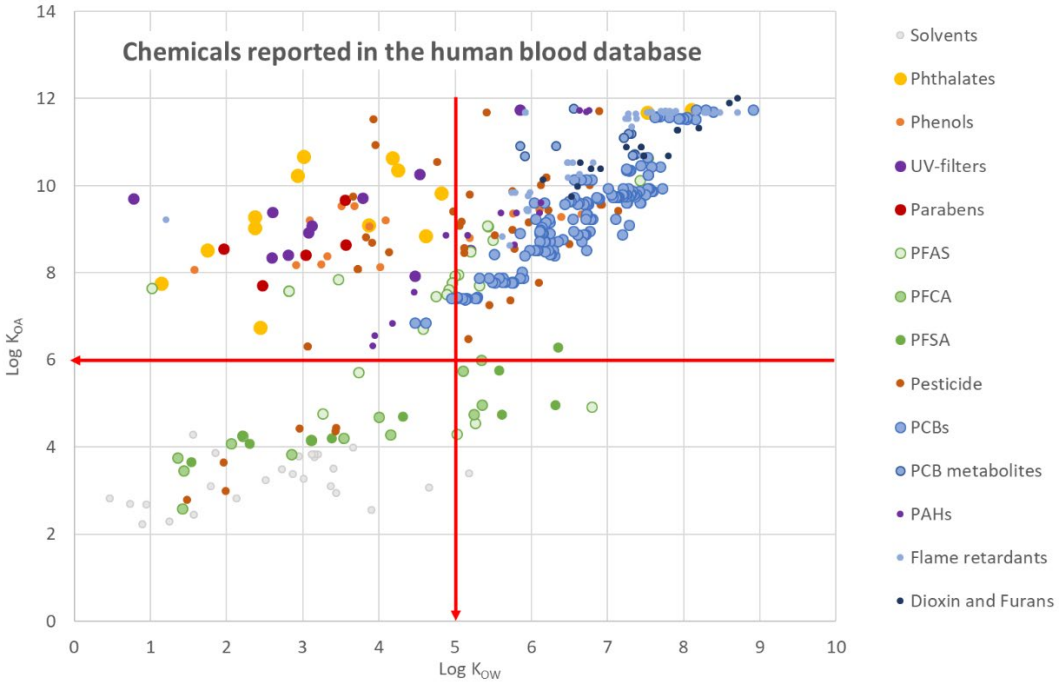

Figure 1. The log K_{OA} and log K_{OW} of the chemicals reported to have been detected in human blood. The red lines indicate the cut-off values for the prioritization.

In this study, the focus was on the identification of lipophilic and bioaccumulative chemicals. Lipophilicity is not a general requirement for risk chemicals, as is demonstrated by the phthalates, parabens and phenols in human serum (Figure 1). Antioxidants and pigments are highlighted in the SE-PR dataset to illustrate the inherent span of log K_{OW} for these chemicals (Figure 2). In addition, a high log K_{OA} seem to be of importance for air-breathing organisms such as humans, which is well illustrated in the HBDB. Looking at the chemicals with a high $EI_{consumer}$ in SE-PR it can be seen that the majority (72%) of the chemicals have a log K_{OA} >6. This indicates that several chemicals on the market which humans are exposed to could end up in our blood. The strategy used here can be redirected to prioritize more hydrophilic chemicals for further investigation.

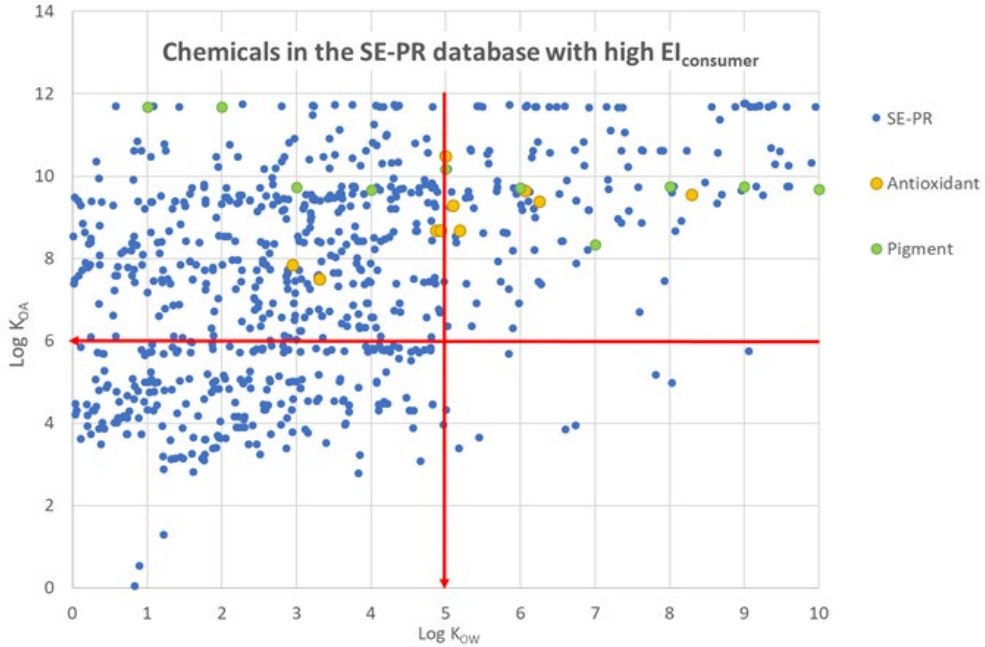

Figure 2. The log K_{OA} and log K_{OW} of the chemicals with a high $EI_{consumer}$ in SE-PR. The red line indicates the cut-off values for the prioritization, leaving the upper right corner to represent the prioritized chemicals for further investigation

There are two studies that have attempted to validate the EI, focusing on sewage and wastewater [4,10]. This is the first time the EI has been used for validation of human exposure. Chemical analysis of the prioritized antioxidant (and similar chemicals with high $EI_{consumer}$) is ongoing and will be reported elsewhere. Optimally, the properties identified here as influencing the exposure to humans should be taken into consideration in chemical safe-by-design.

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