Begränsad delning

RISKMIX
Risk assessment of mixtures

EUROTOX 2024
COPENHAGEN | DENMARK
8-11 SEPTEMBER 2024

Risk modeling of mixtures of endocrine disrupting chemicals relevant to human exposure, using zebrafish (*Danio rerio*) embryo as model organism

Jana M. Weiss[1], Josefin Engelhardt[1], Patrik L. Andersson[2], Elena Golosovskaia[2], Pim E.G. Leonards[3], Lara Z. Fanali[4], Stefan Örn[4]

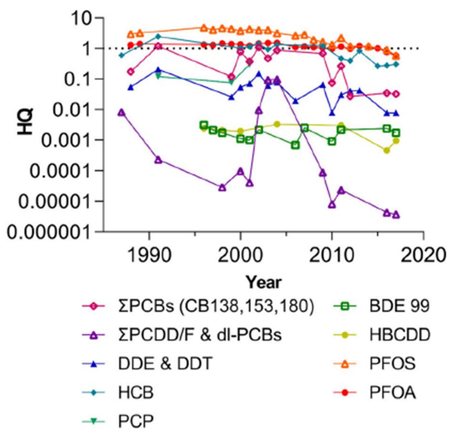
[1]Stockholm University, Environmental Science, Stockholm, Sweden; [2]Umeå University, Chemistry Department, Umeå, Sweden; [3]Vrije University, A-LIFE, Amsterdam, Netherlands; [4]Swedish University of Agricultural Sciences, Biomedical Sience and Veterinary Public Health, Uppsala, Sweden

BACKGROUND

Between 2019-2024, the FORMAS funded project RiskMix addressed different aspects of potential health effects posed by exposure to complex mixtures of anthropogenic chemicals, focusing on the general background exposure of the Swedish population.

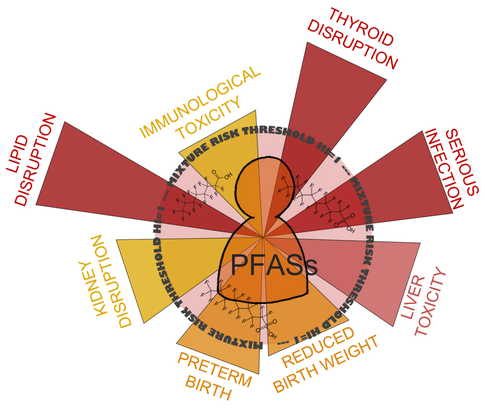
A generic mixture risk assessment (MRA) showed that the risk from exposure to Persistent Organic Pollutants (POPs) cannot be excluded (hazard index >1) for the general population in Sweden.[1] Risk drivers were the per- and polyfluoroalkyl substances (PFASs).

Generic MRA of POPs

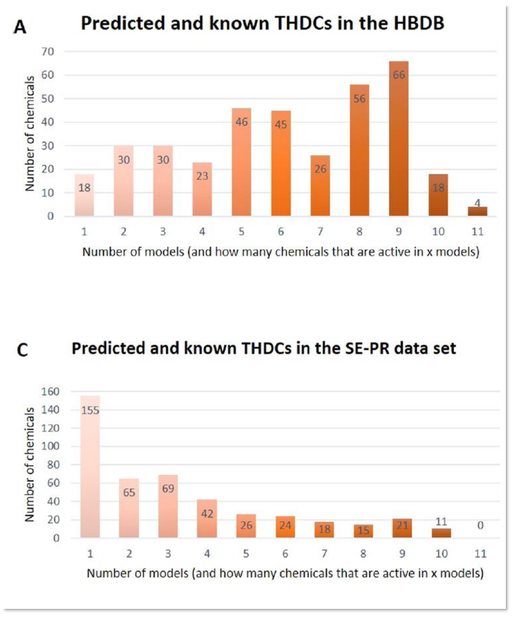


PFAS specific MRA

A specific MRA addressing PFAS exposure indicated that the majority of the general Swedish population is at risk for several health implications.[2]

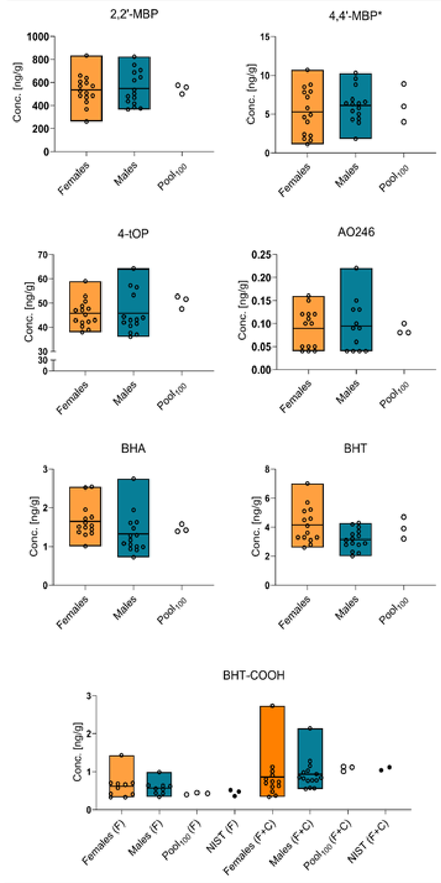


QSAR models and prioritization of risk chemicals



Novel *in silico* models were applied to predict thyroid hormone disrupting chemicals (THDCs) in two datasets, the Human Blood Database (HBDB),[1] and to chemicals in the Swedish Product Register (SE-PR).[4]

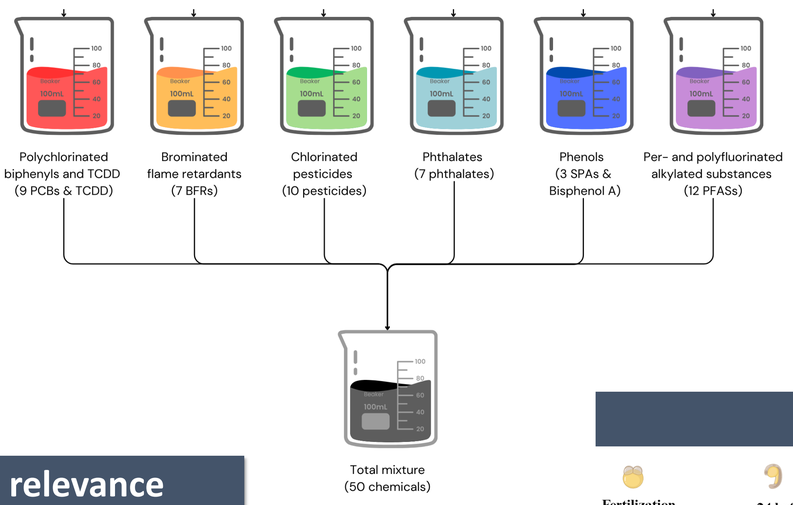
Extended chemical exposure assessment



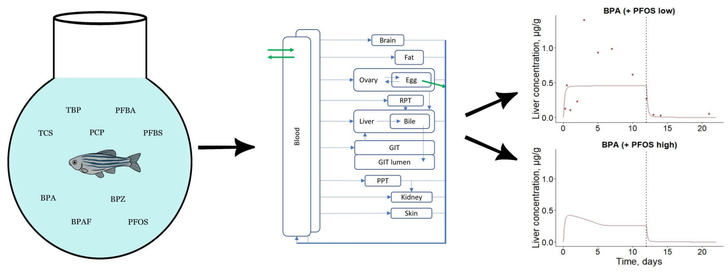
The analysis of phenolic bisphenols, UV-filters, parabens and synthetic phenolic antioxidants (SPAs) revealed high levels of SPAs in human blood.[3]
29 analytes were found in at least one sample either in free or deconjugated fraction
High background contamination challenged the analysis.

Human relevant complex chemical mixtures

Based on exposure reviews, identification of drivers and prioritization of potential risk chemicals based on *in silico* models; 6 chemical group mixtures were created in a human exposure relevant molar ratio.[6]



PBK modeling in adult Zebrafish

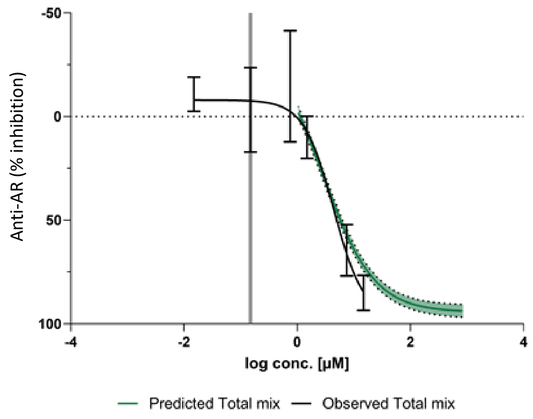


The PBK mixture model predicted that PFOS levels close to those observed in surface waters do not influence the ADME of bisphenols. However, combined exposure of bisphenols with PFOS at higher levels could lead to different tissue distribution of the former.[5]

Toxicity testing of chemical mixtures of human relevance

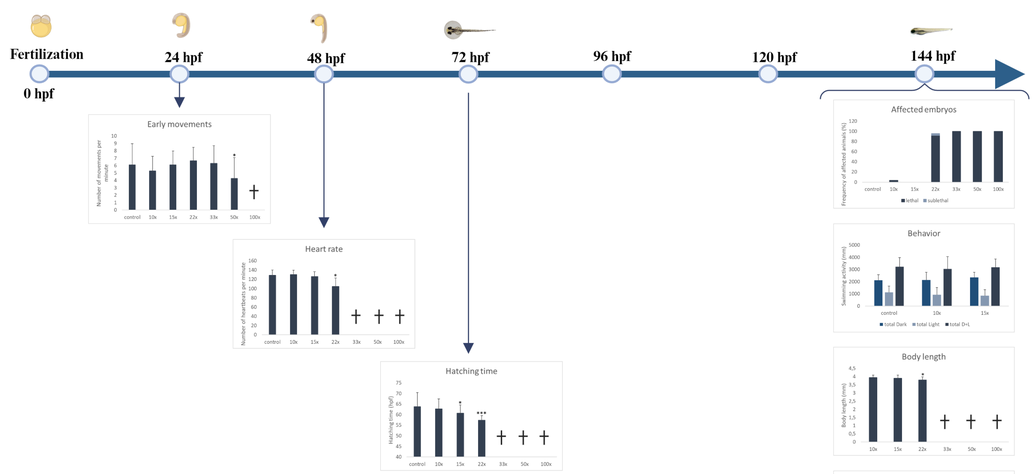
The individual chemical group mixtures, as well as the complex mixture was tested in a range of different toxicity assays at human relevant concentrations (HRCs):

1. Zebrafish Embryo Toxicity (ZFET) assay[7]
2. Human based cell-assays (adipogenesis and a battery of CALUX® assays)[6]
3. Proteome Integral Solubility Alteration (PISA) assay on zebrafish[8]



The mixtures tested in cell assays follow the dose addition model in the anti-AR CALUX.[6] At 100x HRC effects on the adipogenesis (LOEC) could be seen. At 0.12x HRC effects reach EC_{15} in the DR-CALUX and at 11x HRC in ER-CALUX. At 16x HRC effects reach EC_{20} in the anti-AR-CALUX.

Zebrafish embryo toxicity test



At 15x HRC heart rate and hatching time were affected, and from 22x HRC the levels were lethal.[7] Non-monotonic concentration-dependent alterations in lipid levels were observed, peaking at 0.1x HRC. phosphatidylcholine lipids were mostly down regulated, and lysophosphatidylcholine and lysophosphatidylethanolamine lipids upregulated.

References:
[1]Engelhardt *et al.* 2022. https://doi.org/10.1007/s12403-022-00507-y [2]Engelhardt *et al.* 2024 (and **poster P19-34**). Submitted to Environmental Health Perspective. [3]Engelhardt *et al.* manuscript. [4]Dracheva *et al.* 2022. https://doi.org/10.1021/acs.est.1c07762 [5]Golosovskaia *et al.* manuscript. [6]Struwe and Engelhardt et al. manuscript. [7]Zacari Fanali et al. manuscript. [8]Work in progress together with Professor S. Cristobal (LiU).

Project partners:
Stockholm University, SLU, VU Vrije Universiteit Amsterdam, Umeå Universitet

Collaborators:
Örebro Universitet, Karolinska Institutet, Linköping University

Funder:
FORMAS