A review of the human exposure to persistent and mobile chemicals and their potential health risk assessments

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Kim et al., The Science of the total environment 2023:164764

Introduction

Persistent and mobile chemicals (PMs) are highly polar organic chemicals of anthropogenic origin and are an emerging issue of concern for environmental and human health.

- **New hazard classes have been established for PMTs and for vPvMs** under the EU Regulation on Classification, Labelling and Packaging (CLP). A substance shall be considered to **fulfil the "mobile" (M) and "very mobile" (vM) criterion (vM)** when **log K_{oc} < 3** and **log K_{oc} < 2**, respectively (Commission Delegated Regulation (EU) 2023/707 of 19 December 2022). (Table 1)
- This follows a proposal for **evaluation of PMs** (Neumann and Schliebner, 2019) and a proposal for a **list of PMs** (Arp and Hale, 2019).
- The REACH revised impact assessment proposed amendments to Article 57 of REACH **to add PMT and vPvM as criteria** for adding substances to the Registry of Substances of Very High Concern (SVHC) (ECHA, 2021a).

However, comprehensive scientific information regarding the occurrence of PMs in human exposure is still limited.

The aim of this work was to review the recent knowledge on human exposure to PMs and to assess potential health risks based on the relevant published reference values.

Table 1. New PMTs and for vPvMs criteria established by the EU Regulation on Classification, Labelling and Packaging (CLP)

Persistency criteria			
Persistence (P): degradation half-lives			
P	Water	Marine	>60 days
		Fresh or estuarine water	>40 days
	Sediment	Marine	>180 days
		Fresh or estuarine water	>120 days
	Soil		>120 days
vP	Water	Marine	>60 days
		Fresh or estuarine water	>60 days
	Sediment	Marine	>180 days
		Fresh or estuarine water	>180 days
	Soil		>180 days
Mobility criteria			
Mobility (M): the lowest *log* K_{oc} over the pH = 4 - 9			
M			< 3.0
vM			< 2.0

The assessments are based on test results on degradation half-lives and/or biodegradability (P, vP) adsorption/desorption testing (M, vM) and/or (Q)SAR models or other suitable and reliable information for P, vP, M and vM.

Methods

Eight groups of PMs were selected refereeing to the ***previous persistency and mobility criteria*** provided *by Neumann and Schliebner (2019).* In total, 28 PMs, including their derivatives that have *logD_{ow}/K_{ow} or logD_{oc}/K_{oc}* ranging from -3.0 to 2.5, were included in this study:

- **Melamine (MEL) and derivatives**
- **Quaternary ammonium compounds (QACs)**
- **Benzotriazoles (BTRs) and benzothiazoles (BTHs)**
- **1,4-dioxane (1,4-D)**
- **1,3-di-o-tolylguanidine (DTG) and 1,3-diphenylguanidine (DPG)**
- **Trifluoromethane sulfonic acid (TFMS)**

Estimated daily intakes (EDIs) from both internal and external exposure ⟷ **Tolerable daily intake (TDI)**, **Acceptable daily intake (ADI)**, **Reference dose (RfD)**

Results and Discussions

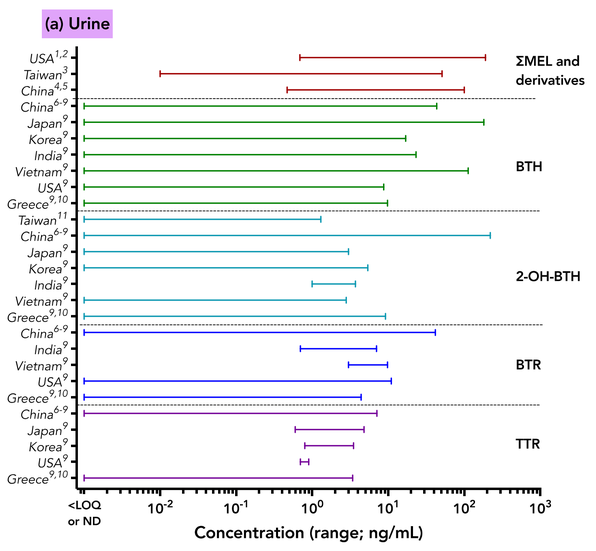
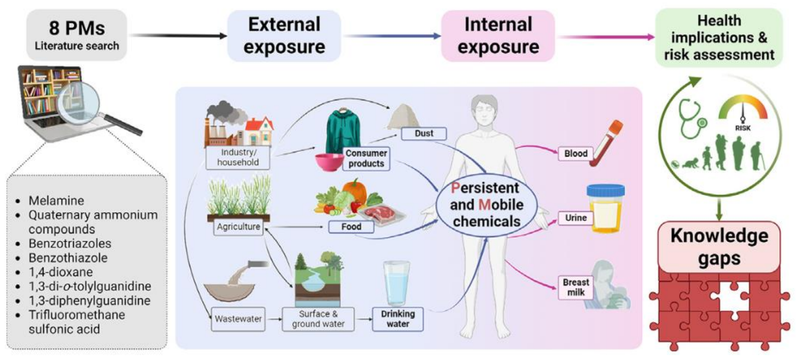


Figure 1. Concentration ranges of PMs in (a) urine, (b) breast milk, and (c) blood reported in previous studies.



- General adult population was mostly investigated, followed by pregnant women.
- Urine was the most used matrix for human biomonitoring of ΣMELs, BTRs, and BTHs, while blood was the most common matrix for QACs, 1,4-D, DPG, and DTG.

- Higher concentrations of ΣMELs and BTH were observed in urine.
- MELs was detected in all urine samples (DF=100%).
- MELs and QACs were detected also in breast milk, whereby 10-fold higher concentration were observed for MELs compared to QACs.
- Both MELs and QACs were higher in urine than in breast milk.

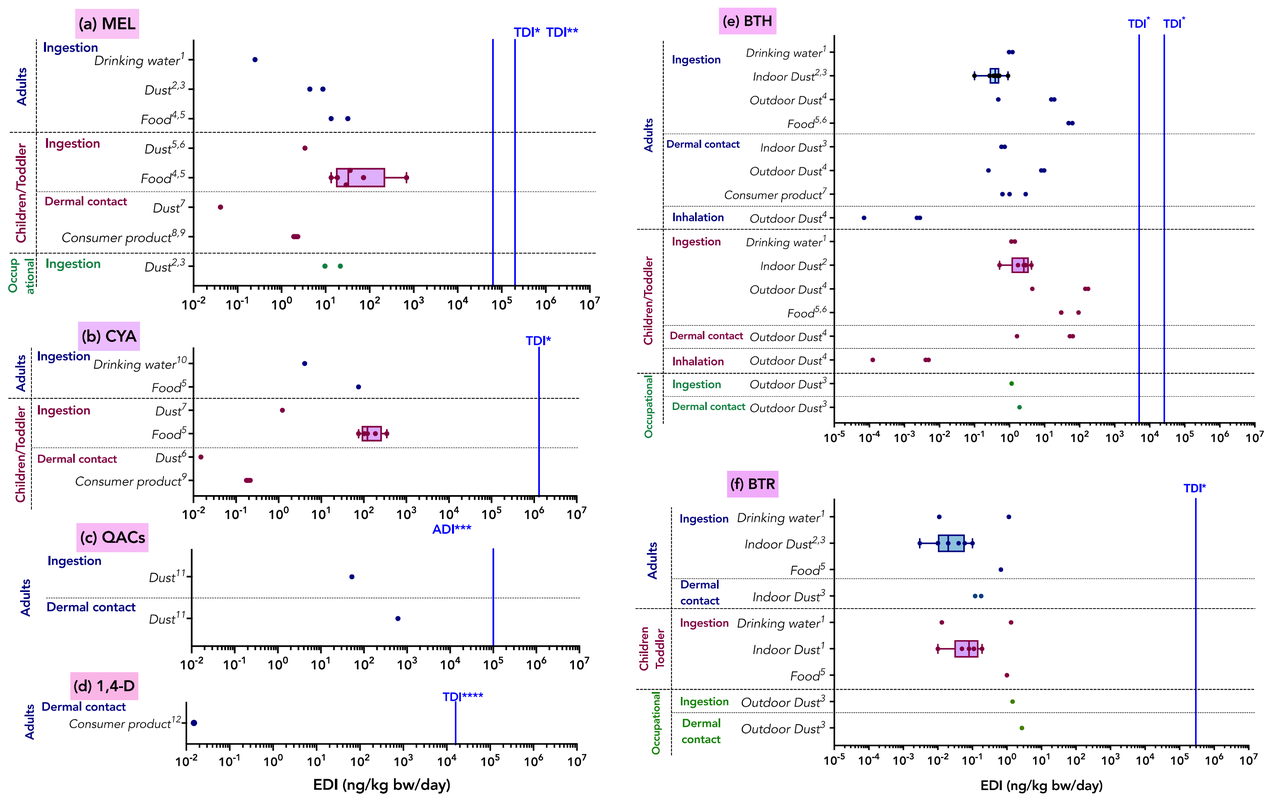


Figure 2. Estimated daily intakes (EDI) of (a) melamine (MEL), (b) cyanuric acid (CYA), (c) ammonium compounds (QACs), (d) 1,4-dioxane (1,4-D), (e) benzothiazole (BTH), and (f) benzotriazole (BTR) through external exposure reported in previous studies.

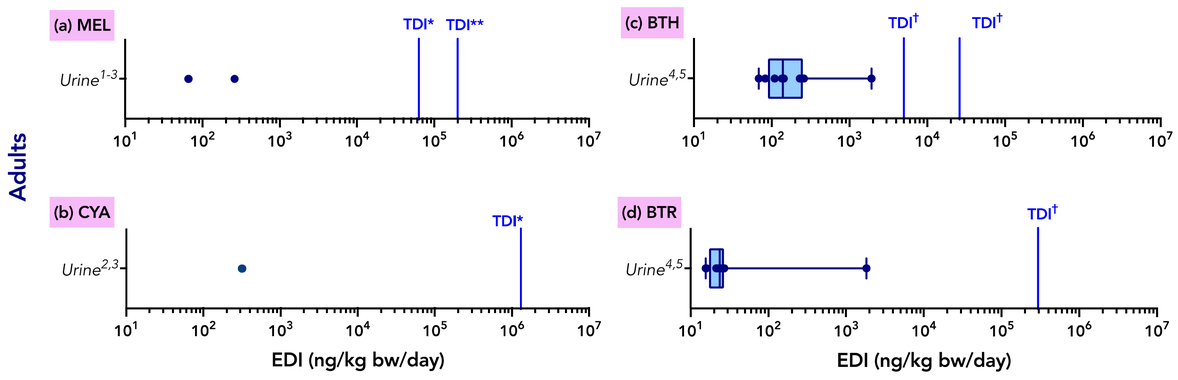


Figure 3. Estimated daily intakes (EDI) of (a) melamine (MEL), (b) cyanuric acid (CYA), (c) benzothiazole (BTH), and (d) benzotriazole (BTR) through internal exposure reported in previous studies.

- Very limited biomonitoring studies on DPG and DTG were available. No reports regarding TFMS were available.
- None of the reviewed PMs showed EDIs, calculated from the internal and external exposure levels, exceeding the current TDI or RfD values. Indicating that internal and external exposure levels of these PMs and in the studied general populations are less probable to lead to health effects.
- However, the upper bound measurements of BTH are not more than three-fold below the TDI. If exposure would increase, the EDI would become rather close to or even exceed the TDI.
- Calculation of the EDIs are based on a simple extrapolation from measured HBM values. Dedicated elaboration of health-based HBM Guidance Values (HBM-GV) with additional measurements of human toxicokinetics seems to be warranted in order to reduce significant uncertainties in the internal exposure-based risk assessments.

Conclusions

- EDIs of PMs from internal and external exposure levels were compared to relevant TDI or other RfD, and it was concluded that none of the PMs in this review resulted in EDIs exceeding the TDI or RfD values.
- However, exposure levels are unknown for many other PMs and in vulnerable populations.
- It is necessary to identify and assess the human exposure to other PMs or potential PMs that were not covered in this review to achieve a comprehensive understanding of the potential risks associated with PMs.

References:

Fig 1: *[1]Liu et al., 2022a; [2]Shi et al., 2020; [3]Tsai et al., 2021; [4]Melough et al., 2020; [5]Zhu and Kannan, 2019a; [6]Asimakopoulos et al., 2013a; [7]Asimakopoulos et al., 2013b; [8]Chen et al., 2022b; [9]Li et al., 2018; [10]Li et al., 2017; [11]Li and Ding, 2021; [12]Zheng et al., 2022; [13]Zheng et al., 2021; [14]Tang et al., 2022.*

Fig 2 (left): *[1]Zhu and Kannan, 2020b; [2]Zhao et al., 2022; [3]Li et al., 2022; [4]Zhu and Kannan, 2018a; [5]Zhu and Kannan, 2019b; [6]Zheng et al., 2020a; [7]Zheng et al., 2020b; [8]Zheng and Salamova, 2020; [9]Zhu and Kannan, 2020a; [10]Zhu and Kannan, 2020b; [11]Zheng et al., 2020b; [12]Lin et al., 2017; *EFSA, 2010; **FDA, 2008 and Hsieh et al., 2009; ***BfR, 2012 and BfR, 2013; ****Nishimura et al., 2004.*

Fig 2 (right): *[1]Wang et al., 2022; [2]Wang et al., 2013; [3]Li et al., 2020a; [4]Zhang et al., 2018; [5]Jia et al., 2019; [6]Trabalon et al., 2017; [7]Ge et al., 2021; *calculated with an established LO(A)EL and/or NO(A)EL (Ginsberg et al., 2011).*

Fig 3: *[1]Shi et al., 2020; [2]Liu et al., 2022a; [3]Zhu and Kannan, 2019a; [4]Li et al., 2018; [5]Asimakopoulos et al., 2013b; *EFSA, 2010; **FDA, 2008 and Hsieh et al., 2009; †calculated with an established LO(A) EL and/or NO(A)EL (Ginsberg et al., 2011).*