Human exposure to persistent and mobile chemicals : a review of sources, internal levels and health implications

Human Exposure to Persistent and Mobile Chemicals: A Review of Sources, Internal Levels and Health Implications

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Abstract

Persistent and mobile chemicals (PMs) are highly polar organic chemicals of anthropogenic origin, which have been documented as an emerging issue of concern for environmental and human health and for which policy needs have recently been identified. Since PMs are recognized as a serious threat to water resources and drinking water, many studies have focused on the occurrence and fate of PMs in aqueous environmental matrices, especially surface water, groundwater and drinking water but considerably less so directly on human exposure. Consequently, our understanding of human exposure to PMs is still limited. In this context, the main objectives of this review are to provide reliable information on PMs and comprehensive knowledge about human internal and relevant external exposure to PMs. This review highlights the occurrence of eight selected PMs: melamine and its derivatives and transformation products, quaternary ammonium compounds, benzotriazoles, benzothiazole and their derivatives and transformation products, 1,4-dioxane, 1,3-di-*o*-tolylguanidine, 1,3-diphenylguanidine and trifluoromethane sulfonic acid in human matrices (blood, urine, etc.) and environmental samples relevant to human exposure (drinking water, food, indoor dust, etc.). In addition, human biomonitoring data is discussed in the framework of the chemicals risk management policy. Current knowledge gaps of selected PMs from a human exposure perspective, as well as future research needs were also identified. While PMs discussed in this review have been found in various environmental matrices relevant for human exposure, it is important to note that human biomonitoring data for some PMs is very limited. Available data on the estimated daily intakes of some PMs suggest that they do not pose an immediate concern for human exposure.

Keywords

Persistent and mobile chemicals, Biomonitoring, Drinking water, Dust, Food, Health implications

1. Introduction

Persistent and mobile chemicals (PMs) represent a large group of anthropogenic organic compounds with specific combinations of intrinsic properties that make them persistent and mobile in the aquatic environment. Since various classes of organic compounds including pharmaceuticals, pesticides, and perfluoroalkyl substances (PFAS) can be PMs, emission sources of PMs may vary widely (industry, agriculture, households). Once released into the environment, PMs can rapidly distribute, recirculate, and accumulate without being removed from the water cycle because of their intrinsic properties, being high water solubility, and weak or negligible sorption to soils and sediment. Consequently, PMs may well end up in drinking water, potentially threatening human health (Angeles and Aga, 2020; Arp and Hale, 2019; Arp et al., 2017; Knepper et al., 2020; Neumann and Schliebner, 2019; Reemtsma et al., 2016; Rüdel et al., 2020).

In recent years, the occurrence and fate of PMs in the aqueous environment have been documented as a key emerging issue of concern among scientists, regulators, and the general public, and many studies have been conducted to identify PMs in the environment for potential regulatory actions, primarily within Europe. Neumann and Schliebner (2019) first proposed to establish new hazard categories for PMs under the European Union Regulations on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and on Classification, Labelling and Packaging (CLP) which are additionally toxic (referred to as PMTs) and for very persistent and very mobile chemicals (vPvMs) and has reported criteria for the evaluation of PMs (Neumann and Schliebner, 2019). Arp and Hale (2019) suggested a list of PMs based on substance data in REACH-registrations in 2019 (Arp and Hale, 2019). In the REACH Revision Impact Assessment, it has been proposed to amend REACH Article 57 in order to add PMT and vPvM as criteria to add a substance to the Registry of SVHC (Substance of Very High Concern) Intentions (ECHA, 2021a).

Table 1 presents an overview of the criteria proposed by Neumann and Schliebner (2019) for degradation half-lives for persistent and very persistent chemicals in marine, fresh or estuarine water, in marine, fresh or estuarine water sediment, and in soil at specific temperature and pH. Criteria and screening criteria for mobile and very mobile chemicals were presented by Neumann and Schliebner (2019) and Arp and Hale (2019) based on the lowest logarithmic organic carbon-water coefficient (log K_{oc}) in the pH range 4-9, the lowest pH-dependent octanol-water distribution coefficient, or the logarithmic octanol-water partition coefficient (log K_{ow}) in the pH range 4-9 being ≤ 4 and 3 for M and vM, respectively (Table 1) (Arp and Hale, 2019; Neumann and Schliebner, 2019).

However, less stringent mobility criteria (log K_{oc} ≤ 3 and 2, respectively) were proposed more recently by the European Commission in 2021. Thus, the criteria of mobility are still under discussion. Neumann and Schliebner (2019) has also suggested toxicity criteria based on REACH annex XIII section 1.1.3 or other hazardous properties, such as the derived-No-Adverse-Effect-Level (NOAEL) of ≤ 9 μg/kg bw/day and suspected endocrine disruption (Neumann and Schliebner, 2019). Some PMs would not be classified as PMT according to Arp and Hale (2019) as not fulfilling the current T-criterion. It is stressed however that considerable uncertainty about their toxicity may exist and their continuous release and accumulation in the water cycle suggest that adverse effects may occur and would therefore be of concern.

To date, many studies have focused on the occurrence and fate of diverse PMs in aqueous environmental matrices, such as surface water, groundwater and drinking water, since PMs are recognized as a serious threat to drinking water quality (Arp and Hale, 2019; Hale et al., 2020). In addition, some recent reviews on PMs summarized the current state of knowledge, the existing analytical techniques and the occurrence in the aquatic environment; however, there are no published reviews actually addressing human internal and external exposure to PMs. Our understanding of human exposure to PMs is thus still limited.

Therefore, the main objectives of this review were to provide an overview of the published studies related to internal human exposure and occurrence in environmental samples relevant to human exposure to PMs, with a focus on recent studies. To select PMs for this review, a list of PMT/vPvM and chemicals listed to prioritize for biomonitoring in Pellizzari et al. were considered and PMs with some available human and environmental data but with research gaps were chosen. As a result, information for eight relevant PMs was presented in this review: melamine (MEL), quaternary ammonium compounds (QACs), benzotriazoles (BTRs), benzothiazoles (BTHs), 1,4-dioxane (1,4-D), 1,3-di-*o*-tolylguanidine (DTG), 1,3-diphenylguanidine (DPG) and trifluoromethane sulfonic acid (TFMS). Their persistency (half-lives) and mobility (log K_{oc}, D_{ow}, or K_{ow}) properties meet the criteria of PM or potential PM from Neumann and Schliebner (2019) and Arp and Hale (2019) (Table 1) and the rationale for these properties is shown in Table 2. Legacy poly- and perfluorinated alkylated substances (PFAS), pesticides, and pharmaceuticals were not discussed here, because several recent reviews focusing on the environmental occurrence and human exposure already exist. This review summarized data on the eight selected PMs from studies published within the past five years, and older publications are included only if limited data were available. In addition, we discuss their available human biomonitoring data representing the internal exposure to these PMs from a chemicals risk management policy framework and identify the future research needs from a human exposure perspective.

1.1. Melamine and its derivatives and transformation products

Melamine (MEL), a heterocyclic aromatic amine synthesized as first in the 1830s, is the raw material to produce melamine formaldehyde resin (Skinner et al., 2010). It is a high production volume chemical with estimated annual production volumes of over 1 million tons (EPA, 2020). MEL is extensively applied in a wide variety of consumer products, including plastic kitchenware and dinnerware, flooring, paint pigments, furniture, and coatings (Bolden et al., 2017; Zhao et al., 2022). It is also a minor metabolite and degradation product of the pesticide and veterinary drug cyromazine. Cyanuric acid (CYA) is a degradation product of MEL, and it is widely applied as disinfectant for swimming pool chlorination, or as chlorine stabilizer, sanitizer, and bleaching agent. Ammelide (AMD) and ammeline (AMN) are impurities in the melamine manufacturing process and are also intermediates formed via melamine hydrolysis (Zhao et al., 2022).

MEL is hydrophilic and highly mobile, and has longer half-life than 60 days in water (Table 2 and Table S1.1). As a result, MEL has been recently suggested to be a vPvM and PMT compound and was included in the SIN - Substitute It Now - List in November 2019 (Lennquist, 2020), gaining an increasing public attention (Liu et al., 2021). Due to their widespread use, MEL and its derivatives and transformation products (TPs) have been detected in a wide range of different environmental and human matrices, including soil and sediments (Zhu et al., 2019b), surface waters (Johannessen et al., 2022), indoor dust (Li et al., 2022; Zhu and Kannan, 2018b), food (Zhu and Kannan, 2019b), human and animal urine (Karthikraj et al., 2018) and breast milk (Yalcin et al., 2020; Zhu and Kannan, 2019c).

Suggested human exposure pathways involve ingestion of contaminated food, possibly due to leaching from tableware (Takazawa et al., 2020), food packaging and contaminated water (Bouma et al., 2022), inadvertent dust ingestion (Choi et al., 2022; Li et al., 2022; Zhu and Kannan, 2018b), and dermal contact with treated clothing (Zheng and Salamova, 2020). In the body, MEL appears to be rapidly absorbed in the gastrointestinal tract and to be rapidly excreted in the urine with little or no metabolism (Bolden et al., 2017; Dobson et al., 2008). The limited information available for CYA also indicates rapid absorption in the gastrointestinal tract followed by elimination via the urine with little or no biotransformation (EFSA, 2010).

MEL and its derivatives and TPs are perhaps most well-known for the unfortunate consequences of adulteration incidences in pet food in 2007 and infant formula in 2008, which resulted in renal damage and failure or even death among pets and infants (Guan et al., 2009). MEL and CYA are known nephrotoxicants and, while they individually exhibit relatively low acute toxicities (LD_{50}s > 1 g/kg body weight), upon combination they can form insoluble crystals in the kidney and induce renal damage and failure (Liu et al., 2017a). Beyond nephrotoxicity,

124 growing evidence suggests that MEL and CYA have also endocrine disruptive properties (Bolden et al., 2017),
125 reproductive (Chu et al., 2017) and neurological (An and Sun, 2017) toxicity. The toxicological profile of MEL and
126 CYA was evaluated in the scientific opinion of the European Food Safety Authority on melamine in food and feed
127 and resulted in a tolerable daily intake (TDI) of 0.2 mg/kg bw/day and 1.3 mg/kg bw/day, respectively (EFSA,
128 2010). The toxicological databases for AMD and AMN are however very limited and no TDI could thus be
129 established. In addition, EFSA concluded that, in case of significant concomitant exposure with CYA, AMD or
130 AMN, the TDI for MEL is not applicable due to the increased potential for formation of urinary crystals (EFSA,
131 2010). In the US, the FDA initially established a TDI of 0.63 mg/kg bw/day, then lowered it at 0.063 mg/kg bw/day
132 (FDA, 2008; Hsieh et al., 2009). Finally, to protect public health and food safety, the maximum amount of MEL
133 allowed in powdered infant formula and in other foods and in animal feed was set at 1 mg/kg and 2.5 mg/kg,
134 respectively (FAO, 2010).

135

136 **1.2. Quaternary ammonium compounds**

137 QACs represent a group of surface-active substances characterized by a cationic headgroup (with nitrogen
138 carrying the positive charge) and at least one hydrophobic hydrocarbon side chain (Bures, 2019). The QAC salt
139 is usually formed with chlorine or bromine as the corresponding anion. Most prevalent QACs include three major
140 classes: 1) alkyltrimethylammonium compounds (ATMACs), 2) benzylalkyldimethylammonium compounds
141 (BACs) and 3) dialkyldimethylammonium compounds (DDACs). Thereby, the alkyl side chains most commonly
142 include 6 to 18 carbon atoms for BACs and 8 to 18 carbon atoms for DDACs and ATMACs (Table 2; (Zhang et al.,
143 2015). The amphiphilic properties of QACs lead to a wide range of applications, such as surfactants in fabric
144 softeners, household cleaners and personal care products such as hair conditioning creams (Ying, 2006). More
145 importantly, QACs show antimicrobial activity against various pathogens, such as bacteria, viruses and fungi, by
146 disruption of their phospholipid membrane which ultimately leads to cell lysis (Schrank et al., 2020). This allows
147 a wide application of QACs in disinfectant products, hand wipes, (alcohol-free) hand sanitizers and soaps.
148 Especially with the start of the COVID-19 pandemic in early 2020, and hence a significant increase in disinfecting
149 practices, the usage of QACs rose posing the question of potential human exposure to these compounds (Hora
150 et al., 2020). Already before the pandemic, QACs were high production chemicals with annual production
151 volumes of up to 25,000 tons as reported by the US Environmental Protection Agency (EPA) for 2019 (EPA, 2020).

152 QACs are not currently included in the list of PMs reported by Arp and Hale (2019) but can be characterized as
153 potential PMs according to the criteria listed in Table 1. Most QACs included here show log K_{ow} values < 4.5

suggesting their high mobility. This is further supported by the high water solubility of some of the QAC derivatives. Regarding persistence, consistent data of the half-lives of different QAC derivatives (as highlighted in Table 1) is lacking. However, recent studies suggest a high persistency of these compounds both in environmental matrices (such as sediment, and water bodies), as well as human samples (blood and breast milk) (Mohapatra et al., 2022; Zheng et al., 2022; Zheng et al., 2021). Therefore, the assignment of QACs to the group of potential PMs seems justified. Furthermore, QACs have recently been identified as emerging contaminants exposure which might lead to health effects in children (Pellizzari et al., 2019).

The various applications of QACs as disinfectants described above follow a wide approval of QACs in disinfecting products in the US. Following the outbreak of COVID-19, a list of 430 disinfecting products to be used against the SARS coronavirus 2 was released by EPA (EPA, 2022). 216 of these disinfecting agents contained QACs corresponding to their approval in a brought selection of products. In the European Union, the Biocidal Products Regulation ((EU) No 528/2012 (BPR)) requires a separate application for an approval of a certain QAC in a particular product type (EC, 2012). At present, C10-DDAC (CAS: 7173-51-5) is permitted in products for human hygiene and, together with C8- to C18-BACs, in wood preservatives in the EU. The approval of various other QACs in several product types is currently under evaluation in the EU.

Several possible pathways have been described for human exposure to QACs. These include the intake of food contaminated with QACs due to their use as biocides or for the cleaning and disinfection of production tools or storage containers (EFSA et al., 2021; Xian et al., 2016). Furthermore, high levels of QACs have been reported in indoor dust samples indicating dust inhalation as another possible exposure route (Zheng et al., 2020b). Lastly, dermal exposure through contact with disinfected surfaces must also be considered (Li et al., 2020a).

The toxicity of QACs and resulting hazards for both human health and aquatic environments have been reviewed in detail elsewhere (Luz et al., 2020; Zhang et al., 2015). In brief, based on the currently available data, no evidence for mutagenicity, genotoxicity or carcinogenicity of QACs could be obtained (Luz et al., 2020). The same applies to reproductive toxicity (ECHA, 2015; EPA, 2017a). However, DDACs and BACs were identified as potent skin and eye irritants. Additionally, QACs were associated with ocular hypersensitivity and inflammation as well as contact dermatitis (Peyneau et al., 2022). Reported LD_{50} (rat) values, reflecting the oral acute toxicity, ranged from 238 to 329 mg/kg bw and 304.5 to 344 mg/kg bw for DDACs and BACs, respectively (ECHA, 2016; Luz et al., 2020). Evaluating the known toxic effects of QACs under the Biocidal Products Regulation, the European Food Safety Authority (EFSA) established an Acceptable Daily Intake (ADI) of 0.1 mg/kg bw per day for both DDACs and BACs within a reasoned opinion on the dietary risk assessment (EFSA, 2014). Latter defined DDACs and BACs to which the given ADIs apply as dialkyldimethylammonium and benzylalkyldimethylammonium with an even

number of chain lengths ranging between C8-C12 and C8-C18, respectively. It must be noted that for QACs, in contrast to other contaminants, and ADI (instead of a TDI) is provided as some QACs are approved for use in different biocide products. For example, the use of dodecyl dimethyl ammonium chloride has recently been approved for the use in disinfectant product types 3 and 4 (according to the definitions given in EU Regulation (EU) No 528/2012 and 2021/1045).

Despite toxic effects described for QACs, studies on chronic human exposure and associated health effects are scarce. Hrubec et al. identified an association between chronic human exposure to QACs (as found by blood monitoring) and decreased mitochondrial function, an increase in inflammatory cytokines, and a disruption of cholesterol homeostasis (Hrubec et al., 2021). However, the study was limited by a small sampling group consisting of 41 participants. Extensive studies covering a larger population are still lacking.

1.3. Benzotriazoles and benzothiazoles

Benzotriazoles (BTRs) and benzothiazoles (BTHs) are heterocyclic aromatic compounds with 1,2,3-triazole ring and 1,3-thiazole ring fused to a benzene ring, respectively with a wide variety of uses in commercial and industrial applications.

BTRs are mostly used as corrosion inhibitors in various consumer products (e.g., in dishwasher detergents, fungicides, antifogging fluids, and as stabilizer in paper), as brake fluids in the metal industry or as antifreeze in cooling agents and at airports (Liu et al., 2017b; Vendemiatti et al., 2021). A commonly known BTR is 1-H-benzotriazole (BTR, CAS: 95-14-7), which is classified as a vPvM and PMT under Arp and Hale (2019) (Table 2). It is registered under the REACH Regulation and is manufactured in and/or imported to the European Economic Area, at $\geq$ 1 000 to < 10 000 tonnes per annum (ECHA, 2022c). Other important BTRs are 5-methyl-1-H-benzotriazole (MeBTR, CAS: 136-85-6), 5-chloro benzotriazole (5-Cl-BTR, CAS: 94-97-3). Generally, BTRs are classified into 2 groups according to their use: 1) anti-corrosive agents and 2) UV light absorbers and stabilizers. In this review, however, we do not discuss BTR-UV filters because they are not mobile.

BTHs are used as vulcanization accelerators in rubber production, fungicides in leather and paper production, corrosion inhibitors in antifreeze formulations, herbicides, algicides, and UV light stabilizers in textiles and plastics (Liao et al., 2018). Commonly known BTHs include benzothiazole (BTH, CAS: 95-16-9), 2-hydroxybenzothiazole (2-OH-BTH, CAS: 934-34-9), and 2-methylthio-benzothiazole (2-Me-S-BTH, CAS: 615-22-5). In particular, BTH is classified as potential PMT and vPvM by Arp and Hale (2019) due to their high persistency and mobile properties (Table 2). Log K_{ow} of BTRs and BTHs are shown in Table 2, Table S1.1 and Table S1.2.

Briefly, log K_{ow} of BTRs and BTHs considered in this review range between 0.3 and 1.8 for BTRs, and 1.5 and 5.95 for BTHs, respectively, which indicates that BTHs have more hydrophobic properties and partition mostly into organic phase than BTRs.

Exposure sources of BTRs and BTHs to humans are similar to other classes of compounds listed in this review, and include drinking water, food, dust, consumer products, and personal care products. One unique possible exposure source for BTHs is crumb rubber from recycled end-of-life tires (Schneider et al., 2020a), which is widely used as infill material for synthetic turfs at sport fields and playgrounds.

The toxicity of BTRs and BTHs has been reported from several *in vitro* and *in vivo* species. Studies regarding toxicity of BTRs have been examined acute and high-level exposure to microorganisms (Cornell et al., 2000), plants (Seeland et al., 2012), invertebrates (Giraudo et al., 2017), and vertebrates (Damalas et al., 2018; Pillard et al., 2001). However, for our knowledge, the studies focused on chronic low-level exposure to BTRs on the species have not been done. There are some studies which examined the endocrine disrupting effects of BTRs, such as *in vitro* (Harris et al., 2007) and *in vivo* estrogenic activity (Tangtian et al., 2012). However, toxicity studies on humans are very limited. Studies on the toxicity of BTHs have been reported from *in vitro* and *in vivo* experiments. Thyroid hormone activity (Hornung et al., 2015), genotoxicity and cytotoxicity (Ye et al., 2014), and aryl hydrocarbon receptor (AhR)-mediated activity (Noguerol et al., 2006) of BTHs have been reported *in vitro* settings. As for *in vivo*, acute toxicity (Ginsberg et al., 2011), dermatitis and irritation (allergic) reactions (Ikarashi et al., 1993), and thyroid hormone-related effects (Hornung et al., 2015) of BTHs have been reported. However, most of these studies investigated the toxic effects of BTHs at high exposure doses.

1.4. 1,4-Dioxane

1,4-D is a cyclic diether, historically used as a stabilizer in chlorinated solvents, wetting and dispersing agent, and aerosol additive in industrial processes (Godri Pollitt et al., 2019; Goen et al., 2016). The manufacture and/or import volume of 1,4-D into the European Union is registered at 1,000 – 10,000 tons/year (ECHA, 2022b). According to the Chemical Data Reporting database and the Toxics Release Inventory (TRI) for 2016, approximately 500 tons/year of 1,4-D was produced or imported (EPA, 2016a) and 300 tons was released to the environment in U.S. (EPA, 2016b). Although the use of 1,4-D as a solvent stabilizer was terminated (EPA, 2017b), it has also been used for various consumer products, such as personal care products, and food packaging adhesives, and as a food additive (ATSDR, 2012; EPA, 2006). The physico-chemical properties of 1,4-D are presented in Table 2 and S1.1. 1,4-D is completely miscible with water and resistant to biodegradation in water

and soil (ATSDR, 2012). Its half-life in groundwater and surface water is 2 to 5 years and 56 days, respectively (Adamson et al., 2017), indicating the persistent nature of 1,4-D. It is classified as PMT and added to and candidate list of candidate list of SVHC for authorization.

Human exposure to 1,4-D has been suggested to occur through the consumption of contaminated food and water, or dermal contact (EPA, 2017b). 1,4-D is a probable human carcinogen (Chen et al., 2022a; Dourson et al., 2014; Kano et al., 2009; Wang et al., 2022). The EPA has derived a reference dose (RfD) of 0.03 mg/kg bw/day for 1,4-D based on a NOAEL of 9.6 mg/kg bw/day for liver and kidney toxicity in male rats (Table S1.1) (IRIS, 2010). Exposure to a high level (> 50 ppm) of 1,4-D has been suggested to lead to several adverse effects, including headache, and irritation of the eyes, nose, and throat (ATSDR, 2012). In addition, recent toxicological studies revealed that 1,4-D may cause DNA damage and alteration of oxidative stress (Wang et al., 2022) and imperceptible injury to the kidney by environmentally relevant concentration (~ 0.5 mg/L) of 1,4-D without no clinical changes (Qiu et al., 2019). Some studies published in 1990 have described the pharmacokinetics of 1,4-D in humans and animals (Braun and Young, 1977; Young et al., 1978; Young et al., 1977) and have shown that 1,4-D is absorbed and eliminated rapidly in the urine. In humans and animals, 1,4-D is metabolized to β-hydroxyethoxyacetic acid (HEAA) and 1,4-dioxane-2-one (ATSDR, 2012; Braun and Young, 1977).

1.5.1,3-di-o-tolylguanidine and 1,3-diphenylguanidine

DTG and DPG are emerging synthetic antioxidants, primarily used as vulcanization agents in the manufacture of rubber including synthetic gloves and other polymers (Table 2 and S1.1) (Shin et al., 2020; Zahn et al., 2019). The manufacture and/or import volumes of DTG and DPG into the European Union are registered at 10 – 100 tons/year and 10,000 – 100,000 tons/year, respectively (ECHA, 2022a). Especially, tire production is the main application of DTG and DPG, so leachate from road run-off is suggested as an emission source of DTG and DPG (Neuwald et al., 2022). Log D_{ow}/K_{ow} of DTG and DPG are -3.0 and 1.4, respectively (Arp and Hale, 2019). Water solubility is 70 mg/L for DTG and 475 mg/L for DPG. The dissociation constant (pK_a) is 10.67 for DTG and 10.12 for DPG, so they mainly exist in their protonated form in the environment. They are currently classified as vPvM and PMT, and, especially DTG has been identified as one of the most prevalent PMs in water (Schulze et al., 2019).

The current knowledge on the adverse effects of exposure to DTG on human and environmental health is limited. However, some toxicological studies have observed that DTG may be teratogenic and cause maternal neurobehavioral changes (Ema et al., 2006a; Ema et al., 2006b). In addition, Arp and Hale (2019) reported that

DTG fulfils the criteria for classification as carcinogenic (category 1B), and as reproductive toxicity (category 2) (Arp and Hale, 2019). DPG is suggested to have serious health and environmental hazards including skin irritation, eye irritation, developmental toxicity, teratogenicity, and reproductive toxicity (ECHA, 2022a). Potential genotoxic effects of DPG were observed in an *in-vitro* study (Marques Dos Santos et al., 2022). In addition, DPG was the most commonly identified allergen through patch tests for healthcare workers (Dejonckheere et al., 2019). The metabolism and disposition of DTG are not completely understood, whereas there are rat studies that investigated the distribution and possible metabolism of DPG (Ioannou and Matthews, 1984; Shah et al., 1985). One study identified that radiolabelled DPG is distributed throughout the body tissues including blood, liver, muscle, brain, heart, etc. and liver and intestines seemed to preferentially accumulate DPG (Shah et al., 1985). However, DPG was readily eliminated from most of the tissues within 24 h after exposure. Another research showed a similar result to Ioannous and Matthews (1984) that more than 80% of the adsorbed dose DPG-derived radioactivity was cleared into urine and faeces within 5 days (Shah et al., 1985). Additionally, both studies reported that the DPG-derived radioactivity in the urine was present in the form of DPG and metabolites and only metabolites were detected in faeces (Ioannou and Matthews, 1984; Shah et al., 1985).

1.6. Trifluoromethane sulfonic acid

TFMS, which belongs to the ultra-short-chain PFAS, is vPvM classified in Arp and Hale (2019). The manufacture and/or import volume of TFMS into the European Union is registered at 100 – 1,000 tons/year (ECHA, 2022c). It has been used as firefighting foam. TFMS is miscible in water (1,600 g/L) and is a very strong acid (pK_a = -14.7; Table 2 and S1.1). TFMS is a vPvM chemical and has a 'very high' REACH Emission Likelihood classified in Arp and Hale (2019). Although the knowledge on toxicokinetics, environmental fate and exposure pathways to humans of TFMS is still limited, TFMS was identified as one of the most prevalent novel PM in water (Schulze et al., 2019). In addition, TFMS may be globally distributed and has been detected in surface snow in the Arctic (Bjornsdotter et al., 2021). TFMS exposure may induce eye and skin irritation in humans (ECHA, 2022) and disturb liver lipid metabolism (Zhou et al., 2020a).

2. Occurrence of PMs in the relevant external exposure source for humans

A number of 8 relevant PMs were reviewed for their occurrence in drinking water and other water sources, dust, consumer products, and food. Concentrations of wastewater, sediment, and sludge were discussed in Supplementary Materials section 1 (S1).

2.1. Melamine

The occurrence of MEL and its derivatives and TPs in wastewater, sediment, and sludge was reviewed in Supplementary Materials section S1.1.

Drinking water and other water sources

Concentrations of MEL and its derivatives and TPs were determined between 2015 and 2019 in more than 220 water samples, comprising river and lake water, seawater, drinking water, rainwater, wastewater, and swimming pool water, collected from New York State, USA (Figure 1) (Zhu and Kannan, 2020b). The total concentrations of MEL and its derivatives and TPs were measured in the following order: swimming pool water (median: 1.5×10^7 ng/L, represented almost entirely by CYA), wastewater (1240), rainwater (739), tap water (512), river water (370), lake water (347), seawater (186), and bottled water (98) (Table S2.1). MEL was the major compound in river and lake water, while CYA was dominant in swimming pool water, wastewater, rainwater, tap water, seawater, and bottled water. The elevated concentrations of CYA detected in water from swimming pools was identified by the authors as a priority for further research, especially to prevent exposure in children from swimming. The EDI of MEL and CYA via ingestion of tap water was estimated between 0.18 and 0.79 and between 2.9 and 13 ng/kg bw/day, respectively, suggesting that drinking water is only a minor contributor to exposure to MEL and CYA in humans (Figure 4 and Table S2.12) (Zhu and Kannan, 2020b). The leaching of MEL from melamine based kitchenware (table bowls) to water-based simulants (including drinking water) was investigated by (Takazawa et al., 2020). The highest concentration of MEL leached was 0.37-70.2 ng/cm^2 to hot water (90-100 °C), followed by <0.03-49 ng/cm^2 to drinking water at room temperature (25 °C). The median EDI of MEL based on the ingestion of drinking water at room temperature was calculated at 44,300 ng/kg bw/day, suggesting that kitchenware can be a significant contributor for human exposure to melamine.

Soils

Since the contamination of soils with melamine can lead to plant uptake and food chain transfer of these chemicals, Zhu et al. investigated the concentrations of MEL and its derivatives and TPs in 98 surface soils and 16 fertilizers collected across China in 2017. High concentrations of MEL and its derivatives and TPs were found in soils (concentration range: 0.09-2.02 μg/g dw, mean: 0.21 μg/g dw), and MEL accounted for 63% of the total concentrations, followed by CYA (28%). The measured concentrations in fertilizers were 3 to 4 orders of magnitude higher than those found in soils, suggesting that that fertilizers are a relevant source of MEL and CYA in farm soils (Table S2.1) (Zhu et al., 2019b).

Dust

The occurrence of MEL and its derivatives and TPs was determined in 341 samples of indoor dust, collected from 12 countries (i.e. U.S., Japan, China, South Korea, Saudi Arabia, Romania, Greece, Kuwait, Vietnam, Colombia, Pakistan, and India) between 2010 and 2014 (Zhu and Kannan, 2018b). The targeted analytes were detected in all indoor dust samples, with global median concentrations of 1.8, 1.1, 0.048, and 0.045 μg/g for MEL, CYA, AMD, and AMN, respectively. The total concentrations of MEL and its derivatives and TPs varied among countries and were the highest in the U.S. (median: 17 μg/g), followed by Japan (8.4 μg/g) and South Korea (7.3 μg/g), and were the lowest in India (0.43 μg/g) (Figure 1 and Table S2.1). The high concentrations measured in indoor dust from more developed countries was related by the authors to the use of these compounds as flame retardants in various indoor products and electric appliances. The median estimated daily intakes (EDIs) of MEL and CYA through dust ingestion and inhalation for different age groups ranged from 0.206 to 80 ng/kg bw/day for MEL and from 0.127 to 19.3 ng/kg bw/day for CYA (Figure 4 and Table S2.12). These results suggested that the exposure doses of MEL and its derivatives and TPs via indoor dust ingestion did not represent a risk to human health (Zhu and Kannan, 2018b).

Zheng et al. investigated the occurrence and distribution of MEL and its derivatives and TPs in 20 indoor dust samples collected in 2016 from childcare centres located in Seattle and Indiana (USA) and in 26 nap mat samples from Seattle. Total MEL concentrations ranged from 0.43 to 117 μg/g in dust (Figure 1 and Table S2.1) and from 0.0002 to 35.7 μg/g in nap mat samples (Figure 2 and Table S2.1). Median EDIs of MEL and CYA estimated for toddlers through dust ingestion were 3.40 and 1.23 ng/kg bw/day, respectively, almost 2 orders of magnitude higher than the EDIs via dermal absorption (0.041 and 0.015 ng/kg bw/day, respectively) (Figure 4 and Table S2.12). Both values were anyway below the established TDI levels (Zheng et al., 2020b).

The occurrence of MEL and its derivatives and TPs was studied by Li et al. in indoor dust collected between 2016 and 2017 from typical e-waste recycling areas and adjacent rural communities. The total median concentrations of MEL and its related compounds varied among sampling locations and were 14 μg/g in e-waste recycling workshops > 9.8 μg/g in urban houses > 6.6 μg/g in local rural houses > 0.23 μg/g in local streets (Figure 1 and Table S2.1). The median exposure of the e-waste recycling workers to MEL and its derivatives and TPs was 21.7 ng/kg bw/day, higher than that of urban adult residents (8.7 ng/kg bw/day) (Figure 4 and Table S2.12), suggesting that e-waste recycling workers might suffer from potentially high occupational exposure to MEL and its derivatives (Li et al., 2022).

In the study by Zhao et al., the concentrations of MEL and its derivatives and TPs were analysed in 273 dust and 170 hand wipe samples collected from different microenvironments, including e-waste sites, homes, dormitories, and hotel rooms in 2020. Results showed that MEL levels in both dust (median: 24.1 μg/g) and hand wipes (803 ng/m^2) collected from e-waste dismantling workshops were significantly higher than those from homes (15.6 μg/g and 196 ng/m^2), dormitories (13.1 μg/g and 227 ng/m^2) and hotel rooms (11.8 μg/g and 154 ng/m^2) (Figure 1 and Table S2.1) (Zhao et al., 2022). In addition, while MEL dominated in dust samples collected in e-waste dismantling workshops, CYA was the main compound in hand wipes. Median EDIs of MEL and related compounds among e-waste dismantling workers was 9.70 ng/kg bw/day, significantly higher than those occurring in homes (4.40 ng/kg bw/day), dormitories (2.75 ng/kg bw/day) and hotels (1.95 ng/kg bw/day) (Figure 4 and Table S2.12). This study supports the conclusions drawn by Li et al. (Li et al., 2022) and suggested that e-waste dismantling activities contributed to elevated emissions of MEL and related compounds into the surrounding environment.

Consumer products

The occurrence of MEL and its derivatives and TPs was investigated in textiles and infant clothing purchased in the U.S. in 2016 (Zhu and Kannan, 2020a) and 2019 (Zheng and Salamova, 2020). In the former study, the targeted compounds were detected in all textile samples at concentrations ranging 0.002–81.8 μg/g for MEL, 0.003–17.8 μg/g for CYA, <0.001–25.7 μg/g for AMN, and <0.0005–0.55 μg/g for AMD (Figure 2 and Table S2.1). Significant positive correlations were observed among MEL derivatives and TPs in textile samples, suggesting that CYA, AMN, and AMD are present as impurities in MEL mixtures and resins used in textiles or are formed during textile production and processing. The exposure to MEL and CYA via dermal absorption from the analysed textiles ranged from 1.89 to 2.34 ng/kg bw/day and from 0.175 to 0.217 ng/kg bw/day, respectively (Figure 4 and Table S2.12), both below the recommended TDI values (Zhu and Kannan, 2020a). In the other study, the concentrations of MEL and its derivatives and TPs were up to 250 μg/g, with a median of 0.078 μg/g (Figure 2 and Table S2.1) (Zheng and Salamova, 2020). Although detected only in 21% of the samples, AMN was the most abundant compound, with a median concentration of 1.53 μg/g. The MEL EDIs from infant clothing were estimated in the rage of 0.012-0.015 ng/kg bw/day for non-nylon clothes and 6.94-8.59 ng/kg bw/day for nylon clothes (Figure 4 and Table S2.12) (Zheng and Salamova, 2020).

Food

The occurrence of MEL in more than 130 nutritional supplements from South Africa was investigated by Gabriels et al. (Gabriels et al., 2015). The median MEL concentration in the supplements produced and purchased in

South Africa (8,860 ng/g) was higher than that of products imported and purchased in South Africa (6,940 ng/g) (Table S2.1). The EDI values calculated based on the levels of MEL measured in this study were within the TDI limit guidelines of 0.2 mg/kg (EFSA, 2010) and were thus not of concern for the consumer (Gabriels et al., 2015).

MEL levels were measured in 40 samples of milk powder collected from Uruguay between 2013 and 2014. MEL values ranged between 170 to 820 ng/g, with a mean of 280 ng/g (Table S2.1). Also in this case, the consumption of milk powder did not constitute a health risk for consumers ((Garcia Londono et al., 2018)). The occurrence of MEL and its derivatives and TPs was also investigated in 52 infant formulas (collected in 2008 and 2018) and 42 dairy products (from 2018) from the U.S. (Zhu and Kannan, 2018a). In 2008, the total MEL concentrations ranged between 0.78 and 60 ng/g ww, but were significantly lower in 2018, below 8.2 ng/g ww. In dairy products, concentrations of MEL and its derivatives and TPs ranged between <LOQ to 54 ng/g ww (Figure 2 and Table S2.1). The average daily intakes of MEL by U.S. infants via formula and adults via dairy products were estimated at 687 and 32 ng/kg bw/day, respectively (Figure 4 and Table S2.12), suggesting a low-level contamination of the marketed food (Zhu and Kannan, 2018a).

Concentrations of MEL, CYA, AMN, AMD were determined in 121 foodstuffs, 24 food packaging and 12 animal feed collected from the U.S. in 2018 (Zhu and Kannan, 2019b). Median cumulative concentrations ranged from 2.17 and 23.6 ng/g ww in food and were 36.2 ng/g in food packaging and 56.5 ng/g ww in feed (Figure 2 and Table S2.1). The highest median EDI values for MEL and CYA were found for toddlers (72.7 and 347 ng/kg bw/day, respectively) (Figure 4 and Table S2.12), yet the estimated level of MEL exposure did not represent a significant health risk for consumers (Zhu and Kannan, 2019b).

2.2. Quaternary ammonium compounds

The occurrence of QACs in sediment, wastewater, and sludge was reviewed in Supplementary Materials section S1.2.

Dust

Nineteen target QACs (C6- to C18-BAC, C8:C8- to C18-DDAC, C8- to C18-ATMAC) were analysed in indoor dust samples collected before (n = 21) and during (n= 40) the COVID-19 pandemic. All analytes were detected with DFs ranging between 95-100% and 93-100% for the samples collected before and during the pandemic, respectively. Summed QAC concentrations ranged between 1.95 and 531 μg/g dust (Figure 1). BACs were the homologues with the highest individual concentrations and accounted for 56% of the total QAC concentration

in the samples collected during the pandemic. C11-BAC was the homologue with the highest individual median concentration of 12.6 µg/g. Based on the obtained data, a significant increase in total QAC concentrations could be identified when comparing levels before and during the pandemic. Additionally, calculated EDIs through dust ingestion corresponded to values up to 615 ng/kg bw/day for toddlers (∑QAC; Figure 4). None of the EDIs calculated for BACs and DDACs exceeded the ADI value of 10^5 ng/kg bw/day which was set by the EFSA (Zheng et al., 2020a).

Food

Bertuzzi et al. quantified four homologues of BACs (C10- to C16-BAC), as well as C10-DDAC in 30 and 17 powdered and liquid milk samples, respectively. All investigated samples contained QACs. After calculating the corresponding dry matter for the liquid milk samples, powdered milk samples still showed substantially higher QAC levels with the highest concentration of 29.4 ± 43.8 ng/g observed for C12-BAC. Summed QAC concentrations corresponded to 82.5 ± 131 ng/g and 2.6 ± 3.9 µg/L for the powdered and liquid milk, respectively (Figure 2). For one of the analysed samples, the sum QAC concentration exceeded 500 ng/g. This value was stated by Standing Committee on the Food Chain and Animal Health (SCoFCAH) as the maximum value accepted in food and feed which is placed on the market (Bertuzzi and Pietri, 2014).

Within the study conducted by Xiang et al., a GC-MS method was developed for the quantification of C12-ATMAC, C16-ATMAC and C12-DDAC in vegetable samples. The samples included the following nine types of vegetables (n = 3 for each type): white radish, potato, eggplant, water spinach, Chinese flowering cabbage, lettuce, cucumber, carrot and pumpkin. Samples were purchased at various markets in Guangzhou, China. At least two QACs were quantifiable in every vegetable type, except for the carrot samples in which no QACs were detected. Detection frequencies (DFs) of 33%, 89% and 78% were observed for C12-ATMAC, C16-ATMAC and C12-DDAC, respectively. C16-ATMAC showed the highest average concentrations which ranged from 23 to 122 ng/g dw (Table 2.3). The study pointed out the need to estimate potential human exposure to QACs through the intake of contaminated vegetables (Xiang et al., 2015).

Xian et al. quantified five QACs in dairy products which were treated using a QuEChERS-based sample preparation approach. The targeted QACs included C12-, C14-, C16-BAC, C12-ATMAC and C10-DDAC. A total of 37 dairy products which included 27 and 10 infant formula milk powder and liquid milk samples, respectively, were included. In six milk powder and one liquid milk samples, QACs were quantified with concentrations ranging between 31.9 and 122 ng/g, with C12- and C16-BAC being the most abundant detected homologues.

Two of the powder milk samples exceeded the limit of 0.1 mg/kg which was set as the maximum residual limit by EFSA (Xian et al., 2016).

2.3. Benzotriazoles and benzothiazoles

The occurrence of BTRs and BTHs in sediments was reviewed in Supplementary Materials section S1.3.

Drinking water and other water sources

The extensive use of both BTRs and BTHs has resulted in their emission/release into environment matrices. Consequently, these chemicals have been reported in various environmental matrices related to the aquatic ecosystem, including wastewater, groundwater, freshwater (surface water), drinking water and sediment and sludge (Table S2.5 and section S1.3). Comprehensive monitoring data for BTHs and BTRs in drinking water sources are scarce (Figure 1a). One recent study reported concentrations of 4 BTRs (BTR, MeBTR, 5-Cl-BTR, and XTR) and 5 BTHs (2-ABTH, BTH, 2-OH-BTH, 2-MeBTH, and 2-Me-S-BTH) in treated water from drinking water treatment plants (DWTPs) and in bottled water (Wang et al., 2023). High DFs (> 50% DF) were observed for both BTRs (except 5-Cl-BTR and XTR) and BTHs compounds in the treated water samples. Interestingly, BTHs except 2-ABTH were detected in all bottled water samples. The study estimated HQs for treated and bottled water consumption ranged from 10^{-5} to 10^{-2} for BTRs and 10^{-4} for BTHs. This study indicated that the risks were acceptable (defined as HQ < 1) with a safety margin of 2–5 orders of magnitude. Moreover, directly drinking the treated water from DWTPs may result in a BTR exposure risk that is two- or three-times higher than that of bottled water. Wang et al. measured 2 BTRs and 2 BTHs (BTR, TTR, BTH and 2-OH-BHT) in tap water in China. The contributions of intake of tap water to their internal exposure estimated by their urinary levels were 12.3% for BTH, while for the other three, contributions of tap water were <2% (Wang et al., 2016). However, it should be noted that this contribution was roughly estimated because the samples of tap water samples from Wang et al (2016) and urinary internal exposure from Li et al. (2017) were not matching in time and location.

Recently, 7 Chinese studies have reported the levels of BTRs and/or BTHs in river surface waters (Han et al., 2020; Hu et al., 2021; Lu et al., 2017; Peng et al., 2020; Wu et al., 2023; Xiong et al., 2022; Zhang et al., 2023) (Table S2.5). Dominant BTHs were 2-OH-BTH and 2-SH-BTH in Pearl River, which is most frequently investigated river in China. As shown in Table S2.5, BTR was the most abundant BTRs in the surface water (both highly detected and high concentration) in Chinese rivers. Zhang et al. measured BTHs and BTRs in the surface water, groundwater, stormwater and suspended particles from the Liuxi River and reported that BTR or BTH concentrations in surface water were strongly correlated with distance from industrial area, which indicates

that industrial activities were the main sources of these chemicals. Moreover, the mean total BTRs and BTHs concentrations were ranked as follows: groundwater > surface water > stormwater > suspended particle samples (Zhang et al., 2023). Occurrence of BTRs or BTHs in surface water has been reported also in other countries, such as in Germany, Brazil, Taiwan, Greece, Slovenia, Australia, and Antarctica (Ao et al., 2021; Chung et al., 2018; Díaz-Cruz et al., 2019; Domínguez-Morueco et al., 2021; Neuwald et al., 2022; Rauert et al., 2022; Trček et al., 2018; Vimalkumar et al., 2018). Generally, the reported concentrations of BTH, 2-Me-S-BTH, 2-SH-BTH, BTR, MeBTR in surface water are higher in Chinese rivers compared to other countries listed in Table S2.5. Surveys regarding BTHs and BTRs in groundwater are limited to BTR, 2,4-dMeBT, and 2-MeBTH (Guillemoto et al., 2022; Neuwald et al., 2022; Selak et al., 2022; Trček et al., 2018) (Table S2.5).

Dust

Recent studies have reported the presence of BTRs and BTHs in outdoor (Deng et al., 2022; Li et al., 2020b; Maceira et al., 2018; Zhang et al., 2018) and indoor dust (Li et al., 2020b; Nunez et al., 2022; Wang et al., 2013) (Table S2.5 and Figure 1b). As BTHs are commonly used as vulcanization accelerators in rubber production, the major outdoor sources of BTHs are assumed to be tire rubber. Outdoor dust was collected from road, indoor parking and tunnel road and investigated for the presence of BTHs (Deng et al., 2022; Klockner et al., 2021). BTH, 2-Cl-BTH, 2-Me-S-BTH, and 2-OH-BTH were found in road dust and indoor parking lot. Concentrations of BTHs in dust were higher in the smaller size fractions (< 125 μm or PM2.5) than in the larger fractions (125 -1000 μm or PM10) (Deng et al., 2022; Wang et al., 2013). The total EDI of BTHs, calculated based on the concentrations of BTHs detected in the road dust samples, via ingestion was highest, followed by dermal absorption and inhalation (Zhang et al., 2018). The order of intake of BTHs in the three different sizes was PM2.5 (children: 239 ng/kg bw/day; adults: 28.5 ng/kg bw/day) > PM10 (198 ng/kg bw/day; 23.6 ng/kg bw/day) > total dust (6.10 ng/kg bw/day; 0.73 ng/kg bw/day), indicating that smaller particles resulted in greater health risks to humans (Figure 5a and 5b).

BTRs and BTHs were detected in indoor dust samples collected from a typical e-waste area and residential areas, as well as from a control urban area in China (Li et al., 2020b) (Table S2.5). The median sum of BTRs in e-waste dismantling workshop dust (3830 ng/g) was 21 and 17 times higher than medians in the local residential house dust (180 ng/g) and the control urban residential house dust (231 ng/g), respectively. Similarly, significantly higher total concentrations of BTHs were also found in indoor dust from e-waste workshops (median: 2070 ng/g) compared to the local residential houses (823 ng/g) and the control urban residential houses (930 ng/g), indicating that e-waste dismantling activities contribute to considerable residues of BTRs and BTHs in indoor dust. BTR, BTH and 2-OH-BTH were the major compounds in three types of dust samples, cumulatively

representing more than 80% of total BTRs and BTHs. Only BTR (<17 - 3230 ng/g) was detected out of 3 BTRs and 5 BTHs in indoor floor dust collected from Spanish houses (n=16) (Nunez et al., 2022) (Figure 1b).

In total, 158 indoor dust from residences in the U.S., China, Japan, and South Korea were measured for 5 BTRs and 5 BTHs (Wang et al., 2013). Highest median concentration of the sum of 5 BTRs in dust was found in samples from South Korea with a value of 87.1 ng/g, followed by U.S. with 36.2 ng/g, and Japan with 33.7 ng/g. The lowest median concentration was the samples from China with 19.3 ng/g. Highest median concentration for the sum of 5 BTHs was found in dust samples from South Korea with a value of 2000 ng/g, followed by U.S. with 1290 ng/g, China with 857 ng/g, and Japan with 605 ng/g, respectively. Dust samples from the U.S. contained TTR as the major derivative, followed by 5-Cl-BTR. Similar to U.S, TTR and 5-Cl-BTR were major found in dust samples in Japan and South Korea. In dust from China, concentrations of TTR and 5-Cl-BTR were lower than those found in the other three countries. On the other hand, BTR was the major BTRs detected in dust from China (Wang et al., 2013), suggested that the distribution of BTRs in dust varied among the four countries studied. The distribution of BTHs in dust were similar between U.S, Japan, and South Korea. On the other hand, BTH concentrations were high in the samples from China, suggested the existence of specific sources of this compound in indoor environments (Figure 1b). Occurrence of BTHs in indoor air has also been reported (Armada et al., 2022b; Wan et al., 2016; Xue et al., 2017). Armada et al. performed measurements of BTH in the air above rubber football pitches (outdoor), playgrounds (indoor and outdoor), and tire warehouses in Spain (Armada et al., 2022b). BTH concentrations collected from tire warehouse was highest (125 ± 28 ng/m^3) followed by indoor playground (2.05 ± 0.33 ng/m^3), outdoor playground (0.99 ± 0.65 ng/m^3), and outdoor football pitch (0.25 ng/m^3). The results indicated the ubiquity and diffusion of BTH from the tire rubber facilities to the air, which can suppose a health risk for the users of these surfaces, as well as for workers of the tire industry and those laying the recycled rubber (Armada et al., 2022b). Wan et al. investigated BTHs in indoor air and the inhalation exposure of humans to these substances (Wan et al., 2016). The highest ΣBTH concentrations (geometric mean: 148 ng/m^3) were found in automobiles, followed by homes (49.5) > automobile garages (46.0) > public places (24.2 ng/m^3).

The studies of Wang et al. and Li et al. further calculated EDIs from BTRs and BTHs resulting from indoor dust ingestion (Li et al., 2020b; Wang et al., 2013) (Figure 5a and 5b). The EDI of BTRs in Korean children was higher than that found for other countries, with a GM value of 0.19 ng/kg bw/day. The EDI of BTRs was the lowest for Chinese children. The GM EDI of BTHs for Korean children was 4.22 ng/kg bw/day, followed by U.S. children (2.87), Chinese urban children (2.56), and Japanese children (1.74) (Wang et al., 2013). Li et al. calculated EDI of BTRs and BTHs through dust ingestion and dermal absorption by e-waste dismantling workers, local adult

residents, and urban adult residents under median- and high-end exposure scenarios. EDI values of BTRs and BTHs was 4.17 ng/kg bw/day and 3.10 ng/kg bw/day for e-waste dismantling workers, respectively, which were 2.5 to 20 times higher than that for local adult residents (BTRs: 0.18 ng/kg bw/day; BTHs: 0.86 ng/kg bw/day) and urban adult residents (0.28 ng/kg bw/day; 1.12 ng/kg bw/day), respectively. This indicates that occupational workers (e-waste dismantling area) suffer from potentially high risk from BTRs and BTHs exposure. EDI of BTRs of the study by Li et al. for urban adult residents was approximately 2 orders of magnitude higher than that for Chinese adult residents conducted in 2010 (Wang et al., 2013), suggesting that residents of urban areas currently face a higher risk of BTRs exposure than in the past (Figure 5a and 5b).

Consumer products

BTRs and BTHs in consumer products, such as textile and rubber products, have been commonly investigated (Armada et al., 2022a; Armada et al., 2022b; Avagyan et al., 2013; Chang et al., 2015; Chisvert et al., 2013; Ge et al., 2021; Liu et al., 2017b; Llompart et al., 2013; Luongo et al., 2016; Schneider et al., 2020a; Schneider et al., 2020b; Skoczynska et al., 2021; Zhang et al., 2018). As some BTRs are used as UV-stabilizers, BTRs in cosmetics and personal care products were also investigated (Table S2.5 and Figure 2a) (Armada et al., 2022a; Armada et al., 2022b; Avagyan et al., 2013; Chang et al., 2015; Chisvert et al., 2013; Ge et al., 2021; Liu et al., 2017b; Llompart et al., 2013; Luongo et al., 2016; Schneider et al., 2020a; Schneider et al., 2020b; Skoczynska et al., 2021; Zhang et al., 2018).

(a) *Rubber and tires*

Due to the impact of increased tire disposal, recycling end-of-life tires (ELT) has been implemented to give old tires a useful second life, such as crumb rubber for artificial football pitch and children's playground. Seven targeted BTHs were analysed in seventeen major brands of automobile tires from eight countries (Zhang et al., 2018). Most dominant BTH was BTH (mean 52.4 μg/g; range 25.4 – 175 μg/g), followed by 2-OH-BTH, 2-SH-BTH, 2-ABTH, and 2-Me-S-BTH. Avagyan et al. measured 5 BTHs and 6 BTRs from 15-year-old tire rubber. BTH, 2-Me-S-BTH, 2-SH-BTH, and MBTS were detected, but BTR and MeBTR, were not detected from the tire samples (Avagyan et al., 2013). BTH was the highest (23.5 μg/g), followed by 2-SH-BTH (12.3 μg/g), and 2-Me-S-BTH (0.46 μg/g) (Table S2.5 and Figure 2a).

Armada et al. collected crumb rubber samples from synthetic turf football pitches in 17 countries on 4 continents, and alternative materials, such as cork crumb, coconut fibre and thermoplastic elastomers for comparison. BTH was detected from all crumb rubber samples with concentrations ranging of 0.03 – 36 μg/g, except for samples from Thailand (not detected). The highest BTH concentration was detected from crumb

574 rubber samples in Sweden (36 μg/g), followed by one in Spain (26 μg/g). On the other hand, 2-SH-BTH was less
575 detected, with range from 40 to 146 μg/g (Armada et al., 2022a) (Table S2.5 and Figure 2a).

576 Llompart et al. and Skoczyńska et al. also measured BTHs from playgrounds ((Llompart et al., 2013)) and from
577 football pitches, new rubber mattress, and ELT tires (Skoczynska et al., 2021), respectively. BTH was found in all
578 playground samples with mean concentration of 10 μg/g and the highest concentration was 40 μg/g (Llompart
579 et al., 2013). Skoczyńska et al. reported that the BTH levels in new rubber mattress (72 μg/g) were the highest,
580 followed by ELT-tires (14 μg/g) and football pitch (9.4 μg/g) (Table S2.5 and Figure 2a).

581 Three selected BTHs (BTH, HO-BTH, and SH-BTH) in ELT-derived rubber samples collected from sport fields and
582 recycling companies in 15 European countries were measured (Schneider et al., 2020a), indicated the presence
583 of BTH, HO-BTH, and SH-BTH at concentrations < 100 μg/g. This study further indicated that BTH can migrate
584 from rubber to the air and from rubber to artificial body fluids (sweat, saliva, and gastric juice) (Schneider et al.,
585 2020b). Concentrations of BTH, HO-BTH, and SH-BTH in sweat, saliva, and gastric juice were below LOQ,
586 indicated that internal exposure to selected BTH compounds from rubber products is rather limited and might
587 not need large cautions (Table S2.5 and Figure 2a).

588 To examine dermal exposure to BTHs from consumer products, Ge et al. conducted on the migration of BTH and
589 2-Me-S-BTH from three different mouse pads, leather, silicon, and rubber, to artificial sweat (Ge et al., 2021).
590 The detection frequencies of 4 BTH compounds (BTH, 2-OH-BTH, 2-Me-S-BTH, and 2-SH-BTH) from mouse pad
591 were 72–100%. Migration ratio (%) of BTHs from mouse pads into artificial sweat after 1-d and 20-d incubation
592 were examined. In 1-day incubation, migration ratios of both BTH and 2-Me-S-BTH from leather mouse pad
593 were 0 %, however, in 20-d incubation as long-term exposure, migration ratios from silicon pad were highest in
594 both BTH (88 %) and 2-Me-S-BTH (95 %), followed by rubber (84 %; 89 %) and leather (23%; 100%)(Ge et al.,
595 2021).

596 *b) Textile and clothes*

597 The occurrence of BTHs and BTRs in textiles has also been investigated (Avagyan et al., 2013; Liu et al., 2017b;
598 Luongo et al., 2016a) (Table S2.5 and Figure 2a). BTH was most frequently detected with higher concentrations
599 than other BTHs and BTRs in 3 studies. Levels of BTH, 2-OH-BTH, and TTR were higher in socks than other textile
600 samples, such as diaper, blanket, and infant clothes. Higher levels of BTR (0.027 – 14 μg/g) and TTR (0.007 – 0.27
601 μg/g) were detected from infant clothes (Liu et al., 2017b). The investigated BTRs and BTHs are slowly released
602 from clothes by washing after 5 and 10 times washing. Percentage of the average concentration decreased,
603 which indicates that the emission to household wastewater. The estimated dermal exposure doses of BTHs and

BTRs by infants through direct skin contact with textiles were up to 3740 pg/kg bw/day, with a mean value of 92 pg/kg bw/day. Furthermore, socks made up of 98% polyester contributed to BTH exposures in the range of 244 to 395 pg/kg bw/day, with combined BTH and BTR exposures ranging from 369 to 533 pg/kg bw/day, indicating that textiles are a possible source of exposure to BTHs and BTRs to infants (Figure 5a and 5b) (Liu et al., 2017b).

Food

Bioaccumulation of BTRs and BTHs on foods could result in human health effects, however, the studies that examined the occurrence of BTRs and BTHs from foods are scarce. A few publications regarding the occurrence of BTRs and BTHs in marine and freshwater fish or shellfish were available (Table S2.5 and Figure 2b).

Concentrations of BTRs and BTHs were measured in marketed fish samples from Taiwan (Chen et al., 2020a) and Spain (Trabalon et al., 2017). In the Taiwanese study, BTR, 5Cl-BTR and 2OH-BTH were detected in all four marketed fish samples (DF: 100%), whereas 2-ABTH and XTR were not detected in any samples. BTR was the major compound and ranged from 41.5 to 72.3 ng/g dry weight (dw), followed by 2OH-BTH (15.5 – 26.1 ng/g). In Spanish study, BTH followed by 2-ABTH were frequently detected in the group of whitefish, mussels, and shrimps, whereas, 2-Cl-BTH was dominant in fatty fishes (Trabalon et al., 2017). Squid had the highest value of BTH (82.0 ng/g), while tuna showed the lowest levels. Mussels were the only species in which all 5 BTHs were detected. Although BTH was the dominant compound in the marketed fish, the EDI of 2-Me-S-BTH in general population of Spain (Catalonia) was the highest in older women (22 ng/kg bw/day) followed by BTH (11 ng/kg bw/day) in adult women, which indicated that women, both older and adult, showed the greatest intake of all BTHs (Figure 5a and 5b).

Most of studies regarding the occurrence of BTRs and BTHs in the foods reported in this review investigated a limited number of BTRs and BTHs (Table S2.5). Jia et al. reported that wider range of BTRs and BTHs in molluscs collected from the Bohai Sea, China between 2006–2014 (Jia et al., 2019). BTH (range: 132 - 13400 ng/g dw) was the most dominant in molluscs followed by XTR (3.17 - 103 ng/g dw). In addition, BTH, 2-Me-BTH, and 2-MeS-BTH were present in all mollusc samples (100%), followed by 2-MeBTH (99.4 %), 2-OH-BTH (89.2 %), and 2-ABTH (71.1 %). BTH concentrations in molluscs from the study from Jia et al were considerably higher than those in fish and shellfish observed in Spain (range: ND - 82.0 ng/g) (Trabalon et al., 2017) (Table S2.5). XTR was found in 100 % of Chinese samples, followed by BTR (82.5 %), 5-Cl-BTR (71.0 %), and 5-MeBTR (63.9 %). Positive

633 correlations between concentrations of BTRs in various molluscs were found, which indicates potential common
634 sources, such as corrosion inhibitors in de-icing fluids for aircraft and cars (Jia et al., 2019).

635 EDIs of BTHs and BTRs for Chinese general population in different age groups (children and teenagers, and
636 adults) based on concentration of BTHs and BTRs in mollusc samples (ng/g dw) and the daily consumption rate
637 of molluscs (g/day) have been reported. The highest EDI values ranged from 58.2 (female adults) to 94.9 ng/kg
638 bw/day (female children and teenagers) for BTH and from 1.41 (female adults) to 2.29 ng/kg bw/day (female
639 children and teenagers) for XTR, respectively. Higher EDIs in younger age group compared to in adults. EDIs of
640 BTH in studies from Jia et al. were 1-3 orders of magnitude lower than the RfD of BTH (5000 ng/kg bw/day)
641 (Ginsberg et al., 2011) (Figure 5a and 5b). Although all mollusc species generally contained relatively high levels
642 of BTHs/BTRs indicating the high bioaccumulation potential of BTHs/BTRs, EDIs of BTHs/BTRs through
643 consumption of molluscs appear minor, due to limited contribution of molluscs to the overall diet.

644 Bioaccumulation potential and human health risks were investigated from the concentrations of BTR and MeBTR
645 in muscle and liver of wild fish in Pearl River and Yangtze River in China (Yao et al., 2019; Yao et al., 2018). Levels
646 of MeBTR were higher in liver (ND - 54.5 ng/g ww) than those in muscle (ND - 1.0 ng/g ww). BTR was detected
647 in fish muscle at a maximum concentration of 54.5 ng/g ww. The highest HQ values as the worst-case scenario
648 exposure risks of BTR via consumption of fish muscle was in the range from 1.19E-07 (mullet) to 7.87E-06
649 (tilapia), which indicated that the health risks of BTR to humans is not related with the intake of different fish
650 species (Table S2.5).

651

652 **2.4. 1,4-Dioxane**

653 The occurrence of 1,4-D in sediment was reviewed in Supplementary Materials section S1.4.

654 *Drinking water and other water sources*

655 The occurrence of 1,4-D in drinking water and its source (e.g., surface water and groundwater) has been
656 reported in several studies from 2017 (Table S2.7). A survey of 1,4-D in drinking water collected in 4,864 public
657 water systems throughout the U.S. between 2013-2016 under the Unregulated Contaminant Monitoring Rule
658 showed that 1,4-D was detected in 21% of samples at concentrations of 0.1 – 50 μg/L and in 7% of public water
659 systems concentrations exceed the health-based reference concentration (0.35 μg/L) (Adamson et al., 2017).
660 The study also found a significant association between 1,4-D detection in drinking water and the detection of
661 other chlorinated compounds, in particular 1,1-dichloroethane, which may relate to the use of 1,4-D as a
662 chlorinated solvent stabilizer. In addition, a higher detection of 1,4-D was observed in samples from

groundwater sources than in samples from surface water sources, suggesting that people may be at higher risk from 1,4-D exposure through the consumption of groundwater- than from surface water-derived drinking water.

Karges et al. investigated the occurrence of 1,4-D in drinking water and surface water collected throughout Germany between 2015 and 2018 (Karges et al., 2022; Karges et al., 2020). 1,4-D was detected in over 75% of drinking water and surface water at concentrations of ND–2.05 µg/L and ND–10.7 µg/L, respectively (Figure 1a). Concentrations of 1,4-D in drinking water did not exceed the German drinking water guidance level (5 µg/L).

Neuwald et al. reported 1,4-D concentrations in the range of around 0.05-1 µg/L in surface water, groundwater, bank filtrate, and raw water obtained in 2020-2021 (Neuwald et al., 2022). Another German study examined 1,4-D in ground water from eight polluted groundwater sites (five sites with volatile chlorinated hydrocarbons, two sites by leachate from landfills, one site by the discharge from a detergent manufacturing plant), located in Western Germany and found that 1,4-D detected all groundwater samples at concentrations of 0.04-152 µg/L (Karges et al., 2018). The results from these German studies indicate that 1,4-D is widespread in Germany.

Consumer products

Household detergents, cleaners and cosmetic products contained 1,4-D at levels up to the µg/g range (Figure 2a) (Alsohaimi et al., 2020; Lin et al., 2017; Saraji and Shirvani, 2017; Zhou, 2019). Lin et al. reported that 1,4-D was detected in the range of <LOD to 3.73 µg/g (mean: 1.22 µg/g; median: 0.75 µg/g; DF: 89%) in various food detergents on dishware, fruits, and vegetables commercially purchased from supermarkets and local stores in Taiwan (Lin et al., 2017). The maximum daily intake of 1,4-D through skin absorption from food detergent was reported as 0.015 ng/g/day, which was three orders of magnitude lower than the chronic no-observed-adverse-effect level (NOAL; rat, oral) for 1,4-D (10 mg/kg/day) (Lin et al., 2017). This indicates that 1,4-D exposure through dermal contact with food detergents is not considered to pose a significant health risk to humans.

In a study from Iran, 1,4-D was measured in 8 surfactants and cleaning agents including shampoo, and hand and dishwashing liquid at concentrations ranging from <0.05–201 µg/g, with DF 75% (Saraji and Shirvani, 2017). 1,4-D was also detected in various cosmetic products collected in the U.S. and Saudi Arabia in the range of 0.25 – 15.3 µg/g (mean: 1.54 µg/g; Zhou, 2019), and ND – 9.92 µg/mL (Alsohaimi et al., 2020). These results indicate that the general population can be expose to 1,4-D through dermal contact with personal care and household products.

1,4-D is listed in the European Union cosmetics regulation No 1223/2009 and the Scientific Committee on Consumer Safety (SCCS) concluded that the residual concentration of 1,4-D in cosmetic products is considered safe for consumers at below 10 µg/g. Nevertheless, 1,4-D has been identified in some cosmetic products at

levels above 10 μg/g by previous studies (Saraji and Shirvani, 2017; Zhou, 2019). Therefore, it is required to continuously examine the 1,4-D concentrations in finished cosmetics and prepare relevant actions to reduce the amount of 1,4-D in cosmetics and protect the health of consumers.

Food

To date, there are only two papers about 1,4-D in food (Table S.7) (Nishimura et al., 2004; Nishimura et al., 2005). One of them investigated the exposure to 1,4-D in 12 food groups including rice, vegetables, fruit, oils, fish, meat, etc. and found that 1,4-D ranged between ND and 15 ng/g (Figure 2b) (Nishimura et al., 2004). The authors showed the EDI of 1,4-D corresponded to 0.055% of the calculated TDI value with regard to a cancer endpoint (16 ng/g/day). In the other study, 1,4-D was detected in meals from 3 days collected from 3 homes in 7 prefectures of Japan (total 63 composite food) at concentrations of ND–3 mg/g, with a very low DF (1.6%) (Nishimura et al., 2005). According to these rather old studies on food, human exposure to 1,4-D through the food consumption appears to be very low.

2.5.1,3-di-o-tolylguanidine and 1,3-diphenylguanidine

The occurrence of BTRs and BTHs in sludge was reviewed in Supplementary Materials section S1.5.

Drinking water and other water sources

There are some data on the presence of DPG in various aqueous matrices including surface water, groundwater, and drinking water, whereas relatively few studies are available on the occurrence of DTG in water samples (Table S2.9 and Figure 1a). Except for surface water, most of previous studies have reported the occurrence of DPG and DTG in less than 10 samples.

For DPG, some studies conducted in Germany reported various ranges of concentrations in surface water collected in Hesse (<LOQ–60 ng/L) (Zahn et al., 2019), in Tegeler See (191 ng/L) (Schulze et al., 2020), and river Rhine (median: 23 ng/L) (Scheurer et al., 2022). In Spain, DPG was detected in the range of ND–173 ng/L with DF 58% in surface water, and in the range of ND–7.3 ng/L with DF 67% in drinking water (Montes et al., 2019). DPG was also reported in surface water, groundwater, and bank filtrate from Spain, Germany, and the Netherlands, with approximate concentrations of 5–100 ng/L (Schulze et al., 2019). Similarly, Neuwald et al. analysed DPG in diverse drinking water sources, surface water, groundwater, bank filtrate, and raw water taken throughout Germany and revealed the widespread presence of DPG (around 0.1–500 ng/L) (Neuwald et al., 2022).

For DTG, few studies have been conducted in Spain, Germany, and the Netherlands. Schulze et al. reported DTG presence in surface water, groundwater and bank filtrate at concentrations of 5–50 ng/L (Schulze et al., 2019). In Spain, DTG was detected in surface water (ND–9 ng/L), but was not detected in drinking water (Montes et al., 2019). DTG was not detected in 120 surface water from river Rhine, Germany (Scheurer et al., 2022).

Since DPG and DTG are mainly used as vulcanization agents in rubber products and tires, their exposure to the aquatic environment might be related to leaching from tire wear particles and street run-off (Scheurer et al., 2022; Zahn et al., 2019). Additionally, a previous study identified the migration of DPG from high-density polyethylene pipes, which can be an additional source of DPG in drinking water (Tang et al., 2015).

Dust

Since DPG is used in household products, such as rubber products, food packaging, drug products, etc. (EC, 2013; Shin et al., 2020), it may migrate to the indoor environment and may have been detected in house dust. So far, two studies have been conducted on DPG and DTG exposure to house dust from 5 countries (Australia, California, China, U.S., and Vietnam) and reported high DFs of DPG and DTG in most samples (DF > 80%) (Shin et al., 2020; Tan et al., 2021). DPG was measured in house dust with median concentrations of 3,218 ng/g in California (Shin et al., 2020), 5,030 ng/g in Australia, 5,100 ng/g in China, 11,400 ng/g in the U.S., and 305 ng/g in Vietnam (Tan et al., 2021) (Table S2.9 and Figure 1b).

The concentration of DTG was lower than of DPG and the highest concentration of DTG was observed in Australia (ND–56.3 ng/g; median: 2.2 ng/g), following the U.S. (ND–43.2 ng/g; 5.8 ng/g), China (ND–41.4 ng/g; 0.9 ng/g), and Vietnam (ND–8.0 ng/g; ND) (Figure 1b) (Tan et al., 2021). Lower DTG concentrations than DPG are consistent with lower manufacture and /or import volume of DTG than DPG into the European Union. Dust concentrations from previous studies show that DPG and DTG can be exposed to the human body in the indoor environment.

Consumer products

Since DPG and DTG have been used as vulcanization agents in the manufacture of synthetic gloves (Shin et al., 2020; Zahn et al., 2019) and DPG is reported as the most common allergen to healthcare workers (Dejonckheere et al., 2019), an exposure route is by wearing disposable gloves. In this regard, the presence of DPG was examined on the inside and outside of sterile non-latex protective gloves to evaluate patients with occupational contact dermatitis caused by their gloves (Ponten et al., 2013). DPG was found at higher concentrations on the inside of the gloves (<LOQ–26.7 μg/cm^2) than on the outside (<LOQ–7.1 μg/cm^2) (Table S2.9).

DPG is used in various household products such as rubber products, food packaging, drug products, etc. (Table S2.9) (Shin et al., 2020). Therefore, it is needed to evaluate the human risk from exposure to DPG through consumer products. Yet, to the best of our knowledge, the investigation on DPG and DTG concentrations in other consumer products has not been performed.

2.6. Trifluoromethane sulfonic acid

The occurrence of TFMS has been reported in only aqueous environmental matrices until now.

Drinking water and other water sources

TFMS was reported to occur in surface water, groundwater, and drinking water from Spain, Germany, France, the Netherlands, and Switzerland, with estimated concentrations of 44–6,325 ng/L (DF 41%) (Table S2.11) (Montes et al., 2017). A study from Sweden investigated TFMS in surface water, and groundwater from suspected point sources, firefighting training sites, and non-contaminated drinking water collected from water treatment facilities (Björnsdotter et al., 2019). The range of TFMS concentration was <1.8–30 ng/L (DF 78%) in surface water, 3.9–24 ng/L (DF 100%) in groundwater, and <1.8–7.8 ng/L (DF 50%; Table S2.11 and Figure 1a) in drinking water. Two German studies reported the detection of TFMS in surface water, groundwater, and drinking water. One study reported that TFMS was found at concentrations of <13–380 ng/L (Scheurer et al., 2022). Another study analysed a few real samples because the main purpose of them was to optimize the analytical method (Schulze et al., 2020). They showed no detection of TFMS in surface water and drinking water and detected TFMS in only groundwater with a relatively high concentration of 18,000 ng/L than other previous studies. TFMS concentrations (1–1000 ng/L) were also reported in surface water, groundwater, and drinking water collected from Spain, Germany, and the Netherlands, consequently TFMS was classified as high priority PM (Montes et al., 2019). Additionally, TFMS presence was reported in diverse water samples (surface water, groundwater, and drinking water) in EU countries through two research, but it was not quantified (Zahn et al., 2016).

3. The internal exposure levels of PMs

3.1. Melamine

Urine

MEL and CYA were measured in 109 children (4 months to 8 years) from Seattle, USA. The median levels of MEL and CYA in urine were 4.7 and 27.4 ng/mL, respectively (Figure 3 and Table S2.2). The concentrations of MEL were generally higher in older and male kids. These results suggested a widespread exposure in the population, given the multiple sources of MEL in consumer products (Sathyanarayana et al., 2019).

Since diet has been recognized as one major source of MEL exposure, the associations of dietary intake with concentrations of urinary MEL and its derivative were investigated in 123 US children (4–6 years) (Melough et al., 2022). Mean concentrations of MEL, CYA, and AMD were 6.1 ± 12.4 ng/mL, 60.6 ± 221 ng/mL, and 1.9 ± 2.1 ng/mL, respectively (Figure 3 and Table S2.2). Results showed a ubiquitous exposure of children to MEL and its derivatives and TPs, and identified certain foods (i.e., red meat, certain starchy vegetables, and yogurt) as potential dietary sources of exposure (Melough et al., 2022). Similarly, MEL was determined in 478 urine samples from American children (aged 8 years) and adults (between 18 and 40 years and above 40 years) (Melough et al., 2020). Mean concentrations per age class were 0.69 ± 0.20 ng/mL, 1.05 ± 0.21 ng/mL, and 1.96 ± 0.2 ng/mL, respectively (Figure 3 and Table S2.2). In the same study, consumption of processed meats, whole grains, and other plant-based food items was considered an important source of MEL exposure in the US diet. In another study, the concentrations of urinary MEL were measured in 908 adults from Shanghai in association with food consumption (Shi et al., 2020). A few participants (n = 22) had EDIs exceeding the TDI, suggesting that a small percentage (~4%) of the Shanghai adult population might be at health risk following MEL exposure. In the same study, MEL concentration in urine was positively associated with consumption of processed meat, rice, fruits, and eggs.

MEL and its derivatives and TPs were analysed in urine from 171 pregnant US women belonging to nine diverse ECHO cohorts (Environmental influences on Child Health Outcomes) during 2008–2020. Median concentrations were 1.6 ng/mL for MEL and 28 ng/mL for CYA, and <0.05 ng/mL for AMD (Figure 3 and Table S2.2) (Choi et al., 2022). In a study of (Tsai et al., 2021), creatinine-adjusted concentration ranged from 0.01 to 50.97 µg/mmoL creatinine, with an adjusted median of 0.63 µg/mmoL creatinine in urine samples from 1433 pregnant women from Taiwan (Figure 3 and Table S2.2).

The concentrations of MEL and its derivatives and TPs were detected in 239 urines from Chinese adults with a median value of 40.7 ng/mL (Figure 3 and Table S2.2) (Liu et al., 2022a). The median EDI values for MEL and CYA were 260 and 320 ng/kg bw/day, respectively (Figure 6 and Table S2.13). According to the performed cumulative risk assessment, the authors suggested that the studied population may suffer potential health risk associated with the exposure of CYA and MEL.

The variability in urinary concentrations of MEL and its derivatives and TPs was investigated in 213 samples collected from 19 US volunteers in 2018 (Zhu and Kannan, 2019a). Total concentrations ranged between 3.5 and 190 ng/mL, with a median concentration of 13 ng/mL (Figure 3 and Table S2.2). The mean cumulative daily intake of MEL and CYA, calculated based on concentrations in urine, was 65.5 and 315 ng/kg bw/day, at least an order of magnitude below the current TDI (Figure 6 and Table S2.13). Still, a high degree of variability in urinary MEL concentrations was found with a moderate reliability over time (Zhu and Kannan, 2019a).

MEL urinary concentrations were measured in 80 Taiwanese workers from MEL tableware factories and 309 adult patients with calcium urolithiasis. Median concentrations were 18.4 and 4.86 ng/mL, respectively (Figure 3 and Table S2.2) (Liu et al., 2020). In that study, the urinary levels of MEL and urinary biomarkers of oxidative stress were significantly and positively correlated, indicating that MEL exposure can increase oxidative stress (Liu et al., 2020). Urinary concentrations of MEL were also measured in Taiwanese workers from another melamine factory, and specifically from four worksites at the end and at the beginning of their shifts (on Friday and Monday, respectively) (Hsu et al., 2022). Concentrations were lowest among packing and administrative workers (12.8 and 26.2 ng/mL on Friday; 13.4 and 1.6 ng/mL on Monday) and highest among manufacturing and grinding workers (2771 and 188 ng/mL on Friday; 282 and 31.1 ng/mL on Monday) (Figure 3 and Table S2.2).

Finally, the occurrence of MEL and its derivatives and TPs was investigated also in pets which can be seen as proxy for human exposure. In a study of (Karthikraj et al., 2018), the concentrations of MEL, CYA, AMN, and AMD were measured in urine from 30 dogs and 30 cats collected in 2017 from the US. In dogs, total concentrations ranged from 13.4 to 510 ng/mL, while in cats they ranged from 5.8 to 760 ng/mL (Table S2.2). For both pet categories, age and gender were found to be important concentrations determinants. The cumulative daily intake of MEL and its derivatives and TPs, calculated based on urinary concentrations, was between 2100 and 5700 ng/g bw/d for dogs and between 5830 and 9400 ng/kg bw/d for cats, estimated to be below the TDI (Table S2.13). The occurrence of MEL and its derivatives and TPs was also explored in 183 bovine urine and 29 matched feed samples from China, India, and the US collected in 2018 (Zhu et al., 2019a). Total median concentrations were 610, 27, and 180 ng/mL in China, India, and USA, respectively (Table S2.2). CYA was the predominant compound found in bovine urine, whose source the authors attributed to direct exposure via feed. However, the daily intakes of MEL and CYA in bovines were at least an order of magnitude below the current human TDI (Zhu et al., 2019a).

Breast milk

The presence of MEL and its derivatives and TPs was investigated in 100 human breast milk samples collected from the US between 2009 and 2012 (Zhu and Kannan, 2019c). Total concentrations of MEL and derivatives and TPs ranged from 0.176 to 10.0 ng/mL (median: 1.40 ng/mL) (Figure 3 and Table S2.2). The cumulative daily intakes calculated for breast-fed infants were 16.9 to 30.6 ng/kg bw/day for MEL and 88.8 to 161 ng/kg bw/day for CYA, 1-2 orders of magnitude below the current TDI (Figure 6 and Table S2.13) (Zhu and Kannan, 2019c).

Overall, MEL and its TPs seems to be widely present in human matrices in many countries all over the world indicating their widespread use and exposure in line with findings presented in Chapter 2.

3.2. Quaternary ammonium compounds

Blood

Extensive studies on the internal human exposure to QACs are scarce (Table S2.4). Recently, a study on the occurrence of QACs in human blood samples was published by Hrubec et al. (Hrubec et al., 2021). Five QACs, namely C10-DDAC, C10-, C12-, C14- and C16-BAC) were analysed in blood samples of 43 participants. QACs were detected in 80% of the samples, of which 50% showed summed QAC concentrations between 10 and 150 nM. The major QACs showed median concentrations of 1.9, 4.5, 2.4 and 5 nm for C12-, C14-, C16-BAC and C10:C10-DDAC, respectively. Further tests conducted on the blood samples allowed the identification of a positive correlation between QAC levels and a disruption of cholesterol homeostasis, an increase in inflammatory cytokines and a decrease in mitochondrial function. This study can therefore be seen as a first proof of potential health effects of QACs on humans (Hrubec et al. 2021).

Zheng et al. quantified 18 QACs (C8- to C18-BAC, C8- to C18-DDAC, C8- to C18-ATMAC) in 222 blood samples, half of which were collected before and the other half during the COVID-19 pandemic in Indiana, USA. Out of the investigated QACs, 15 analytes were detected in the blood samples, nine of which showed DFs > 50% (Zheng et al. 2021). The highest DFs were observed for C12-, C14-BAC and C14-ATMAC with values of 97%, 95% and 94%, respectively. Median summed concentrations of 2.84 ng/mL, 2.45 ng/mL and 0.35 ng/mL were reported for ATMACs, BACs and DDACs, respectively. The most abundant individual homologues were C14-BAC (Median concentration of 1.14 ng/mL) and C14-ATMAC (median concentration of 0.93 ng/mL) (Figure 3). Similar to the results observed in indoor dust samples (see above), a significant increase in the summed internal blood concentrations of QACs could be identified when comparing samples collected before and during the pandemic. Thereby, the overall increase corresponded to 77% (Zheng et al. 2021).

Breast milk

The same 18 QACs (C8- to C18-BAC, C8- to C18-DDAC, C8- to C18-ATMAC) were also quantified in breast milk samples (n = 48) collected in Seattle, USA, from 48 primiparous women. The sample collection was accompanied by a questionnaire in which information about the use of personal care products, household cleaners and the frequency of disinfection within the household was collected. Thirteen target QACs were detected in breast milk samples, of which seven QACs showed DFs > 50%. Summed QAC concentrations ranged between 0.33 and 7.4 ng/mL. BACs were the most abundant class with a median summed BAC concentration of 0.92 ng/mL. This corresponded to 71% of the median summed QAC concentration. C14-BAC was the most abundant individual QAC showing a median concentration of 0.45 ng/mL. Based on the data obtained from the questionnaires, an effect of the disinfecting practices on the quantified QAC levels was assumed as higher QAC concentrations were observed for mothers using disinfectants in comparison to mother who do not use such products (Zheng et al., 2022).

Urine and serum

Lastly, a recent study from Li et al. analysed 19 QACs (C6- to C18-BAC, C8- to C18-DDAC, C8- to C18-ATMAC) in human urine and serum. The sample set included 11 and 27 serum and urine samples collected in 2002-2003 and 2022 in the US, respectively. Additionally, the study reported the first quantification of eight BAC metabolites in human urine. The latter included the hydroxylated and carboxylated analogues of C6- to C12-BAC (Table S2.4). In human serum, four QACs (C14-, C16-BAC, C18-DDAC and C14-ATMAC) were detected with concentrations ranging between 0.28 and 3.4 ng/mL. Thereby, C14- and C16-BAC could only be detected in pooled serum (and not in individual) serum samples. All other QACs were below the method limit of detection (MLOD). While no parent QACs were detectable in human urine above the MLOD, five BAC metabolites including carboxylated C6-BAC and hydroxylated C6- to C12-BAC were detected with DFs and mean concentrations ranging between 30.8 - 96.2% and 0.05 - 0.35 ng/mL, respectively. These findings indicate a fast metabolization of QACs in humans and point out the necessity to consider QAC metabolites in future biomonitoring studies.

In summary and despite significant differences found between the various QAC homologues, the above findings indicate for QACs occurrence in blood (USA) and breast milk in several countries (Spain, China, USA). This is in line with findings reported in Chapter 2 regarding widespread occurrence in media relevant for human exposure (indoor dust and food).

3.3. Benzotriazoles and benzothiazoles

Despite the extensive use of both BTRs and BTHs in a wide range of industrial and household products, studies investigating the internal human exposure to BTRs and BTHs are very limited (Table S2.6). Urine samples from the general population (Asimakopoulos et al., 2013a; Asimakopoulos et al., 2013c; Li and Ding, 2021), women (Chen et al., 2020b; Chen et al., 2022b; Li et al., 2018; Zhou et al., 2020b; Zhou et al., 2018; Zhou et al., 2020c), and children (Murawski et al., 2020) and breast milk samples (Kim et al., 2019; Liu et al., 2022b), amniotic fluid (Li et al., 2018), and adipose tissue (Wang et al., 2015) were investigated for the human biomonitoring of BTRs and BTHs (Table S2.6).

Urine

Asimakopoulos et al. reported 5 targeted BTRs and 5 BTHs in urine of 100 individuals from the general population (2 - 85 years old) in Greece (Asimakopoulos et al., 2013a) (Table S2.6 and Figure 3a). All targeted compounds were detected in < 50 % of the samples. Among them, BTH was the dominant BTHs with 32 % and 22 % of detections in the samples (GM male: 5.36 ng/mL; female: 4.84 ng/mL). Asimakopoulos et al. further conducted a similar study and added 2 BTHs (2-Me-S-BTH and 2-SCNMeS-BTH) with larger study population in 7 countries, China, Japan, India, the U.S., Korea, Vietnam, and Greece (Asimakopoulos et al., 2013b) (Table S2.6 and Figure 3 a). All BTRs and BTHs, except for 5-Cl-1H-BTR, 1-OH-BTR, 2-Me-S-BTH, and 2-SCNMeS-BTH were found in urine. The highest median concentration of ΣBTRs was found in urine samples from India (2.8 ng/mL) and China (2.3 ng/mL), followed by samples from Vietnam, Japan, Greece, the U.S., and Korea. The highest median concentration of ΣBTHs was found in urine samples from Japan (10.9 ng/mL) and Vietnam (9.1 ng/mL), followed by samples from Korea, China, Greece, India, and the U.S. The distribution profiles of BTRs varied among the investigated countries, whereas, those of BTHs did not vary among the 7 countries. GM EDI values in 7 countries ranged from 0.7 to 3.6 μg/kg bw/day for Σ_5BTRs, and 4.8 to 18.2 μg/kg bw/day for Σ_6BTHs (Figure 6 c and d).

Li et al. measured 3 BTRs and 5 BTHs from 20 healthy young Taiwanese adults (10 males and 10 females; 22 - 26 years old) (Li and Ding, 2021) (Table S2.6 and Figure 3a). XTR was the major BTR with 80% of detection in the samples. 2-ABTH had the highest concentration detected a value of 24.1 ng/mL with a detection frequency of 35 %. BTR, BTH, and 2-Me-S-BTH were not detected in any sample. Concentrations and detection frequencies of XTR, 2-OH-BTH, 2-ABTH, and 2-Cl-BTH were higher in females than in males.

Four BTRs and 2 BTHs were measured in urine from 83 Chinese pregnant women collected before delivery (Li et al., 2018) (Table S2.6 and Figure 3a). Corresponding BTRs and BTHs were also measured from amniotic fluid. In both urine and amniotic fluid samples, BTH were detected in all urine (100%) and in 85 % of amniotic fluid

samples. BTR was secondly dominant in urine, while 2-OH-BTH was in amniotic fluid. No significant correlations between levels of sum BTRs/BTHs in urine and amniotic fluid were observed, however, there were significant positive correlations between individual levels of BTRs/BTHs in both biological samples. The median concentrations of Σ_4BTRs and Σ_2BTHs (0.03 and 0.72 ng/mL) in amniotic fluid were much lower than those (0.88 and 1.35 ng/mL) in maternal urine. The GMs of the EDIs of Σ_4BTRs and Σ_2BTHs were 1.15 μg/kg bw/day and 1.92 μg/kg bw/day, respectively. The GMs of the EDIs of TTR, BTR, and 5-Cl-BTR were 0.39, 1.83, and 0.026 μg/kg bw/day, respectively. These three EDIs are higher than the allowed daily intake value of TTR from drinking water (14 ng/kg bw/day) (Figure 6c and 6d).

In a prospective birth cohort study in Wuhan, China, 2568 urine samples from 856 pregnant women were collected across three trimesters and measured for five BTRs and five BTHs (Zhou et al., 2018) (Table S2.6 and Figure 3a). All targeted BTRs and BTHs, except 5-Cl-BTR, were detected in more than 50 % of samples. The highest median concentration was for BTH (1.4 ng/mL; DF 88 %), followed by 2-MeS-BTH, 1-OH-BTR and 2-OH-BTH, BTR, and XTR and TTR. Temporal variability of urinary BTRs and BTHs during pregnancy were estimated using the inter-class correlation coefficients (ICCs). ICCs for BTRs ranged from 0.12 (BTR) to 0.56 (TTR) and for BTHs from 0.42 (2-OH-BTH) to 0.85 (2-MeS-BTH), suggesting that TTR and 2-MeS-BTH have a high reproducibility of levels during pregnancy. Pregnant women from high income family tended to have higher levels of urinary TTR, 2-OH-BTH, and 2-NH2-BTH. Similarly, women who were employed during pregnancy had higher levels of urinary 2-OH-BTH, 2-MeS-BTH, and 2-NH2-BTH (Zhou et al., 2018). This cohort study has further investigated the associations between urinary BTRs and BTHs during pregnancy and several adverse health effects, such as gestational diabetes mellitus (Zhou et al., 2020c), fetal birth size (Zhou et al., 2020b), preterm birth (Chen et al., 2022b), and cord blood mitochondrial DNA copy number (Chen et al., 2020b). Higher BTH and 2-OH-BTH levels were positively associated with 2-h blood glucose level. Moreover, the high exposure group of 2-OH-BTH showed an elevated risk of gestational diabetes mellitus (Zhou et al., 2020c), Higher levels of BTR, 1-OH-BTR, and 2-ABTH were positively associated with birth length z-scores among girls. On the other hands, higher BTH levels were associated with decrement birth length z-score among boys. These findings suggest that the associations between prenatal exposure to BTRs/BTHs and fetal growth may be in a sex-specific difference and the 2nd and 3rd trimesters may increase the susceptibility of BTH exposure (Zhou et al., 2020b).

Trimester-specific exposure to 13 EDCs, including 4 phthalates, 2 parabens, 3 phenols, 3 BTRs and BTH, and preterm birth have been investigated. Findings showed that the exposure to a mixture of 13 EDCs in the 1st trimester was significantly associated with an elevated risk of preterm birth. However, BTRs and BTH were not independently associated the risk of preterm birth (Chen et al., 2022b). A positive association between urinary

2-MeS-BTH concentrations in the 1st trimester and cord blood mitochondrial DNA copy number (mtDNAcn), while urinary 2-ABTH in 3rd trimester was significantly negatively associated with cord blood mtDNAcn. Similar patterns of associations were demonstrated between urinary BTR and XTR concentrations in the 3rd trimester and cord blood mtDNAcn. This indicates that the impact of prenatal exposure to 2-MeS-BTH, BTR, and XTR has a link between cord blood mtDNAcn, however, since the observed associations were controversial, interpretation should be taken with caution (Chen et al., 2020b).

To our knowledge, only one study measured BTHs in children's urine (Murawski et al., 2020) Urinary 2-SH-BTH was measured from a total of 516 urine samples collected from 3-17-years-old-children of the German Environmental Survey (2015-2017) (Table S2.6). 2-SH-BTH was detected in 61% of urine sample of the 3-5-year-old children (GM 1.2 ng/mL), and in 50%, 35%, and 52% of the age group of 6–10 years (< 1.0 ng/mL), 11-13 years (< 1.0 ng/mL), and 14–17 years (< 1.0 ng/mL), respectively. The GM of 2-SH-BTH concentrations in urine of 3- to 17-year- old children was 1.02 ng/mL (0.89 µg/g cr). The maximum urinary 2-SH-BTH concentration was 43.5 ng/mL (42.7 µg/g cr). Despite its ubiquitous usage of 2-SH-BTH, exposure levels were below the existing health-based guidance value for systemic exposure.

Adipose tissue

Human adipose fat samples collected from 20 volunteers who underwent liposuction surgery in New York City were analysed for the presence of 3 phenols, 7 parabens, as well as 5 BTRs and 4 BTHs (Wang et al., 2015) (Table S2.6). Among the 5 BTRs, TTR and XTR were frequently detected at GM 1.55 ng/g and 0.73 ng/g, respectively. Other BTRs, such as BTR, 1-OH-BTR, and 5-Cl-BTR were detected at concentrations < 1 ng/g. Among 4 BTHs, 2-OH-BTH was the dominant BTH found in 55% of the adipose samples, at GM 5.5 ng/g with maximum concentration of 62.5 ng/g, followed by BTH detected in 30 % of the samples with maximum concentration of 20.2 ng/g. Measured BTRs and BTHs were compared with a previous study that conducted measurements of urinary BTRs and BTHs in U.S general population (Asimakopoulos et al., 2013b) (Table S2.6). Urinary concentrations of TTR, XTR, BTH, and 2-OH-BTH were lower than those in adipose tissue samples, suggesting that BTRs and BTHs may have potentially bioaccumulated in fat tissue.

In summary, BTRs and BTHs (including a TP) were found in urine collected from various parts of the world (Asia, USA, Europe) in significant concentrations up to 200 ng/mL. As BTR was found in drinking water, indoor dust, consumer products and food and BTH in drinking water, consumer products and food (Figures 1 and 2), the biomonitoring results indicate that this widespread occurrence in human exposure relevant media results as well in internal human exposure (Figure 3).

3.4. 1,4-Dioxane

Blood

Very few studies are available on the biomonitoring of 1,4-D. A study performed by the U.S. Centers of Disease Control and Prevention (CDC) collected 3125 whole blood samples in 2013–2014 from U.S. general population aged equal to and above 12 years old and showed that 1,4-D was not detected in any sample (Table S2.8) (CDC, 2017). Since 1,4-D is reported to be quickly excreted in urine and metabolized to HEAA and 1,4-dioxane-2-one (ATSDR, 2012; Braun and Young, 1977; Young et al., 1978; Young et al., 1977), 1,4-D and its metabolites, HEAA and 1,4-dioxane-2-one may be measurable in urine rather than blood which should be considered in future biomonitoring studies.

3.5. 1,3-di-o-tolylguanidine and 1,3-diphenylguanidine

Blood

Tang et al. investigated DTG and DPG concentrations in maternal and cord serum pairs collected from 109 mothers. DTG was not detected in both maternal and cord serum, while DPG was found with median and maximum concentrations of 1.7 and 8.8 ng/mL in maternal serum (DF: 91%), and 0.35 and 2.1 ng/mL in cord serum (80%), respectively (Table 2.10 and Figure 3c) (Tang et al., 2022). This finding indicates the potential for DPG to cross the human placenta and exposure to the foetus.

Gil-Solsona et al. reported that DPG was detected in 70% of maternal blood (collected during delivery) at a concentration range of ND–28 ng/mL, but not in the placenta (Table 2.10) (Gil-Solsona et al., 2021). This is contrary to the speculation from the previous study (Tang et al., 2022) that DPG may cross the human placenta.

3.6. Trifluoromethane sulfonic acid

To date, there is no available data on biomonitoring for TFMS. The results of TFMS detection in diverse water samples, especially drinking water from previous studies indicate that TFMS is exposed to the general population. Therefore, human biomonitoring of TFMS and assessment of human exposure to TFMS should be urgently needed to confirm the current status of TFMS exposure to the general population.

4. Interpretation of human biomonitoring data in the policy framework

Human biomonitoring data, reflecting internal exposure, can be used for various purposes which are of more or less relevance directly to environment and health policy under chemicals management legislation such as REACH in the EU and TOSCA in the US in general or more specific (vertical) chemical products legislations such as for pesticides, biocides, food contact materials, human and animal pharmaceuticals, cosmetics etcetera. First use of HBM data is just an indication and proof, not only that human exposure does occur, but also that the pollutant or a metabolite is absorbed via skin, lungs or gastro-intestinal tract resulting in actual internal exposure. As such (without additional information on 'safe internal values'), a HBM measurement is a scientific finding that by itself does not have any direct regulatory or policy significance. Sensitive analytical chemistry techniques will be able to measure more and more chemicals or their metabolites in whatever biological matrix. Subsequently, HBM-based knowledge regarding internal exposure to the parent substances and/or metabolites can be used for human risk assessment purposes in comparison with established internal exposure HBM guidance values ('safe values' or HBM-GVs). Internal exposure best reflects real-life exposure of potential target organs and systems. This might have regulatory or policy consequences in general when measured HBM-concentrations are above the relevant HBM-GVs. Third, it can also inform policy makers on exposure differences and risk differences between different age groups, between males and females, differences linked to socioeconomic status (SES) or living in rural or urban areas or between countries and regions and this might help focussing policy measures to decreased potential risks indicated. Fourth, the risk assessment outcome and knowledge on highly exposed (sub)populations can inform policymakers whether specific or general exposure mitigation is needed. Lastly, sequential HBM sampling results obtained as such over the years in the same population can inform policy makers on the effectiveness of exposure mitigation policies as well as on the need to take a closer look at them in case detection frequencies and/or concentrations do rise over time. Several time-trends indicating impact of exposure mitigation policies have been presented, such as on PFAS (Buekers et al., 2018), on blood lead in children (Hwang et al., 2019) and on various phthalates (Dominguez-Romero et al., 2023). Human risk assessment using all possible data regarding hazards and external and internal exposure should indicate whether there are (sub)populations at risk and whether policy action is needed.

Risk assessment can be based on external limit values (legally binding or not), such as ADI, TDI, derived no-effect level (DNEL), acceptable operator exposure level (AOEL), RfD, reference concentration (RfC) and obviously for this, sufficient knowledge regarding the hazardous properties of the chemical, risk assessment is needed. With high-quality or only screening level information on the human toxicokinetics of the chemicals, the limit values

can be converted into (screening-level) internal values. Examples of these are the human biomonitoring guidance values (HBM-GV), as derived for several chemicals in the HBM4EU project (https://www.hbm4eu.eu/?s=HBM-GV), the biomonitoring equivalent (BE) screening values, as derived various chemical substances for Health Canada (Nakayama et al., 2023) and the German HBM-I values (https://www.umweltbundesamt.de/en/image/current-human-biomonitoring-hbm-values-for-blood). The BE screening values are estimates of average blood concentrations that are consistent with what would be expected in a typical adult human exposed at steady state to the reference values identified here. These are rough screening values than can allow comparison of measured blood VOC concentrations to a benchmark that is consistent with existing risk assessments for these compounds, rather than bright lines separating safe from unsafe exposure levels (Aylward et al., 2010).

Many of these screening values are listed in the recently developed Human Biomonitoring Health-Based Guidance Value (HB2GV) Dashboard as presented in Nakayama et al. (2023). A regularly updated overview of actually available internal HBM-GV (internal RfDs) is available (https://biomonitoring.shinyapps.io/guidance/). Actual HBM measurement values can then be compared to these internal guidance values for human risk assessment based on internal exposure. A second option is to take a reasonable worst-case internal exposure (HBM) value, usually the P95 of the distribution of HBM measurements, and estimate the external exposure that has resulted in that P95 internal exposure value: the estimated daily intake or EDI. This is called reverse dosimetry and can be done at screening level with empirics-based assumptions on key toxicokinetic factors such as the urinary excretion factor (FUE) or with sophisticated physiologically-based kinetic (PBK) modelling (https://www.epa.gov/expobox/exposure-assessment-tools-approaches-exposure-reconstruction-biomonitoring-and-reverse). This approach has been taken likely in most of the papers that have been presented regarding EDI values in Section 3.

In Figures 4 and 5, a graphical overview is presented on EDIs for various PM and TPs (MEL, CYA, QACs, 1,4-D, BTH and BTR) calculated using human external exposure models including the actually measured values in the various relevant exposure media drinking water, (indoor or outdoor) dust, consumer products or food as reported in the papers included in this review. In addition, the TDIs of the PMs and the TP CYA and the ADI for QACs are presented in the same Figures 4 and 5 to enable comparison with EDIs. It is clear in both figures that the differences between EDIs and TDIs/ADIs are still one to two orders of magnitude or more indicating no immediate health concern.

In Figure 6, EDIs calculated using human biomonitoring data in the original papers and reverse dosimetry models are shown for MEL, CYA, BTH and BTR, together with the corresponding TDIs. Figure 6 presents point estimates

(MEL and CYA) or distributions of EDIs (BTH and BTR) as reported in the original papers. Overall, none of the relatively few HBM measurements that were found on the investigated PMs and presented in Figure 6 are alarming. When EDIs were calculated from the internal exposure levels presented, none of them seemed to indicate exceedance of the TDI. Caution is needed however as only relatively few measurements were done. Furthermore, the calculation of the EDIs as found in the literature seems to be mostly based on a rather simple extrapolation from measured HBM values. Dedicated elaboration of health-based HBM Guidance Values (HBM-GV) with proper consideration and potentially (additional) measurements of human toxicokinetics seems to be warranted in order to reduce significant uncertainties in the internal exposure-based risk assessments.

Also, it is noticed that 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. In addition, as far as we have been able to assess, the TDIs as presented in the papers included in this review are specific for one substance (one PM). In practice, various PM, like BTHs and BTRs might exhibit similar health effects, warranting mixtures risk assessment in which in its most simple form, exposures to different but similarly acting PM would be added-up (additivity principle) and the sum EDI would then be compared to a "to be established" group TDI as EFSA has e.g. done for PFAS (EFSA, 2020).

Interestingly, and as mentioned already in chapter 1, Hrubec et al (2021) demonstrated statistically significant relationships between the sum of QAC in blood (BAC and DDAC) and meaningful health related biomarkers (increase in inflammatory cytokines, decreased mitochondrial function, and disruption of cholesterol homeostasis in a dose dependent manner). While the current review focusses on the human exposure to PMs with a bit of consideration of potential human risks that do not immediately seem to be present based on single substance risk assessment, it is possible that the occurrence of these chemicals in the environment may pose a risk for various other organisms and environmental species.

5. Research gaps and future perspectives for research on human exposure to PMs

Most of PMs discussed in this review were found to be detected in various environmental matrices relevant to human exposure. In particular, as expected from their intrinsic properties, exposure to targeted PMs was observed in drinking water and various water bodies in diverse countries. PMs were also frequently detected in dust and various consumer products, indicating their various application and persistency in the environment. These results also suggest that PMs can be exposed to the human body through various sources and pathways,

not only through drinking water, where PMs may primarily accumulate (Arp et al., 2017). Additionally, biomonitoring studies have identified human exposure to targeted PMs. In particular, the detection of MEL, QACs, BTHs, BTRs, and DPG in breast milk and blood samples was confirmed, suggesting that some PMs can bioaccumulate.

Although exposure to PMs in various human and environmental matrices relevant to human exposure has been reported, limited information on pharmacokinetics, toxicokinetic parfameters and reference values (e.g. RfD) is available for the 8 PMs. Additionally, few or no biomonitoring studies exist for some PMs (TFMS and 1,4-D). This makes accurate risk assessment of PMs and identification of potential threats of them to human health difficult and prohibits our understanding of the current exposure status of PMs. To narrow current knowledge gaps and better elucidate human exposure to PMs, continuous biomonitoring and environmental monitoring programs, as well as research on risk assessment of PMs, should be performed.

Specific research gaps and future perspectives of each of the 8 PMs discussed in this review are presented:

Human exposure to **MEL and its derivatives and TPs** has been well-studied compared to other PMs discussed in this review. Growing evidence suggests that MEL and CYA are not only kidney toxicants at high concentrations, but they can also have reproductive and neurological toxicity and endocrine disruptive properties. However, due to the limited information available on toxicokinetic parameters of MEL and its derivatives and TPs in humans, and to the lack of unequivocal TDI values, exposure dose calculations and risk assessment are still subject to high uncertainty. All studies presented here highlight the critical need for further assessment of health risk associated with exposure to MEL both in the general population and in more vulnerable groups, such as infants and pregnant women. Research in this direction should also focus on examining the potential health risks of chronic low-level co-exposure to MEL and its derivatives and TPs including other health effects than renal toxicity that might result in further lowering of the TDI. Additional biomonitoring is also needed to characterize exposure temporal variability and across population sub-types. Other identified research gaps which should be addressed in the future include the measurement of internal biomarkers of exposure in the general population, the identification of major predictors of exposure and associated health effects, and the assessment of early markers of kidney injury and disease.

An increased occurrence of **QACs** at high concentrations in various matrices has been observed during the Covid-19 pandemic leading to an increasing interest in this chemical class. Before that, no data on human exposure to QACs were available. Currently, there are only three studies available investigating human exposure to QACs. Two of these studies covered human blood samples and confirmed a wide occurrence of QACs through high DFs

(>50 %) for most of the investigated analytes (Hrubec et al., 2021; Zheng et al., 2021). QACs were also detected in breast milk samples suggesting an exposure of infants to these compounds (Zheng et al., 2022). These studies covered the general population in the US. Investigations of populations in other parts of the world are lacking. Furthermore, future biomonitoring studies are limited due to several research gaps identified within this review. Firstly, the listed studies investigated only parent QAC compounds in human samples without taking into account any potential biotransformation products. Latter would be especially relevant for the investigation of QACs in human urine, hypothesized as a possible excretion pathway. To the best of our knowledge, only one study characterized the biotransformation products of some BACs. Seguin et al. investigated the *in vitro* metabolism of BACs using human liver microsomes (HLM) and human hepatic cytochrome P450 (CYP) enzymes. Oxidation of the alkyl side chain was identified as an important metabolic reaction through reporting of *ω*-hydroxy-, (*ω*-1)-hydroxy-, (*ω*, *ω*-1)-diol-, (*ω*-1)-ketone-, and *ω*-carboxylic acid-metabolites for C10-BAC (Seguin et al., 2019). Comparable studies investigating the metabolism of the other BACs and QAC classes (ATMACs and DDACs) are still lacking. In order to estimate a potential risk of human exposure to QACs, EFSA established TDIs of 0.1 mg/kg bw per day for DDACs and BACs based on the recommendations provided by the German BfR agency (BfR, 2012; BfR, 2013). Within the studies on the occurrence of QACs in indoor dust and food samples listed in section 2.2, all EDIs calculated from the quantified concentrations were below the established TDIs. However, TDI values for ATMACs are lacking, and thus a risk assessment for this compound group is not possible. Furthermore, a comprehensive and combined assessment of as many possible exposure sources, including cleaning and personal care products, other foods etc., is needed for the estimation of human exposure to all classes of QACs.

BTHs and BTRs are most widely investigated PMs discussed in this review, especially, BTH and BTR are most studied compounds in both human and environmental samples. As external exposure sources, dust, surface water, and consumer products have been commonly studied. Not only indoor dust sample, but also outdoor dust collected from the road have been considered as important exposure source of BTHs due to the leaching of BTHs from road and tire wear particles. Interestingly, reported concentration of BTHs in PM_{10} and $PM_{2.5}$ were 2 orders higher than outdoor dust samples (Zhang et al., 2018). EDIs have been estimated by several studies investigated BTHs in dust samples and indicated that EDIs of BTH(s) and BTR(s) in general and occupational population were below the current RfDs. However, according to the occurrence of BTHs in $PM_{2.5}$ and PM_{10}, which are most harmful particle size for exposure via inhalation, more comprehensive studies are crucial to investigate not only dust, but also PMs in future. Studies included in this review have measured a wider range of BTH and BTR derivatives in surface water than previous studies due to improvement in the sensitivity of measurements. While most studies have investigated river water samples, studies reporting BTHs and/or BTRs

in tap and bottled water are scarce. Food and drinking water are important exposure sources of BTRs and BTHs. In this review, only two studies from China (Wang et al., 2016) and Korea (Wang et al., 2023) have reported BTRs and/or BTHs in tap and commercial bottled water and indicated that concentrations of BTHs and BTRs were higher in tap water than bottled water. Moreover, current evidence indicates that the contributions of BTH and BTH derivatives in tap water to internal exposure were low (12% and < 2 %, respectively). EDIs of BTRs and BTHs from seafood were below current RfD, however, the potential to cause long- term or risks to sea organisms should not be ignored. Recycled rubber products, such as floor materials of sports fields and children's playgrounds, together with textiles and child clothing were commonly investigated as consumer products. EDIs from children's clothing showed that dermal exposure of BTRs and BTHs from clothes to skin was below RfD. Although dermal exposure to BTRs and BTHs via clothes was shown negligible, these exposures are possibly chronic exposures. Therefore, comprehensive studies regarding integrative exposure scenario of BTRs and BTHs from consumer products, drinking water, and foods are required. Lastly, to our knowledge, only few studies have investigated human health effects resulting from exposure to BTRs and BTHs. Adverse effects of BTRs and BTHs have been reported regarding adverse pregnancy health outcomes, such as gestational diabetes, preterm birth, and birth weight from one birth cohort study in China. Current scientific evidence is limited in health outcomes of a specific study population, therefore, future studies investing a wider range of health outcomes in different age groups (infant, toddler, children, adolescent, and adult) are essential.

Studies presented in this review for **1,4-D** have shown its occurrence in drinking water and its sources, food, and consumer products, in agreement with the exposure pathways of 1,4-D to humans (the consumption of contaminated food and water, or dermal contact) suggested by EPA (EPA, 2017b). In particular, high DFs of 1,4-D were observed in drinking water and its sources, and in consumer products, which is a result of the extensive use of 1,4-D in consumer products and its intrinsic properties. Despite the occurrence of 1,4-D in relevant environmental matrices to human exposure which indicates potential exposure of the general population to 1,4-D, there are few human biomonitoring data for 1,4-D. Therefore, epidemiological studies investigating the general population should be conducted to understand human exposure and the health implications of 1,4-D. Such studies can also establish the major determinants of exposure to 1,4-D in the general population. Additionally, our understanding of human exposure to 1,4-D will be enhanced by the development of efficient biomarkers of exposure. Because 1,4-D is mainly metabolized to HEAA and 1,4-dioxane-2-one, those two metabolites can be used as specific biomarkers of 1,4-D exposure. It is required to identify 1,4-D along with these markers in the future investigation of human exposure to 1,4-D, because it might be difficult to detect 1,4-D itself in biological samples.

Multiple exposure sources of **DPG** and **DTG** to humans, especially drinking water, indoor dust, and consumer products, were identified in this review. However, it is difficult to find the major contributor to DPG and DTG exposure in the general population. In addition, DPG was detected in maternal and cord blood confirming that the general population is exposed to DPG and that DPG may bioaccumulate and cross the human placenta. This finding indicates that the bioaccumulation and mobility properties are not inherently exclusive, as previously suggested by Arp et al. (2017). However, existing data on DPG and DTG do not allow the elucidation of the internal exposure levels in the general population, and the potential adverse health outcomes of DPG and DTG. To assess human risks to DPG and DTG, future biomonitoring and epidemiological studies, and a better understanding of their toxicokinetics, and toxic thresholds are necessary. The monitoring of their biotransformation products may also be required for an accurate estimation of human exposure. DPG was found to migrate into water from high-density polyethylene pipes (Tang et al., 2015). Detailed investigations of such phenomena could promote appropriate management of the polyethylene pipes used in the distribution of drinking water and control the risk of DPG.

The general population is exposed to **TFMS**, as evidenced by its occurrence and high DFs in drinking water and its sources. However, studies on the exposure sources, pathways, and fate in humans and in other environmental matrices relevant to human exposure are very limited. This is closely linked to the lack of specific, sensitive, and reliable analytical methods for TFMS. It is difficult to analyse TFMS with general analytical methods for PFAS because TFMS has higher water solubility than other PFAS and is eluted very early in PFAS chromatographic analysis resulting in poor sensitivity, poor peak shape, difficult separation, and unreliable quantification. Recently, alternative analytical approaches, such as mixed-mode liquid chromatography (Montes et al., 2017; Schulze et al., 2019), hydrophilic interaction liquid chromatography (Zahn et al., 2016; Schulze et al., 2019), and supercritical fluid chromatography (Bjornsdotte et al., 2019; Schulze et al., 2020; Schulze et al., 2019) have been employed for TFMS for aqueous environmental matrices. In this regard, the development of novel, sensitive, and reliable analytical methods as well as improvement of already available methods for TFMS in various environmental and human matrices should be conducted. In addition, the pharmacokinetics of TFMS have not been clearly elucidated. To the best of our knowledge, an RfD of TFMS has not been established, hampering thus appropriate interpretation of environmental and human exposure data. The establishment of an RfD value for TFMS would allow an effective management of risks derived from TFMS exposure.

6. Conclusions

This review illustrated the occurrence of 8 PMs in humans and environmental matrices relevant to human exposure. While data on a few PMs in different environmental and human matrices is limited, most PMs discussed in this review have been frequently detected in drinking water and other water sources, as expected from their mobility characteristics. Furthermore, some of these PMs have been detected in dust and various consumer products, which is consistent with their various applications and persistency properties. In addition, evidence of human exposure to PMs has been found. EDIs of PMs from environmental matrices and HBM data were compared to relevant TDI or other RfD, and it was concluded that none of the PMs in this review resulted in EDIs exceed the current TDI or RfD values. While there seems not to be an imminent concern for human exposure, it is currently unclear in PMs discussed in this review are chemicals of concern for other species, in particular in the aquatic environment. It is clear that further studies focusing on the unbiased exposure and risk assessment of PMs in humans are necessary. Additionally, 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 more comprehensive understanding of the potential risks associated with PMs.

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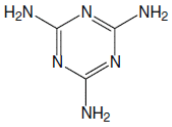
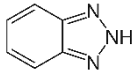
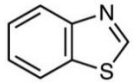
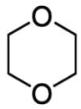
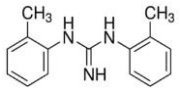
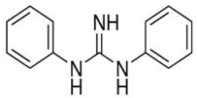
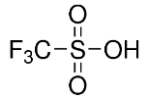
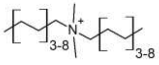
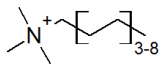
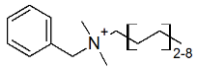
Table 1. Persistency and mobility criteria for the PM/vPvM assessment proposed by Neumann and Schliebner (2019)

Persistency criteria			
i) High-quality experimental half-lives or expert evaluations (e.g. SVHC-PBT)			
P	water	Marine water (at 9℃)	>60 days
		Fresh water (at 12℃ and pH 4-9)	>40 days
		Estuarine water (at 12℃ and pH 4-9)	>40 days
	Sediment	Marine sediment (at 9℃)	>180 days
		Fresh water sediment (at 12℃ and pH 4-9)	>120 days
		Estuarine water sediment (at 12℃ and pH 4-9)	>120 days
	Soil (at 12℃ and pH 4-9)		>120 days
vP	water	Marine water (at 9℃)	>60 days
		Fresh water (at 12℃ and pH 4-9)	>60 days
		Estuarine water (at 12℃ and pH 4-9)	>60 days
	Sediment	Marine sediment (at 9℃)	>180 days
		Fresh water sediment (at 12℃ and pH 4-9)	>180 days
		Estuarine water sediment (at 12℃ and pH 4-9)	>180 days
	Soil (at 12℃ and pH 4-9)		>180 days
ii) Inherent/readily biodegradable tests and weight-of-evidence (experimental data, QSARs, read-across, etc.)			
Potential P/vP++	The weight-of-evidence suggests it is quite likely the P criterion is met, due to all lines of evidence indicating persistency, though half-lives are not available		
Potential P/vP	There is only screening level date from inherent or readily biodegradable tests or QSAR data that indicate potential persistency		
Mobility criteria			
i) The lowest organic carbon-water coefficient log K_{oc} over the pH range of 4–9			
M	<4.0		
vM	<3.0		
ii) If high-quality experimental K_{oc} data is not available*			
M	$logK_{ow}$ (neutral); $logD_{ow}$ (anions or ionisable with exp. pK_a)		<2.5
	$logD_{ow}$ (zwitterions, ionisable no exp. pK_a)		<1.5
	$logD_{ow}$ (cations)		<0.5
vM	$logK_{ow}$ (neutral); $logD_{ow}$ (anions or ionisable with exp. pK_a)		<3.5
	$logD_{ow}$ (zwitterions, ionisable no exp. pK_a)		<2.5
	$logD_{ow}$ (cations)		<1.5
Potential M/vM	$logK_{ow}$ (neutral); $logD_{ow}$ (anions or ionisable with exp. pK_a)		<4.5
	$logD_{ow}$ (zwitterions, ionisable no exp. pK_a)		<5.5
	$logD_{ow}$ (cations)		<4.5

*This is mobility screening criteria. The German Environment Agency has recommended to screen for mobility if no K_{oc} data is available (Arp and Hale, 2019; Neumann and Schliebner, 2019)

Table 2. Persistent and mobile chemicals (PMs) discussed in this review

Name	Acronym	Formula	CAS number	Molecular weight	Structure	P (half-life)	Rationale M		Class[b]
							$logK_{oc}$[a]	$logD_{ow}/K_{ow}$ or $logD_{oc}/K_{oc}$ (pH 4-9)[b]	
Melamine	MEL	$C_3H_6N_6$	108-78-1	126.12		>60 days (in water)[c]	1.51	-2.3	vPvM & PMT
2H-benzotriazole	BTR	$C_6H_5N_3$	95-14-7	119.12		268-345 days (in soils)[d]	1.72	1.5	vPvM & PMT
1,3-benzothiazole	BTH	C_7H_5NS	95-16-9	135.19		>60 days (in water)[e]	2.93	2.0	Pot.PMT / vPvM
1,4-Dioxane	1,4-D	$C_4H_8O_2$	123-91-1	88.11		>60 days (in surface water)[f]	0.42	-0.5	PMT
1,3-Di-o-tolylguanidine	DTG	$C_{15}H_{17}N_3$	97-39-2	239.32		107 days (estimated using QSAR)[b]	4.17	-3.0	vPvM & PMT
1,3-Diphenylguanidine	DPG	$C_{13}H_{13}N_3$	102-06-7	211.26		68 days (estimated using QSAR)[b]	3.74	1.4	vPvM & PMT
Trifluoromethane sulfonic acid	TFMS	CF_3SO_3H	1493-13-6	150.08		39 days (estimated using QSAR)[b]	0.29	0.3	vPvM
Dialkyldimethyl ammonium chlorides	DDAC	$[CH_3(CH_3)_{7\text{-}17}]N(CH_3)_2Cl$	C8: 5538-94-3 C10: 7173-51-5 C12: 3401-74-9 C14: 10108-91-5 C16: 1812-53-9 C18: 107-64-2	C8: 306.0 C10: 362.1 C12: 418.2 C14: 474.3 C16: 530.4 C18: 586.5		180 days (in river water)[g] 1048 days (in soil)[h]	4.64 (C8) 5.68 (C10) 6.73 (C12) 7.71 (C14) 8.81 (C16) 9.86 (C18)	1.57 (C8*) 2.59 (C10) 4.31 (C12*) 6.25 (C14*) 7.98 (C16*) 9.52 (C18*)	Pot. PM
Alkyltrimethyl ammonium chlorides	ATMAC	$CH_3(CH_3)_{7\text{-}17}N(CH_3)_3Cl$	C8: 10108-86-8 C10: 10108-87-9 C12: 112-00-5 C14: 4574-04-3 C16: 112-02-7 C18: 112-03-8	C8: 207.8 C10: 235.8 C12: 263.9 C14: 291.9 C16: 320.0 C18: 348.0		NA	2.78 (C8) 3.30 (C10) 3.82 (C12) 4.34 (C14) 4.86 (C16) 5.38 (C18)	-1.05 (C8*) -0.189 (C10*) 0.857 (C12*) 1.77 (C14*) 2.53 (C16*) 3.25 (C18*)	(Pot. PM)

Benzylalkyl dimethylammonium chloride	BAC	$CH_3(CH_3)_{5\text{-}17}N(Cl)(CH_3)_2CH_2C_6H_5$	C6: 22559-57-5 C8: 959-55-7 C10: 965-32-2 C12: 139-07-1 C14: 139-08-2 C16: 122-18-9 C18: 122-19-0	C6: 255.8 C8: 283.9 C10: 311.9 C12: 340.0 C14: 368.0 C16: 396.1 C18: 424.1		379 days (in water at pH 9)[i]	3.87 (C6) 4.39 (C8) 4.91 (C10) 5.43 (C12) 5.96 (C14) 6.48 (C16) 7.00 (C18)	C6*: -0.763 C8*: 0.233 C10*: 1.31 C12*: 2.10 C14*: 2.78 C16*: 3.54 C18*: 4.28	(Pot. PM)

NA: not applicable; a: from KOWWIN v. 1.68 estimate in EPI suite; b: Arp and Hale, 2019; c: ECHA, 2022c; d: (Lai et al., 2014); e: (Lyman et al., 1990); f: (ECHA, 2021b); g: EPA, 2017a; h: (Juergensen et al., 2000); i: (Frank, 2006)

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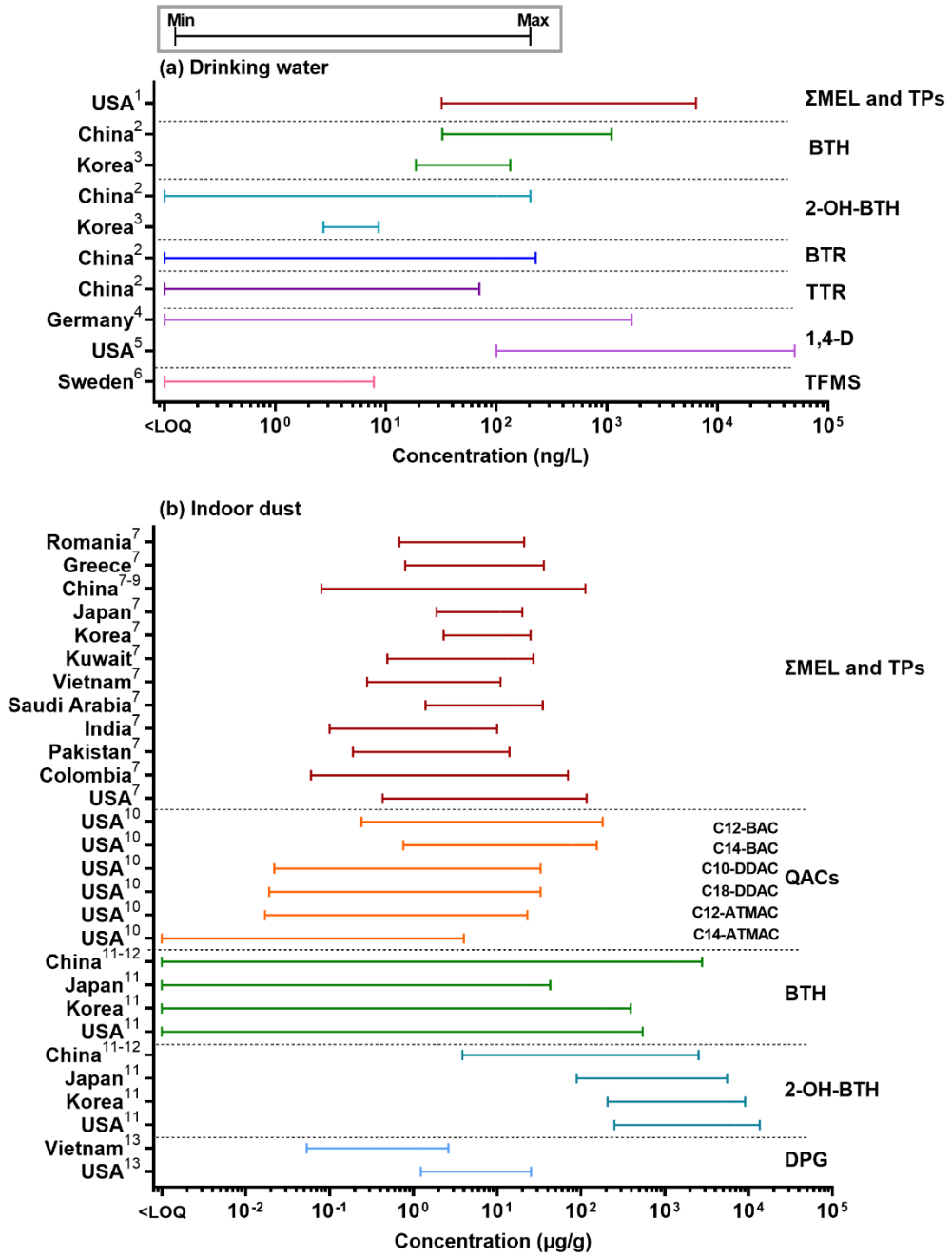


Figure 1. Concentration ranges of persistent and mobile chemicals (PMs) in (a) drinking water and (b) indoor dust reported in previous studies. Detailed concentrations and limit of quantifications (LOQs) of each compound and country are given in the supplementary material (Tables S2.1 to S2.11). [1]Zhu and Kannan, 2020; [2]Wang et al., 2016; [3]Wang et al., 2022; [4]Karges et al. 2022; [5]Adamson et al. 2017; [6]Bjornsdotte et al., 2019; [7]Zhu and Kannan, 2018; [8]Li et al., 2022; [9]Zhao et al., 2022; [10]Zheng et al. 2020a; [11]Wang et al., 2013; [12]Li et al., 2020; [13]Tan et al. 2021

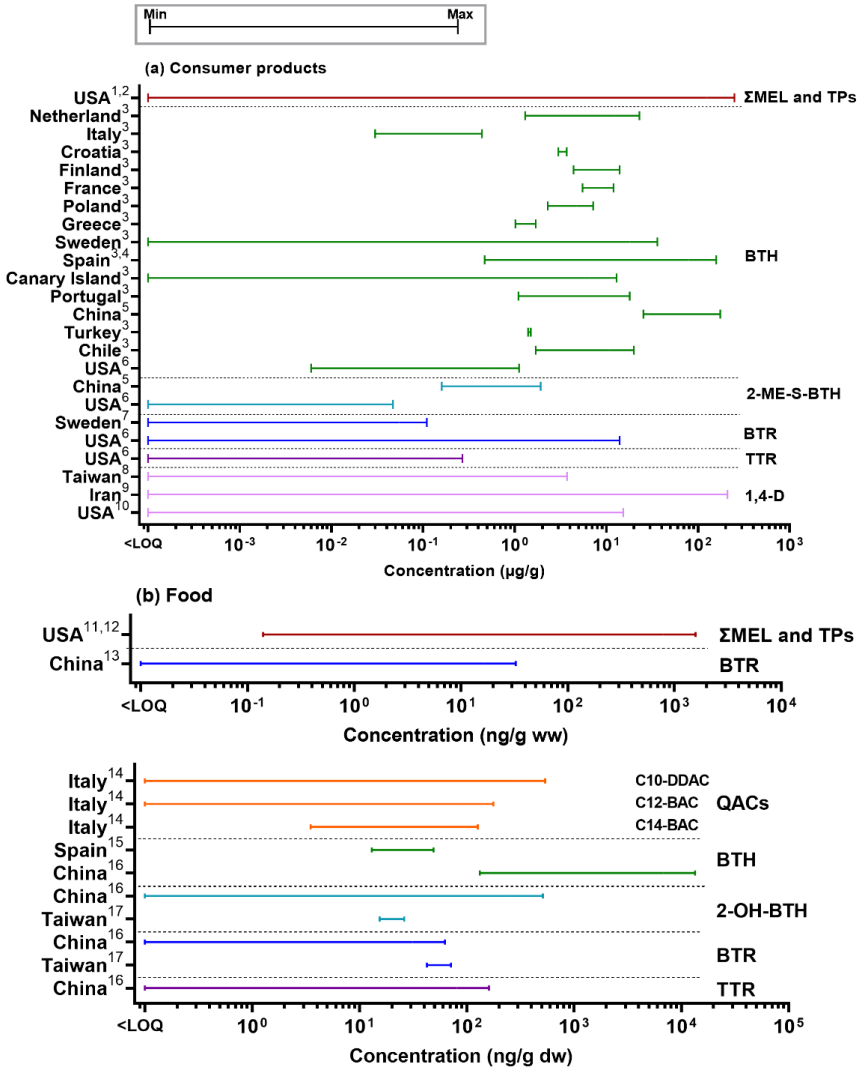


Figure 2. Concentration ranges of persistent and mobile chemicals (PMs) in (a) consumer products and (b) food reported in previous studies. Detailed concentrations and limit of quantifications (LOQs) of each compound and country are given in the supplementary material (Tables S2.1 to S2.11).[1]Zheng et al., 2020a; [2]Zheng and Salamova, 2020; [3] Armada et al., 2022a; [4]Llompart et al., 2013; [5]Zhang et al., 2018; [6]Liu et al, 2017; [7]Luongo et al., 2016; [8]Lin et al. 2017; [9]Saraji et al. 2016; [10]Zhou, 2019; [11]Zhu and Kannan, 2018; [12] Zhu and Kannan, 2019; [13]Yao et al., 2018; [14]Bertuzzi et al. 2014; [15]Trabalon et al., 2017; [16]Jia et al., 2019; [17]Chen et al., 2020

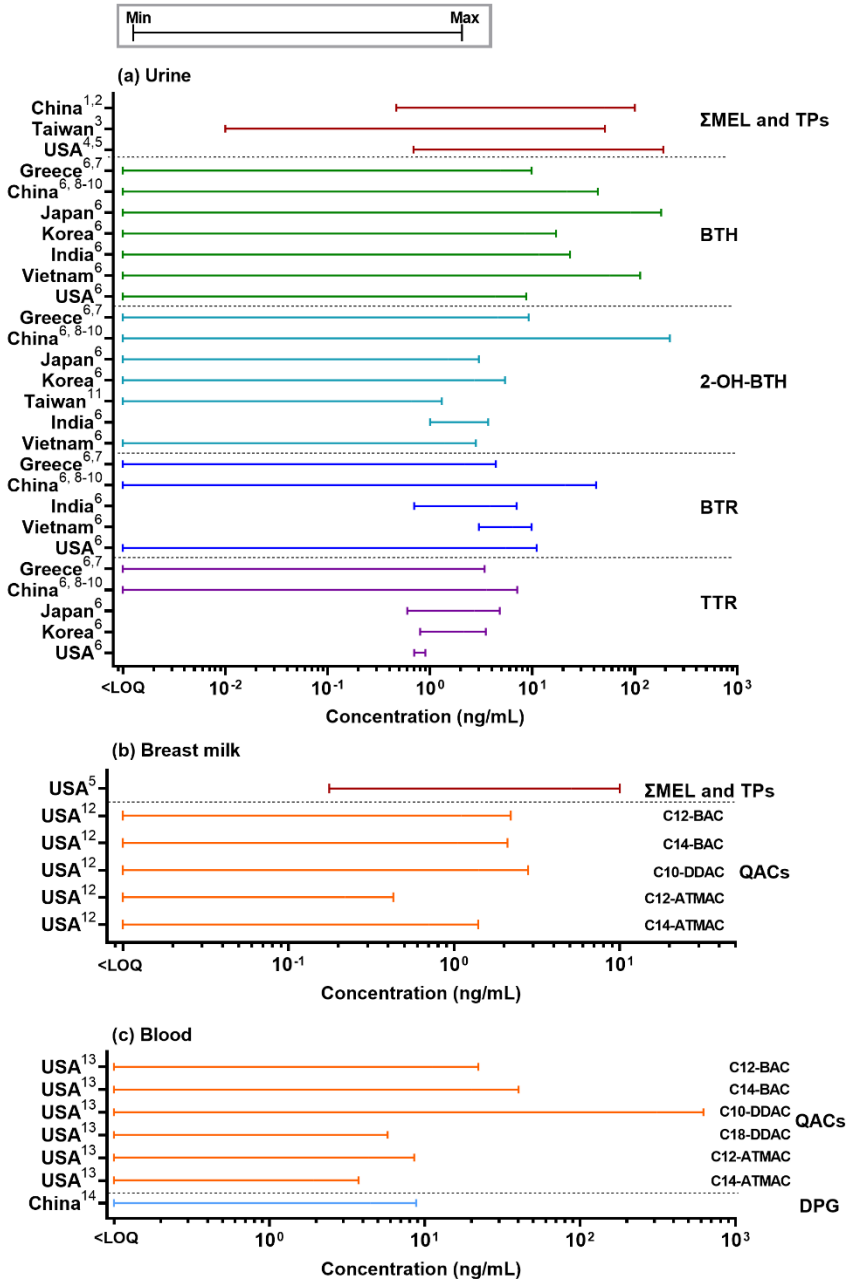
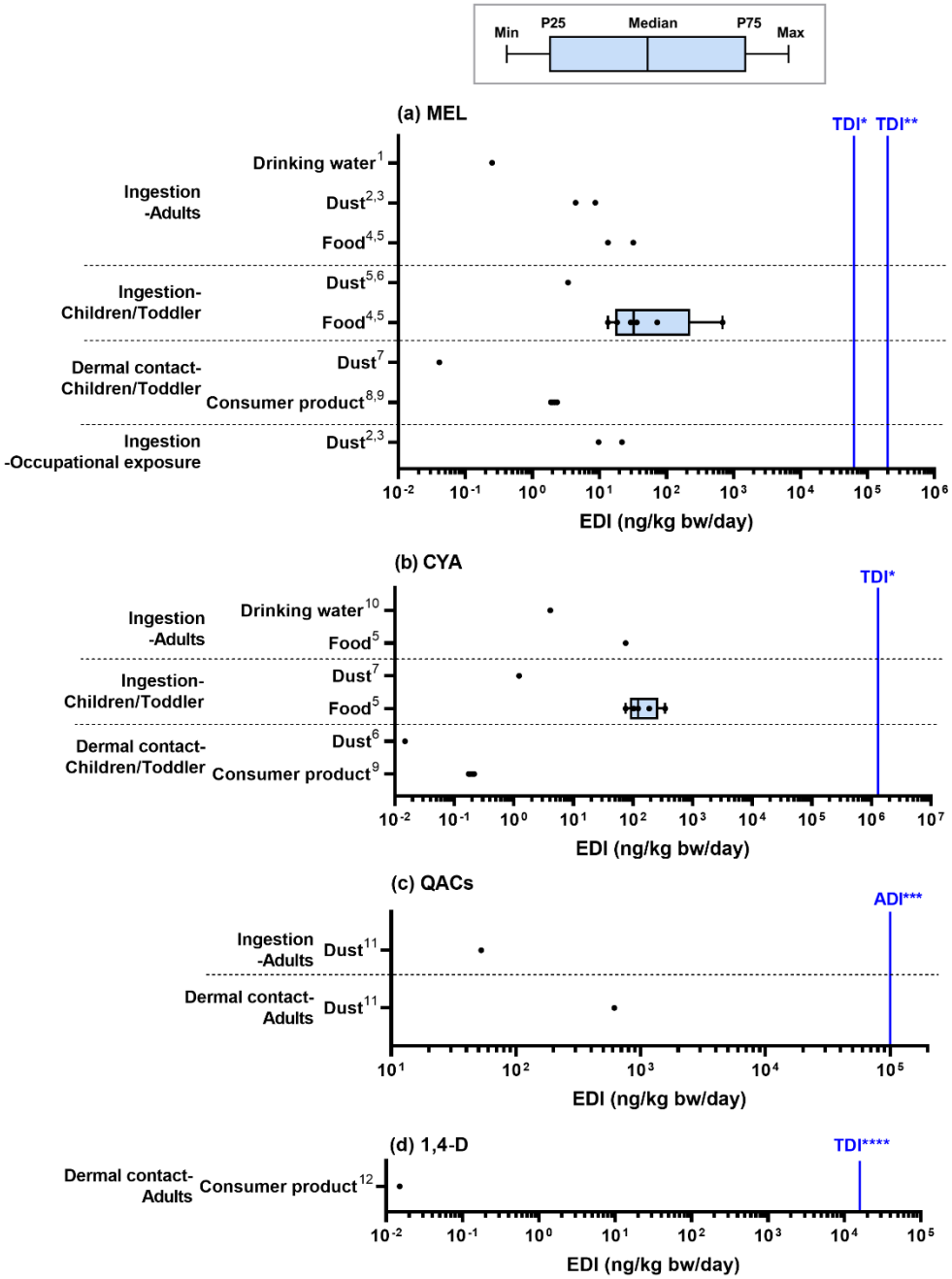


Figure 3. Concentration ranges of PMs in (a) Urine, (b) Breast milk, and (c) blood reported in previous studies. Detailed concentrations and limit of quantifications (LOQs) of each compound and country are given in the supplementary material (Tables S2.1 to S2.11). [1]Liu et al., 2022; [2]Shi et al., 2020; [3]Tsai et al., 2022; [4]Melough et al., 2020; [5]Zhu and Kannan, 2019; [6]Asimakopoulos et al., 2013a; [7]Asimakopoulos et al., 2013b; [8]Chen Y, 2018; [9]Li et al., 2018; [10]Li et al., 2017; [11]Li et al., 2021; [12]Zheng et al. 2022; [13]Zheng et al. 2021; [14]Ting et al. 2022



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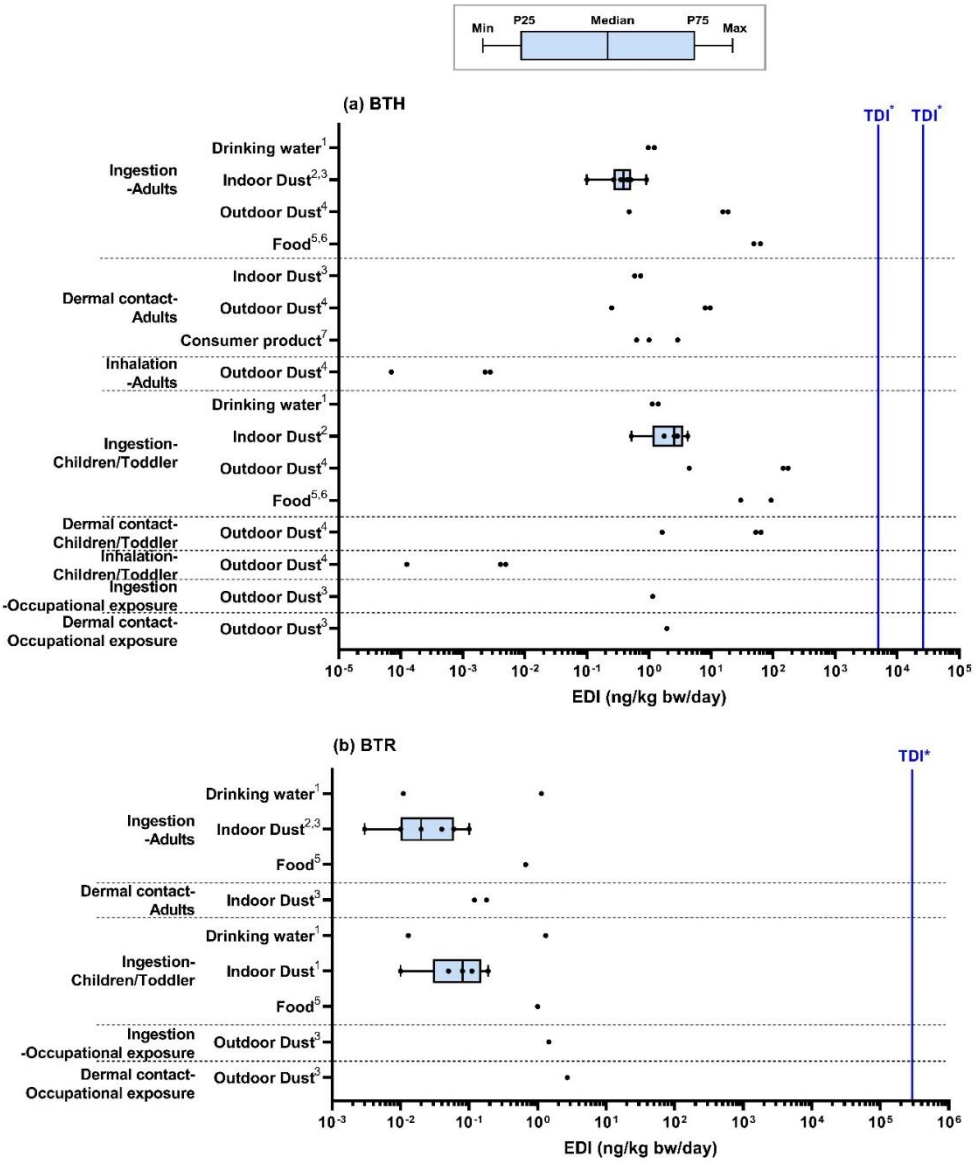
1278 **Figure 4.** Estimated daily intakes (EDIs; ng/kg bw/day) of (a) melamine (MEL), (b) cyanuric acid (CYA), (c)
1279 ammonium compounds (QACs), and (d) 1,4-dioxane (1,4-D) through the external exposure reported in previous
1280 studies. Detailed EDIs of each compound are given in the supplementary material (Tables S2.12 and S2.13). [1]Zhu
1281 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
1282 et al., 2020a; [7]Zheng et al., 2020b; [8]Zheng and Salamova, 2020; [9]Zhu and Kannan, 2020a; [10]Zhu and Kannan,
1283 2020b; [11]Zheng et al., 2020b; [12]Lin et al. 2017; *EFSA, 2010; **FDA, 2008 and Hsieh et al., 2009; ***BfR, 2012
1284 and BfR, 2023; ****Nishimura et al. 2004



1285

1286 **Figure 5.** Estimated daily intakes (EDIs; ng/kg bw/day) of (a) benzothiazole (BTH), and (b) benzotriazole (BTR)
1287 through the external exposure reported in previous studies. Detailed EDIs of each compound are given in the
1288 supplementary material (Table S2.12). [1]Wang et al., 2022; [2]Wang et al., 2013; [3]Li et al., 2020; [4]Zhang et al., 2018;
1289 [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
1290 (Ginsberg et al., 2011)

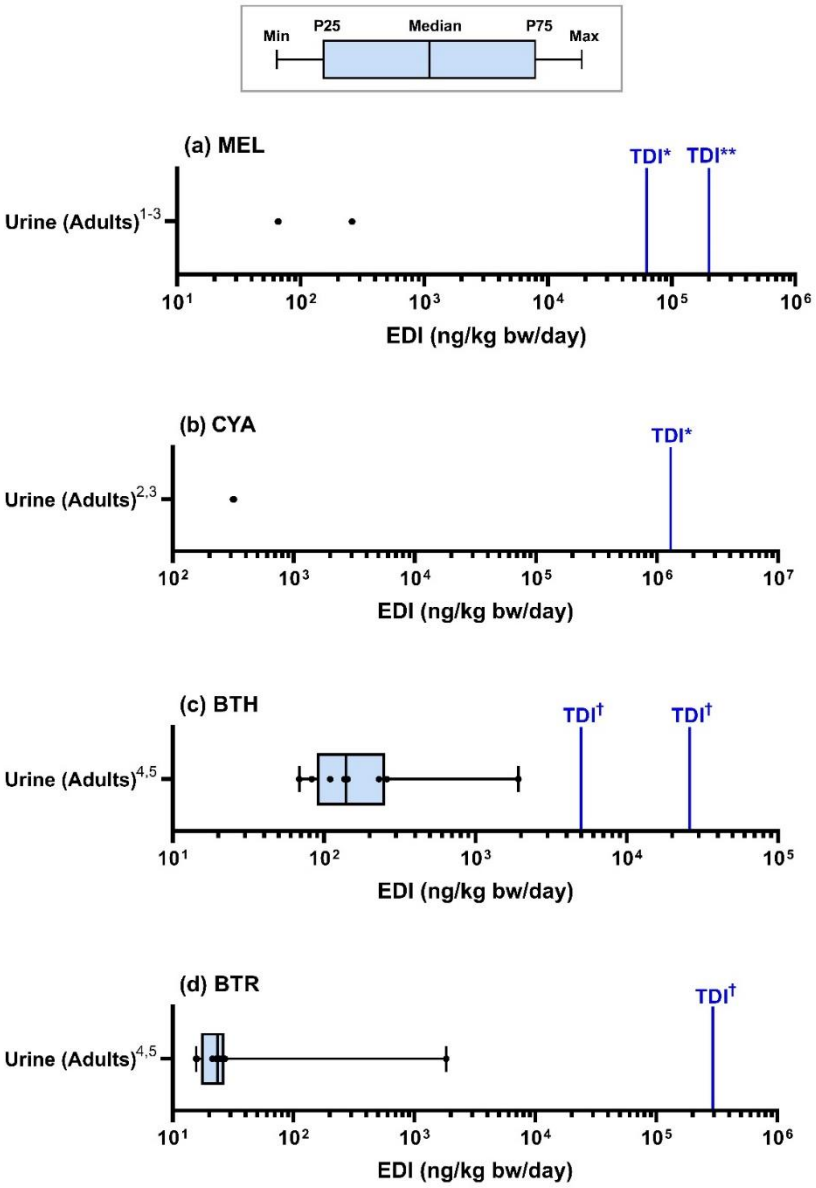


Figure 6. Estimated daily intakes (EDIs; ng/kg bw/day) of (a) melamine (MEL), (b) cyanuric acid (CYA), (c) benzothiazole (BTH), and (d) benzotriazole (BTR) through the internal exposure reported in previous studies. Detailed EDIs of each compound are given in the supplementary material (Table S2.13). [1]Shi et al., 2020; [2]Liu et al., 2022; [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)

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