



Interactions of human drug transporters with chemical additives present in plastics: Potential consequences for toxicokinetics and health

Valentin Tastet, M Le Vee, Arnaud Bruyère, Olivier Fardel

► To cite this version:

Valentin Tastet, M Le Vee, Arnaud Bruyère, Olivier Fardel. Interactions of human drug transporters with chemical additives present in plastics: Potential consequences for toxicokinetics and health. *Environmental Pollution*, 2023, 331 (Pt 2), pp.121882. <10.1016/j.envpol.2023.121882>. <hal-04121151>

HAL Id: hal-04121151

<https://hal.science/hal-04121151v1>

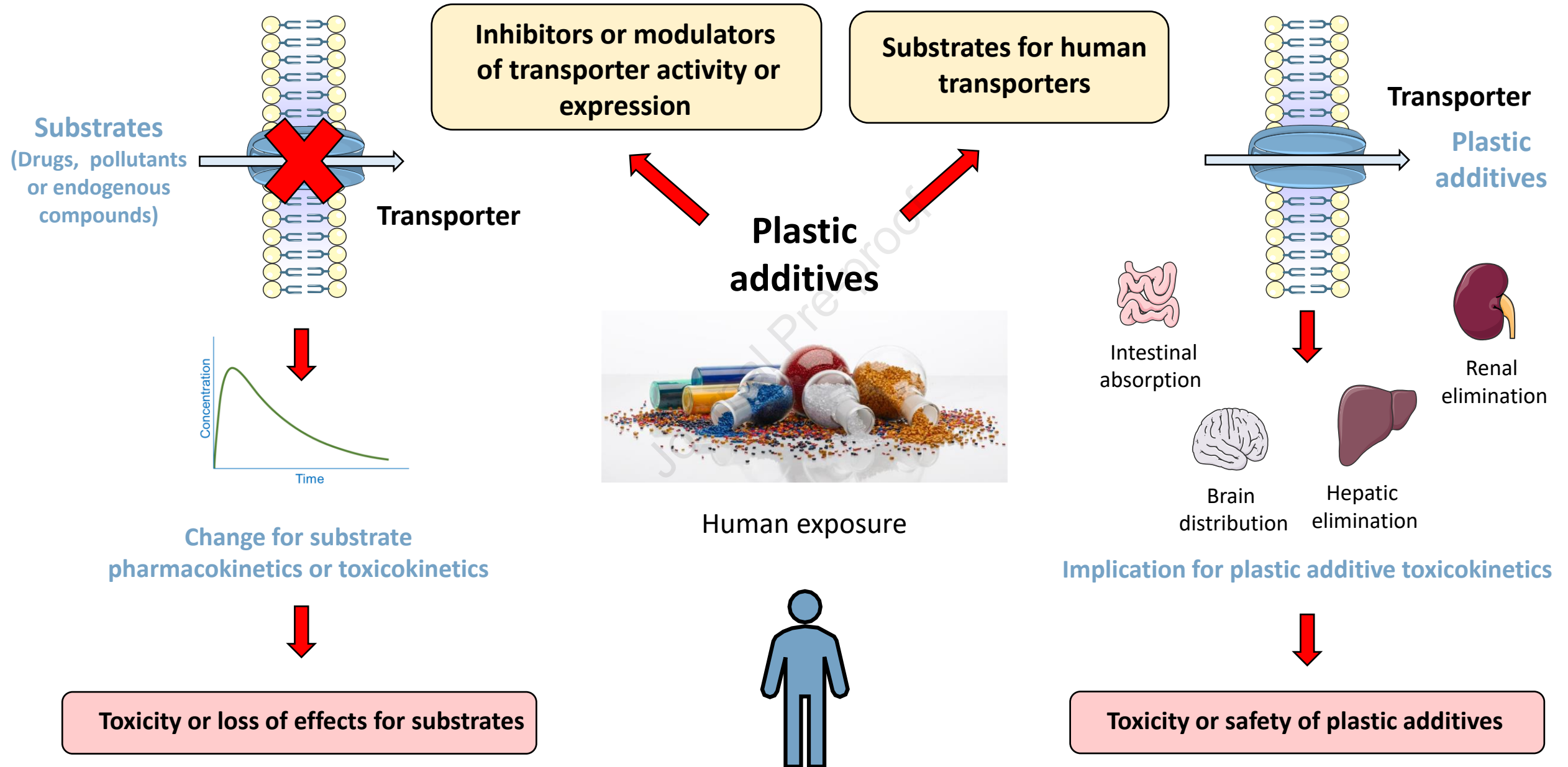
Submitted on 27 Jun 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC 4.0 - Attribution - Non-commercial use - International License



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21

**Interactions of human drug transporters with chemical additives present in plastics:
Potential consequences for toxicokinetics and health**

Valentin Tastet¹, Marc Le Vée¹, Arnaud Bruyère¹ and Olivier Fardel²

¹Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail)
- UMR_S 1085, F-35000 Rennes, France

²Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé,
environnement et travail) - UMR_S 1085, F-35000 Rennes, France

Corresponding author: Olivier Fardel, Irset, Faculté de Pharmacie, 2 Avenue Pr Léon
Bernard, 35043 Rennes, France. E-mail: olivier.fardel@univ-rennes.fr

Abstract

Human membrane drug transporters are recognized as major actors of pharmacokinetics; they also handle endogenous compounds, including hormones and metabolites. Chemical additives present in plastics interact with human drug transporters, which may have consequences for the toxicokinetics and toxicity of these widely-distributed environmental and/or dietary pollutants, to which humans are highly exposed. The present review summarizes key findings about this topic. *In vitro* assays have demonstrated that various plastic additives, including bisphenols, phthalates, brominated flame retardants, poly-alkyl phenols and per- and poly-fluoroalkyl substances, can inhibit the activities of solute carrier uptake transporters and/or ATP-binding cassette efflux pumps. Some are substrates for transporters or can regulate their expression. The relatively low human concentration of plastic additives from environmental or dietary exposure is a key parameter to consider to appreciate the *in vivo* relevance of plasticizer-transporter interactions and their consequences for human toxicokinetics and toxicity of plastic additives, although even low concentrations of pollutants (in the nM range) may have clinical effects. Existing data about interactions of plastic additives with drug transporters remain somewhat sparse and incomplete. A more systematic characterization of plasticizer-transporter relationships is needed. The potential effects of chemical additive mixtures towards transporter activities and the identification of transporter substrates among plasticizers, as well as their interactions with transporters of emerging relevance deserve particular attention. A better understanding of the human toxicokinetics of plastic additives may help to fully integrate the possible contribution of transporters to the absorption, distribution, metabolism and excretion of plastics-related chemicals, as well as to their deleterious effects towards human health.

Key-words

Drug transporters, plastic additives, pollutants, toxicity, toxicokinetics.

1. Introduction

Human drug transporters are membrane proteins, implicated in the uptake or secretion of drugs at the plasma membrane (Petzinger and Geyer, 2006). They segregate into ATP-binding cassette (ABC) transporter and solute carrier (SLC) superfamilies (Roberts, 2021). Drug transporters are located in main organs/tissues implicated in drug absorption, disposition and/or elimination, such as the intestine, the liver, the kidney and blood-tissue barriers, including the blood-brain barrier, the blood-testis barrier and the placental barrier (Giacomini and Huang, 2013). Drug transporters thus play a key role in pharmacokinetics, and are notably involved in the phases of absorption, distribution and excretion of drugs (Liu, 2019). Moreover, drugs are not only substrates for transporters, but can also act as potential inhibitors, which can lead to drug-drug interactions (DDIs) when the pharmacokinetics features of a drug, *i.e.*, the “victim”, are impaired, due to inhibition of its membrane transport by a co-administrated drug, *i.e.*, the “perpetrator” (König et al., 2013). Blockage of transporter activity can additionally result in altered transport of endogenous substrates, thereby triggering adverse drug effects (Zolk and Fromm, 2011). Endogenous substrates for transporters include hormones, signalling molecules, nutrients, neuromediators, metabolites, nucleosides, and bile acids (Nigam, 2015). Some of them have been proposed as clinical biomarkers for transporters-related DDI evaluation (Chu et al., 2018). It is noteworthy that inhibition of hormone transport may represent a contributing mechanism to endocrine disruption, an adverse effect of various chemical pollutants (Lisco et al., 2022). In addition to inhibition of their activity, changes in the expression of drug transporters, caused by drug treatment or pathophysiological situations such as inflammation, can impair pharmacokinetics and be the source of DDIs or toxicity (Brouwer et al., 2022; Cressman et al., 2012). Genetic polymorphisms of certain transporters can also cause pharmacokinetics variability among human populations (Yee et al., 2018). For all these reasons, transporters are now fully recognized by the pharmacology community and by regulatory agencies, as major actors of drug disposition in the body (Giacomini et al., 2010).

Consequently, from a regulatory standpoint, interactions of novel small drugs with main drug transporters have to be studied and characterized during their pharmaceutical development (Lee et al., 2017). This has to be performed using human, and not animal, transporter models, owing to the known interspecies differences in drug transporter activity and expression (Hammer et al., 2021; Morse et al., 2021; Wang et al., 2015).

In addition to drugs, other chemicals, especially pollutants of public health concern, are likely to interact with human drug transporters (Clerbaux et al., 2019; Nicklisch and Hamdoun, 2020), which may have important consequences for chemical risk assessment (Clerbaux et al., 2018; Darney et al., 2020). In contrast to drugs, the handling of pollutants by human drug transporters and their potential inhibitory effects remain rather poorly studied (Fardel et al., 2012). The exact implications of these potential interactions for pollutant toxicokinetics or toxicity are consequently poorly understood (Abu-Qare et al., 2003). The proof of concept for the interaction of environmental chemicals with human drug transporters was, however, provided more than twenty five years ago, through the demonstration that various pesticides belonging to different chemical classes can inhibit the ABC transporter P-glycoprotein (P-gp, *ABCB1*) (Bain and LeBlanc, 1996). Pesticides have since been shown to interact with other ABC transporters and with SLCs, as recently reviewed (Chedik et al., 2018; Guéniche et al., 2020). Transporters notably contribute to the pharmacokinetics, and moreover to the toxicity of certain pesticides, such as those of the herbicide paraquat (Wang et al., 2021). Besides pesticides, chemicals belonging to various classes of environment, food or drinking water contaminants also interfere with human transporters (Nicklisch and Hamdoun, 2020). This is notably the case for chemical additives present in plastics (Bruyere et al., 2017; Kim et al., 2007), known to also interact with xenobiotic transporters of aquatic organisms (Anselmo et al., 2012; Horion et al., 2015; Keiter et al., 2016; Nicklisch et al., 2021; Popovic et al., 2014). More than 400 of these plastics-related chemicals, basically used for enhancing polymer

properties and prolonging their life, are in use (Gunaalan et al., 2020). The most common plastic additives are phthalates (used as plasticizers), bisphenols (used as monomers/plasticizers/antioxidants), brominated flame retardants (BFRs) such as polybrominated diphenyls ethers (PBDE) or tetrabromobisphenol A (TBBPA, 4,4'-(propane-2,2-diyl)bis(2,6-dibromophenol)), alkylphenols (used as antioxidants/plasticizers), and per- and poly-fluoroalkyl substances (PFASs) (used as coating agents) (Barhoumi et al., 2022; Groh et al., 2019; Hahladakis et al., 2018; Hermabessiere et al., 2017; Wiesinger et al., 2021). Because these additives are usually not chemically bound to plastics, they can migrate out of them and are consequently widely released in the environment, notably when plastics degrade (Hermabessiere et al., 2017). They are, in particular, found in food and drinking water, where they can originate from plastic packaging or bottling, and are also closely associated with nanoplastics and microplastics, which are now recognized as major emerging environmental pollutants (Sangkham et al., 2022). Humans are thus highly exposed to these plastic additives through ingestion, inhalation and dermal contact. This is problematic because of the established deleterious effects of many of these additives; for example, bisphenols, phthalates and BFRs cause endocrine disruption, fertility problems, metabolic diseases and cancers (Benjamin et al., 2017; Campanale et al., 2020; Feiteiro et al., 2021; Ma et al., 2019; Tarafdar et al., 2022). Plastic additives are therefore chemicals of considerable concern with respect to the human exposome and the public health. This led us to survey the interactions of plastic additives with human drug transporters in the present review, with a special emphasis on possible consequences for human exposure, toxicokinetics and health. The plastic additives considered are mainly those for which interactions with at least one human drug transporter are documented in the literature, according to a search of the PubMed database (<https://pubmed.ncbi.nlm.nih.gov/>), as of 08/31/2022; these plastic additives are listed in Table 1.

2. Brief overview of drug transporters

2.1. ABC transporters

Plasma membrane drug transporters belonging to the ABC protein family mediate primary active efflux of drugs, through hydrolysis of ATP via their intrinsic ATPase activity (Schinkel and Jonker, 2003). They comprise P-gp, encoded by the multidrug resistance gene 1 (*MDR1*), multidrug resistance-associated proteins (MRPs) such as MRP1 (*ABCC1*), MRP2 (*ABCC2*), MRP3 (*ABCC3*) and MRP4 (*ABCC4*), breast cancer resistance protein (BCRP/*ABCG2*), as well as the hepatic bile salt export pump (BSEP/*ABCB11*). The main types of substrates for these efflux pumps are given in Table 2. It is noteworthy that most of these transporters, particularly P-gp, MRP1, MRP2 and BCRP, usually exhibit broad and sometimes overlapping substrate specificity. Several of them, especially P-gp, have been historically implicated in multidrug resistance of cancer cells (Amawi et al., 2019), thus illustrating the protective effect of these efflux pumps towards xenobiotics (Leslie et al., 2005).

The tissue location of ABC transporters is shown in Fig. 1. P-gp and BCRP are notably found at the brush-border membrane of enterocytes, where they actively expel their substrates into the digestive lumen, thereby preventing or limiting their intestinal absorption (Müller et al., 2017). These pumps are also present at the luminal pole of brain microvessel endothelial cells, at the apical pole of syncytiotrophoblasts and at the basolateral pole of Sertoli cells, where they contribute to the blood–brain, blood-placenta and blood-testis barriers, respectively (Liu and Liu, 2019; Miller, 2015; Mruk et al., 2011). P-gp and BCRP, as well as MRP2 and BSEP, are additionally found at the canalicular pole of hepatocytes, where they secrete their substrates into the bile canaliculus lumen (Jetter and Kullak-Ublick, 2020); in this context, drug-mediated inhibition of BSEP transport has been associated with cholestasis (Chatterjee and Annaert, 2018). In the kidney, P-gp, BCRP and MRP2 are located at the apical pole of proximal tubular cells, where they contribute to tubular secretion of drugs (Lee and Kim, 2004).

2.2. SLC transporters

SLCs mediate secondary active transport or facilitated diffusion of drugs (Zhou and Shu, 2022). They belong mainly to the *SLCO*, *SLC22*, and *SLC47* transporter subfamilies. The list of these transporters and their main types of substrates are indicated in Table 2. *SLCO* transporters, also known as organic anion transporting polypeptides (OATPs), include three members recognized as important drug transporters, *i.e.*, OATP1B1 (*SLCO1B1*), OATP1B3 (*SLCO1B3*) and OATP2B1 (*SLCO2B1*) (Roth et al., 2012). *SLC22* drug transporters correspond to organic cation transporters (OCTs) such as OCT1 (*SLC22A1*) and OCT2 (*SLC22A2*), and organic anion transporters (OATs) like OAT1 (*SLC22A6*), OAT2 (*SLC22A7*), OAT3 (*SLC22A8*) and OAT4 (*SLC22A11*) (Ciarimboli, 2008; Koepsell, 2020; Roth et al., 2012). *SLC47* transporters are multidrug and toxin extrusion (MATE) proteins and comprise two members, *i.e.*, MATE1 (*SLC47A1*) and MATE2 (*SLC47A2*) (Nies et al., 2016). Similarly to ABC transporters, there is a high degree of overlapping substrates between SLC transporters, notably between OCTs and MATEs and between OATPs and OATs (Table 2).

OATPs, OCTs and OATs are notably expressed at the basolateral side of hepatocytes and kidney proximal tubular cells (Fig. 1) and primarily act as uptake drug transporters enabling the entry of drugs from blood into cells (Ciarimboli, 2008; Roth et al., 2012). By contrast, MATE1 and MATE2-K, the functional splice variant of MATE2, function as pH-dependent efflux transporters, at the apical surface of hepatocytes or proximal tubular cells (Koepsell, 2020) (Fig. 1). OAT4 is implicated in drug reabsorption from the primitive urine at the apical pole of proximal tubular cells and also in compound uptake into the placenta from the foetus blood at the basal pole of syncytiotrophoblasts (Rizwan and Burckhardt, 2007). SLC transporters also include the proton-coupled peptide transporter (PEPT) 1 (*SLC15A1*), involved in absorption of peptidomimetic drugs at the apical pole of enterocytes (Inui et al., 2000), the sodium-taurocholate cotransporting polypeptide (NTCP/*SLC10A1*) and the apical sodium-dependent bile acid transporter (ASBT/*SLC10A2*), implicated in bile acid uptake at the

basolateral pole of hepatocytes and the apical pole of enterocytes, respectively (Meier and Stieger, 2002), and the human organic solute transporter (OST) α/β (*SLC51A/SLC51B*), implicated in the efflux of bile acids at the basolateral pole of enterocytes and hepatocytes (Beaudoin et al., 2020).

3. Modulation of transporter activities by plastic additives

Direct modulation of human transporter activities by plastic additives have been studied using conventional *in vitro* methods, based on vesicular or cellular assays (Brouwer et al., 2013). Vesicular transport assays, used mainly for ABC transporters, rely upon the ATP-dependent translocation of reference substrates into the vesicular compartment of inside-out plasma membrane vesicles prepared from cells expressing the transporter of interest (Volpe, 2016); the inhibition or stimulation of transporter activity is visualized by the decreased or increased accumulation of the reference substrate into the vesicular compartment in response to the chemical tested for its transporter activity modulating potential. Cellular assays, used for ABC and SLC transporters, correspond to uptake or efflux of reference substrates in, or from, recombinant cells overexpressing the transporter of interest, or to bidirectional transport of reference substrates across transporter-expressing polarized cells (Jani and Krajcsi, 2014); the potential transporter modulating activity of compounds is demonstrated by the alteration of reference substrate uptake, efflux or transcellular passage.

Modulations of ABC transporter activities by plastic additives are summarized in Table 3. Plastic additives usually act as inhibitors of ABC transporter activities or fail to interfere with them. Only bisphenol A (BPA, 4,4'-(propane-2,2-diyl)diphenol) was reported to stimulate the activity of an ABC transporter, *i.e.*, that of P-gp (Table 3), which is consistent with the fact that most ABC transporter modulators behave as inhibitors (Cui et al., 2015). It is, however, noteworthy that the stimulating effect of BPA towards P-gp activity observed in cellular assays (Jin and Audus, 2005) has not been confirmed in vesicular assays (Dankers et al., 2013), which

may reflect differential sensitivities of cellular and vesicular assays to modulators. Other discrepancies have been observed between cellular and vesicular assays notably with diethylhexylphthalate (DEHP, bis(2-ethylhexyl) benzene-1,2-dicarboxylate) which acts as a P-gp inhibitor in cellular assays (Kim et al., 2007) but not in vesicular assays (Dankers et al., 2013), and the BFR 2,2',4,4'-tetrabromodiphenyl ether (BDE-47, 3,5-dibromo-2-(2,4-dibromophenoxy)phenol), which inhibits BCRP in vesicular assays but not in cellular assays (Marchitti et al., 2017). Overall, among plastic additives, phthalates like DEHP and its metabolite monoethylhexylphthalate (MEHP, 2-(2-ethylhexoxycarbonyl)benzoate) interact poorly with ABC transporter activity; they notably fail to inhibit MRP1, MRP4 or BCRP activity (Table 3). By contrast, the BFR TBBPA, as well as the PFASs perfluorooctanoic acid (PFOA, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoic acid) and perfluorooctane sulfonate (PFOS, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctane-1-sulfonic acid), appear to be potent inhibitors of ABC transporters as they block P-gp, MRP1, MRP4 and BCRP activities (Table 3); PFOS additionally inhibits BSEP and MRP2. Among ABC transporters, BCRP is the most sensitive to plastic additives, as it is inhibited by BPA, BFRs and PFASs (Table 3). It is noteworthy that the concentrations of plastic additives required to inhibit ABC transporters are usually in the 10-100 μM range (Table 3); only the alkylphenol 4-nonylphenol (NP) blocks P-gp activity when used at low concentrations in the 0.1-1 μM range (Doo et al., 2005).

Modulations of SLC drug transporter activities by plastic additives are summarized in Table 4. Some additives, *e.g.*, bisphenols used at 100 μM , stimulate the activity of SLCs; this is the case for bisphenol F (BPF, 4-[(4-hydroxyphenyl)methyl]phenol), proposed as a substitute for BPA, which increases the activity of OCT2, OATP1B3, and OAT1, whereas BPA stimulates only that of OAT1 (Table 4). Inhibition of SLC activities by plastic additives is nevertheless a more common situation (Table 4). It occurs notably for TBBPA which blocks OCT1, OCT2,

OATP1B1, OATP1B3, MATE1, OAT3 and NTCP activities, but fails to alter MATE2-K and OAT1 activities. Other BFRs like BDE-47 and PFASs target OATPs and/or OATs (Table 4), whereas effects of phthalates towards SLC transporters have not yet been investigated. The concentrations of bisphenols, BFRs or PFAS acting on SLC transporter activities are often in the 10-100 μ M range (Table 4), as reported above for those acting on ABC transporters. Low concentrations of TBBPA (in the 0.5-5 μ M range), however, inhibit OAT3 and NTCP activity, whereas inhibition of OATP activities is caused by much lower concentrations of BDE (in the 100 pM-100 nM range) (Table 4).

The mechanisms by which plastic additives modulate transporter activities remain to be clarified. Competitive or non-competitive interactions with drug binding sites on transporter proteins are likely involved, as proposed for drugs inhibiting transporters (Wigler and Patterson, 1993). The fact that BPA has been demonstrated to inhibit OAT3-mediated transport of estrone 3-sulfate in a competitive manner (Bruyere et al., 2017) and that PFOA, perfluorononanoic acid (PFNA, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptafluorooctanoic acid) and perfluorodecanoic acid (PFDA, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-nonadecafluorodecanoic acid) competitively block OATP2B1-mediated uptake of sulfobromophthalein in Caco-2 cells (Kimura et al., 2020) fully supports this conclusion. BDEs probably also inhibit OATPs by competitive mechanisms because they are high affinity ligands for these SLCs (Pacyniak et al., 2010) (Table 5).

4. Plastic additives as substrates for transporters

Handling of plastic additives by human drug transporters has mainly been investigated using conventional *in vitro* methods addressing whether a compound is a substrate for a plasma membrane transporter (Jani and Krajcsi, 2014). Such methods correspond to (i) cellular assays based on the uptake, efflux or transcellular passage of the chemicals in, from or across transporter-expressing cells, in the presence or absence of reference inhibitors for the

considered transporter, (ii) vesicular assays, based on the transport of the compounds into the intravesicular compartment of transporter-expressing inside-outside membrane vesicles and (iii) ATPase assays, which indirectly measure ABC drug transporter activity through quantifying the stimulation of ATPase activity by substrates in plasma membrane preparations from ABC transporter-expressing cells. Additionally, the perfused human placenta model has been used to demonstrate that bisphenol S (BPS, 4-(4-hydroxyphenyl)sulfonylphenol) is transported by P-gp (Grandin et al., 2019).

The plastic additives which are either substrates or non substrates for human ABC and SLC transporters are listed in Table 5. With respect to P-gp, DEHP and alkylphenols such as nonylphenol ethoxylate (NPE, 2-(4-nonylphenoxy)ethanol), but not its metabolite NP, are substrates. For BPA, conflicting results have been obtained with respect to P-gp. BPA has thus been shown to be transported by P-gp across human intestinal Caco-2 cells (Yoshikawa et al., 2002), but not across P-gp-overexpressing MDCK cells (Dankers et al., 2013); moreover, BPA failed to stimulate ATPase activity of P-gp (Mazur et al., 2012). Further studies are therefore required to more precisely determine whether BPA is a substrate for P-gp. With respect to other ABC transporters, MRP2, MRP3 and BCRP transport BPA, whereas PFOA is a substrate for BCRP (Table 5). Various BDEs, including BDE-47, have been demonstrated to be transported by OATP1B1, OATP1B3 and OATP2B1, with rather low K_m values (around 0.3-1.9 μM) (Table 5), indicating that they are high affinity substrates for OATPs. Whereas OATs transport PFOA with K_m values in the 50-310 μM range. Other PFASs such as PFOS have additionally been found to be substrates for the bile salt transporters NTCP, ASBT and OST α/β (Table 5). Finally, the trans-epithelial transport of various BDEs across Caco-2 cells has been shown to be altered by various transporter inhibitors, suggesting that several transporters, *i.e.*, P-gp, MRPs, BCRP and OCTs, may participate in the transcellular passage of these chemicals, even

if passive diffusion may predominate (Yu et al., 2017). Further studies are required to confirm whether BDEs are substrates for these transporters in intestinal cells.

5. Regulation of human drug transporter expression by plastic additives

Regulations of human drug transporter expression by plastic additives have been mostly studied using cellular *in vitro* models and are listed in Table 6. These regulations, either induction or repression of transporter expression, depend on the nature of both the transporter and the plastic additive. For P-gp, chronic exposure (48 h) of placental BeWo cells to 10 μ M BPA results in enhanced expression of the efflux pump, but in a rather modest manner (55% increase) (Jin and Audus, 2005). By contrast, BPA exposure at 80 μ M for 24 h fails to induce P-gp expression in human hepatic HepG2 cells, despite an increase in *MDR1* mRNA levels (Hanet et al., 2008). These contradicting results may reflect a cell type-dependent regulation of P-gp by BPA. This chemical also increases the activity of the *MDR1* gene promoter in an haplotype-dependent manner (Speidel et al., 2018). Phthalates such as DEHP used at 10 μ M for 24 h-72 h enhance P-gp expression in colon cancer and sarcoma cells (Angelini et al., 2011; Chen et al., 2018; Takeshita et al., 2006), which is associated with increased resistance to chemotherapeutics drugs (Chen et al., 2018). P-gp induction and multidrug resistance also occur in response to chronic exposure to 100 nM DEHP for three months in breast cancer MDA-MB-231 cells (Jadhao et al., 2021). P-gp expression has additionally been shown to be induced in a rat epididymal epithelial cell line in response to treatment by NP (20 μ M) for 24 h (Jones and Cyr, 2011). Effects of PFASs towards P-gp expression remain to be characterized, whereas the bile salt efflux pump BSEP has been shown to be repressed by both PFOA and PFOS in human hepatic HepaRG cells (Table 6).

With respect to MRPs, MRP1, MRP2 and MRP3, but not MRP4, have been demonstrated to be up-regulated by BPA (80 μ M) in human hepatic HepG2 cells (Hanet et al., 2008) (Table 6). By contrast, DEHP tends to decrease Mrp2 protein levels in rat liver (Johnson

and Klaassen, 2002), whereas it induces expression of Mdr2 (*Abcb4*), involved in canalicular secretion of phospholipids, in the mouse liver (Miranda et al., 1997). MRP3 mRNA expression is repressed by the PFASs PFOA and PFOS, but is increased by the PFASs PFNA and PFDA in HepaRG cells, thus highlighting that regulation of this ABC transporter depends on the nature of the PFAS. BCRP is repressed in human term placental explant cultures exposed to 1 nM BPA; NP has a similar effect. BPA also reduces BCRP expression in placental BeWo cells, when used, however, at very high concentration (100 mM) (Table 6). PFNA and PFDA also repress BCRP expression in human hepatic HepaRG cells. On the other hand, PFOA enhances expression of Bcrp in the liver, but not in the kidney, of mice (Eldasher et al., 2013); this suggests that regulation of hepatic BCRP by PFAS may be complex and species-dependent.

Regarding the regulation of SLC transporter expression, PFASs are the only plastic additives that have been shown to play a role. They notably decrease mRNA expression of hepatic OATP1B1, OATP2B1 and NTCP, whereas they increase that of OST β (Table 6).

The mechanisms of transporter expression regulation by plastic additives remain to be fully characterized. Drug-sensing receptors, such as the pregnane-X-receptor (PXR), the aryl hydrocarbon receptor (AhR) or the constitutive androstane receptor (CAR), may be implicated because (i) such receptors regulate expression of various transporters, including P-gp, MRP2 and BCRP (Tirona, 2011), and (ii) plastic additives can activate them, notably CAR is activated by PFASs and BDE-47 and PXR is activated by BDE-47 and BPA (Abe et al., 2017; Grimaldi et al., 2019; Sueyoshi et al., 2014). Plastic additives-related oxidative stress and subsequent activation of the antioxidant nuclear factor erythroid-derived 2-like 2 (Nrf2) pathway may also be contributing factors, notably for BDEs (Dunnick et al., 2018). Additionally, repression of BCRP protein expression in human term placenta explant cultures and BeWo cells by BPA likely involves the estrogenic-like effects of this chemical (Cao et al., 2022; Sieppi et al., 2016).

6. Consequences for toxicokinetics and human health

6.1 Consequences for plastic additives altering transporter activity and/or expression

The possible consequences of the alteration of drug transporter activity and/or expression by plastic additives may be drawn from what is now well-established regarding drug-mediated modulation of transporters (Giacomini and Huang, 2013). Plastic additives acting as transporter modulators, considered as “perpetrators”, are likely to impair membrane passage of transporter substrates, considered as “victims”, and thus possibly impair their pharmacokinetics features, *i.e.*, intestinal absorption, distribution and liver or kidney elimination. For drugs or pollutants as “victims”, this may ultimately result in toxicity (if plasma victim concentrations/ area under the curve (AUC) of plasma victim concentration versus time are increased) or lack of effect (if plasma victim concentration/AUC of victims are decreased) (Fig. 2). This may theoretically result in drug-pollutant or pollutant-pollutant interactions. On the other hand, if the victim substrates are endogenous substrates such as, for example, bile acids, toxicity, such as cholestasis due to inhibition of bile acid transport, may develop (Chatterjee and Annaert, 2018). Altered transport of hormones as substrates may also contribute to endocrine disruptive effects, as already suggested for inhibition of testosterone precursor secretion by TBBPA in Leydig cells (Dankers et al., 2013).

The potential drug-pollutant or pollutant-pollutant interactions as well as pollutant toxicity due to an abrogation of endogenous substrate transport have not yet been reported for plastic additives, even for those inhibiting transporter activity or expression. This may likely be due to the fact that human plasma concentrations of plastic additives, such as BPA, phthalates, alkylphenols, BDEs, TBBPA and PFASs, due to environmental exposure or food intake, are usually low, *i.e.*, in the nM or pM range (Asimakopoulos et al., 2012; Huang et al., 2014; Li et al., 2020; Teeguarden et al., 2013; Wang et al., 2012; Wang et al., 2019). Their unbound fraction, which is the one pharmacologically active towards transporters according to the free drug theory (Summerfield et al., 2022), may even be much lower, but it is not commonly

347 considered in studies investigating serum pollutant concentrations. By contrast, the
348 concentrations of plastic additives required to modulate transporter activity and/or expression
349 are mostly in the 10-100 μM range according to *in vitro* studies (Table 3, Table 4 and Table 6).
350 *In vivo* inhibition of most drug transporters might therefore be unlikely to occur in response to
351 environmental exposure or food intake of plastic additives. This conclusion notably applies to
352 inhibition of SLC activities by BPA. Indeed, when applying the criterion initially defined by
353 the International Transporter Consortium for predicting *in vivo* inhibition of SLC transporters,
354 based on the ratio between the unbound maximum plasma concentration (C_{max}) of the drug
355 perpetrator and its IC_{50} value (which has to be ≥ 0.1 to consider *in vivo* inhibition of SLCs)
356 (Giacomini et al., 2010), human plasma concentrations of BPA (less than 50 nM) are very
357 unlikely to block the activity of OCT1, MATE1, OATP1B1, OATP1B3 or OAT3, as previously
358 reported (Bruyere et al., 2017). However, this general lack of *in vivo* modulation of SLCs by
359 plastic additives may be challenged for those exhibiting potent *in vitro* inhibitory effects
360 towards transporters or those regulating transporter expression when used at low
361 concentrations. Thus, BDE-47 at 100 pM inhibits OATP1B1 activity *in vitro* by approximately
362 50% (Pacyniak et al., 2010), thus suggesting that the IC_{50} value of this BDE towards this OATP
363 is around 100 pM. With total BDE-47 concentrations observed in human plasma in the 500-
364 1000 pM range (Wang et al., 2012), the $C_{\text{max}}/\text{IC}_{50}$ ratio is in the 5-10 range, indicating that
365 OATP1B1 activity may be inhibited in humans by circulating BDE-47 and that BDE-47 may
366 consequently potentially interfere with OATP1B1 substrates like statins. Nevertheless, this
367 conclusion can be questioned by considering what is the unbound maximum plasma
368 concentration of BDE-47, or even the unbound maximum plasma concentration of BDE-47 at
369 the liver inlet, instead of the total plasma concentration of BDE-47, if taking into account the
370 hepatic location of OATP1B1. With respect to regulation of transporter expression, repression
371 of BCRP by 1 nM of BPA in placenta explants (Sieppi et al., 2016) may be hypothesized to

occur *in vivo*, because human plasma concentration of BPA in pregnant women is around 28.5 nM (Yang et al., 2021), even though the limit of the free concentration of BPA has to be considered. Through repressing placental BCRP expression, BPA may alter the function of the blood placenta barrier and may thereby decrease the protection of the fetus against toxicant substrates of BCRP, such as carcinogenic heterocyclic aromatic amines (Myllynen et al., 2008), thus indicating a possible pollutant-pollutant interaction.

For P-gp and BCRP, it is noteworthy that their intestinal inhibition is predicted to potentially occur if the ratio between the perpetrator maximal gastrointestinal concentration (calculated as the ingested dose of perpetrator in a volume of 250 mL) and the IC₅₀ value is ≥ 10 (Giacomini et al., 2010). The daily dietary intake of plastic additives has therefore to be considered when calculating theoretical concentrations to evaluate inhibitory effects towards P-gp and/or BCRP. With respect to BPA, TBBPA and BDEs, they can be estimated to be approximately 2.38 μg , 70 ng and 75.4 ng, respectively, for a standard adult male weighing 70 kg (Colnot et al., 2014; Domingo et al., 2008; Huang et al., 2017), leading to gut concentrations in the 1-100 nM range, which is lower than the concentrations needed to inhibit P-gp or BCRP *in vitro* (in the 500 nM-100 μM range) (Table 3). Similarly, and despite daily DEHP intakes being higher, *i.e.*, up to 840 μg (Cheng et al., 2016), the DEHP concentrations in the gut lumen, up to 8.6 μM , remain much lower than the 30.1 mM DEHP concentration active on P-gp *in vitro*. Overall, these data suggest that inhibition of intestinal P-gp or BCRP by plastic additives in response to common contamination by the diet is rather unlikely. The risk of inhibition remains to be considered, however, for highly-exposed subjects, notably in the case of exposure to a mixture of pollutants, including plastic additives, whose inhibitory effects towards P-gp and/or BCRP may be additive or synergic, as already demonstrated for inhibition of P-gp by mixtures of marine pollutants (Nicklisch et al., 2016).

6.2 Consequences for plastic additives that are transporter substrates

Handling of plastic additives by transporters is likely to contribute to the various steps of their toxicokinetics. In particular, transport by P-gp or BCRP at the apical pole of enterocytes may limit their intestinal absorption, especially since saturation of these intestinal pumps is unlikely to occur, owing to the relative low concentrations of plastic additives in the gut lumen, as already discussed above. Transport of plastic additives by P-gp and/or BCRP at the blood-brain barrier may contribute to limit their entry into the brain and prevent any neurotoxicity. A similar conclusion also applies to handling by P-gp and/or BCRP at the blood-placenta barrier and protection of the fetus. Globally, transport of plastic additives by ABC efflux pumps can be considered as a general protective mechanism against the potential toxicity of these compounds.

SLC transporters may play a key-role in liver and kidney uptake of their plastic additive substrates. This is notably the case for BDE-47, BDE-99 and BDE-153, recognized as high affinity substrates for OATPs, which probably explains their liver-specific accumulation (Pacyniak et al., 2010). For PFOA, its transport by OAT1 and OAT3 likely contributes to its renal secretion (Nakagawa et al., 2008) whereas its transport by OAT4 probably mediates its tubular reabsorption, thus resulting in the final detection of only a small amount of PFOA in urine in humans (Nakagawa et al., 2009). PFOS has additionally been demonstrated to be a substrate for intestinal and hepatic uptake transporters of bile salts, *i.e.*, ASBT and NTCP, which likely participate to its enterohepatic circulation and, furthermore, to its long half-life and its hepatic accumulation (Zhao et al., 2015).

In the case of plastic additive substrates of transporters, especially for those with a marked lipophilic nature, it is noteworthy that passive diffusion probably also contributes to their passage across the plasma membrane. The net transport is therefore the sum of active and passive transport, as already suggested for drugs (Sugano et al., 2010). For SLC transporters, the uptake velocity is consequently the addition of transporter-mediated saturable transport and

of transporter-independent non-saturable passage. As illustrated in Fig. 3, for low concentrations of plastic additives, relevant to those occurring in response to environmental exposures, the fraction of saturable transporter-dependent passage across the plasma membrane may be preponderant, thus highlighting the theoretical importance of transporters for the toxicokinetics of these environmental contaminants.

7. Conclusion and perspectives

The studies summarized in this review clearly indicate that various plastic additives can interact with drug transporters, as inhibitors of their activity, as their substrates or as modulators of their expression. However, these regulatory effects have been mostly demonstrated *in vitro* and their *in vivo* relevance remains a crucial point to determine. The rather low concentrations of plastic additives in humans in response to environmental exposure (when compared to those of drugs administrated to patients) probably limits the *in vivo* effects of plastic additives as single agents towards the activity or expression of transporters. However, a caveat to this conclusion is the fact that humans are commonly exposed to mixtures of pollutants, including plastic additives, whose inhibitory effects towards transporters may add up or synergise, as already discussed above for marine pollutants inhibiting P-gp (Nicklisch et al., 2016), or as demonstrated for a binary mixture of heterocyclic amines blocking OAT3 (Sayyed et al., 2017) or for the inhibitory effects of pesticides towards P-gp activity (Pivčević and Zaja, 2006). The study of potential inhibitory effects of mixtures of pollutants, such as mixtures of plastic additives or mixtures of plastic additives and other pollutants, towards drug transporters is therefore warranted. In this context, the recently described inhibitory effects of microplastics towards ABC transporters (Koepsell, 2020) is particularly noteworthy because they are likely to add up with those of plasticizers that are commonly released from plastic microparticles or nanoparticles (Gulizia et al., 2023). Moreover, although plastic additive concentrations are usually rather low in plasma of exposed humans, the specific accumulation of some of them in

certain tissues cannot be ruled out (Cimmino et al., 2020), potentially resulting in intra-tissular concentrations of plastic additives reaching levels active on transporter activity or expression. A better characterization of the human toxicokinetics of plastic additives, including predictions of their intra-tissular concentrations and evaluation of their unbound form, in response to environmental exposure, may therefore be useful to apprehend the possible *in vivo* relevance of their effects on drug transporter activity and/or expression and their putative toxicity. This may be done through physiologically-based toxicokinetic (PBTK) approaches, already developed for plasticizers (Jeong et al., 2020; Sarigiannis et al., 2016). Other *in silico* methods, including those based on quantitative structure-activity relationships (QSAR) or molecular docking (Ai et al., 2015), may also be useful for predicting interactions of plastic additives with drug transporters, especially for emerging plastic additives such as organophosphate flame retardants for which data are currently lacking. The recent use of molecular docking to determine the binding affinities of various chemicals, including PFASs, to P-gp, BCRP and MRP1, fully supports this methodology (Barhoumi et al., 2022). New approaches to study clinical inhibition of transporter activities by measuring altered pharmacokinetics of endogenous substrates, reported notably for OATP1B1 and OAT inhibition by drugs (Neuvonen et al., 2021; Willemin et al., 2021), may additionally be effective to study putative inhibitory effects of plasticizers in humans.

The handling of plastic additives by transporters and their pharmacokinetics consequences have been determined for some additives, such as BDEs and PFOA. This fully validates the concept that transporters can participate in the pharmacokinetics of plastic additives. However, data about the nature of plastic additives, and of chemical pollutants overall, as substrates of drug transporters, remain rather scarce. An extensive analysis of the potential handling of plastic additives, including emergent ones, by drug transporters is therefore warranted. It is noteworthy that the traditionnal approach for such analyses, *i.e.*,

comparing the uptake of putative substrates in cellular or vesicular models overexpressing or not the transporter of interest and in the absence or presence of specific transporter inhibitors, requires the precise quantification of cellular or vesicular accumulation of plastic additives through sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS). This method can, however, be extremely consuming in time and/or money, and may be difficult to integrate into high throughput processes. Experimental approaches such as *trans*-stimulation or competitive counterflow assays (Schäfer et al., 2018; Severance et al., 2017) may be interesting alternatives. Indeed, these assays, based on the ability of candidate substrates to *trans*-stimulate uptake or efflux of a reference tracer substrate, do not require measurement of intracellular levels of candidate substrates such as plastic additives and may be applied to large series of chemicals when using a fluorescent dye as a tracer substrate; this is noteworthy for plastic additives, of which there are more than 400. The relatively low sensitivity of the *trans*-stimulation assay can, nevertheless, be limiting (Lefèvre et al., 2021). In addition to identifying the plastic additives that are substrates for transporters, the possible effect of transporter polymorphisms towards plasticizer toxicokinetics, as was reported for drugs (Yee et al., 2018), will need to be investigated. This implication of transporter polymorphism could apply for environmental chemicals overall (Darney et al., 2020), and it may help to identify individual susceptibility factors to pollutants, including plastic additives.

Finally, it is noteworthy that the list of membrane transporters of interest for drug pharmacokinetics and toxicity is rather evolutive and emerging transporters of clinical significance, including plasma membrane transporters of vitamins or lysosomal and mitochondrial transporters, likely merit attention for drug candidates (Chu et al., 2018; Giacomini et al., 2022; Yee and Giacomini, 2021). These emerging transporters are also potentially targeted by pollutants and may therefore be considered in the future for plastic additives. Amino-acid transporters, such as aspartate transporters (*SLC1A2* and *SLC1A3*)

regulated by BPA in human hepatic HepG2 cells (Jiménez-Torres et al., 2020), as well as glucose transporters, norepinephrine transporter (*SLC6A2*) and thyroid hormone transporters, impacted by BPA or phthalates (Bereketoglu and Pradhan, 2022; Li et al., 2016; Quesnot et al., 2014; Sakurai et al., 2004; Toyohira et al., 2003), may additionally be of interest.

Author contribution statement

Valentin Tastet - conceptualization, writing; Marc Le Vée - reviewing; Arnaud Bruyère - reviewing; Olivier Fardel - conceptualization, writing, editing.

Declaration of competing interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

This study has received funding from the European Union's Horizon Europe research and innovation program under Grant Agreement N° 101057014 (European Partnership for the Assessment of Risks from Chemicals) and from the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) under Grant Agreement N° 2020/01/124. The authors thank Dr Catherine Lavau for proofreading the manuscript.

References

- Abe, T., Takahashi, M., Kano, M., Amaike, Y., Ishii, C., Maeda, K., Kudoh, Y., Morishita, T., Hosaka, T., Sasaki, T., Kodama, S., Matsuzawa, A., Kojima, H., Yoshinari, K., 2017. Activation of nuclear receptor CAR by an environmental pollutant perfluorooctanoic acid. *Arch Toxicol* 91, 2365-2374.
- Abu-Qare, A.W., Elmasry, E., Abou-Donia, M.B., 2003. A role for P-glycoprotein in environmental toxicology. *J Toxicol Environ Health B Crit Rev* 6, 279-288.
- Ai, N., Fan, X., Ekins, S., 2015. In silico methods for predicting drug-drug interactions with cytochrome P-450s, transporters and beyond. *Adv Drug Deliv Rev* 86, 46-60.
- Amawi, H., Sim, H.M., Tiwari, A.K., Ambudkar, S.V., Shukla, S., 2019. ABC Transporter-Mediated Multidrug-Resistant Cancer. *Adv Exp Med Biol* 1141, 549-580.
- Angelini, A., Centurione, L., Sancilio, S., Castellani, M.L., Conti, P., Di Ilio, C., Porreca, E., Cuccurullo, F., Di Pietro, R., 2011. The effect of the plasticizer diethylhexyl phthalate on transport activity and expression of P-glycoprotein in parental and doxo-resistant human sarcoma cell lines. *J Biol Regul Homeost Agents* 25, 203-211.
- Anselmo, H.M., van den Berg, J.H., Rietjens, I.M., Murk, A.J., 2012. Inhibition of cellular efflux pumps involved in multi xenobiotic resistance (MXR) in echinoid larvae as a possible mode of action for increased ecotoxicological risk of mixtures. *Ecotoxicology* 21, 2276-2287.
- Asimakopoulos, A.G., Thomaidis, N.S., Koupparis, M.A., 2012. Recent trends in biomonitoring of bisphenol A, 4-t-octylphenol, and 4-nonylphenol. *Toxicol Lett* 210, 141-154.
- Bain, L.J., LeBlanc, G.A., 1996. Interaction of structurally diverse pesticides with the human MDR1 gene product P-glycoprotein. *Toxicol Appl Pharmacol* 141, 288-298.
- Barhoumi, B., Sander, S.G., Tolosa, I., 2022. A review on per- and polyfluorinated alkyl substances (PFASs) in microplastic and food-contact materials. *Environ Res* 206, 112595.
- Beaudoin, J.J., Brouwer, K.L.R., Malinen, M.M., 2020. Novel insights into the organic solute transporter alpha/beta, OST α/β : From the bench to the bedside. *Pharmacol Ther* 211, 107542.
- Behr, A.C., Kwiatkowski, A., Ståhlman, M., Schmidt, F.F., Luckert, C., Braeuning, A., Buhrke, T., 2020. Impairment of bile acid metabolism by perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) in human HepaRG hepatoma cells. *Arch Toxicol* 94, 1673-1686.
- Benjamin, S., Masai, E., Kamimura, N., Takahashi, K., Anderson, R.C., Faisal, P.A., 2017. Phthalates impact human health: Epidemiological evidences and plausible mechanism of action. *J Hazard Mater* 340, 360-383.
- Bereketoglu, C., Pradhan, A., 2022. Plasticizers: negative impacts on the thyroid hormone system. *Environ Sci Pollut Res Int* 29, 38912-38927.

Brouwer, K.L., Keppler, D., Hoffmaster, K.A., Bow, D.A., Cheng, Y., Lai, Y., Palm, J.E., Stieger, B., Evers, R., 2013. In vitro methods to support transporter evaluation in drug discovery and development. *Clin Pharmacol Ther* 94, 95-112.

Brouwer, K.L.R., Evers, R., Hayden, E., Hu, S., Li, C.Y., Meyer Zu Schwabedissen, H.E., Neuhoﬀ, S., Oswald, S., Piquette-Miller, M., Saran, C., Sjöstedt, N., Sprowl, J.A., Stahl, S.H., Yue, W., 2022. Regulation of Drug Transport Proteins-From Mechanisms to Clinical Impact: A White Paper on Behalf of the International Transporter Consortium. *Clin Pharmacol Ther*.

Bruyere, A., Hubert, C., Le Vee, M., Chedik, L., Sayyed, K., Stieger, B., Denizot, C., Parmentier, Y., Fardel, O., 2017. Inhibition of SLC drug transporter activities by environmental bisphenols. *Toxicol In Vitro* 40, 34-44.

Burckhardt, G., 2012. Drug transport by Organic Anion Transporters (OATs). *Pharmacol Ther* 136, 106-130.

Campanale, C., Massarelli, C., Savino, I., Locaputo, V., Uricchio, V.F., 2020. A Detailed Review Study on Potential Effects of Microplastics and Additives of Concern on Human Health. *Int J Environ Res Public Health* 17.

Cao, Y., Chen, Z., Zhang, M., Shi, L., Qin, S., Lv, D., Li, D., Ma, L., Zhang, Y., 2022. Maternal exposure to bisphenol A induces fetal growth restriction via upregulating the expression of estrogen receptors. *Chemosphere* 287, 132244.

Charuk, M.H., Grey, A.A., Reithmeier, R.A., 1998. Identification of the synthetic surfactant nonylphenol ethoxylate: a P-glycoprotein substrate in human urine. *Am J Physiol* 274, F1127-1139.

Chatterjee, S., Annaert, P., 2018. Drug-induced Cholestasis: Mechanisms, Models, and Markers. *Curr Drug Metab* 19, 808-818.

Chedik, L., Bruyere, A., Bacle, A., Potin, S., Le Vée, M., Fardel, O., 2018. Interactions of pesticides with membrane drug transporters: implications for toxicokinetics and toxicity. *Expert Opin Drug Metab Toxicol* 14, 739-752.

Chen, H.P., Lee, Y.K., Huang, S.Y., Shi, P.C., Hsu, P.C., Chang, C.F., 2018. Phthalate exposure promotes chemotherapeutic drug resistance in colon cancer cells. *Oncotarget* 9, 13167-13180.

Cheng, Z., Li, H.H., Wang, H.S., Zhu, X.M., Sthiannopkao, S., Kim, K.W., Yasin, M.S.M., Hashim, J.H., Wong, M.H., 2016. Dietary exposure and human risk assessment of phthalate esters based on total diet study in Cambodia. *Environ Res* 150, 423-430.

Choi, Y.H., Yu, A.M., 2014. ABC transporters in multidrug resistance and pharmacokinetics, and strategies for drug development. *Curr Pharm Des* 20, 793-807.

Chu, X., Liao, M., Shen, H., Yoshida, K., Zur, A.A., Arya, V., Galetin, A., Giacomini, K.M., Hanna, I., Kusuhara, H., Lai, Y., Rodrigues, D., Sugiyama, Y., Zamek-Gliszczynski, M.J., Zhang, L., 2018. Clinical Probes and Endogenous Biomarkers as Substrates for Transporter Drug-Drug Interaction Evaluation: Perspectives From the International Transporter Consortium. *Clin Pharmacol Ther* 104, 836-864.

Ciarimboli, G., 2008. Organic cation transporters. *Xenobiotica* 38, 936-971.

- Cimmino, I., Fiory, F., Perruolo, G., Miele, C., Beguinot, F., Formisano, P., Oriente, F., 2020. Potential Mechanisms of Bisphenol A (BPA) Contributing to Human Disease. *Int J Mol Sci* 21.
- Clerbaux, L.A., Coecke, S., Lumen, A., Kliment, T., Worth, A.P., Paini, A., 2018. Capturing the applicability of in vitro-in silico membrane transporter data in chemical risk assessment and biomedical research. *Sci Total Environ* 645, 97-108.
- Clerbaux, L.A., Paini, A., Lumen, A., Osman-Ponchet, H., Worth, A.P., Fardel, O., 2019. Membrane transporter data to support kinetically-informed chemical risk assessment using non-animal methods: Scientific and regulatory perspectives. *Environ Int* 126, 659-671.
- Colnot, T., Kacew, S., Dekant, W., 2014. Mammalian toxicology and human exposures to the flame retardant 2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol (TBBPA): implications for risk assessment. *Arch Toxicol* 88, 553-573.
- Cressman, A.M., Petrovic, V., Piquette-Miller, M., 2012. Inflammation-mediated changes in drug transporter expression/activity: implications for therapeutic drug response. *Expert Rev Clin Pharmacol* 5, 69-89.
- Cui, H., Zhang, A.J., Chen, M., Liu, J.J., 2015. ABC Transporter Inhibitors in Reversing Multidrug Resistance to Chemotherapy. *Curr Drug Targets* 16, 1356-1371.
- Dankers, A.C., Roelofs, M.J., Piersma, A.H., Sweep, F.C., Russel, F.G., van den Berg, M., van Duursen, M.B., Masereeuw, R., 2013. Endocrine disruptors differentially target ATP-binding cassette transporters in the blood-testis barrier and affect Leydig cell testosterone secretion in vitro. *Toxicol Sci* 136, 382-391.
- Darney, K., Turco, L., Buratti, F.M., Di Consiglio, E., Vichi, S., Roudot, A.C., Béchaux, C., Testai, E., Dorne, J., Lautz, L.S., 2020. Human variability in influx and efflux transporters in relation to uncertainty factors for chemical risk assessment. *Food Chem Toxicol* 140, 111305.
- Domingo, J.L., Martí-Cid, R., Castell, V., Llobet, J.M., 2008. Human exposure to PBDEs through the diet in Catalonia, Spain: temporal trend. A review of recent literature on dietary PBDE intake. *Toxicology* 248, 25-32.
- Doo, M.H., Li, H., Jang, H.I., Song, I.S., Chung, S.J., Shim, C.K., 2005. Effect of nonylphenol ethoxylates (NPEs) on barrier functions of epithelial cell membranes: opening of tight junctions and competitive inhibition of P-gp-mediated efflux. *Int J Pharm* 302, 145-153.
- Dunnick, J.K., Shockley, K.R., Pandiri, A.R., Kissling, G.E., Gerrish, K.E., Ton, T.V., Wilson, R.E., Brar, S.S., Brix, A.E., Waidyanatha, S., Mutlu, E., Morgan, D.L., 2018. PBDE-47 and PBDE mixture (DE-71) toxicities and liver transcriptomic changes at PND 22 after in utero/postnatal exposure in the rat. *Arch Toxicol* 92, 3415-3433.
- Eldasher, L.M., Wen, X., Little, M.S., Bircsak, K.M., Yacovino, L.L., Aleksunes, L.M., 2013. Hepatic and renal Bcrp transporter expression in mice treated with perfluorooctanoic acid. *Toxicology* 306, 108-113.
- Engdahl, E., van Schijndel, M.D.M., Voulgaris, D., Di Criscio, M., Ramsbottom, K.A., Rigden, D.J., Herland, A., Rüegg, J., 2021. Bisphenol A Inhibits the Transporter Function of

- 638 the Blood-Brain Barrier by Directly Interacting with the ABC Transporter Breast Cancer
639 Resistance Protein (BCRP). *Int J Mol Sci* 22.
- 640 Fardel, O., Kolasa, E., Le Vee, M., 2012. Environmental chemicals as substrates, inhibitors
641 or inducers of drug transporters: implication for toxicokinetics, toxicity and pharmacokinetics.
642 *Expert Opin Drug Metab Toxicol* 8, 29-46.
- 643 Feiteiro, J., Mariana, M., Cairrão, E., 2021. Health toxicity effects of brominated flame
644 retardants: From environmental to human exposure. *Environ Pollut* 285, 117475.
- 645 Giacomini, K.M., Huang, S.M., 2013. Transporters in drug development and clinical
646 pharmacology. *Clin Pharmacol Ther* 94, 3-9.
- 647 Giacomini, K.M., Huang, S.M., Tweedie, D.J., Benet, L.Z., Brouwer, K.L., Chu, X.,
648 Dahlin, A., Evers, R., Fischer, V., Hillgren, K.M., Hoffmaster, K.A., Ishikawa, T., Keppler, D.,
649 Kim, R.B., Lee, C.A., Niemi, M., Polli, J.W., Sugiyama, Y., Swaan, P.W., Ware, J.A., Wright,
650 S.H., Yee, S.W., Zamek-Gliszczynski, M.J., Zhang, L., 2010. Membrane transporters in drug
651 development. *Nat Rev Drug Discov* 9, 215-236.
- 652 Giacomini, K.M., Yee, S.W., Koleske, M.L., Zou, L., Matsson, P., Chen, E.C., Kroetz,
653 D.L., Miller, M.A., Gozalpour, E., Chu, X., 2022. New and Emerging Research on Solute
654 Carrier and ATP Binding Cassette Transporters in Drug Discovery and Development: Outlook
655 From the International Transporter Consortium. *Clin Pharmacol Ther* 112, 540-561.
- 656 Gottesman, M.M., Pastan, I., 1993. Biochemistry of multidrug resistance mediated by the
657 multidrug transporter. *Annu Rev Biochem* 62, 385-427.
- 658 Grandin, F.C., Lacroix, M.Z., Gayrard, V., Viguié, C., Mila, H., de Place, A., Vayssière,
659 C., Morin, M., Corbett, J., Gayrard, C., Gely, C.A., Toutain, P.L., Picard-Hagen, N., 2019. Is
660 bisphenol S a safer alternative to bisphenol A in terms of potential fetal exposure ? Placental
661 transfer across the perfused human placenta. *Chemosphere* 221, 471-478.
- 662 Grimaldi, M., Boulahtouf, A., Toporova, L., Balaguer, P., 2019. Functional profiling of
663 bisphenols for nuclear receptors. *Toxicology* 420, 39-45.
- 664 Groh, K.J., Backhaus, T., Carney-Almroth, B., Geueke, B., Inostroza, P.A., Lennquist, A.,
665 Leslie, H.A., Maffini, M., Slunge, D., Trasande, L., Warhurst, A.M., Muncke, J., 2019.
666 Overview of known plastic packaging-associated chemicals and their hazards. *Sci Total*
667 *Environ* 651, 3253-3268.
- 668 Guéniche, N., Bruyere, A., Le Vée, M., Fardel, O., 2020. Implication of human drug
669 transporters to toxicokinetics and toxicity of pesticides. *Pest Manag Sci* 76, 18-25.
- 670 Gulizia, A.M., Patel, K., Philippa, B., Motti, C.A., van Herwerden, L., Vamvounis, G.,
671 2023. Understanding plasticiser leaching from polystyrene microplastics. *Sci Total Environ*
672 857, 159099.
- 673 Gunaalan, K., Fabbri, E., Capolupo, M., 2020. The hidden threat of plastic leachates: A
674 critical review on their impacts on aquatic organisms. *Water Res* 184, 116170.
- 675 Hahladakis, J.N., Velis, C.A., Weber, R., Iacovidou, E., Purnell, P., 2018. An overview of
676 chemical additives present in plastics: Migration, release, fate and environmental impact during
677 their use, disposal and recycling. *J Hazard Mater* 344, 179-199.

- Hammer, H., Schmidt, F., Marx-Stoelting, P., Pötz, O., Braeuning, A., 2021. Cross-species analysis of hepatic cytochrome P450 and transport protein expression. *Arch Toxicol* 95, 117-133.
- Hanet, N., Lancon, A., Delmas, D., Jannin, B., Chagnon, M.C., Cherkaoui-Malki, M., Latruffe, N., Artur, Y., Heydel, J.M., 2008. Effects of endocrine disruptors on genes associated with 17beta-estradiol metabolism and excretion. *Steroids* 73, 1242-1251.
- Hermabessiere, L., Dehaut, A., Paul-Pont, I., Lacroix, C., Jezequel, R., Soudant, P., Duflos, G., 2017. Occurrence and effects of plastic additives on marine environments and organisms: A review. *Chemosphere* 182, 781-793.
- Horion, S., Thomé, J.P., Gismondi, É., 2015. Changes in antitoxic defense systems of the freshwater amphipod *Gammarus pulex* exposed to BDE-47 and BDE-99. *Ecotoxicology* 24, 959-966.
- Huang, F., Wen, S., Li, J., Zhong, Y., Zhao, Y., Wu, Y., 2014. The human body burden of polybrominated diphenyl ethers and their relationships with thyroid hormones in the general population in Northern China. *Sci Total Environ* 466-467, 609-615.
- Huang, R.P., Liu, Z.H., Yuan, S.F., Yin, H., Dang, Z., Wu, P.X., 2017. Worldwide human daily intakes of bisphenol A (BPA) estimated from global urinary concentration data (2000-2016) and its risk analysis. *Environ Pollut* 230, 143-152.
- Inui, K., Terada, T., Masuda, S., Saito, H., 2000. Physiological and pharmacological implications of peptide transporters, PEPT1 and PEPT2. *Nephrol Dial Transplant* 15 Suppl 6, 11-13.
- Jadhao, M., Tsai, E.M., Yang, H.C., Chen, Y.F., Liang, S.S., Wang, T.N., Teng, Y.N., Huang, H.W., Wang, L.F., Chiu, C.C., 2021. The Long-Term DEHP Exposure Confers Multidrug Resistance of Triple-Negative Breast Cancer Cells through ABC Transporters and Intracellular ROS. *Antioxidants (Basel)* 10.
- Jani, M., Krajcsi, P., 2014. In vitro methods in drug transporter interaction assessment. *Drug Discov Today Technol* 12, e105-112.
- Jeong, S.H., Jang, J.H., Cho, H.Y., Lee, Y.B., 2020. Risk assessment for humans using physiologically based pharmacokinetic model of diethyl phthalate and its major metabolite, monoethyl phthalate. *Arch Toxicol* 94, 2377-2400.
- Jetter, A., Kullak-Ublick, G.A., 2020. Drugs and hepatic transporters: A review. *Pharmacol Res* 154, 104234.
- Jiménez-Torres, C., Hernández-Kelly, L.C., Najimi, M., Ortega, A., 2020. Bisphenol A exposure disrupts aspartate transport in HepG2 cells. *J Biochem Mol Toxicol* 34, e22516.
- Jin, H., Audus, K.L., 2005. Effect of bisphenol A on drug efflux in BeWo, a human trophoblast-like cell line. *Placenta* 26 Suppl A, S96-s103.
- Johnson, D.R., Klaassen, C.D., 2002. Regulation of rat multidrug resistance protein 2 by classes of prototypical microsomal enzyme inducers that activate distinct transcription pathways. *Toxicol Sci* 67, 182-189.

- Jones, S.R., Cyr, D.G., 2011. Regulation and characterization of the ATP-binding cassette transporter-B1 in the epididymis and epididymal spermatozoa of the rat. *Toxicol Sci* 119, 369-379.
- Kalliokoski, A., Niemi, M., 2009. Impact of OATP transporters on pharmacokinetics. *Br J Pharmacol* 158, 693-705.
- Keiter, S., Burkhardt-Medicke, K., Wellner, P., Kais, B., Färber, H., Skutlarek, D., Engwall, M., Braunbeck, T., Keiter, S.H., Luckenbach, T., 2016. Does perfluorooctane sulfonate (PFOS) act as chemosensitizer in zebrafish embryos? *Sci Total Environ* 548-549, 317-324.
- Kim, J.H., Yun, J., Sohng, J.K., Cha, J.M., Choi, B.C., Jeon, H.J., Kim, S.H., Choi, C.H., 2007. Di(2-ethylhexyl)phthalate leached from medical PVC devices serves as a substrate and inhibitor for the P-glycoprotein. *Environ Toxicol Pharmacol* 23, 272-278.
- Kimura, O., Fujii, Y., Haraguchi, K., Kato, Y., Ohta, C., Koga, N., Endo, T., 2017. Uptake of perfluorooctanoic acid by Caco-2 cells: Involvement of organic anion transporting polypeptides. *Toxicology Letters* 277, 18-23.
- Kimura, O., Fujii, Y., Haraguchi, K., Kato, Y., Ohta, C., Koga, N., Endo, T., 2020. Effects of perfluoroalkyl carboxylic acids on the uptake of sulfobromophthalein via organic anion transporting polypeptides in human intestinal Caco-2 cells. *Biochem Biophys Res Commun* 548, 100807.
- Koepsell, H., 2020. Organic Cation Transporters in Health and Disease. *Pharmacol Rev* 72, 253-319.
- König, J., Müller, F., Fromm, M.F., 2013. Transporters and drug-drug interactions: important determinants of drug disposition and effects. *Pharmacol Rev* 65, 944-966.
- Lee, S.C., Arya, V., Yang, X., Volpe, D.A., Zhang, L., 2017. Evaluation of transporters in drug development: Current status and contemporary issues. *Adv Drug Deliv Rev* 116, 100-118.
- Lee, W., Kim, R.B., 2004. Transporters and renal drug elimination. *Annu Rev Pharmacol Toxicol* 44, 137-166.
- Lefèvre, C.R., Le Vée, M., Gaubert, S., Jouan, E., Bruyere, A., Moreau, C., Fardel, O., 2021. Substrate-Dependent Trans-Stimulation of Organic Cation Transporter 2 Activity. *Int J Mol Sci* 22.
- Leslie, E.M., Deeley, R.G., Cole, S.P., 2005. Multidrug resistance proteins: role of P-glycoprotein, MRP1, MRP2, and BCRP (ABCG2) in tissue defense. *Toxicol Appl Pharmacol* 204, 216-237.
- Li, A., Zhuang, T., Shi, W., Liang, Y., Liao, C., Song, M., Jiang, G., 2020. Serum concentration of bisphenol analogues in pregnant women in China. *Sci Total Environ* 707, 136100.
- Li, J., Wang, Y., Fang, F., Chen, D., Gao, Y., Liu, J., Gao, R., Wang, J., Xiao, H., 2016. Bisphenol A disrupts glucose transport and neurophysiological role of IR/IRS/AKT/GSK3 β axis in the brain of male mice. *Environ Toxicol Pharmacol* 43, 7-12.

755 Lim, J.J., Suh, Y., Faustman, E.M., Cui, J.Y., 2021. Regulation of transporters by
756 perfluorinated carboxylic acids in HepaRG cells. *Drug Metab Dispos.*

757 Lisco, G., Giagulli, V.A., Iovino, M., Guastamacchia, E., Pergola, G., Triggiani, V., 2022.
758 Endocrine-Disrupting Chemicals: Introduction to the Theme. *Endocr Metab Immune Disord*
759 *Drug Targets* 22, 677-685.

760 Liu, L., Liu, X., 2019. Contributions of Drug Transporters to Blood-Placental Barrier. *Adv*
761 *Exp Med Biol* 1141, 505-548.

762 Liu, X., 2019. Overview: Role of Drug Transporters in Drug Disposition and Its Clinical
763 Significance. *Adv Exp Med Biol* 1141, 1-12.

764 Loo, T.W., Clarke, D.M., 1998. Nonylphenol ethoxylates, but not nonylphenol, are
765 substrates of the human multidrug resistance P-glycoprotein. *Biochem Biophys Res Commun*
766 247, 478-480.

767 Ma, Y., Liu, H., Wu, J., Yuan, L., Wang, Y., Du, X., Wang, R., Marwa, P.W., Petlulu, P.,
768 Chen, X., Zhang, H., 2019. The adverse health effects of bisphenol A and related toxicity
769 mechanisms. *Environ Res* 176, 108575.

770 Mao, Q., Unadkat, J.D., 2015. Role of the breast cancer resistance protein (BCRP/ABCG2)
771 in drug transport--an update. *Aaps j* 17, 65-82.

772 Marchitti, S.A., Mazur, C.S., Dillingham, C.M., Rawat, S., Sharma, A., Zastre, J., Kenneke,
773 J.F., 2017. Inhibition of the Human ABC Efflux Transporters P-gp and BCRP by the BDE-47
774 Hydroxylated Metabolite 6-OH-BDE-47: Considerations for Human Exposure. *Toxicol Sci*
775 155, 270-282.

776 Mazur, C.S., Marchitti, S.A., Dimova, M., Kenneke, J.F., Lumen, A., Fisher, J., 2012.
777 Human and rat ABC transporter efflux of bisphenol a and bisphenol a glucuronide: interspecies
778 comparison and implications for pharmacokinetic assessment. *Toxicol Sci* 128, 317-325.

779 Meier, P.J., Stieger, B., 2002. Bile salt transporters. *Annu Rev Physiol* 64, 635-661.

780 Miller, D.S., 2015. Regulation of ABC transporters at the blood-brain barrier. *Clin*
781 *Pharmacol Ther* 97, 395-403.

782 Miranda, S., Vollrath, V., Wielandt, A.M., Loyola, G., Bronfman, M., Chianale, J., 1997.
783 Overexpression of *mdr2* gene by peroxisome proliferators in the mouse liver. *J Hepatol* 26,
784 1331-1339.

785 Morse, B.L., Fallon, J.K., Kolur, A., Hogan, A.T., Smith, P.C., Hillgren, K.M., 2021.
786 Comparison of Hepatic Transporter Tissue Expression in Rodents and Interspecies Hepatic
787 OCT1 Activity. *Aaps j* 23, 58.

788 Mruk, D.D., Su, L., Cheng, C.Y., 2011. Emerging role for drug transporters at the blood-
789 testis barrier. *Trends Pharmacol Sci* 32, 99-106.

790 Müller, J., Keiser, M., Drozdik, M., Oswald, S., 2017. Expression, regulation and function
791 of intestinal drug transporters: an update. *Biol Chem* 398, 175-192.

792 Myllynen, P., Kumm, M., Kangas, T., Ilves, M., Immonen, E., Rysä, J., Pirilä, R.,
793 Lastumäki, A., Vähäkangas, K.H., 2008. ABCG2/BCRP decreases the transfer of a food-born

- 794 chemical carcinogen, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in perfused
795 term human placenta. *Toxicol Appl Pharmacol* 232, 210-217.
- 796 Nakagawa, H., Hirata, T., Terada, T., Jutabha, P., Miura, D., Harada, K.H., Inoue, K.,
797 Anzai, N., Endou, H., Inui, K., Kanai, Y., Koizumi, A., 2008. Roles of organic anion
798 transporters in the renal excretion of perfluorooctanoic acid. *Basic Clin Pharmacol Toxicol* 103,
799 1-8.
- 800 Nakagawa, H., Terada, T., Harada, K.H., Hitomi, T., Inoue, K., Inui, K., Koizumi, A.,
801 2009. Human organic anion transporter hOAT4 is a transporter of perfluorooctanoic acid. *Basic*
802 *Clin Pharmacol Toxicol* 105, 136-138.
- 803 Neuvonen, M., Tornio, A., Hirvensalo, P., Backman, J.T., Niemi, M., 2021. Performance
804 of Plasma Coproporphyrin I and III as OATP1B1 Biomarkers in Humans. *Clin Pharmacol Ther*
805 110, 1622-1632.
- 806 Nicklisch, S.C., Rees, S.D., McGrath, A.P., Gökirmak, T., Bonito, L.T., Vermeer, L.M.,
807 Cregger, C., Loewen, G., Sandin, S., Chang, G., Hamdoun, A., 2016. Global marine pollutants
808 inhibit P-glycoprotein: Environmental levels, inhibitory effects, and cocrystal structure. *Sci*
809 *Adv* 2, e1600001.
- 810 Nicklisch, S.C.T., Hamdoun, A., 2020. Disruption of small molecule transporter systems
811 by Transporter-Interfering Chemicals (TICs). *FEBS Lett* 594, 4158-4185.
- 812 Nicklisch, S.C.T., Pouv, A.K., Rees, S.D., McGrath, A.P., Chang, G., Hamdoun, A., 2021.
813 Transporter-interfering chemicals inhibit P-glycoprotein of yellowfin tuna (*Thunnus albacares*).
814 *Comp Biochem Physiol C Toxicol Pharmacol* 248, 109101.
- 815 Nies, A.T., Damme, K., Kruck, S., Schaeffeler, E., Schwab, M., 2016. Structure and
816 function of multidrug and toxin extrusion proteins (MATEs) and their relevance to drug therapy
817 and personalized medicine. *Arch Toxicol* 90, 1555-1584.
- 818 Nies, A.T., Keppler, D., 2007. The apical conjugate efflux pump ABCC2 (MRP2). *Pflugers*
819 *Arch* 453, 643-659.
- 820 Nigam, S.K., 2015. What do drug transporters really do? *Nat Rev Drug Discov* 14, 29-44.
- 821 Pacyniak, E., Roth, M., Hagenbuch, B., Guo, G.L., 2010. Mechanism of polybrominated
822 diphenyl ether uptake into the liver: PBDE congeners are substrates of human hepatic OATP
823 transporters. *Toxicol Sci* 115, 344-353.
- 824 Petzinger, E., Geyer, J., 2006. Drug transporters in pharmacokinetics. *Naunyn*
825 *Schmiedebergs Arch Pharmacol* 372, 465-475.
- 826 Pivčević, B., Zaja, R., 2006. Pesticides and their binary combinations as P-glycoprotein
827 inhibitors in NIH 3T3/MDR1 cells. *Environ Toxicol Pharmacol* 22, 268-276.
- 828 Popovic, M., Zaja, R., Fent, K., Smital, T., 2014. Interaction of environmental
829 contaminants with zebrafish organic anion transporting polypeptide, Oatp1d1 (Slc01d1).
830 *Toxicol Appl Pharmacol* 280, 149-158.
- 831 Quesnot, N., Bucher, S., Fromenty, B., Robin, M.A., 2014. Modulation of metabolizing
832 enzymes by bisphenol a in human and animal models. *Chem Res Toxicol* 27, 1463-1473.

- Rizwan, A.N., Burckhardt, G., 2007. Organic anion transporters of the SLC22 family: biopharmaceutical, physiological, and pathological roles. *Pharm Res* 24, 450-470.
- Roberts, A.G., 2021. The Structure and Mechanism of Drug Transporters. *Methods Mol Biol* 2342, 193-234.
- Roth, M., Obaidat, A., Hagenbuch, B., 2012. OATPs, OATs and OCTs: the organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. *Br J Pharmacol* 165, 1260-1287.
- Russel, F.G., Koenderink, J.B., Masereeuw, R., 2008. Multidrug resistance protein 4 (MRP4/ABCC4): a versatile efflux transporter for drugs and signalling molecules. *Trends Pharmacol Sci* 29, 200-207.
- Sakurai, K., Kawazuma, M., Adachi, T., Harigaya, T., Saito, Y., Hashimoto, N., Mori, C., 2004. Bisphenol A affects glucose transport in mouse 3T3-F442A adipocytes. *Br J Pharmacol* 141, 209-214.
- Sangkham, S., Faikhaw, O., Munkong, N., Sakunkoo, P., Arunlertaree, C., Chavali, M., Mousazadeh, M., Tiwari, A., 2022. A review on microplastics and nanoplastics in the environment: Their occurrence, exposure routes, toxic studies, and potential effects on human health. *Mar Pollut Bull* 181, 113832.
- Sarigiannis, D.A., Karakitsios, S.P., Handakas, E., Simou, K., Solomou, E., Gotti, A., 2016. Integrated exposure and risk characterization of bisphenol-A in Europe. *Food Chem Toxicol* 98, 134-147.
- Sayyed, K., Le Vee, M., Abdel-Razzak, Z., Fardel, O., 2017. Inhibition of organic anion transporter (OAT) activity by cigarette smoke condensate. *Toxicol In Vitro* 44, 27-35.
- Schäfer, A.M., Bock, T., Meyer Zu Schwabedissen, H.E., 2018. Establishment and Validation of Competitive Counterflow as a Method To Detect Substrates of the Organic Anion Transporting Polypeptide 2B1. *Mol Pharm* 15, 5501-5513.
- Schinkel, A.H., Jonker, J.W., 2003. Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: an overview. *Adv Drug Deliv Rev* 55, 3-29.
- Severance, A.C., Sandoval, P.J., Wright, S.H., 2017. Correlation between Apparent Substrate Affinity and OCT2 Transport Turnover. *J Pharmacol Exp Ther* 362, 405-412.
- Shen, H., Lai, Y., Rodrigues, A.D., 2017. Organic Anion Transporter 2: An Enigmatic Human Solute Carrier. *Drug Metab Dispos* 45, 228-236.
- Sieppi, E., Vähäkangas, K., Rautio, A., Ietta, F., Paulesu, L., Myllynen, P., 2016. The xenoestrogens, bisphenol A and para-nonylphenol, decrease the expression of the ABCG2 transporter protein in human term placental explant cultures. *Mol Cell Endocrinol* 429, 41-49.
- Speidel, J.T., Xu, M., Abdel-Rahman, S.Z., 2018. Bisphenol A (BPA) and bisphenol S (BPS) alter the promoter activity of the ABCB1 gene encoding P-glycoprotein in the human placenta in a haplotype-dependent manner. *Toxicol Appl Pharmacol* 359, 47-54.

- Sueyoshi, T., Li, L., Wang, H., Moore, R., Kodavanti, P.R., Lehmler, H.J., Negishi, M., Birnbaum, L.S., 2014. Flame retardant BDE-47 effectively activates nuclear receptor CAR in human primary hepatocytes. *Toxicol Sci* 137, 292-302.
- Sugano, K., Kansy, M., Artursson, P., Avdeef, A., Bendels, S., Di, L., Ecker, G.F., Faller, B., Fischer, H., Gerebtzoff, G., Lennernaes, H., Senner, F., 2010. Coexistence of passive and carrier-mediated processes in drug transport. *Nat Rev Drug Discov* 9, 597-614.
- Summerfield, S.G., Yates, J.W.T., Fairman, D.A., 2022. Free Drug Theory - No Longer Just a Hypothesis? *Pharm Res* 39, 213-222.
- Takeshita, A., Inagaki, K., Igarashi-Migitaka, J., Ozawa, Y., Koibuchi, N., 2006. The endocrine disrupting chemical, diethylhexyl phthalate, activates MDR1 gene expression in human colon cancer LS174T cells. *J Endocrinol* 190, 897-902.
- Tarafdar, A., Sirohi, R., Balakumaran, P.A., Reshmy, R., Madhavan, A., Sindhu, R., Binod, P., Kumar, Y., Kumar, D., Sim, S.J., 2022. The hazardous threat of Bisphenol A: Toxicity, detection and remediation. *J Hazard Mater* 423, 127097.
- Teeguarden, J., Hanson-Drury, S., Fisher, J.W., Doerge, D.R., 2013. Are typical human serum BPA concentrations measurable and sufficient to be estrogenic in the general population? *Food Chem Toxicol* 62, 949-963.
- Tirona, R.G., 2011. Molecular mechanisms of drug transporter regulation. *Handb Exp Pharmacol*, 373-402.
- Toyohira, Y., Utsunomiya, K., Ueno, S., Minami, K., Uezono, Y., Yoshimura, R., Tsutsui, M., Izumi, F., Yanagihara, N., 2003. Inhibition of the norepinephrine transporter function in cultured bovine adrenal medullary cells by bisphenol A. *Biochem Pharmacol* 65, 2049-2054.
- van der Schoor, L.W., Verkade, H.J., Kuipers, F., Jonker, J.W., 2015. New insights in the biology of ABC transporters ABCC2 and ABCC3: impact on drug disposition. *Expert Opin Drug Metab Toxicol* 11, 273-293.
- Volpe, D.A., 2016. Transporter assays as useful in vitro tools in drug discovery and development. *Expert Opin Drug Discov* 11, 91-103.
- Wang, C., Lin, Z., Dong, Q., Lin, Z., Lin, K., Wang, J., Huang, J., Huang, X., He, Y., Huang, C., Yang, D., Huang, C., 2012. Polybrominated diphenyl ethers (PBDEs) in human serum from Southeast China. *Ecotoxicol Environ Saf* 78, 206-211.
- Wang, L., Prasad, B., Salphati, L., Chu, X., Gupta, A., Hop, C.E., Evers, R., Unadkat, J.D., 2015. Interspecies variability in expression of hepatobiliary transporters across human, dog, monkey, and rat as determined by quantitative proteomics. *Drug Metab Dispos* 43, 367-374.
- Wang, X., Wang, X., Zhu, Y., Chen, X., 2021. ADME/T-based strategies for paraquat detoxification: Transporters and enzymes. *Environ Pollut* 291, 118137.
- Wang, Y., Zhu, H., Kannan, K., 2019. A Review of Biomonitoring of Phthalate Exposures. *Toxics* 7.
- Wiesinger, H., Wang, Z., Hellweg, S., 2021. Deep Dive into Plastic Monomers, Additives, and Processing Aids. *Environ Sci Technol* 55, 9339-9351.

- Wigler, P.W., Patterson, F.K., 1993. Inhibition of the multidrug resistance efflux pump. *Biochim Biophys Acta* 1154, 173-181.
- Willemin, M.E., Van Der Made, T.K., Pijpers, I., Dillen, L., Kunze, A., Jonkers, S., Steemans, K., Tuytelaars, A., Jacobs, F., Monshouwer, M., Scotcher, D., Rostami-Hodjegan, A., Galetin, A., Snoeys, J., 2021. Clinical Investigation on Endogenous Biomarkers to Predict Strong OAT-Mediated Drug-Drug Interactions. *Clin Pharmacokinet* 60, 1187-1199.
- Yang, C.H., Glover, K.P., Han, X., 2010. Characterization of cellular uptake of perfluorooctanoate via organic anion-transporting polypeptide 1A2, organic anion transporter 4, and urate transporter 1 for their potential roles in mediating human renal reabsorption of perfluorocarboxylates. *Toxicol Sci* 117, 294-302.
- Yang, J., Wang, H., Du, H., Xu, L., Liu, S., Yi, J., Chen, Y., Jiang, Q., He, G., 2021. Serum Bisphenol A, glucose homeostasis, and gestational diabetes mellitus in Chinese pregnant women: a prospective study. *Environ Sci Pollut Res Int* 28, 12546-12554.
- Yee, S.W., Brackman, D.J., Ennis, E.A., Sugiyama, Y., Kamdem, L.K., Blanchard, R., Galetin, A., Zhang, L., Giacomini, K.M., 2018. Influence of Transporter Polymorphisms on Drug Disposition and Response: A Perspective From the International Transporter Consortium. *Clin Pharmacol Ther* 104, 803-817.
- Yee, S.W., Giacomini, K.M., 2021. Emerging Roles of the Human Solute Carrier 22 Family. *Drug Metab Dispos* 50, 1193-1210.
- Yoshikawa, Y., Hayashi, A., Inai, M., Matsushita, A., Shibata, N., Takada, K., 2002. Permeability characteristics of endocrine-disrupting chemicals using an in vitro cell culture model, Caco-2 cells. *Curr Drug Metab* 3, 551-557.
- Yu, Y., Wang, M., Zhang, K., Yang, D., Zhong, Y., An, J., Lei, B., Zhang, X., 2017. The transepithelial transport mechanism of polybrominated diphenyl ethers in human intestine determined using a Caco-2 cell monolayer. *Environ Res* 154, 93-100.
- Zhao, W., Zitzow, J.D., Ehresman, D.J., Chang, S.C., Butenhoff, J.L., Forster, J., Hagenbuch, B., 2015. Na⁺/Taurocholate Cotransporting Polypeptide and Apical Sodium-Dependent Bile Acid Transporter Are Involved in the Disposition of Perfluoroalkyl Sulfonates in Humans and Rats. *Toxicol Sci* 146, 363-373.
- Zhou, S., Shu, Y., 2022. Transcriptional Regulation of Solute Carrier (SLC) Drug Transporters. *Drug Metab Dispos*.
- Zolk, O., Fromm, M.F., 2011. Transporter-mediated drug uptake and efflux: important determinants of adverse drug reactions. *Clin Pharmacol Ther* 89, 798-805.

Table 1. Plastic additives considered in this review.

Chemical class	Function	Name
Phthalates	Plasticizers	Di(2-ethylhexyl) phthalate (DEHP) Mono(2-ethylhexyl) phthalate (MEHP) (metabolite of DEHP) Butylbenzyl phthalate (BBP) Diethyl phthalate (DEP) Dibutyl phthalate (DBP)
Bisphenols	Monomers/ plasticizers/ antioxidants	Bisphenol A (BPA) BPA glucuronide (metabolite of BPA) Bisphenol F (BPF) Bisphenol S (BPS)
Brominated flame retardants (BFRs)	Flame retardants	Polybrominated diphenyl ethers (PBDE): BDE-47, BDE-99, BDE-100, BDE-153, 6-hydroxy-BDE-47 (metabolite of BDE-47) Tetrabromobisphenol A (TBBPA)
Alkylphenols	Plasticizers/antioxidants	tert-Butylphenol (tBP) tert-Octylphenol (tOP) Nonylphenol ethoxylate (NPE) Nonylphenol (NP) (metabolite of NPE)
Per- and poly- fluorinated alkyl substances (PFASs)	Coating agents	Perfluorobutane sulfonate (PFBS) Perfluorooctanoic acid (PFOA) Perfluorononanoic acid (PFNA) Perfluorodecanoic acid (PFDA) Perfluorohexane sulfonate (PFHxS) Perfluorooctane sulfonate (PFOS)

954 Table 2. Main types of substrates for human drug transporters.

Subfamily	Transporter	Type of substrates	Reference
ABCB	P-gp (<i>MDR1/ABCB1</i>)	Neutral or positively charged hydrophobic drugs (Example: etoposide, digoxin, doxorubicin, fexofenadine, paclitaxel, vinblastine)	(Gottesman and Pastan, 1993)
	BSEP (<i>ABCB11</i>)	Bile acids (Example: taurocholate)	(Jetter and Kullak-Ublick, 2020)
ABCC	MRP1 (<i>ABCC1</i>)	Hydrophobic and anionic drugs; glucuronide and glutathione conjugates; leukotriene C4 (Example: ciprofloxacin, doxorubicin, etoposide, irinotecan, ritonavir, saquinavir, vincristine)	(Choi and Yu, 2014)
	MRP2 (<i>ABCC2</i>)	Anionic drugs; glucuronide, glutathione and sulfate conjugates; sulphated bile salts; leukotriene C4 (Example: adefovir, ampicillin, bilirubin glucuronides, ritonavir, sequinavir)	(Nies and Keppler, 2007)
	MRP3 (<i>ABCC3</i>)	Anionic drugs; glucuronide conjugates; bile salts (Example: morphine-3-glucuronide, estradiol-17 β -glucuronide, taurocholate)	(van der Schoor et al., 2015)
	MRP4 (<i>ABCC4</i>)	Anionic drugs; antiviral nucleoside analogues; signalling molecules (Example: adefovir, cAMP, cGMP, furosemide, tenofovir)	(Russel et al., 2008)
ABCG	BCRP (<i>ABCG2</i>)	Hydrophobic drugs; hydrophilic conjugated organic anions (Example: cimetidine, doxorubicin, estrone 3-sulfate, mitoxantrone, prazosine, rosuvastatin, uric acid)	(Mao and Unadkat, 2015)
SLC10	NTCP (<i>SLC10A1</i>) ASBT (<i>SLC10A2</i>)	Bile acids (Example: taurocholate)	(Meier and Stieger, 2002)
SLC15	PEPT1 (<i>SLC15A1</i>)	Peptidomimetic drugs (Example: β -lactam antibiotics)	(Inui et al., 2000)
SLCO	OATP1B1 (<i>SLC01B1</i>)	Anionic drugs; bile acids; bilirubin; steroid and thyroid hormones (Example: bromosulphophthalein, estrone 3-sulfate, statins, valsartan)	(Kalliokoski and Niemi, 2009)
	OATP1B3 (<i>SLC01B3</i>)	Anionic drugs; bile acids; bilirubin; steroid and thyroid hormones (Example: cholecystokinin, estrone 3 sulfate, statins)	
	OATP2B1 (<i>SLC02B1</i>)	Anionic drugs; bile acids; steroid hormones (Example: estrone 3-sulfate, fexofenadine, statins)	
SLC22	OCT1 (<i>SLC22A1</i>) OCT2 (<i>SLC22A2</i>)	Cationic drugs; monoamine neurotransmitters (Example: acyclovir, cimetidine, cisplatin, metformin, oxaliplatin, choline, dopamine)	(Koepsell, 2020)
	OAT1 (<i>SLC22A6</i>) OAT3 (<i>SLC22A8</i>)	Anionic drugs; cyclic nucleotides; dicarboxylic acids (Example : adefovir, zidovudine, ciprofloxacin, cephaloridin, methotrexate, para-aminohippurate, pravastatin)	(Burckhardt, 2012)
	OAT2 (<i>SLC22A8</i>)	Anionic drugs; cyclic nucleotides; prostaglandins; steroid hormones (Example: bumetanide, cGMP, creatinine, diclofenac, erythromycin, estrone 3-sulfate, uric acid)	(Shen et al., 2017)
SLC47	MATE1 (<i>SLC47A1</i>) MATE2-K (<i>SLC47A2</i>)	Cationic drugs (Example: cimetidine, creatinine, ganciclovir, metformin, oxaliplatin)	(Koepsell, 2020)
SLC51	OST α (<i>SLC51A</i>) OST β (<i>SLC51B</i>)	Bile acids; conjugated steroids (Example: taurocholate, estrone 3-sulfate, digoxin)	(Beaudoin et al., 2020)

955 Note: P-gp - P-glycoprotein; *MDR* - multidrug resistance gene; BSEP - bile salt export pump; MRP - multidrug
 956 resistance-associated protein; BCRP - breast cancer resistance protein; NTCP - sodium-taurocholate
 957 cotransporting polypeptide; ASBT - apical sodium-dependent bile acid transporter; PEPT - peptide transporter;
 958 OATP - organic anion transporting polypeptide; OCT - organic cation transporter; OAT - organic anion
 959 transporter; MATE - multidrug and toxin extrusion protein; OST - organic solute transporter.

Table 3. Modulation of human ABC drug transporter activities by plastic additives.

Transporter	Chemical class	Transporter activity		
		Stimulation	Inhibition	Lack of effect
P-gp	Bisphenols	BPA (100 nM ^{CA}) (Jin and Audus, 2005)		BPA (100 μM ^{VA}) (Dankers et al., 2013)
	Phthalates		DEHP (30.1 mM ^{CA}) (Kim et al., 2007) DEP (16.1 mM ^{CA}) (Kim et al., 2007) DBP (32.1 mM ^{CA}) (Kim et al., 2007)	DEHP (100 μM ^{VA}) (Dankers et al., 2013) MEHP (100 μM ^{VA}) (Dankers et al., 2013)
	BFRs		BDE-47 (50 μM ^{VA}) (Nicklisch et al., 2016) 6-OH-BDE-47 (IC ₅₀ =11.4 μM ^{VA} , 50 μM ^{CA}) (Marchitti et al., 2017) TBBPA (IC ₅₀ =22.9 μM ^{VA}) (Dankers et al., 2013)	PBDE-47 (300 μM ^{VA} , 100 μM ^{CA}) (Marchitti et al., 2017) PBDE-100 (50 μM ^{VA}) (Nicklisch et al., 2016)
	Alkylphenols		NPE (0.1-1 μM ^{CA}) (Doo et al., 2005)	
	PFASs		PFOA (100 μM ^{VA}) (Dankers et al., 2013) PFOS (100 μM ^{VA}) (Dankers et al., 2013)	
BSEP	PFASs		PFOS (100 μM ^{VA}) (Zhao et al., 2015)	PFBS (100 μM ^{VA}) (Zhao et al., 2015) PFHxS (100 μM ^{VA}) (Zhao et al., 2015)
MRP1	Bisphenols			BPA (100 μM ^{VA}) (Dankers et al., 2013)
	Phthalates			DEHP (100 μM ^{VA}) (Dankers et al., 2013) MEHP (100 μM ^{VA}) (Dankers et al., 2013)
	BFRs		TBBPA (100 μM ^{VA}) (Dankers et al., 2013)	
	PFASs		PFOA (100 μM ^{VA}) (Dankers et al., 2013) PFOS (100 μM ^{VA}) (Dankers et al., 2013)	
MRP2	PFASs		PFHxS (100 μM ^{VA}) (Zhao et al., 2015) PFOS (100 μM ^{VA}) (Zhao et al., 2015)	PFBS (100 μM ^{VA}) (Zhao et al., 2015)
MRP4	Bisphenols			BPA (100 μM ^{VA}) (Dankers et al., 2013)
	Phthalates			DEHP (100 μM ^{VA}) (Dankers et al., 2013) MEHP (100 μM ^{VA}) (Dankers et al., 2013)
	BFRs		TBBPA (IC ₅₀ =24.0 μM ^{VA}) (Dankers et al., 2013)	
	PFASs		PFOA (100 μM ^{VA}) (Dankers et al., 2013) PFOS (100 μM ^{VA}) (Dankers et al., 2013)	
BCRP	Bisphenols		BPA (500 nM ^{CA} , 100 μM ^{VA}) (Dankers et al., 2013; Engdahl et al., 2021)	
	Phthalates			DEHP (100 μM ^{VA}) (Dankers et al., 2013) MEHP (100 μM ^{VA}) (Dankers et al., 2013)
	BFRs		BDE-47 (IC ₅₀ =45.7 μM ^{VA}) (Marchitti et al., 2017) 6-hydroxy-BDE-47 (IC ₅₀ =9.4 μM ^{VA} , 50 μM ^{CA}) (Marchitti et al., 2017) TBBPA (100 μM ^{VA}) (Dankers et al., 2013)	BDE-47 (100 μM ^{CA}) (Marchitti et al., 2017)
	PFASs		PFOA (5-100 μM ^{VA}) (Dankers et al., 2013; Eldasher et al., 2013) PFOS (100 μM ^{VA}) (Dankers et al., 2013) PFHxS (100 μM ^{VA}) (Zhao et al., 2015)	

Note: Abbreviations for plastic additives and transporters are those defined in Table 1 and Table 2, respectively; CA - cellular assay; VA - vesicular assay; IC₅₀ - half maximal inhibitory concentration.

974

975 Table 4. Modulation of human SLC drug transporter activities by plastic additives.

Transporter	Chemical class	Transporter activity		
		Stimulation	Inhibition	Lack of effect
OCT1	Bisphenols	BPS (100 μ M) (Bruyere et al., 2017)	BPA (IC ₅₀ =39.0 μ M) (Bruyere et al., 2017) BPF (100 μ M) (Bruyere et al., 2017)	
	BFRs		TBBPA (IC ₅₀ =37.5 μ M) (Bruyere et al., 2017)	
OCT2	Bisphenols	BPF (100 μ M) (Bruyere et al., 2017) BPS (100 μ M) (Bruyere et al., 2017)		BPA (100 μ M) (Bruyere et al., 2017)
	BFRs		TBBPA (100 μ M) (Bruyere et al., 2017)	
MATE1	Bisphenols		BPA (IC ₅₀ =73.5 μ M) (Bruyere et al., 2017) BPF (100 μ M) (Bruyere et al., 2017) BPS (100 μ M) (Bruyere et al., 2017)	
	BFRs		TBBPA (IC ₅₀ =23.1 μ M) (Bruyere et al., 2017)	
MATE2-K	Bisphenols			BPA (100 μ M) (Bruyere et al., 2017) BPF (100 μ M) (Bruyere et al., 2017) BPS (100 μ M) (Bruyere et al., 2017)
	BFRs			TBBPA (100 μ M) (Bruyere et al., 2017)
OATP1B1	Bisphenols		BPA (IC ₅₀ =18.7 μ M) (Bruyere et al., 2017) BPF (IC ₅₀ =13.4 μ M) (Bruyere et al., 2017)	BPS (100 μ M) (Bruyere et al., 2017)
	BFRs		TBBPA (IC ₅₀ =0.6 μ M) (Bruyere et al., 2017) BDE-47 (100 pM) (Pacyniak et al., 2010) BDE-99 (100 nM) (Pacyniak et al., 2010) BDE-153 (100 nM) (Pacyniak et al., 2010)	
OATP1B3	Bisphenols	BPF (100 μ M) (Bruyere et al., 2017)	BPA (100 μ M) (Bruyere et al., 2017)	BPS (100 μ M) (Bruyere et al., 2017)
	BFRs		TBBPA (IC ₅₀ =12.3 μ M) (Bruyere et al., 2017) BDE-47 (100 pM) (Pacyniak et al., 2010) BDE-99 (100 nM) (Pacyniak et al., 2010) BDE-153 (100 nM) (Pacyniak et al., 2010)	
OATP2B1	BFRs		BDE-47 (100 pM) (Pacyniak et al., 2010) BDE-99 (100 nM) (Pacyniak et al., 2010) BDE-153 (100 nM) (Pacyniak et al., 2010)	
	PFASs		PFOA (Ki=62.2 μ M) (Kimura et al., 2020) PFNA (Ki=35.3 μ M) (Kimura et al., 2020) PFDA (Ki=43.2 μ M) (Kimura et al., 2020)	
OAT1	Bisphenols	BPA (100 μ M) (Bruyere et al., 2017) BPF (100 μ M) (Bruyere et al., 2017)	BPS (100 μ M) (Bruyere et al., 2017)	
	BFRs			TBBPA (100 μ M) (Bruyere et al., 2017)
	PFASs		PFOA (10 μ M) (Nakagawa et al., 2008)	
OAT2	PFASs		PFOA (10 μ M) (Nakagawa et al., 2008)	
OAT3	Bisphenols		BPA (IC ₅₀ =9.2 μ M) (Bruyere et al., 2017) BPF (IC ₅₀ =26.8 μ M) (Bruyere et al., 2017) BPS (IC ₅₀ =23.3 μ M) (Bruyere et al., 2017)	
	BFRs		TBBPA (IC ₅₀ =0.5 μ M) (Bruyere et al., 2017)	
	PFASs		PFOA (10 μ M) (Nakagawa et al., 2008)	
NTCP	Bisphenols		BPA (100 μ M) (Bruyere et al., 2017) BPF (100 μ M) (Bruyere et al., 2017)	BPS (100 μ M) (Bruyere et al., 2017)
	BFRs		TBBPA (IC ₅₀ =4.5 μ M) (Bruyere et al., 2017) PFBS (10 μ M) (Zhao et al., 2015) PFHxS (10 μ M) (Zhao et al., 2015) PFOS (10 μ M) (Zhao et al., 2015)	

976 Note: Abbreviations for plastic additives and transporters are those defined in Table 1 and Table 2, respectively; IC₅₀ - half
 977 maximal inhibitory concentration; Ki - inhibition constant.

978

979

980

981 Table 5. Plastic additives as substrates for human ABC and SLC drug transporters.

Transporter	Plastic additive		
	Chemical class	Substrate	Not substrate
P-gp	Bisphenols	BPA ^{CA} (Yoshikawa et al., 2002)	BPA ^{ATA, CA} (Dankers et al., 2013; Mazur et al., 2012) BPA-Glucuronide ^{ATA} (Mazur et al., 2012) BPS ^{Perfused human placenta} (Grandin et al., 2019)
	Phthalates	DEHP ^{CA, ATA} (Kim et al., 2007; Yoshikawa et al., 2002)	BBP ^{CA} (Yoshikawa et al., 2002) DBP ^{CA, ATA} (Kim et al., 2007; Yoshikawa et al., 2002) DEP ^{CA, ATA} (Kim et al., 2007)
	BFRs		TBBPA ^{CA} (Dankers et al., 2013)
	Alkylphenols	tBP ^{CA} (Yoshikawa et al., 2002) tOP ^{CA} (Yoshikawa et al., 2002) NPE ^{ATA, CA} (Charuk et al., 1998; Loo and Clarke, 1998)	NP ^{CA} (Loo and Clarke, 1998)
	PFASs		PFOA ^{CA, ATA} (Dankers et al., 2013)
MRP2	Bisphenols	BPA ^{ATA} (Mazur et al., 2012)	BPA-Glucuronide ^{ATA} (Mazur et al., 2012)
MRP3	Bisphenols	BPA ^{ATA} (Mazur et al., 2012) BPA-Glucuronide ^{ATA} (Mazur et al., 2012)	
BCRP	Bisphenols	BPA ^{ATA, CA} (Dankers et al., 2013; Mazur et al., 2012)	BPA-Glucuronide ^{ATA} (Mazur et al., 2012) TBBPA ^{CA} (Dankers et al., 2013)
	BFRs		TBBPA ^{CA} (Dankers et al., 2013)
	PFASs	PFOA ^{CA} (Dankers et al., 2013)	
OATP1B1	BFRs	BDE-47 (Km=0.31 μM^{CA}) (Pacyniak et al., 2010) BDE-99 (Km=0.91 μM^{CA}) (Pacyniak et al., 2010) BDE-153 (Km=1.91 μM^{CA}) (Pacyniak et al., 2010)	
OATP2B1	BFRs	BDE-47 (Km=0.41 μM^{CA}) (Pacyniak et al., 2010) BDE-99 (Km=0.70 μM^{CA}) (Pacyniak et al., 2010) BDE-153 (Km=1.66 μM^{CA}) (Pacyniak et al., 2010)	
	PFASs	PFOA (Km=8.3 μM^{CA}) (Kimura et al., 2017)	
OATP1B3	BFRs	BDE-47 (Km=0.81 μM^{CA}) (Pacyniak et al., 2010) BDE-99 (Km=0.87 μM^{CA}) (Pacyniak et al., 2010) BDE-153 (Km=0.65 μM^{CA}) (Pacyniak et al., 2010)	
OAT1	PFASs	PFOA (Km=48.0 μM^{CA}) (Nakagawa et al., 2008)	
OAT3	Bisphenols		BPA ^{CA} (Bruyere et al., 2017)
	PFASs	PFOA (Km=49.1 μM^{CA}) (Nakagawa et al., 2008)	
OAT4	PFASs	PFOA (Km=310.3 μM^{CA}) (Nakagawa et al., 2009; Yang et al., 2010)	
NTCP	PFASs	PFBS (Km=39.6 μM^{CA}) (Zhao et al., 2015) PFHxS (Km=112 μM^{CA}) (Zhao et al., 2015) PFOS (Km=130 μM^{CA}) (Zhao et al., 2015)	
ASBT	PFASs	PFOS ^{CA} (Zhao et al., 2015)	PFBS ^{CA} (Zhao et al., 2015) PFHxS ^{CA} (Zhao et al., 2015)
OST α/β	PFASs	PFBS ^{CA} (Zhao et al., 2015) PFHxS ^{CA} (Zhao et al., 2015) PFOS ^{CA} (Zhao et al., 2015)	

982 Note: Abbreviations for plastic additives and transporters are those defined in Table 1 and Table 2, respectively; CA - cellular
 983 assay; ATA - vesicular ATPase assay; Km - Michaelis constant.

984

985

986 Table 6. Regulation of human drug transporter expression by plastic additives.

Transporter	Chemical class (Plastic additive)	Regulation	Reference
P-gp/ <i>MDR1</i>	Bisphenols	Induction of <i>MDR1</i> promoter activity by BPA (50 nM/acute exposure/15 min or 3 nM/chronic exposure/12 days), BPS (0.3 nM/chronic exposure/12 days) or a mixture BPA/BPS (5 nM BPA/1.5 nM BPS/chronic exposure/12 days) in an haplotype-dependent manner.	(Speidel et al., 2018)
		Repression of <i>MDR1</i> promoter activity by BPS (0.5 nM/acute exposure/15 min) in an haplotype-dependent manner.	
		Induction of <i>MDR1</i> mRNA expression, but not that of P-gp, by BPA (80 μ M/24 h) in human hepatic HepG2 cells.	(Hanet et al., 2008)
	Phthalates	Modest induction of P-gp expression by BPA (10 μ M/48 h) in placental BeWo cells.	(Jin and Audus, 2005)
		Induction of P-gp expression by DEHP (10 μ M/24-72 h) and MEHP (10 μ M/24-72 h) in cancer colon cell lines.	(Chen et al., 2018)
		Induction of P-gp expression by DEHP (6 and 12 μ M/24 h) in sarcoma cells.	(Angelini et al., 2011)
		Induction of <i>MDR1</i> mRNA expression by DEHP (1-10 μ M/24 h) in human cancer colon cells.	(Takeshita et al., 2006)
		Induction of <i>MDR1</i> mRNA and P-gp expression in breast cancer MDA-MB-231 cells by chronic exposure to DEHP (100 nM/three months).	(Jadhao et al., 2021)
	Alkylphenols	No apparent induction of P-gp expression in human intestinal Caco-2 cells exposed to NPE (up to 1 μ M/72 h).	(Doo et al., 2005)
BSEP	PFASs	Repression of BSEP mRNA expression by PFOA (250 and 500 μ M/24 h) and PFOS (25-100 μ M/24 h) in human hepatic HepaRG cells.	(Behr et al., 2020)
MRP1	Bisphenols	Induction of MRP1 mRNA expression by BPA (80 μ M/24 h) in HepG2 cells.	(Hanet et al., 2008)
MRP2	Bisphenols	Induction of MRP2 mRNA and protein expression by BPA (80 μ M/24 h) in HepG2 cells.	(Hanet et al., 2008)
	PFASs	Repression of MRP2 mRNA expression by PFOA (250 and 500 μ M/24 h) and PFOS (25 μ M/24 h) in HepaRG cells.	(Behr et al., 2020)
MRP3	Bisphenols	Induction of MRP3 mRNA and protein expression by BPA (80 μ M/24 h) in HepG2 cells.	(Hanet et al., 2008)
	PFASs	Induction of MRP3 mRNA expression by PFNA (45 μ M/24 h) and PFDA (45 μ M/24 h), but repression by PFOA (500 μ M/24 h) and PFOS (100 μ M/24 h) in HepaRG cells.	(Behr et al., 2020; Lim et al., 2021)
MRP4	Bisphenols	Lack of effects of BPA (80 μ M/24 h) towards MRP4 mRNA expression in human hepatic HepG2 cells.	(Hanet et al., 2008)
BCRP	Bisphenols	Repression of BCRP protein expression by BPA (1 nM/48 h) in human term placental explant cultures.	(Sieppi et al., 2016)
		Repression of BCRP mRNA and protein expression by BPA (100 mM/48 h) in BeWo cells.	(Cao et al., 2022)
	Alkylphenols	Repression of BCRP protein expression by NP (1 nM/48 h) in human term placental explant cultures.	(Sieppi et al., 2016)
	PFASs	Induction of BCRP mRNA expression by PFNA (45 μ M/24 h) and PFDA (45 μ M/24 h) in HepaRG cells.	(Lim et al., 2021)
OATP1B1	PFASs	Repression of OATP1B1 mRNA expression by PFOA (250 and 500 μ M/24 h) and PFOS (100 μ M/24 h) in HepaRG cells.	(Behr et al., 2020)
OATP2B1	PFASs	Repression of OATP2B1 mRNA expression by PFDA (45 μ M/24 h) in HepaRG cells.	(Lim et al., 2021)
MATE2-K	PFASs	Induction of MATE2-K mRNA expression by PFDA (45 μ M/24 h) in HepaRG cells.	(Lim et al., 2021)
NTCP	PFASs	Repression of NTCP mRNA expression by PFDA (45 μ M/24 h), PFOA (10-500 μ M/24 h) and PFOS (10-100 μ M/24 h) in HepaRG cells.	(Behr et al., 2020; Lim et al., 2021)
OST β	PFAS	Induction of OST β mRNA expression by PFOA (50-250 μ M/24 h) and PFOS (25-100 μ M/24 h) in HepaRG cells.	(Behr et al., 2020)

987 Note: Abbreviations for plastic additives and transporters are those defined in Table 1 and Table 2, respectively.

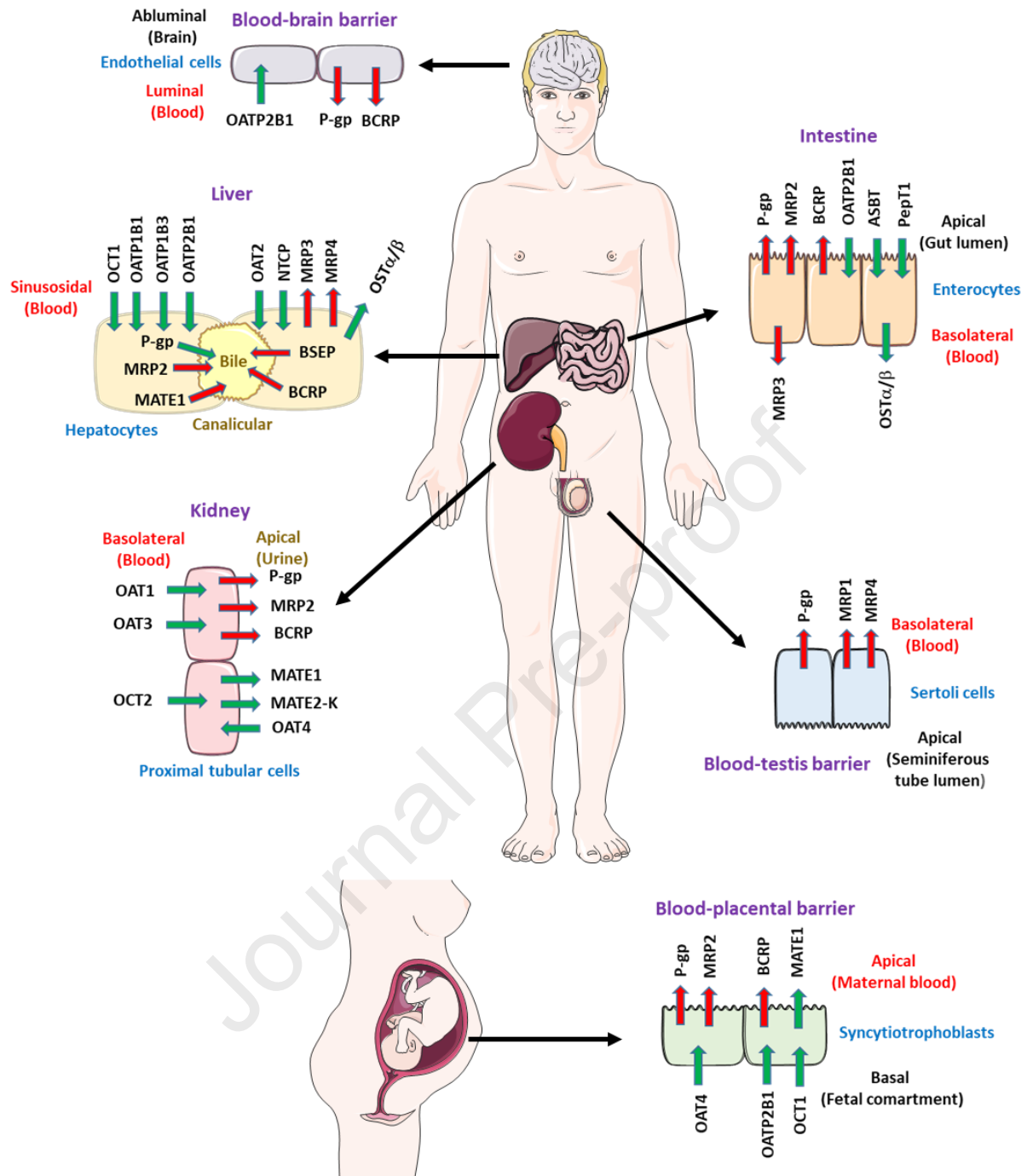


Fig. 1. Schematic representation of human drug transporter expression. Red and green arrows correspond to ATP-binding cassette (ABC) and solute carrier (SLC) transporters, respectively.

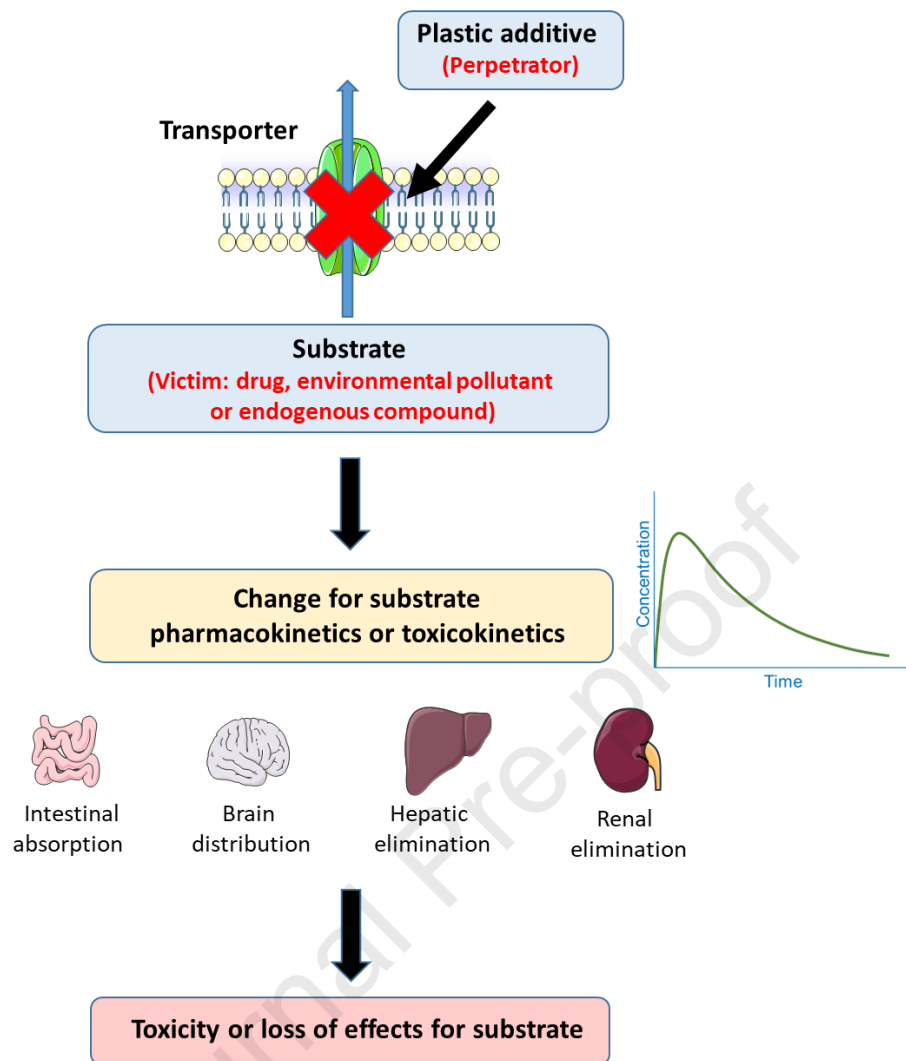


Fig. 2. Schematic representation of the possible deleterious consequences of drug transporter inhibition by a plastic additive, considered here as a perpetrator.

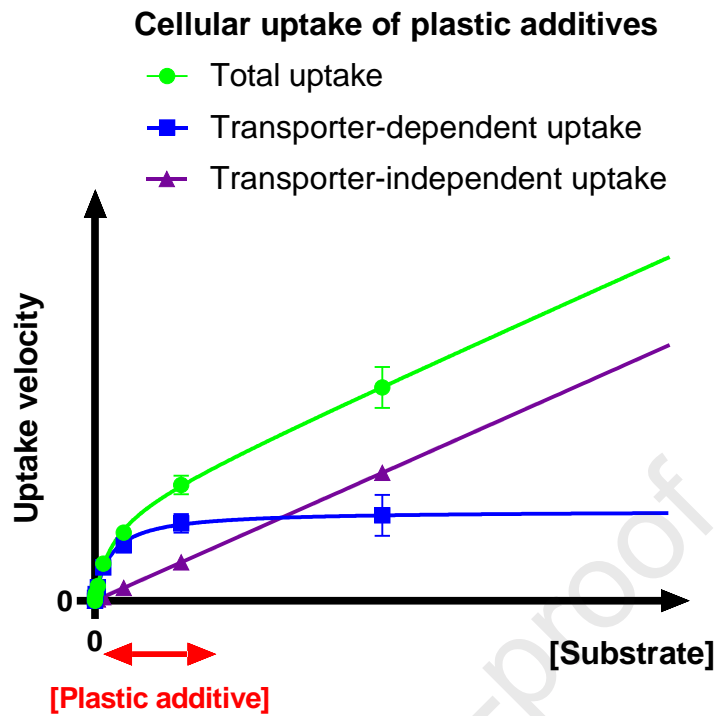


Fig. 3. Relative contribution of SLC transporter-mediated uptake and transporter-unrelated passive diffusion across the plasma membrane for plastic additives. At low plastic additive concentrations (usually the case for these pollutants in response to environmental or dietary exposure), the relative contribution of transporter-mediated uptake velocity to total uptake velocity is maximal.

Highlights

- Human drug transporters are key actors of pharmacokinetics for drugs and pollutants
- Various plastic additives inhibit *in vitro* activities of human drug transporters
- Some plasticizers regulate human drug transporter expression in cellular systems
- Plastic additives can behave as substrates for human drug transporters
- *In vivo* relevance of plasticizers-transporters interactions remains to elucidate

Author statement

This paper, entitled “Interactions of human drug transporters with chemical additives present in plastics: Potential consequences for toxicokinetics and health”, by Tastet et al., has been approved by all the authors and is not being considered elsewhere. This paper does not involve the use of human subjects or animal experiments.

On behalf of all co-authors,



Olivier Fardel

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: