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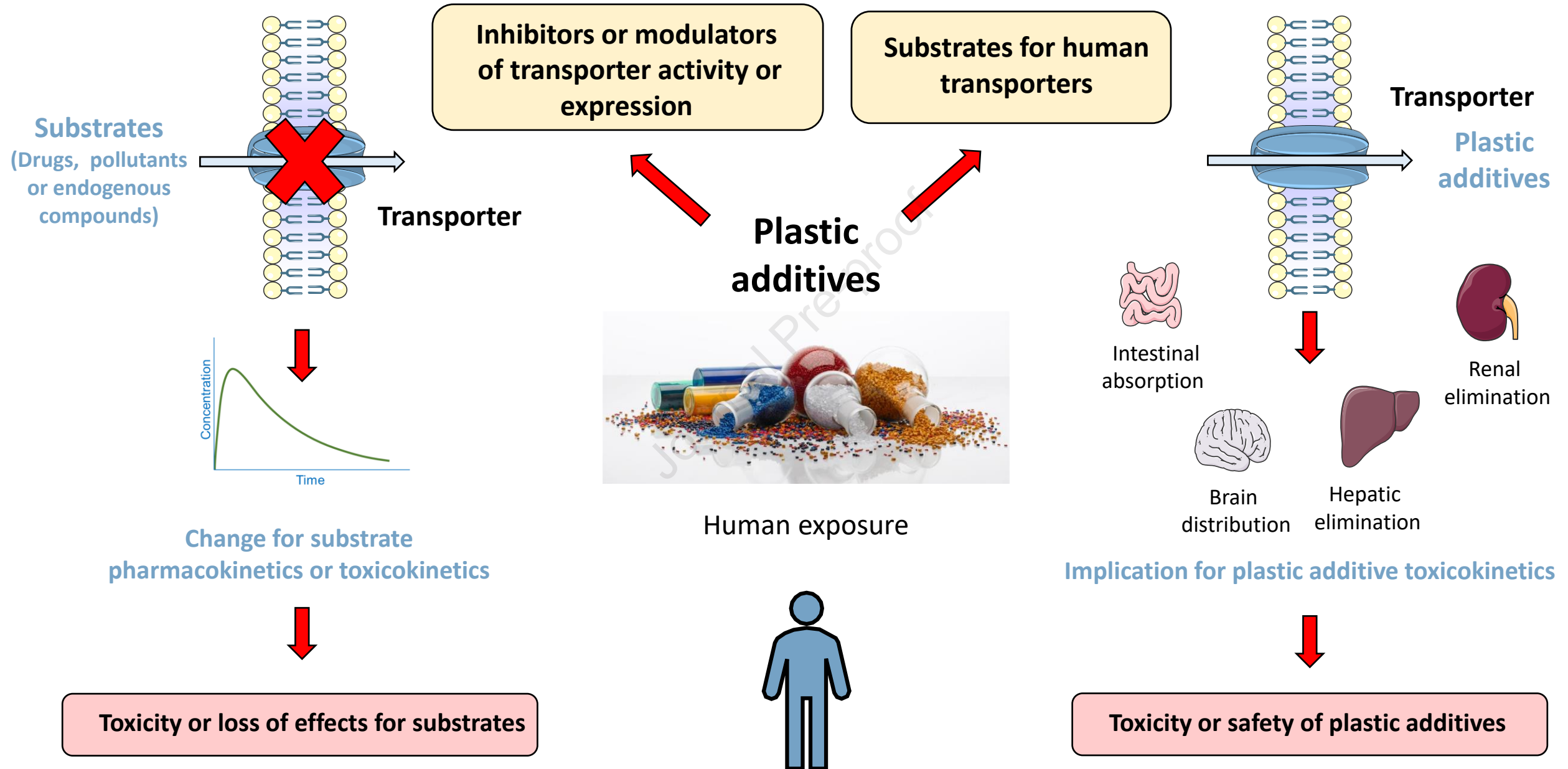
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**Interactions of human drug transporters with chemical additives present in plastics:  
Potential consequences for toxicokinetics and health**

Valentin Tastet<sup>1</sup>, Marc Le Vée<sup>1</sup>, Arnaud Bruyère<sup>1</sup> and Olivier Fardel<sup>2</sup>

<sup>1</sup>Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail)  
- UMR\_S 1085, F-35000 Rennes, France

<sup>2</sup>Univ 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](mailto:olivier.fardel@univ-rennes.fr)

**22 Abstract**

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

**44 Key-words**

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

## 47 **1. Introduction**

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

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

78 In addition to drugs, other chemicals, especially pollutants of public health concern, are  
79 likely to interact with human drug transporters (Clerbaux et al., 2019; Nicklisch and Hamdoun,  
80 2020), which may have important consequences for chemical risk assessment (Clerbaux et al.,  
81 2018; Darney et al., 2020). In contrast to drugs, the handling of pollutants by human drug  
82 transporters and their potential inhibitory effects remain rather poorly studied (Fardel et al.,  
83 2012). The exact implications of these potential interactions for pollutant toxicokinetics or  
84 toxicity are consequently poorly understood (Abu-Qare et al., 2003). The proof of concept for  
85 the interaction of environmental chemicals with human drug transporters was, however,  
86 provided more than twenty five years ago, through the demonstration that various pesticides  
87 belonging to different chemical classes can inhibit the ABC transporter P-glycoprotein (P-gp,  
88 *ABCB1*) (Bain and LeBlanc, 1996). Pesticides have since been shown to interact with other  
89 ABC transporters and with SLCs, as recently reviewed (Chedik et al., 2018; Guéniche et al.,  
90 2020). Transporters notably contribute to the pharmacokinetics, and moreover to the toxicity of  
91 certain pesticides, such as those of the herbicide paraquat (Wang et al., 2021). Besides  
92 pesticides, chemicals belonging to various classes of environment, food or drinking water  
93 contaminants also interfere with human transporters (Nicklisch and Hamdoun, 2020). This is  
94 notably the case for chemical additives present in plastics (Bruyere et al., 2017; Kim et al.,  
95 2007), known to also interact with xenobiotic transporters of aquatic organisms (Anselmo et  
96 al., 2012; Horion et al., 2015; Keiter et al., 2016; Nicklisch et al., 2021; Popovic et al., 2014).  
97 More than 400 of these plastics-related chemicals, basically used for enhancing polymer

98 properties and prolonging their life, are in use (Gunaalan et al., 2020). The most common plastic  
99 additives are phthalates (used as plasticizers), bisphenols (used as  
100 monomers/plasticizers/antioxidants), brominated flame retardants (BFRs) such as  
101 polybrominated diphenyls ethers (PBDE) or tetrabromobisphenol A (TBBPA, 4,4'-(propane-  
102 2,2-diyl)bis(2,6-dibromophenol)), alkylphenols (used as antioxidants/plasticizers), and per- and  
103 poly-fluoroalkyl substances (PFASs) (used as coating agents) (Barhoumi et al., 2022; Groh et  
104 al., 2019; Hahladakis et al., 2018; Hermabessiere et al., 2017; Wiesinger et al., 2021). Because  
105 these additives are usually not chemically bound to plastics, they can migrate out of them and  
106 are consequently widely released in the environment, notably when plastics degrade  
107 (Hermabessiere et al., 2017). They are, in particular, found in food and drinking water, where  
108 they can originate from plastic packaging or bottling, and are also closely associated with  
109 nanoplastics and microplastics, which are now recognized as major emerging environmental  
110 pollutants (Sangkham et al., 2022). Humans are thus highly exposed to these plastic additives  
111 through ingestion, inhalation and dermal contact. This is problematic because of the established  
112 deleterious effects of many of these additives; for example, bisphenols, phthalates and BFRs  
113 cause endocrine disruption, fertility problems, metabolic diseases and cancers (Benjamin et al.,  
114 2017; Campanale et al., 2020; Feiteiro et al., 2021; Ma et al., 2019; Tarafdar et al., 2022). Plastic  
115 additives are therefore chemicals of considerable concern with respect to the human exposome  
116 and the public health. This led us to survey the interactions of plastic additives with human drug  
117 transporters in the present review, with a special emphasis on possible consequences for human  
118 exposure, toxicokinetics and health. The plastic additives considered are mainly those for which  
119 interactions with at least one human drug transporter are documented in the literature, according  
120 to a search of the PubMed database (<https://pubmed.ncbi.nlm.nih.gov/>), as of 08/31/2022; these  
121 plastic additives are listed in Table 1.

## 122 **2. Brief overview of drug transporters**

## 123 2.1. ABC transporters

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

135 The tissue location of ABC transporters is shown in Fig. 1. P-gp and BCRP are notably  
136 found at the brush-border membrane of enterocytes, where they actively expel their substrates  
137 into the digestive lumen, thereby preventing or limiting their intestinal absorption (Müller et  
138 al., 2017). These pumps are also present at the luminal pole of brain microvessel endothelial  
139 cells, at the apical pole of syncytiotrophoblasts and at the basolateral pole of Sertoli cells, where  
140 they contribute to the blood–brain, blood-placenta and blood-testis barriers, respectively (Liu  
141 and Liu, 2019; Miller, 2015; Mruk et al., 2011). P-gp and BCRP, as well as MRP2 and BSEP,  
142 are additionally found at the canalicular pole of hepatocytes, where they secrete their substrates  
143 into the bile canaliculus lumen (Jetter and Kullak-Ublick, 2020); in this context, drug-mediated  
144 inhibition of BSEP transport has been associated with cholestasis (Chatterjee and Annaert,  
145 2018). In the kidney, P-gp, BCRP and MRP2 are located at the apical pole of proximal tubular  
146 cells, where they contribute to tubular secretion of drugs (Lee and Kim, 2004).

## 147 2.2. SLC transporters



148 SLCs mediate secondary active transport or facilitated diffusion of drugs (Zhou and Shu,  
149 2022). They belong mainly to the *SLCO*, *SLC22*, and *SLC47* transporter subfamilies. The list  
150 of these transporters and their main types of substrates are indicated in Table  
151 2. *SLCO* transporters, also known as organic anion transporting polypeptides (OATPs), include  
152 three members recognized as important drug transporters, *i.e.*, OATP1B1 (*SLCO1B1*),  
153 OATP1B3 (*SLCO1B3*) and OATP2B1 (*SLCO2B1*) (Roth et al., 2012). *SLC22* drug transporters  
154 correspond to organic cation transporters (OCTs) such as OCT1 (*SLC22A1*) and OCT2  
155 (*SLC22A2*), and organic anion transporters (OATs) like OAT1 (*SLC22A6*), OAT2 (*SLC22A7*),  
156 OAT3 (*SLC22A8*) and OAT4 (*SLC22A11*) (Ciarimboli, 2008; Koepsell, 2020; Roth et al.,  
157 2012). *SLC47* transporters are multidrug and toxin extrusion (MATE) proteins and comprise  
158 two members, *i.e.*, MATE1 (*SLC47A1*) and MATE2 (*SLC47A2*) (Nies et al., 2016). Similarly  
159 to ABC transporters, there is a high degree of overlapping substrates between SLC transporters,  
160 notably between OCTs and MATEs and between OATPs and OATs (Table 2).

161 OATPs, OCTs and OATs are notably expressed at the basolateral side of hepatocytes  
162 and kidney proximal tubular cells (Fig. 1) and primarily act as uptake drug transporters enabling  
163 the entry of drugs from blood into cells (Ciarimboli, 2008; Roth et al., 2012). By contrast,  
164 MATE1 and MATE2-K, the functional splice variant of MATE2, function as pH-dependent  
165 efflux transporters, at the apical surface of hepatocytes or proximal tubular cells (Koepsell,  
166 2020) (Fig. 1). OAT4 is implicated in drug reabsorption from the primitive urine at the apical  
167 pole of proximal tubular cells and also in compound uptake into the placenta from the foetus  
168 blood at the basal pole of syncytiotrophoblasts (Rizwan and Burckhardt, 2007). SLC  
169 transporters also include the proton-coupled peptide transporter (PEPT) 1 (*SLC15A1*), involved  
170 in absorption of peptidomimetic drugs at the apical pole of enterocytes (Inui et al., 2000), the  
171 sodium-taurocholate cotransporting polypeptide (NTCP/*SLC10A1*) and the apical sodium-  
172 dependent bile acid transporter (ASBT/*SLC10A2*), implicated in bile acid uptake at the

173 basolateral pole of hepatocytes and the apical pole of enterocytes, respectively (Meier and  
174 Stieger, 2002), and the human organic solute transporter (OST)  $\alpha/\beta$  (*SLC51A/SLC51B*),  
175 implicated in the efflux of bile acids at the basolateral pole of enterocytes and hepatocytes  
176 (Beaudoin et al., 2020).

### 177 **3. Modulation of transporter activities by plastic additives**

178 Direct modulation of human transporter activities by plastic additives have been studied  
179 using conventional *in vitro* methods, based on vesicular or cellular assays (Brouwer et al.,  
180 2013). Vesicular transport assays, used mainly for ABC transporters, rely upon the ATP-  
181 dependent translocation of reference substrates into the vesicular compartment of inside-out  
182 plasma membrane vesicles prepared from cells expressing the transporter of interest (Volpe,  
183 2016); the inhibition or stimulation of transporter activity is visualized by the decreased or  
184 increased accumulation of the reference substrate into the vesicular compartment in response  
185 to the chemical tested for its transporter activity modulating potential. Cellular assays, used for  
186 ABC and SLC transporters, correspond to uptake or efflux of reference substrates in, or from,  
187 recombinant cells overexpressing the transporter of interest, or to bidirectional transport of  
188 reference substrates across transporter-expressing polarized cells (Jani and Krajcsi, 2014); the  
189 potential transporter modulating activity of compounds is demonstrated by the alteration of  
190 reference substrate uptake, efflux or transcellular passage.

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

198 may reflect differential sensitivities of cellular and vesicular assays to modulators. Other  
199 discrepancies have been observed between cellular and vesicular assays notably with  
200 diethylhexylphthalate (DEHP, bis(2-ethylhexyl) benzene-1,2-dicarboxylate) which acts as a P-  
201 gp inhibitor in cellular assays (Kim et al., 2007) but not in vesicular assays (Dankers et al.,  
202 2013), and the BFR 2,2',4,4'-tetrabromodiphenyl ether (BDE-47, 3,5-dibromo-2-(2,4-  
203 dibromophenoxy)phenol), which inhibits BCRP in vesicular assays but not in cellular assays  
204 (Marchitti et al., 2017). Overall, among plastic additives, phthalates like DEHP and its  
205 metabolite monoethylhexylphthalate (MEHP, 2-(2-ethylhexoxycarbonyl)benzoate) interact  
206 poorly with ABC transporter activity; they notably fail to inhibit MRP1, MRP4 or BCRP  
207 activity (Table 3). By contrast, the BFR TBBPA, as well as the PFASs perfluorooctanoic acid  
208 (PFOA, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoic acid) and perfluorooctane  
209 sulfonate (PFOS, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctane-1-sulfonic acid),  
210 appear to be potent inhibitors of ABC transporters as they block P-gp, MRP1, MRP4 and BCRP  
211 activities (Table 3); PFOS additionally inhibits BSEP and MRP2. Among ABC transporters,  
212 BCRP is the most sensitive to plastic additives, as it is inhibited by BPA, BFRs and PFASs  
213 (Table 3). It is noteworthy that the concentrations of plastic additives required to inhibit ABC  
214 transporters are usually in the 10-100  $\mu\text{M}$  range (Table 3); only the alkylphenol 4-nonylphenol  
215 (NP) blocks P-gp activity when used at low concentrations in the 0.1-1  $\mu\text{M}$  range (Doo et al.,  
216 2005).

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

223 OATP1B1, OATP1B3, MATE1, OAT3 and NTCP activities, but fails to alter MATE2-K and  
224 OAT1 activities. Other BFRs like BDE-47 and PFASs target OATPs and/or OATs (Table 4),  
225 whereas effects of phthalates towards SLC transporters have not yet been investigated. The  
226 concentrations of bisphenols, BFRs or PFAS acting on SLC transporter activities are often in  
227 the 10-100  $\mu\text{M}$  range (Table 4), as reported above for those acting on ABC transporters. Low  
228 concentrations of TBBPA (in the 0.5-5  $\mu\text{M}$  range), however, inhibit OAT3 and NTCP activity,  
229 whereas inhibition of OATP activities is caused by much lower concentrations of BDE (in the  
230 100 pM-100 nM range) (Table 4).

231 The mechanisms by which plastic additives modulate transporter activities remain to be  
232 clarified. Competitive or non-competitive interactions with drug binding sites on transporter  
233 proteins are likely involved, as proposed for drugs inhibiting transporters (Wigler and Patterson,  
234 1993). The fact that BPA has been demonstrated to inhibit OAT3-mediated transport of estrone  
235 3-sulfate in a competitive manner (Bruyere et al., 2017) and that PFOA, perfluorononanoic acid  
236 (PFNA, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluorononanoic acid) and perfluorodecanoic  
237 acid (PFDA, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-nonadecafluorodecanoic acid)  
238 competitively block OATP2B1-mediated uptake of sulfobromophthalein in Caco-2 cells  
239 (Kimura et al., 2020) fully supports this conclusion. BDEs probably also inhibit OATPs by  
240 competitive mechanisms because they are high affinity ligands for these SLCs (Pacyniak et al.,  
241 2010) (Table 5).

#### 242 **4. Plastic additives as substrates for transporters**

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

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

255         The plastic additives which are either substrates or non substrates for human ABC and  
256 SLC transporters are listed in Table 5. With respect to P-gp, DEHP and alkyphenols such as  
257 nonylphenol ethoxylate (NPE, 2-(4-nonylphenoxy)ethanol), but not its metabolite NP, are  
258 substrates. For BPA, conflicting results have been obtained with respect to P-gp. BPA has thus  
259 been shown to be transported by P-gp across human intestinal Caco-2 cells (Yoshikawa et al.,  
260 2002), but not across P-gp-overexpressing MDCK cells (Dankers et al., 2013); moreover, BPA  
261 failed to stimulate ATPase activity of P-gp (Mazur et al., 2012). Further studies are therefore  
262 required to more precisely determine whether BPA is a substrate for P-gp. With respect to other  
263 ABC transporters, MRP2, MRP3 and BCRP transport BPA, whereas PFOA is a substrate for  
264 BCRP (Table 5). Various BDEs, including BDE-47, have been demonstrated to be transported  
265 by OATP1B1, OATP1B3 and OATP2B1, with rather low  $K_m$  values (around 0.3-1.9  $\mu\text{M}$ )  
266 (Table 5), indicating that they are high affinity substrates for OATPs. Whereas OATs transport  
267 PFOA with  $K_m$  values in the 50-310  $\mu\text{M}$  range. Other PFASs such as PFOS have additionally  
268 been found to be substrates for the bile salt transporters NTCP, ASBT and OST $\alpha/\beta$  (Table 5).  
269 Finally, the trans-epithelial transport of various BDEs across Caco-2 cells has been shown to  
270 be altered by various transporter inhibitors, suggesting that several transporters, *i.e.*, P-gp,  
271 MRPs, BCRP and OCTs, may participate in the transcellular passage of these chemicals, even

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

## 274 **5. Regulation of human drug transporter expression by plastic additives**

275 Regulations of human drug transporter expression by plastic additives have been mostly  
276 studied using cellular *in vitro* models and are listed in Table 6. These regulations, either  
277 induction or repression of transporter expression, depend on the nature of both the transporter  
278 and the plastic additive. For P-gp, chronic exposure (48 h) of placental BeWo cells to 10  $\mu\text{M}$   
279 BPA results in enhanced expression of the efflux pump, but in a rather modest manner (55%  
280 increase) (Jin and Audus, 2005). By contrast, BPA exposure at 80  $\mu\text{M}$  for 24 h fails to induce  
281 P-gp expression in human hepatic HepG2 cells, despite an increase in *MDR1* mRNA levels  
282 (Hanet et al., 2008). These contradicting results may reflect a cell type-dependent regulation of  
283 P-gp by BPA. This chemical also increases the activity of the *MDR1* gene promoter in an  
284 haplotype-dependent manner (Speidel et al., 2018). Phthalates such as DEHP used at 10  $\mu\text{M}$   
285 for 24 h-72 h enhance P-gp expression in colon cancer and sarcoma cells (Angelini et al., 2011;  
286 Chen et al., 2018; Takeshita et al., 2006), which is associated with increased resistance to  
287 chemotherapeutics drugs (Chen et al., 2018). P-gp induction and multidrug resistance also occur  
288 in response to chronic exposure to 100 nM DEHP for three months in breast cancer MDA-MB-  
289 231 cells (Jadhao et al., 2021). P-gp expression has additionally been shown to be induced in a  
290 rat epididymal epithelial cell line in response to treatment by NP (20  $\mu\text{M}$ ) for 24 h (Jones and  
291 Cyr, 2011). Effects of PFASs towards P-gp expression remain to be characterized, whereas the  
292 bile salt efflux pump BSEP has been shown to be repressed by both PFOA and PFOS in human  
293 hepatic HepaRG cells (Table 6).

294 With respect to MRPs, MRP1, MRP2 and MRP3, but not MRP4, have been  
295 demonstrated to be up-regulated by BPA (80  $\mu\text{M}$ ) in human hepatic HepG2 cells (Hanet et al.,  
296 2008) (Table 6). By contrast, DEHP tends to decrease Mrp2 protein levels in rat liver (Johnson

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

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

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

## 321 **6. Consequences for toxicokinetics and human health**

## 322 6.1 Consequences for plastic additives altering transporter activity and/or expression

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

338 The potential drug-pollutant or pollutant-pollutant interactions as well as pollutant  
339 toxicity due to an abrogation of endogenous substrate transport have not yet been reported for  
340 plastic additives, even for those inhibiting transporter activity or expression. This may likely be  
341 due to the fact that human plasma concentrations of plastic additives, such as BPA, phthalates,  
342 alkylphenols, BDEs, TBBPA and PFASs, due to environmental exposure or food intake, are  
343 usually low, *i.e.*, in the nM or pM range (Asimakopoulos et al., 2012; Huang et al., 2014; Li et  
344 al., 2020; Teeguarden et al., 2013; Wang et al., 2012; Wang et al., 2019). Their unbound  
345 fraction, which is the one pharmacologically active towards transporters according to the free  
346 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  $\mu\text{M}$  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 ( $C_{\text{max}}$ ) of the drug  
355 perpetrator and its  $\text{IC}_{50}$  value (which has to be  $\geq 0.1$  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  $\text{IC}_{50}$  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

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

378 For P-gp and BCRP, it is noteworthy that their intestinal inhibition is predicted to  
379 potentially occur if the ratio between the perpetrator maximal gastrointestinal concentration  
380 (calculated as the ingested dose of perpetrator in a volume of 250 mL) and the  $IC_{50}$  value is  $\geq$   
381 10 (Giacomini et al., 2010). The daily dietary intake of plastic additives has therefore to be  
382 considered when calculating theoretical concentrations to evaluate inhibitory effects towards  
383 P-gp and/or BCRP. With respect to BPA, TBBPA and BDEs, they can be estimated to be  
384 approximately 2.38  $\mu$ g, 70 ng and 75.4 ng, respectively, for a standard adult male weighing 70  
385 kg (Colnot et al., 2014; Domingo et al., 2008; Huang et al., 2017), leading to gut concentrations  
386 in the 1-100 nM range, which is lower than the concentrations needed to inhibit P-gp or BCRP  
387 *in vitro* (in the 500 nM-100  $\mu$ M range) (Table 3). Similarly, and despite daily DEHP intakes  
388 being higher, *i.e.*, up to 840  $\mu$ g (Cheng et al., 2016), the DEHP concentrations in the gut lumen,  
389 up to 8.6  $\mu$ M, remain much lower than the 30.1 mM DEHP concentration active on P-gp *in*  
390 *vitro*. Overall, these data suggest that inhibition of intestinal P-gp or BCRP by plastic additives  
391 in response to common contamination by the diet is rather unlikely. The risk of inhibition  
392 remains to be considered, however, for highly-exposed subjects, notably in the case of exposure  
393 to a mixture of pollutants, including plastic additives, whose inhibitory effects towards P-gp  
394 and/or BCRP may be additive or synergic, as already demonstrated for inhibition of P-gp by  
395 mixtures of marine pollutants (Nicklisch et al., 2016).

396 6.2 Consequences for plastic additives that are transporter substrates

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

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

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

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

## 427 **7. Conclusion and perspectives**

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

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

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

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

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

497 regulated by BPA in human hepatic HepG2 cells (Jiménez-Torres et al., 2020), as well as  
498 glucose transporters, norepinephrine transporter (*SLC6A2*) and thyroid hormone transporters,  
499 impacted by BPA or phthalates (Bereketoglu and Pradhan, 2022; Li et al., 2016; Quesnot et al.,  
500 2014; Sakurai et al., 2004; Toyohira et al., 2003), may additionally be of interest.

501

#### 502 **Author contribution statement**

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

#### 505 **Declaration of competing interest**

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

#### 508 **Data availability**

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

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947 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)

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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 $\beta$ - 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: $\beta$ -lactam antibiotics)	(Inui et al., 2000)
SLCO	OATP1B1 ( <i>SLCO1B1</i> )	Anionic drugs; bile acids; bilirubin; steroid and thyroid hormones (Example: bromosulphophthalein, estrone 3-sulfate, statins, valsartan)	(Kalliokoski and Niemi, 2009)
	OATP1B3 ( <i>SLCO1B3</i> )	Anionic drugs; bile acids; bilirubin; steroid and thyroid hormones (Example: cholecystokinin, estrone 3 sulfate, statins)	
	OATP2B1 ( <i>SLCO2B1</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 $\alpha$ ( <i>SLC51A</i> ) OST $\beta$ ( <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.

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962 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 <sup>CA</sup> ) (Jin and Audus, 2005)		BPA (100 μM <sup>VA</sup> ) (Dankers et al., 2013)
	Phthalates		DEHP (30.1 mM <sup>CA</sup> ) (Kim et al., 2007) DEP (16.1 mM <sup>CA</sup> ) (Kim et al., 2007) DBP (32.1 mM <sup>CA</sup> ) (Kim et al., 2007)	DEHP (100 μM <sup>VA</sup> ) (Dankers et al., 2013) MEHP (100 μM <sup>VA</sup> ) (Dankers et al., 2013)
	BFRs		BDE-47 (50 μM <sup>VA</sup> ) (Nicklisch et al., 2016) 6-OH-BDE-47 (IC <sub>50</sub> =11.4 μM <sup>VA</sup> , 50 μM <sup>CA</sup> ) (Marchitti et al., 2017) TBBPA (IC <sub>50</sub> =22.9 μM <sup>VA</sup> ) (Dankers et al., 2013)	PBDE-47 (300 μM <sup>VA</sup> , 100 μM <sup>CA</sup> ) (Marchitti et al., 2017) PBDE-100 (50 μM <sup>VA</sup> ) (Nicklisch et al., 2016)
	Alkylphenols		NPE (0.1-1 μM <sup>CA</sup> ) (Doo et al., 2005)	
	PFASs		PFOA (100 μM <sup>VA</sup> ) (Dankers et al., 2013) PFOS (100 μM <sup>VA</sup> ) (Dankers et al., 2013)	
BSEP	PFASs		PFOS (100 μM <sup>VA</sup> ) (Zhao et al., 2015)	PFBS (100 μM <sup>VA</sup> ) (Zhao et al., 2015) PFHxS (100 μM <sup>VA</sup> ) (Zhao et al., 2015)
MRP1	Bisphenols			BPA (100 μM <sup>VA</sup> ) (Dankers et al., 2013)
	Phthalates			DEHP (100 μM <sup>VA</sup> ) (Dankers et al., 2013) MEHP (100 μM <sup>VA</sup> ) (Dankers et al., 2013)
	BFRs		TBBPA (100 μM <sup>VA</sup> ) (Dankers et al., 2013)	
	PFASs		PFOA (100 μM <sup>VA</sup> ) (Dankers et al., 2013) PFOS (100 μM <sup>VA</sup> ) (Dankers et al., 2013)	
MRP2	PFASs		PFHxS (100 μM <sup>VA</sup> ) (Zhao et al., 2015) PFOS (100 μM <sup>VA</sup> ) (Zhao et al., 2015)	PFBS (100 μM <sup>VA</sup> ) (Zhao et al., 2015)
MRP4	Bisphenols			BPA (100 μM <sup>VA</sup> ) (Dankers et al., 2013)
	Phthalates			DEHP (100 μM <sup>VA</sup> ) (Dankers et al., 2013) MEHP (100 μM <sup>VA</sup> ) (Dankers et al., 2013)
	BFRs		TBBPA (IC <sub>50</sub> =24.0 μM <sup>VA</sup> ) (Dankers et al., 2013)	
	PFASs		PFOA (100 μM <sup>VA</sup> ) (Dankers et al., 2013) PFOS (100 μM <sup>VA</sup> ) (Dankers et al., 2013)	
BCRP	Bisphenols		BPA (500 nM <sup>CA</sup> , 100 μM <sup>VA</sup> ) (Dankers et al., 2013; Engdahl et al., 2021)	
	Phthalates			DEHP (100 μM <sup>VA</sup> ) (Dankers et al., 2013) MEHP (100 μM <sup>VA</sup> ) (Dankers et al., 2013)
	BFRs		BDE-47 (IC <sub>50</sub> =45.7 μM <sup>VA</sup> ) (Marchitti et al., 2017) 6-hydroxy-BDE-47 (IC <sub>50</sub> =9.4 μM <sup>VA</sup> , 50 μM <sup>CA</sup> ) (Marchitti et al., 2017) TBBPA (100 μM <sup>VA</sup> ) (Dankers et al., 2013)	BDE-47 (100 μM <sup>CA</sup> ) (Marchitti et al., 2017)
	PFASs		PFOA (5-100 μM <sup>VA</sup> ) (Dankers et al., 2013; Eldasher et al., 2013) PFOS (100 μM <sup>VA</sup> ) (Dankers et al., 2013) PFHxS (100 μM <sup>VA</sup> ) (Zhao et al., 2015)	

963 Note: Abbreviations for plastic additives and transporters are those defined in Table 1 and Table 2, respectively; CA - cellular  
 964 assay; VA - vesicular assay; IC<sub>50</sub> - half maximal inhibitory concentration.

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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 $\mu$ M) (Bruyere et al., 2017)	BPA (IC <sub>50</sub> =39.0 $\mu$ M) (Bruyere et al., 2017) BPF (100 $\mu$ M) (Bruyere et al., 2017)	
	BFRs		TBBPA (IC <sub>50</sub> =37.5 $\mu$ M) (Bruyere et al., 2017)	
OCT2	Bisphenols	BPF (100 $\mu$ M) (Bruyere et al., 2017) BPS (100 $\mu$ M) (Bruyere et al., 2017)		BPA (100 $\mu$ M) (Bruyere et al., 2017)
	BFRs		TBBPA (100 $\mu$ M) (Bruyere et al., 2017)	
MATE1	Bisphenols		BPA (IC <sub>50</sub> =73.5 $\mu$ M) (Bruyere et al., 2017) BPF (100 $\mu$ M) (Bruyere et al., 2017) BPS (100 $\mu$ M) (Bruyere et al., 2017)	
	BFRs		TBBPA (IC <sub>50</sub> =23.1 $\mu$ M) (Bruyere et al., 2017)	
MATE2-K	Bisphenols			BPA (100 $\mu$ M) (Bruyere et al., 2017) BPF (100 $\mu$ M) (Bruyere et al., 2017) BPS (100 $\mu$ M) (Bruyere et al., 2017)
	BFRs			TBBPA (100 $\mu$ M) (Bruyere et al., 2017)
OATP1B1	Bisphenols		BPA (IC <sub>50</sub> =18.7 $\mu$ M) (Bruyere et al., 2017) BPF (IC <sub>50</sub> =13.4 $\mu$ M) (Bruyere et al., 2017)	BPS (100 $\mu$ M) (Bruyere et al., 2017)
	BFRs		TBBPA (IC <sub>50</sub> =0.6 $\mu$ 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 $\mu$ M) (Bruyere et al., 2017)	BPA (100 $\mu$ M) (Bruyere et al., 2017)	BPS (100 $\mu$ M) (Bruyere et al., 2017)
	BFRs		TBBPA (IC <sub>50</sub> =12.3 $\mu$ 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 $\mu$ M) (Kimura et al., 2020) PFNA (Ki=35.3 $\mu$ M) (Kimura et al., 2020) PFDA (Ki=43.2 $\mu$ M) (Kimura et al., 2020)	
OAT1	Bisphenols	BPA (100 $\mu$ M) (Bruyere et al., 2017) BPF (100 $\mu$ M) (Bruyere et al., 2017)	BPS (100 $\mu$ M) (Bruyere et al., 2017)	
	BFRs			TBBPA (100 $\mu$ M) (Bruyere et al., 2017)
	PFASs		PFOA (10 $\mu$ M) (Nakagawa et al., 2008)	
OAT2	PFASs		PFOA (10 $\mu$ M) (Nakagawa et al., 2008)	
OAT3	Bisphenols		BPA (IC <sub>50</sub> =9.2 $\mu$ M) (Bruyere et al., 2017) BPF (IC <sub>50</sub> =26.8 $\mu$ M) (Bruyere et al., 2017) BPS (IC <sub>50</sub> =23.3 $\mu$ M) (Bruyere et al., 2017)	
	BFRs		TBBPA (IC <sub>50</sub> =0.5 $\mu$ M) (Bruyere et al., 2017)	
	PFASs		PFOA (10 $\mu$ M) (Nakagawa et al., 2008)	
NTCP	Bisphenols		BPA (100 $\mu$ M) (Bruyere et al., 2017) BPF (100 $\mu$ M) (Bruyere et al., 2017)	BPS (100 $\mu$ M) (Bruyere et al., 2017)
	BFRs		TBBPA (IC <sub>50</sub> =4.5 $\mu$ M) (Bruyere et al., 2017) PFBS (10 $\mu$ M) (Zhao et al., 2015) PFHxS (10 $\mu$ M) (Zhao et al., 2015) PFOS (10 $\mu$ M) (Zhao et al., 2015)	

976 Note: Abbreviations for plastic additives and transporters are those defined in Table 1 and Table 2, respectively; IC<sub>50</sub> - half  
 977 maximal inhibitory concentration; Ki - inhibition constant.

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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 <sup>CA</sup> (Yoshikawa et al., 2002)	BPA <sup>ATA, CA</sup> (Dankers et al., 2013; Mazur et al., 2012) BPA-Glucuronide <sup>ATA</sup> (Mazur et al., 2012) BPS <sup>Perfused human placenta</sup> (Grandin et al., 2019)
	Phthalates	DEHP <sup>CA, ATA</sup> (Kim et al., 2007; Yoshikawa et al., 2002)	BBP <sup>CA</sup> (Yoshikawa et al., 2002) DBP <sup>CA, ATA</sup> (Kim et al., 2007; Yoshikawa et al., 2002) DEP <sup>CA, ATA</sup> (Kim et al., 2007)
	BFRs		TBBPA <sup>CA</sup> (Dankers et al., 2013)
	Alkylphenols	tBP <sup>CA</sup> (Yoshikawa et al., 2002) tOP <sup>CA</sup> (Yoshikawa et al., 2002) NPE <sup>ATA, CA</sup> (Charuk et al., 1998; Loo and Clarke, 1998)	NP <sup>CA</sup> (Loo and Clarke, 1998)
	PFASs		PFOA <sup>CA, ATA</sup> (Dankers et al., 2013)
MRP2	Bisphenols	BPA <sup>ATA</sup> (Mazur et al., 2012)	BPA-Glucuronide <sup>ATA</sup> (Mazur et al., 2012)
MRP3	Bisphenols	BPA <sup>ATA</sup> (Mazur et al., 2012) BPA-Glucuronide <sup>ATA</sup> (Mazur et al., 2012)	
BCRP	Bisphenols	BPA <sup>ATA, CA</sup> (Dankers et al., 2013; Mazur et al., 2012)	BPA-Glucuronide <sup>ATA</sup> (Mazur et al., 2012) TBBPA <sup>CA</sup> (Dankers et al., 2013)
	BFRs		TBBPA <sup>CA</sup> (Dankers et al., 2013)
	PFASs	PFOA <sup>CA</sup> (Dankers et al., 2013)	
OATP1B1	BFRs	BDE-47 (Km=0.31 $\mu\text{M}^{\text{CA}}$ ) (Pacyniak et al., 2010) BDE-99 (Km=0.91 $\mu\text{M}^{\text{CA}}$ ) (Pacyniak et al., 2010) BDE-153 (Km=1.91 $\mu\text{M}^{\text{CA}}$ ) (Pacyniak et al., 2010)	
OATP2B1	BFRs	BDE-47 (Km=0.41 $\mu\text{M}^{\text{CA}}$ ) (Pacyniak et al., 2010) BDE-99 (Km=0.70 $\mu\text{M}^{\text{CA}}$ ) (Pacyniak et al., 2010) BDE-153 (Km=1.66 $\mu\text{M}^{\text{CA}}$ ) (Pacyniak et al., 2010)	
	PFASs	PFOA (Km=8.3 $\mu\text{M}^{\text{CA}}$ ) (Kimura et al., 2017)	
OATP1B3	BFRs	BDE-47 (Km=0.81 $\mu\text{M}^{\text{CA}}$ ) (Pacyniak et al., 2010) BDE-99 (Km=0.87 $\mu\text{M}^{\text{CA}}$ ) (Pacyniak et al., 2010) BDE-153 (Km=0.65 $\mu\text{M}^{\text{CA}}$ ) (Pacyniak et al., 2010)	
OAT1	PFASs	PFOA (Km=48.0 $\mu\text{M}^{\text{CA}}$ ) (Nakagawa et al., 2008)	
OAT3	Bisphenols		BPA <sup>CA</sup> (Bruyere et al., 2017)
	PFASs	PFOA (Km=49.1 $\mu\text{M}^{\text{CA}}$ ) (Nakagawa et al., 2008)	
OAT4	PFASs	PFOA (Km=310.3 $\mu\text{M}^{\text{CA}}$ ) (Nakagawa et al., 2009; Yang et al., 2010)	
NTCP	PFASs	PFBS (Km=39.6 $\mu\text{M}^{\text{CA}}$ ) (Zhao et al., 2015) PFHxS (Km=112 $\mu\text{M}^{\text{CA}}$ ) (Zhao et al., 2015) PFOS (Km=130 $\mu\text{M}^{\text{CA}}$ ) (Zhao et al., 2015)	
ASBT	PFASs	PFOS <sup>CA</sup> (Zhao et al., 2015)	PFBS <sup>CA</sup> (Zhao et al., 2015) PFHxS <sup>CA</sup> (Zhao et al., 2015)
OST $\alpha/\beta$	PFASs	PFBS <sup>CA</sup> (Zhao et al., 2015) PFHxS <sup>CA</sup> (Zhao et al., 2015) PFOS <sup>CA</sup> (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.

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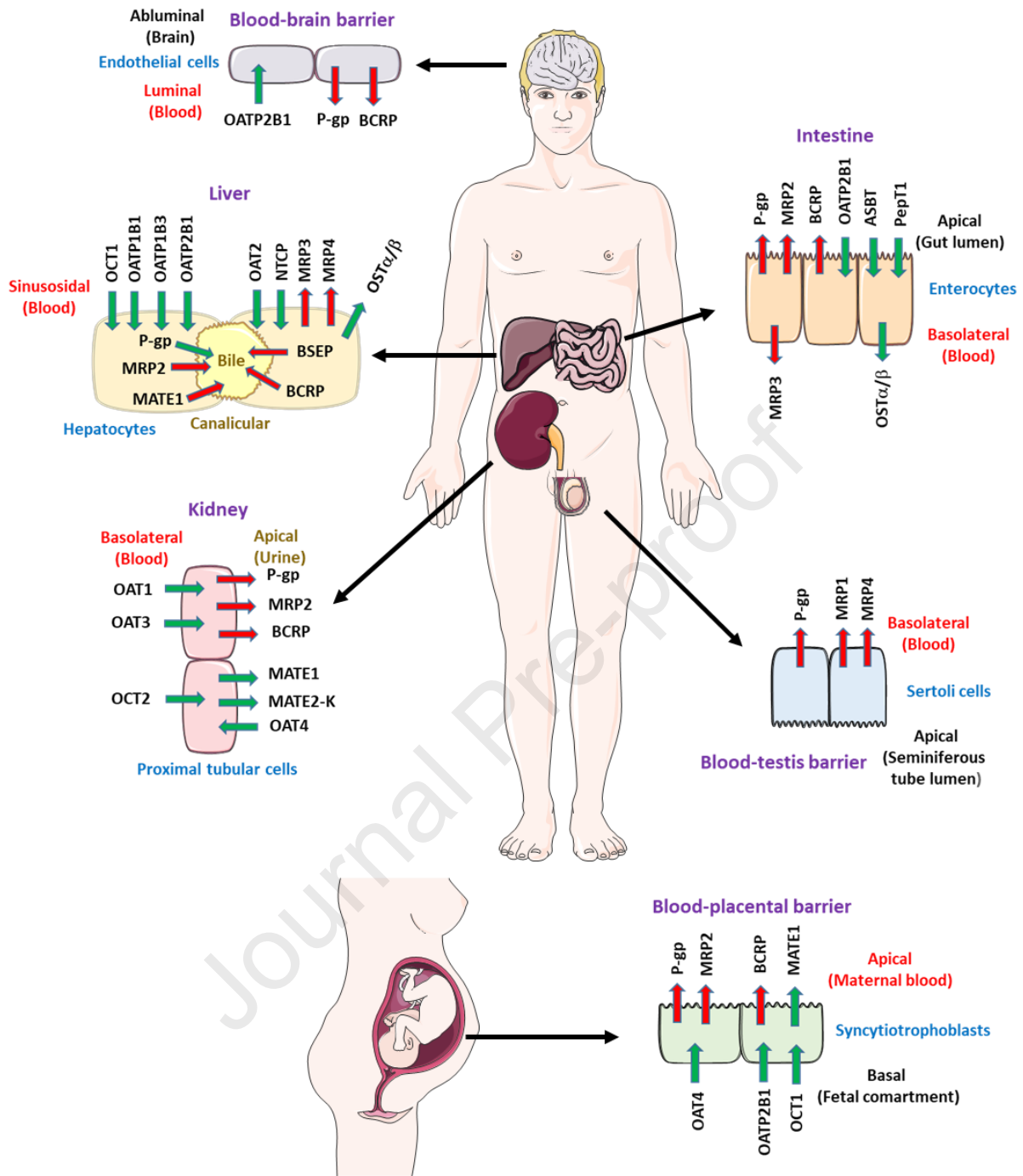
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986 Table 6. Regulation of human drug transporter expression by plastic additives.

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. Repression of <i>MDR1</i> promoter activity by BPS (0.5 nM/acute exposure/15 min) in an haplotype-dependent manner.	(Speidel et al., 2018)
		Induction of <i>MDR1</i> mRNA expression, but not that of P-gp, by BPA (80 $\mu$ M/24 h) in human hepatic HepG2 cells.	(Hanet et al., 2008)
		Modest induction of P-gp expression by BPA (10 $\mu$ M/48 h) in placental BeWo cells.	(Jin and Audus, 2005)
	Phthalates	Induction of P-gp expression by DEHP (10 $\mu$ M/24-72 h) and MEHP (10 $\mu$ M/24-72 h) in cancer colon cell lines.	(Chen et al., 2018)
		Induction of P-gp expression by DEHP (6 and 12 $\mu$ M/24 h) in sarcoma cells.	(Angelini et al., 2011)
		Induction of <i>MDR1</i> mRNA expression by DEHP (1-10 $\mu$ 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).	(Jadhaio et al., 2021)
Alkylphenols	No apparent induction of P-gp expression in human intestinal Caco-2 cells exposed to NPE (up to 1 $\mu$ M/72 h).	(Doo et al., 2005)	
BSEP	PFASs	Repression of BSEP mRNA expression by PFOA (250 and 500 $\mu$ M/24 h) and PFOS (25-100 $\mu$ M/24 h) in human hepatic HepaRG cells.	(Behr et al., 2020)
MRP1	Bisphenols	Induction of MRP1 mRNA expression by BPA (80 $\mu$ M/24 h) in HepG2 cells.	(Hanet et al., 2008)
MRP2	Bisphenols	Induction of MRP2 mRNA and protein expression by BPA (80 $\mu$ M/24 h) in HepG2 cells.	(Hanet et al., 2008)
	PFASs	Repression of MRP2 mRNA expression by PFOA (250 and 500 $\mu$ M/24 h) and PFOS (25 $\mu$ M/24 h) in HepaRG cells.	(Behr et al., 2020)
MRP3	Bisphenols	Induction of MRP3 mRNA and protein expression by BPA (80 $\mu$ M/24 h) in HepG2 cells.	(Hanet et al., 2008)
	PFASs	Induction of MRP3 mRNA expression by PFNA (45 $\mu$ M/24 h) and PFDA (45 $\mu$ M/24 h), but repression by PFOA (500 $\mu$ M/24 h) and PFOS (100 $\mu$ M/24 h) in HepaRG cells.	(Behr et al., 2020; Lim et al., 2021)
MRP4	Bisphenols	Lack of effects of BPA (80 $\mu$ 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 $\mu$ M/24 h) and PFDA (45 $\mu$ M/24 h) in HepaRG cells.	(Lim et al., 2021)
OATP1B1	PFASs	Repression of OATP1B1 mRNA expression by PFOA (250 and 500 $\mu$ M/24 h) and PFOS (100 $\mu$ M/24 h) in HepaRG cells.	(Behr et al., 2020)
OATP2B1	PFASs	Repression of OATP2B1 mRNA expression by PFDA (45 $\mu$ M/24 h) in HepaRG cells.	(Lim et al., 2021)
MATE2-K	PFASs	Induction of MATE2-K mRNA expression by PFDA (45 $\mu$ M/24 h) in HepaRG cells.	(Lim et al., 2021)
NTCP	PFASs	Repression of NTCP mRNA expression by PFDA (45 $\mu$ M/24 h), PFOA (10-500 $\mu$ M/24 h) and PFOS (10-100 $\mu$ M/24 h) in HepaRG cells.	(Behr et al., 2020; Lim et al., 2021)
OST $\beta$	PFAS	Induction of OST $\beta$ mRNA expression by PFOA (50-250 $\mu$ M/24 h) and PFOS (25-100 $\mu$ 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.





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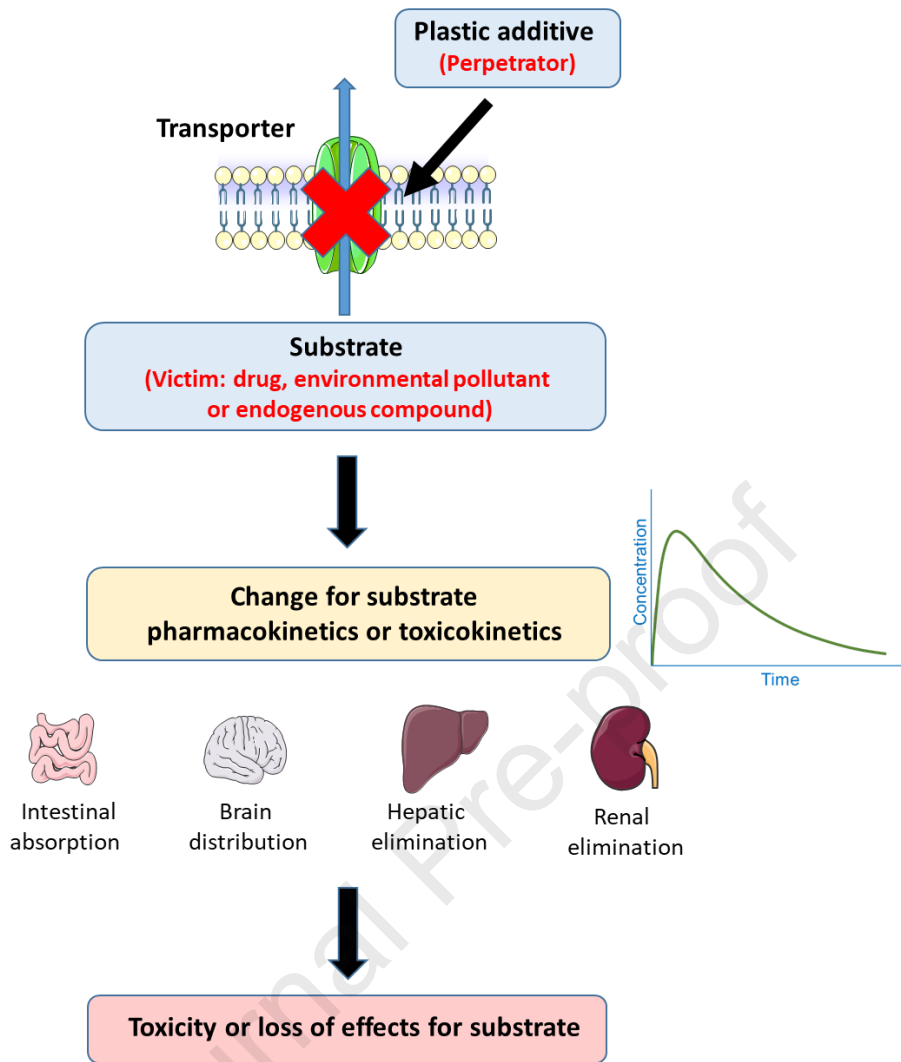
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991 Fig. 1. Schematic representation of human drug transporter expression. Red and green arrows

992 correspond to ATP-binding cassette (ABC) and solute carrier (SLC) transporters, respectively.

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997 Fig. 2. Schematic representation of the possible deleterious consequences of drug transporter

998 inhibition by a plastic additive, considered here as a perpetrator.

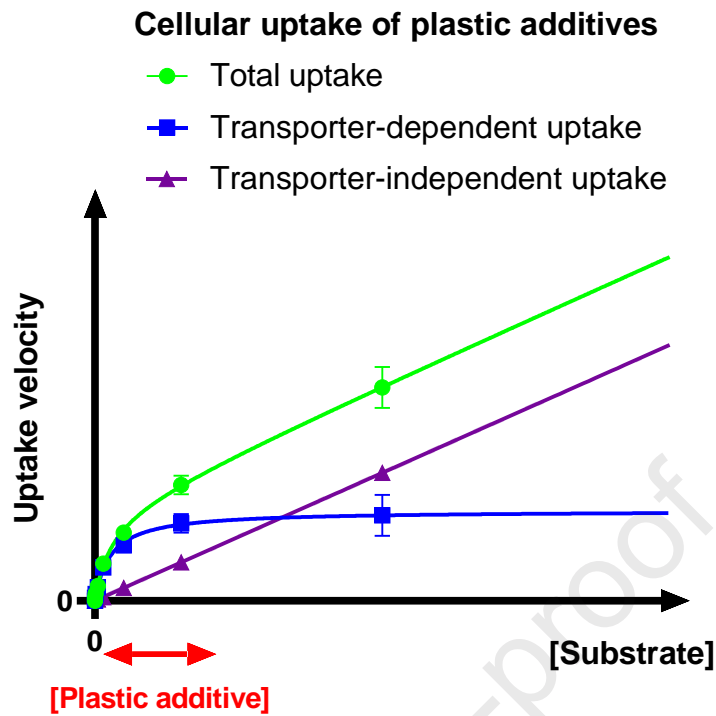
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1006 Fig. 3. Relative contribution of SLC transporter-mediated uptake and transporter-unrelated  
1007 passive diffusion across the plasma membrane for plastic additives. At low plastic additive  
1008 concentrations (usually the case for these pollutants in response to environmental or dietary  
1009 exposure), the relative contribution of transporter-mediated uptake velocity to total uptake  
1010 velocity is maximal.

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### **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

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**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

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**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:

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