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## Interactions of organophosphate flame retardants with human drug transporters

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### ABSTRACT

Organophosphate flame retardants (OPFRs) are environmental pollutants of increasing interest, widely distributed in the environment and exerting possible deleterious effects towards the human health. The present study investigates *in vitro* their possible interactions with human drug transporters, which are targets for environmental chemicals and actors of their toxicokinetics. Some OPFRs, *i.e.*, tris(2-butoxyethyl) phosphate (TBOEP), tris(1,3-dichloroisopropyl) phosphate (TDCPP), tri-*o*-cresyl phosphate (TOCP) and triphenyl phosphate (TPHP), were found to inhibit activities of some transporters, such as organic anion transporter 3 (OAT3), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter 2 (OCT2) or breast cancer resistance protein (BCRP). These effects were concentration-dependent, with IC<sub>50</sub> values ranging from 6.1 μM (for TDCPP-mediated inhibition of OCT2) to 51.4 μM (for TOCP-mediated inhibition of BCRP). OPFRs also blocked the transporter-dependent membrane passage of endogenous substrates, notably that of hormones. OAT3 however failed to transport TBOEP and TPHP. OPFRs additionally repressed mRNA expressions of some transporters in cultured human hepatic HepaRG cells, especially those of OAT2 and OCT1 in response to TOCP, with IC<sub>50</sub> values of 2.3 μM and 2.5 μM, respectively. These data therefore add OPFRs to the expanding list of pollutants interacting with drug transporters, even if OPFR concentrations required to impact transporters, in the 2–50 μM range, are rather higher than those observed in humans environmentally or dietarily exposed to these chemicals.

### 1. Introduction

Flame retardants (FRs) constitute a diverse group of functional chemicals used in many materials in order to meet fire safety regulations and standards (Green, 1996). They decrease flammability and hinder the starting or spreading of fires when added to combustible materials, by creating a flame shielding layer of char on the product (Camino et al., 1991). They are therefore widely used in various industries, notably as additives in plastics, furniture, textiles, printed circuit boards and building products like insulation material. FRs segregate into two main classes: the halogenated FRs, such as the polybrominated diphenyl ethers (PBDEs), and the organophosphate FRs (OPFRs) (Gill et al., 2020). The OPFRs comprise three main categories of chemicals: (i) halogenated alkyl phosphate esters, (ii) alkyl phosphate esters and (iii) aryl phosphate esters (van der Veen and de Boer, 2012). Due to their persistence in the environment and their toxicity towards humans and animals, halogenated FRs are now either banned or highly restricted.

The OPFRs are increasingly considered as alternatives to halogenated FR, even if this assertion is challenged (Blum et al., 2019). Indeed, OPFRs are thought to be less toxic and more suitable for use because of their moderate accumulation potential in the environment. Nevertheless, there is now evidence that OPFRs can be widely released into the environment, notably through leaching and volatilization (Marklund et al., 2005; Salthammer et al., 2003; Wei et al., 2015). They are therefore detected in various media (Yao et al., 2021), including water (Fernández-Arribas et al., 2023; Huang et al., 2023), dust (Cao et al., 2019), air (Li et al., 2022) and sediment (Liao et al., 2020). Humans can consequently be exposed to these emerging pollutants (Hou et al., 2021; Saillenfait et al., 2018), notably *via* inhalation or ingestion of household dusts or by dermal absorption *via* contact with furniture fabrics (Abou-Elwafa Abdallah and Harrad, 2022; Chen et al., 2020; Chupeau et al., 2020). In particular, fire fighters may represent a specific highly-exposed population (Gill et al., 2020). Although rapidly metabolized in the human body and initially considered to be rather safe,

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OPFRs are now suspected to cause toxic effects for humans, including carcinogenic effects, endocrine disruption and neurotoxicity (Dou and Wang, 2023; Hales and Robaire, 2020; Patisaul et al., 2021; Wei et al., 2015; J.-Y. Zhao et al., 2022). In particular, OPFRs may favor the development of thyroid, renal or cervical cancers (Liu et al., 2022; Y. Liu et al., 2021; Zhou et al., 2022) and the progression of colorectal, bladder and hepatic cancers (Hong et al., 2022; Ye et al., 2022; Yu et al., 2022). The neurotoxicity of these chemicals is supported by *in vitro*, *in vivo* and epidemiological studies (Choi et al., 2021; Esplugas et al., 2023; W. Liu et al., 2021; Newell et al., 2023; Y. Zhao et al., 2022). In addition, endocrine disrupting effects of OPFRs are documented in cultured cells, animals and humans (Chen et al., 2015; Liu et al., 2023; Rosenmai et al., 2021; Xiaotong Wang et al., 2023; Xu et al., 2017). Exposure to OPFRs is notably associated with type 2 diabetes (G. Zhang et al., 2023), thyroid dysfunction (Yan et al., 2022) and altered levels of reproductive hormones (Siddique et al., 2022).

Drug transporters are plasma membrane proteins that consist of ATP-binding cassette (ABC) transporters, which behave as drug efflux pumps, and solute carriers (SLCs), which mediate a facilitated diffusion or a secondary active transport (Giacomini et al., 2010). SLCs are usually implicated in drug entry into cells, with the exception of multidrug and toxin extrusion proteins (MATEs/*SLC47A*), which are involved in drug secretion at the apical pole of hepatocytes and human proximal tubular cells, like ABC transporters (Liu, 2019; Nies et al., 2011; Roth et al., 2012). ABC transporters additionally contribute to blood-tissue barriers and to intestinal efflux of xenobiotics, thereby restricting brain passage or intestinal absorption of drugs (Petzinger and Geyer, 2006). Besides drugs, various environmental chemicals interact with transporters (Clerbaux et al., 2018; Nicklisch and Hamdoun, 2020; Tastet et al., 2023). Thus, pesticides, as well as the FR tetrabromobisphenol A and carcinogenic heterocyclic aromatic amines, can inhibit the activity of various drug transporters (Bain and LeBlanc, 1996; Bruyere et al., 2017; Guéniche et al., 2020a; Nie et al., 2023; Sayyed et al., 2019), whereas perfluoroalkyl substances as well as PBDEs can be either inhibitors or substrates for drug transporters (Pacyniak et al., 2010; Zhao et al., 2017). Pollutants can additionally regulate transporter expression, as demonstrated by the repression of the ABC pump P-glycoprotein (P-gp), encoded by the multidrug resistance gene 1 (*MDR1/ABCB1*), at the blood-brain barrier level by the brominated FR 2,4,6-tribromophenol (Trexler et al., 2019). Such transporter-pollutant interactions may therefore contribute to pollutant toxicokinetics and/or toxicity or may cause pollutant-drug interactions (Fardel et al., 2012). Thus, it is important to identify and investigate these transporter-pollutant interactions (Clerbaux et al., 2019; Darney et al., 2020). In this context, putative interactions of OPFRs with transporters remain very poorly characterized (Hou et al., 2022). The present study aims at investigating *in vitro* putative interactions of seven common prototypical OPFRs with the activity and expression of main human ABC and SLC drug transporters involved in pharmacokinetics. Our data demonstrate that some of these OPFRs can regulate activity and/or expression of transporters, thus supporting the conclusion that human drug transporters may be targeted by these environmental pollutants.

## 2. Materials and methods

### 2.1. Chemicals

Seven OPFRs, *i.e.*, the chlorinated alkyl phosphates tris(1,3-dichloroisopropyl) phosphate (TDCPP, also known as TDCIPP), tris(2-chloroethyl) phosphate (TCEP) and tris(1-chloro-2-propyl) phosphate (TCPP, also known as tris(2-chloroisopropyl)phosphate/TCIPP), the alkyl phosphates tri-*n*-butyl phosphate (TNBP) and tris(2-butoxyethyl) phosphate (TBOEP, also known as TBEP) and the aryl phosphates tri-phenyl phosphate (TPHP) and tri-*o*-cresyl phosphate (TOCP), were provided by Sigma-Aldrich (Saint-Quentin-Fallavier, France). The chemical structures of these prototypical OPFRs, to which humans are

exposed (Chupeau et al., 2020), are shown in Fig. S1. The suppliers of other used chemicals are indicated in Table S1. Stock solutions of chemicals were usually prepared in dimethyl sulfoxide, except those of probenecid and rhodamine 123, prepared in NaOH and ethanol, respectively. Concentrations of solvents in transport assay medium or culture medium were lower or equal to 0.2% (vol/vol); control cells received the same dose of solvent.

### 2.2. Cell culture

P-gp-positive MCF7R cells (Jouan et al., 2016b), hepatoma HuH-7 cells, expressing human multidrug resistance-associated protein (MRP) 2/*ABCC2* and MRP4/*ABCC4* (Jouan et al., 2016a) and human breast cancer resistance protein (BCRP/*ABCG2*)-transfected HEK-293 cells (HEK-BCRP cells) were cultured as already reported (Chedik et al., 2017). Human HEK-293 cells expressing human SLC transporters, *i.e.*, organic cation transporter (OCT) 1 (*SLC22A1*) (HEK-OCT1 cells), OCT2 (*SLC22A2*) (HEK-OCT2 cells), MATE1 (*SLC47A1*) (HEK-MATE1 cells), MATE2-K (*SLC47A2*) (HEK-MATE2-K cells), organic anion transporter (OAT) 1 (*SLC22A6*) (HEK-OAT1 cells), OAT3 (*SLC22A8*) (HEK-OAT3 cells), organic anion transporting polypeptide (OATP) 1B1 (*SLCO1B1*) (HEK-OATP1B1 cells) or OATP1B3 (*SLCO1B3*) (HEK-OATP1B3 cells), as well as control HEK-MOCK cells, human hepatoma HepaRG cells and fresh or cryopreserved primary human hepatocytes were maintained in culture as previously described (Chedik et al., 2017; Le Vee et al., 2015, 2013; Sayyed et al., 2019).

### 2.3. Drug transporter assays

OPFR effects on the activity of ABC and SLC transporters were investigated through the measurement of cellular uptake or retention of reference substrates for transporters, in the presence or absence of reference inhibitors (Chedik et al., 2017; Guéniche et al., 2020b; Sayyed et al., 2019). The nature of reference substrates and inhibitors as well as the times of incubation, the used cell lines/clones and the analytical methods for measuring cellular levels of reference substrates have been characterized and validated (Bruyère et al., 2021; Guéniche et al., 2020b; Jouan et al., 2016b, 2016a); they are summarized in Table S2.

Data were expressed as percentages of substrate accumulation in control cells not exposed to reference inhibitors or OPFRs, arbitrarily set at 100%, or as transporter activity percentages, as described in the following equations (Guéniche et al., 2020b):

For SLC transporters:

$$\text{Transporter activity (\%)} = \frac{([\text{Substrate}_{\text{OPFR}}] - [\text{Substrate}_{\text{Reference inhibitor}}]) \times 100}{[\text{Substrate}_{\text{Control}} - \text{Substrate}_{\text{Reference inhibitor}}]} \quad (\text{A})$$

For ABC transporters:

$$\text{Transporter activity (\%)} = \frac{([\text{Substrate}_{\text{OPFR}}] - [\text{Substrate}_{\text{Control}}]) \times 100}{[\text{Substrate}_{\text{Reference inhibitor}} - \text{Substrate}_{\text{Control}}]} \quad (\text{B})$$

with  $[\text{Substrate}_{\text{OPFR}}]$  = cellular concentration of the reference substrate incubated with one OPFR,  $[\text{Substrate}_{\text{Reference inhibitor}}]$  = cellular concentration of the reference substrate incubated with the reference inhibitor and  $[\text{Substrate}_{\text{Control}}]$  = cellular concentration of the reference substrate in control cells not incubated with OPFRs or the reference inhibitor.

The percentage of inhibition of transporter activity by OPFRs was finally determined as following:

$$\text{Transporter activity inhibition (\%)} = 100\% - \text{transporter activity (\%)} \quad (\text{C})$$

with transporter activity (%) determined as described in Eq. (A) (for SLC transporters) or Eq. (B) (for ABC transporters).

## 2.4. OPFR accumulation assays

HEK-MOCK and HEK-OAT3 cells were incubated for 5 min at 37 °C with 100 μM TBOEP, 100 μM TPHP or the reference OAT3 substrate 6-carboxyfluorescein (6-CF) in the assay medium previously described (Guéniche et al., 2020b), in the absence (control) or presence of 2 mM probenecid used as a reference OAT3 inhibitor. At the end of the incubation period with OPFRs, cells were washed twice with ice-cold phosphate-buffered saline (PBS) and lysed in distilled water. Cellular proteins were next precipitated using 50% (vol/vol) acetonitrile. After centrifugation, supernatants were collected for OPFR measurements using a liquid chromatography-tandem mass spectroscopy (LC-MS/MS) system (Guéniche et al., 2020b). For TBOEP and TPHP, monitored ion transitions were at 399.3 > 199.1 *m/z* and at 327.2 > 215.1 *m/z*, respectively. Cellular accumulation of 6-CF was investigated by spectrofluorimetry, as indicated in Table S2. Cellular accumulations of substrates were finally normalized to protein content.

## 2.5. Cell viability assay

Cellular viability was investigated with the colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Carmichael et al., 1987). Data were expressed as cell viability percentages comparatively to control untreated cells.

## 2.6. RNA isolation and analysis

Total RNAs were prepared from cultured HepaRG cells or human hepatocytes either untreated or exposed to OPFRs, using the TRIzol reagent (Invitrogen/Thermo Fisher Scientific, Waltham, MA, USA) protocol. Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) assays were next performed as already reported (Le Vee et al., 2013). The sequences of gene primers are indicated in Table S3. Relative quantification of the steady-state target mRNA levels was performed after normalization to the 18 S rRNA endogenous reference, through the  $2^{(-\Delta\Delta Ct)}$  method, knowing that the amount of 18 S rRNA was arbitrarily set to 10<sup>6</sup> arbitrary units. Data were commonly expressed as percentages of drug transporter mRNA levels detected in control OPFR-untreated cells.

The percentage of inhibition of transporter mRNA expression by OPFR was determined as following:

$$\text{Transporter expression inhibition (\%)} = 100\% - \text{transporter expression (\%)(D)}$$

## 2.7. Prediction of *in vivo* modulation of transporter activity or expression by OPFRs

The *in vivo* inhibition of transport activities by OPFRs was predicted from *in vitro* generated data using the criteria defined by the International Transporter Consortium (ITC) (Giacomini et al., 2010). Briefly, drug transporters present in the liver, kidney or blood-tissue barriers, can be inhibited *in vivo* by plasma concentrations of xenobiotics if the ratio half maximal inhibitory concentration (IC<sub>50</sub>) towards activity/-maximum unbound plasma concentration of chemicals (I<sub>max,u</sub>) ≥ 0.1. Because data about human pharmacokinetics of OPFRs are rather scarce, I<sub>max,u</sub> values for OPFRs were approximately and by default estimated to correspond to the product of human maximal blood OPFR measurements reported in the literature (Wang et al., 2021; Zhao et al., 2016) and the unbound plasma fractions of OPFRs, predicted *in silico* using the online tool Admetlab2.0 (<https://admetmesh.scbdd.com/>) (Xiong et al., 2021). With respect to the P-gp and BCRP expressed at the brush-border membrane of enterocytes, it can be predicted that they are inhibited *in vivo* by luminal gut concentrations of xenobiotics if the ratio IC<sub>50</sub>/luminal gut concentration (I<sub>gut</sub>) ≥ 10 (I<sub>gut</sub> being defined by the ratio

“orally ingested dose/250 mL”) (Giacomini et al., 2010). To define the orally ingested dose of OPFR, we considered the estimated daily intake *via* dust ingestion in highly exposed subjects, *i.e.*, a value of 4.99 ng/kg for TOCP (Hoang et al., 2023). This value was normalized to a subject weighing 70 kg, corresponding to a standardized body weight in pharmacokinetic studies (Anderson et al., 2000), and arbitrarily considered to be ingested all at once. This resulted in the oral dose of 349.3 ng (0.95 nmole) for TOCP, with which TOCP I<sub>gut</sub> value was calculated, as described above.

*In vivo* predictions of hepatic transporter expression regulations by OPFRs were performed according to the correlation approach developed for drug metabolizing enzyme inductions (Fahmi and Ripp, 2010), whose criteria were extended to transporter expression repression. The ratio I<sub>max,u</sub> versus IC<sub>50</sub> towards transporter mRNA expression was calculated and considered for the prediction: ratio ≤ 0.001, 0.001 < ratio ≤ 0.01 and ratio > 0.01 would predict an OPFR to be a weak, moderate and strong transporter repressor, respectively (Fahmi and Ripp, 2010).

## 2.8. Data analysis

Data are expressed as means ± SD of at least three independent assays, which is common for *in vitro* transporter studies with cultured cells (Guéniche et al., 2020b; Louise et al., 2023; Nicklisch et al., 2016); each independent assay was moreover usually performed in triplicate (for transporter activity assays) or in duplicate (for RT-qPCR assays). The analysis of variance (ANOVA) and Dunnett's or Tukey's post-hoc tests were performed with the Prism 8.3 software (GraphPad, San Diego, CA, USA). The significance criterion was p < 0.05.

The IC<sub>50</sub> values of OPFRs towards transporter activity or expression were calculated from nonlinear regression of concentration-response data, as previously described (Guéniche et al., 2020b).

## 3. Results

### 3.1. Effects of OPFRs on the activity of drug transporters

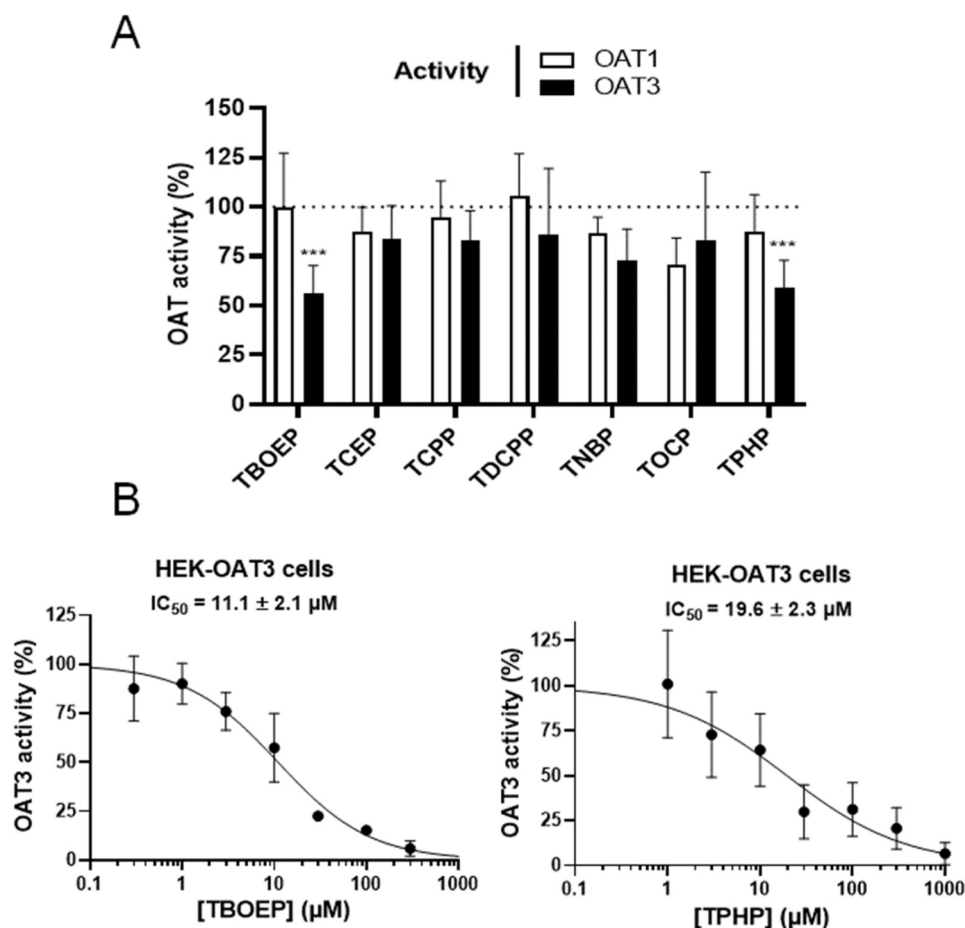
The concentration of OPFRs initially tested towards transporter activities was 10 μM, in the range of those commonly used in *in vitro* OPFR studies (Li et al., 2014, 2020; Yuan et al., 2020; Z.-N. Zhang et al., 2023).

With respect to SLC handling organic anions, none of the seven OPFRs used at 10 μM altered the OAT1 activity; on the other hand, the OAT3 activity was significantly decreased by TBOEP and TPHP, by 44.0% and 41.1%, respectively (Fig. 1A). These two OPFRs were next found to block OAT3-mediated transport of 6-CF in a concentration-dependent manner, with IC<sub>50</sub> values of 11.1 ± 2.1 and 19.6 ± 2.3 μM, for TBOEP and TPHP, respectively (Fig. 1B). Regarding other transporters of organic anions such as OATPs, 10 μM TPHP inhibited OATP1B1 activity (by 40.5%) and 10 μM TBOEP that of OATP1B3 (by 29.9%); furthermore, 10 μM TDCPP decreased both OATP1B1 and OATP1B3 activities by 45.1% and 46.8%, respectively (Fig. 2A). Analysis of the concentration-dependent effects of these OPFRs towards OATP activities indicated that TDCPP was a more potent OATP1B1 inhibitor (IC<sub>50</sub> = 23.4 ± 1.9 μM) than TPHP (IC<sub>50</sub> = 44.1 ± 2.4 μM) (Fig. 2B). In the same way, TDCPP was a stronger inhibitor of OATP1B3 activity (IC<sub>50</sub> = 8.3 ± 1.8 μM) compared to TBOEP (IC<sub>50</sub> = 43.2 ± 2.6 μM) (Fig. 2B).

Concerning the organic cations-transporting SLCs, none of the OPFRs used at 10 μM impaired MATE1 or MATE2-K activities (Fig. 3A) or that of OCT1 (Fig. 3B), whereas OCT2 activity was found to be reduced only by 10 μM TDCPP (inhibition by 47.0%) (Fig. 3B). This inhibitory effect of TDCPP towards OCT2-mediated transport of 4-(4-(dimethylamino)styryl)-N-methylpyridinium iodide (4-Di-ASP) was concentration-dependent (IC<sub>50</sub> = 6.1 ± 1.8 μM) (Fig. 3C).

For ABC transporters, none of the OPFRs used at 10 μM were found to inhibit activities of P-gp or MRPs (Fig. 4A). TOCP was the only OPFR





**Fig. 1.** OPFR effects towards activities of OATs. (A) The effects of OPFRs (each used at 10 μM) on OAT1- and OAT3-mediated transport of the fluorescent dye 6-CF in HEK-OAT1 and HEK-OAT3 cells. Data are expressed as percentages of OAT1 and OAT3 activities found in control untreated cells, set at 100% and visualized by the dashed line on the graph. Data correspond to means ± SD of independent experiments (n = 4 for OAT1; n = 4–7 for OAT3). \*\*\*, p < 0.001 comparatively to OAT activities in control cells. (B) The effects of various concentrations of TBOEP and TPHP on OAT3 activity. Data are expressed as percentages of OAT3 activity found in control untreated cells and correspond to means ± SD of independent experiments (n = 4). The IC<sub>50</sub> values for OPFRs are shown at the top of the graphs.

which significantly reduced BCRP activity (inhibition by 25.6% for 10 μM TOCP) (Fig. 4A), with an IC<sub>50</sub> value of 51.4 ± 2.0 μM (Fig. 4B).

### 3.2. Effects of OPFRs on membrane transport of endogenous compounds

We next investigated whether the inhibition of transporters by OPFRs may have functional consequences for membrane transport of endogenous compounds handled by the targeted transporters. As shown in Fig. 5, OAT3-mediated transport of estrone-3-sulfate (E3S) was markedly blocked by TBOEP and TPHP in a concentration-dependent manner; in particular, the concentration of 3 μM significantly reduced the OAT3-mediated uptake of E3S by more than 20.0%. With respect to endogenous substrates of OATPs, the OATP1B3-mediated transport of cholecystinin octapeptide (CCK-8) was reduced by TDCPP in a concentration-dependent manner (Fig. 5); treatment by 1 μM TDCPP was sufficient to significantly reduce CCK-8 uptake by 15.7%, whereas the higher concentration of 30 μM diminished it by 70.9% (Fig. 5). By contrast, a 100 μM concentration of TDCPP was required to inhibit significantly the OATP1B1-mediated transport of E3S by 31.6% (Fig. 5). Furthermore, TCDPP also decreased the OCT2-mediated accumulation of dopamine in HEK-OCT2 cells in a concentration-dependent manner (Fig. 5).

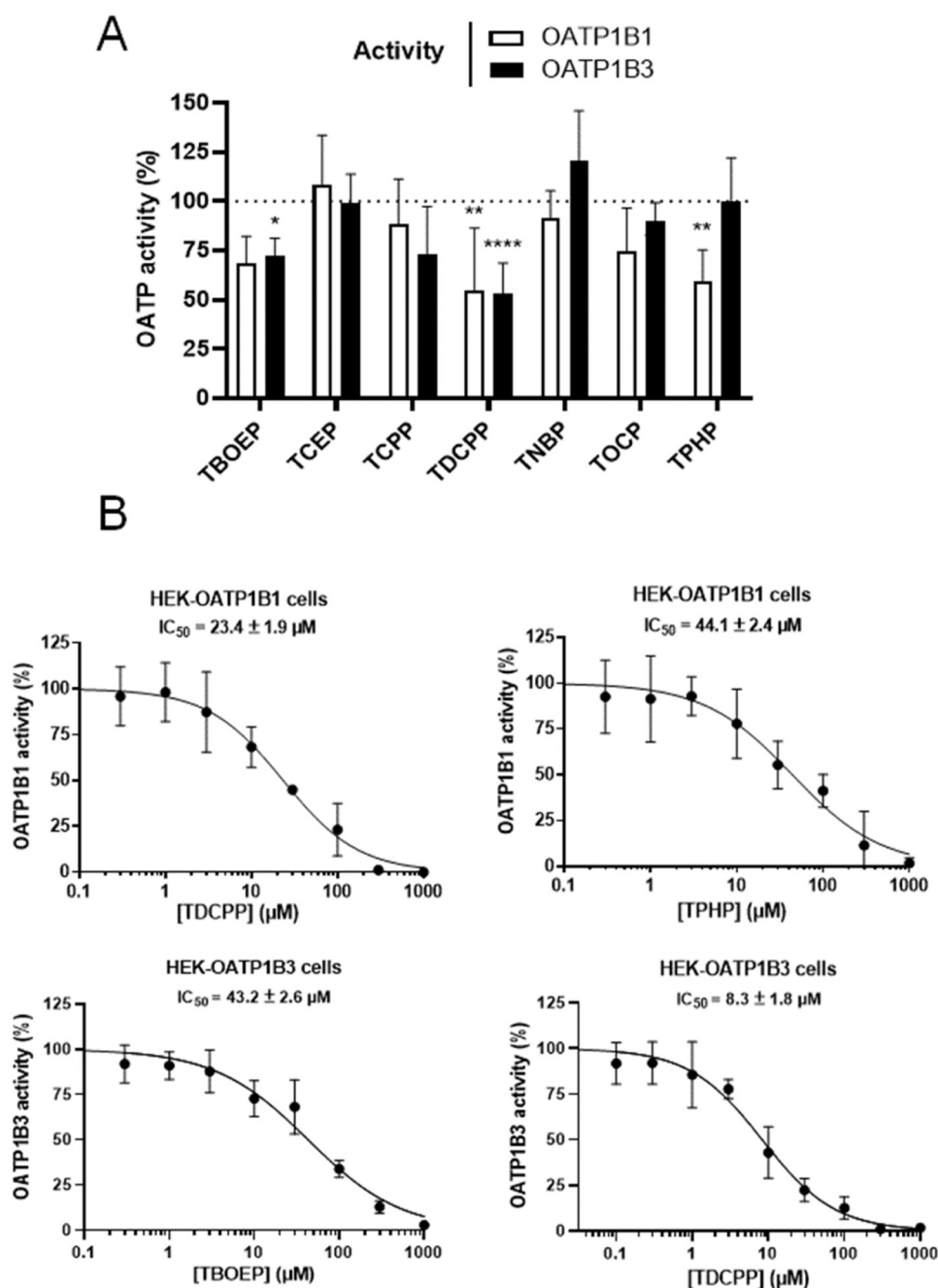
### 3.3. Transport of OPFRs by SLCs

To determine whether OPFRs may be substrates for transporters, we have studied the cellular uptake of TBOEP and TPHP in HEK-OAT3 cells and HEK-MOCK cells, in the presence or absence of the reference OAT3 inhibitor probenecid. This experimental approach, based on the use of control and transporter-overexpressing cell clones associated with that

of reference transporter inhibitors, is widely applied for identifying substrates of SLC transporters (Brouwer et al., 2013). TBOEP and TPHP were analyzed in these transport assays because (i) they interacted with OAT3 in a rather marked manner (IC<sub>50</sub> values < 20 μM) (Fig. 1B) and (ii) their cellular accumulation could be detected with a rather notable sensitivity by our LC-MS/MS system, in contrast to other OPFRs, notably TDCPP (Tastet et al., unpublished results). As indicated in Fig. S2, HEK-OAT3 cells and HEK-MOCK cells similarly accumulated these two OPFRs, without any inhibitory effect of the reference OAT3 inhibitor probenecid. This likely discards any contribution of OAT3 activity to cellular accumulation of the two OPFRs. By contrast, the OAT3 substrate 6-CF exhibited high uptake in HEK-OAT3 cells comparatively to HEK-MOCK cells; in addition, probenecid was able to strongly prevent this uptake of 6-CF in HEK-OAT3 cells (Fig. S2). Such data indicate that OAT3 was fully functional in these accumulation assays.

### 3.4. Regulation of drug transporter mRNA expression by OPFRs

To study the effects of OPFRs towards drug transporter expression, we used mainly human differentiated hepatoma HepaRG cells, which exhibit notable expression of main hepatic drug transporters (Le Vee et al., 2013), including sinusoidal transporters such as OATPs, OAT2 (SLC22A7) and OCT1, and canalicular transporters such as P-gp, MRP2 and BCRP. HepaRG cells are considered as a suitable alternative to human hepatocytes for drug detoxifying protein studies (Andersson et al., 2012; Tátrai et al., 2022). In the current study, HepaRG cells were treated by 10 μM OPFRs for 48 h before analysis of transporter mRNA levels. Such treatments were not found to cause cellular toxicity, as revealed by MTT assays (Fig. S3) and phase-contrast microscopic examination of cells (data not shown).



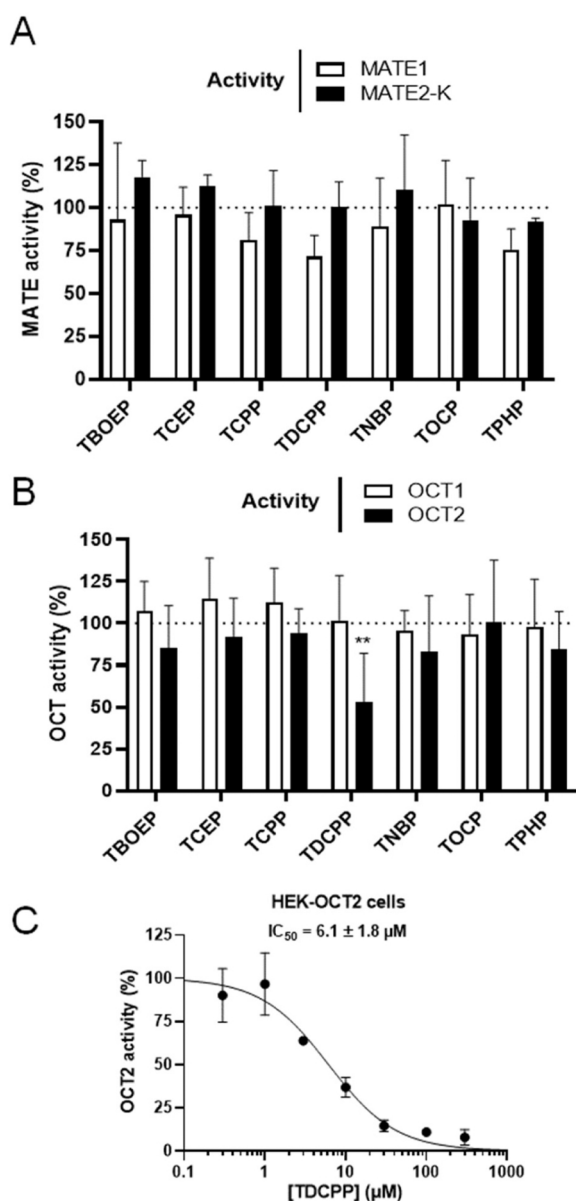
**Fig. 2.** OPFR effects towards activities of OATPs. (A) The effects of OPFRs (each used at 10 μM) on OATP1B1- and OATP1B3-mediated transport of the fluorescent dyes 2',7'-dichloro-fluorescein (DCF) and 8- (2- [fluoresceinyl] aminoethylthio) adenosine- 3', 5'- cyclic monophosphate (8-FcA), respectively, in HEK-OATP1B1 and HEK-OATP1B3 cells. Data are expressed as percentages of OATP1B1 and OATP1B3 activities found in control untreated cells, set at 100% and visualized by the dashed line on the graph. Data correspond to means ± SD of independent experiments (n = 5–6 for OATP1B1; n = 4–7 for OATP1B3). \*, p < 0.05, \*\*, p < 0.01 and \*\*\*\*, p < 0.0001 comparatively to OATP activities in control cells. (B) The effects of various concentrations of TBOEP, TDCPP and TPHP towards OATP activities. Data are expressed as percentages of OATP activities found in control untreated cells and correspond to means ± SD of independent experiments (n = 3–6). The IC<sub>50</sub> values for OPFRs are shown at the top of the graphs.

Treatment of HepaRG cells by OPFRs failed to alter mRNA expression of OATP1B3, P-gp/*MDR1*, MRP2, MRP3 or BCRP (Fig. 6A and Fig. S4). The mRNA levels of OATP1B1 and OATP2B1 (*SLCO2B1*) were repressed only by 10 μM TOCP, with inhibition percentages of 47.8% (for OATP1B1) or 62.5% (for OATP2B1). OAT2 and OCT1 mRNA levels decreased in response to five OPFRs, each used at 10 μM, *i.e.*, TCPP, TDCPP, TNBP, TOCP and TPHP (Fig. 6A). TOCP exerted the greater inhibitory effect towards OAT2 and OCT1 mRNA expression, *i.e.*, inhibition by 83.8% and 77.0%, whereas the range of OAT2 or OCT1 repression by TCPP, TDCPP, TNBP and TPHP was approximately 40–60%. TOCP effects towards OATP1B1, OATP2B1, OAT2 and OCT1 mRNA expression in HepaRG cells were concentration-dependent (Fig. 6B); IC<sub>50</sub> values were lower for repressions of OAT2 mRNAs (IC<sub>50</sub> = 2.3 ± 1.9 μM) and OCT1 mRNAs (IC<sub>50</sub> = 2.5 ± 1.8 μM) than for those of OATP2B1 mRNAs (IC<sub>50</sub> = 5.6 ± 1.9 μM) or OATP1B1 mRNAs (IC<sub>50</sub> = 12.1 ± 1.9 μM). In addition, TOCP used at 10 μM was found to

significantly repress OAT2 and OCT1 expression in cultured human hepatocytes (Fig. S5). By contrast, it failed to reduce OATP1B1 and OATP2B1 mRNA levels in hepatocytes (Fig. S5), suggesting that a TOCP concentration higher than 10 μM may be required to repress OATP1B1 and OATP2B1 mRNA expression in human hepatocytes.

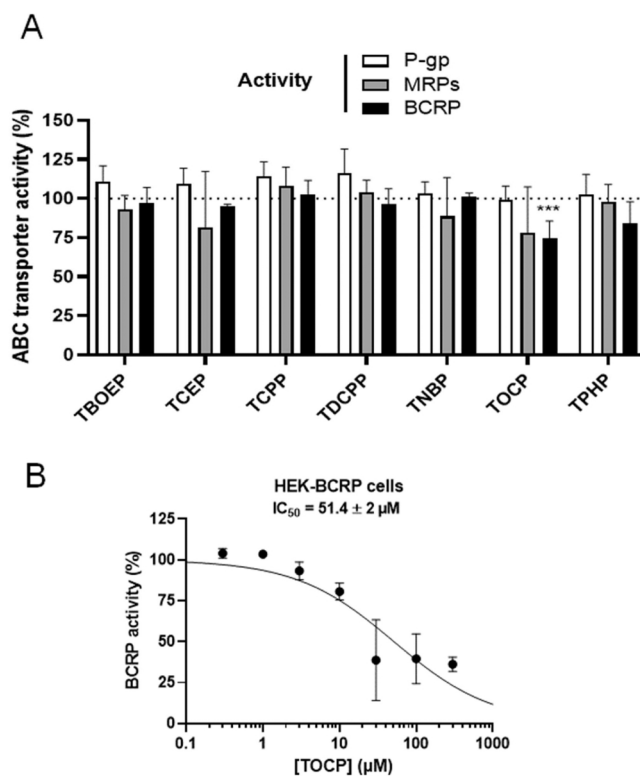
### 3.5. Prediction of *in vivo* modulation of drug transporter activity or expression by OPFRs

*In vivo* inhibition of transporter activities by blood concentrations of OPFRs was predicted from the *in vitro* data described above, using (i) the criteria defined by the ITC (Giacomini et al., 2010) and (ii) the reported blood levels and predicted unbound plasma fraction of OPFRs in humans. As shown in Table 1, none of transporters whose *in vitro* activity is inhibited by OPFRs, *i.e.*, OATP1B1, OATP1B3, OAT3, OCT2 and BCRP, were predicted to be inhibited *in vivo* by human plasma concentrations



**Fig. 3.** OPFR effects towards MATE and OCT activities. (A, B) The effects of OPFRs (each used at 10  $\mu M$ ) on (A) MATE1- and MATE2-K mediated transport of tetraethylammonium (TEA) in HEK-MATE1 and HEK-MATE2-K cells and (B) OCT1- and OCT2-mediated transport of the fluorescent dye 4-Di-ASP in HEK-OCT1 and HEK-OCT2 cells. Data are expressed as percentages of MATE or OCT activities found in control untreated cells, set at 100% and visualized by the dashed lines on the graphs. Data correspond to means  $\pm$  SD of independent experiments ( $n = 3$  for MATE2-K;  $n = 4$  for MATE1 and OCT1;  $n = 4-7$  for OCT2). \*\*,  $p < 0.01$  comparatively to MATE or OCT activities in control cells. (C) The effects of various concentrations of TDCPP towards OCT2 activity. Data are expressed as percentages of OCT2 activity found in control untreated cells and correspond to means  $\pm$  SD of independent experiments ( $n = 3$ ). The TDCPP  $IC_{50}$  value is shown at the top of the graph.

of OPFRs expected in response to environmental exposure. In the same way, intestinal BCRP was not predicted to be blocked by estimated luminal gut concentration of TOCP in humans, according to the ITC criteria (Table S4). Finally, we found that TOCP was predicted to only weakly repress expression of hepatic drug transporters *in vivo*, when applying the criteria developed for drug metabolizing enzyme induction (Fahmi and Ripp, 2010) to transporter repression (Table S5).



**Fig. 4.** OPFR effects towards ABC pump activities. (A) The effects of OPFRs (each used at 10  $\mu M$ ) towards efflux of the P-gp substrate rhodamine 123 from MCF7R cells, of the MRP substrate carboxy-2',7'-dichlorofluorescein (CDFC) from HuH-7 cells and of the BCRP substrate Hoechst 33342 from HEK-BCRP cells. Data are expressed as percentages of ABC transporter activities found in control untreated cells, set at 100% and visualized by the dashed line on the graph. Data correspond to means  $\pm$  SD of independent experiments ( $n = 4$  for P-gp and MRPs;  $n = 3-6$  for BCRP). \*\*\*,  $p < 0.001$  comparatively to transport activities in control cells. (B) The effects of various concentrations of TOCP towards BCRP activity. Data are expressed as percentages of BCRP activity found in control untreated cells and correspond to means  $\pm$  SD of independent experiments ( $n = 3$ ). The  $IC_{50}$  value for TOCP is shown at the top of the graph.

#### 4. Discussion

OPFRs are used as substitutive FRs to brominated FRs. In consequence, they are ubiquitously distributed in the environment and humans are highly exposed to these environmental chemicals, which highlights the need for predictions of their concentrations in human tissues (Xiaolei Wang et al., 2023). Although initially considered as safe for human health, recent data indicate that OPFRs may cause some toxicity and can interact with human cellular and molecular regulatory pathways (Patisaul et al., 2021; Yuan et al., 2020). The data shown in the present study support this conclusion, by reporting that human drug transporters may be targeted by some OPFRs, with possible consequences in terms of inhibition of hormone transport and endocrine disruptive effects.

Indeed, OPFRs were able to inhibit activities of some drug transporters, acting as uptake transporters such as OAT3, OATP1B1, OATP1B3 and OCT2, or as efflux pumps, such as BCRP. OPFRs can additionally repress the expression of hepatic transporters, especially those of OAT2 and OCT1 (See Table S6 for a summary of OPFR effects towards drug transporters). This modulation of transporter activity and/or expression depends on the nature of OPFRs, with at least one OPFR, *i. e.*, TCEP, having no effect towards transporters. This confirms that interactions with transporters are not shared by all the members of a chemical or pharmacological class of pollutants, as already reported for pyrethroids and organophosphorus pesticides (Chedik et al., 2019,

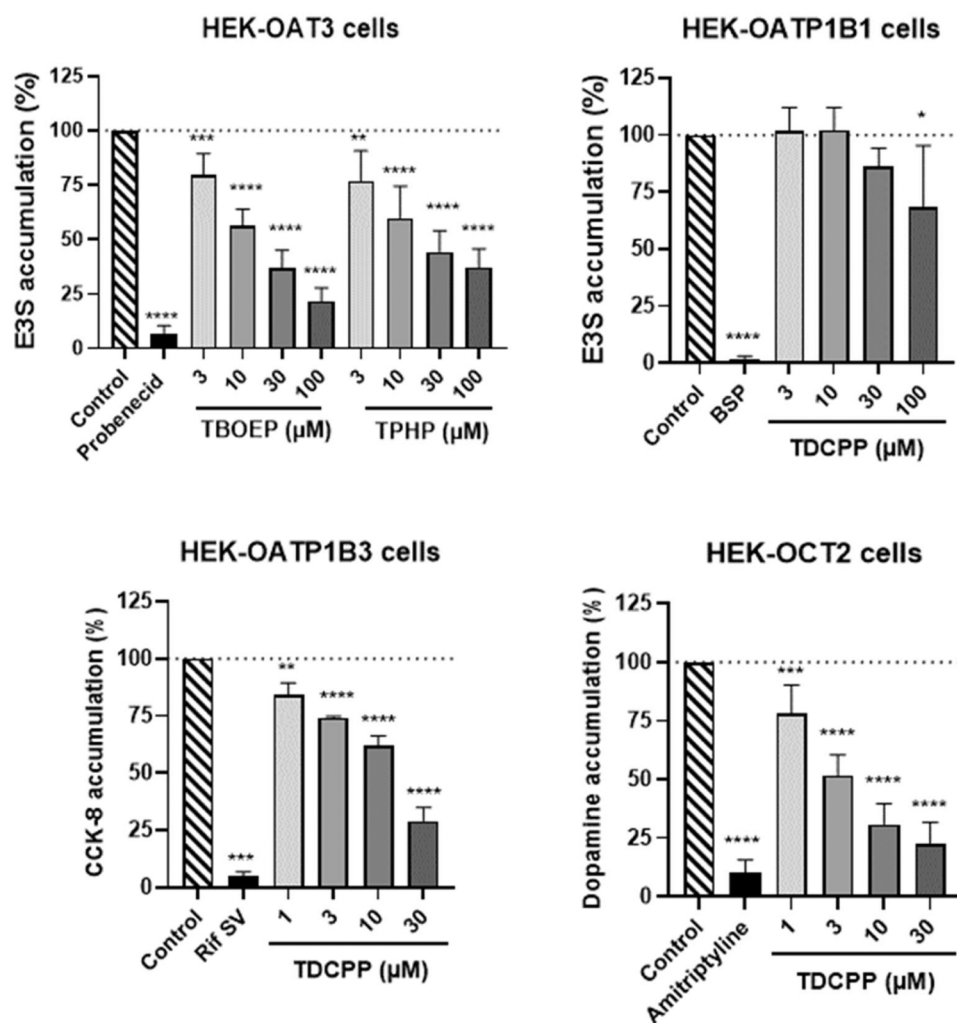


Fig. 5. Effects of OPFRs towards handling of endogenous substrates by OAT3, OATP1B1, OATP1B3 or OCT2. HEK-OAT3, HEK-OATP1B1, HEK-OATP1B3 and HEK-OCT2 cells were incubated for 5 min at 37 °C with endogenous substrates for OAT3/OATP1B1 (E3S), OATP1B3 (CCK-8) or OCT2 (dopamine), without (control) or with OPFRs used at various concentrations or reference transporter inhibitors (2 mM probenecid for OAT3, 100 μM sulfobromophthalein (BSP) for OATP1B1, 100 μM rifamycin SV (Rif SV) for OATP1B3 and 200 μM amitriptyline for OCT2). Intracellular accumulations of endogenous substrates were next determined by scintillation counting. Data are expressed as percentages of endogenous substrate accumulations in control cells, set at 100% and visualized by the dashed lines on the graphs. Data correspond to means ± SD of independent experiments (n = 3–7). \*, p < 0.05, \*\*, p < 0.01, \*\*\*, p < 0.001 and \*\*\*\*, p < 0.0001 comparatively to substrate accumulation in control cells.

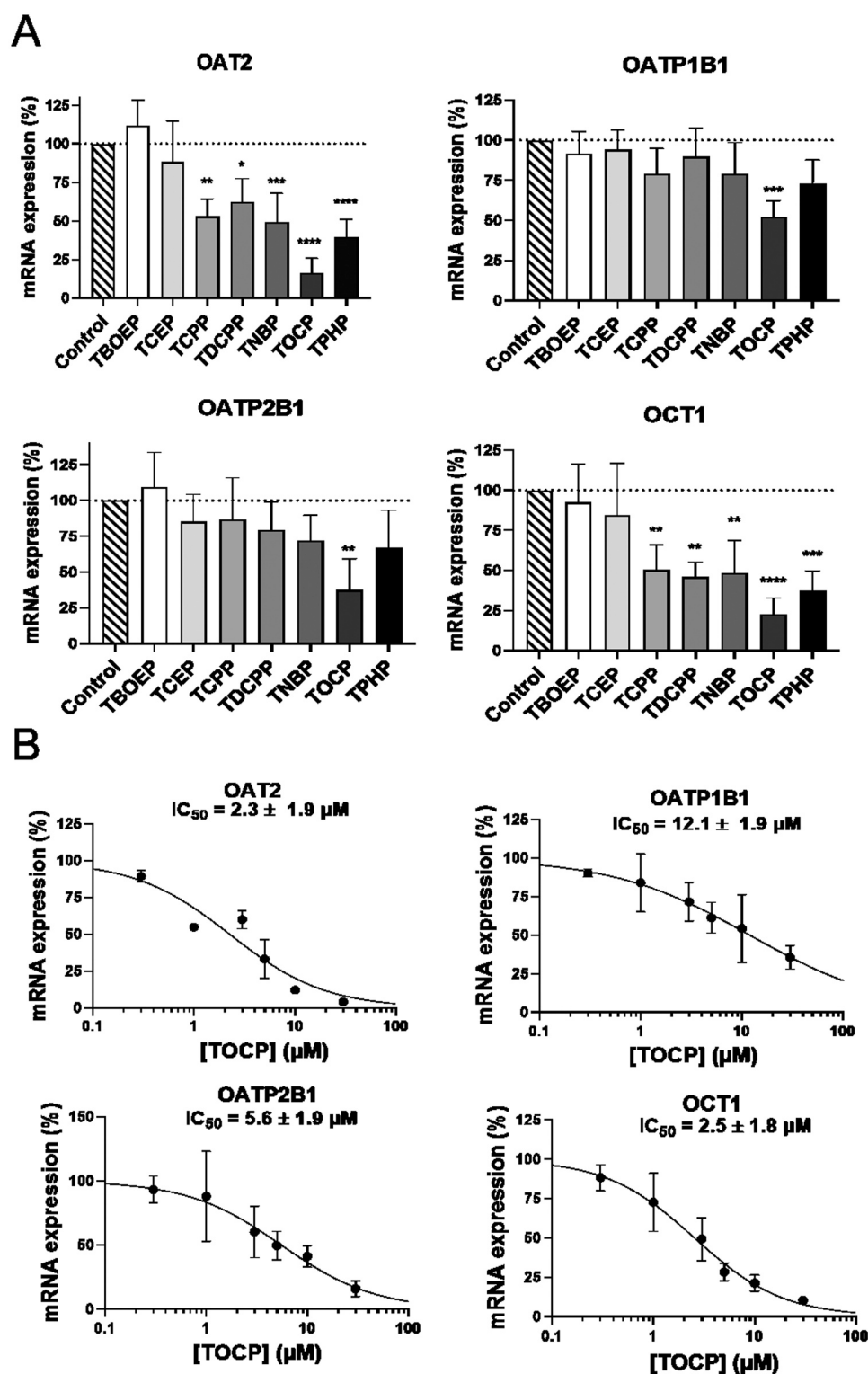
2017) and for environmental bisphenols (Bruyere et al., 2017). Moreover, activity and/or expression of MATEs, MRPs and P-gp transporters were not impacted by OPFRs (Table S6), suggesting that transporters are not general and unspecific targets for OPFRs, as already reported for other environmental chemicals, e.g., carbamate and neonicotinoid pesticides which interact with some, but not all, drug transporters (Guéniche et al., 2020b; Le Vée et al., 2019). The absence of interactions of TCEP and TCPP with P-gp is coherent with their high penetration efficiencies across the blood-cerebrospinal fluid barrier, indicating that these two OPFRs are unlikely to be substrates of P-gp (Hou et al., 2022), which restricts xenobiotic access through this barrier (Yasuda et al., 2013). By contrast, TPHP displayed reduced passage into human cerebrospinal fluid, associated with strong binding affinity to P-gp according to molecular docking analyses, suggesting that P-gp-mediated efflux of TPHP at the blood-cerebrospinal barrier is implicated (Hou et al., 2022). TPHP could therefore behave as a substrate for P-gp, without however inhibiting its activity, as demonstrated in the present study. The fact that many P-gp substrates do not block P-gp-mediated transport supports this hypothesis (Barecki-Roach et al., 2003).

Inhibition of drug transporter activity or repression of hepatic transporter expression in response to OPFRs, acting here as “perpetrators”, may impair the handling and thus the pharmacokinetics of drugs substrates for the incriminated transporters, behaving as “victims”. Such putative pollutant-drug interactions have however not been clinically reported, according to the best of our knowledge. They cannot be formally discarded according to a theoretical point of view and may concern various important drugs, including the hypoglycemic agent

metformin (substrate for OCT1, repressed by various OPFRs) and the cholesterol-lowering agents statins (substrates notably for OATP1B1, inhibited by TDCPP and repressed by TOCP). Besides, it is noteworthy that the *in vitro* transport of endogenous hormonal compounds, such as E3S, CCK-8 or dopamine, is significantly altered by OPFRs inhibiting OAT3 (TBOEP and TPHP), OATP1B3 (TDCPP) or OCT2 (TDCPP), even when using relatively low OPFR concentrations (in the 1–3 μM range). Such inhibitions of hormone transport may therefore be hypothesized to contribute to endocrine disrupting and metabolic effects of the concerned OPFRs (Dou and Wang, 2023; Wang et al., 2022). Repression of hepatic OATP1B1 and OATP2B1 by TOCP may additionally impair liver uptake of steroid hormones substrates of these SLCs, thereby impacting their elimination. OCT1 repression by OPFRs may result in altered liver accumulation of the physiological substrates of this SLC, especially thiamine (Chen et al., 2014), which may in turn promote cardiometabolic diseases (Liang et al., 2018) that are well-known to be favored by exposure to OPFRs (Ding et al., 2023). Lowered levels of hepatic OAT2 in response to OPFRs may similarly decrease accumulation of its physiological substrates, including endogenous prostaglandins, hormones, cyclic nucleotides and nucleosides (Shen et al., 2017), into hepatocytes, which may result in toxicity.

The possible implications of transporter inhibitions or repressions in toxic effects of OPFRs depend nevertheless on the *in vivo* relevance of *in vitro* interactions of OPFRs with transporters described in the present study. When applying criteria from the ITC, no OPFR was predicted to inhibit the activity of drug transporters in response to environmental or dietary exposure (Table 1 and Table S4). In the same way, TOCP was





**Fig. 6.** OPFR effects towards mRNA levels of SLC drug transporters in hepatic HepaRG cells. HepaRG cells were either untreated (control) or treated for 48 h by (A) 10  $\mu$ M OPFRs or (B) various concentrations of TOCP. SLC transporter mRNA levels were next analysed by RT-qPCR. Data are expressed as percentages of SLC mRNA levels found in control cells, set at 100% for each SLC and visualized by the dashed lines on the graphs (A). Data correspond to means  $\pm$  SD of independent experiments ( $n = 3-4$ ). (A) \*,  $p < 0.05$ , \*\*,  $p < 0.01$ , \*\*\*,  $p < 0.001$  and \*\*\*\*,  $p < 0.0001$  comparatively to control cells. (B) The IC<sub>50</sub> values for TOCP are shown at the top of the graphs.

predicted to only weakly repress *in vivo* hepatic expression of transporters (Table S5). Taken together, these predictions do not indicate major *in vivo* interactions of OPFRs with transporters. Such a conclusion may however be challenged by the fact that human pharmacokinetics data regarding OPFRs, especially their free plasma concentration, remain rather poor, notably in the case of high environmental exposure; moreover, OPFR plasma concentrations may vary among subpopulations. Extensive characterization of OPFR pharmacokinetics in environmentally-exposed humans, as well as the specific consideration

of human subpopulations highly exposed to OPFRs, may consequently be welcome in the future. Moreover, although OPFR concentrations are expected to be rather low in humans, the specific accumulation of some OPFRs in some tissues cannot be discarded, especially in the liver which is recognized as a target organ for OPFRs (Li et al., 2022). Besides, humans are frequently exposed to mixtures of pollutants, including OPFRs (Hoang et al., 2023), whose effects towards transporters may be additive or synergistic, as already demonstrated for marine pollutants blocking P-gp activity (Nicklisch et al., 2016). The study of pollutant

**Table 1**  
Prediction of *in vivo* inhibition of transporter activity by OPFR concentrations<sup>a</sup>.

OPFR	Approximated $I_{\max}^b$	$F_u^c$	$I_{\max, u}^d$	Transporter	IC <sub>50</sub>	Ratio $I_{\max, u}/IC_{50}$	Predicted <i>in vivo</i> inhibition
TBOEP	40 nM	0.054	2.2 nM	OAT3	11.1 μM	< 0.001	No inhibition
	(Zhao et al., 2016)			OATP1B3	43.2 μM	< 0.001	No inhibition
TPHP	12.1 nM	0.007	0.08 nM	OAT3	19.6 μM	< 0.001	No inhibition
	(Wang et al., 2021)			OATP1B1	44.1 μM	< 0.001	No inhibition
TDCPP	17.8 nM	0.016	0.29 nM	OATP1B1	23.4 μM	< 0.001	No inhibition
	(Wang et al., 2021)			OATP1B3	8.3 μM	< 0.001	No inhibition
				OCT2	6.1 μM	< 0.001	No inhibition
TOCP	35.9 nM	0.008	0.29 nM	BCRP <sup>e</sup>	51.4 μM	< 0.001	No inhibition
	(Wang et al., 2021)						

<sup>a</sup> *In vivo* inhibition of drug transporter activity can be predicted if the ratio  $I_{\max, u}/IC_{50} \geq 0.1$  (Giacomini et al., 2010).

<sup>b</sup> defined as the maximum plasma concentration.

<sup>c</sup> defined as the unbound plasma fraction and *in silico* predicted using ADMETlab 2.0.

<sup>d</sup> defined as the maximum unbound plasma concentration.

<sup>e</sup> related to non-intestinal BCRP.

mixtures, including mixtures of OPFRs or mixtures of OPFRs and other pollutants, towards drug transporters is consequently warranted. Whether OPFRs may interfere with activities of emerging drug transporters of clinical relevance, such as OATP2B1 or OAT2 (Zamek-Gliszczynski et al., 2022), may also be worthy of interest. In addition, for some specific populations of subjects, especially those suffering from inflammatory diseases, the repressing effects of OPFRs, especially those of TOCP, towards transporters may add up to those caused by pro-inflammatory cytokines (Cressman et al., 2012; Fardel and Le Vée, 2009), which likely deserves interest. Finally, some parameters related to transporter inhibitors, such as their time-dependent effects or their long-lasting activity (Shitara and Sugiyama, 2017; Tátrai et al., 2019), may be interesting to evaluate for OPFRs.

Despite interacting with OAT3 through inhibiting its activity, TBOEP and TPHP were not transported by this SLC, as demonstrated by their similar accumulation in HEK-MOCK and HEK-OAT3 cells and the lack of effect of the OAT3 inhibitor probenecid. TBOEP and TPHP thus probably inhibit OAT3 by interacting with the transporter outside of its drug binding site or may alternatively bind to it without however being transported. Whether TBOEP and TPHP, as well as other OPFRs, may be handled by other transporters is not known and likely deserves further studies, due to the established role of transporters in pharmacokinetics and toxicokinetics.

## 5. Conclusion

In summary, some OPFRs, including TBOEP, TDCPP, TOCP and TPHP, were found to interact *in vitro* with human drug transporters such as OAT2, OAT3, OATP1B1, OATP1B3, OCT1, OCT2 and/or BCRP. OPFRs inhibit the activity of these transporters or repress their hepatic mRNA levels. OPFRs can thus be added to the expanding list of environmental pollutants that target drug transporters, despite the concentrations of OPFRs reached in humans in response to environmental exposure being likely too low to allow single OPFRs to act *in vivo* on transporter activities or expressions. The handling of OPFRs by drug transporters and the possible contribution to their toxicokinetics remain important issues to clarify in the future.

## CRedit authorship contribution statement

**Valentin Tastet:** Conceptualization, Formal analysis, Investigation, Validation, Writing - original draft. **Marc Le Vée:** Conceptualization, Methodology, Supervision, Validation. **Marie Kerhoas:** Investigation; **Anna ZerDoug:** Investigation; **Elodie Jouan:** Resources; **Arnaud Bruyère:** Conceptualization, Investigation, Methodology, Supervision. **Olivier Fardel:** Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Writing - original draft, Writing - review & editing.

## Declaration of Competing Interest

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.

## Data Availability

Data will be made available on request.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ecoenv.2023.115348](https://doi.org/10.1016/j.ecoenv.2023.115348).

## References

- Abou-Elwafa Abdallah, M., Harrad, S., 2022. Dermal uptake of chlorinated organophosphate flame retardants via contact with furniture fabrics; implications for human exposure. *Environ. Res.* 209, 112847 <https://doi.org/10.1016/j.envres.2022.112847>.
- Anderson, B.J., Woollard, G.A., Holford, N.H.G., 2000. A model for size and age changes in the pharmacokinetics of paracetamol in neonates, infants and children. *Br. J. Clin. Pharmacol.* 50, 125–134. <https://doi.org/10.1046/j.1365-2125.2000.00231.x>.
- Andersson, T.B., Kanebratt, K.P., Kenna, J.G., 2012. The HepaRG cell line: a unique *in vitro* tool for understanding drug metabolism and toxicology in human. *Expert Opin. Drug Metab. Toxicol.* 8, 909–920. <https://doi.org/10.1517/17425255.2012.685159>.
- 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. <https://doi.org/10.1006/taap.1996.0286>.
- Barecki-Roach, M., Wang, E.-J., Johnson, W.W., 2003. Many P-glycoprotein substrates do not inhibit the transport process across cell membranes. *Xenobiotica Fate Foreign Compd. Biol. Syst.* 33, 131–140. <https://doi.org/10.1080/0049825021000035326>.
- Blum, A., Behl, M., Birnbaum, L.S., Diamond, M.L., Phillips, A., Singla, V., Sipes, N.S., Stapleton, H.M., Venier, M., 2019. Organophosphate ester flame retardants: are they a regrettable substitution for polybrominated diphenyl ethers? *Environ. Sci. Technol. Lett.* 6, 638–649. <https://doi.org/10.1021/acs.estlett.9b00582>.
- Brouwer, K.L.R., Keppler, D., Hoffmaster, K.A., Bow, D. a J., Cheng, Y., Lai, Y., Palm, J.E., Stieger, B., Evers, R., International Transporter Consortium, 2013. *In vitro* methods to support transporter evaluation in drug discovery and development. *Clin. Pharmacol. Ther.* 94, 95–112. <https://doi.org/10.1038/clpt.2013.81>.
- 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. Vit. Int. J. Publ. Assoc. BIBRA* 40, 34–44. <https://doi.org/10.1016/j.tiv.2016.12.009>.

- Bruyère, A., Le Vée, M., Jouan, E., Molez, S., Nies, A.T., Fardel, O., 2021. Differential in vitro interactions of the Janus kinase inhibitor ruxolitinib with human SLC drug transporters. *Xenobiotica Fate Foreign Compd. Biol. Syst.* 51, 467–478. <https://doi.org/10.1080/00498254.2021.1875516>.
- Camino, G., Costa, L., Dicortemiglia, M., 1991. Overview of fire retardant mechanisms. *Polym. Degrad. Stab.* 33, 131–154. [https://doi.org/10.1016/0141-3910\(91\)90014-1](https://doi.org/10.1016/0141-3910(91)90014-1).
- Cao, D., Lv, K., Gao, W., Fu, Jie, Wu, J., Fu, Jianjie, Wang, Y., Jiang, G., 2019. Presence and human exposure assessment of organophosphate flame retardants (OPEs) in indoor dust and air in Beijing, China. *Ecotoxicol. Environ. Saf.* 169, 383–391. <https://doi.org/10.1016/j.ecoenv.2018.11.038>.
- Carmichael, J., DeGraff, W.G., Gazdar, A.F., Minna, J.D., Mitchell, J.B., 1987. Evaluation of a tetrazolium-based semiautomated colorimetric assay: assessment of chemosensitivity testing. *Cancer Res* 47, 936–942.
- Chedik, L., Bruyere, A., Le Vee, M., Stieger, B., Denizot, C., Parmentier, Y., Potin, S., Fardel, O., 2017. Inhibition of human drug transporter activities by the pyrethroid pesticides allethrin and tetramethrin. *PLoS One* 12, e0169480. <https://doi.org/10.1371/journal.pone.0169480>.
- Chedik, L., Bruyere, A., Fardel, O., 2019. Interactions of organophosphorus pesticides with solute carrier (SLC) drug transporters. *Xenobiotica Fate Foreign Compd. Biol. Syst.* 49, 363–374. <https://doi.org/10.1080/00498254.2018.1442030>.
- Chen, G., Jin, Y., Wu, Y., Liu, L., Fu, Z., 2015. Exposure of male mice to two kinds of organophosphate flame retardants (OPFRs) induced oxidative stress and endocrine disruption. *Environ. Toxicol. Pharmacol.* 40, 310–318. <https://doi.org/10.1016/j.etap.2015.06.021>.
- Chen, L., Shu, Y., Liang, X., Chen, E.C., Yee, S.W., Zur, A.A., Li, S., Xu, L., Keshari, K.R., Lin, M.J., Chien, H.-C., Zhang, Y., Morrissey, K.M., Liu, J., Ostrem, J., Younger, N.S., Kurhanewicz, J., Shokat, K.M., Ashrafi, G., Giacomini, K.M., 2014. OCT1 is a high-capacity thiamine transporter that regulates hepatic steatosis and is a target of metformin. *Proc. Natl. Acad. Sci. U. S. A.* 111, 9983–9988. <https://doi.org/10.1073/pnas.1314939111>.
- Chen, Y., Liu, Q., Ma, J., Yang, S., Wu, Y., An, Y., 2020. A review on organophosphate flame retardants in indoor dust from China: Implications for human exposure. *Chemosphere* 260, 127633. <https://doi.org/10.1016/j.chemosphere.2020.127633>.
- Choi, G., Keil, A.P., Richardson, D.B., Daniels, J.L., Hoffman, K., Villanger, G.D., Sakhi, A.K., Thomsen, C., Reichborn-Kjennerud, T., Aase, H., Engel, S.M., 2021. Pregnancy exposure to organophosphate esters and the risk of attention-deficit hyperactivity disorder in the Norwegian mother, father and child cohort study. *Environ. Int.* 154, 106549. <https://doi.org/10.1016/j.envint.2021.106549>.
- Chupeau, Z., Bonvallot, N., Mercier, F., Le Bot, B., Chevrier, C., Glorennec, P., 2020. Organophosphorus flame retardants: a global review of indoor contamination and human exposure in Europe and epidemiological evidence. *Int. J. Environ. Res. Public Health* 17, 6713. <https://doi.org/10.3390/ijerph17186713>.
- 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. <https://doi.org/10.1016/j.scitotenv.2018.07.122>.
- 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. <https://doi.org/10.1016/j.envint.2019.03.003>.
- 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. <https://doi.org/10.1586/ecp.11.66>.
- Darney, K., Turco, L., Buratti, F.M., Di Consiglio, E., Vichi, S., Roudot, A.C., Béchaux, C., Testai, E., Dorne, J.L.C.M., Lautz, L.S., 2020. Human variability in influx and efflux transporters in relation to uncertainty factors for chemical risk assessment. *Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc.* 140, 111305. <https://doi.org/10.1016/j.fct.2020.111305>.
- Ding, E., Deng, F., Fang, J., Li, T., Hou, M., Liu, J., Miao, K., Yan, W., Fang, K., Shi, W., Fu, Y., Liu, Y., Dong, H., Dong, L., Ding, C., Liu, X., Pollitt, K.J.G., Ji, J.S., Shi, Y., Cai, Y., Tang, S., Shi, X., 2023. Association between organophosphate ester exposure and insulin resistance with glycometabolic disorders among older Chinese adults 60–69 years of age: evidence from the China BAPE study. *Environ. Health Perspect.* 131, 47009. <https://doi.org/10.1289/EHP11896>.
- Dou, M., Wang, L., 2023. A review on organophosphate esters: physicochemical properties, applications, and toxicities as well as occurrence and human exposure in dust environment. *J. Environ. Manag.* 325, 116601. <https://doi.org/10.1016/j.jenvman.2022.116601>.
- Espugras, R., Linares, V., Bellés, M., Domingo, J.L., Schuhmacher, M., 2023. In vitro neurotoxic potential of emerging flame retardants on neuroblastoma cells in an acute exposure scenario. *Toxicol. Vitr. Int. J. Publ. Assoc. BIBRA* 87, 105523. <https://doi.org/10.1016/j.tiv.2022.105523>.
- Fahmi, O.A., Ripp, S.L., 2010. Evaluation of models for predicting drug-drug interactions due to induction. *Expert Opin. Drug Metab. Toxicol.* 6, 1399–1416. <https://doi.org/10.1517/17425255.2010.516251>.
- Fardel, O., Le Vée, M., 2009. Regulation of human hepatic drug transporter expression by pro-inflammatory cytokines. *Expert Opin. Drug Metab. Toxicol.* 5, 1469–1481. <https://doi.org/10.1517/17425255.2009.3304056>.
- Fardel, O., Kolasa, E., Le Vee, M., 2012. Environmental chemicals as substrates, inhibitors or inducers of drug transporters: implication for toxicokinetics, toxicity and pharmacokinetics. *Expert Opin. Drug Metab. Toxicol.* 8, 29–46. <https://doi.org/10.1517/17425255.2012.637918>.
- Fernández-Arribas, J., Moreno, T., Eljarrat, E., 2023. Human exposure to organophosphate esters in water and packed beverages. *Environ. Int.* 175, 107936. <https://doi.org/10.1016/j.envint.2023.107936>.
- Giacomini, K.M., Huang, S.-M., Tweedie, D.J., Benet, L.Z., Brouwer, K.L.R., Chu, X., Dahlin, A., Evers, R., Fischer, V., Hillgren, K.M., Hoffmaster, K.A., Ishikawa, T., Keppler, D., Kim, R.B., Lee, C.A., Niemi, M., Polli, J.W., Stugiama, Y., Swaan, P.W., Ware, J.A., Wright, S.H., Yee, S.W., Zamek-Gliszczyński, M.J., Zhang, L., 2010. Membrane transporters in drug development. *Nat. Rev. Drug Discov.* 9, 215–236. <https://doi.org/10.1038/nrd3028>.
- Gill, R., Hurley, S., Brown, R., Tarrant, D., Dhaliwal, J., Sarala, R., Park, J.-S., Patton, S., Petreas, M., 2020. Polybrominated diphenyl ether and organophosphate flame retardants in Canadian fire station dust. *Chemosphere* 253, 126669. <https://doi.org/10.1016/j.chemosphere.2020.126669>.
- Green, J., 1996. Mechanisms for flame retardancy and smoke suppression - a review. *J. FIRE Sci.* 14, 426–442. <https://doi.org/10.1177/073490419601400602>.
- Guéniche, N., Bruyere, A., Le Vée, M., Fardel, O., 2020a. Implication of human drug transporters to toxicokinetics and toxicity of pesticides. *Pest Manag. Sci.* 76, 18–25. <https://doi.org/10.1002/ps.5577>.
- Guéniche, N., Bruyere, A., Ringeval, M., Jouan, E., Huguët, A., Le Hégarat, L., Fardel, O., 2020b. Differential interactions of carbamate pesticides with drug transporters. *Xenobiotica Fate Foreign Compd. Biol. Syst.* 50, 1380–1392. <https://doi.org/10.1080/00498254.2020.1771473>.
- Hales, B.F., Robaire, B., 2020. Effects of brominated and organophosphate ester flame retardants on male reproduction. *Andrology* 8, 915–923. <https://doi.org/10.1111/andr.12789>.
- Hoang, M.T.T., Le, G.T., Kiwao, K., Duong, H.T., Nguyen, T.Q., Phan, T.Q., Bui, M.Q., Truong, D.A., Trinh, H.T., 2023. Occurrence and risk of human exposure to organophosphate flame retardants in indoor air and dust in Hanoi, Vietnam. *Chemosphere* 328, 138597. <https://doi.org/10.1016/j.chemosphere.2023.138597>.
- Hong, Z., Li, Y., Deng, X., Chen, M., Pan, J., Chen, Z., Zhang, X., Wang, C., Qiu, C., 2022. Comprehensive analysis of triphenyl phosphazene: An environmental explanation of colorectal cancer progression. *Ecotoxicol. Environ. Saf.* 241, 113778. <https://doi.org/10.1016/j.ecoenv.2022.113778>.
- Hou, M., Shi, Y., Na, G., Cai, Y., 2021. A review of organophosphate esters in indoor dust, air, hand wipes and silicone wristbands: Implications for human exposure. *Environ. Int.* 146, 106261. <https://doi.org/10.1016/j.envint.2020.106261>.
- Hou, M., Zhang, B., Fu, S., Cai, Y., Shi, Y., 2022. Penetration of organophosphate triesters and diesters across the blood-cerebrospinal fluid barrier: efficiencies, impact factors, and mechanisms. *Environ. Sci. Technol.* 56, 8221–8230. <https://doi.org/10.1021/acs.est.2c01850>.
- Huang, Q., Mao, X., Pan, F., Hu, X., He, Z., Wang, Y., Wan, Y., 2023. Organophosphate esters in source, finished, and tap water in Wuhan, China. *Chemosphere* 325, 138288. <https://doi.org/10.1016/j.chemosphere.2023.138288>.
- Jouan, E., Le Vée, M., Denizot, C., Parmentier, Y., Fardel, O., 2016a. Drug transporter expression and activity in human hepatoma HuH-7 cells. *Pharmaceutics* 9, 3. <https://doi.org/10.3390/pharmaceutics9010003>.
- Jouan, E., Le Vée, M., Mayati, A., Denizot, C., Parmentier, Y., Fardel, O., 2016b. Evaluation of P-glycoprotein inhibitory potential using a rhodamine 123 accumulation assay. *Pharmaceutics* 8, 12. <https://doi.org/10.3390/pharmaceutics8020012>.
- Le Vee, M., Noel, G., Jouan, E., Stieger, B., Fardel, O., 2013. Polarized expression of drug transporters in differentiated human hepatoma HepaRG cells. *Toxicol. Vitr. Int. J. Publ. Assoc. BIBRA* 27, 1979–1986. <https://doi.org/10.1016/j.tiv.2013.07.003>.
- Le Vee, M., Jouan, E., Noel, G., Stieger, B., Fardel, O., 2015. Polarized location of SLC and ABC drug transporters in monolayer-cultured human hepatocytes. *Toxicol. Vitr. Int. J. Publ. Assoc. BIBRA* 29, 938–946. <https://doi.org/10.1016/j.tiv.2015.03.019>.
- Le Vée, M., Baclé, A., Bruyere, A., Fardel, O., 2019. Neonicotinoid pesticides poorly interact with human drug transporters. *J. Biochem. Mol. Toxicol.* 33, e22379. <https://doi.org/10.1002/jbt.22379>.
- Li, F., Yang, X., Li, X., Li, R., Zhao, J., Wu, H., 2014. Determination and prediction of the binding interaction between organophosphate flame retardants and p53. *Chem. Res. Toxicol.* 27, 1918–1925. <https://doi.org/10.1021/tx5002157>.
- Li, Y., Xiong, S., Hao, Y., Yang, R., Zhang, Q., Wania, F., Jiang, G., 2022. Organophosphate esters in Arctic air from 2011 to 2019: Concentrations, temporal trends, and potential sources. *J. Hazard. Mater.* 434, 128872. <https://doi.org/10.1016/j.jhazmat.2022.128872>.
- Li, Z., Sun, J., Liu, W., Wu, J., Peng, H., Zhao, Y., Qiao, H., Fang, Y., 2020. Changes in the circRNA expression profile of PC12 cells induced by TDCIPP exposure may regulate the downstream NF- $\kappa$ B pathway via the Traf2 gene. *Chemosphere* 254, 126834. <https://doi.org/10.1016/j.chemosphere.2020.126834>.
- Liang, X., Yee, S.W., Chien, H.-C., Chen, E.C., Luo, Q., Zou, L., Piao, M., Mifune, A., Chen, L., Calvert, M.E., King, S., Norheim, F., Abad, J., Krauss, R.M., Giacomini, K.M., 2018. Organic cation transporter 1 (OCT1) modulates multiple cardiometabolic traits through effects on hepatic thiamine content. *PLoS Biol.* 16, e2002907. <https://doi.org/10.1371/journal.pbio.2002907>.
- Liao, C., Kim, U.-J., Kannan, K., 2020. Occurrence and distribution of organophosphate esters in sediment from northern Chinese coastal waters. *Sci. Total Environ.* 704, 135328. <https://doi.org/10.1016/j.scitotenv.2019.135328>.
- Liu, M., Li, A., Meng, L., Zhang, G., Guan, X., Zhu, J., Li, Y., Zhang, Q., Jiang, G., 2022. Exposure to novel brominated flame retardants and organophosphate esters and associations with thyroid cancer risk: a case-control study in Eastern China. *Environ. Sci. Technol.* 56, 17825–17835. <https://doi.org/10.1021/acs.est.2c04759>.
- Liu, W., Luo, D., Xia, W., Tao, Y., Wang, L., Yu, M., Hu, L., Zhou, A., Covaci, A., Lin, C., Xu, S., Mei, S., Li, Y., 2021. Prenatal exposure to halogenated, aryl, and alkyl organophosphate esters and child neurodevelopment at two years of age. *J. Hazard. Mater.* 408, 124856. <https://doi.org/10.1016/j.jhazmat.2020.124856>.
- Liu, X., 2019. Overview: role of drug transporters in drug disposition and its clinical significance. *Adv. Exp. Med. Biol.* 1141, 1–12. <https://doi.org/10.1007/978-981-13-7647-4-1>.



- Liu, Y., Li, Y., Dong, S., Han, L., Guo, R., Fu, Y., Zhang, S., Chen, J., 2021. The risk and impact of organophosphate esters on the development of female-specific cancers: comparative analysis of patients with benign and malignant tumors. *J. Hazard. Mater.* 404, 124020 <https://doi.org/10.1016/j.jhazmat.2020.124020>.
- Liu, Y., Li, Y., Xiao, N., Liu, M., Wang, Y., Luo, H., Yao, Y., Feng, Y., Wang, S., 2023. Serum organophosphate flame retardants and plasticizers in Chinese females of childbearing age: association with serum reproductive and thyroid hormones. *Chemosphere* 337, 139237. <https://doi.org/10.1016/j.chemosphere.2023.139237>.
- Louise, J., Dellafiora, L., van den Heuvel, J.J.M.W., Rijkers, D., Leenders, L., Dorne, J.-L. C.M., Punt, A., Russel, F.G.M., Koenderink, J.B., 2023. Perfluoroalkyl substances (PFASs) are substrates of the renal human organic anion transporter 4 (OAT4). *Arch. Toxicol.* 97, 685–696. <https://doi.org/10.1007/s00204-022-03428-6>.
- Marklund, A., Andersson, B., Haglund, P., 2005. Traffic as a source of organophosphorus flame retardants and plasticizers in snow. *Environ. Sci. Technol.* 39, 3555–3562. <https://doi.org/10.1021/es0482177>.
- Newell, A.J., Kapps, V.A., Cai, Y., Rai, M.R., St Armour, G., Horman, B.M., Rock, K.D., Witchev, S.K., Greenbaum, A., Patisaul, H.B., 2023. Maternal organophosphate flame retardant exposure alters the developing mesencephalic dopamine system in fetal rat. *Toxicol. Sci. J. Soc. Toxicol.* 191, 357–373. <https://doi.org/10.1093/toxsci/kfac137>.
- Nicklisch, S.C.T., Hamdoun, A., 2020. Disruption of small molecule transporter systems by transporter-interfering chemicals (TICs). *FEBS Lett.* 594, 4158–4185. <https://doi.org/10.1002/1873-3468.14005>.
- Nicklisch, S.C.T., Rees, S.D., McGrath, A.P., Gökirmak, T., Bonito, L.T., Vermeer, L.M., Cregger, C., Loewen, G., Sandin, S., Chang, G., Hamdoun, A., 2016. Global marine pollutants inhibit P-glycoprotein: environmental levels, inhibitory effects, and cocrystal structure. *Sci. Adv.* 2, e1600001 <https://doi.org/10.1126/sciadv.1600001>.
- Nie, J., Zhou, J., Shen, Y., Lin, R., Hu, H., Zeng, K., Bi, H., Huang, M., Yu, L., Zeng, S., Miao, J., 2023. Studies on the interaction of five triazole fungicides with human renal transporters in cells. *Toxicol. Vit. Int. J. Publ. Assoc. BIBRA* 88, 105555. <https://doi.org/10.1016/j.tiv.2023.105555>.
- Nies, A.T., Koepsell, H., Damme, K., Schwab, M., 2011. Organic cation transporters (OCTs, MATes), in vitro and in vivo evidence for the importance in drug therapy. *Handb. Exp. Pharmacol.* 105–167. [https://doi.org/10.1007/978-3-642-14541-4\\_3](https://doi.org/10.1007/978-3-642-14541-4_3).
- Pacyniak, E., Roth, M., Hagenbuch, B., Guo, G.L., 2010. Mechanism of polybrominated diphenyl ether uptake into the liver: PBDE congeners are substrates of human hepatic OATP transporters. *Toxicol. Sci. J. Soc. Toxicol.* 115, 344–353. <https://doi.org/10.1093/toxsci/kfq059>.
- Patisaul, H.B., Behl, M., Birnbaum, L.S., Blum, A., Diamond, M.L., Rojello Fernández, S., Hogberg, H.T., Kwiatkowski, C.F., Page, J.D., Soehl, A., Stapleton, H.M., 2021. Beyond cholinesterase inhibition: developmental neurotoxicity of organophosphate ester flame retardants and plasticizers. *Environ. Health Perspect.* 129, 105001 <https://doi.org/10.1289/EHP9285>.
- Petzinger, E., Geyer, J., 2006. Drug transporters in pharmacokinetics. *Naunyn. Schmiede Arch. Pharmacol.* 372, 465–475. <https://doi.org/10.1007/s00210-006-0042-9>.
- Rosenmai, A.K., Winge, S.B., Möller, M., Lundqvist, J., Wedebye, E.B., Nikolov, N.G., Lilith Johansson, H.K., Vinggaard, A.M., 2021. Organophosphate ester flame retardants have antiandrogenic potential and affect other endocrine related endpoints in vitro and in silico. *Chemosphere* 263, 127703. <https://doi.org/10.1016/j.chemosphere.2020.127703>.
- 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. <https://doi.org/10.1111/j.1476-5381.2011.01724.x>.
- Saillenfait, A.-M., Ndaw, S., Robert, A., Sabaté, J.-P., 2018. Recent biomonitoring reports on phosphate ester flame retardants: a short review. *Arch. Toxicol.* 92, 2749–2778. <https://doi.org/10.1007/s00204-018-2275-z>.
- Salthammer, T., Fuhrmann, F., Uhde, E., 2003. Flame retardants in the indoor environment – Part II: release of VOCs (triethylphosphate and halogenated degradation products) from polyurethane. *Indoor Air* 13, 49–52. <https://doi.org/10.1034/j.1600-0668.2003.01150.x>.
- Sayyed, K., Camillerapp, C., Le Vée, M., Bruyère, A., Nies, A.T., Abdel-Razzak, Z., Fardel, O., 2019. Inhibition of organic cation transporter (OCT) activities by carcinogenic heterocyclic aromatic amines. *Toxicol. Vit. Int. J. Publ. Assoc. BIBRA* 54, 10–22. <https://doi.org/10.1016/j.tiv.2018.08.015>.
- Shen, H., Lai, Y., Rodrigues, A.D., 2017. Organic anion transporter 2: an enigmatic human solute carrier. *Drug Metab. Dispos. Biol. Fate Chem.* 45, 228–236. <https://doi.org/10.1124/dmd.116.072264>.
- Shitara, Y., Sugiyama, Y., 2017. Preincubation-dependent and long-lasting inhibition of organic anion transporting polypeptide (OATP) and its impact on drug-drug interactions. *Pharmacol. Ther.* 177, 67–80. <https://doi.org/10.1016/j.pharmthera.2017.02.042>.
- Siddique, S., Farhat, I., Kubwabo, C., Chan, P., Goodyer, C.G., Robaire, B., Chevrier, J., Hales, B.F., 2022. Exposure of men living in the greater Montreal area to organophosphate esters: association with hormonal balance and semen quality. *Environ. Int.* 166, 107402 <https://doi.org/10.1016/j.envint.2022.107402>.
- Tastet, V., Le Vée, M., Bruyère, A., Fardel, O., 2023. Interactions of human drug transporters with chemical additives present in plastics: Potential consequences for toxicokinetics and health. *Environ. Pollut.* 121882 <https://doi.org/10.1016/j.envpol.2023.121882>.
- Tátrai, P., Schweigler, P., Poller, B., Domange, N., de Wilde, R., Hanna, I., Gáborik, Z., Huth, F., 2019. A systematic in vitro investigation of the inhibitor preincubation effect on multiple classes of clinically relevant transporters. *Drug Metab. Dispos. Biol. Fate Chem.* 47, 768–778. <https://doi.org/10.1124/dmd.118.085993>.
- Tátrai, P., Erdő, F., Krajcsi, P., 2022. Role of hepatocyte transporters in drug-induced liver injury (DILI)-in vitro testing. *Pharmaceutics* 15, 29. <https://doi.org/10.3390/pharmaceutics15010029>.
- Trexler, A.W., Knudsen, G.A., Nicklisch, S.C.T., Birnbaum, L.S., Cannon, R.E., 2019. 2,4,6-tribromophenol exposure decreases p-glycoprotein transport at the blood-brain barrier. *Toxicol. Sci. J. Soc. Toxicol.* 171, 463–472. <https://doi.org/10.1093/toxsci/kfz155>.
- van der Veen, I., de Boer, J., 2012. Phosphorus flame retardants: properties, production, environmental occurrence, toxicity and analysis. *Chemosphere* 88, 1119–1153. <https://doi.org/10.1016/j.chemosphere.2012.03.067>.
- Wang, X., Chen, P., Zhao, L., Zhu, L., Wu, F., 2021. Transplacental behaviors of organophosphate tri- and diesters based on paired human maternal and cord whole blood: efficiencies and impact factors. *Environ. Sci. Technol.* 55, 3091–3100. <https://doi.org/10.1021/acs.est.0c06095>.
- Wang, X., Li, F., Teng, Y., Ji, C., Wu, H., 2022. Potential adverse outcome pathways with hazard identification of organophosphate esters. *Sci. Total Environ.* 851, 158093 <https://doi.org/10.1016/j.scitotenv.2022.158093>.
- Wang, Xiaolei, Zhao, X., Shi, D., Dong, Z., Zhang, X., Liang, W., Liu, L., Wang, Xia, Wu, F., 2023. Integrating physiologically based pharmacokinetic modeling-based forward dosimetry and in vitro bioassays to improve the risk assessment of organophosphate esters on human health. *Environ. Sci. Technol.* 57, 1764–1775. <https://doi.org/10.1021/acs.est.2c04576>.
- Wang, Xiaotong, Lee, E., Hales, B.F., Robaire, B., 2023. Organophosphate esters disrupt steroidogenesis in KGN human ovarian granulosa cells. *Endocrinology* 164, bqad089. <https://doi.org/10.1210/endo.cr/bqad089>.
- Wei, G.-L., Li, D.-Q., Zhuo, M.-N., Liao, Y.-S., Xie, Z.-Y., Guo, T.-L., Li, J.-J., Zhang, S.-Y., Liang, Z.-Q., 2015. Organophosphorus flame retardants and plasticizers: Sources, occurrence, toxicity and human exposure. *Environ. Pollut.* 196, 29–46. <https://doi.org/10.1016/j.envpol.2014.09.012>.
- Xiong, G., Wu, Z., Yi, J., Fu, L., Yang, Z., Hsieh, C., Yin, M., Zeng, X., Wu, C., Lu, A., Chen, X., Hou, T., Cao, D., 2021. ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties. *Nucleic Acids Res* 49, W5–W14. <https://doi.org/10.1093/nar/gkab255>.
- Xu, Q., Wu, D., Dang, Y., Yu, L., Liu, C., Wang, J., 2017. Reproduction impairment and endocrine disruption in adult zebrafish (*Danio rerio*) after waterborne exposure to TBOEP. *Aquat. Toxicol. Amst. Neth.* 182, 163–171. <https://doi.org/10.1016/j.aquatox.2016.11.019>.
- Yan, Z., Feng, C., Jin, X., Wang, F., Liu, C., Li, N., Qiao, Y., Bai, Y., Wu, F., Giesy, J.P., 2022. Organophosphate esters cause thyroid dysfunction via multiple signaling pathways in zebrafish brain. *Environ. Sci. Ecotechnol.* 12, 100198 <https://doi.org/10.1016/j.ese.2022.100198>.
- Yao, C., Yang, H., Li, Y., 2021. A review on organophosphate flame retardants in the environment: Occurrence, accumulation, metabolism and toxicity. *Sci. Total Environ.* 795, 148837 <https://doi.org/10.1016/j.scitotenv.2021.148837>.
- Yasuda, K., Cline, C., Vogel, P., Onciu, M., Fatima, S., Sorrentino, B.P., Thirumaran, R.K., Ekins, S., Urade, Y., Fujimori, K., Schuetz, E.G., 2013. Drug transporters on arachnoid barrier cells contribute to the blood-cerebrospinal fluid barrier. *Drug Metab. Dispos. Biol. Fate Chem.* 41, 923–931. <https://doi.org/10.1124/dmd.112.050344>.
- Ye, L., Zhang, X., Wang, P., Zhang, Y., He, S., Li, Y., Li, S., Liang, K., Liao, S., Gao, Y., Zhou, S., Peng, Q., 2022. Low concentration triphenyl phosphate fuels proliferation and migration of hepatocellular carcinoma cells. *Environ. Toxicol.* 37, 2445–2459. <https://doi.org/10.1002/tox.23609>.
- Yu, K., Du, Z., Xuan, H., Chen, Q., 2022. Comprehensive analysis based in silico study of organophosphate flame retardants - environmental explanation of bladder cancer progression. *Environ. Toxicol. Pharmacol.* 92, 103851 <https://doi.org/10.1016/j.etap.2022.103851>.
- Yuan, S., Zhu, K., Ma, M., Zhu, X., Rao, K., Wang, Z., 2020. In vitro oxidative stress, mitochondrial impairment and G1 phase cell cycle arrest induced by alkyl-phosphorus-containing flame retardants. *Chemosphere* 248, 126026. <https://doi.org/10.1016/j.chemosphere.2020.126026>.
- Zhang, G., Meng, L., Guo, J., Guan, X., Liu, M., Han, X., Li, Y., Zhang, Q., Jiang, G., 2023. Exposure to novel brominated and organophosphate flame retardants and associations with type 2 diabetes in East China: a case-control study. *Sci. Total Environ.* 871, 162107 <https://doi.org/10.1016/j.scitotenv.2023.162107>.
- Zhang, Z.-N., Yang, D.-L., Liu, H., Bi, J., Bao, Y.-B., Ma, J.-Y., Zheng, Q.-X., Cui, D.-L., Chen, W., Xiang, P., 2023. Effects of TCP and TCEP exposure on human corneal epithelial cells: Oxidative damage, cell cycle arrest, and pyroptosis. *Chemosphere* 331, 138817. <https://doi.org/10.1016/j.chemosphere.2023.138817>.
- Zhao, F., Wan, Y., Zhao, H., Hu, W., Mu, D., Webster, T.F., Hu, J., 2016. Levels of blood organophosphorus flame retardants and association with changes in human sphingolipid homeostasis. *Environ. Sci. Technol.* 50, 8896–8903. <https://doi.org/10.1021/acs.est.6b02474>.
- Zhao, J.-Y., Zhan, Z.-X., Lu, M.-J., Tao, F.-B., Wu, D., Gao, H., 2022. A systematic scoping review of epidemiological studies on the association between organophosphate flame retardants and neurotoxicity. *Ecotoxicol. Environ. Saf.* 243, 113973 <https://doi.org/10.1016/j.ecoenv.2022.113973>.
- Zhao, W., Zitzow, J.D., Weaver, Y., Ehresman, D.J., Chang, S.-C., Butenhoff, J.L., Hagenbuch, B., 2017. Organic anion transporting polypeptides contribute to the disposition of perfluoroalkyl acids in humans and rats. *Toxicol. Sci. J. Soc. Toxicol.* 156, 84–95. <https://doi.org/10.1093/toxsci/kfw236>.
- Zhao, Y., Liu, W., Zhang, D., Shen, J., Huang, X., Xiao, L., Chen, X., Lin, X., Du, S., Liu, J., Lu, S., 2022. Association between organophosphorus flame retardants exposure and cognitive impairment among elderly population in southern China. *Sci. Total Environ.* 848, 157763 <https://doi.org/10.1016/j.scitotenv.2022.157763>.
- Zhou, X., Zhou, X., Yao, L., Zhang, X., Cong, R., Luan, J., Zhang, T., Song, N., 2022. Organophosphate flame retardant TDCPP: a risk factor for renal cancer? *Chemosphere* 305, 135485. <https://doi.org/10.1016/j.chemosphere.2022.135485>.