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TICBase: Integrated Resource for Data on Drug and Environmental Chemical Interactions with Mammalian Drug Transporters

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Environmental health science seeks to predict how environmental toxins, chemical toxicants, and prescription drugs accumulate and interact within the body. Xenobiotic transporters of the ATP-binding cassette (ABC) and solute carrier (SLC) superfamilies are major determinants of the uptake and disposition of xenobiotics across the kingdoms of life. The goal of this study was to integrate drug and environmental chemical interactions of mammalian ABC and SLC proteins in a centralized, integrative database. We built upon an existing publicly accessible platform—the "TransPortal"—which was updated with novel data and searchable features on transporter-interfering chemicals from manually curated literature data. The integrated resource TransPortal-TICBase (https://transportal.compbio.ucsf.edu) now contains information on 46 different mammalian xenobiotic transporters of the ABC- and SLC-type superfamilies, including 13 newly added rodent and 2 additional human drug transporters, 126 clinical drug–drug interactions, and a more than quadrupled expansion of the initial *in vitro* chemical interaction data from 1,402 to 6,296 total interactions. Based on our updated database, environmental interference with major human and rodent drug transporters occurs across the ABC- and SLC-type superfamilies, with kinetics indicating that some chemicals, such as the ionic liquid 1-hexylpyridinium chloride and the antiseptic chlorhexidine, can act as strong inhibitors with potencies similar or even higher than pharmacological model inhibitors. The new integrated web portal serves as a central repository of current and emerging data for interactions of prescription drugs and environmental chemicals with human drug transporters. This archive has important implications for predicting adverse drug–drug and drug-environmental chemical interactions and can serve as a reference website for the broader scientific community of clinicians and researchers.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Xenobiotic transporters are major rate-limiting determinants of human drug uptake and disposition. However, knowledge of how these proteins interact with environmental chemicals is limited, fragmented, and historically focused on aquatic organisms.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study addresses the urgent need to systematically evaluate existing kinetic interaction data to identify key transporter targets of environmental chemicals in the human body.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ We generated a centralized web resource to catalog and identify drug and environmental chemical interactions of immediate relevance to public health. Our metadata analysis revealed that the majority of environmental chemicals can interfere with mammalian drug transporters, thereby acting as strong inhibitors.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The new database serves as a free resource for the broader community of clinicians, researchers, and regulatory agencies to provide a detailed understanding of the molecular interactions kinetics between drugs and environmental chemicals, enabling the identification of novel drug-environmental chemical interactions and the mitigation of potentially harmful interactions.

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Humans and wildlife are continuously exposed to a wide-ranging mixture of manmade chemicals, with over 86,000 currently in commercial use in the United States (https://www.epa.gov/tsca-inventory). Many of these chemicals, such as persistent organic pollutants (POPs), resist degradation and remain in the environment for long periods. Continuous exposure to POPs in the air we breathe, the water we drink, and, in particular, the food we eat leads to their accumulation in samples of human blood and urine.[1–3] The Centers for Disease Control (CDC) currently monitors over 400 of these bioaccumulative chemicals, many of which can have harmful effects on health. These compounds and their complex mixtures have been associated with adverse outcomes, including cancer, hormone disruption, and developmental, cardiovascular, reproductive, and neurological disorders.[4,5]

Understanding the interaction of our xenobiotic defenses with these chemicals is key to understanding the biological basis for their bioaccumulation as well as determining safe levels of exposure. To act as xenobiotic defenses, drug transporters, expressed in specific tissues or a ubiquitous manner, play a crucial role in both the uptake and elimination of small molecules.[6,7] Clinical pharmacology and regulatory sciences have established that inhibiting intestinal efflux transporters through drugs, herbs, or food products can significantly increase the bioavailability of drug substrates, leading to adverse effects.[8,9] As a result, the US Food and Drug Administration (FDA) recommends *in vitro* and *in vivo* testing of all new drugs to determine interactions with essential transporters such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), as well as 7 SLC transporters—OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2.[10] The list of transporters relevant to drug discovery and development has since been expanded by the International Transporter Consortium (ITC) to include de-orphaned SLC transporters and intestinal uptake transporters that interact with microbial metabolites.[10] This testing aims to identify any drugs that might increase plasma or tissue-specific drug levels and potential drug toxicities by inhibiting the major intestinal efflux transporters (P-gp and BCRP) as well as influx transporters in the liver and kidneys (OATPs, OATs, MATEs, and OCT2). For example, concurrently using a statin and another drug that inhibits BCRP or OATPs may cause increased statin levels, leading to statin-induced muscle toxicities and even rhabdomyolysis.[11]

Targeting drug transporters can sometimes be advantageous, as seen in chemotherapy, where researchers are actively exploring the pharmacological inhibition of drug transporters to intentionally chemosensitize cancer cells and reverse multidrug resistance.[12] Nonetheless, accurately predicting the uptake, disposition, and toxicity of new drugs based on drug transporter-mediated drug–drug interactions (DDIs) remains a significant challenge for researchers, clinicians, the pharmaceutical industry, and regulatory agencies.[13,14]

Similar challenges exist regarding environmental chemicals. In aquatic organisms, drug transporter inhibition and the resulting chemosensitization of cells and organisms toward toxic environmental chemical bioaccumulation was first described over 30 years ago and has since been confirmed in non-aquatic organisms.[15–17] Recent research has shown that environmental chemicals similarly bind and inhibit vertebrate drug transporter function for mouse ABCB1 and tuna ABCB1.[18,19] These so-called transporter-interfering chemicals (or TICs) are typically present at low levels in food, but the sum of individual compounds can reach levels high enough to inhibit drug transporters and trigger consumption advisories based on the risk of developing cancer.[3,20] Determining exposure levels and characterizing the potencies of such environmental chemical modulators of xenobiotic transporter activity is crucial for better predicting the adverse effects of unintentional exposure to chemical mixtures on human and environmental health.

To assist in meeting these goals, we present TransPortal-TICBase (https://transportal.compbio.ucsf.edu), a new central repository for information on drug and environmental chemical interactions (DECIs) with mammalian drug transporters. In what follows, we discuss how this integrated web portal includes updates to the original University of California – San Francisco (UCSF)/FDA TransPortal database and review the additions of clinically relevant transporters, new mammalian model organisms, and relevant interactions. We also highlight the strong transporter inhibition potencies of several environmental chemicals identified in the UCSD/UCD-NIEHS TICBase. Finally, we emphasize the need for continuous biomonitoring of these drug TICs in food and humans and offer clinical and regulatory guidance to mitigate possible adverse health effects of drug-environmental chemical interactions.

METHODS

General database formatting

Primary research articles were searched for inhibition constant (K_i), half-maximal inhibitory concentration (IC_{50}), and Michaelis–Menten constant (K_M) values pertaining to transporter-chemical interactions. All analyzed data were derived from published human clinical studies and *in vitro* assays on transporters from model mammalian organisms, including human, rat, mouse, and monkey. The data collected about each *in vitro* transporter-chemical interaction includes transporter name, chemical name, quantitative kinetic value (K_i, IC_{50}, or K_M), *in vitro* assay system, reporter molecule, and article reference. Interactions are indexed by both transporter and chemical and divided into inhibition and substrate interactions. The clinical DDI data are listed as implicated transporter(s), interacting drug, affected drug, and the quantitative effects on pharmacokinetic parameters (area under the curve, maximum plasma concentration, renal clearance, total apparent clearance, and terminal half-life).

Transporter and chemical nomenclature

The ABC, SLC, SLCO, and OST transporter family naming systems were used according to the HUGO Gene Nomenclature Committee at the European Bioinformatics Institute (https://www.genenames.org) to standardize the protein nomenclature. Homologous proteins from different organisms, such as mouse Abcb1a and human ABCB1, are indexed as different proteins in the database and their respective data are displayed separately. When applicable, chemical nomenclature regarding geometric (i.e., ortho, para, and meta) and optical (i.e., − and +) stereoisomerism was accounted for.

Environmental chemical classification

The updated database includes novel environmental chemical interactions with drug transporters. The basic criteria for this classification are that chemicals have to be synthetic, are (or have previously been) used in consumer products or industrial applications but are not intended for

human exposure. These compounds are distinguished from pharmaceuticals, endogenous compounds, natural chemicals from the environment (such as plant or fungal compounds), and substances found in food or supplements.

RESULTS

Despite a long history of pharmacological investigations into the key role drug transporters play in drug uptake and disposition, information on drug transporter interactions with environmental chemicals is scarce and fragmented. As such, TransPortal-TICBase seeks to establish a holistic approach in pharmacology and toxicology that offers a more complete and comprehensive understanding of the effects of drugs, food, herbs, and environmental chemicals on the body. By systematically expanding and establishing a comprehensive database of clinically relevant transporter proteins that includes both DDIs and novel DECIs, we seek to facilitate communication between pharmacological and (eco)toxicological researchers working at the interface of human and environmental health and harmonize the language of both fields.

Updates to the TransPortal database

The early TransPortal database was the first of its kind and contained information on more than 1,400 DDIs and 31 human drug transporters.[21] However, it lacked interaction data from other important pharmacological and toxicological animal models, such as rodents or primates. In the 10 years since its publication, significant advances in the field of drug transporter research have been made; at the same time, many new drugs have entered the global market, with a 5-year average FDA approval rate of 46 novel therapeutics per year.[22]

This update to the original database now totals 46 different mammalian drug transporters of the ABC- and SLC-type superfamilies, including 13 newly added rodent and 2 additional human drug transporters (**Figure 1**, **Table 1**), 126 clinical DDIs (of which 78 are newly added), and a more than quadrupled expansion of the initial *in vitro* interaction data (from 1,402 to 6,296 total interactions). This update reflects the current state of understanding regarding drug transporters of clinical relevance that are known targets of pharmacokinetic DDIs.[10,23] Approximately 70% of those transporters are human SLC- ($n = 23$) and ABC-type ($n = 10$) transporters, with the remainder consisting of rodent SLC ($n = 9$), mouse ABC ($n = 3$), and grivet ($n = 1$) ABCB1 transporters. Over 85% ($n = 5{,}480$) of the listed kinetic interactions of chemicals with drug transporters in the updated database are inhibitory, emphasizing the need for developing novel methods for the improved discovery of transporter substrates.[16] Besides the drug interaction data, the updated database also contains transporter protein localization and gene expression data for five different human organs (the brain, kidneys, liver, placenta, and small intestine).

Drug transporter interactions with environmental chemicals

For the first time, the updated TransPortal-TICBase database features coherently integrated environmental chemical interactions with mammalian drug transporters. TICBase was originally developed as a collaborative, in-house collection of all known drug transporter-interfering chemicals established in the Hamdoun and Nicklisch laboratories. The integration of this information with TransPortal not only allows global dissemination and free access to those data but also creates a central repository for connecting pharmacological and toxicological research at the interface of DECIs.

A total of 134 environmental chemical interactions with mammalian drug transporters have been added to the new database, with over 90% of those ($n = 121$) being inhibitory and 13 substrate interactions. Among those 134 interactions, 94 (9 substrates and 85 inhibitors) were measured with human drug transporters, whereas 31 (all inhibitors) and 9 (4 substrates and 5 inhibitors) were determined with mouse and rat transporters, respectively. When separated by superfamily, 71 interactions (3 substrates and 68 inhibitors) were determined with ABC-type transporters, and 63 (10 substrates and 53 inhibitors) were measured with SLC-type transporters.

The IC_{50} of the top 30 most potent inhibitory environmental chemicals range from 0.35 to 5.7 µM (**Table 2**) and are well within the range of the IC_{50} values for FDA-recommended model inhibitors of drug transporters (**Table 3**). The most potent inhibitor found among the environmental chemicals is the ionic liquid 1-hexylpyridinium chloride (HPy-Cl) acting on human SLC22A2 (OCT2) with an IC_{50} of 0.35 µM, followed by the antiseptic chlorhexidine acting on human SLC22A2 (OCT2) and SLC22A3 (OCT3) with an IC_{50} of 0.4 µM (**Table 2**). These chemicals, together with the flame retardant Tetrabromobisphenol A (TBBPA)—acting on SLC22A8 (OAT3) and SLCO1B1 (OATP1B1)—and the ionic liquid *N*-butyl-*N*-methylpyrrolidinium chloride (BmPy-Cl)—acting on SLC22A2 (OCT2), SLC22A3 (OCT3), SLC47A1 (MATE1), and SLC47A2 (MATE2-K)—have IC_{50} values below 1 µM when interacting with SLC-type transporters (**Figure 2**).

Ionic liquids (ILs) are liquid salts often described as "green solvents" due to their low volatility at room temperature, low flammability, high chemical stability, and their organic and inorganic ion composition. Their unique tunable physical and chemical properties inspired a continuous evolution of second and third-generation ILs with tailored biological and chemical properties in the last 2 decades with an eye toward their application in the pharmaceutical and chemical industries.[24] Due to their poor degradability in the environment, ILs have been regularly detected in aquatic and terrestrial ecosystems.[25] Given the strong positive growth rates in IL patent applications since 2004 and a predicted market size reaching $4.5 billion by 2027, human exposure to these ubiquitous environmental chemicals is likely to increase.[25]

Chlorhexidine and its salts are one of the most widely used over-the-counter disinfectant and antiseptic agents used for oral hygiene and cleaning skin and wounds to reduce the risk of surgical site infections in humans and livestock. As such, human exposure to this potent class of transporter-interfering compounds is intentional and is likely to increase due to its known overuse in healthcare settings and existing regulatory guidance on its impregnation in wound dressings and catheters.[26] Notably, one

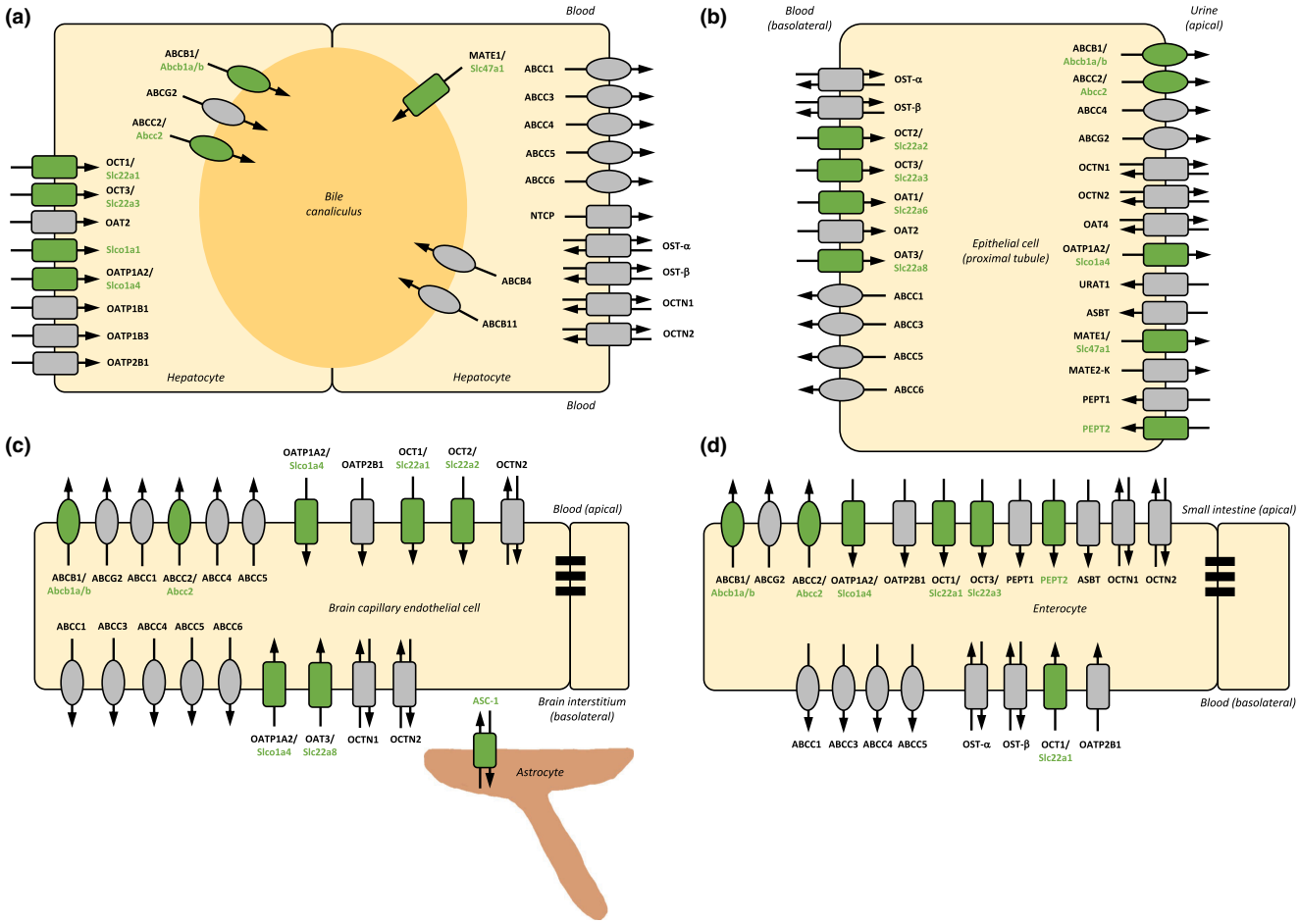

Figure 1 Drug transporter localization in four representative biological barriers in human. Shown are apical and basolateral membrane localization of all ABC and SLC transporters listed in the database for (**a**) liver, (**b**) kidneys, (**c**) brain, and (**d**) small intestine (adapted fromref. 16). The anticipated direction of substrate and co-substrate flow are marked with arrows. Tight junctions are displayed as a group of three black bars in the indicated cell type. Newly added human, rodent, and monkey transporters are highlighted in green.

of the highest medical chlorhexidine concentrations (7.1% chlorhexidine digluconate) is currently used for newborn umbilical cord care and is included in the World Health Organization (WHO) Model List of Essential Medicines (https://list.essentialmeds.org).

TBBPA is still one of the highest-selling brominated flame retardants worldwide, primarily used in epoxy and polycarbonate resins for electronics, appliances, and computer boards.[27,28] Although current production volumes of TBBPA are often difficult to obtain, it is estimated that TBBPA accounts for almost 60% of all brominated flame retardants manufactured worldwide, with an annual global production volume of 150,000 tons.[28] One of the major pathways for non-occupational exposure to TBBPA is through the intake of contaminated food, contact with consumer goods, and even inhaling the dust of indoor environments.[29,30]

It is important to stress that despite the limited data on the 134 tested environmental chemicals (approximately covering 2% of the total database), several of these compounds that show high drug transporter inhibition potencies are still produced and in use in the United States and worldwide. Furthermore, some of those inhibitors can be readily detected in human biofluids, indicating that they can exert systemic effects on drug transporters throughout the body (**Table 2**).

DISCUSSION

Levels of TICs in human body fluids

Arguably, the gold standard of cumulative human biomonitoring data on environmental chemical exposures is the CDC's biannual National Exposure Report.[2] From a random 2,500-participant subsample of the National Health and Nutrition Examination Survey (NHANES), the levels of more than 400 environmental chemicals, and their metabolites in human blood, urine, and saliva samples are calculated (https://www.cdc.gov/nchs/nhanes). The report summarizes the representative and cumulative biomonitoring data collected from surveys on the US population's exposure to environmental chemicals between 1999 and 2018 with categories defined by race/ethnicity, gender, age group, and survey years.

Of the top 30 environmental chemical inhibitors listed in **Table 2**, only 4—p,p′-DDE, p,p′-DDT, pentachlorophenol, and mirex—are currently measured under CDC's National Biomonitoring Program (https://www.cdc.gov/biomonitor

Table 1 List of all 46 drug transporters and host organisms described in the updated TransPortal-TICBase repository

#	Human	Rodents	Monkey
ABC Transporters			
1	ABCB1 (MDR1)[EC]	***mouse_Abcb1a*[EC]**	***grivet_ABCB1***
2	ABCB11 (BSEP)	***mouse_Abcb1b***	
3	ABCB4 (MDR3)	***mouse_Abcc2***	
4	ABCC1 (MRP1)		
5	ABCC2 (MRP2)[EC]		
6	ABCC3 (MRP3)		
7	ABCC4 (MRP4)[EC]		
8	ABCC5 (MRP5)		
9	ABCC6 (MRP6)		
10	ABCG2 (BCRP)[EC]		
SLCs			
1	***SLC7A10 (ASC-1)***	***mouse_Slco1a4***	
2	SLC10A1 (NTCP)[EC]	***rat_Slc22a1***	
3	SLC10A2 (ASBT)	***rat_Slc22a2***	
4	SLC15A1 (PEPT1)	***rat_Slc22a3***	
5	***SLC15A2 (PEPT2)***	***rat_Slc22a6*[EC]**	
6	SLC22A1 (OCT1)[EC]	***rat_Slc22a8*[EC]**	
7	SLC22A11 (OAT4)	***rat_Slc47a1*[EC]**	
8	SLC22A12 (URAT1)[EC]	***rat_Slc7a10***	
9	SLC22A2 (OCT2)[EC]	***rat_Slco1a1***	
10	SLC22A3 (OCT3)[EC]		
11	SLC22A4 (OCTN1)		
12	SLC22A5 (OCTN2)		
13	SLC22A6 (OAT1)[EC]		
14	SLC22A7 (OAT2)		
15	SLC22A8 (OAT3)[EC]		
16	SLC47A1 (MATE1)[EC]		
17	SLC47A2 (MATE2-K)[EC]		
18	SLC51A (OSTalpha)		
19	SLC51B (OSTbeta)		
20	SLCO1A2 (OATP1A2)		
21	SLCO1B1 (OATP1B1)[EC]		
22	SLCO1B3 (OATP1B3)[EC]		
23	SLCO2B1 (OATP2B1)		

Transporters in bold and italics ($n=15$) are completely new additions to the database. Transporter aliases are written in parentheses.
[EC]=Transporters ($n=20$) with data on environmental chemical interactions; mouse=Mus musculus (House mouse); rat=Rattus norvegicus (Brown rat); grivet=Cercopithecus aethiops (African green monkey).

ing/). Between survey years 1999 and 2004, p,p′-DDE was detected at high levels in all sera, whereas the levels of the other 3 chemicals in blood and urine samples often registered below the limit of detection. Yet, for some groups, concentrations are significantly higher (95th percentile) than expected. For example, in survey years 2003–2004, pentachlorophenol in urine for those aged 6 to 11 years in the total population ranged from 3.6 to 10.6 μg/g creatinine. The levels of p,p′-DDT in the serum of Mexican Americans (1999–2000 survey) and Mirex in Non-Hispanic Blacks (2001–2002 survey) ranged unexpectedly higher as well—between 59.3–590 ng/g lipid and 30.5–425 ng/g lipid, respectively. For p,p′-DDE, the geometric mean of serum levels ranged from 84.7 ng/g lipid for teenagers aged 12–19 years (2003–2004 survey) to 792 ng/g lipid for Mexican Americans (1999–2000 survey). In some extreme cases, p,p′-DDE levels of up to 6,900 ng/g lipid and 15,600 ng/g lipid were detected in the 2001–2002 survey for Non-Hispanic Blacks and Mexican Americans, respectively. Assuming an average serum lipoprotein mass density of 1.01[31] and a molecular weight of 318 g/mol for p,p′-DDE, these extreme concentrations translate to 21.7 and 49.1 μM, which is well within the range of the measured IC_{50} for human ABCG2 (p,p′-DDE $IC_{50}=4$ μM) and mouse ABCB1a (p,p′-DDE $IC_{50}=31.3$ μM) in our database. Mirex and the three DDT congeners (p,p′-DDD, p,p′-DDE, and p,p′-DDT) have been previously shown to act on human, mouse, and fish ABCB1 transporters.[18,19]

An important consideration for evaluating the toxic effects of bioaccumulative TICs is that they typically occur as mixtures in human food sources.[3,32,33] Hence, whereas individual compounds can be present at low levels, the sum of compounds can reach levels high enough to inhibit drug transporters and trigger consumption advisories for both general and vulnerable populations.[3,20] Those inhibitory effects can be further amplified by dietary habits, lifestyle, and specific metabolism, accumulation, and elimination rates.[34] For instance, the accumulation and risk of adverse DDIs with toxic chemicals that occur in meat and dairy products might be lower than the average in vegan and vegetarian populations, but higher in communities that rely on them as primary food sources.

Genetic, developmental, and occupational susceptibilities to TICs

Higher exposure levels to toxic environmental chemicals in different ethnic groups can have important impacts on xenobiotic disposition and elimination.[35] Clinical observations have shown that genetic variations in drug transporter genes, based on an individual's ethnic background, can introduce complexity into therapeutic treatment plans.[10,36,37] For example, individuals of African ancestry have a low allele frequency of functional variants in BCRP-Q141K and OATP1B1-V174A compared with those with European or Asian heritage.[37] This may potentially result in altered bioavailability and disposition of statins, methotrexates, and other drugs that are substrates of one or both of these transporters.[38] According to the 2020 US Census Bureau (https://www.census.gov), the US population has a wide range of ethnic and racial groups, including ~60.6% White, 18.1% Hispanic or Latino, 12.3% Black or African American, 5.5% Asian, 0.7% American Indian and Alaska Native, 0.2% Native Hawaiian and other Pacific Islander, with 0.3% reporting other races and 2.4% identifying as 2 or more races. Predicting interethnic pharmacogenetic susceptibility toward co-administered drugs as well as from unintentional exposure to environmental

Table 2 Top 30 environmental chemicals in TICBase ranked by transporter inhibition potency

Environmental chemical	PubChem CID	Classification	Transporter	IC_{50} (μM)	Assay environment	References
HPy-Cl	2,734,172	Ionic liquid	SLC22A2	0.35	CHO cells	66
Chlorhexidine	9,552,079	Antiseptic	SLC22A2	0.4	HEK293 cells	67
Chlorhexidine	9,552,079	Antiseptic	SLC22A3	0.4	HEK293 cells	68
BmPy-Cl	11,769,095	Ionic liquid	SLC22A2	0.48	CHO cells	66
Chlorhexidine	9,552,079	Antiseptic	SLC47A2	0.5	HEK293 cells	67
Tetrabromobisphenol A	6,618	Flame retardant	SLC22A8	0.5	HEK293 cells	69
Tetrabromobisphenol A	6,618	Flame retardant	SLCO1B1	0.6	CHO cells	69
Chlorhexidine	9,552,079	Antiseptic	SLC47A1	0.7	HEK293 cells	67
Endrin	3,048	OC pesticide	mouse_ Abcb1a	1.1	Purified protein	18
Bmim-Cl	2,734,161	Ionic liquid	SLC22A2	1.5	CHO cells	66
Pentachlorophenol*	992	OC pesticide	ABCB1	1.6	MDCK II cells	70
NBuPy-Cl	2,734,171	Ionic liquid	SLC22A6	1.6	CHO cells	66
NBuPy-Cl	2,734,171	Ionic liquid	ABCB1	2.29	CHO cells	66
Allethrin	11,442	Pyrethroid insecticide	SLC22A1	2.6	HEK293 cells	71
Endosulfan	3,224	OC pesticide	ABCB1	2.8	NIH 3T3 cells	72
Fenamiphos	31,070	OP pesticide	SLC22A2	2.8	HEK293 cells	73
Phosalone	4,793	OP pesticide	ABCB1	3	NIH 3T3 cells	72
p,p′-DDD** (DDT metabolite)	6,294	OC pesticide	ABCG2	3	Sf9 membranes	74
Mirex*	16,945	OC pesticide	mouse_ Abcb1a	3	Purified protein	18
Propiconazole	43,234	Triazole fungicide	ABCB1	3.6	NIH 3T3 cells	72
Phosmet	12,901	OP pesticide	SLC22A2	3.6	HEK293 cells	73
Chlorhexidine	9,552,079	Antiseptic	SLC22A3	3.7	HEK293 cells	68
p,p′-DDT*	3,036	OC pesticide	ABCB1	3.8	Sf9 membranes	74
p,p′-DDE* (DDT metabolite)	3,035	OC pesticide	ABCG2	4	Sf9 membranes	74
PCB-145	93,442	PCB	mouse_ Abcb1a	4.4	Purified protein	18
Tetrabromobisphenol A	6,618	Flame retardant	SLC10A1	4.5	HEK293 cells	69
Tetramethrin	83,975	Pyrethroid pesticide	SLC22A1	4.9	HEK293 cells	71
p,p′-DDT*	3,036	OC pesticide	ABCG2	5	Sf9 membranes	74
Resmethrin	5,053	Pyrethroid pesticide	ABCG2	5.6	Sf9 membranes	74
Tetramethrin	83,975	Pyrethroid pesticide	SLCO1B1	5.7	CHO cells	71

Listed are the interacting chemical, the target transporter, the determined IC_{50} value in micromolar (μM), the chemical classification, the originating reference, and the assay environment (i.e., cellular, membrane patches, or purified protein). The chemicals marked with an asterisk are directly measured (*) or known metabolites (**) of the detected compounds in human blood or urine samples.[2]
Bmim-Cl, 1-butyl-3-methylimidazolium chloride; BmPy-Cl, *N*-butyl-*N*-methylpyrrolidinium-chloride; HPy-Cl, 1-hexylpyridinium-chloride; IC_{50}, half-maximal inhibitory concentration; NBuPy-Cl, *N*-butylpyridinium-chloride; OC, organochlorine; OP, organophosphate; PCB, polychlorinated biphenyl.

chemicals is an understudied but crucial dimension to clinical and regulatory decision making for precision medicine and improved patient care.

In addition, higher exposure levels to toxic environmental chemicals during human development can have important impacts on xenobiotic disposition and elimination. Drug transporter localization and expression levels are known to change during development, typically involving an increase in transporter expression from the fetal to adult stage.[39,40] Reduced expression of drug transporters during early development makes infants and young children particularly vulnerable to xenobiotic insult.[41] This scenario is further aggravated in cases where nursing infants suffer increased exposure

Table 3 Ranges of IC_{50} values (in micromolar) of *in vitro* inhibitors of clinically relevant drug transporters listed in the updated TransPortal database

FDA-recommended inhibitors	SLC22A2 (μM)	SLC22A6/A8 (μM)	SLCO1B1/B3 (μM)	ABCB1 (μM)	ABCG2 (μM)	SLC47A1/A2 (μM)
Benzylpenicillin		137				
Cimetidine	25.4–373					1.2–39
Cyclosporine			0.05–3.5	0.1–9.3		
Elacridar (GF120918)				0.027–0.18	0.31	
Estradiol glucuronide			n.a.			
Estrone sulfate			0.06–0.79			
Fumitremorgin C					0.25–0.47	
Ketoconazole				1.2–53.4		
Ko134					n.a.	
Ko143					0.01–0.4	
Novobiocin					1.4	
Probenecid		1.9–24.6				
Pyrimethamine						0.01–0.07
Quinidine				1–340		
Reserpine				0.5–6.1		
Rifampicin			0.24–120			
Ritonavir				3.8–28.2		
Sulfasalazine					0.61–2.9	
Tacrolimus				n.a.		
Valspodar (PSC833)				0.11–3.2		
Verapamil				0.2–446.5		
Zosuquidar (LY335979)				0.024–0.1		

Shown are the FDA-recommended *in vitro* inhibitors for drug development and drug interactions (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table4-2). Model inhibitors in italics are not available (n.a.) in the current transporter database.
FDA, US Food and Drug Administration; IC_{50}, half-maximal inhibitory concentration.

to maternally mobilized xenobiotics that can be concentrated in colostrum, transitional, and mature breast milk.[42,43] Pregnant and nursing women often take multiple transporter-active prescription and illicit drugs during and after pregnancy, including antidepressants, antipsychotics, and cannabis, which can accumulate in breast milk.[44,45] A better understanding of the breast milk levels of environmental chemicals and drugs during the different stages of lactation could allow for proper mitigation strategies (e.g., "pump and dump") to protect infant health.

Another vulnerable population is the elderly, who often take different types of drugs simultaneously (i.e., polypharmacy) to treat multiple medical conditions.[46] The interference of TICs with drug or drug metabolite elimination processes could further complicate medication management and safe dosing regimens in elderly patients. Drugs and TICs in mixtures can act on the same drug transporters, effectively reducing the concentration levels needed for individual compounds to inhibit these proteins.[16,18] As such, strategies to safely manage or reduce polypharmacy in the elderly could be supported by toxico-nutritional information on dietary intakes and eating patterns of elderly people that ultimately reduce TIC body burden.

Nor are the only groups at higher risk of adverse DECIs acting on drug transporters and other metabolic enzymes defined by age. Among commonly consumed dietary items contaminated with multiple environmental chemicals, fish and fish oil often have the highest detected levels.[1,3] As such, coastal communities that primarily rely on fish and seafood as their primary protein source are at higher risk of exposure to environmental contaminants.[47] From an occupational perspective, firefighters also face increased exposure to hazardous airborne environmental chemicals and regularly have flame retardants and other chemicals detected in their blood,[48] whereas farmworkers directly inhale fumigants and semi-volatile pesticides when working in fields and indirectly ingest them through contaminated food and water.[49,50]

CONCLUSION AND FUTURE DIRECTIONS

By systematically collating and summarizing existing kinetic interaction data on environmental chemicals with mammalian drug transporters, the TransPortal-TICBase is a crucial first step toward identifying key molecular targets of environmental chemicals. The future central repository will include additional

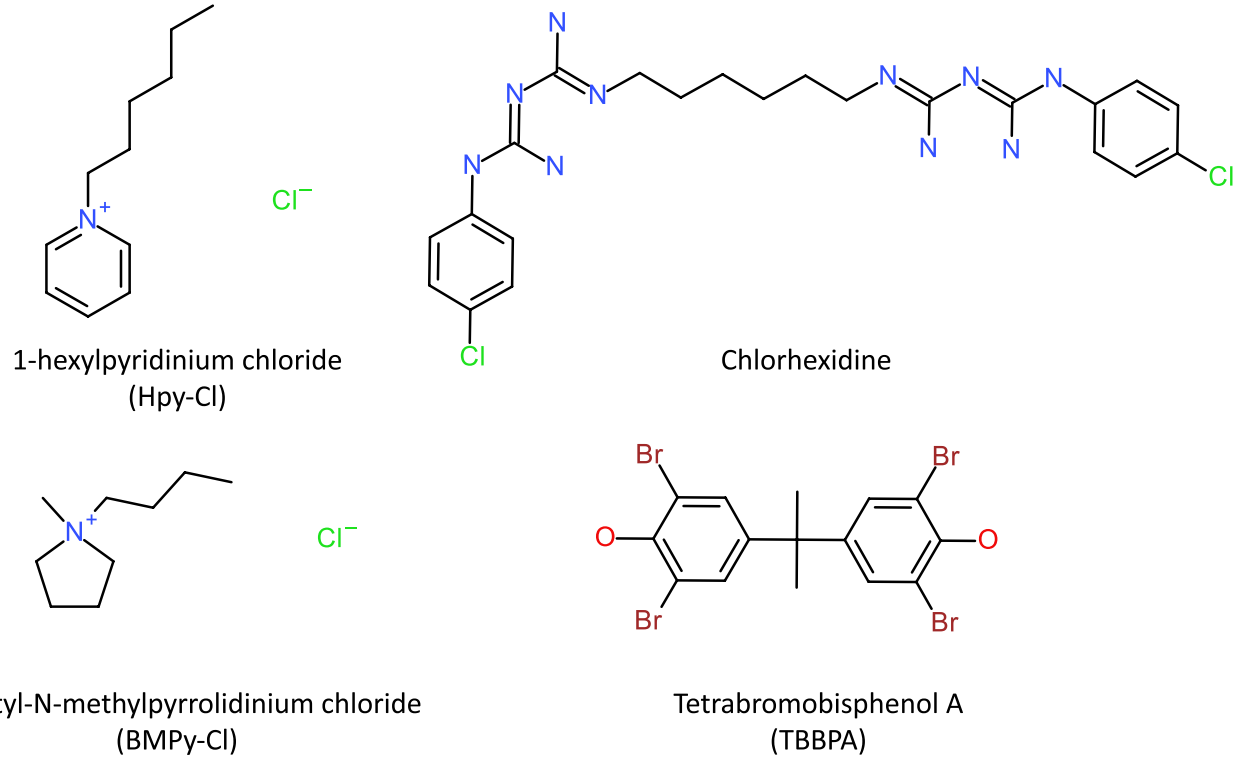

Figure 2 Chemical structures of the most potent inhibitory TICs in the database with IC_{50} values below 1 μM. Shown are the two ionic liquids (1-hexylpyridinium chloride and *N*-butyl-*N*-methylpyrrolidinium chloride) which are potent inhibitors of SLC22A2 (OCT2), SLC22A3 (OCT3), SLC47A1 (MATE1), and SLC47A2 (MATE2-K), the antiseptic Chlorhexidine, which is a potent inhibitor of SLC22A2 (OCT2), and the brominated flame retardant Tetrabromobisphenol A (TBBPA) which potently inhibits two anion transporters SLC22A8 (OAT3) and SLCO1B1 (OATP1B1; **Table 2**). IC_{50}, half-maximal inhibitory concentration.

drug transporter information, including gene (mRNA) and protein expression levels and localization stratified by organ, tissue, cellular, and subcellular levels to better understand loci of absorption and directional transport of chemicals within the body. Furthermore, comprehensive metadata on chemical classes and physicochemical properties, such as molecular weight, pKa, and K_{ow}, will be added to allow the prediction of chemical bioavailability and disposition. This open-access web platform will help researchers, clinicians, the pharmaceutical industry, and regulatory agencies understand how these chemicals may inhibit transporter function as well as how to mitigate possible adverse DDIs and DECIs.

Incorporating data from a broader swath of the exposome should also be a priority goal for this central repository. Of the total drug transporter interactions listed in the updated database, approximately only 2% ($n = 134$) involve environmental chemicals, most of which are legacy POPs that have already been banned or restricted for use or production worldwide (http://chm.pops.int/). However, critically lacking is human biomonitoring data regarding drug transporter interactions with emerging chemical compounds, such as the ever-increasing number of congeners of environmental Per- and Polyfluoroalkyl Substances[51] and natural or synthetic cannabinoids.[52] As such, the future version of TransPortal-TICBase is anticipated to include human exposome and biomonitoring data, such as from blood, breast milk, and urine samples, to provide information on physiological levels of the drug transporter inhibitors in the database.[2,53,54]

Given the pace at which these new synthetic chemicals and polymers enter the global market,[55,56] it is important both to develop modern high throughput assays to rapidly identify and predict environmental chemical accumulation potential and to validate those observations by continuing to monitor chemical contamination in food and their incidence in human body fluids. Data-driven approaches that combine computational methods (such as machine learning and network analysis) with exposome and metabolome data are an emerging strategy to rapidly identify and predict relationships between co-accumulating drugs and xenobiotics and their adverse health effects on organisms.[57] Implementing analogous data visualization and discovery tools in a future version of the TransPortal-TICBase could help prioritize the selection of drugs and chemicals for pharmacokinetic and toxicokinetic laboratory analysis.[58]

The fact that drug transporters of the ABC and SLC families also transport endogenous compounds adds another layer of complexity toward a holistic understanding of the effects of inhibitory environmental chemicals on the disposition of drug substrates and the overall balance of endogenous compound substrates in the body.[7,59] The significance of ABC and SLC in regulating intracellular levels of endogenous metabolites, antioxidants, and signaling molecules in different human tissues are well-documented.[59,60] Drug and environmental

chemical-induced inhibition or induction of these transporters can affect the uptake and distribution of endogenous compounds, ultimately disrupting the normal physiological functions and possibly leading to altered therapeutic responses. Further research on the physiological impacts of environmental chemical-induced inhibition of drug transporters is necessary to fully understand their toxicological and clinical significance.

As outlined above, some of the remaining challenges in using human pharmacokinetic parameters and plasma-concentration time curves for *in vitro* to *in vivo* extrapolation and physiologically-based pharmacokinetic modeling (to better predict transporter-mediated disposition and elimination of drugs and other xenobiotics within the body) are related to confounding factors, such as organ- and tissue-specific differences in compound concentrations, substrate- and time-dependent transporter inhibition,[61–63] plasma protein binding, and bioavailability,[64,65] as well as age-dependent transporter gene expression levels[39–41] and interindividual and interethnic differences in genetic polymorphism.[10,36,37] A future version of TransPortal-TICBase is anticipated to include polymorphic transporter gene variants to personalize interaction prediction.

A detailed understanding of the molecular interaction kinetics of drugs and environmental chemicals with drug transporters from humans and other organisms is necessary to provide new avenues for the design of "greener" chemicals that are less persistent, bioaccumulative, and toxic for human and non-target organisms. In addition, being able to foresee and mitigate potential adverse interactions of TICs and novel drug candidates with human drug transporters will be crucial for the development of safe and effective drug dosing regimens for both susceptible and vulnerable populations.

Relational databases that list DDI data on metabolic enzymes and drug transporters have been developed in the past, including the qualitative interaction data in the Comparative Toxicogenomics Database (https://ctdbase.org), the Antifungal Drug Interaction Database (https://antifungalinteractions.org), as well as commercially available qualitative and quantitative interaction databases, such as the DrugBank (https://www.drugbank.com), DDInter (http://ddinter.scbdd.com), and Certara's Drug Interactions Solutions (https://www.druginteractionsolutions.org), formerly known as the University of Washington Drug Interaction Database or DIDB. To our knowledge, these databases do not include kinetic interaction data on rodent or primate drug transporters. Furthermore, none of these databases contains human drug transporter interaction data on legacy and emerging environmental chemicals that are unique to the updated TransPortal-TICBase.

Since its launch in 2012, TransPortal-TICBase has been frequently accessed, with over 484,000 views by more than 58,000 users from 163 countries. To keep the TransPortal-TICBase current, accurate, and freely accessible, the authors aim to roll out annual database updates that will include new kinetic interaction data generated in continuing student research projects in each of the involved laboratories. In addition, we encourage the ongoing expansion and support of the database through external contributions from multiple research collaborations and projects across disciplines.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

M.E.M., K.M.G., A.H., and S.C.T.N. wrote the manuscript. A.H., and S.C.T.N. designed the research. M.E.M., C.C.W., and S.W.Y. performed the research. M.E.M., S.W.Y., and S.C.T.N. analyzed the data. K.M.G. contributed new reagents/analytical tools. S.C.T.N. designed the research, wrote the manuscript, and analyzed the data.

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