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Human variability in influx and efflux transporters in relation to uncertainty factors for chemical risk assessment

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ABSTRACT

Transporters are divided into the ABC and SLC super-families, mediating the cellular efflux and influx of various xenobiotic and endogenous substrates. Here, an extensive literature search was performed to identify *in vivo* probe substrates for P-gp, BCRP and OAT1/3. For other transporters (e.g. OCT, OATP), no *in vivo* probe substrates could be identified from the available literature. Human kinetic data (Cmax, clearance, AUC) were extracted from 142 publications and Bayesian meta-analyses were performed using a hierarchical model to derive variability distributions and related uncertainty factors (UFs). For P-gp, human variability indicated that the kinetic default UF (3.16) would cover over 97.5% of healthy individuals, when considering the median value, while the upper confidence interval is exceeded. For BCRP and OAT1/3 human variability indicated that the default kinetic UF would not be exceeded while considering the upper confidence interval. Although limited kinetic data on transporter polymorphisms were available, inter-phenotypic variability for probe substrates was reported, which may indicate that the current default kinetic UF may be insufficient to cover such polymorphisms. Overall, it is recommended to investigate human genetic polymorphisms across geographical ancestry since they provide more robust surrogate measures of genetic differences compared to geographical ancestry alone. This analysis is based on pharmaceutical probe substrates which are often eliminated relatively fast from the human body. The transport of environmental contaminants and food-relevant chemicals should be investigated to broaden the chemical space of this analysis and assess the likelihood of potential interactions with transporters at environmental concentrations.

1. Introduction

Over the last two decades, efflux and influx transport proteins, expressed in a wide range of organs in the human body, have become increasingly important due to their critical role in the pharmacokinetics (PK) and toxicokinetics (TK) of xenobiotics, potentially affecting their absorption, distribution, and excretion (ADE) along with phase I and phase II metabolism (Clerbaux et al., 2019). Significant differences in substrate specificity, tissue distribution, and relative abundance of transporters have been described between experimental animal models and humans and such knowledge bring another level of complexity to ADME processes as well as the potential to improve inter-species extrapolations for hazard characterisation and risk assessment purposes. In addition, inter-phenotypic differences in transporter expression and activities have been demonstrated and can ultimately result in further modulation of the kinetics and toxicity of chemicals (Burt et al., 2016; Harwood et al., 2019; Zhang and Lauschke, 2019). In this context, the Adenosine Triphosphate Binding Cassette Protein (ABC) superfamily of efflux transporters mediate the removal of exogenous compounds, import of nutrients, transport of endogenous substances, and impact on signal transduction. ABC transporters include multidrug-resistance protein 1 (ABCB1/MDR1) also named P-glycoprotein, the multidrug resistance-associated protein (MRP) family, the bile salt export pump (BSEP/*ABCB11*), the multidrug and toxin extrusions (MATE1/MATE2-K) and breast cancer resistant proteins (BCRP/ABCG2). P-glycoprotein (P-gp) is extensively expressed in key organs including the liver, kidney,

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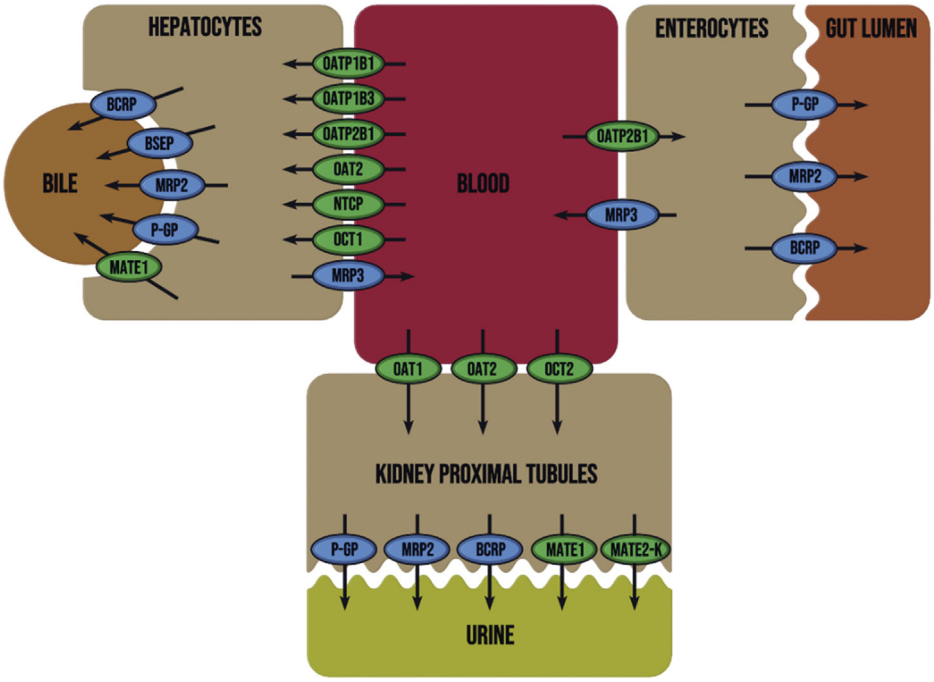

Fig. 1. Membrane transporters in the human liver, kidney and intestine (blue: ABC transporters, green: SLC transporters). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

central nervous system, small intestine and lymphoid tissues, and is involved in the transport of a range of substrates including fats, sugars, amino acids, drugs and other xenobiotics (Calcagno et al., 2017) (Fig. 1). Likewise, BCRP is present in many organs and transports xenobiotics and endogenous substrates (Heyes et al., 2018; Hira and Terada, 2018; Urquhart et al., 2008). A second superfamily of membrane transporter are solute carriers, acting mostly but not exclusively as influx or chemical uptake transporters. This group includes organic cation transporters (OCTs), organic anion transporters (OATs) as well as organic-anion-transporting polypeptides (OATPs).

Information and data on the kinetic of probe substrates, inducers and inhibitors of such transporters are increasingly available particularly for pharmaceuticals for potential drug-drug interactions but also for food and environmental chemicals such as pesticides, mycotoxins, perfluoroalkyl compounds, flavonoids and other natural bioactive compounds (e.g. coumarins, resins, saponins, terpenoids) (Chedik et al., 2017, 2018, 2019; Clerbaux et al., 2019; Dewanjee et al., 2017; Fardel et al., 2012; Guéniche et al., 2020). Examples of relevance to food safety include flavonoids and curcumin as inhibitors of BCRP and capsaicin and piperine as P-gp inhibitors (Fan et al., 2019; Kusuhara et al., 2012). Several food-drug interactions have also been described for OATPs, particularly with grapefruit juice, which inhibits OATP1A2 (Fan et al., 2008; Kalliokoski and Niemi, 2009; Oswald, 2019).

The role of phase I and phase II xenobiotic-metabolising enzymes is well documented in chemical risk assessment (Ginsberg et al., 2009), while transporters are less well characterised, although they can contribute significantly to human variability in kinetic and dynamic processes. Such quantitative understanding can contribute to the refinement of default uncertainty factors (UF) with pathway-related UFs, chemical-specific adjustment factors (CSAFs) and the development of physiologically based kinetic models (Clerbaux et al., 2018; Clerbaux et al., 2019; Ginsberg et al., 2002; Ginsberg et al., 2009; Hattis et al., 1999; Valcke and Krishnan, 2013). Based on the WHO guidance of uncertainty in hazard assessment (WHO, 2017), the geometric standard deviation for inter-individual variability in the human equipotent dose distribution ($\log(GSD_H)$) has been proposed to calculate UFs (P95/P50) (Hattis and Lynch, 2007). Next to this, meta-analysis has been conducted to derive pathway-related UFs for several phase I and phase II metabolic pathways and renal excretion (Dorne, 2010; Dorne et al., 2001a, 2001b, 2002, 2003a, 2003b, 2004a, 2004b) and recently, this methodology has been update using hierarchical Bayesian models (Darney et al., 2019, 2020; Quignot et al., 2019; Wiecek et al., 2019). Since human variability in the kinetics of probe substrates for efflux and influx transporters has not been investigated to date, this paper aims to fill this data gap particularly for the most clinically relevant representatives of efflux and influx transporters.

This manuscript, as part of an EFSA funded project addressing human variability in metabolism and transporters aims specifically to i) quantify human variability associated with efflux and influx transporter proteins for well-characterised probe substrates of P-gp, BCRP, MATE1/MATE2-K, OAT1/3, OCTs, and OATPs using hierarchical Bayesian meta-analysis ii) derive UFs from the variability analysis and assess whether the default kinetic UF is sufficiently protective. In addition, inter-phenotypic differences for well characterised single nucleotide polymorphisms (SNPs) in the human population as well inter- and intra-ethnic differences are investigated for transporters with available data.

2. Material and methods

2.1. Extensive literature search

In vivo probe substrates for P-gp, BCRP and OAT1/3 were identified from the FDA website and datasheets while for other transporters (OCT, OATPs, MATE1/MATE2-K), no *in vivo* specific probe substrates were available (FDA, 2017). For each probe substrate, extensive literature searches (ELS) were conducted in PubMed and Scopus (1966–June 2019) according to the EFSA guidance document using search terms related to human PK studies provided in Table 1 (EFSA, 2010). Specifically, data from human PK studies reporting markers of oral (single) or intravenous (bolus) acute (Cmax) and chronic exposure (area under the curve (AUC), clearance) were collected for healthy adults from different geographical ancestry or ethnic backgrounds. In addition, data for inter-phenotypic differences were investigated from the literature for three different SNPs in P-gp (3435C > T, 1236C > T,

Table 1
List of search queries for the Extensive Literature Searches on human kinetic for probe substrates of efflux and influx transporters.

Search probe substrate	TITLE-ABS (“*name of probe substrate*”)
Population	(TITLE-ABS (human) OR TITLE-ABS (adult*) OR TITLE-ABS (child) OR TITLE-ABS (children) OR TITLE-ABS (infant) OR TITLE-ABS (neonate) OR TITLE-ABS (newborn*) OR TITLE-ABS (elderly) OR TITLE-ABS (“pregnant women”) OR TITLE-ABS (men) OR TITLE-ABS (women) OR TITLE-ABS (“ethnic group”) OR TITLE-ABS (caucasian) OR TITLE-ABS (asian) OR TITLE-ABS (african) OR TITLE-ABS (“genetic polymorphism*") OR TITLE-ABS (“individual susceptibility”) OR TITLE-ABS (“gene environment”) OR TITLE-ABS (“ethnic variability”) OR TITLE-ABS (“Afro American”) OR TITLE-ABS (hispanic) OR TITLE-ABS (“race difference*") OR TITLE-ABS (“age difference*") OR TITLE-ABS (“gender difference”) OR TITLE-ABS (“sex difference*"))
Outcome	(TITLE-ABS (auc) OR TITLE-ABS (area under the curve) OR TITLE-ABS (area under curve) OR TITLE-ABS (half life) OR TITLE-ABS (half-life) OR TITLE-ABS (half-lives) OR TITLE-ABS (clearance) OR TITLE-ABS (cmax) OR TITLE-ABS (pharmacokinetic*) OR TITLE-ABS (toxicokinetic*))
Exclusion	(TITLE-ABS (“cell line*") OR TITLE-ABS (“cell culture*"))
Search genotypic data	(TITLE-ABS (“polymorphism*“) OR TITLE-ABS (genotype) OR TITLE-ABS (SNP) OR TITLE-ABS (human) OR TITLE-ABS (“*name of transporter*”))

TITLE-ABS: term searched only in the title and the abstract of the paper.

2677G > A/T) and two SNPs for BCRP (34G > A, 421C > A).

Table 1 provides a summary of the keywords applied to the ELS. Screening of the literature was performed as previously described starting with screening of titles and abstracts after removal of duplicates and application of exclusion criteria including: species other than humans, *in vitro* studies, development of analytical methods, modelling approaches, pharmacodynamic investigations, studies for unhealthy individuals, substrates other than those identified as relevant (Darney et al., 2019). Only publications written in English were considered.

2.2. Standardisation of datasets

PK parameters collected from literature were standardised to perform the analyses in a harmonised manner for each parameter while correcting to dose and body weight namely AUC, Cmax and clearance expressed in mg/kg BW, ng.h/ml/dose, ng/ml/dose and ml/min/kg BW. Body weight correction from the parameters were performed using mean body weight (kg) recorded from the study when available or allocating them to the country of origin using data from Walpole et al. (2012). Kinetic data were often either reported as arithmetic mean (X) and standard deviation (SD) or as geometric means (GM) and geometric standard deviation (GSD). Since PK data are well recognised to follow a lognormal distribution, all PK parameters were transformed, when needed, and expressed as GM and GSD using the following equations:

$$GM = \frac{X}{\sqrt{1 + CV_N^2}} \quad (1)$$

$$GSD = exp(\sqrt{\ln(1 + CV_N^2)}) \quad (2)$$

where CV_N is the coefficient of variation for normally distributed data:

$$CV_N = \frac{SD}{X} \quad (3)$$

In some studies, SD was not reported and was derived from the standard error (SE, SEM), CV, or 95% confidence interval of the mean as described previously (Darney et al., 2019).

2.3. Meta-analyses

A number of meta-analyses were performed while integrating results from multiple independent kinetic studies to provide quantitative information regarding inter-individual variability of the PK parameters per chemical and results were expressed as distributions. For each substrate and parameter, variability related to inter-study, inter-substrate and inter-individual differences were analysed through a decomposition of the PK parameter variance (clearance, AUC or Cmax) using a hierarchical Bayesian model described previously (Darney et al., 2019; Wiecek et al., 2019). Since this paper constitutes the first comprehensive meta-analyses of PK variability associated to the human transporters BCRP, P-gp, and OAT1/3 using *in vivo* probe substrates, non-informative prior distributions expressed as uniform distributions were selected.

The meta-analyses provided probabilistic variability and uncertainty distributions describing inter-individual differences for each PK parameter using median values and 95% confidence intervals. The coefficient of variation (CV) were also estimated as follows:

$$CV = \sqrt{exp(\ln(\sqrt{\exp(1/\tau_j)}))^2 - 1} \quad (4)$$

where τ_j is the inter-individual variability of the activity for a substrate ‘j’.

UFs related to BCRP-, P-gp-, and OAT probe substrates were calculated as the ratio between the percentile of choice (95th and 97.5th centiles) and the median of the distribution for each PK parameter (Fig. 2).

Kinetic differences in internal dose between each healthy adult subgroup and general healthy adults and other healthy adult subgroups (inter-phenotypic and inter-ethnic differences) were derived as GM ratios so that a value > 1 indicated a higher internal dose or slower elimination (Dorne, 2010).

2.4. Software

All statistical analyses and graphical display of the data were performed using R (version 3.5). The Bayesian modelling was implemented with Jags (4.2.0) (Plummer, 2003). References from the ELS were computed in EndNote (X8) files. The R codes used for the meta-analyses are published previously (Darney et al., 2019).

3. Results

3.1. Data collection for P-gp, BCRP, and OAT1/3

2643 papers were retrieved from Scopus and PubMed for seven P-gp probe substrates (dabigatran, digoxin, fexofenadine, loperamide, quinidine, talinolol, and vinblastine) and for the OAT1 and OAT3 probe substrate adefovir and sitagliptin. For BCRP, 1115 peer reviewed publications were retrieved for sulfasalazine and rosuvastatin with 20 papers reporting PK data. 496 papers were considered eligible after the first screening while 354 were then as review articles or publications with scarce information or of poor quality Overall, 142 papers were considered eligible and relevant for data extraction and were included in the database. A full account of the screening procedure, inclusion/exclusion criteria and data collection is reported in Darney et al. (2019). Fig. 3 summarises the flow of information for the available PK studies on P-gp, BCRP and OAT1/3 probe substrates while the full list of relevant peer reviewed publications is provided in supplementary information [A] and the full database can be accessed on EFSA knowledge junction under DOI: 10.5281/zenodo.3739015 with a Creative Common Attribute 4.0 license.

Fig. 4 illustrates the raw data for each probe substrate and kinetic parameters reflecting acute oral (Cmax) and chronic exposure

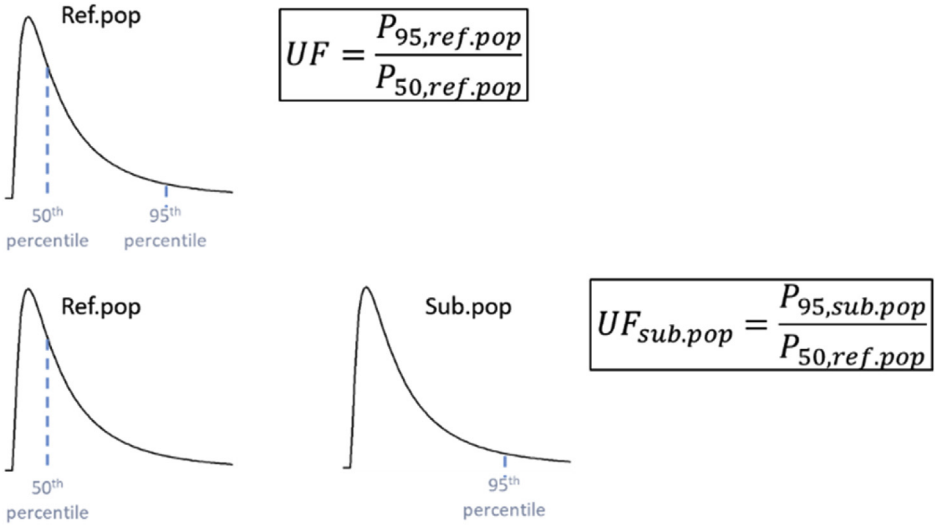

Fig. 2. Derivation of probabilistic distributions and uncertainty factors (UF) from PK data for reference and sub-populations of healthy adults.

(clearance and AUC) after intravenous and oral dosing. The amount of data available varied from one substrate to another and route as well as the reported geometric means (GM) for all kinetic parameters due to inter-substrate differences in kinetics.

3.2. P-glycoprotein

3.2.1. Data analysis

Kinetic data were available for European, East Asian, South Asian, Southeast Asian, North American and Middle East healthy adults with the majority of the datasets from North America, East Asian and European studies. In order to estimate inter-ethnic differences, European healthy adults were used as the reference group with the

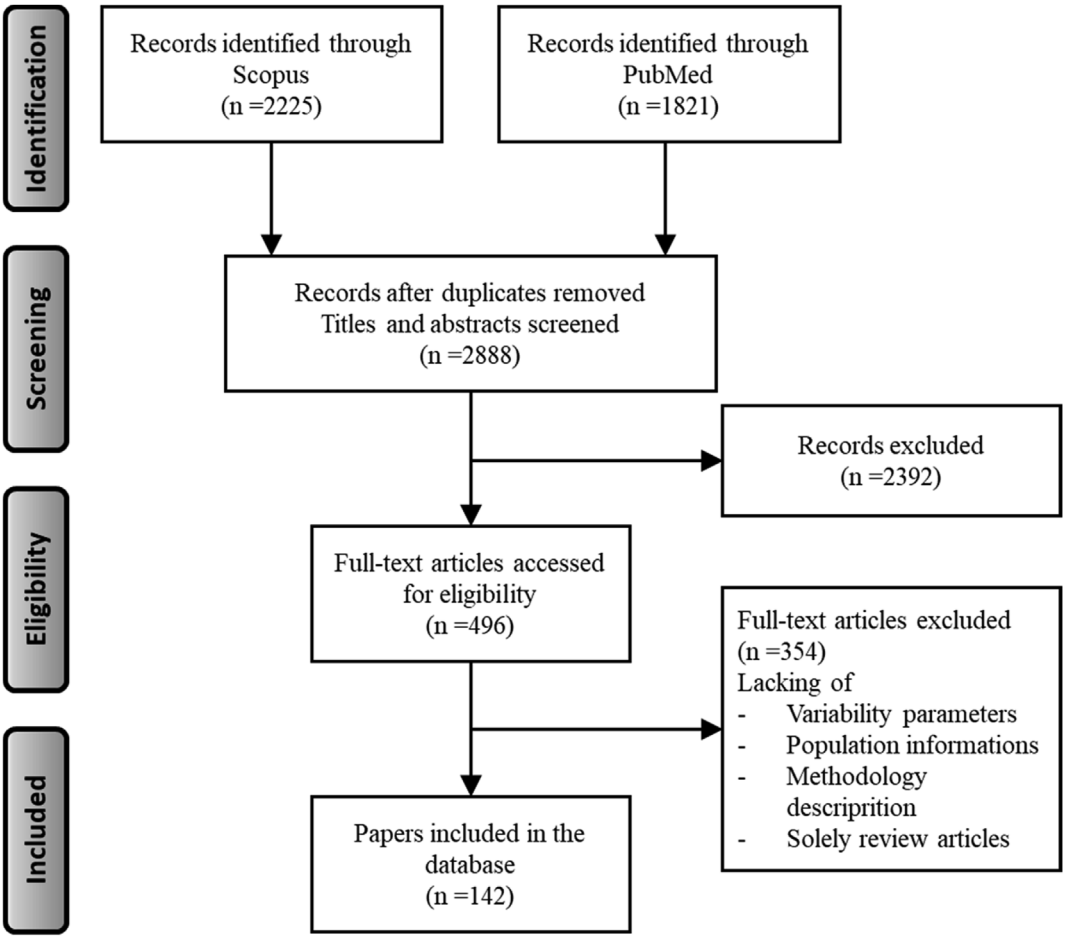

Fig. 3. Flow diagram for the extensive literature search of human pharmacokinetic studies for P-gp, BCRP, and OAT1/3 probe substrates.

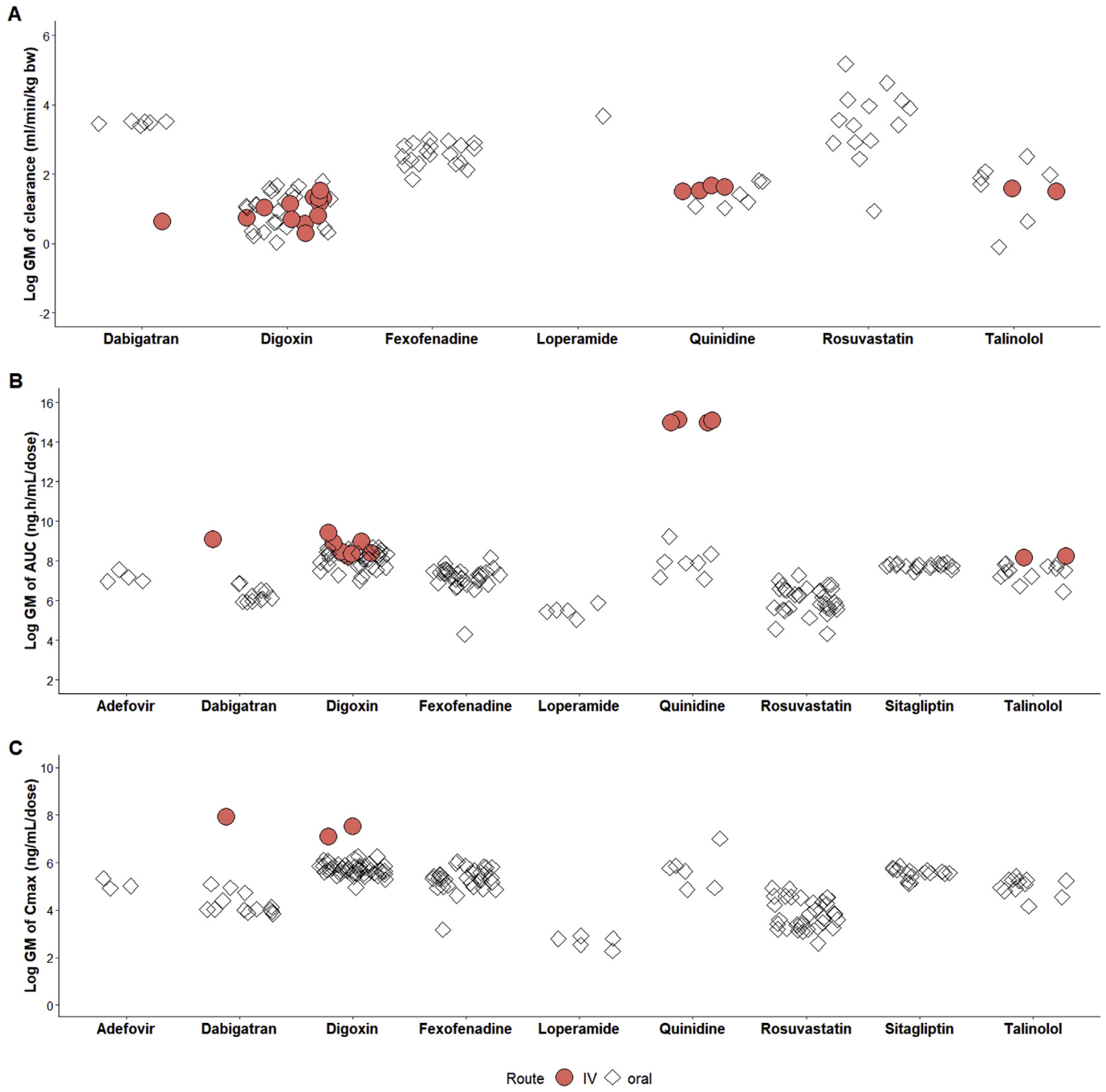

Fig. 4. Log geometric mean of human kinetic parameters for probe substrates of P-gp, BRCP and OAT1/3. A: clearance; B: AUC; C: Cmax. Squares: oral exposure; red circles: IV exposure. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

highest number of P-gp substrates and parameters for the oral and intravenous routes. Data gaps were identified for specific groups including Central and Southern Americans, as well as North and sub-Saharan Africans. CV values from the meta-analyses provide inter-individual variability considering all substrates and highlight lower inter-individual variability for the IV route compared to the oral route (Table 2). Overall, inter-individual variability in kinetic parameters for healthy adults is around 40% for the oral route (AUC/clearance and Cmax respectively) and 20% for the IV route (AUC/clearance). Intra-ethnic and inter-ethnic differences for healthy North American, East Asian and South Asian adults showed similar P-gp-related UFs compared to healthy European adults. However, discrepancies for specific substrates with limited data, such as talinolol were evidenced between European and North American healthy adults, with a 3-fold lower internal dose for AUC (oral administration) in the North American subgroup (data from a single study). Overall, the default kinetic UF (3.16) would be protective of at least 97.5% of the healthy adult population when considering the median value. However, the Bayesian analysis taking into account uncertainty around the estimation of the UF shows that, given the available data (number of studies and number of individuals per study), variability may be higher than that covered by the kinetic default UF, as demonstrated by the upper bound of the 95% confidence interval. Regarding healthy Middle Eastern, South Asian, and Southeast Asian adults, the number of studies was much lower compared to that for other populations. As a consequence, these results have to be taken with caution. Differences in AUC between healthy

Table 2
Differences in pharmacokinetic parameters for healthy adults of different geographical ancestry after oral administration of P-gp probe substrates: intra and inter-ethnic differences.

		ns	nc	n	CV	Intra-ethnic				Inter-ethnic			
						UF95 [95% CI]		UF97.5 [95% CI]		UF95 [95% CI]		UF97.5 [95% CI]	
oral	**AUC (ng.h/ml/dose)**												
	Europe	37	6	496	41.6	1.9	[1.5–6.1]	2.2	[1.6–8.4]				
	East Asia	37	5	457	31.6	1.7	[1.2–3.2]	1.8	[1.3–4.0]	2.0	[0.4–9.0]	2.2	[0.5–9.8]
	North America	23	5	343	40.4	1.9	[1.4–3.9]	2.2	[1.5–5.1]	2.5	[0.7–9.4]	2.8	[0.7–10.0]
	Middle East	5	3	66	40.5	1.9	[1.4–4.2]	2.2	[1.5–5.5]	3.3	[0.5–11.0]	3.7	[0.5–13.0]
	South Asia	5	2	104	37.5	1.8	[1.4–4.9]	2.0	[1.5–6.5]	2.3	[0.8–4.5]	2.4	[0.8–5.0]
	Southeast Asia	4	1	136	21.9	1.4	[1.3–1.6]	1.5	[1.4–1.7]	3.0	[1.6–5.6]	3.2	[1.7–6.0]
	Cmax (ng/ml/dose)												
	Europe	35	5	433	37.2	1.9	[1.5–3.2]	2.1	[1.6–4.0]				
	East Asia[a]	29	5	361	37.5	1.8	[1.2–3.4]	2.0	[1.3–4.2]	1.7	[0.3–7.1]	1.8	[0.3–7.8]
	North America[a]	23	5	339	45.6	2.1	[1.5–4.6]	2.4	[1.7–6.2]	2.1	[0.9–11.0]	2.3	[0.9–13.0]
	Middle East[a]	5	3	66	31.5	1.7	[1.3–3.2]	1.8	[1.4–4.0]	1.4	[0.2–6.5]	1.4	[0.2–7.1]
	South Asia[b]	5	2	104	28.7	1.6	[1.5–2.5]	1.7	[1.4–3.0]	1.9	[1.1–4.1]	2.1	[1.2–4.9]
	Southeast Asia[a]	4	1	136	30.5	1.6	[1.5–1.9]	1.8	[1.6–2.1]				
	Clearance (ml/min/kg)												
	Europe	20	4	239	34.7	1.8	[1.4–3.6]	2.0	[1.5–4.6]				
	East Asia[a]	23	3	280	33.6	1.7	[1.4–2.3]	1.9	[1.5–2.7]	3.1	[1.9–5.2]	3.3	[2.0–5.5]
	North America[a]	13	4	160	41.7	1.9	[1.4–4.6]	2.2	[1.6–6.1]	2.3	[1.2–6.2]	2.5	[1.3–8.1]
	Middle East[b]	3	3	42	52.5	2.3	[1.2–7.8]	2.7	[1.3–11.0]	1.9	[0.1–14.0]	2.0	[0.1–15.0]
	South Asia[a]	2	1	24	29.7	1.6	[1.3–2.6]	1.8	[1.4–3.1]				
	Southeast Asia[a]	3	1	103	16.5	1.3	[1.2–1.4]	1.4	[1.3–1.5]				
iv	**AUC (ng.h/ml/dose)**												
	Europe	6	3	52	14.5	1.3	[1.1–2.4]	1.3	[1.1–2.9]				
	East Asia[b]	6	2	78	20	1.3	[1.1–2.4]	1.4	[1.2–2.8]	2.5	[1.6–3.6]	2.9	[1.9–4.3]
	North America[b]	3	2	24	20	1.4	[1.1–3.0]	1.5	[1.2–3.6]	2.7	[0.5–5.1]	3.3	[0.5–6.2]
	Clearance (ml/min/kg)												
	Europe	9	3	77	16	1.3	[1.1–1.8]	1.4	[1.1–2.1]				
	East Asia[b]	6	2	78	19	1.4	[1.1–2.7]	1.4	[1.2–3.3]	1.4	[1.0–2.0]	1.4	[1.0–2.0]
	North America[b]	4	2	31	28.1	1.6	[1.3–3.1]	1.7	[1.3–3.9]	1.7	[0.9–3.4]	1.9	[0.9–3.6]

[a] Fexofenadine was not studied in the reference group.
[b] Digoxin was the only common substrate with the reference group; ns: number of studies, nc: number of compounds, n: number of individuals, CV: coefficient of variation (lognormal distribution), GM: geometric mean (lognormal distribution), ratio GM: ratio of geometric mean between healthy adults from Europe and subgroup (lognormal distribution, 1/ratio GM for AUC and Cmax).

Middle Eastern, Southeast Asian and European adults for P-gp substrates were around 1.5–2.3 fold (3 substrates) and 2-fold (1 substrate) respectively and these inter-ethnic differences were associated with UFs of variability (95th and 97.5th centiles) of 3.3–3.7 (Middle East) and 3–3.4 (Southeast Asian) healthy adults. Results of the meta-analyses of CVs and GMs for each substrate are given in supplementary information A.

3.2.2. Impact of P-gp polymorphism on human variability

An additional important aspect of the contribution of P-gp to human variability is the impact of polymorphic genotypes on kinetics, although few studies provide these types of data and it is not currently feasible to quantitatively link allelic frequencies and inter-ethnic differences. The *MDR1* gene is highly polymorphic and several SNPs have been identified, among which the 3435C > T (rs1045642), 1236C > T (rs1128503), and 2677G > A/T (rs2032582) are commonly studied. The 3435C allele is associated with increased P-gp expression, while the 3435T allele is associated with decreased P-gp expression, which might lead to altered plasma levels of substrates (Hoffmeyer et al., 2000; Sipeky et al., 2011), although results regarding the effects of SNPs in P-gp on pharmacokinetic parameters are conflicting (Wolking et al., 2015). For both 1236C > T and 2677G > A/T no conclusive findings on the functionality of P-gp could be determined (Sipeky et al., 2011).

However, it has been demonstrated that 2677A bearing subjects show higher P-gp activity for some substrates (Yi et al., 2004). The three variants show a strong linkage disequilibrium with *CGC* and *TTT* as the most common haplotypes (Kroetz et al., 2003; Leschziner et al., 2006; Sai et al., 2003; Tang et al., 2004). There is an indication that *3435T* carriers have higher drug concentrations as well as those with a *TTT* haplotype, which results in a higher response rate or an increased frequency of adverse effects (Wolking et al., 2015). The distributions of the genotypes for the SNPs C1236T, G2677 A/T and C3435T in P-gp are shown in Fig. 5. Overall, in Central and Southern Africa, the wildtype of each SNP was dominantly present. For C1236T, the genotypes frequencies were similar between North African, South American, European and Middle Eastern populations. In the Asian population, the wildtype is less frequently observed (< 20%) compared to the 1236CT and 1236 TT variant. For G2677 A/T, similar patterns between the different ethnicities can be observed, except for the Southern African population, where the wildtype is predominantly present. The 3435CC genotype is frequently observed in Southern and Central African population, while in the Northern African population the genotypes 3435CC and 3435CT were equally observed. Overall, the homozygous 3435 TT genotype in the African population was below 11%. Variability in the P-gp SNP C3435T was similar in the American, Asian, European, Middle Eastern and Oceanian population. However, larger variability in the South American population was observed.

3.3. BCRP

3.3.1. Data analysis

Kinetic data on rosuvastatin were available for healthy adults after single oral exposure. PK data did not show differences between included subpopulations, so that variability and uncertainty were determined for the total human population. Values from the meta-analysis for inter-individual variability (Table 3) highlight that the default kinetic UF of 3.16 would be protective of at least 97.5% of the healthy adult population. However, the results should be considered with

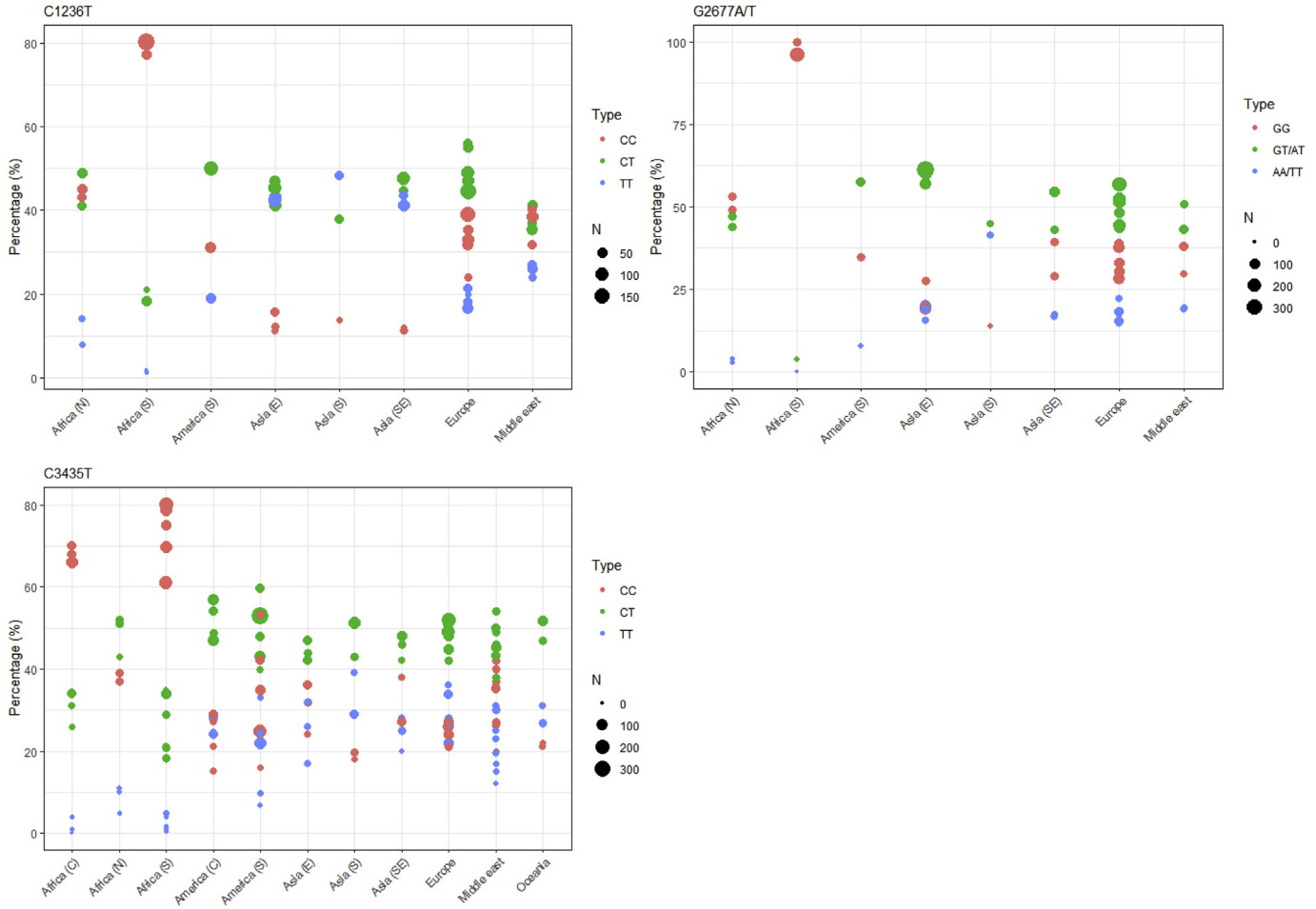

Fig. 5. Frequency of SNPs in P-gp (C1236T, G2677 A/T, C3435T) in various ethnic groups. *Reference C1236T:* (Abuhaliema et al., 2016; Al-Mohizea et al., 2012; Bellusci et al., 2013; Bouzidi et al., 2016; Kassogue et al., 2013; Pechandova et al., 2006; Phuthong et al., 2017; Qiu et al., 2012; Sipeky et al., 2011; Swart et al., 2012); Reference G2677 A/T: (Abuhaliema et al., 2016; Al-Mohizea et al., 2012; Bouzidi et al., 2016; Brown et al., 2012; Kassogue et al., 2013; Pechandova et al., 2006; Phuthong et al., 2017; Qiu et al., 2012; Rosales et al., 2012; Sipeky et al., 2011; Swart et al., 2012); References C3435T: (Abuhaliema et al., 2016; Al-Mohizea et al., 2012; Ameyaw et al., 2001; Baldissera et al., 2012; Balram et al., 2003; Bellusci et al., 2013; Bernal et al., 2003; Bouzidi et al., 2016; Brown et al., 2012; Chelule et al., 2003; Cizmarikova et al., 2010; Isaza et al., 2013; Jaramillo-Rangel et al., 2018; Kassogue et al., 2013; Komoto et al., 2006; Leal-Ugarte et al., 2008; Marsh et al., 2015; Masebe et al., 2012; Miladpour et al., 2009; Ngaimisi et al., 2013; Omar and Hughes, 2013; Ostrovsky et al., 2004; Pechandova et al., 2006; Phuthong et al., 2017; Rao et al., 2010; Roberts et al., 2002; Rosales et al., 2012; Sinues et al., 2008; Sipeky et al., 2011; Swart et al., 2012; Vicente et al., 2008). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

caution, since only one chemical was included for the variability and UF calculation. Most PK data included in the meta-analysis was measured in Asians, showing large variability in measured data, which may be due to polymorphisms. Less PK data was available for Caucasians and no differences between Asian and Caucasian population could be identified.

3.3.2. Impact of breast cancer resistant protein (BCRP) polymorphism and human variability

Various SNPs of the *ABCG2* gene have been identified, whereof 34G > A and 421C > A (p.Q141, rs2231142) are most commonly studied (Mao and Unadkat, 2015). 34G > A is associated with deceased BCRP activity, but studies investigating differences in drug response in relation to 34G > A are inconclusive (Niebudek et al., 2019). Variability in the frequency of G34A in BCRP between different populations is illustrated in Fig. 6. While in most populations, the wildtype genotype is more frequently detected (> 70%), in Asians and inhabitants of Oceania the wildtype 34 GG and the homozygous mutation were less frequently observed compared to the heterozygous genotype. In East Asian populations, the wildtype genotype is more frequently observed (50–75%) compared to Southeast Asians, but is still more often observed compared to African, American, European and Middle Eastern populations. 421C > A is associated with decreased expression of the BCRP protein (Kondo et al., 2004; Mizuarai et al.,

Table 3
Inter-individual differences in the rosuvastatin PK in healthy adults after oral administration.

Parameter	ns	N	CV	GM	UF95 [95% CI]		UF97.5 [95% CI]	
AUC (ng.h/ml/dose)	33	445	47	411	2.1	[1.9–2.4]	2.4	[2.1–2.8]
Clearance (ml/min/kg bw)	14	134	43	1.9	2.0	[1.7–2.4]	2.2	[1.9–2.9]
Cmax (ng/ml/dose)	32	430	49	46.5	2.1	[1.9–2.5]	2.5	[2.2–2.9]

ns: number of studies, n: number of individuals, CV: coefficient of variation (lognormal distribution), GM: geometric mean (lognormal distribution).

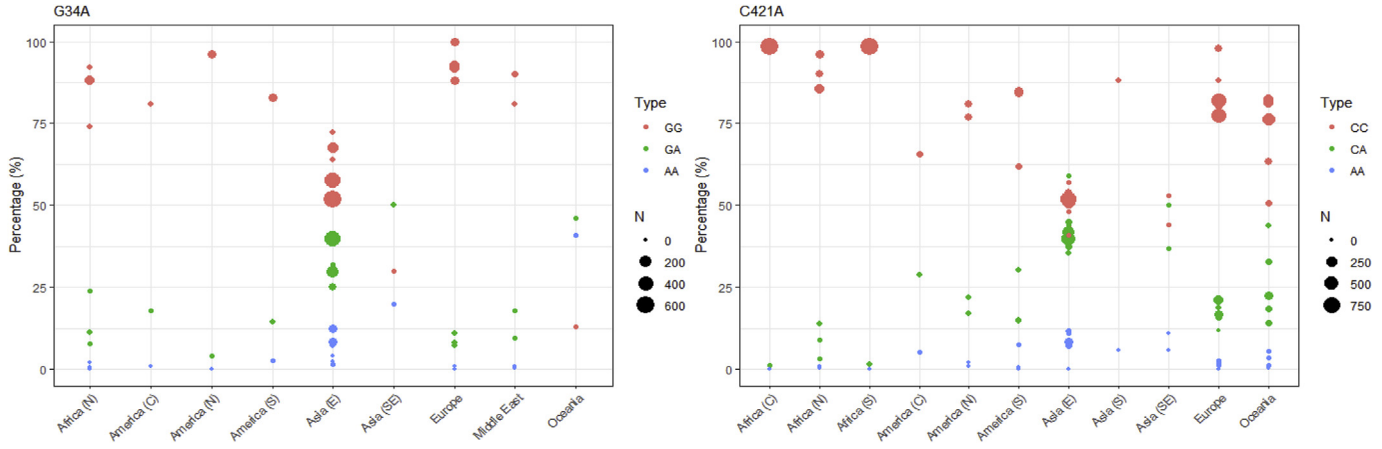

Fig. 6. Frequency of SNPs in BCRP (G34A, C421A) in various ethnic groups. *References G34A:* (Bosch et al., 2005; de Lima et al., 2014; Fischer et al., 2007; Kim et al., 2010; Kobayashi et al., 2005; Niebudek et al., 2019; Wan et al., 2015; Wu et al., 2015; Zamber et al., 2003); References C241A: (Andersen et al., 2009; Birmingham et al., 2015; de Jong et al., 2004; de Lima et al., 2014; El Mesallamy et al., 2014; Feher et al., 2013; Fischer et al., 2007; Genvigir et al., 2017; Hammann et al., 2012; Imai et al., 2002; Keskitalo et al., 2009; Kim et al., 2010; Kobayashi et al., 2005; Marsh et al., 2015; Niebudek et al., 2019; Oh et al., 2013; Phipps-Green et al., 2010; Soko et al., 2016; Wan et al., 2015; Wu et al., 2015; Yen-Revollo et al., 2009). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 4
Effects of genetic polymorphisms on the pharmacokinetics of rosuvastatin.

Population	Parameter	Ratio CC/CA	Ratio CC/AA	Reference
Finnish	AUC	0.82	0.41	Keskitalo et al. (2009)
Finnish	Cmax	0.90	0.43	
Finnish	Clearance	0.95	1.07	
Chinese	AUC	0.93	0.63	Zhou et al. (2013)
Chinese	Cmax	0.99	0.71	
Chinese	AUC	0.97	0.38	Wan et al. (2015)
Chinese	Cmax	0.92	0.31	
Chinese	Clearance	0.97	2.68	

2004), leading to altered PK parameters of several drugs (de Jong et al., 2004; Lee et al., 2015; Tanaka et al., 2015). Regarding the pattern of distributions, the homozygous mutation 421AA is detected only in < 12% of the population. Nevertheless, in Southeast and East Asian populations, the genotype 421CC and 421CA are equally detected and the 421A allele is more frequently present in East and Southeast Asians compared to that in Caucasian populations. C421A SNP is considered an important BCRP variation in terms of cancer chemotherapy and drug resistance (Noguchi et al., 2009) (Table 4). Indeed, both the European Medicine Agency and the US Food and Drug Administration recommend to test for the effect of C421A SNP to take into account potentially sensitive populations (Lee et al., 2015).

3.4. Other efflux transporters

The MRP family consists of nine members, whereof MRP2 (ABCC2) and MRP4 (ABCC4) are in particular involved in the disposition of drugs and conjugates (Terada and Hira, 2015). MRP2 can transport both the parent chemical and its metabolites, unconjugated bile acids, organic anions, GSH conjugates, glucuronides, and sulphates (Kumar and Jaitak, 2019). MATE transporters are mainly expressed in the kidneys and are involved in the tubular elimination of cationic drugs and endogenous compounds. MATE1 is also expressed in the canalicular membrane of hepatocytes and shares various neutral and cationic substrates with P-gp, such as fexofenadine, levofloxacin and quinidine. Furthermore, MATE transporters are involved in the elimination of substrates which are taken up by OCTs. Examples for these substrates are metformin and cimetidine (Jetter and Kullak-Ublick, 2019; Trueck et al., 2019). However, for none of these transporters, *in vivo* probe substrates have been identified and therefore the analysis was not carried out.

3.5. OAT1/3

An ELS was performed for OATs to identify human PK studies in healthy adults from different geographical ancestry or ethnic background. The literature data highlight a broad overlapping substrate specificity among different OATs that does not allow to draw conclusions clearly referred to a single transporter; the PK parameters measured are in most cases based on the net result of the actions of more than one carrier. Adefovir and sitagliptin have been identified as *in vivo* probe substrates for OAT1 and OAT3, respectively. The meta-analysis showed that the overall variability of the OAT1/3 transporters is lower compared to P-gp and BCRP (Table 5). The default kinetic UF would be protective of 97.5% of the healthy adult population considering median value, but number of subjects available from kinetic studies is limited, especially regarding adefovir, and therefore results should be considered with caution. Coding regions of *OAT1* and *OAT3* have low genetic and functional diversity suggesting that coding region variants of these transporters may not contribute substantially to inter-individual differences observed in pharmacokinetics of chemicals (Yee et al.,

Table 5
Differences in pharmacokinetic parameters in healthy adults after oral administration of OAT1/3 probe substrates.

Drug	Parameter	ns	n	CV	GM	UF95 (95% IC)		UF97.5 (95% IC)	
Adefovir	AUC (ng.h/ml/dose)	4	67	23	1323	1.5	[1.3–1.7]	1.6	[1.1–1.9]
	Cmax (ng/ml/dose)	3	43	25	169	1.5	[1.3–1.9]	1.6	[1.4–2.2]
Sitagliptin	AUC (ng.h/ml/dose)	17	219	20	2300	1.4	[1.3–1.5]	1.5	[1.4–1.6]
	Cmax (ng/ml/dose)	16	195	32	256	1.7	[1.5–1.9]	1.9	[1.6–2.2]

ns: number of studies, n: number of individuals, CV: coefficient of variation (lognormal distribution), GM: geometric mean (lognormal distribution).

2018).

3.6. OATPs

The OATP family consists of 11 members, whereof OATP1A2, OATP1B1, OATP1B3, and OATP2B1 are most extensively characterised and are involved in the disposition of drugs and xenobiotics (Konig et al., 2006; Zhang and Lauschke, 2019). For this class of carriers, the ELS evidenced that different OATP isoforms show a broad overlapping substrate specificity and in many cases transporters other than OATPs can act on the same substrate. A good example is provided by various studies on statins: as discussed above, rosuvastatin's cellular influx and efflux are mediated by OATP1B1 and BCRP, respectively and the measured PK parameters are the net result of multiple transporters. *In vivo* studies on statins PK showed that OATP1B1 polymorphisms can influence the internal concentration of rosuvastatin and other statins (Giacomini et al., 2013; Pasanen et al., 2007; Wu et al., 2017), but the impact of OATP1B1 genotypes on drug disposition is highly compound-specific (Giacomini et al., 2013). Nevertheless, since no clear probe substrates have been established for OATP transporters *in vivo,* analysis of human variability for these transporters could not be carried out.

3.7. OCTs

OCTs and MATEs are transporters that transcellularly translocate cationic drugs: together they represent an essential system for renal elimination of therapeutic drugs and other xenobiotics (Ayrton and Morgan, 2008; Matsushima et al., 2009; Wang et al., 2008). These two families of carriers share several substrates and inhibitors (Motohashi and Inui, 2013; Nies et al., 2011). Metformin is recommended as a probe drug for the renal proximal tubular transporter OCT2, but it lacks specificity because excretion of metformin across the apical membrane is carried out by MATE1 and MATE2-K (Trueck et al., 2019). Furthermore, OCT1 is involved in apical transport and may mediate metformin reabsorption (Momper et al., 2016). There are indications that polymorphisms in OCT2 can influence the *in vivo* PK of metformin causing variability in drug response (Islam et al., 2018; Song et al., 2008; Wang et al., 2008; Yee et al., 2018). However, no probe substrates were available for *in vivo* OCT transporters so that analysis of pharmacokinetic variability in this transporter was not performed.

4. Discussion and conclusion

Data for human variability in the pharmacokinetics of transporter substrates are scarce for non-phenotyped individuals, let alone polymorphisms and until now such information has not been integrated in human health risk assessment for pharmaceuticals and environmental chemicals (Clerbaux et al., 2018, 2019). Nevertheless, several studies have indicated that variable BCRP and P-gp expression/function may determine variation in PK parameters for specific substrates. Both transporters are highly expressed at the apical membrane of enterocytes and may limit the oral bioavailability of a range of chemicals (Clerbaux et al., 2019; Harwood et al., 2019; Maliepaard et al., 2001; Thiebaut et al., 1987). This observation is also relevant for other barrier systems such as the blood-brain barrier and the placenta in which both BCRP and P-gp are highly expressed to protect the fetus. A number of variant alleles have been hypothesised as risk factors for fetal toxicity with no clear conclusions so far (Allikmets et al., 1998; Hitzl et al., 2004; Maliepaard et al., 2001; Tanabe et al., 2001).

Here, data obtained by means of extensive literature searches on well characterised *in vivo* probe substrates of P-gp, BCRP, and organic anionic transporters (OAT1/3) were analysed to identify the associated human variability. For other transporters (e.g. OCT, OATP), no *in vivo* probe substrates could be identified and therefore the analysis of pharmacokinetic variability was not performed. The impact of polymorphisms on P-gP, BCRP and OAT1/3 was analysed as well as the effects of the SNPs on transporters seem to be substrate specific, due to changes of the substrate-binding domain which alters substrate affinity.

Based on the available data for P-gp, limited to the adult life stage and certain ethnic groups (largely Caucasian), the calculated human variability indicated that the kinetic default UF of 3.16 would be protective of 97.5% of healthy individuals, when considering the median value, while it is exceeded when considering the upper confidence interval. The variability of kinetic parameters observed following IV injection is generally 50% lower when compared to the oral administration. This can be explained by the aforementioned expression of P-gp in the intestine, that will influence the bioavailability of orally administered chemicals (Li et al., 2017; Thiebaut et al., 1987).

Our assessment reflects the total variability related to the probe substrates. Indeed, the contribution of P-gp to the overall pharmacokinetics of drugs is in most cases unknown and dual- or multiple-transporter mediated transporting of chemicals may mask the net *in vivo* function of P-gp. Indeed, digoxin, the most frequently tested drug for P-gp, is also a substrate of a sodium-dependent transporter (Taub et al., 2011). Another P-gp probe substrate, fexofenadine, is suspected to be a substrate for the drug transporters MRP2 and OATP2B1/OATP1A2, which are all polymorphic (Ming et al., 2011). Compounds like quercetin can competitively inhibit the members of MDR family, P-gp, MRP1 and BCRP (Ofer et al., 2005) as well as CYP3A4 (Wink et al., 2012). The interplay between P-gp and CYP3A4 can be relevant in determining inter-individual differences since they share substrate affinity and are co-inducible in response to at least some xenobiotics. For this reason, P-gp potentiates CYP3A4-mediated drug disappearance during intestinal secretory detoxification for a range of compounds (Chan et al., 2004).

For BCRP and OAT1/3, human variability data were limited to healthy adults and indicated that the default kinetic UF of 3.16 was not exceeded and provides a sufficient level of protection considering the upper confidence interval (95%CI). For BCRP, some literature data indicate that rosuvastatin plasma concentrations are significantly higher in an Asian population compared to Caucasian populations (Birmingham et al., 2015; Keskitalo et al., 2009; Lee et al., 2005). This could be attributed to the presence of the C421C > A SNP which has been reported to markedly affect the PK parameters of rosuvastatin (Birmingham et al., 2015; Keskitalo et al., 2009). The same polymorphism also significantly affects the PK of other drugs, such as topotecan and diflomotecan (Heyes et al., 2018; Hira and Terada, 2018; Sparreboom et al., 2004; Sparreboom et al., 2005). However, for these compounds, the contribution of metabolism to the inter-individual variability cannot be underestimated. Indeed, topotecan and diflomotecan undergo CYP3A4 metabolism, which can have an influence on the PK parameters (Graham et al., 2009; Rodriguez-Antona and Ingelman-Sundberg, 2006). For rosuvastatin only approximately 10% of the parent compound is metabolised (primarily by CYP2C9). Due to the small contribution to rosuvastatin's internal dose, and to the lack of the most common CYP2C9 variant alleles in Asian populations, it is not expected that the higher systemic exposure in Asians is based on CYP2C9-mediated metabolism (Yasuda et al., 2008). In addition, while BCRP mediates rosuvastatin excretion from the cell, another carrier, namely OATP1B1, mediates rosuvastatin uptake into the cells. This suggests that also polymorphisms in OATP1B1 may influence the *in vivo* kinetics of this substrate (Giacomini et al., 2013; Pasanen et al., 2007; Wu et al., 2017).

We are aware, as stated above, that the contribution of transporter variability alone cannot be distinguished from other factors that can also contribute to variability of the PK parameters. However, the results suggest that based on the available data on healthy adults, inter-individual differences associated with the activity of transporters is mostly covered by the 3.16 default kinetic UF using data for pharmaceutical probe substrates. A rationale for such limited variability lies in the fact that very few probe substrates are transported by one specific carrier-mediated process, so it is reasonable to assume that the

overlapping substrate specificity of transporters (from same or different classes) may reduce the variability due to possible compensation mechanisms (Chedik et al., 2018; Clerbaux et al., 2019). The involvement of multiple transporters can also influence the occurrence of chemical interactions mediated by transport processes induction or inhibition; these have been observed *in vitro* but *in vivo* evidence is mostly lacking, likely due to low exposure to environmental chemicals or food components which are generally well below the concentrations of administered therapeutic drugs (Chedik et al., 2018). Accidental exposure to very high levels or intoxication events with high peak blood concentrations may represent an exception.

The methodology and modelling presented here has been previously applied to the CYP3A4 isoform (Darney et al., 2019) and it is currently being explored for other phase I and phase II isoforms enzymes to generate variability distributions for human inter-individual differences in PK parameters (Darney et al., 2020). Here, it is foreseen that *in vitro* kinetic data and transporter variability can be integrated in quantitative *in vitro in vivo* extrapolation (QIVIVE) to estimate intrinsic clearance for the human population. Non-invasive *in vitro* techniques are now available to investigate the involvement of transporters and generate chemical-specific data using human cell lines or human liver microsomes (Harwood et al., 2016; Kumar et al., 2015; Poulin, 2013; Prasad and Unadkat, 2014; Yoon et al., 2013; Zhang et al., 2019). The variability derived here for specific transporters can then be integrated in physiologically-based kinetic models with Markov-Chain Monte Carlo, allowing full probabilistic integration, instead of using a single deterministic mean value. In addition, data for protein abundance of transporters and their activity can also further support the modelling of transporter kinetics by physiologically-based kinetic-QIVIVE link models including the mechanistic modelling of chemical oral absorption as well as chemical-chemical and drug-drug interactions (Barton et al., 2013; Harwood et al., 2013, 2014; Jamei et al., 2014; Neuhoff et al., 2013).

Since only healthy adults were considered in this study, due to the lack of data for other subgroups the transporter-related variability described here may not be applicable to sensitive subpopulations, such as neonates, children and elderly as well as non-healthy individuals or specific ethnic groups for which data are not available. However, almost no studies have been performed investigating transporter-dependent pharmacokinetics in children and studies in neonates are not available (Rodieux et al., 2016).

There is a current trend to replace traditional default UFs by using data-derived UFs based on a quantitative understanding of population characteristics, PK data and/or toxicodynamic data to reduce uncertainty in chemical risk assessment (Bhat et al., 2017). Although limited kinetic data on transporter polymorphisms were available, inter-phenotypic variability for probe substrates was reported, which may contribute to human variability in PK parameters, and can therefore result in exceedance of the default kinetic UF. Overall, to predict whether the kinetic portion of the intra-individual UF is protective of humans, it is recommended that genetic polymorphisms across all human groups are investigated since polymorphisms provide a better predictor in altered pharmacokinetics than ethnicity alone (Darney et al., 2020; Wu et al., 2017).

Kinetic data were mostly available for on pharmaceutical probe substrates which are eliminated relatively fast from the human body (i.e. short half-lives). However, data on the transport of environmental contaminants and food-relevant chemicals, particularly persistent ones, are very scarce and it is not certain that the UFs derived for pharmaceuticals are applicable to these chemicals as well. Therefore, assessment of such chemicals would need to be performed on a case by case basis either using the default factor, the transporter-related UFs or chemical specific adjustment factors. The chemical-specific adjustment factors will be necessary when 1. the compound is handled by a combination of phase I, Phase II pathways and transporters. 2. the compound is persistent with long half-lives. 3. pharmacokinetic data shows inter-phenotypic differences in the substance's specific transporter(s) handling. This suggests a need to investigate their kinetic and transport profile to broaden the chemical groups of this analysis to such persistent compounds. Relevant examples for transporters as P-gp, BCRP2, OCTs are food additives (sweeteners), organochlorines, pyrethroids such as allethrin and tetramethrin, and organophosphorus pesticides (Chedik et al., 2017, 2018; Guéniche et al., 2020; Sjöstedt et al., 2017). Overall, these investigations should include environmental concentrations to investigate the likelihood of such interactions with transporters to occur.

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CRediT authorship contribution statement

K. Darney: Conceptualization, Methodology, Formal analysis, Writing - original draft, Visualization. **L. Turco:** Writing - original draft, Writing - review & editing. **F.M. Buratti:** Investigation. **E. Di Consiglio:** Investigation. **S. Vichi:** Investigation. **A.C. Roudot:** Supervision. **C. Béchaux:** Software. **E. Testai:** Writing - review & editing, Project administration. **J.L.C.M. Dorne:** Writing - review & editing, Supervision, Project administration. **L.S. Lautz:** Conceptualization, Data curation, Writing - original draft, Writing - review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This work was supported by the European Food Safety Authority (EFSA) [Contract number: GP/EFSA/SCER/2015/01].

Appendix A. Supplementary data

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