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Human variability for metabolic pathways with limited data (CYP2A6, CYP2C9, CYP2E1, ADH, esterases, glycine and sulphate conjugation)

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Abstract

Human variability in the kinetics of a number of phase I (CYP2A6, CYP2C9, CYP2E1, alcohol dehydrogenase and hydrolysis) and phase II enzymes (glycine and sulphate conjugation) was analysed using probe substrates metabolised extensively (>60%) by these routes. Published pharmacokinetic studies (after oral and intravenous dosing) in healthy adults and available data on subgroups of the population (effects of ethnicity, age and disease) were abstracted using parameters relating primarily to chronic exposure [metabolic and total clearances, area under the plasma concentration time-curve (AUC)] and acute exposure (C_{max}). Interindividual differences in kinetics for all these pathways were low in healthy adults ranging from 21 to 34%. Pathway-related uncertainty factors to cover the 95th, 97.5th and 99th centiles of healthy adults were derived for each metabolic route and were all below the 3.16 kinetic default uncertainty factor in healthy adults, with the possible exception of CYP2C9*3/*3 poor metabolisers (based on a very limited number of subjects). Previous analyses of other pathways have shown that neonates represent the most susceptible subgroup and this was true also for glycine conjugation for which an uncertainty factor of 29 would be required to cover 99% of this subgroup. Neonatal data were not available for any other pathway analysed.
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1. Introduction

Pathway-related default uncertainty factors to allow for human variability in toxicokinetics have been developed from the Renwick and Lazarus proposal (1998), and applied to metabolism by several phase I enzymes (CYP1A2, CYP3A4, polymorphic CYP2D6 and CYP2C19), phase II enzymes (glucuronidation, polymorphic N-acetyltransferase) and renal excretion (Dorne et al., 2001a,b, 2002, 2003a,b, submitted for publication). Potentially sensitive subgroups of the human population have been identified as neonates for CYP1A2, CYP3A4, glucuronidation and renal excretion (Dorne et al., 2001a,b, 2003a, 2003c), for whom the default uncertainty factor of 3.16 (WHO, 1999) would be inadequate. The default would also be inadequate for most subgroups of the population (including healthy adults) for all three polymorphic pathways (CYP2C19, CYP2D6 and N-acetylation) analysed previously (Dorne et al., 2002, 2003b). For each pathway of elimination analysed previously, pathway-related uncertainty factors that cover each subpopulation to the 95th, 97.5th or 99th centile have been calculated to provide several risk management options (Dorne et al., 2001a,b, 2002, 2003a,b,c).

This paper aims to quantify inter-individual differences in human metabolic pathways for which limited data were available. Human data for the kinetics of probe substrates handled by phase I (CYP2A6, CYP2C9, CYP2E1, alcohol dehydrogenase and hydrolysis) and phase II enzymes (glycine and sulphate conjugation) have been analysed for the healthy adult population and subgroups of the population (effects of ethnicity, age and disease). A meta-analysis of the

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Nomenclature

ADH	Alcohol dehydrogenase
ALDH	Aldehyde dehydrogenase
AUC	Area under the plasma-concentration-time-curve
CL	Total plasma clearance
C_{max}	Maximum plasma concentration
CV_N	Coefficient of variation (normal distribution)
CV_{LN}	Coefficient of variation (lognormal distribution)
CYP	Cytochrome P450
GM_W	Geometric weighted mean (lognormal distribution)
GSD_w	Weighted geometric standard deviation (lognormal distribution)
n	number of subjects
NAT	N-acetyl transferase
N_p	Number of publications
N_s	Number of studies
SD_w	Weighted standard deviation (normal distribution)
X_W	Arithmetic weighted mean (normal distribution)

kinetic data in healthy adults and subgroups of the population has been performed to quantify variability in parameters reflecting chronic exposure (clearances and AUCs) and acute exposure (C_{max}) and to define the magnitude of any differences between healthy adults and any potentially susceptible subgroups of the population. The results have been used to derive pathway-related uncertainty factors for each metabolic route in order to provide risk assessors with a more refined method of allowing for uncertainty and variability.

2. Methods

The methods used in this paper have been described previously (Dorne et al., 2001a, 2002).

2.1. Literature search and selection of probe substrates

Published literature was searched with online databases: BIDS-EMBASE (1980–October 2002), MEDLINE (1966–October 2002) and TOXLINE (1966–October 2002) to select substrates handled by essentially monomorphic pathways of metabolism (CYP2E1, alcohol dehydrogenase, hydrolysis and glycine and sulphate conjugation). Data for polymorphic phase I enzymes (CYP2A6 and CYP2C9) were also searched in the above databases and searches included the current literature (up to April 2003), because data describing kinetics in phenotyped individuals have been published recently.

Probe substrates for each metabolic route were selected on the basis that their oral absorption was high (>90%) and that between 60 and 100% of an oral dose were excreted as metabolites of the relevant pathway in the urine and/or the faeces.

2.2. Data analysis

The kinetic data abstracted and analysed were parameters related primarily to chronic exposure (clearances and AUC) and to acute (oral) exposure (maximum plasma concentration (C_{max}). Data in each original kinetic study were published assuming a normal distribution [mean (X), standard deviation (SD) and (CV_N)]. Analysis of population distributions in all groups of the population required the transformation of the data on the log-scale to describe a lognormal distribution [geometric mean (GM), geometric standard deviation (GSD) and respective CV: CV_{LN}] (Aitchison and Brown, 1966; Dorne et al., 2002).

Data from individual studies for a particular kinetic parameter, compound and subgroup of the population were combined using the weighted mean method described previously (Dorne et al., 2001a) for both assumptions [normal (X_w and SD_w) and lognormal (GM_w and GSDw)] (Dorne et al., 2002). The overall CVs (CV_N and CV_{LN}) for each parameter and subgroup of the population were then combined for all the drugs as a simple average of the normal data, whereas the CV_{LN} were averaged on the log-scale. When available, both metabolic clearances (CLm) and clearances (CL) were extracted for the same subjects but only CL data were used for the calculation of pathway-related uncertainty factors.

Differences in internal dose for subgroups of the population [including healthy adults in different ethnic groups, neonates (<1 month), infants (>1 month to <1year), children (>1 year to <16 years), the elderly (healthy adults older than 70 years), and patients with liver or renal disease] were calculated by comparing each subgroup (for both means and variability) to healthy adults using the lognormal data. The difference in geometric means and variability between healthy adults and the subgroup were expressed as ratios (ratio GM and ratio CV_{LN}) and represented the magnitude of any increase in internal dose or increase in variability in the subpopulation compared to healthy adults.

Pathway-related uncertainty factors necessary to cover healthy adults to the 95th, 97.5th and 99th centile were calculated for each kinetic parameter and combined using the weighted mean analysis. For subpopulations, the uncertainty factors were calculated

using the mean ratios for the subgroup compared to that for healthy adults (ratio GM), and the variability within the subgroup (Dorne et al., 2002, 2003a,b,c).

3. Results

3.1. Metabolism data for phase I and phase II probe substrates

3.1.1. Metabolism data for phase I probe substrates

3.1.1.1. CYP2A6. Coumarin is a recognised in vitro and in vivo probe substrate for CYP2A6, because it is totally and exclusively metabolised by this isoform to 7-hydroxycoumarin (Cholerton et al., 1992, Rautio et al., 1992, Oscarson et al., 1998).

More than 70–80% of an intravenous dose of nicotine undergoes C-oxidation to cotinine via CYP2A6 in a two-step reaction, an initial rate limiting C-oxidation of nicotine to nicotine-$\Delta^{1'(5')}$-iminium ion (CYP2A6) and subsequent oxidation of the iminium to cotinine (via cytosolic aldehyde oxidase) (Benowitz and Jacob, 1994; Nakajima et al., 1996a).

Cotinine itself also constitutes a good CYP2A6 probe substrate since the main three oxidation reactions to trans-3′-hydroxycotinine, 5′-hydroxycotinine and norcotinine are mediated via CYP2A6 (Nakajima et al., 1996b; Murphy et al., 1999).

3.1.1.2. CYP2C9. Three probe substrates have been identified for the polymorphic CYP2C9 isoform: glibenclamide (glyburide), the S-enantiomer of warfarin and tolbutamide.

Glibenclamide is extensively metabolised via CYP2C9 to *trans*-4- and *cis*-3-hydroxyglibenclamide which constitute 90–95% of the urinary metabolites (Dahl-Puustinen et al., 1990). Moreover, glibenclamide clearance has been shown to be lower in carriers of different poor metaboliser CYP2C9 genotypes (CYP2C9*1/*3, *2/*2, *2/*3and *3/*3) compared to the extensive metabolisers (CYP2C9*1/*1 and *1/*2) (Kircheiner et al., 2002a).

Tolbutamide is oxidised to its 4-hydroxy derivative via CYP2C9 (>80%) and further metabolised to carboxy-tolbutamide via alcohol dehydrogenase and CYP2C9 (Back et al., 1988; Relling et al., 1990; Thomas and Ikeda, 1966; Veronese et al., 1986) with CYP2C9 making the major contribution. Tolbutamide clearance has also been shown to be affected by the CYP2C9 polymorphism (Kirchheiner et al., 2002b; Lee et al., 2002, 2003).

S-Warfarin is mainly metabolised to 6- and 7-hydroxywarfarin (80–85% of an oral dose) via CYP2C9 (Rettie et al., 1992; Takahashi et al., 1998). A decrease in the oral clearance of racemic warfarin clearance was reported for different CYP2C9 genotypes, but no pharmacokinetic studies were available for S-warfarin (Loebstein et al., 2001).

3.1.1.3. CYP2E1. Two probe substrates for CYP2E1 have been identified (chlorzoxazone and trimethadione) both of which are well absorbed after oral administration. Chlorzoxazone 6-hydroxylation is mediated by CYP2E1 and 71% of an oral dose was recovered as 6-hydroxy metabolites in the urine of healthy adult volunteers (Kharasch et al., 1993).

Trimethadione (TMO) undergoes N-demethylation by CYP2E1 (Kurata et al., 1998) to dimethadione that accounts for more than 60% of the total recovered dose in the urine (Tanaka et al., 1989). The N-demethylation activity was strongly correlated to the total clearance.

3.1.1.4. Alcohol dehydrogenase. Ethanol was the only substrate available for alcohol dehydrogenase (ADH) and its elimination is recognised to be catalysed largely by this enzyme (>80–90%) (Lands, 1998). CYP2E1 and CYP1A2 have also been shown to contribute to a minor extent (5%) (Lands, 1998). Chronic ethanol consumption results in induction of its own metabolism with an increase in microsomal ethanol-oxidizing system associated with the rise in CYP2E1. This induction is associated with proliferation of the endoplasmic reticulum, both in experimental animals and in humans (Lieber, 1999).

3.1.1.5. Hydrolysis. Substrates that were well absorbed from the gastrointestinal tract and for which hydrolysis is a major route of metabolism were aspirin, fosinopril, flumazenil. Cocaine, etodimate, esmolol, and flestolol are also totally hydrolysed, but are only partially absorbed from the GI tract, and therefore only the intravenous data have been analysed. The metabolism data for these compounds are summarised in Table 1.

Table 1
Metabolism data for probe substrates metabolised via hydrolysis in healthy adult volunteers

Drug	*n*	Route	% Metabolism via hydrolysis[a]
Aspirin[1]	7	PO	90–100
Cocaine[2]	5	IV	>60
Esmolol[3]	8	IV	80
Etodimate[4]	7	IV	75–90
Flestolol[5]	7	IV	>80
Flumazenil[6]	6	PO	80
Fosinopril[7]	9	PO	75

n number of subjects; PO oral administration; IV intravenous administration. [1]Montgomery et al. (1986); [2]Chow et al. (1985); [3]Achari et al. (1986); [4]Ghonheim and Van Hamme (1979); [5]Achari et al. (1987); [6]Klotz et al. (1984); [7]Singhvi et al. (1988).

[a] Expressed as the percentage of the dose recovered as hydrolysis dependent metabolites in the urine.

3.1.2. Metabolism data for phase II probe substrates

3.1.2.1. Glycine conjugation. Salicylic acid and benzoate are probe substrates for glycine conjugation with more than 84 and 83–90% excreted as salicyluric acid and hippuric acid respectively after an oral dose in healthy adults (Montgomery et al., 1986; Kubota and Ishizaki, 1991).

3.1.2.2. Sulphate conjugation. Prenalterol was selected as a probe substrate for sulphation because more than 76% of an oral dose was recovered as the sulphate conjugate in the urine of healthy adult volunteers (Hoffmann et al., 1982). No other probe substrates were found for this route of metabolism, however metabolic clearances via sulphation were available for diflunisal, paracetamol and salbutamol.

3.2. Kinetic data for phase I and phase II probe substrates

3.2.1. Variability between studies

Figs. 1–4 present the variability between studies for all pathways for markers of chronic exposure (Figs. 1 and 2) and for a marker of acute exposure (Figs. 3 and 4). The data are calculated as the ratio of the value for a particular study to the overall weighted value for all studies that reported the same parameter for the same compound.

For clearance and AUC data (Figs. 1 and 2), the ratios of geometric means and coefficients of variation from individual studies were mostly within a 40% range of the overall mean and CV for each pathway. A few outliers were found for studies of small sample size in the analysis of mean ratios (CYP2C9, glycine conjugation) and the analysis of CV ratios (ADH, and glycine conjugation). Greater study-to-study variability was found for C_{max} (Figs. 3 and 4), as would be expected, because this would be influenced by a variety of factors including the rate of gastric emptying.

3.2.2. Inter-individual differences

All inter-individual differences are described in the text as lognormal (CV_{LN}).

3.2.2.1. Phase I probe enzymes. CYP2A6. Data for human variability in healthy adults for CYP2A6 metabolism (Tables 2 and 3) were mostly available for the intravenous route. Clearance data for the oral route included only 15 subjects, two compounds and ranged from 23 to 46%. Clearance data for the intravenous route included 115 subjects for ml/min/kg and 72 subjects for ml/min and the variability ranged from 12 to 35%. The variability in total clearance was similar to that reported for the equivalent metabolic clearances (23–28%).

The data available for smokers and ethnic minorities of the population (healthy adult smokers, black American smokers, Chinese American smokers) did not show a difference in internal dose or variability compared with healthy adults (Tables 2 and 3). Intravenous clearances for the elderly and patients with renal diseases were 1.3–1.5 lower than for healthy adults. Variability was similar in the elderly and 1.5-fold higher in patients with renal disease compared to healthy adults.

CYP2C9. The data describing the human variability in kinetics for the CYP2C9 pathway are presented in Tables 4–7. Inter-individual differences in non-phenotyped healthy adults (Table 4) ranged from 12 to 47% for all kinetic parameters after oral administration. Inter-individual differences for the metabolic clearances were similar with a CV_{LN} of 37% (body weight adjusted, one compound, 27 subjects) and 44% (not adjusted to body weight, one compound, eight subjects). Lower variability was observed for clearance adjusted to body weight (CV_{LN} of 27%; three compounds, 102 subjects) than for unadjusted clearance (CV_{LN} of 40%; three compounds, 240 subjects). Variability in the AUC was much lower with a value of 16% (three compounds, 139 subjects). Data for C_{max} showed an overall similar CV_{LN} value of 34% (three compounds, 329 subjects). Variability for the intravenous route (Table 5) was similar to the oral route (range 23–34%).

Data on phenotyped healthy adults (Tables 4 and 7) were only available for a small number of subjects ($n < 15$). Differences in internal dose were observed between subjects with different poor metaboliser CYP2C9 genotypes [CYP2C9*1/*3 (1.3–1.8-fold), *2/*2 (1.2-fold), *2/*3 (1.7–2-fold) and *3/*3 (4.8-fold)] compared to the extensive metabolisers (CYP2C9*1/*1 and *1/*2) for both glibenclamide and tolbutamide (Kircheiner et al., 2002a,b). Variability was low for each phenotype (<40%, overall average 20%).

The available data for the different subgroups of the population [Arabian, Chinese healthy subjects, elderly and patients with liver disease (acute viral hepatitis)] (Tables 6 and 8) did not show any major differences in internal dose and variability compared with general healthy adults.

CYP2E1 Interindividual differences were relatively low when comparing the different kinetic parameters for healthy adults (Tables 9 and 10) with a CV_{LN} of 32% for metabolic clearance (ml/min/kg, one compound, 91 subjects), 23% for total clearance (ml/min/kg, two compounds, 182 subjects) and 29% for unadjusted clearance (ml/min, two compounds and 81 subjects). The variability in C_{max} was overall lower than that for clearances or AUC at 16% (Tables 9 and 10).

Data on chlorzoxazone kinetics were also available for Japanese healthy adults with different CYP2E1 genotypes (Marchand et al., 1999) and the oral clearance not adjusted to body weight was shown to decrease

Table 2
Pharmacokinetics of CYP2A6 probe substrates: comparisons between healthy adults (non-smokers and smokers) and (Caucasian, African, and Asian subjects), the elderly and patients with renal disease after intravenous administration

Parameter	Drug	N_s	N_p	n	X_w	SD_w	CV_N	GM_w	GSD_w	CV_{LN}	Ratio GM	Ratio CV
Oral administration												
Healthy adult non-smokers												
CL[a]	Cotinine	1	1[1]	9	0.83	0.29	23	0.78	1.4	23		
CL[a]	Nicotine	1	1[2]	6	22	10	46	20	1.6	46		
Intravenous administration												
Healthy adult non-smokers												
CLm 2A6[b]	Nicotine	1	1[3]	12	880	250	28	850	1.3	28		
CLm[b]	Nicotine	2	2[4]	29	1300	290	23	1200	1.3	23		
CL[a]	Coumarin	2	2[5]	9	14	3.2	23	13	1.2	22		
CL[a]	Nicotine	9	8[6]	100	19	6.5	34	17	1.4	36		
CL[b]	Cotinine	1	1[7]	4	61	8	12	60	1.1	12		
CL[b]	Coumarin	1	1[8]	5	1600	550	34	1500	1.4	34		
CL[b]	Nicotine	5	5[9]	63	1300	310	24	1200	1.3	25		
Healthy adult smokers												
CLm 2A6[a]	Nicotine	2	1[10]	94	18	7.8	43	16	1.5	43	0.76	1.5
CLm[a]	Nicotine	2	2[11]	53	18	5.7	38	17	1.4	31	1.0	1.4
CLm[b]	Cotinine	1	1[12]	8	60	12	24	59	1.2	25	1.0	2.0
CL[a]	Cotinine	1	1[12]	8	0.94	0.15	66	0.93	1.2	37	0.94	1.1
CL[a]	Nicotine	6	5[13]	164	20	7.3	37	19	1.4	36	0.90	1.0
Black American smokers												
CLm[a]	Nicotine	1	1[14]	40	17	4.8	28	17	1.3	28	1.0	0.9
CL[a]	Nicotine	1	1[14]	40	18	4.9	28	17	1.3	28	1.0	0.8
Chinese American smokers												
CLm 2A6[a]	Nicotine	1	1[15]	37	14	6.3	46	13	1.5	46	1.3	1.1
CL[a]	Nicotine	1	1[15]	37	17	7.6	44	16	1.5	44	1.1	1.2
Elderly												
CLm[b]	Nicotine	1	1[16]	20	980	240	24	960	1.3	24	1.3	1.1
CL[b]	Nicotine	1	1[16]	20	1000	240	24	970	1.3	24	1.3	1.0
Patients with renal disease												
CLm[b]	Nicotine	3	3[17]	15	960	290	31	860	1.4	35	1.5	1.5
CL[b]	Nicotine	3	3[17]	15	980	300	30	880	1.4	34	1.4	1.4

N_s Number of studies; N_p Number of publications; n number of subjects; X_W Arithmetic weighted mean (normal distribution); SD_w Weighted standard deviation (normal distribution); CV_N coefficient of variation (normal distribution); GM_W Geometric weighted mean (lognormal distribution); GSD_w Weighted geometric standard deviation (lognormal distribution); CV_{LN} Coefficient of variation; (lognormal distribution); Ratio GM Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio GM was calculated) (lognormal distribution); Ratio CV_{LN} Variability ratio between healthy adults and subgroup (lognormal distribution); (n) given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.; CLm2A6[a] Metabolic clearance adjusted to body weight (ml/min/kg) corresponding to the oxidation of nicotine to cotinine (CYP2A6 specific reaction); Clm 2A6[b] Metabolic clearance not adjusted to body weight (ml/min) corresponding to the oxidation of nicotine to cotinine (CYP2A6 specific reaction); CLm[a] Total metabolic clearance (including CYP2A6-specific and other minor multiple CYP reactions) adjusted to body weight (ml/min/kg); Clm[b] Total metabolic clearance (including CYP2A6-specific and other minor multiple CYP reactions) not adjusted to body weight (ml/min); CL[a] Total clearance adjusted to body weight (ml/min/kg); CL[b] Total clearance not adjusted to body weight (ml/min). [1]Curvall et al. (1990); [2]Zins et al. (1997); [3]Benowitz and Jacob (2000); [4]Molander et al. (2000, 2001); [5]Ritschel et al. (1976), Ritschel and Hoffmann (1981); [6] Rosenberg et al. (1980), Benowitz et al. (1982), Kyerematen et al. (1982) (2), Feyerabend et al. (1985), Benowitz and Jacob (1993, 1994), Compton et al. (1997), Zevin et al. (1997); [7]De Schepper et al. (1987); [8] Ritschel et al. (1977); [9]Benowitz et al. (1991, 1992), Benowitz and Jacob (2000), Molander et al. (2000, 2001); [10]Benowitz et al. (2002) (2); [11]Benowitz et al. (1982), Perez-Stable et al. (1998); [12]Benowitz et al. (1983); [13]Benowitz et al. (1982) (2002) (2), Scherer et al. (1988), Benowitz and Jacob (1993), Perez-Stable et al. (1998); [14]Perez-Stable et al. (1998); [15] Benowitz et al. (2002); [16]Molander et al. (2001); [17]Molander et al. (2000).

with the number of C2 alleles (c2/c2; 147 ml/min) compared to the homozygous wild type (c1/c1; 238 ml/min) or the heterozygous wild type (c1/c2; 201 ml/min).

The data in elderly subjects (Tables 9 and 10) revealed a slightly higher internal dose (1.3-fold) associated with similar variability to that in healthy adults (26%, 22 subjects).

Data for patients with liver disease (Tables 9 and 10) showed lower clearances for both estimates (1.3-fold and 6-fold) and higher variability than that in healthy

Table 3
Pooled analysis for interindividual differences in CYP2A6 metabolism; data for healthy adults (non-smokers and smokers), Black American and Chinese American healthy adult smokers, elderly and patients with renal disease

PK parameter	Route	N_c	N_s	N_p	n	CV_{LN}	Mean ratio GM	Mean ratio CV
Healthy adult non-smokers								
CL[a]	PO	2	2	2	15	33		
CLm[b] CYP2A6	IV	1	1	1	12	28		
CLm[b]	IV	1	2	2	29	23		
CL[a]	IV	2	11	10	109	28		
CL[b]	IV	2	7	7	72	31		
Healthy adult smokers								
CLm[a] CYP2A6	IV	1	2	1	94	43	0.76	1.5
CLm[a]	IV	1	2	2	53	31	1.0	1.4
CLm[b]	IV	1	1	1	8	25	1.0	2.0
CL[a]	IV	2	7	6	172	36	0.92	1.0
Black American smokers								
CLm[a]	IV	1	1	1	40	28	1.0	0.90
CL[a]	IV	1	1	1	40	28	1.0	0.80
Chinese American smokers								
CLm[a] CYP2A6	IV	1	1	1	37	46	1.3	1.1
CL[a]	IV	1	1	1	37	44	1.1	1.2
Elderly								
CLm[b]	IV	1	1	1	20	24	1.3	1.1
CL[b]	IV	1	1	1	20	24	1.3	1.0
Patients with renal disease								
CLm[b]	IV	1	3	3	15	35	1.5	1.5
CL[b]	IV	1	3	3	15	34	1.4	1.4

N_c Number of compounds; Ns Number of studies; Np Number of publications; n Number of subjects; Mean ratio GM Mean Ratio between healthy volunteers and subgroup (lognormal distribution); Mean ratio CV_{LN} Ratio between the variability of the subgroup and the healthy volunteers; CLm[a] Total metabolic clearance (including CYP2A6-specific and other minor multiple CYP reactions) adjusted to body weight (ml/min/kg); CLm[b] total metabolic clearance specific (including CYP2A6-specific and other minor multiple CYP reactions) and not adjusted to body weight (ml/min); CLm[a]CYP2A6 metabolic clearance specific to CYP2A6 (nicotine to cotinine) adjusted to body weight; CLm[b]CYP2A6 metabolic clearance specific to CYP2A6 (nicotine to cotinine) not adjusted to body weight; CL[a] total clearance adjusted to body weight (ml/min/kg); CL[b] total clearance not adjusted to body weight (ml/min); PO oral administration; IV intravenous administration.

adults with CV_{LN} values of 37 and 58% respectively (one compound, 71 and 10 subjects). Data for patients with renal disease showed a three- and two-fold greater internal dose and variability respectively (one compound, 13 subjects).

Alcohol dehydrogenase. The coefficients of variation for metabolism via ADH in general healthy adults were between 20 and 30% for both routes and for the different kinetic parameters reflecting either chronic or acute exposure (Table 11).

Interindividual variability for Oriental individuals was lower than that in healthy adults and ranged between 11 and 21% and was not related to the ADH phenotype. Differences in internal dose were not significant with only a slightly lower elimination rate for the ADH− phenotype compared with the ADH+ phenotype (1.2-fold). The elderly data did not indicate a higher internal dose based on AUC and C_{max}, but, a two-fold greater variability was observed for both parameters compared to healthy adults (Table 11).

Hydrolysis. Data on metabolism via hydrolysis in healthy adults showed CV_{LN} values between 25 and 30% overall for both the oral and intravenous routes, and for different kinetic parameters (Table 12). The intravenous data showed similar variability for both systemic clearances although the variability in metabolic clearance was higher, but this was based on only 1 compound and 11 subjects.

The comparison between healthy adults and Chinese from two intravenous studies describing the kinetics of fosinopril showed nearly two-fold lower metabolic clearances and total clearances associated with greater variability (Tables 13 and 14). No major differences were observed between healthy adults and either children or the elderly; clearance and variability were slightly higher for both groups (Tables 13 and 14).

Patients with liver disease (Tables 13 and 14) showed 1.5–2-fold lower intravenous clearances compared to healthy adults, but the variability data were inconsistent across the different parameters. A similar observation

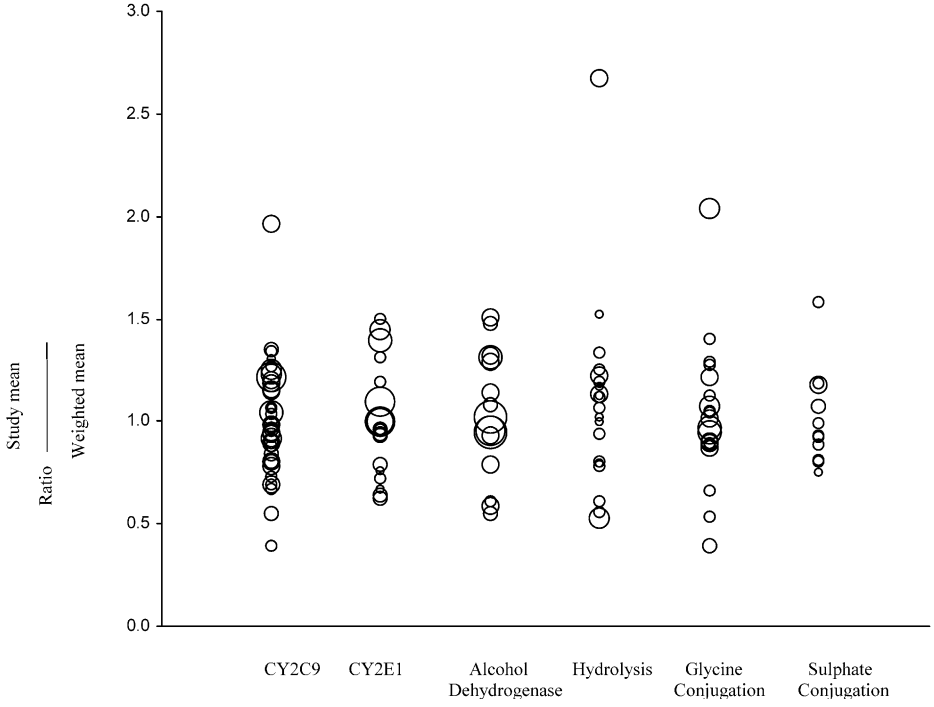
Table 4
Pharmacokinetics of CYP2C9 probe substrates in phenotyped and non-phenotyped healthy adults after oral administration

Parameter/(phenotype)	Drug	N_s	N_p	n	X_w	SD_w	CV_N	GM_w	GSD_w	CV_{LN}	Ratio GM	Ratio CV_{LN}
Non-phenotyoped healthy adults												
CLm[a] 3-OH (NP)	Glibenclamide	1	1[1]	15	0.11	0.04	32	0.10	1.4	32		
CLm[a] 4-OH (NP)	Glibenclamide	3	2[2]	27	0.36	0.14	39	0.34	1.4	37		
CL[a] (NP)	Glibenclamide	6	5[3]	71	1.5	0.54	37	1.3	1.4	35		
CL[a] (NP)	S-Warfarin	1	1[4]	5	0.19	0.04	22	2.6	1.3	25		
CL[a] (NP)	Tolbutamide	3	3[5]	26	0.19	0.04	22	0.19	1.2	22		
CLm[b] (NP)	Glibenclamide	1	1[6]	8	17	7.3	44	15	1.5	44		
CL[b] (NP)	Glibenclamide	10	9[7]	113	75	30	41	66	1.5	40		
CL[b] (NP)	S-Warfarin	7	5[8]	93	4.5	1.9	43	4.0	1.4	38		
CL[b] (NP)	Tolbutamide	3	3[9]	34	14	6.5	47	12	1.5	43		
AUC (NP)	Glibenclamide	8	8[10]	101	10,300	3500	33	9500	1.4	33		
AUC (NP)	S-Warfarin	1	1[11]	12	140,000	16,000	12	140,000	1.1	12		
AUC (NP)	Tolbutamide	2	2[12]	26	95,000	28,000	29	90,000	1.3	26		
C_{max} (NP)	Glibenclamide	24	22[13]	287	3700	550	15	3000	1.4	34		
C_{max} (NP)	S-Warfarin	2	2[14]	24	3200	540	17	2300	1.3	27		
C_{max} (NP)	Tolbutamide	2	2[15]	18	6400	1300	20	6300	1.2	18		
Phenotyped healthy adults												
CLm[a] (*1/*1)	Tolbutamide	2	2[16]	10	16	2	12	16	1.1	11		
CLm[a] (*1/*2)	Tolbutamide	2	2[16]	10	11	3	32	10	1.3	32	1.6	2.9
CLm[a] (*1/*3)	Tolbutamide	2	2[16]	10	8	1.3	15	8.1	1.2	14	2.0	1.3
CL[a] (*1/*1)	Tolbutamide	2	2[17]	11	16	3	16	15	1.2	16		
CL[a] (*1/*2)	Tolbutamide	2	2[17]	9	12	2	20	12	1.2	20	1.3	1.3
CL[a] (*1/*3)	Tolbutamide	2	2[17]	11	9	1.4	16	9	1.2	15	1.8	1.0
CL[a] (*2/*2)	Tolbutamide	1	1[18]	3	13	3	20	12	1.2	20	1.2	1.3
CL[a] (*2/*3)	Tolbutamide	1	1[18]	3	2.5	0.5	20	7	1.2	20	2.0	1.3
CL[b](*1/*1)	Glibenclamide	1	1[19]	4	54	12	21	53	21	21		
CL[b](*1/*2)	Glibenclamide	1	1[19]	4	72	26	37	67	24	37	0.79	1.7
CL[b] (*1/*3)	Glibenclamide	1	1[19]	4	49	16	33	46	23	33	1.3	0.19
CL[b] (*2/*2)	Glibenclamide	1	1[19]	3	42	1.7	4.0	42	17	4	1.1	1.6
CL[b] (*2/*3)	Glibenclamide	1	1[19]	3	32	3.0	9.0	32	18	9	1.7	0.44
CL[b] (*3/*3)	Glibenclamide	1	1[19]	3	11	1.5	13	11	19	13	4.8	0.64

Ns Number of studies; Np Number of publications; n number of subjects; X_W Arithmetic weighted mean (normal distribution); SD_w Weighted standard deviation (normal distribution); CV_N coefficient of variation (normal distribution); GM_W Geometric weighted mean (lognormal distribution); GSD_w Weighted geometric standard deviation (lognormal distribution); CV_{LN} Coefficient of variation (lognormal distribution); Ratio GM Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); Ratio CV_{LN} Variability ratio between healthy adults and subgroup (lognormal distribution); (n) given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.; CLm[a] Metabolic clearance adjusted to body weight (ml/min/kg); Clm[b] Metabolic clearance not adjusted to body weight (ml/min); CL[a] Total clearance adjusted to body weight (ml/min/kg) CL[b] Total clearance not adjusted to body weight (ml/min); AUC AUC/dose ((ng/ml)h) with mean data corrected for dose expressed per mean body weight (mg/kg); C_{max} C_{max}/dose (ng/ml) with mean data corrected for dose expressed per mean body weight (mg/kg); NP non-phenotyped healthy adults. [1]Dahl-Puustinen et al. (1990); [2]Peart et al. (1989) (2), Dahl-Puustinen et al. (1990); [3] Peart et al. (1989) (2), Dahl-Puustinen et al. (1990), Schwinghammer et al. (1991), Muller et al. (1993), Boni et al. (1997); [4]Heimark et al. (1992); [5]Whiting et al. (1981), Robson et al. (1987), Gross et al. (1999); [6]Rydberg et al. (1995); [7]Malerczyk et al. (1994), Fleishaker and Phillips (1991), Jaber et al. (1993) (2), (1994), Rydberg et al. (1995), Jaber et al. (1996), Kubacka et al. (1996), Brier et al. (1997), Jonsson et al. (1998); [8]Chan et al. (1984), Toon et al. (1986) (2), Awni et al. (1995) (2), Priskorn et al. (1997), Tiseo et al. (1998); [9] Day et al. (1995), Madsen et al. (2001), Wang et al. (2001); [10]Molz et al. (1989), Zuccaro et al. (1989), Coppack et al. (1990), Kivisto et al. (1993), Appel et al. (1995), Gleiter et al. (1999), Niemi et al. (2001), Niopas and Daftios, (2002); [11]Tiseo et al. (1998); [12]Sartor et al. (1980), Antal et al. (1982); [13]Malerczyk et al. (1994), Peart et al. (1989) (2), Molz et al. (1989), Zuccaro et al. (1989), Coppack et al. (1990), Dahl-Puustinen et al. (1990), Fleishaker and Phillips (1991), Schwinghammer et al. (1991), Jaber et al. (1993) (2) (1994, 1996), Kivisto et al. (1993), Muller et al. (1993), Appel et al. (1995), Rydberg et al. (1995), Kubacka et al. (1996), Boni et al. (1997), Jonsson et al. (1998), Courtois et al. (1999), Gleiter et al. (1999), Niemi et al. (2001), Niopas and Daftsios (2002); [14]Priskorn et al. (1997), Robertson et al. (2002); [15]Sartor et al. (1980), Day et al. (1995); [16]Lee et al. (2002, 2003); [17]Kirchheiner et al. (2002b), Lee et al. (2002); [18]Kirchheiner et al. (2002b); [19]Kirchheiner et al. (2002a).

was made with the intravenous clearance data for patients with renal disease, the variability was however similar to that in healthy adults.

3.2.2.2. Phase II enzymes. Glycine conjugation. Inter-individual differences for glycine conjugation gave CV_{LN} values between 15 and 24% in healthy adults for both routes of exposure with an overall mean of 21% for the oral route (205 subjects); variability for C_{max} was lower at 16% (262 subjects) (Tables 15 and 17). No significant differences were observed in the mean values between healthy adults and children (20 subjects) or elderly (40 subjects) or patients with liver disease (eight subjects), but there was higher variability for patients



The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; [1]Clearance (ml/min/kg); [2]Clearance (ml/min); [3]AUC/dose ((ng/ml)h) corrected for dose and body weight (mg/kg); [4]extraction rate (mg/min/kg); [5]Metabolic Clearance (ml/min/kg); [6]Metabolic Clearance (ml/min).

CY2C9: [1]data for glibenclamide (6 studies), tolbutamide (3 studies), [2]data for glibenclamide (10 studies), S-Warfarin (7 studies), tolbutamide (3 studies), [3]data for glibenclamide (8 studies), tolbutamide (2 studies); **CY2E1**: [1]data for chlorzoxazone (6 studies) and trimethadione (8 studies), [2]data for chlorzoxazone (4 studies) and trimethadione (2 studies); **Alcohol dehydrogenase**: [4]data for ethanol (3 studies), [3]data for ethanol (11 studies); **Hydrolysis**: [1]data for aspirin (2 studies), [3]data for aspirin (9 studies), fosinopril (9 studies) and flumazenil (2 studies); **Glycine Conjugation**: [1]data for salicylate (2 studies), [2]data for salicylate (3 studies), [3]data for salicylate (15 studies); **Sulphate Conjugation**:, [5]data for diflunisal (3 studies) and paracetamol (3 studies), [6]data for paracetamol (6 studies).

Fig. 1. Inter-study variation in kinetic parameters for phase I (CYP2C9, CYP2E1, alcohol dehydrogenase, hydrolysis) and phase II (glycine and sulphate conjugation) pathways after oral administration in healthy adult volunteers. Comparisons of individual study means versus weighted geometric means for markers of chronic exposure (clearances and AUC).

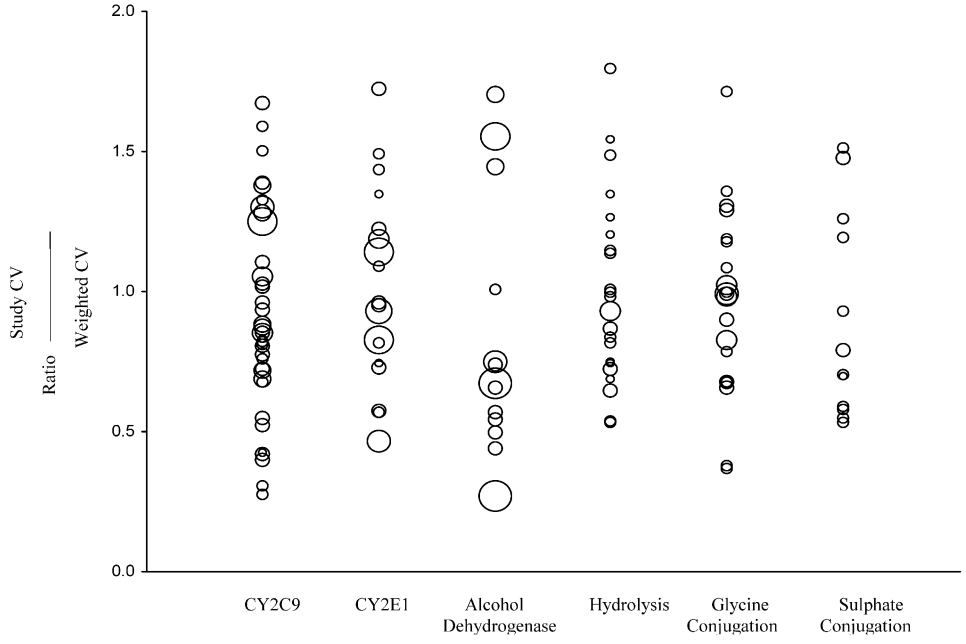
with liver disease, particularly for the intravenous data (2.5-fold, 30 subjects). Neonates showed a markedly higher internal dose compared with adults (19-fold, data based on only one compound and 10 subjects) (Tables 15 and 17).

Sulphate conjugation. Data for the sulphation pathway (Tables 16 and 17) in healthy adults showed that variability was below 30% for the oral route (CV_{LN} 17–39%, 97 subjects) and was slightly higher for the intravenous route (36%), however the number of subjects was much lower (18) for the latter route. Variability in the elderly was lower than that in healthy adults for both routes of exposure, and no differences in internal dose were shown (Tables 16 and 17).

The metabolic clearance of paracetamol via sulphation was higher and more variable in Chinese healthy adults than that in Caucasian healthy adults (1.3- and 2-fold) (Tables 16 and 17).

3.3. Pathway-related uncertainty factors

The pathway-related uncertainty factors were below the 3.16 toxicokinetic default factor for most subgroups of the population available (healthy adults and elderly) (Table 18). The values to cover each subgroup to the 99th centile were similar for all the pathways with values up to 2–2.3 for healthy adults (with the exception of CYP2C9*3/*3 genotype which had a value of 6.5) (Table 18). The 3.16 kinetic default uncertainty factor would not cover Asian healthy adults for compounds metabolised via hydrolysis and pathway-related factors of 3.4, 3.9 and 4.6 would be required to cover 95th, 97.5th and 99th centiles respectively. The most significant deviation from the default factor was for neonates who would need uncertainty factors up to 28 (for the 99th centile) for compounds handled by glycine conjugation. Unfortunately, no clearance data were



The overall weighted CV_{LN} for each compound has been normalised to one, and the ratio of the mean CV_{LN} for each study to the weighted mean CV_{LN} is shown as a circle with the number of subjects in the study indicated by the size of the circle; [1]Clearance (ml/min/kg); [2]Clearance (ml/min); [3]AUC/dose ((ng/ml)h) corrected for dose and body weight (mg/kg); [4]extraction rate (mg/min/kg); [5]Metabolic Clearance (ml/min/kg); [6]Metabolic Clearance (ml/min).

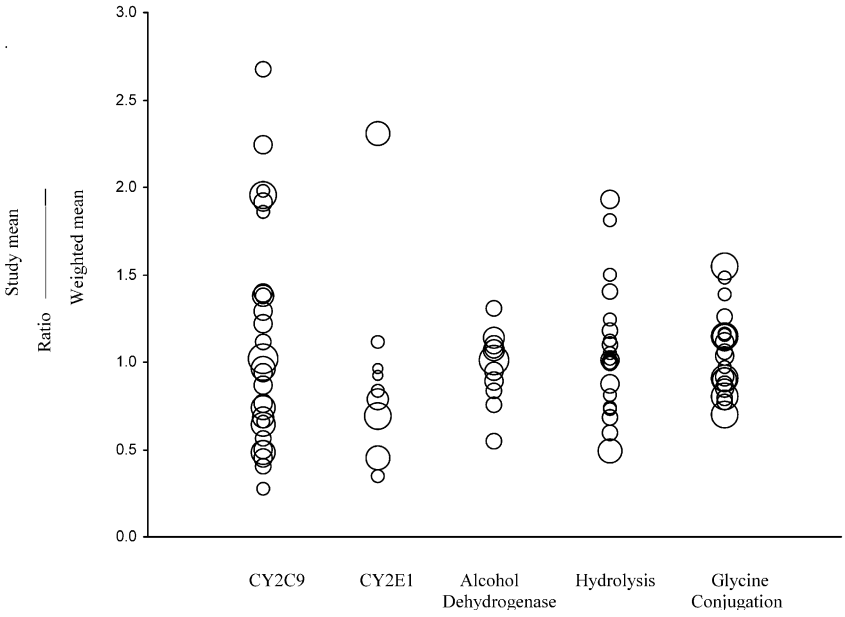
CY2C9: [1]data for glibenclamide (6 studies), tolbutamide (3 studies), [2]data for glibenclamide (10 studies), S-Warfarin (7 studies), tolbutamide (3 studies), [3]data for glibenclamide (8 studies), tolbutamide (2 studies); **CY2E1**: [1]data for chlorzoxazone (6 studies) and trimethadione (8 studies), [2]data for chlorzoxazone (4 studies) and trimethadione (2 studies); **Alcohol dehydrogenase**: [4]data for ethanol (3 studies), [3]data for ethanol (11 studies); **Hydrolysis**: [1]data for aspirin (2 studies), [3]data for aspirin (9 studies), fosinopril (9 studies) and flumazenil (2 studies); **Glycine Conjugation**: [1]data for salicylate (2 studies), [2]data for salicylate (3 studies), [3]data for salicylate (15 studies); **Sulphate Conjugation**:, [5]data for diflunisal (3 studies) and paracetamol (3 studies), [6]data for paracetamol (6 studies).

Fig. 2. Inter-study variation in kinetic parameters for phase I (CYP2C9, CYP2E1, alcohol dehydrogenase, hydrolysis) and phase II (glycine and sulphate conjugation) pathways after oral administration in healthy adult volunteers. Comparisons of individual study coefficients of variation versus weighted coefficients of variation for markers of chronic exposure (clearances and AUC).

Table 5
Pharmacokinetics of CYP2C9 probe substrates in non-phenoyped healthy adults after intravenous administration

Parameter (phenotype)	Drug	N_s	N_p	n	X_w	SD_w	CV_N	GM_w	GSD_w	CV_{LN}
CLm^a	Tolbutamide	1	1[1]	7	0.18	0.06	33	0.17	1.4	34
CLm^{a2}	Tolbutamide	1	1[1]	7	0.21	0.07	34	0.20	1.4	34
CL^a	Tolbutamide	1	1[1]	7	0.26	0.10	39	0.24	1.4	38
CL^b	Glibenclamide	1	1[2]	52	49	11	23	48	1.2	23
CL^b	S-Warfarin	1	1[3]	4	4.2	1.1	26	4.1	1.3	26
CL^b	Tolbutamide	1	1[4]	12	21	5.40	26	20	1.3	26

N_s Number of studies; N_p Number of publications; n number of subjects; X_W Arithmetic weighted mean (normal distribution); SD_w Weighted standard deviation (normal distribution); CV_N coefficient of variation (normal distribution); GM_W Geometric weighted mean (lognormal distribution); GSD_w Weighted geometric standard deviation (lognormal distribution); CV_{LN} Coefficient of variation; (lognormal distribution); CLm^a Metabolic clearance (carboxy group) adjusted to body weight (ml/min/kg); Clm^{a2} Metabolic clearance (hydroxy group) adjusted to body weight (ml/min/kg); CL^a Total clearance adjusted to body weight (ml/min/kg) CL^b Total clearance not adjusted to body weight (ml/min). [1]Back et al. (1988); [2]Spraul et al. (1989); [3]Abernethy et al. (1991); [4]Tremaine et al. (1997).



The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; [1]Cmax (maximum plasma concentration in ng/ml per mg/kg).

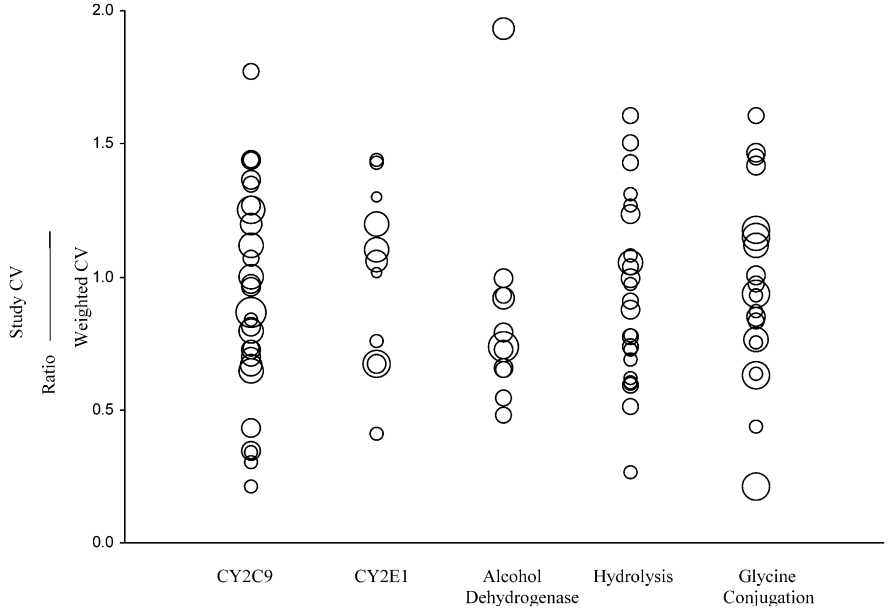
CY2C9: [1]data for glibenclamide (24 studies), [1]S-Warfarin (2 studies), [1]tolbutamide (3 studies); **CY2E1**: [1]data for chlorzoxazone (8 studies) and trimethadione (3 studies); **Alcohol dehydrogenase**: [1]data for ethanol (9 studies); **Hydrolysis**: [1]data for aspirin (13 studies), [1]fosinopril (9 studies) and [1]flumazenil (2 studies). **Glycine Conjugation**: [1]data for salicylate (21 studies).

Fig. 3. Inter-study variation in kinetic parameters for phase I (CYP2C9, CYP2E1, alcohol dehydrogenase, hydrolysis) and phase II (glycine conjugation) pathways after oral administration in healthy adult volunteers. Comparisons of individual study means versus weighted geometric means for a marker of acute exposure (C_{max}).

Table 6
Pharmacokinetics of CYP2C9 probe substrates: comparison between healthy adults and subgroups of the population, (Arabian, Chinese, elderly, liver disease patients) after oral administration

Parameter/(phenotype)	Drug	N_s	N_p	n	X_w	SD_w	CV_N	GM_w	GSD_w	CV_{LN}	Ratio GM	Ratio CV
Arabian (Oral administration)												
AUC (NP)	Glibenclamide	1	1[1]	16	13,000	4100	32	12,000	1.4	32	1.4	0.66
C_{max} (NP)	Glibenclamide	1	1[1]	16	2500	620	25	2400	1.3	25	0.81	1.0
Chinese (Oral administration)												
CL[a] (NP)	Glibenclamide	1	1[2]	4	0.67	0.11	16	0.66	1.2	16	2.0	0.47
CL[a] (NP)	Tolbutamide	1	1[3]	12	0.17	0.02	12	0.17	1.1	12	1.1	0.55
CL[a] (*1/*1)	Tolbutamide	2	1[4]	12	0.20	0.01	6.3	0.20	1.1	6	1.1	0.40
CL[a] (*1/*3)	Tolbutamide	1	1[5]	6	0.20	0.01	6.6	0.20	1.1	7	1.1	0.40
C_{max} (NP)	Glibenclamide	1	1[2]	4	1300	190	15	1300	1.2	15	0.45	0.58
C_{max} (*1/*1)	Tolbutamide	2	1[4]	12	6900	450	6.5	6900	1.1	7	1.1	0.30
C_{max} (*1/*3)	Tolbutamide	1	1[5]	6	8200	1400	17	8100	1.2	17	1.3	0.90
Elderly (Oral administration)												
CL[a] (NP)	Glibenclamide	1	1[6]	20	1.9	0.75	41	1.7	1.5	41	0.78	1.2
CL[b] (NP)	Glibenclamide	1	1[7]	10	59	15	25	57	1.3	25	1.1	0.61
AUC (NP)	Tolbutamide	1	1[8]	12	70,000	21,000	30	67,000	1.3	29	0.74	1.1
C_{max} (NP)	Glibenclamide	3	3[9]	35	2700	1300	49	2050	1.4	38	0.69	1.5
C_{max} (NP)	Tolbutamide	1	1[8]	12	5600	2100	38	5200	1.4	38	0.83	2.2
Liver disease (Oral administration)												
CL[a] (NP)	Tolbutamide	1	1[10]	5	0.43	0.09	21	0.42	1.2	21	0.44	0.96

N_s Number of studies; N_p Number of publications; n number of subjects; X_W Arithmetic weighted mean (normal distribution); SD_w Weighted standard deviation (normal distribution); CV_N coefficient of variation (normal distribution); GM_W Geometric weighted mean (lognormal distribution); GSD_w Weighted geometric standard deviation (lognormal distribution); CV_{LN} Coefficient of variation; (lognormal distribution); Ratio GM Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); Ratio CV_{LN} Variability ratio between healthy adults and subgroup (lognormal distribution); (n) given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.; CL[a] Total clearance adjusted to body weight (ml/min/kg) CL[b] Total clearance not adjusted to body weight (ml/min); AUC AUC/dose ((ng/ml)h)with mean data corrected for dose expressed per mean body weight (mg/kg); C_{max} C_{max}/dose (ng/ml) with mean data corrected for dose expressed per mean body weight (mg/kg); NP non-phenotyped. [1]El Sayed et al. (1989); [2]Cui et al. (1993); [3]Gross et al. (1999); [4]Shon et al. (2002) (2); [5]Shon et al. (2002); [6]Schwinghammer et al. (1991); [7]Jaber et al. (1996); [8]Sartor et al. (1980); [9]Schwinghammer et al. (1991), Jaber et al. (1996), Courtois et al. (1999); [10]Williams et al. (1977).



The overall weighted CV_{LN} for each compound has been normalised to one, and the ratio of the mean CV_{LN} for each study to the weighted mean CV_{LN} is shown as a circle with the number of subjects in the study indicated by the size of the circle; [1]Cmax (maximum plasma concentration in ng/ml per mg/kg).

CY2C9: [1]data for glibenclamide (24 studies), [1]S-Warfarin (2 studies), [1]tolbutamide (3 studies); **CY2E1**: [1]data for chlorzoxazone (8 studies) and trimethadione (3 studies); **Alcohol dehydrogenase**: [1]data for ethanol (9 studies); **Hydrolysis**: [1]data for aspirin (13 studies), [1]fosinopril (9 studies) and [1]flumazenil (2 studies). **Glycine Conjugation**: [1]data for salicylate (21 studies).

Fig. 4. Inter-study variation in kinetic parameters for phase I (CYP2C9, CYP2E1, alcohol dehydrogenase, hydrolysis) and phase II (glycine conjugation) pathways after oral administration in healthy adult volunteers. Comparisons of individual study coefficients of variation versus weighted coefficients of variation for a marker of acute exposure (C_{max}).

available for any other pathways of metabolism for this subgroup.

4. Discussion

Human variability in kinetics for Phase I (CYP2A6, CYP2C9, CYP2E1, alcohol dehydrogenase and hydrolysis) and phase II enzymes (glycine and sulphate conjugation) has been analysed using probe substrates metabolised extensively (>60%) by these routes. Inter-individual differences in kinetics for all these pathways were low in healthy adults with CV_{LN} values ranging from 21 to 34%, resulting in pathway-related uncertainty factors ranging from 1.6 to 2.3 (at the 99th centile). Some of the enzymes, AHD, glycine conjugation and sulphate conjugation, are saturable at normal doses, and therefore part of the variability in the data may reflect inter-individual differences in the Km value of the enzyme.

The variability estimates in this paper are similar to the values that we have reported for most other metabolic pathways (Dorne et al., 2001a,b, 2002, 2003a,b,c), despite the more limited database available for these particular enzymes. CYP2C9 *3/*3 poor metabolisers were the only group requiring an uncertainty factor greater than 3.16, with a value of 6.5 necessary to cover the 99th centile, but this conclusion must be considered tentative as it is based on a single study with only three individuals. More in vivo pharmacokinetic studies are required to characterise the magnitude of the difference in internal dose and the true variability between the different CYP2C9 genotypes.

The frequency of the different CYP2C9 genotypes (excluding allele *4, *5, 6*) has been characterised recently in 516 individuals (Kircheiner et al., 2002a); the homozygous (*1/*1) and heterozygous (*1/*2) extensive metabolisers would constitute most of the human population (68 and 18% respectively). Another major genotype is *1/*3 at 11%, whereas the *2/*2, *2/*3 and *3/*3 genotypes would represent 1, 1 and 0.8% respectively. A recent review indicates that patients carrying the variant genotypes (mainly 2* and 3*) for CYP2C9 appear to be significantly more susceptible to adverse reactions (especially with drugs such as warfarin and phenytoin which have a narrow therapeutic index) (Lee et al., 2002). CYP2C9 constitutes approximately 20% of all CYP in the human liver (Miners and Birkett, 1998) and this isoform together with CYP2C19 has been shown to catalyse the O-demethylation of the endocrine disrupter methoxychlor (Hu and Kupfer, 2002). As we have previously discussed for CYP2D6, CYP2C19 and

Table 7
Interindividual differences for CYP2C9 metabolism of probe substrates in non-phenotyped and phenotyped healthy adults and subgroups of the population; pooled analysis

PK parameter	N_c	N_s	N_p	n	Mean CV_{LN}	Mean ratio EM/PM_{LN}	Mean ratio CV_{LN}
Non-phenotyped individuals							
CLm^a	1	3	2	27	37		
CL^a	3	10	9	102	27		
CLm^b	1	1	1	8	44		
CL^b	3	20	17	240	40		
AUC	3	11	11	139	22		
C_{max}	3	28	26	329	25		
Phenotyped individuals							
CLm^a (*1/*1)	1	2	2	10	11		
CLm^a (*1/*2)	1	2	2	10	32	1.6	2.9
CLm^a (*1/*3)	1	2	2	10	14	2.0	1.3
CL^a (*1/*1)	1	2	2	11	16		
CL^a (*1/*2)	1	2	2	9	20	1.3	1.3
CL^a (*1/*3)	1	2	2	11	15	1.8	1.0
CL^a (*2/*2)	1	1	1	3	20	1.2	1.3
CL^a (*2/*3)	1	1	1	3	20	2.0	1.3
CL^b (*1/*1)	1	1	1	4	21		
CL^b (*1/*2)	1	1	1	4	37	0.79	1.7
CL^b (*1/*3)	1	1	1	4	4	1.3	0.19
CL^b (*2/*2)	1	1	1	3	33	1.1	1.6
CL^b (*2/*3)	1	1	1	3	9	1.7	0.44
CL^b (*3/*3)	1	1	1	3	13	4.8	0.64

N_c Number of compounds; N_s Number of studies; N_p Number of publications; n Number of subjects; Mean CV_{LN} Mean coefficient of variation for all compounds (lognormal distribution); Mean ratio EM/PM_{LN} Mean ratio between the poor (*1/*2,*1/*3, *2/*2, *2/*3, *3/*3) and the extensive metabolisers (*1/*1) for all compounds (lognormal distribution); Mean ratio CV_{LN} mean ratio of the variability between the poor (*1/*2,*1/*3, *2/*2, *2/*3, *3/*3) and the extensive metabolisers (*1/*1) for all compounds (lognormal distribution); CL^a, CLm^a Individual Clearance corrected for body weight (ml/min/kg); CL^b, CLm^b Clearance not corrected for body weight (ml/min); AUC and C_{max} Mean AUC [(ng/ml)h] and C_{max} (ng/ml) corrected for dose expressed per mean body weight (mg/kg).

NAT2 metabolism (Dorne et al., 2002, 2003b), CYP2C9 polymorphism would have important implications for the risk assessment of environmental contaminants, because poor metabolisers would be a potential susceptible subgroup if the parent compound were the proximate toxicant, but would be at reduced risk if the metabolite were the proximate toxicant.

CYP2A6 polymorphism has also been described (Raunio et al., 2001) but no clearance or AUC data were available for any subgroup of the population so that quantification of phenotypic differences in internal dose and variability was not possible. The same conclusion would apply to CYP2E1, ADH and esterases (especially in the case of paraoxonase or PON1) (Bolt et al., 2003; Norberg et al., 2003; Costa et al., 2003).

Data for different subgroups of the population were scarce and included only African healthy adults (CYP2A6 and CYP2C9), Asian healthy adults (CYP2A6, CYP2C9, CYP2E1, ADH and hydrolysis), elderly (all pathways), children (hydrolysis and glycine conjugation) and neonates (glycine conjugation) (Table 18). Asian healthy adults would require a higher pathway-related factor for compounds metabolised via hydrolysis (only 10 subjects) but unexpectedly no major ethnic differences were observed in ethanol pharmacokinetics. The alcohol-induced flushing in Asians, which is associated with an increase in cortisol levels, occurs in individuals carrying aldehyde dehydrogenase isoform ALDH2*2 alleles and no pharmacokinetic data were available for these subjects (Wall et al., 1998). The data available for subjects described as ADH+or ADH−would have included ALDH2 homozygotes (*2/*2) and heterozygotes (ALDH2*1/2*1). A recent study of ALDH2 polymorphism in Japanese subjects (Ginsberg et al., 2002) investigated the population differences in acetaldehyde peak blood levels using data from the literature and Monte Carlo simulation for the homozygous variant (ALDH*2/*2), the heterozygous variant (ALDH*2/*1/2) and the wild type (ALDH2*1/1). The heterozygous variant is common in the Asian population (40%) and large differences were observed such that the ratio of the 95th/99th percentiles compared to the median of the US population was 14- to 26-fold. The authors concluded that these values for the variants of aldehyde dehydrogenase were much larger than the 3.16-kinetic default. However, these observed and simulated differences were based on peak blood levels (not plasma) and studies reporting clearances (when

Table 8
Interindividual differences for CYP2C9 metabolism in subgroups of the population (Arabian and Chinese healthy adults, elderly and patients with liver disease); pooled analysis

PK parameter	N_c	N_s	N_p	n	Mean CV_{LN}	Mean ratio GM	Mean ratio CV_{LN}
Arabian healthy adults							
AUC	1	1	1	16	32	1.4	0.66
C_{max}	1	1	1	16	25	0.81	1.0
Chinese healthy adults							
CL[a]	2	2	2	16	14	1.5	0.5
CL[a] (*1/*1)	1	2	2	12	6	1.1	0.4
CL[a] (*1/*3)	1	1	1	6	7	1.1	0.4
C_{max}	1	1	1	4	15	0.45	0.58
C_{max} (*1/*1)	1	2	1	12	7	1.1	0.30
C_{max} (*1/*3)	1	1	1	6	17	1.3	0.90
Elderly							
CL[a]	1	1	1	20	41	0.78	1.2
CL[b]	1	1	1	10	25	1.1	0.61
AUC	1	1	1	12	29	0.74	1.1
C_{max}	2	4	4	47	38	0.76	1.8
Patients with liver disease							
CL[a]	1	1	1	5	21	0.44	0.96

N_c Number of compounds; N_s Number of studies; N_p Number of publications; n Number of subjects; Mean CV_{LN} Mean coefficient of variation for all compounds (lognormal distribution); Mean ratio GM Mean ratio between healthy volunteers and subgroup (for the AUC and C_{max} the 1/Ratio was calculated) (lognormal distribution); Mean ratio CV_{LN} mean ratio of the variability between healthy volunteers and subgroup (lognormal distribution); CL[a], Individual clearance corrected for body weight (ml/min/kg); CLm[a] Individual metabolic clearance corrected for body weight (ml/min/kg); CL[b] clearance not corrected for body weight (ml/min); CLm[b] metabolic clearnace not corrected for body weight (ml/min); AUC and C_{max} Mean AUC [(ng/ml)h] and Cmax (ng/ml) corrected for dose expressed per mean body weight (mg/kg).

Table 9
Inter-individual differences in the pharmacokinetics of CYP2E1 probe substrates: Comparison between healthy adults, elderly, patients with liver disease and patients with renal disease after oral administration

Parameter	Drug	N_s	N_p	n	X_w	SD_w	CV_N	GM_w	GSD_w	CV_{LN}	Ratio GM	Ratio CV
Healthy												
CLm[a]	Chlorzoxazone	5	3[1]	91	3.0	0.98	33	2.8	1.4	32		
CL[a]	Chlorzoxazone	6	4[2]	101	4.4	1.7	29	4.2	1.3	29		
CL[a]	Trimethadione	8	6[3]	81	0.75	0.13	17	0.72	1.2	19		
CL[b]	Chlorzoxazone	4	4[4]	65	300	110	37	260	1.4	33		
CL[b]	Trimethadione	2	2[5]	16	68	19	28	63	1.3	25		
C_{max}	Chlorzoxazone	6	5[6]	73	940	390	41	690	1.4	32		
C_{max}	Trimethadione	3	1[7]	14	1300	115	9	1300	1.1	8		
Elderly												
CL[a]	Trimethadione	2	2[8]	22	0.58	0.15	25	0.56	1.3	26	1.3	1.4
Patients with Liver disease												
CL[a]	Trimethadione	6	3[9]	71	0.63	0.16	26	0.54	1.4	37	1.3	2.0
CL[b]	Trimethadione	1	1[10]	10	11.8	6.8	58	10.2	1.7	58	6.1	2.3
Patients with Renal disease												
CL[a]	Trimethadione	1	1[11]	13	0.26	0.10	39	0.25	1.4	39	2.9	2.1

N_s Number of studies; N_p Number of publications; n number of subjects; X_W Arithmetic weighted mean (normal distribution); SD_w Weighted standard deviation (normal distribution); CV_N coefficient of variation (normal distribution); GM_W Geometric weighted mean (lognormal distribution); GSD_w Weighted geometric standard deviation (lognormal distribution); CV_{LN} Coefficient of variation; (lognormal distribution); Ratio GM Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); Ratio CV_{LN} Variability ratio between healthy adults and subgroup (lognormal distribution); (n) given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.; CLm[a]: Metabolic clearance adjusted to body weight (ml/min/kg); CL[a]: Total clearance adjusted to body weight (ml/min/kg) CL[b]: Total clearance not adjusted to body weight (ml/min); C_{max} C_{max}/dose (ng/ml) with mean data corrected for dose expressed per mean body weight (mg/kg). [1]Kharasch et al. (1993), Kim et al. (1995) (2), O'Shea et al. (1997) (2); [2]Kharasch et al. (1993), Kim et al. (1995) (2), O'Shea et al. (1997) (2), Leclercq et al. (1998); [3]Kobayashi et al. (1984) (3), Tanaka et al. (1987a,b, 1993, 1999), Abei et al. (1995); [4]Desiraju et al. (1983), De Vries et al. (1994), Girre et al. (1994), Eap et al. (1999); [5]Tanaka and Nakamura (1989), Ohashi et al. (1991); [6]Kharasch et al. (1993), De Vries et al. (1994), Girre et al. (1994) (2), Leclercq et al. (1998), Eap et al. (1998); [7]Kobayashi et al. (1984) (3); [8]Tanaka et al. (1987a, 1994); [9]Tanaka et al. (1987b, 1994), Abei et al. (1995) (4); [10]Tanaka and Nakamura (1989; [11]Abei et al. (1995).

Table 10
Pooled analysis for interindividual differences in CYP2E1 metabolism for the oral route of exposure; data for healthy adults, elderly and patients with liver disease

PK parameter	N_c	N_s	N_p	n	Mean CV_{LN}	Mean ratio GM	Mean ratio CV_{LN}
Healthy adults							
CLm[b]	1	5	3	91	32		
CL[a]	2	14	10	182	23		
CL[b]	2	6	6	81	29		
C_{max}	2	9	6	87	16		
Elderly							
CL[a]	1	2	2	22	26	1.3	1.4
Patients with liver disease							
CL[a]	1	6	3	71	37	1.3	2.0
CL[b]	1	1	1	10	58	6.1	2.3
Patients with renal disease							
CL[a]	1	1	1	13	39	2.9	2.1

N_c Number of compounds; N_s Number of studies; N_p Number of publications; n Number of subjects; Mean CV_{LN} Mean coefficient of variation for all compounds (lognormal distribution); Mean Ratio GM Mean ratio between healthy volunteers and the subgroup (for the C_{max} the 1/Ratio was calculated) (lognormal distribution); Mean ratio $CV_{LN,}$ Mean ratio of the variability between healthy volunteers and the subgroup (lognormal distribution); CL[a] Individual clearance corrected for body weight (ml/min/kg); CLm[b] CL[b] Clearances not corrected for body weight (ml/min); C_{max} C_{max}/dose (ng/ml) corrected for dose expressed per mean body weight (mg/kg).

Table 11
Interindividual differences for compounds handled via alcohol dehydrogenase: Comparison between healthy adults, healthy oriental subjects and elderly after oral and intravenous administration

Parameter (route)	N_s	N_p	n	X_w	SD_w	CV_N	GM_w	GSD_w	CV_{LN}	Ratio GM	Ratio CV
Healthy adults											
Oral administration											
ER	4	4[1]	145	1.9	0.37	20	1.8	1.2	18		
AUC	11	8[2]	136	3.6	1.0	29	3.2	1.3	30		
AUC (Sigma ADH)	1	1[3]	10	0.96	0.22	22	0.9	1.3	23		
C_{max}	9	7[4]	112	1.4	0.32	23	1.3	1.2	21		
Intravenous administration											
CL	2	1[5]	12	290	89	31	273	1.3	29		
AUC	1	1[6]	24	4.9	1.2	25	4.8	1.3	25		
Orientals (Oral administration)											
ER	5	2[7]	154	2.1	0.46	21	2.1	1.2	21	0.87	1.2
ER (ADH+)	4	1[8]	114	1.7	0.20	11	1.5	1.1	14	1.18	0.74
ER (ADH−)	4	1[8]	166	1.6	0.21	14	1.7	1.1	11	1.21	0.62
AUC (Sigma ADH)	1	1[3]	10	0.88	0.10	12	0.9	1.1	11	1.07	0.50
Elderly (Oral administration)											
AUC	2	1[9]	29	3.3	2.5	75	2.7	1.9	73	0.82	2.4
C_{max}	2	1[9]	29	1.7	0.74	43	1.5	1.5	46	0.88	2.1

N_s Number of studies; N_p Number of publications; n number of subjects; X_W Arithmetic weighted mean (normal distribution); SD_w Weighted standard deviation (normal distribution); CV_N coefficient of variation (normal distribution); GM_W Geometric weighted mean (lognormal distribution); GSD_w Weighted geometric standard deviation (lognormal distribution); CV_{LN} Coefficient of variation; (lognormal distribution); Ratio GM Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); Ratio CV_{LN} Variability ratio between healthy adults and subgroup (lognormal distribution); (n) given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation; Sigma ADH Phenotype for ADH described in the publication as Sigma (slow metabolism); ADH+ Fast phenotype for ADH; ADH- Slow type for ADH; ER Elimination rate in mg/min/kg; CL Total clearance not adjusted to body weight (ml/min); AUC AUC/dose ((ng/ml)h) with mean data corrected for dose expressed per mean body weight (mg/kg); C_{max} C_{max}/dose (ng/ml) with mean data corrected for dose expressed per mean body weight (mg/kg).[1]Fenna et al. (1971), Farris and Jones (1978), Hanna (1978), Nuutinen et al. (1985); [2]Marshall et al. (1983) (2), Jones and Jonsson (1994), Kamali (1994), Minocha et al. (1995), Ammon et al. (1996) (2), Jones et al. (1997), Lucey et al. (1999) (2), Mumenthaler et al. (1999); [3]Dohmen et al. (1996); [4]Marshall et al. (1983) (2), Jones and Jonsson (1994), Kamali (1994), Minocha et al. (1995), Jones et al. (1997), Lucey et al. (1999) (2), Mumenthaler et al. (1999); [5]Hahn et al. (1994) (2); [6]Jones et al. (1992); [7]Hanna (1978) (2), Mizoi et al. (1985) (3); [8]Mizoi et al. (1987) (4); [9]Lucey et al. (1999).

Table 12
Interindividual differences for compounds handled via esterase hydrolysis in healthy adults after oral and intravenous administration

Drug	N_s	N_p	n	X_w	SD_w	CV_N	GM_w	GSD_w	CV_{LN}
Oral administration									
CL (ml/min/kg)									
Aspirin	2	1[1]	15	19	3.6	19	18	1.2	19
AUC/dose [(ng/ml)h] per mg/kg									
Aspirin	9	8[2]	89	920	201	22	770	1.2	22
Flumazenil	2	2[3]	12	210	82	39	190	1.4	38
Fosinopril	9	1[4]	50	6500	2000	31	6100	1.3	30
C_{max}/*dose (ng/ml) per mg/kg*									
Aspirin	13	11[5]	115	1200	430	34	1000	1.4	31
Flumazenil	2	2[6]	14	180	60	34	170	1.4	33
Fosinopril	9	1[4]	50	860	240	28	830	1.3	27
Intravenous administration									
CLm (ml/min/kg)									
Fosinopril	1	1[7]	9	0.26	0.09	33	0.25	1.4	33
CLm (ml/min)									
Fosinopril	1	1[8]	11	17	8.9	53	15	1.6	53
CL (ml/min/kg)									
Aspirin	1	1[9]	6	9.3	1.2	13	9.3	1.1	13
Cocaine	3	3[10]	12	28	5.4	20	27	1.2	19
Esmolol	3	3[11]	27	193	84	43	170	1.4	37
Etodimate	7	7[12]	44	17	6.5	38	15	1.3	31
Flestolol	2	2[13]	13	190	69	36	180	1.4	36
Flumazenil	1	1[14]	12	15	3.3	22	15	1.2	22
Fosinopril	1	1[8]	9	0.50	0.11	21	0.49	1.2	21
CL (ml/min)									
Cocaine	3	3[15]	16	1800	494	27	1600	1.3	24
Flumazenil	4	4[16]	30	1000	196	20	980	1.2	19
Fosinopril	3	2[17]	25	25	9.7	40	23	1.4	37

N_s Number of studies; N_p Number of publications; n number of subjects; X_W Arithmetic weighted mean (normal distribution); SD_w Weighted standard deviation (normal distribution); CV_N coefficient of variation (normal distribution); GM_W Geometric weighted mean (lognormal distribution); GSD_w Weighted geometric standard deviation (lognormal distribution); CV_{LN} Coefficient of variation (lognormal distribution). [1]Siegmund et al. (1994) (2); [2]Brantmark et al. (1982), Ho et al. (1985) (2), Hsyu et al. (1989), Mason and Winer (1981), Moolenaar et al. (1979), Roberts et al. (1983), Shrurer et al. (1996), Vigano et al. (1991); [3]Roncari et al. (1986, 1993); [4]Duchin et al. (1991) (9); [5]Benedek et al. (1995), Bochner et al. (1988), Brantmark et al. (1982), Ho et al. (1985) (2), Hsyu et al. (1989), Mason and Winer (1981), Montgomery et al. (1986), Moolenaar et al. (1979), Roberts et al. (1983), Siegmund et al. (1994) (2), Vigano et al. (1991); [6]Janssen et al. (1989), Roncari et al. (1993); [7]Hu et al. (1997); [8]Kostis et al. (1995); [9]Bochner et al. (1988); [10]Barnett et al. (1981), Chow et al. (1985), Jeffcoat et al. (1989); [11]De Bruijn et al. (1987), Flaherty et al. (1989), Sum et al. (1983); [12]Bonnardot et al. (1991), De Ruiter et al. (1981), Hebron et al. (1983), Schuttler et al. (1980), Sfez et al. (1990), Van Beem et al. (1983), Van Hamme et al. (1978); [13]Achari et al. (1985, 1987); [14]Short et al. (1994); [15]Cone et al. (1988), Javaid et al. (1983), Kumor et al. (1988); [16]Breimer et al. (1991), Debruyne et al. (1991), Janssen et al. (1989), Klotz et al. (1985); [17]Hui et al. (1991), Kostis et al. (1995) (2).

available) may be more appropriate to describe the inter-individual differences in overall elimination relevant to a chronic exposure scenario and uncertainty factors.

The very limited data available for the elderly did not show any major differences compared to healthy adults. The available data indicated that neonates would represent the most susceptible subgroup with uncertainty factors up to a 28 for compounds handled via glycine conjugation. Glycine conjugation has been recognised to be mature in neonates, but it is a highly saturable metabolic pathway and the only data available were for the formation of hippuric acid from benzoate after intravenous dosage to 10 premature newborn babies (Le Bel et al., 1988; Gow et al., 2001). Data on oral kinetics would be required in term neonates to derive a pathway-related factor relevant to risk assessment.

The variability in the phase I (CYP2A6, CYP2E1, ADH, esterases) and the phase II metabolic pathways (sulphate and glycine conjugation) analysed in this paper demonstrated that the 3.16 default factor would be a relatively conservative option to cover the healthy

Table 13
Interindividual differences for compounds handled via esterase hydrolysis: Comparison between healthy adults, healthy Chinese, children, elderly, patients with liver disease and patients with renal disease after oral and intravenous administration

Parameter (Route)	Drug	N_s	N_p	n	X_w	SD_w	CV_N	GM_w	GSD_w	CV_{LN}	Ratio GM	Ratio CV
Chinese healthy adults												
CLm[a](IV)	Fosinopril	1	1[1]	12	0.27	0.12	43	0.25	1.5	43	1.9	2.0
CLm[b](IV)	Fosinopril	1	1[2]	12	10.3	4.1	40	9.6	1.5	40	1.6	0.75
CL[a](IV)	Fosinopril	1	1[1]	12	0.16	0.08	54	0.14	1.7	54	1.8	1.3
CL[b](IV)	Fosinopril	1	1[2]	12	18	7.3	40	17	1.5	40	1.4	1.1
Children												
CL[a](IV)	Esmolol	1	1[3]	19	320	240	74	260	1.9	72	0.65	1.9
CL[a](IV)	Etodimate	1	1[4]	12	17	4.6	27	17	1.3	27	0.91	0.88
CL[a](IV)	Flumazenil	1	1[5]	12	21	6.9	34	20	1.4	34	0.85	1.3
Elderly												
AUC (PO)	Aspirin	3	2[6]	19	730	380	52	640	1.5	39	0.83	1.8
AUC (PO)	Flumazenil	1	1[7]	12	360	110	32	340	1.4	32	0.53	0.80
C_{max} (PO)	Aspirin	3	2[6]	19	1200	470	40	1040	1.5	40	1.0	1.3
C_{max} (PO)	Flumazenil	1	1[7]	12	204	82	34	190	1.5	40	0.18	1.0
Patients with Liver disease												
AUC (PO)	Aspirin	1	1[8]	4	960	403	42	880	1.5	42	1.1	1.9
CL[a] (IV)	Etodimate	1	1[9]	12	12	3.6	31	11	1.4	31	1.4	1.0
CL[a] (IV)	Esmolol	1	1[10]	9	151	44	29	145	1.3	29	1.3	0.67
CL[b] (IV)	Flumazenil	2	2[11]	11	560	310	56	440	1.6	48	2.2	2.6
C_{max} (PO)	Aspirin	1	1[8]	4	1040	630	60	890	1.7	60	0.89	1.9
C_{max} (PO)	Flumazelil	1	1[7]	8	590	180	31	560	1.3	31	0.64	0.72
Patients with Renal disease												
CL[b] (IV)	Fosinopril	3	1[12]	13	14	4.2	30	13	1.4	30	1.7	0.82

Ns Number of studies; Np Number of publications; n number of subjects; X_W Arithmetic weighted mean (normal distribution); SD_w Weighted standard deviation (normal distribution); CV_N coefficient of variation (normal distribution); GM_W Geometric weighted mean (lognormal distribution); GSD_w Weighted geometric standard deviation (lognormal distribution); CV_{LN} Coefficient of variation; (lognormal distribution); Ratio GM Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); Ratio CV_{LN} Variability ratio between healthy adults and subgroup (lognormal distribution); (n) given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.; Clm[a] Metabolic clearance adjusted to body weight (ml/min/kg); CLm[b] Metabolic clearance not adjusted to body weight (ml/min); CL[a] Total clearance adjusted to body weight (ml/min/kg); CL[b] Total clearance not adjusted to body weight (ml/min); AUC AUC/dose [(ng/ml)h] with mean data corrected for dose expressed per mean body weight (mg/kg); C_{max} C_{max}/dose (ng/ml) with mean data corrected for dose expressed per mean body weight (mg/kg); (IV) intravenous; (PO) oral. [1]Hu et al. (1997); [2]Ding et al. (1999); [3]Wiest et al. (1991); [4]Sfez et al. (1990); [5]Jones et al. (1993); [6]Roberts et al. (1983), Ho et al. (1985) (2); [7]Roncari et al. (1993); [8]Roberts et al. (1983); [9]Bonnardot et al. (1991); [10]Buchi et al. (1987); [11]Janssen et al. (1989), Van der Rijt et al. (1991); [12]Hui et al. (1991) (3).

Table 14
Interindividual differences for metabolism via hydrolysis (oral and intravenous route) in subgroups of the population: Comparison between healthy adults, Asian healthy adults, children, elderly, patients with liver disease and patients with renal disease, pooled analysis

PK parameter/route	N_c	N_s	N_p	n	Mean CV_{LN}	Ratio GM	Ratio CV_{LN}
Healthy adults							
CL[a](PO)	1	2	1	15	19		
AUC(PO)	3	20	11	151	29		
CLm[a](IV)	1	1	1	11	33		
CL[a](IV)	7	18	18	123	24		
CL[b](IV)	3	10	9	71	26		
Chinese							
CLm[a](IV)	1	1	1	12	43	1.9	2.0
CLm[b](IV)	1	1	1	12	40	1.6	0.75
CL[a](IV)	1	1	1	12	54	1.8	1.3
CL[b](IV)	1	1	1	12	40	1.4	1.1
Children							
CL[a] (IV)	3	3	3	43	40	0.80	1.3
Elderly							
AUC (PO)	2	4	3	31	35	0.66	1.20
Liver disease							
CL[a] (IV)	2	2	2	21	30	1.3	0.82
CL[b] (IV)	1	2	2	11	48	2.2	2.6
AUC (PO)	1	1	1	4	42	1.1	1.9
Renal disease							
CL[b] (IV)	1	3	1	13	30	1.7	0.82
Acute exposure							
C_{max} Healthy adults	3	24	14	179	30		
C_{max} Elderly	2	4	3	31	40	0.44	1.1
C_{max} Liver disease	2	2	2	12	43	0.76	1.2

N_s Number of studies; N_p Number of publications; n number of subjects; CV_{LN} Coefficient of variation; (lognormal distribution); Ratio GM Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); Ratio $CV_{LN,}$ variability ratio between healthy adults and subgroup (lognormal distribution); CL[a] total clearance not adjusted to body weight (ml/min/kg); CL[b] total clearance adjusted to body weight (ml/min); Clm[a] Metabolic clearance adjusted to body weight (ml/min/kg); CLm[b] Metabolic clearance not adjusted to body weight (ml/min); AUC and C_{max} with mean data corrected for dose expressed per mean body weight (mg/kg).

Table 15
Interindividual differences for compounds handled via glycine conjugation: Comparison between healthy adults, neonates, children, elderly and patients with liver disease after oral and intravenous administration

Parameter	Drug	N_s	N_p	n	X_w	SD_w	CV_N	GM_w	GSD_w	CV_{LN}	Ratio GM	Ratio CV
Healthy adults												
CL[a] (PO)	Salicylate	2	1[1]	44	0.37	0.08	21	0.36	1.2	21		
CL[b] (PO)	Salicylate	3	2[2]	24	30	6.8	23	29	1.2	21		
AUC (PO)	Benzoate	1	1[3]	6	5100	790	16	5040	1.2	16		
AUC (PO)	Salicylate	15	13[4]	131	42,000	13,000	31	37,000	1.3	28		
C_{max} (PO)	Benzoate	1	1[3]	6	2400	400	17	2400	1.2	17		
C_{max} (PO)	Salicylate	22	16[5]	256	5500	916	17	5300	1.2	16		
CL[a] (IV)	Salicylate	4	1[6]	25	0.62	0.15	25	0.60	1.3	24		
AUC (IV)	Benzoate	1	1[7]	7	6100	940	15	6050	1.2	15		
Neonates												
AUC (IV)	Benzoate	2	1[8]	10	120,000	18,000	16	110,000	1.2	16	19	1.1
Children												
CL[a](PO)	Salicylate	2	1[9]	20	0.38	0.11	28	0.37	1.3	27	0.98	1.3
C_{max} (PO)	Salicylate	2	1[9]	20	7800	2700	35	7300	1.4	33	1.4	2.1
Elderly												
AUC (PO)	Salicylate	3	2[10]	19	41,000	10,500	26	37,000	1.3	30	1.0	1.1
C_{max} (PO)	Salicylate	5	3[11]	40	4800	840	18	4500	1.2	19	0.85	1.2
CL[a](IV)	Salicylate	2	1[12]	21	0.54	0.13	24	0.52	1.3	23	1.1	0.99
Liver disease												
AUC (PO)	Salicylate	1	1[13]	8	46,000	20,000	43	42,000	1.5	43	1.1	1.5
Cmax (PO)	Salicylate	1	1[13]	8	5300	1900	36	5010	1.4	36	0.94	2.3
AUC (IV)	Benzoate	2	1[14]	30	3200	1300	40	2900	1.4	37	0.48	2.5

N_s Number of studies; N_p Number of publications; n number of subjects; X_W Arithmetic weighted mean (normal distribution); SD_w Weighted standard deviation (normal distribution); CV_N coefficient of variation (normal distribution); GM_W Geometric weighted mean (lognormal distribution); GSD_w Weighted geometric standard deviation (lognormal distribution); CV_{LN} Coefficient of variation; (lognormal distribution); Ratio GM Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); Ratio CV_{LN} Variability ratio between healthy adults and subgroup (lognormal distribution); (n) given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation; CL[a] Total clearance adjusted to body weight (ml/min/kg) CL[b] Total clearance not adjusted to body weight (ml/min); AUC AUC/dose [(ng/ml)h] with mean data corrected for dose expressed per mean body weight (mg/kg); C_{max} C_{max}/dose (ng/ml) with mean data corrected for dose expressed per mean body weight (mg/kg). [1]Montgomery et al. (1986) (2); [2]Trnavska and Trnavska (1983) (2), Abdallah et al. (1991); [3]Kubota and Ishizaki (1991); [4]Jamali et al. (1981), Mason and Winer (1981), Brantmark et al. (1982), Roberts et al. (1983), Borgstrom et al. (1984), Ho et al. (1985) (2) (1989), Bochner et al. (1988), Gatti et al. (1989), Vigano et al. (1991), Siegmund et al. (1994) (2), Benedek et al. (1995), Schrurer et al. (1996); [5]Jamali et al. (1981), Mason and Winer (1981), Brantmark et al. (1982), Roberts et al. (1983), Borgstrom et al. (1984), Ho et al. (1985) (2) (1989), Greenblatt et al. (1986) (4), Montgomery et al. (1986) (2), Bochner et al. (1988), Gatti et al. (1989), Abdallah et al. (1991), Vigano et al. (1991), Siegmund et al. (1994) (2), Benedek et al. (1995), Schrurer et al. (1996); [6]Greenblatt et al. (1986) (4); [7]Yamada et al. (1992); [8]Le Bel et al. (1988) (2); [9]Wilson et al. (1982) (2); [10]Roberts et al. (1983), Ho et al. (1985) (2); [11]Roberts et al. (1983), Ho et al. (1985) (2), Greenblatt et al. (1986) (2); [12]Greenblatt et al. (1986) (2); [13]Roberts et al. (1983); [14]Yamada et al. (1992) (2).

Table 16
Interindividual differences for compounds handled via sulphate conjugation: Comparison between healthy adults, healthy orientals and elderly after oral and intravenous administration

Parameter	Drug	N_s	N_p	n	X_w	SD_w	CV_N	GM_w	GSD_w	CV_{LN}	Ratio GM	Ratio CV
Oral administration												
Healthy adults												
CLm[a]	Diflunisal	3	3[1]	17	1.03	0.42	41	0.90	1.5	39		
CLm[a]	Paracetamol	6	4[2]	48	1.6	0.3	19	1.5	1.2	17		
CLm[b]	Paracetamol	3	3[3]	26	86	25	28	83	1.3	27		
AUC	Prenalterol	1	1[4]	6	2800	770	28	2700	1.3	28		
C_{max}	Prenalterol	1	1[4]	6	1500	480	33	1400	1.4	33		
Asian Healthy adults												
CLm[a]	Paracetamol	1	1[5]	12	2.2	0.77	35	2.1	1.4	35	0.71	2.0
Elderly												
CLm[a]	Paracetamol	1	1[6]	8	1.4	0.23	16	1.4	1.2	16	1.1	0.96
Intravenous administration												
Healthy adults												
CLm[a]	Paracetamol	1	1[7]	10	1.2	0.44	36	1.13	1.4	36		
CLm[b]	Salbutamol	1	1[8]	8	55	21	36	51	1.4	36		
Elderly												
CLm[a]	Paracetamol	3	2[9]	24	1.2	0.28	23	1.18	1.3	23	1.1	0.62

N_s Number of studies; N_p Number of publications; n number of subjects; X_W Arithmetic weighted mean (normal distribution); SD_w Weighted standard deviation (normal distribution); CV_N coefficient of variation (normal distribution); GM_W Geometric weighted mean (lognormal distribution); GSD_w Weighted geometric standard deviation (lognormal distribution); CV_{LN} Coefficient of variation; (lognormal distribution); Ratio GM Ratio of geometric means between healthy adults and subgroups (lognormal distribution); Ratio CV_{LN} Variability ratio between healthy adults and subgroup (lognormal distribution); (n) given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation; CLm[a] Metabolic clearance adjusted to body weight (ml/min/kg); CLm[b] Metabolic clearance not adjusted to body weight (ml/min); AUC AUC/dose [(ng/ml)h] with mean data corrected for dose expressed per mean body weight (mg/kg); C_{max} C_{max}/dose (ng/ml) with mean data corrected for dose expressed per mean body weight (mg/kg). [1]Loewen et al. (1988), Verbeeck et al. (1990), McDonald et al. (1992); [2]Miners et al. (1983) (2), (1984) (2), (1988), Osborne et al. (1991); [3]Miners et al. (1986), Baraka et al. (1990), Rumble et al. (1991); [4]Graffner et al. (1981); [5]Osborne et al. (1991); [6]Miners et al. (1988); [7]Wynne et al. (1990); [8]Morgan et al. (1986); [9]Wynne et al. (1990) (2), Kamali et al. (1993).

Table 17
Interindividual differences for metabolism via glycine conjugation and sulphate conjugation (oral and intravenous route) in subgroups of the population, pooled analysis

PK parameter/route	N_c	N_s	N_p	n	Mean CV_{LN}	Ratio GM	Ratio CV
Glycine conjugation							
Healthy							
CL[a] (PO)	1	2	1	44	21		
CL[a] (IV)	1	4	1	25	24		
CL[b] (PO)	1	3	2	24	21		
AUC (PO)	2	16	14	137	21		
AUC (IV)	1	1	1	7	15		
C_{max} (PO)	2	23	17	262	16		
Neonates							
AUC (IV)	1	2	1	10	16	19	1.1
Children							
CL[a] (PO)	1	2	1	20	27	0.98	1.3
C_{max} (PO)	1	2	1	20	33	1.4	2.1
Elderly							
CL[a] (IV)	1	2	1	21	23	1.1	0.99
AUC (PO)	1	3	2	19	30	1.0	1.1
C_{max} (PO)	1	5	3	40	19	0.85	1.2
Liver Disease							
AUC (PO)	1	1	1	8	43	1.1	1.5
AUC (IV)	1	2	1	30	37	0.48	2.5
C_{max} (PO)	1	1	1	8	36	0.94	2.3
Sulphate conjugation							
Healthy							
CLm[a] (PO)	2	9	7	65	26		
CLm[a] (IV)	1	1	1	10	36		
CLm[b] (PO)	1	3	3	26	27		
CLm[b] (IV)	1	1	1	8	36		
AUC (PO)	1	1	1	6	28		
C_{max} (PO)	1	1	1	6	33		
Elderly							
CLm[a] (PO)	1	1	1	8	16	1.1	0.96
CLm[a] (IV)	1	3	2	24	23	1.1	0.62

N_s Number of studies; N_p Number of publications; n number of subjects; CV_{LN} Coefficient of variation; (lognormal distribution); Ratio GM Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); Ratio CV_{LN}, Variability ratio between healthy adults and subgroup (lognormal distribution); CL[a] Total clearance adjusted to body weight (ml/min/kg); CL[b] Total clearance not adjusted to body weight (ml/min); Clm[a] Metabolic clearance adjusted to body weight (ml/min/kg); CLm[b] Metabolic clearance not adjusted to body weight (ml/min); AUC and C_{max} with mean data corrected for dose expressed per mean body weight (mg/kg).

adult population for compounds handled by these pathways. However, future studies may demonstrate phenotypic differences for these routes in which case new assessments of human variability will be required. Phenotypic differences due to CYP2C9 polymorphism (based on small numbers of individuals) have been shown, but more in vivo data would be necessary to characterise these differences at the population level. Lack of data in neonates constitutes a concern for compounds handled by these pathways, because this subgroup has been characterised as the most susceptible for glycine conjugation (the only pathway for which data were available in this paper) and other pathways including CYP1A2 (Dorne et al., 2001a), glucuronidation (Dorne et al., 2001b) and CYP3A4 (Dorne et al., 2003a).

Although, more data would be required to characterise potentially sensitive subgroups of the population for all these pathways, especially for recently described polymorphisms in healthy adults and subgroups of the population (including neonates), the data reviewed in this paper provide further support for the 3.16-fold default uncertainty factor for human variability in toxicokinetics.

Table 18
Pathway-related uncertainty factors for healthy adults and other subgroups of the population

Pathway	PK parameter/(route)/phenotype	N_c	N_s	n	CV_{LN}	Ratio GM	Pathway-related uncertainty factors (Lognormal distribution)		
							95th	97.5th	99th
Healthy adults									
CYP2A6	CL^a, CL^b (PO)/NP	2	2	15	33		1.7	1.9	2.1
CYP2A6	CL^a, CL^b (IV)/NP	3	18	181	29		1.6	1.7	1.9
CYP2C9	CL^a, CL^b, AUC (PO)/NP	3	41	481	32		1.7	1.9	2.1
CYP2C9	CL^a, CL^b (PO)/*1/*1	2	3	15	17		1.3	1.4	1.5
CYP2C9	CL^a, CL^b (PO)/*1/*2	2	3	13	25	1.1	1.7	1.8	2.0
CYP2C9	CL^a, CL^b (PO)/*1/*3	2	3	15	12	1.7	2.1	2.1	2.2
CYP2C9	CL^b (PO)/*2/*2	1	1	3	33	1.1	1.9	2.1	2.3
CYP2C9	CL^b (PO)/*2/*3	1	1	3	9	1.7	2.0	2.0	2.1
CYP2C9	CL^b (PO)/*3/*3	1	1	3	13	4.8	5.9	6.2	6.5
CYP2E1	CL^a, AUC (PO)	2	20	263	26		1.5	1.7	1.8
ADH	ER, AUC (PO)/NP	1	15	281	24		1.5	1.6	1.8
Hydrolysis	CL^a, AUC (PO)	3	22	166	28		1.6	1.7	1.9
Glycine conjugation	CL^a, CL^b, AUC (PO)	2	21	205	21		1.4	1.5	1.6
Sulphation	CLm^a, CLm^b, AUC (PO)/NP	3	13	97	26		1.5	1.7	1.8
African American healthy adults									
$CYP2A6^+$	CL^a (IV)/NP	1	1	40	28	1.0	1.6	1.7	1.9
Arabian healthy adults									
$CYP2C9^{++}$	AUC (PO)/NP	1	1	16	32	1.4	2.3	2.6	2.9
Asian healthy adults									
$CYP2A6^{+++}$	CL^a (IV)/ NP	1	1	37	44	1.1	2.2	2.5	2.9
CYP2C9	CL^a (PO)/ NP	2	2	16	14	1.5	1.9	1.9	2.1
CYP2C9	CL^a (PO)/*1/*1	2	2	12	6	1.1	1.2	1.2	1.3
CYP2C9	CL^a (PO)/*1/*3	1	1	6	7	1.1	1.2	1.3	1.3
ADH	ER (PO)/NP	1	5	154	21	0.87	1.2	1.3	1.4
Hydrolysis	CL^a (IV)	1	2	24	47	1.6	3.7	3.9	4.6
Sulphation	CLm^a (PO)	1	1	12	35	0.71	1.2	1.4	1.6
Neonates									
Glycine Conjugation	AUC (IV)	2	1	10	16	19	25	26	28
Children									
Hydrolysis	CL^a, AUC (PO)	3	3	43	40	0.80	1.5	1.7	2.0
Glycine Conjugation	CL^a (PO)	1	2	20	27	0.98	1.5	1.6	1.8
Elderly									
CYP2A6	CL^a (IV)	1	1	20	24	1.3	1.9	2.1	2.3
CYP2C9	CL^a, CL^b, AUC (PO)	2	3	42	34	0.84	1.4	1.6	1.8
CYP2E1	CL^a (PO)	1	2	22	26	1.3	1.9	2.1	2.3
ADH	AUC (PO)	1	2	29	73	1.2	2.4	2.8	3.2
Hydrolysis	AUC (PO)	2	4	31	35	0.66	1.2	1.3	1.5
Glycine conjugation	AUC (PO)	1	3	19	26	1.0	1.6	1.8	2.0
Sulphation	CLm^a (IV)	1	3	24	23	1.1	1.6	1.7	1.9

N_c Number of compounds; N_s Number of studies; n Number of subjects; CV_{LN} Coefficient of variation; Ratio GM Ratio of geometric mean between subgroup and health adults; CL^a Clearance adjusted to body weight (ml/min/kg); CL^b Clearance not adjusted to body weight (ml/min); Clm^a Metabolic clearance adjusted to body weight (ml/min/kg); AUC Area-under-the-plasma-concentration-curve [(ng/ml)h] corrected for dose expressed per mean body weight (mg/kg); $^+$Black American healthy adult smokers; $^{++}$Arabian healthy adults; $^{+++}$Chinese American healthy adult smokers; (IV) intravenous; (PO) oral; NP not phenotyped.

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