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Human variability in glutathione-S-transferase activities, tissue distribution and major polymorphic variants: Meta-analysis and implication for chemical risk assessment

Franca Maria Buratti[a,*], Keyvin Darney[b], Susanna Vichi[a], Laura Turco[a], Emma Di Consiglio[a], Leonie S. Lautz[b], Camille Béchaux[b], Jean-Lou Christian Michel Dorne[c], Emanuela Testai[a]

[a] Department of Environment and Health, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161, Rome, Italy
[b] Risk Assessment Department, French Agency for Food, Environmental and Occupational Health & Safety (ANSES), 14 rue Pierre et Marie Curie, Maisons-Alfort, F-94700, France
[c] European Food Safety Authority, 1a, Via Carlo Magno 1A, 43126, Parma, Italy

HIGHLIGHTS

- Extensive literature review performed on *in vivo* GST activity in healthy humans.
- Variability analysis of *in vivo* GST activity due to age, ethnicity, polymorphisms.
- Tissue and organ distribution of GST activity is reported.
- Bayesian meta-analysis was conducted to derive GST-related uncertainty factors.
- Limited datasets highlighted large data gaps.

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ABSTRACT

The input into the QIVIVE and Physiologically-Based kinetic and dynamic models of drug metabolising enzymes performance and their inter-individual differences significantly improve the modelling performance, supporting the development and integration of alternative approaches to animal testing. Bayesian meta-analyses allow generating and integrating statistical distributions with human *in vitro* metabolism data for quantitative *in vitro-in vivo* extrapolation. Such data are lacking on glutathione-S-transferases (GSTs). This paper reports for the first time results on the human variability of GST activities in healthy individuals, their tissue localisation and the frequencies of their major polymorphic variants by means of extensive literature search, data collection, data base creation and meta-analysis.

A limited number of papers focussed on *in vivo* GST inter-individual differences in humans. *Ex-vivo* total GST activity without discriminating amongst isozymes is generally reported, resulting in a high inter-individual variability.

The highest levels of cytosolic GSTs in humans are measured in the kidney, liver, adrenal glands and blood. The frequencies of GST polymorphisms for cytosolic isozymes in populations of different geographical ancestry were also presented. Bayesian meta-analyses to derive GST-related uncertainty factors provided uncertain estimates, due to the limited database.

Considering the relevance of GST activities and their pivotal role in cellular adaptive response mechanisms to chemical stressors, further studies are needed to identify GST probe substrates for specific isozymes and quantify inter-individual differences.

1. Introduction

In the current international context, toxicokinetics (TK), representing the processes of absorption, distribution, metabolism

* Corresponding author.
E-mail address: franca.buratti@iss.it (F.M. Buratti).

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and excretion (ADME), provides very valuable information to risk assessors and researchers: i) to understand the fate and elimination patterns of xenobiotics in organisms in relation to their hazard properties, ii) to address extrapolations between test species and humans as well as iii) to collect *in vitro* data for quantitative *in vitro* to *in vivo* extrapolations. A recent relevant example of the latter is highlighted by the new data requirements for active substances used in plant protection products (EU Regulation 283/2013) for which *in vitro* comparative metabolism studies between test species and humans need to be conducted and submitted to regulatory authorities in the pre-market authorisation dossier.

Over the last two decades, there has been continuous efforts at the EU and international level to develop and integrate alternative approaches to animal testing, wherever possible. Approaches such as *in vitro* and *in silico* methods, integrated testing strategies, OMICs, and Physiologically-Based kinetic and dynamic (PB-K and PB-D) modelling have been addressed as "modern methodologies and tools for human hazard assessment of chemicals" (EFSA, 2014; Coecke et al., 2013; Paini et al., 2019).

In vitro methods and PB-TK modelling have been identified as research priorities in Europe to move towards the reduction of animal testing and a more mechanistic understanding of chemical toxicity, particularly in the food and feed safety area. The applicability of these tools provide means to improve the use of quantitative methods in chemical risk assessment for a large number of chemicals. However, the production of robust *in vitro* data, taking into account *in vitro* kinetics (Kramer et al., 2015), as well as informed parameters such as human variability in the activity of phase I, phase II enzymes and transporters involved in ADME processes, represent critical data needs to obtain reliable estimates (Bessems et al., 2014).

These issues have been addressed in an EFSA funded Project 'Modelling human variability in toxicokinetic and toxicodynamic processes using Bayesian meta-analysis, physiologically-based modelling and *in vitro* systems', with a particular focus on generating and modelling kinetic and dynamic data for sets of chemicals and integrating human variability in these processes for evidence-based risk assessment.

In this context, a number of Bayesian meta-analyses have been performed using human kinetic data on pharmaceuticals and other xenobiotics as a basis to generate probabilistic distributions. *In vivo* enzymatic activity for specific phase I and phase II enzymes, including CYP3A4, PON1, some transporters and UDP-glucuronosyltransferases (UDPGT) (Darney et al., 2019, 2020a, 2020b; Kasteel et al., 2020) have been quantified, similarly to what developed by other authors for UDPGT and carboxylesterases in the pharmaceutical sector (Ladumor et al., 2019). In addition, the studies within the project investigated the frequency of specific polymorphisms within different human populations of different geographical ancestry to integrate this information in PB-K models. To date these meta-analyses are still lacking for most phase II enzymes, including glutathione-S-transferases (GSTs).

The superfamily of GSTs are composed of multi-functional eukaryotic and prokaryotic isozymes with a molecular weight around 25 kDa, which are present in different sub-cellular compartments including cytosol, mitochondria, and endoplasmic reticulum, nucleus or plasma membrane, the latter also known as MAPEG (membrane-associated proteins involved in eicosanoid and glutathione metabolism). The most studied human GSTs are the cytosolic forms, which are characterized by a dimeric structure and classified into eight classes on the basis of their chemical, physical and structural properties: mu (GSTM), alpha (GSTA), pi (GSTP), theta (GSTT), zeta (GSTZ), sigma (GSTS), and omega (GSTO) (Allocati et al., 2018). Each member of the family has multiple isozymes with overlapping substrate specificity.

Amongst the biological functions of GSTs the most important are i) detoxification of a wide range of electrophilic xenobiotics including chemical carcinogens, environmental and food chain contaminants. The conjugation reaction is between reduced glutathione (γ-glutamyl-cysteinyl-glycine (GSH)), *via* a sulfhydryl group, and the xenobiotic electrophilic centers, and produces hydrophilic compounds, that are more readily excreted. In some instances, however, this reaction can also result in xenobiotic bioactivation (Lash et al., 2014; Schlosser et al., 2015); ii) inactivation of endogenous α,β-unsaturated aldehydes, quinones, epoxides, and hydroperoxides; iii) regulation of cell signaling; iv) maintenance of GSH pool as the cellular antioxidant, in different cell compartments. Indeed, these enzymes offer high levels of protection of cell structures against oxidative stress as an integral part of a dynamic and interactive defence mechanism that protects against cytotoxic electrophilic chemicals and allows adaptation to oxidative stress exposure (Hayes et al., 2005).

GSTs exhibit sex-, age-, tissue-, species-, and tumor-specific patterns of expression, which consequently brings complexity to the regulation of their isoenzyme expression and activities. Furthermore, some chemicals, including naturally occurring substances in vegetables and fruits, can act as inducers by transcriptional activation of GST genes through a range of responsive elements (Hayes and Pulford, 1995). Such GST induction is also part of adaptive response mechanisms to chemical stress caused by electrophiles. Beside possible inter-individual phenotypic differences in isoform activities, cytosolic GSTs display genetic polymorphism in humans. This aspect likely contributes to inter-individual differences in responses to xenobiotics and differences in susceptibility particularly in pathologies of inflammatory nature including asthma, allergies, rheumatoid arthritis, and systemic sclerosis (Gilliland et al., 2004; Palmer et al., 2003) or cancerogenesis (Palli et al., 2005; Stoehlmacher et al., 2002; Weich et al., 2016; Shiota et al., 2017).

This manuscript provides the first analysis of inter-individual differences in GST isozyme activities, their tissue distribution and frequencies of the major polymorphic variants by means of extensive literature search, data collection and meta-analysis. Insights on implications for chemical risk assessment in the light of new approach methodologies are provided as well as the need for future research in this area.

Table 1
List of queries used for the ELS (formatted for Scopus) for GST.

STUDY QUESTION	Objective: Data collection of *in vivo* activities of GSTs in humans
Search string	TITLE-ABS-KEY (("population distribution" OR "tissue distribution " OR "tissue localization" OR intestine OR liver OR kidney OR lung OR "expression level*" OR "gene expression" OR "genetic polymorphism*" OR "individual susceptibility" OR "gene environment" OR "ethnic variability" OR caucasian OR asian OR "Afro American" OR hispanic OR "race difference*" OR "age difference*" OR "gender difference*" OR "sex difference*" OR ontogenesis OR "foetal stage" OR neonate* OR children OR "elderly people" OR adult* OR genotype OR induction OR inhibition)) AND TITLE-ABS-KEY ((human* W/50 ("glutathione transferase*" OR "glutathione-S-transferase*" OR "glutathione S-transferase*"))) AND NOT ("cell line*" OR "cell culture*")

TITLE-ABS-KEY: term searched in the title, the abstract and the keywords of the paper.

2. Materials and methods

2.1. Extensive literature search and data collection

Extensive literature searches (ELS) on available data for cytosolic GSTs were performed according to EFSA guidance (EFSA, 2010), searching on available scientific databases and international multidisciplinary platforms namely Scopus, Web of Science, PubMed, Food Science Source and Agricola. The ELS were carried out through formulating relevant queries, specific key words and appropriate syntax as well as Boolean operators, for the period January 1990 –December 2019. Table 1 provides a summary of the individual keywords submitted to the databases for the ELS.

After removal of duplicates, the primary screening, carried out on titles and abstracts, allowed excluding peer reviewed papers which did not meet the inclusion criteria, that is: articles not in the English language, *in vitro* studies or studies on species other than humans. Publications which met the inclusion criteria were imported into an EndNote™ file while studies focusing on: i) calibration of analytical methods; ii) TD studies only; iii) unhealthy individuals (*e.g.* affected by hepatic or renal dysfunction, carcinoma *etc*) were excluded.

Therefore, the final selection of peer reviewed publications included studies on healthy and un-exposed individuals to provide a picture of the background level of cytosolic GST isozyme activities since healthy adults constitute the major protection goal for human risk assessment. Whenever papers included data on healthy, as well as unhealthy or exposed people at the same time, data referring to the later populations were reported in a specific column in the database as additional information (*i.e.* the considered disease or the kind of exposure). Unhealthy individuals were excluded also because the background levels of cytosolic GST isozyme activities can be strongly affected by the presence of specific diseases. Well-known examples include the over-expression of GSTP genes in many human cancers and preneoplastic lesions (Allocati et al., 2018) or the 10-fold increase in GSTA activity reported in thalassemia children compared to healthy adults (Huezo-Diaz et al., 2014).

The full text of the selected studies has been evaluated through a secondary screening to assess methodological quality such as study design, specificity and sensitivity, result analysis and reporting, to avoid biased results. The scoring system used for rating the quality of the studies is shown in Table 2. As previously described (Darney et al., 2019), it was applied as follow: the required score for inclusion was 1–2 for the sections “Population” and “Methodology”, while a score of 2 need to be fulfilled for the “Results” section.

Proceedings, letters to editor, conference papers, short communications, were excluded. Reviews, book chapters and other sources reporting primary datasets, were excluded from the data extraction to avoid multiple inclusions of the same dataset from different references.

Data from eligible studies after the secondary screening were extracted and computed in an MS Excel database using OECD harmonised templates (OHTs), from an EFSA’s data model allowing consistency with EFSA’s chemical hazards database (OpenFoodTox) (Dorne et al., 2017). The database was built to include details for each reference, cytosolic GST isoform activity, factors that may impact on human variability (*e.g.* populations from different geographical ancestry, presence of polymorphisms, age differences), characteristics of the assay and the probe substrate(s), number of individuals, summary statistics for the *in vivo* parameters (*e.g.* sample size, arithmetic or geometric mean, median, standard deviation, confidence intervals, *etc.*). A number of fields were reported as fixed values (*e.g.* quality criteria requires a score ranging from 1 to 3 as a pre-requisite in EFSA databases) to increase reporting harmonization/standardisation

The flow of information performed for the ELS on cytosolic GST isozymes is summarised in Fig. 1. The complete database is available in Supplementary material A.

Table 2
Scoring system for the secondary screening.

Population	0 No information
	1 at least number, age and health status
	2 ethnic group and other information
Methodology	0 insufficient description
	1 inaccurancies in some points
	2 full description
Results	0 no pharma/toxicokinetics data
	1pharma/toxicokinetics data without descriptive statistics
	2 pharma/toxicokinetics data with descriptive statistics

2.2. Data standardisation

Data for cytosolic GST activities were standardised to perform the statistical analysis. Activity was expressed in U/L or μmol/min/mL for each specific activity. GST activities from individual studies were reported as arithmetic means (X) and standard deviations (SD) and were harmonised to geometric mean (GM) and geometric standard deviation (GSD) using the following equations, as reported in Darney et al., 2019:

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

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

Where CV_N provides the coefficient of variation for normally distributed data as:

$$CV_N = SD/X \quad (3)$$

3. Results and discussion

Results from the ELS are presented in Fig. 1 as a Prisma diagram illustrating the very large number of peer-reviewed papers retrieved from all databases (n = 6789) using the search strings (Table 1). The acronym GSTs, which is not univocal for this enzyme family, was excluded from the search. Overall, 58 peer reviewed publications were selected from the ELS for data extraction.

The score of extracted papers was most often 2 for results and methodology, while there was a general lack of information related to the population description for which geographical ancestry was not often reported (giving rise to a score of 1 or 2). However, in some cases, such information could be retrieved from the text using the country of enrollment considering the subjects as native. This was not assumed for the United States where geographical ancestry is very heterogeneous.

During the secondary screening phase, the authors noted that most of the recent peer-reviewed literature (n = 2207), focused on GST polymorphisms in case-control studies, while investigating association with a range of diseases, in some cases even without a specific biological plausibility. The rationale behind such a choice in genotyping studies lies in the fact that some GST variants have high frequencies in Caucasian populations (*e.g.* GSTM1 and GSTT1 null genotype, see below). Hence, the number of enrolled individuals to ensure an appropriate statistical power is relatively limited. In other cases, the GST activity towards specific pharmaceuticals was reported in group of patients, to provide a rationale to explain the high variability in the kinetic parameters

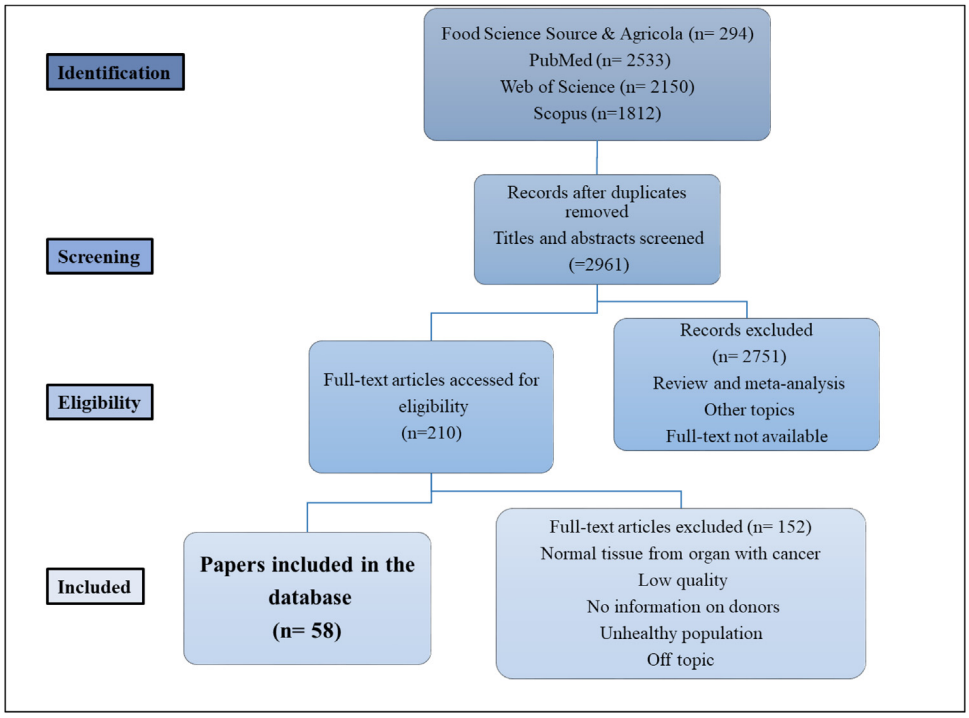

Fig. 1. Flow diagram illustrating the extensive literature search on studies reporting human cytosolic GST activity and localisation (update December 2019).

associated with different therapeutic responses. Since GSTs are overexpressed in cancer cells, a relevant contribution to multidrug resistance has been reported, due to increased detoxification of anti-cancer drugs (Sau et al., 2010). Another set of 192 papers, identified as reviews and meta-analyses of the above-mentioned case-control studies, were used to review the frequency of the polymorphic GST variants.

3.1. Inter-individual differences in GST activities

The vast majority of the papers (73 %) described GST activities in plasma, serum, lymphocytes and erythrocytes. This is most likely because such measurements involve non-invasive procedures to obtain samples from healthy volunteers.

Most studies (67 %) in the database reported total GST activity without discriminating amongst isozymes. The commonly used marker for GST total activity, 1-chloro-2,4-dinitrobenzene (CDNB), reacts almost with any GSTs (Habig et al., 1974; Eaton and Bammler, 1999), although the contribution of some isozymes, such as GSTT, may be under-estimated, due to its negligible affinity with CDNB. Hence for GSTT, 1,2-epoxy-3-(4-nitrophenoxy) propane (EPNP) is a more specific substrate for this class (Eaton and Bammler, 1999; Primavera et al., 2008).

Some of the most recent papers also measured the genotype of donors: therefore case-control studies from the peer reviewed literature from genotyped individuals have been analysed, but they did not fit the purpose, since for the association with a specific disease, only genotype data were used and the associated phenotype in terms of GST activities was rarely reported. Measurements of *in vivo* GST activities were not available, most likely due to the lack of *in vivo* probe substrates. This, on the other hand, would be relevant since the activity can be influenced by other factors such as exposure to inducers or inhibitors (Allocati et al., 2018), acting as possible confounding factors. In some publications, potential differences in GST activities were hypothesised and expressed using qualifiers such as low, intermediate or high activity based on the presence of null variants; however, no measurements were reported. From this rationale, inter-individual differences in GSTs activities were reported and analysed in non-genotyped subjects.

Inter-individual differences in GST activities from populations of different geographical ancestry are not equally represented in the database, with 63 % of data from Caucasian populations, 21 and 16 % from Asian and Indian populations, respectively. Information on the Afro-Americans and sub-Saharan Africans was not explicitly indicated and it should be considered that most studies carried out in the USA (17 out of 19) did not report the description of the geographical ancestry.

Geometric means and associated geometric standard deviations representing inter-individual differences in GST specific

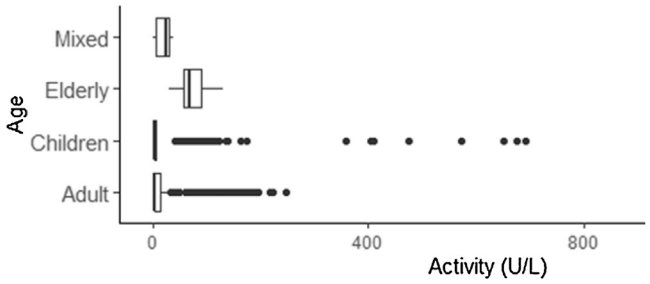

Fig. 2. Inter-individual differences in GST activity in different age groups of the human healthy populations. Data are expressed as geometric means and standard deviations (log normal distribution) and expressed as U/L. Number of studies/samples per age groups: mixed 5/690 ; elderly 2/44 ; children 4/222 ; adult 12/1140. The 'elderly' group includes people >65 years old; the generic group 'children' includes 0-18 years old individuals: no subgrouping was feasible due to the limited number of subjects in each subgroups or lack of indication in the papers. The 'Adults' group includes populations 18-65 years of age, whereas the group 'Mixed' collects papers where mixed aged group were reported together.

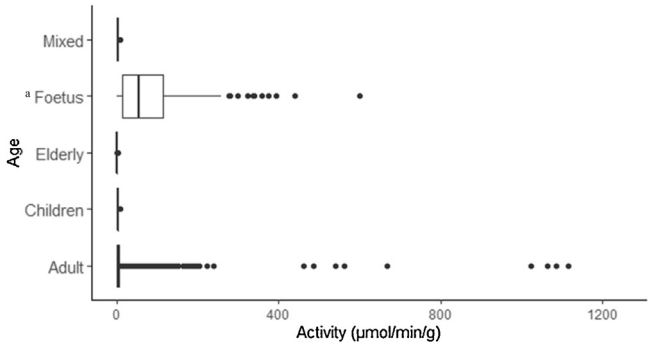

Fig. 3. Inter-individual differences in GST activity in different age groups of the human healthy populations. Data are expressed as geometric means and standard deviations (log normal distribution) and expressed as expressed as µmol/min/g. Number of studies/samples per age groups: mixed 2/167 ; foetus 23/238 ; elderly 8/1310 ; children 1/29 ; adult 81/2691. The 'elderly' group includes people >65 years old; the generic group 'children' includes 0-18 years old individuals: no sub-grouping was feasible due to the limited number of subjects in each subgroups or lack of indication in the papers; the 'foetus' category referrer to 16-39 weeks of gestation. The 'Adults' group includes populations 18-65 years of age, whereas the group 'Mixed' collects papers where mixed aged group were reported together.

activities are plotted in Fig. 2 (expressed as U/L) and Fig.3 (expressed in µmol/min/g) and clustered according to the age group of the individuals, since age has been shown to impact on both expression and activity of GST isozymes. Well known examples include higher GSTA1 activity in young children enterocytes compared to that in adults (Gibbs et al., 1999). Furthermore, higher GSTP1- related activity in the colon mucosa of menopausal women compared to younger women, although the major determinant was not the age *persé*, but the age-dependent hormones level, as demonstrated by the suppressed GSTP1 content among female patients between 50 and 70 years during oral sex hormone substitution therapy (Hoensch et al., 2006).

As shown in Fig. 2 and 3, GST activities in healthy adults are widely variable. This can be explained considering that available data on GST activities have been measured as total activities (using CDNB as a non-specific probe substrate) without considering the genotypic background of the individuals and this may result in large inter-individual differences, particularly since subjects belong to populations from geographical ancestry with variable frequencies of polymorphic variants (Fig. 4). Finally, although the vast majority of measurements were from blood, samples from different tissues expressing different isozymes at variable levels (Fig. 5 and 6) were pooled together.

Results were divided per broad age groups, evidencing that inter-individual differences were generally much more limited in the age groups other than healthy adults, but those estimates were also more uncertain because of the limited number of tested individuals.

Data for GST activities in different human developmental stages were also gathered from foetal organs resulting from spontaneous or voluntary abortions (referring to 16–39 weeks of gestation). Although differences can exist between different development stages, the data available indicate that the GST level remain almost stable from 11 weeks of gestation until birth (Pacifici et al., 1988); therefore it was not deemed necessary to subdivide foetal data in different subgroubs, also considering the limited number of individual samples available. In this context the health status of the donors was considered not specifically spelt out from the studies; these aspects were reported in the notes within the database used for data extraction. Nevertheless, GST activities in the fetal stage is significant, variable and overlaps with values measured throughout adulthood.

The Bayesian method applied here for the meta-analysis of inter-individual differences in GST activities in different isozymes considering age groups and tissues, has been previously applied to phase I enzymes (CYP3A4, PON1), phase II enzymes (UGT isoforms) and transporters (Darney et al., 2019; Darney et al., 2020a, 2020b; Kasteel et al., 2020). When data for populations from the same geographical ancestry were available, the adult population was used as the reference group. Results of geometric means (GM), coefficient of variation (CV), uncertainty factors (UFs) within the population (95th percentile) and UFs compared to the Caucasian adult population, used as reference population (95th percentile), were tentatively derived. Generally the GST-related UF were below the default factor of 3, with few exceptions such as in Asian elderly people showing higher values (≈9). Overall, data were scarce and most UFs were derived from single studies with very limited number of individuals from different specific ethnic groups resulting in uncertain estimates, which did not allow to draw robust conclusions (data not shown).

3.2. Organ and tissue distribution

Organ and tissue distribution of GSTs is very wide and varies according to the class of GSTs. Peer reviewed publications specifically addressing tissue distribution using immunohistochemical techniques reported only a qualitative indication of GST such distribution without information on donors and their related health status, and, as a consequence were attributed a low quality score. Nevertheless, data were extracted and computed into the database to provide a global qualitative picture of organ and tissue distributions of human GSTs and combined with available data on isozyme-specific levels of expression in tissues. This overall picture is illustrated in Table 3 for the most studied cytosolic GSTs in human subgroups of the population (foetal stages, adults, elderly).

In addition, GST distribution and expression showed variation across different organ and tissues, with the liver, testes, kidney, adrenals, and small intestine being characterised by the presence of almost all the isozymes at the highest level, except for GSTA3, which is not present in the liver. GSTP1 is expressed at high level in almost all tested tissues, including the uterus, in which the only other present isoform is GSTT1.

Few peer reviewed papers provided information on GST distribution with quantitative data on GST activity and are reported in Figs. 5 and 6 as estimated geometric means and their associated standard deviations for GSTs expressed as U/L and as specific activity data (µmol/min/g) per organ or tissue. Although the activity is present in many different tissues and organs, the highest activities are measured in whole blood, mostly associated with the cell fraction (Fig. 5) while plasma or serum activities are much lower and are associated with high variability (Fig. 6). High levels are measured also in the kidney (reaching very high individual values), liver, adrenal glands, confirming the results from the qualitative immunohistochemistry and expression data analysis. However, the authors note that GST activity is expressed as total activity measured with the non-specifc probe substrate CDNB (Table 3) and the relative presence of different isozymes in various organs and tissues substantially varies.

3.3. GST polymorphisms

Cytosolic GSTs show genetic polymorphisms for which GSTM1, GSTT1 and GSTP1 are the most extensively studied (Table 4). For GSTM1, nucleotide variation (G2619C) and a complete deletion of the gstm1 gene are responsible for the presence of three named

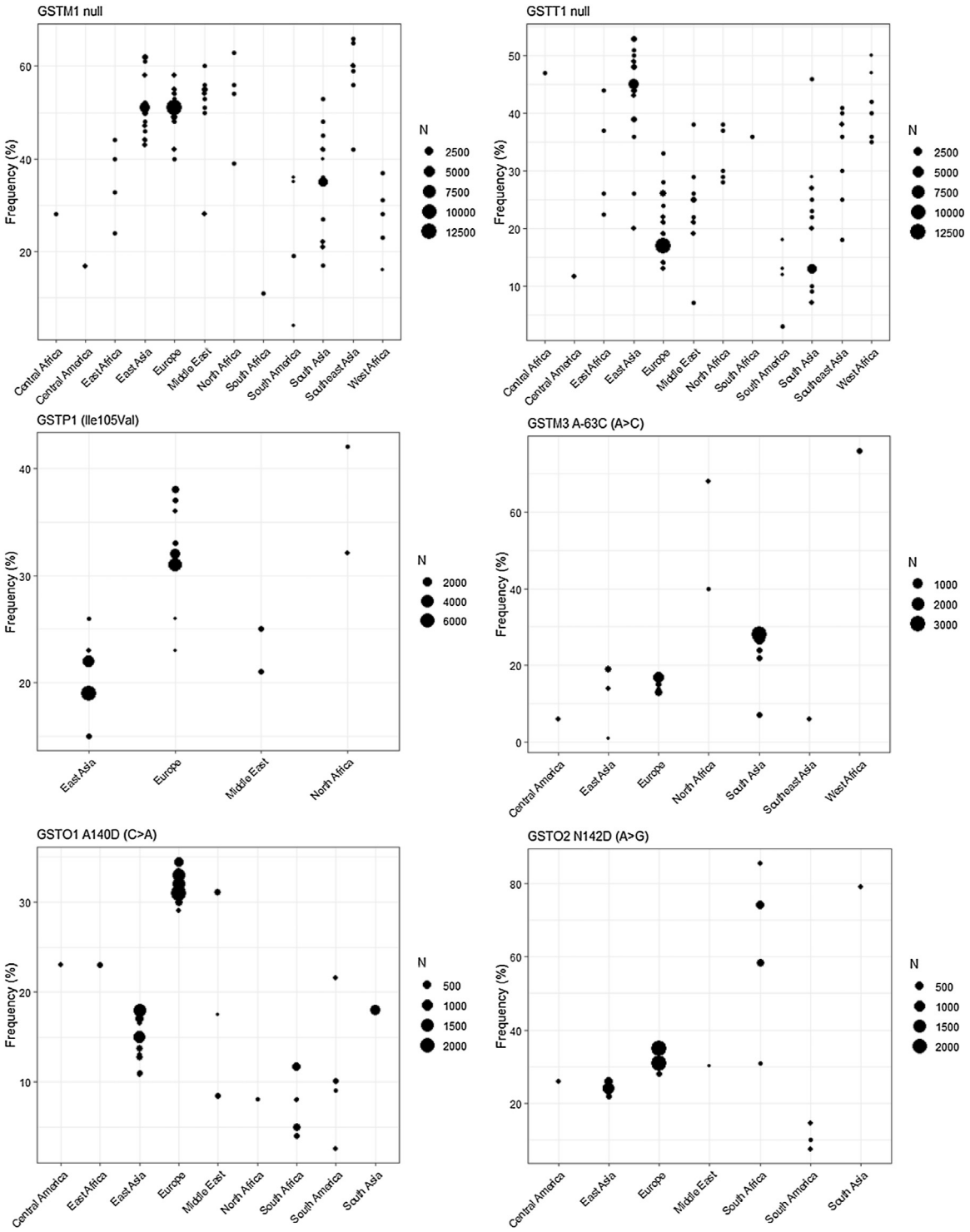

Fig. 4. Frequencies of Glutathione-S-transferases polymorphisms for cytosolic isozymes GSTM1, GSTT1 and GSTP1, GSTM3, GSTO1 and GSTO2 in world population of different geographical ancestry. For the number of studies/samples, please see Table 5 and 6.

alleles: GSTM1*A, GSTM1*B and GSTM1*null*. The first two differ by a single base in exon 7, which was not shown to affect enzyme activity. In contrast, GSTM1*null* results in the absence of GSTM1 and subjects carrying this deletion of the gstm1 gene have been shown to be unable to metabolise epoxides or quinones (Smith et al., 1994; Hayes and Strange, 2000; McIlwain et al., 2006; Dong et al., 2018).

Several studies confirmed the presence of the null phenotype GSTT1 following the deletion of the gstt1 gene (Hayes and Pulford, 1995). A nucleotide variation was found at the level of the gstt1 gene (A310C) which substitutes the threonine residue (Thr) 104 in proline (Pro) (Alexandrie et al., 2002). The GSTT1*B allele confers a decreased catalytic activity when compared to the GSTT1*A allele. Thus, three alleles can be described for GSTT1: GSTT1*A, GSTT1*B

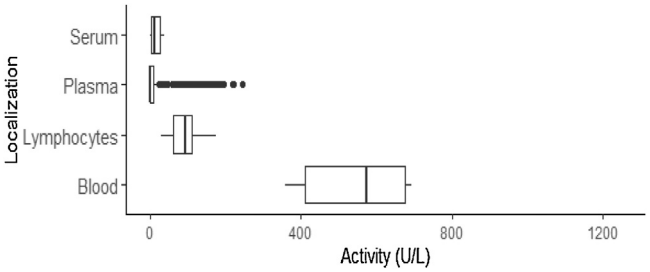

Fig. 5. Inter-individual differences in GST activity in serum, plasma, lymphocytes and blood from healthy individuals. Geometric means and associated GSD (log normal distributions) for GSTs expressed as U/L. Number of studies/samples: serum 7/821 ; plasma 9/1137 ; lymphocytes 6/129 ; blood 1/9.

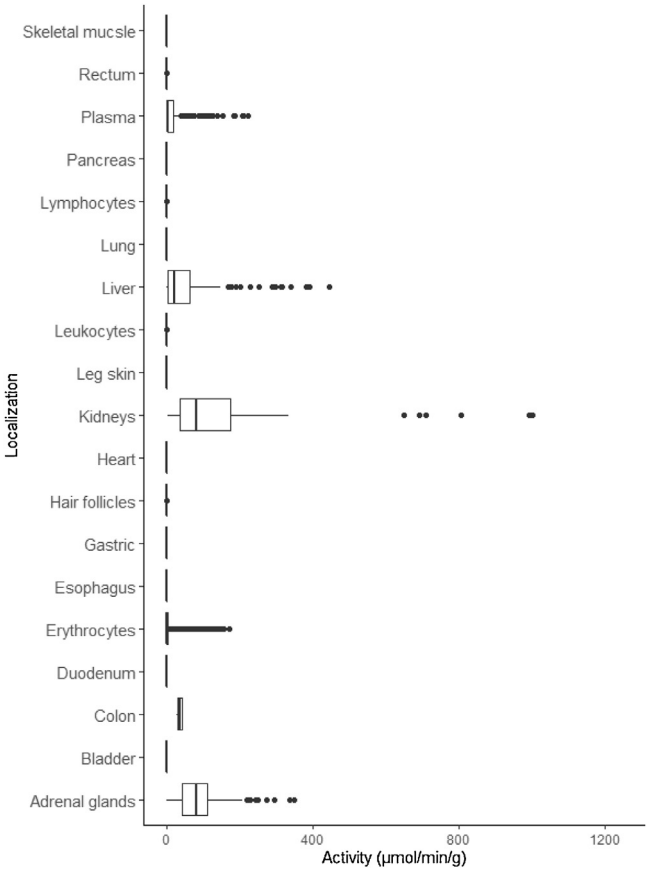

Fig. 6. Inter-individual differences in GST activity in human organs and tissues. Geometric means and geometric standard deviations (log normal distributions) for GSTs specific activity expressed as µmol/min/g. Number of studies/samples: skeletal muscle 2/4 ; rectum 2/97 ; plasma 9/388 ; pancreas 2/5 ; lymphocytes 6/259 ; lung 2/5 ; liver 14/131 ; leukocytes 1/92 ; leg skin 2/8 ; kidneys 6/50 ; heart 2/6 ; gastric 1/34 ; hair follicles 2/152 ; esophagus 1/15 ; erythrocytes 52/1301 ; duodenum 1/5 ; colon 2/8 ; bladder 2/29 ; adrenal gland 8/88.

and GSTT1*null* and their respective GST activity has been previously described as a trimodal distribution so that subjects have been classified into: *null*, slow (*B) and fast (*A) metabolisers with a 20 and 61 % frequency of the null allele GSTT1*null* in Caucasian and Asian population, respectively.

The GSTP1 has four named allelic variants GSTP1*A, GSTP1*B, GSTP1*C and GSTP1*D (Manevich et al., 2013; Dong et al., 2018). These variants result from the presence of two nucleotide variations at the level of the coding sequence (A313 G and C341 T) for which a substitution of the codon ATC (isoleucine (Ile)) occurs at position 105 in GSTP1*A and 1*D in GTC (valine (Val)) in GSTP1*B and 1*C. Another variation at the GCG (alanine (Ala)) codon occurs at position 114, in GSTP1*A and 1*B, with a GTG (valine (Val)) substitution in GSTP1*C and 1*D. These changes have an impact on the three-dimensional structure of the enzyme and on the stereospecificity of the catalytic (active) site (Ali-Osman, 1997) and lead to a decrease in the activity of the encoded protein, suboptimal catalytic efficiency and a decrease in the excretion of conjugated xenobiotics (Dong et al., 2018). The Ile105→Val105 and Ala114→Val114 substitutions do not alter glutathione-binding affinity, but cause a steric change at the substrate-binding site of the enzyme (Manevich et al., 2013). The Val105 variant, compared with Ile105, appears to confer a higher catalytic efficiency for polycyclic aromatic hydrocarbon diol epoxides and a lower one for CDNB (Holley et al., 2007).

Substitutions of amino acids at the 105th position affects the geometry of the substrate binding site of GSTP1 resulting in an approximately three-fold reduction in *in vitro* substrate affinity (Goodrich and Basu, 2012) (Ali-Osman et al., 1997; Hu et al., 1997; Zimniak et al., 1994). The major GSTP1 alleles are Ile105 (frequency >50 %) and Ala114 (>90 %). The two most common allozymes of GSTP1 in human populations are GSTP1*A and *B, though GSTP1 *D and *C exist to a limited extent (estimated $\leq$ 5% based on allele frequencies in HapMap populations). GSTP1 *A and *D had the greatest affinity for the electrophilic substrate, CDNB, and their affinities were 3–4 fold greater than that of GSTP1*B (Goodrich and Basu, 2012).

Results of the data collection are presented in Tables 5 and 6. and report the frequencies of the main genetic polymorphisms for hGSTM1, hGSTT1 and the double null (Table 5), as well as hGSTP1, hGSTM3, hGSTO1 and hGSTO3 (Table 6) in world populations of different geographical ancestry resulting from reviews and meta-analysis studies correlating tissue GST expression and diseases (e.g cancer). The full database is available as an excel file (EFSA DOI) and presented in the supplementary material.

Data for each polymorphism were subdivided for world populations from different geographical ancestry; in one single study, worldwide distribution was available based on the latitudinal position (Saitou and Ishida, 2015). Fig. 4 shows the summary statistics (average, min, max) of the frequency of polymorphisms for each allozyme in relation to sample size. Data stratified by gender were not often reported; however, when gender specific diseases were studied, such as endometriosis and breast cancer for women and varicocele and prostate cancer for men, gender differences in the frequency distribution was analysed: no significant differences between male and female individuals were evidenced in any of the world populations.

The stratification by geographical ancestry showed higher incidence (around 50 % of the population) of the null GSTM1 genotype in Caucasian and Asian populations, when compared with Indians and South and Central Africans, Afro-Brazilians, Afro-Americans (around 30 %). On the other hand, the GSTT1 null genotype frequency was lower in Caucasian, the group of South and Central Africans, Afro-Brazilians, Afro Americans and Indians (around 20 %) compared to that in Asian populations (40 %). The double null GSTM1/T1 frequency for the main populations showed the highest incidence in Asians (23 %) which was twice as low (i.e 10 %) for other populations.

Another well-characterised polymorphism is the GSTP1 Ile105Val (*B), where the amino-acidic substitution gives a lower activity with many substrates. The frequency of Val allele did not

Table 3
Tissue localisation of key cytosolic Glutathione-S-Transferases in humans.

GST	Alpha				Mu					Pi	Theta	
	A 1	A2	A3	A4	M1	M2	M3	M4	M5	P1	T1	T2
Brain	t	t		+	+	+	+	+-	+-	++		+
Bladder	t	t		+-		+-	+-	+-	+-	+++		+
Skin			+-	++	++	++	+	+-	+-	+++	+-	+
Heart	t	t	t	+-	+	+	+-	+-	+-	++	++	+
Testes	+++	++	+-	+	+	+	++	+-	+-	++	+-	+
Liver	+++	+++		+-	++	+	+-	+-	t	+-	+	+
Lung	+-	+-	t	+	+	+	+-	+-	+-	+++	+++	+
Small intestine	+++	++	t	+-	+	+	+-	++	+-	+++	++	+
Kidney	+++	+++	t	+	+	+	++	+	+-	+++	++	+
Ovary	++	+-	t	+	++	++	+	+	++	+++	+-	+
Pancreas	+-	++		+-		+-	+-	+-	t	++	+	t
Placenta	t	t	+-	+		+-		+-	t	+++	+	+
Prostate	+-	+-	t	+	++	++	+	+-	+	++	+++	+
Uterus	t									+	++	
Adrenal	+++	++	+	+++	++	++	+-	+-	+-	++	++	+
Spleen	t		t	+-	+	+	+-	+-	+-	++		+
Thyroid		t		+-	+	+	+	+	+-	+++	+++	+

+++: high expression; ++: medium/high expression; +: medium expression; +-: low level; t traces.
Data collected from histochemical staining studies and RNA-seq databases. (Rowe et al., 1997; Desmots et al., 2001; Tiltman, A. J. and Haffajee, Z. 1999; Sundberg et al., 1993; Eaton and Brommler, 1999; Hayes and Strange, 2000; https://www.ncbi.nlm.nih.gov/gene; http://ds.biogps.org/?dataset=GSE1133&gene=2952).

Table 4
Major human polymorphisms in cytosolic GST classes.

GST class	Gene	allelic variants	Nucleotide variation
M	hGSTM1	hGSTM1*A	Lys173
		hGSTM1*B	Asn 173
		hGSTM1*Null*	Gene deletion
		hGSTM1**1–2*	Duplication
	hGSTM3	hGSTM3*A	Wt
		hGSTM3*B	Protein unchanged
P	hGSTP1	hGSTP1*A	Ile105/Ala114 (Wt)
		hGSTP1*B	Val105/Ala114
		hGSTP1*C	Val105/Val114
		hGSTP1*D	Ile105/Val114
T	hGSTT1	hGSTT1*A	Thr104 (Wt)
		hGSTT1*B	Pro104
		hGSTT1*Null*	Gene deletion
O	hGSTO1	hGSTO1*A	Ala140;Glu155
		hGSTO1*B	Ala140
		hGSTO1*C	Asp140;Glu155
		hGSTO1*D	Asp140
	hGSTO2	hGSTO2*A	Asn142
		hGSTO2*B	Asp142

Wt: Wild type; from (Dong et al., 2018).

show significant differences between the different populations, even if the African population was at the lower end of the frequency range found in Afro-Americans.

For other polymorphic variants, data were more limited and associated with smaller sample sizes to derive population distributions.

GSTM3 3-bp deletion polymorphism (GSTM3*A/*B) has been shown to have a high (*i.e.* 60 %) frequency only in Sub-Saharan Africans (with African populations at the higher end of the range shown in Afro-Americans). The A-63C polymorphism was on the contrary more frequent in Caucasian populations.

Two datasets describing the frequency of GSTO1 (A140D (alanine to aspartate substitution) and GSTO2 polymorphisms ((N142D (asparagine to aspartate substitution)) were available however, with for limited number of individuals. Caucasian showed the highest frequency of O1 A140D (*B) gene polymorphism whereas N142D (*B) O2 frequency was very high (>70 %) in Indian and Sub-saharan Africans. The latter variant allozyme was also associated with a 20 % reduction in GSTO2 expression levels compared to that in the GSTO2 wild type (Khosravi et al., 2013).

Another possibly relevant polymorphism is associated to GSTA1, one of the isoforms mainly expressed in the liver and intestine: its allelic variants can cause altered GSTA1 activity as studied with busulfan, an alkylating agent, used as a therapeutic drug. However, the effects of GST A1*A/*A and GST*B/*B genotype on busulfan clearance gave contrasting results (Michaud et al., 2019). Other GST polymorphisms have been reported in the literature with more limited data and these did not allow deriving a robust population distribution.

Table 5
Frequency of glutathione-S-transferases polymorphisms for isozymes M1 and T1 in population of different geographical ancestry.

GST	Polymorphism	Ethnicity	Allele	Number of cases	Average frequency (range)	References
M1	Null	Caucasian[a]	Null	26,089	0.50 (0.28–0.60) ♀ 0.48 (0.16–0.62) ♂ 0.43 (0.28–0.60)	Saitou and Ishida, 2015; Piacentini et al., 2011; Abid et al., 2016; Yu et al., 2017; Dresler et al., 2000; Karagas et al., 2005; Tang et al., 2015; Song et al., 2016; Millikan et al., 2000; Xin et al., 2016; Khalighinasab et al., 2015; Schnakenberg et al., 2000; Zhu et al., 2015; Safarinejad et al., 2011; Mo et al., 2009; Safarinejad et al., 2010
	Null	Black[b]	Null	5396	0.29 (0.11–0.39) ♀ 0.28 ♂ 0.37 (0.27–0.47)	Saitou and Ishida, 2015; Piacentini et al., 2011; Millikan et al., 2000; Mo et al., 2009; Sharma et al., 2012
	Null	Asian[c]	Null	20,774	0.50 (0.36–0.61) ♀ 0.50 (0.25–0.60) ♂ 0.48 (0.42–0.56)	Saitou and Ishida, 2015; Piacentini et al., 2011; Tang et al., 2015; Xin et al., 2016; Zhu et al., 2015; Mo et al., 2009; Yu et al., 2017
	Null	Indian	Null	5094	0.31 (0.17–0.46) ♀ 0.28 (0.08–0.34) ♂ 0.35 (0.30–0.38)	Saitou and Ishida, 2015; Piacentini et al., 2011; Tang et al., 2015; Xin et al., 2016; Zhu et al., 2015; Mo et al., 2009; Yu et al., 2017; Konwar et al., 2010; Abid et al., 2016; Sharma et al., 2012
	Null	Ameridians[d]	Null	411	0.21 (0.04–0.36)	Saitou and Ishida, 2015; Piacentini et al., 2011
T1	Null	Caucasian[a]	Null	24,032	0.23 (0.07–0.44) ♀ 0.16 (0.08–0.29) ♂ 0.17 (0.10–0.50)	Saitou and Ishida, 2015; Piacentini et al., 2011; Abid et al., 2016; Yu et al., 2017; Dresler et al., 2000; Karagas et al., 2005; Tang et al., 2015; Song et al., 2016; Millikan et al., 2000; Xin et al., 2016; Khalighinasab et al., 2015; Schnakenberg et al., 2000; Zhu et al., 2015; Safarinejad et al., 2011; Mo et al., 2009; Safarinejad et al., 2010;
	Null	Black[b]	Null	5384	0.29 (0.20–0.50) ♀ 0.17 ♂ 0.32 (0.27–0.37)	Saitou and Ishida, 2015; Piacentini et al., 2011; Millikan et al., 2000; Mo et al., 2009; Sharma et al., 2012
	Null	Asian[c]	Null	18,832	0.41 (0.07–0.63) ♀ 0.43 (0.22–0.56) ♂ 0.48 (0.42–0.52)	Saitou and Ishida, 2015; Piacentini et al., 2011; Tang et al., 2015; Xin et al., 2016; Zhu et al., 2015; Mo et al., 2009; Yu et al., 2017
	Null	Indian	Null	1463	0.16 (0.09–0.29) ♀ 0.15 (0.09–0.40) ♂ 0.15 (0.11–0.29)	Saitou and Ishida, 2015; Piacentini et al., 2011; Tang et al., 2015; Xin et al., 2016; Zhu et al., 2015; Mo et al., 2009; Yu et al., 2017; Konwar et al., 2010; Sharma et al., 2012
	Null	Ameridians[d]	Null	411	0.20 (0.12–0.38)	Saitou and Ishida, 2015; Piacentini et al., 2011
M1/T1	Null/Null	Caucasian[a]	Null/Null	1980	0.12 (0.03–0.25) ♀ 0.05 ♂ 0.12	Xin et al., 2016; Safarinejad et al., 2011; Yu et al., 2017; Ali et al., 2015
	Null/Null	Black[b]	Null/Null	3141	0.12 (0.10–0.14)	Ali et al., 2015; Sharma et al., 2012
	Null/Null	Asian[c]	Null/Null	7662	0.23 (0.15–0.31) ♀ 0.08 (0.09–0.25)	Xin et al., 2016; Yu et al., 2017; Sharma et al., 2012; Ali et al., 2015
	Null/Null	Indian[d]	Null/Null	5057	0.08 (0.04–0.11)	Xin et al., 2016; Yu et al., 2017; Sharma et al., 2012

a: Caucasian group, generally the populations of Europe, white people of USA and Canada and also caucasian/arabian (Turkish and Iranian people, Arabian peninsula in general), caucasian/african (North and central-east Africa; Tunisia and Egypt, Somalia and Etyopia). b: Black (South and central African, Afro-Brazilian, Afro American). c: Asian (East Asia: Chinese, Japanese, Korean and Central Asia: Mongolian Pakistan, Afghanistan). d: Ameridians (Brazilian, Mexican, Paraguay). The Indian population even if generally considered in Asian group was reported separately considering that the MAF (Minor allelic frequency) was quite different, in some cases.

Table 6
Frequency of glutathione-s-transferases polymorphisms for isoforms P1, M3, O1 and O2 in population of different geographical ancestry.

GST	Polymorphism	Ethnicity	Allele	Number of cases	Average frequency (range)	Genotype frequency	References
P1	Ile105Val (rs1695)	Caucasian[a]	*B	9599	0.33 (0.31–0.36) ♀ 0.30 (0.17–0.48) ♂ 0.26 (0.23–0.38)	Ile/Ile = 43 % Ile/Val = 48 % Val/Val = 8%	Sharma et al., 2014; Wang et al., 2015; Tang et al., 2015; Song et al., 2016; Millikan et al., 2000; Safarinejad et al., 2011; Mo et al., 2009; Bacic Baronica et al., 2014; Safarinejad et al., 2010
	Ile105Val (rs1695)	Black (Africa and USA)	*B	3006	0.31 (0.12–0.42) ♀ 0.46 ♂ 0.49		Piacentini et al., 2011; Sharma et al., 2014; Wang et al., 2015; Millikan et al., 2000; Kuang et al., 2016; Mo et al., 2009
	Ile105Val (rs1695)	Asian (China, Japan, East Asia)	*B	10,838	0.24 (0.22–0.26) ♀ 0.19 (0.18–0.19) ♂ 0.15 (0.14–0.15)	Ile/Ile = 57 % Ile/Val = 39 % Val/Val = 4%	Sharma et al., 2014; Wang et al., 2015; Tang et al., 2015; Mo et al., 2009
	Ile105Val (rs1695)	Indian	*B	1776	0.28 ♀ 0.27 (0.20–0.32) ♂ 0.23 (0.22–0.25)	Ile/Ile = 50 % Ile/Val = 44 % Val/Val = 6%	Sharma et al., 2014; Tang et al., 2015; Mo et al., 2009; Konwar et al., 2010
M3		Caucasian (European countries and USA)	*B	2188	0.14 (0.05–0.24) ♀ 0.16 (0.08–0.29) ♂ 0.17 (0.10–0.50)	A/A = 74 % A/B = 24 % B/B = 2%	Xu et al., 2014a; Cortessis et al., 2001; Mitrunen et al., 2001; Medeiros et al., 2004
		Black (Africa Sub-saharan and USA)	*B	383	0.61 (0.40–0.78)		Xu et al., 2014a; Cortessis et al., 2001; Teixeira et al., 2010
		Asian	*B	189	0.03 (0.0–0.03)		Cortessis et al., 2001; Alshagga et al., 2011
		Indian	*B	169	0.07 (0.09–0.29)		Kesarwani et al., 2009
		Hispanic	*B	209	0.10 (0.06–0.14)		Cortessis et al., 2001; Jaramillo-Rangel et al., 2015

Table 6 (*Continued*)

GST	Polymorphism	Ethnicity	Allele	Number of cases	Average frequency (range)	Genotype frequency	References
	A-63C (A > C)	Caucasian	*C	175	0.44		Liu et al., 2005; Yoshimura et al., 2003
		Asian		416	0.16 (0.14–0.19)		
		Afro-american		107	0.17		
O1	A140D (C > A)	Caucasian (European countries and USA)	A (*B)	5688	0.31 (0.29–0.35)	C/C = 45 % C/A = 47 % A/A = 18 %	Xu et al., 2014b; Takeshita et al., 2009; Polimanti et al., 2013; Ada et al., 2013
	A140D (C > A)	Black	A (*B)	570	0.08 (0.04–0.12)		Takeshita et al., 2009
	A140D (C > A)	Asian (China, Japan Thailand)	A (*B)	4107	0.15 (0.11–0.37)	C/C = 69 % C/A = 28 % A/A = 3%	Xu et al., 2014a; Takeshita et al., 2009; Luo et al., 2018; Fu et al., 2008
	A140D (C > A)	Indian	A (*B)	925	0.18	C/C = 68 % C/A = 29 % A/A = 3%	Antonelli et al., 2014
O2	N142D (A > G)	Caucasian (European countries and USA)	G (*B)	5014	0.31 (0.28–0.37)	A/A = 46 % A/G = 46 % G/G = 8%	Xu et al., 2014b; Takeshita et al., 2009; Piacentini et al., 2014
	N142D (A > G)	Black (Africa and USA)	G (*B)	570	0.74 (0.58–0.86)		Takeshita et al., 2009
	N142D (A > G)	Asian (China, Japan Thailand)	G (*B)	2560	0.24(0.22–0.27)	A/A = 55 % A/G = 39 % G/G = 6%	Takeshita et al., 2009; Luo et al., 2018
	N142D (A > G)	Indian (Pakistan)	G (*B)	102	0.79	A/A = 7% A/G = 27 % G/G = 66 %	Xu et al., 2014a

4. Conclusions and future perspectives

This manuscript constitutes the first extensive literature search and meta-analysis of inter-individual differences in cytosolic GST activities in healthy adults. The open source database also provides an analysis of the tissue distribution of GSTs and the frequency of the polymorphic variants for which data are available. The availability of inter-individual differences in key metabolic pathways is increasingly important in human risk assessment, it has been shown to significantly improve the performance of QIVIVE and PBPK models for hazard characterisation of chemicals and support the reduction of animal testing as New Approach Methods (NAMs).

This study evidenced that, despite the large number of peer-reviewed publications available on GST enzymes, only a limited number provided data for inter-individual differences in healthy adults and other subgroups of the human population. In addition, current databases, including the Food and Drug Administration one (FDA, 2017), do not provide isoform-specific probe substrates for GSTs of clinical or toxicological relevance to support the modelling of inter-individual differences in kinetic parameters (*e.g.* AUC, clearance, Cmax, $t_{1/2}$) and their integration with differences in dynamics. Data are available for a number of drugs administered to patients affected by a range of pathologies including correlation between GST polymorphic alleles and specific diseases; however, as discussed above, disease status is known to be associated with an alteration of GST activities and data for healthy adults are still limited.

GST activity is most often measured *ex-vivo* using CDNB as a non-specific probe substrate, which reacts with all isozymes, except for GSTT which has very limited affinity for CDNB. In addition, since GST exhibit sex-, age-, tissue-, and species- patterns of expression, the data analysis accounting for these variables (localisation, isoform, geographical ancestry and age group) provided limited number of individuals from each subgroups of the population. Still, a Bayesian meta-analyses provided variability distributions to i) identify GST-related uncertainty factors; ii) implement such variability in generic physiologically based kinetic models or iii) inform quantitative *in vitro/in vivo* extrapolation models. Generally speaking, the GST-related UFs were mostly below the default factor of 3, with few exceptions; however, results were highly uncertain to draw robust conclusions due to the limited datasets highlighting large data gaps.

In the light of the relevance of GST activities in the area of food safety, and their pivotal role in cellular adaptive response mechanisms to chemical stressors caused by electrophiles and ROS, further studies should be conducted to identify and design specific probe substrates for GST isozymes and quantify inter-individual differences in human populations from different geographical ancestry, age groups and polymorphic variants. Refinement of generic human PBK, PBKD and QIVIVE for the risk assessment of chemicals with such data is relevant whenever GSTs is involved in the metabolic pathways, with an isoform specific pattern. This is particularly relevant for those chemicals whose biotransformation is dependent only on GST-catalysed reactions, as in the case of mycrocistins, a group of natural toxins contaminants for seafood and drinking water (Santori et al., 2020).

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CRediT authorship contribution statement

Franca Maria Buratti: Investigation, Data curation, Writing - original draft, Writing - review & editing. **Keyvin Darney:** Methodology, Formal analysis, Visualization. **Susanna Vichi:** Investigation. **Laura Turco:** Investigation. **Emma Di Consiglio:** Investigation. **Leonie S. Lautz:** Methodology, Formal analysis, Visualization. **Camille Béchaux:** Methodology, Software. **Jean-Lou Christian Michel Dorne:** Writing - review & editing, Supervision, Project administration. **Emanuela Testai:** Writing - original draft, Writing - review & editing, Supervision, Project administration.

Declaration of Competing Interest

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

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.toxlet.2020.11.007.

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