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Bayesian meta-analysis of inter-phenotypic differences in human serum paraoxonase-1 activity for chemical risk assessment

K. Darney[a], E.E.J. Kasteel[b], F.M. Buratti[c], L. Turco[c], S. Vichi[c], C. Béchaux[a], A.C. Roudot[d], N.I. Kramer[b], E. Testai[c], J.L.C.M. Dorne[e], E. Di Consiglio[c], L.S. Lautz[a,*]

[a] Risk Assessment Department, French Agency for Food, Environmental and Occupational Health & Safety (ANSES), 14 rue Pierre et Marie Curie, Maisons-Alfort F-94700, France
[b] Institute for Risk Assessment Sciences, Utrecht University, 3508 TD Utrecht, the Netherlands
[c] Department of Environment and Health, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy
[d] Laboratoire des Interactions Epithéliums Neurones, Université Bretagne Loire (UBL), UFR Sciences et Techniques, 6 Av. Victor Le Gorgeu, CS93837, Cedex 3, Brest 29238, France
[e] European Food Safety Authority, 1a, Via Carlo Magno 1A, 43126 Parma, Italy

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ABSTRACT

Human variability in paraoxonase-1 (PON1) activities is driven by genetic polymorphisms that affect the internal dose of active oxons of organophosphorus (OP) insecticides. Here, an extensive literature search has been performed to collect human genotypic frequencies (i.e. L55M, Q192R, and C-108T) in subgroups from a range of geographical ancestry and PON1 activities in three probe substrates (paraoxon, diazoxon and phenyl acetate). Bayesian *meta*-analyses were performed to estimate variability distributions for PON1 activities and PON1-related uncertainty factors (UFs), while integrating quantifiable sources of inter-study, inter-phenotypic and inter-individual differences. Inter-phenotypic differences were quantified using the population with high PON1 activity as the reference group. Results from the *meta*-analyses provided PON1 variability distributions and these can be implemented in generic physiologically based kinetic models to develop quantitative *in vitro in vivo* extrapolation models. PON1-related UFs in the Caucasian population were above the default toxicokinetic UF of 3.16 for two specific genotypes namely −108CC using diazoxon as probe substrate and, −108CT, −108TT, 55MM and 192QQ using paraoxon as probe substrate. However, integration of PON1 genotypic frequencies and activity distributions showed that all UFs were within the default toxicokinetic UF. Quantitative inter-individual differences in PON1 activity are important for chemical risk assessment particularly with regards to the potential sensitivity to organophosphates' toxicity.

1. Introduction

Human paraoxonase 1 (PON1) is a well characterised family member of high-density lipoprotein associated serum enzymes called serum paraoxonases (PONs). PONs have been identified in mammals, vertebrates and invertebrates and are involved in the detoxification process of a range of chemicals, including prodrugs like prulifloxacin, active oxons of organophosphorus (OP) insecticides as well as nerve gas agents such as sarin and soman (Costa et al., 1999; Furlong et al., 2016). PON1 enzymes are also important in protecting the human body against vascular disease through metabolising oxidised lipids (Costa et al., 2011). In the 1960s and 1970s, human studies demonstrated that PON1 activities were polymorphically distributed and the frequency of phenotypes with low activities were variable amongst populations of different geographical or ethnic ancestry (Diepgen and Geldmacher-von Mallinckrodt, 1986).

Nearly 200 single nucleotide polymorphisms (SNPs) have been described in the literature for the PON1 gene with the two most common polymorphisms reported in the coding regions at position 55 and 192 (Gupta et al., 2011; Humbert et al., 1993; Richter et al., 2010; Shunmoogam et al., 2018). The SNP present at position 55, leucine/methionine (L55M) has been associated with altered PON1 serum concentrations, while the SNP at position 192, glutamine/arginine polymorphism (Q192R) has been associated with altered PON1 activity (Ceron et al., 2014; Shunmoogam et al., 2018). Both polymorphisms have been associated with altered protection against lipid peroxidation and an increased risk of heart diseases (Arca et al., 2002; Hernández-Díaz et al., 2016). Especially the 192Q allele has been linked to an

* Corresponding author.
E-mail address: leonie.lautz@anses.fr (L.S. Lautz).

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increased risk to develop coronary artery disease (Hernández-Díaz et al., 2016; Zhang et al., 2018). Within the promoter region of the PON1 gene, another important SNP is C-108T, affecting PON1 enzyme levels (Turgut Cosan et al., 2016). The SNPs described affect PON1 activity, but seems to be substrate dependent, since the 192R alloform hydrolyses chlorpyrifos oxon and paraoxon more rapidly than *192Q *in vitro* (Li et al., 2000). Variability in PON1 activity may not only be introduced by polymorphisms but also by age and lifestyle (Ginsberg et al., 2009; Nalcakan et al., 2016). PON1 activity is very low before birth as indicated by a 24% lower activity in premature babies (33–36 weeks of gestation) compared to babies at term (Ecobichon and Stephens, 1973). PON1 activity increases over time reaching a plateau between 6 months and a few years of age (Augustinsson and Barr, 1963; Cole et al., 2003; Ecobichon and Stephens, 1973; Holland et al., 2006; Huen et al., 2010; Smith et al., 2011).

Polymorphisms in PON1 are well described and constitute an a important source of variability driving potential changes in internal dose of oxon metabolites and have been hypothesised to be involved in OP oxon resistance after OP exposure. Distributions of PON1 activities have been simulated to quantify inter-phenotypic differences while integrating genotypic frequencies and variations across a range of human populations (Ginsberg et al., 2009). This body of evidence shows that quantification of inter-phenotypic differences across different PON1 genotypes provides a basis for the derivation of variability distributions and PON1-related uncertainty factors (UFs) allowing for inter-individual differences in toxicokinetics (TK) (Bhat et al., 2017; Renwick, 1993; Truhaut, 1991).

This manuscripts aims to investigate human variability in PON1 activities by means of extensive literature searches and hierarchical Bayesian meta-analysis for paraoxon, diazoxon and phenyl acetate as probe substrates in healthy adult populations expressing different SNPs (i.e. L55M, Q192R, and C-108T). Variability distributions for PON1 activities and PON1-related UFs have been derived while integrating quantifiable sources of inter-study, inter-individual and inter-phenotypic differences.

2. Material and methods

2.1. Extensive literature search and data collection

Since data collection regarding kinetics requires flexibility, extensive literature searches (ELS) were performed rather than a systematic review (Quignot et al., 2015). The ELS were performed to identify PON1 activity in the serum of healthy human subjects from a range of geographical ancestry or ethnic groups. Inter-phenotypic differences in relation to PON1 polymorphisms (C-108T, L55M, Q192R) were investigated for healthy adults whereas data from populations exposed to pharmaceuticals, environmental contaminants or populations with specific lifestyle or diseases were excluded. The ELS were performed by two independent reviewers (until June 2019) for well-characterised PON1 probe substrates namely paraoxon, diazoxon and phenyl acetate in PubMed and Scopus (EFSA, 2010; Quignot et al., 2015). Data reporting genotypic frequencies of PON1 in human populations from different geographical ancestry (Europe, Africa, Middle East, Asia and Oceania) were collected for the homozygous CC, QQ, LL (wild-type) and for heterozygous (CT, QR, LM) and homozygous TT, RR and MM (mutant). Each polymorphism, whether known from coding or promotor region, was associated with variability in levels of PON1 activity towards each of the three probe substrates. In order to compare different PON1 activity phenotypes, the high activity group has been considered as the reference group which varied across substrates and genotypes (Furlong et al., 2016). The two remaining groups will be considered as sub-groups. Table 1 provides a summary of the individual keywords applied for the ELS. The complete database is available in Supplementary material A.

2.2. Meta-analysis

2.2.1. Data standardisation

Data for PON1 activity were standardised to perform the meta-analysis in a harmonised manner. Activity was expressed in nmol/min/ml (paraoxon and diazoxon studies) or µmol/min/ml (phenyl acetate studies). PON1 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:

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

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

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

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

2.2.2. Derivation of PON1-related variability and uncertainty factors

A Bayesian hierarchical model for the meta-analyses was implemented for PON1 activity as previously described (Darney et al., 2019) using non-informative priors. Two types of uncertainty factors were calculated: (1) UFs were calculated for the different SNPs; (2) UFs were calculated for the human population integrating PON1 activity and genotypic frequencies. Uncertainties in PON1 activities were quantified using median values and 95% confidence intervals. Coefficient of variations (CV) were also estimated as follows:

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

where τ_j is the inter-individual differences of the activity for a substrate 'j'.

Inter-phenotypic differences in PON1 activity and related UFs

PON1 activity related UFs for the reference group within a genotype were derived as ratios between given percentiles (either 95th or 97.5th centiles) and the median of the distribution. For inter-phenotypic differences, PON1-related UFs were calculated as the ratio between the percentiles of choice for the reference group and the median of the subgroup. A confidence interval around the UF is given by calculating 18,000 UFs and providing the values for the median, 2.5th and 97.5th percentile.

Inter-individual differences in PON1 activity and related UFs

Distributions for PON1 activity in the whole adult population were integrated for the reference group and the two remaining sub-groups applying Monte-Carlo simulations. Genotypic frequencies collected from the literature were combined with the estimated PON1 activity distributions. PON1-related UFs were derived as described elsewhere (Wiecek et al., 2019) and illustrated in Fig. 1. (1) Sampling $\alpha \times 10000$ values in the distribution for PON1 activity (α, the genotypic frequency in the population), the same pertains for the two other genotypes with the corresponding frequencies (100 iterations); (2) Calculate UFs based on the 50th and the 95th percentiles of 10^6 values; (3) Derive the distribution of UFs in the human population (18,000 iterations).

2.3. Software

All statistical analyses and graphs were performed in R (version 3.5) and the Bayesian modelling was implemented with Jags (4.2.0) (Plummer, 2003). R codes describing the hierarchical Bayesian model for the meta-analysis have been published elsewhere (Darney et al., 2019; Wiecek et al., 2019). References from the ELS have been saved in EndNote (X8) files.

Table 1
Keyword queries for the Extensive Literature Searches (formatted for Scopus).

General search terms	TITLE-ABS-KEY ("population distribution" 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 african OR children OR elderly OR "elderly people" OR adult* OR genotype)
Search terms for probe substrates	TITLE-ABS-KEY (human* W/50 (paraoxonase* OR diazoxonase* OR arylesterase* OR pon1 OR "PON1 activity"))
Exclusion	TITLE-ABS ("cell line*" OR "cell culture*")

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

3. Results

3.1. Extensive literature searches and data collection

Results from the ELS are presented in Fig. 2 as a prisma diagram. Human PON1 activities are available for a wide range of countries worldwide. Studies focused on healthy adults (range 18–75 years) and data for both genders were equally available. Overall, 67 peer reviewed publications were selected from the ELS and these reported human PON1 enzyme activities for three SNPs (C-108T, L55M and Q192R) using paraoxon, diazoxon and phenyl acetate as probe substrates or genotypic frequencies. The L55M and Q192R SNPs were the most studied while the C-108T SNP was the least studied. Activity data were available for East Asian, European, Middle East, North Africa, North America and South America. In the collected data, PON1 activity was mostly measured in Caucasian population (5469 measurements from adults in regards to paraoxon, Q192R SNPs) while less than 1222 measurements were available for all other populations (East Asian, Middle East, Tunisia, Chile). Moreover, data retrieved from Caucasian population were the only one that cover all genotypes for all studied probe-substrates. Data gaps were identified for Central and Southern Americans, Africans as well as children and neonates.

PON1 genotypic frequencies were available from the literature for the three SNPs C-108T, L55M and Q192R (Fig. 3). The −108CT variant was the most common in the human populations worldwide compared to the homozygous forms with the exception of the Southeast Asians and Middle Eastern populations. The 55LL genotype was dominant in Asian and Central American populations. For human populations, the 55LL and 55LM genotypes were equally present. Overall, the frequency of the 55MM mutation was below 20% worldwide. The 192QQ genotype was predominant in most populations, except for South and Central Americans as well as East Asians for which the 192QR variant was the most common compared to the homozygous forms. In addition, the 192RR mutation was also the most common in these populations.

PON1 activity for diazoxon and phenyl acetate substrates was the highest in the wild-type groups (CC, LL, QQ). PON1 activity towards paraoxon decreased across phenotypes in the following order CC > CT > TT for PON1 C-108T SNP, and between LL > LM > MM for PON1 L55M SNP with the exception of Q192R (Fig. 4) for which the wild type QQ showed a lower activity compared to the mutant RR genotype. An important distinction needs to be highlighted for measurements of PON1 activity using paraoxon with and without salt activation of the enzyme since the latter is not recommended for measurements at the population level. Indeed, salt increases the high-activity allelic form more than other forms while amplifying the variability in the healthy population (Fig. 4). All studies included in the database for diazoxon were conducted with salt activation in the assay and PON1 mean activity and its associated variability using diazoxon should be considered with caution. In contrast, salt addition produces a decrease in PON1 activity while measuring PON1 activity using phenyl acetate and these measurements were performed without salt activation (Ceron et al., 2014).

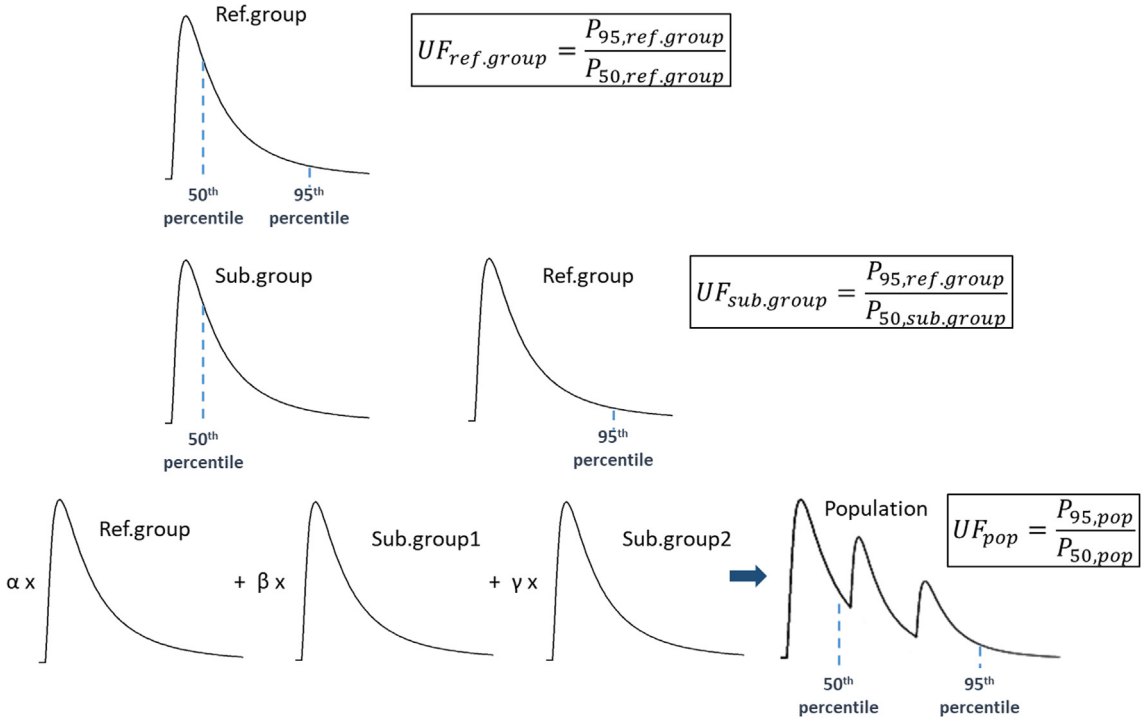

Fig. 1. Population simulations for the derivation of PON1 related uncertainty factors integrating inter-phenotypic differences (reference group and sub-groups) and genotypic frequencies (α, β and γ).

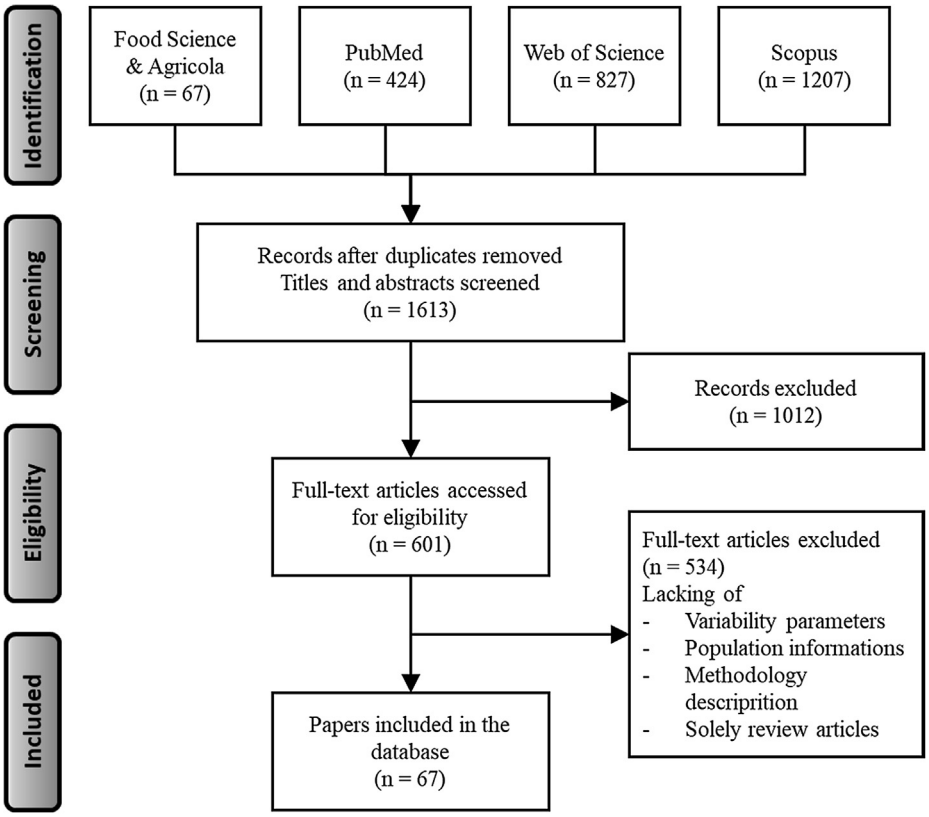

Fig. 2. Flow diagram illustrating the extensive literature search of human PON1 activity studies.

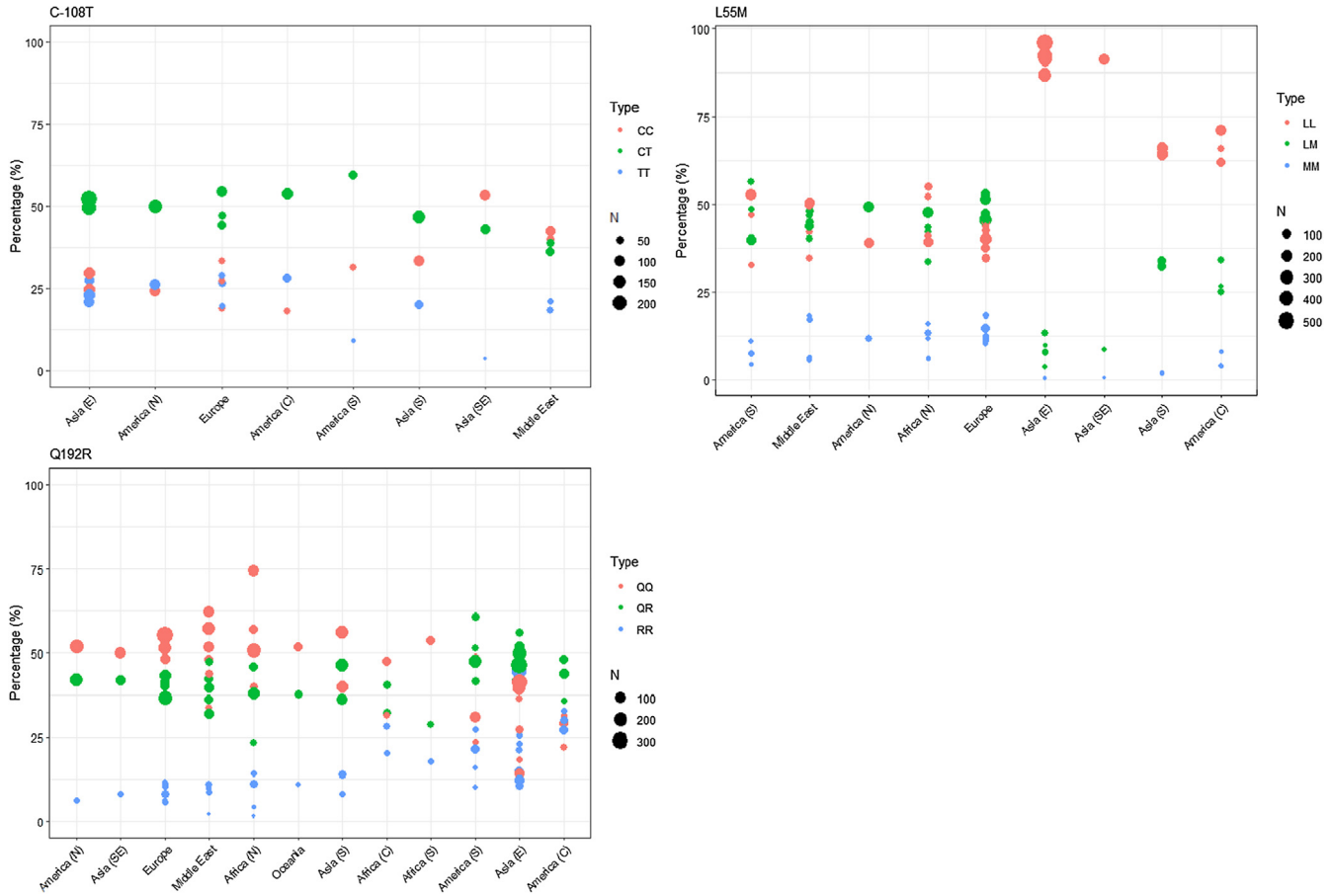

Fig. 3. Genotypic frequencies for PON1 Single Nucleotide Polymorphisms in human populations worldwide (L55M, Q192R, C-108T).

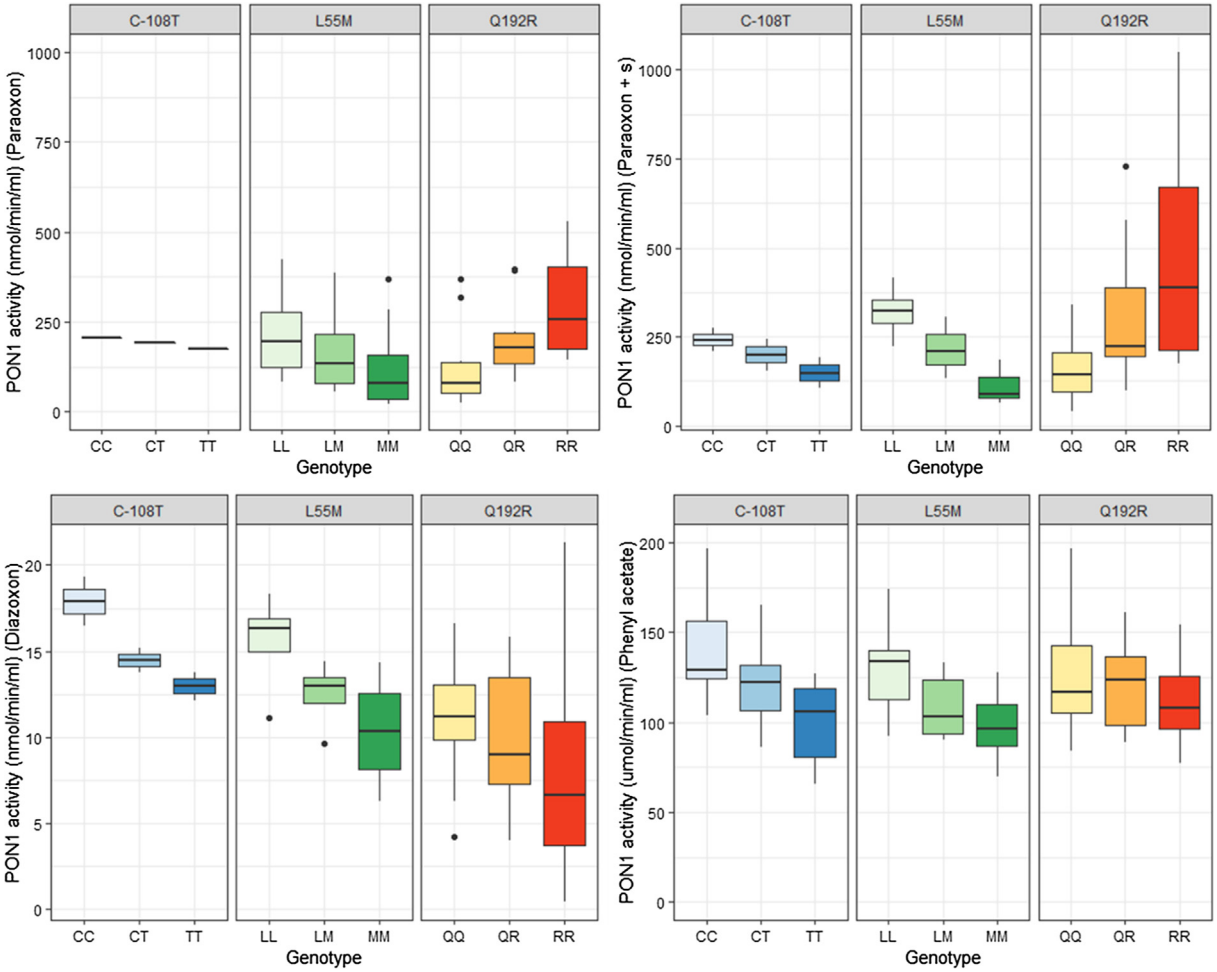

Fig. 4. Inter-phenotypic PON1 activities for major human genotypes. PON1 activity characterised by paraoxon can be divided in salt activated (Paraoxon + s) and not salt activated (Paraoxon). Number of papers included: PON1 activity characterised by paraoxon C-108T (3), L55M (11), Q192R (22); PON1 activity characterised by diazoxon C-108T (2), L55M (4), Q192R (8); PON1 activity characterised by phenyl acetate C-108T (5), L55M (7), Q192R (13).

3.2. Inter-phenotypic differences in PON1 activity and related UFs

Inter-phenotypic differences for PON1 activity in human populations were calculated without including studies with salt activation for paraoxon for the above mentioned reasons. Here, the meta-analyses were performed to quantify for inter-phenotypic differences across all populations. Overall, CV values from the meta-analyses highlight a larger variability in PON1 activity with paraoxon for the L55M genotypes (57–62%) (Table 2). PON1-related UFs across the SNPs also showed inter-phenotypic differences. The wildtypes 55LL and 108CC were considered as the reference group with the high PON1 activity, while the mutant 192RR was considered as the reference group for paraoxon. An exceedance of the default TK UF of 3.16 was observed for the wildtype 192QQ, and the mutants 55MM and 108TT, classified as a group with low PON1 activity, with respectively, 3, 2.4 and 1.2-fold differences compared with the reference groups. For the SNP C-108T, a single study was available for paraoxon and results are associated with high uncertainty and have to be taken with caution. Since salt activated studies were used for diazoxon, the estimated ratio of GM and thus the corresponding UFs were most likely overestimated. All PON1 related UFs were within the default TK UF, except for the genotype −108TT (2 studies, UF97.5 of 3.7- and 1.5- fold difference with −108CC). When considering PON1 activity towards phenyl acetate, estimated CVs were within 23–35% for all SNPs. The largest inter-phenotypic differences between SNPs were 1.5-fold between −108CC and −108TT and PON1-related factors were within the default TK UF.

3.3. Inter-individual differences in PON1 activity and related UFs

From the results of the ELS and meta-analysis, the reference population in the database is the Caucasian population since it is the most data rich. Genotypic frequencies were collected and integrated with inter-phenotypic differences in PON1 activity by means of simulations to derive PON1 variability distributions. The results indicate that the PON1-related UFs did not exceed the default TK UF for median values except for PON1 C-108T and L55M (paraoxon) for a UF97.5 (Table 3). Estimated inter-individual UFs were all lower than those estimated for inter-phenotypic UFs. PON1 variability distributions for Caucasian populations for each genotype are presented in Fig. 5.

4. Discussion and conclusion

An extensive literature search has been conducted to collect data on PON1 genotypic frequencies and activities across healthy adult world populations for three SNPs. The choice of selecting healthy human populations was related to the fact that PON1 hydrolyses phospholipid peroxides in both high-density lipoprotein and low-density lipoprotein. Bayesian meta-analysis was performed to characterise inter-phenotypic differences in PON1 activities using paraoxon, diazoxon and phenyl acetate as probe substrates and genotypic frequencies of the SNPs L55M, Q192R, and C-108T were collected and integrated to simulate PON1 variability distributions across human populations.

Inter-ethnic differences in PON1 genotypic frequencies Q192R and

Table 2
Inter-phenotypic differences in PON1 activity in healthy adult for paraoxon, diazoxon or phenyl acetate probe substrates.

PON1	ns	n	CV	GM	Ratio GM	UF95 (95% CI)		UF97.5 (95% CI)	
Paraoxon (nmol/min/ml)									
−108 CC	1	26	32	197.4		1.7	[1.4–2.6]	1.9	[1.4–3.2]
−108 CT	1	25	45	176.6	1.12	4.1	[0.8–20.0]	5.3	[1.1–25.0]
−108 TT	1	9	46	164.8	1.19	4.3	[0.8–23.0]	5.6	[1.1–30.0]
55 LL	8	1530	58	166		2.4	[2.2–2.7]	2.9	[2.6–3.2]
55 LM	8	1609	62	117.4	1.41	2.2	[1.3–3.8]	2.4	[1.4–4.1]
55 MM	8	481	57	68.4	2.43	3.8	[2.1–6.6]	4.2	[2.3–7.2]
192 QQ	10	1933	32	84.4	3.02	4.6	[2.8–7.5]	5	[3.1–8.2]
192 QR	10	1506	31	167	1.53	2.3	[1.4–2.7]	2.5	[1.6–4.1]
192 RR	10	365	26	254.7		1.5	[1.4–1.6]	1.6	[1.5–1.8]
Diazoxon (nmol/min/ml)									
−108 CC	2	55	39	16.7		1.9	[1.5–2.6]	2.1	[1.7–3.1]
−108 CT	2	81	44	13.3	1.26	2.7	[1.0–6.7]	3.1	[1.2–7.8]
−108 TT	2	54	46	11.4	1.47	3.1	[1.0–8.3]	3.7	[1.5–9.7]
55 LL	4	259	27	14.4		1.5	[1.4–1.7]	1.7	[1.5–1.9]
55 LM	4	341	21	11.9	1.21	2.1	[1.1–3.9]	2.3	[1.2–4.4]
55 MM	4	80	24	9.9	1.45	2.5	[1.3–4.8]	2.8	[1.4–5.4]
192 QQ	8	801	27	9.6		1.6	[1.5–1.6]	1.7	[1.6–1.8]
192 QR	8	699	24	8.6	1.12	1.6	[1.0–2.6]	1.7	[1.1–2.8]
192 RR	8	230	27	4.8	2	2.9	[1.8–4.6]	3.1	[2.0–4.9]
Phenyl acetate (μmol/min/ml)									
−108 CC	7	741	23	133.7		1.4	[1.4–1.5]	1.6	[1.5–1.7]
−108 CT	7	1231	26	113.9	1.17	1.4	[1.1–1.6]	1.4	[1.2–1.6]
−108 TT	7	570	35	86.7	1.54	1.8	[1.5–2.1]	1.8	[1.5–2.2]
55 LL	9	1139	26	119		1.5	[1.5–1.6]	1.7	[1.6–1.8]
55 LM	9	1289	28	101.4	1.17	1.3	[1.1–1.5]	1.4	[1.2–1.6]
55 MM	9	386	32	87.3	1.36	1.5	[1.3–1.8]	1.6	[1.3–1.9]
192 QQ	15	1523	30	118.4		1.6	[1.5–1.7]	1.8	[1.7–1.9]
192 QR	15	1425	27	113	1.05	1.2	[1.0–1.3]	1.2	[1.1–1.3]
192 RR	15	522	23	103.8	1.14	1.3	[1.1–1.4]	1.3	[1.1–1.5]

ns: number of studies, n: number of individuals, CV: coefficient of distribution (lognormal distribution), GM: geometric mean (lognormal distribution), ratio GM: ratio of geometric mean between high activity and sub-group.

Table 3
PON1-related uncertainty factors for Caucasian healthy adults integrating inter-phenotypic differences for 3 SNPs (-108 CC/CT/TT: 25/50/25%; 55 LL/LM/MM: 39/48/13%; 192 QQ/QR/RR: 53/39/8%).

PON1	CV	GM	UF95 (95% CI)		UF97.5 (95% CI)	
Paraoxon (nmol/min/ml)						
−108	44	179	3.0	[1.8–14]	3.6	[2–19]
55	79	125	2.7	[2.5–3.9]	3.3	[3–4.8]
192	53	120	2.5	[1.8–4.1]	2.8	[2–4.8]
Diazoxon (nmol/min/ml)						
−108	44	14.9	2.4	[1.9–4.8]	2.8	[2.1–5.9]
55	27	12.5	1.7	[1.4–3.1]	1.8	[1.6–3.4]
192	32	8.73	1.6	[1.5–2.1]	1.8	[1.6–2.3]
Phenyl acetate (μmol/min/ml)						
−108	32	111	1.6	[1.5–1.7]	1.7	[1.6–1.9]
55	30	106	1.6	[1.5–1.7]	1.7	[1.7–1.9]
192	28	115	1.6	[1.5–1.7]	1.7	[1.7–1.8]

CV: coefficient of distribution (lognormal distribution), GM: geometric mean (lognormal distribution), ratio GM: ratio of geometric mean between high activity and sub-group.

L55M exist, while these were not observed in the regulatory region C-108T (Ginsberg et al., 2009). This may be related to random events or selection pressure which may have acted on PON1 polymorphism to maintain specific allele frequencies across different ethnic groups (Brophy et al., 2001; Hernandez et al., 2003). It has been observed that the 55L allele has strong linkage disequilibrium with −108C and 192R alleles respectively, indicating that high PON1 activity individuals tend to have higher PON1 enzyme levels (Koda et al., 2004; Mohamed Ali and Chia, 2008). The frequency of the *PON1* 192QQ genotype is predominantly present in African, European/North American, and Middle Eastern population, indicating that these subpopulations might be more sensitive to OP toxicity as previously suggested (You et al., 2013). In Asian, and Central/South American populations, the 192RR variant is more frequently detected, which suggest potential decrease in sensitivity to OP toxicity. In addition, the highest PON1 activity toward paraoxon was measured in the *PON1* 192RR genotype in the Asian population (Kujiraoka et al., 2000; Li et al., 2009).

The PON1 activity data showed a high level of variation, especially for the L55M and C-108T genotypes, which has substantial consequences on the results of the Monte Carlo simulations. It is worth noting that PON1 activities were measured *ex vivo*, so the variability presented in the simulations is not directly reflecting oxon internal dose. In addition to PON1 activities, pharmacokinetic parameters reflecting acute exposure (Cmax) and chronic exposure (AUC, clearance) would be needed to simulate the population variability in internal dose. Median values for PON1 related UFs were derived while combining genotypic frequencies for a range of populations and PON1 variability indicated that the PON1-related UFs were generally below the default TK UF with the exception of PON1 C-108T and L55M (paraoxon UF97.5).

PON1 has been described as a good predictor of individual susceptibility to OPs toxicity (Alejo-González et al., 2018; Dardiotis et al., 2019). The meta-analysis confirmed that inter-phenotypic differences in PON1 activity have an impact on the potential susceptibility to OP toxicity in the detoxification of oxon metabolites (Costa et al., 2013). A previous meta-analysis showed that the PON1 192Q and PON1 55L alleles may increase potential susceptibility to OP toxicity for paraoxon, particularly in Caucasian populations (You et al., 2013). While our results confirm that PON1-related UFs are above the 3.16 default TK UF for the PON1 192QQ genotypes, this is not the case for the PON1 55LL genotypes. Since PON1 55MM shows a lower activity of the enzyme, susceptibility to paraoxon toxicity may increase and is indicated by an exceedance of the default TK UF. Overall, this body of evidence has

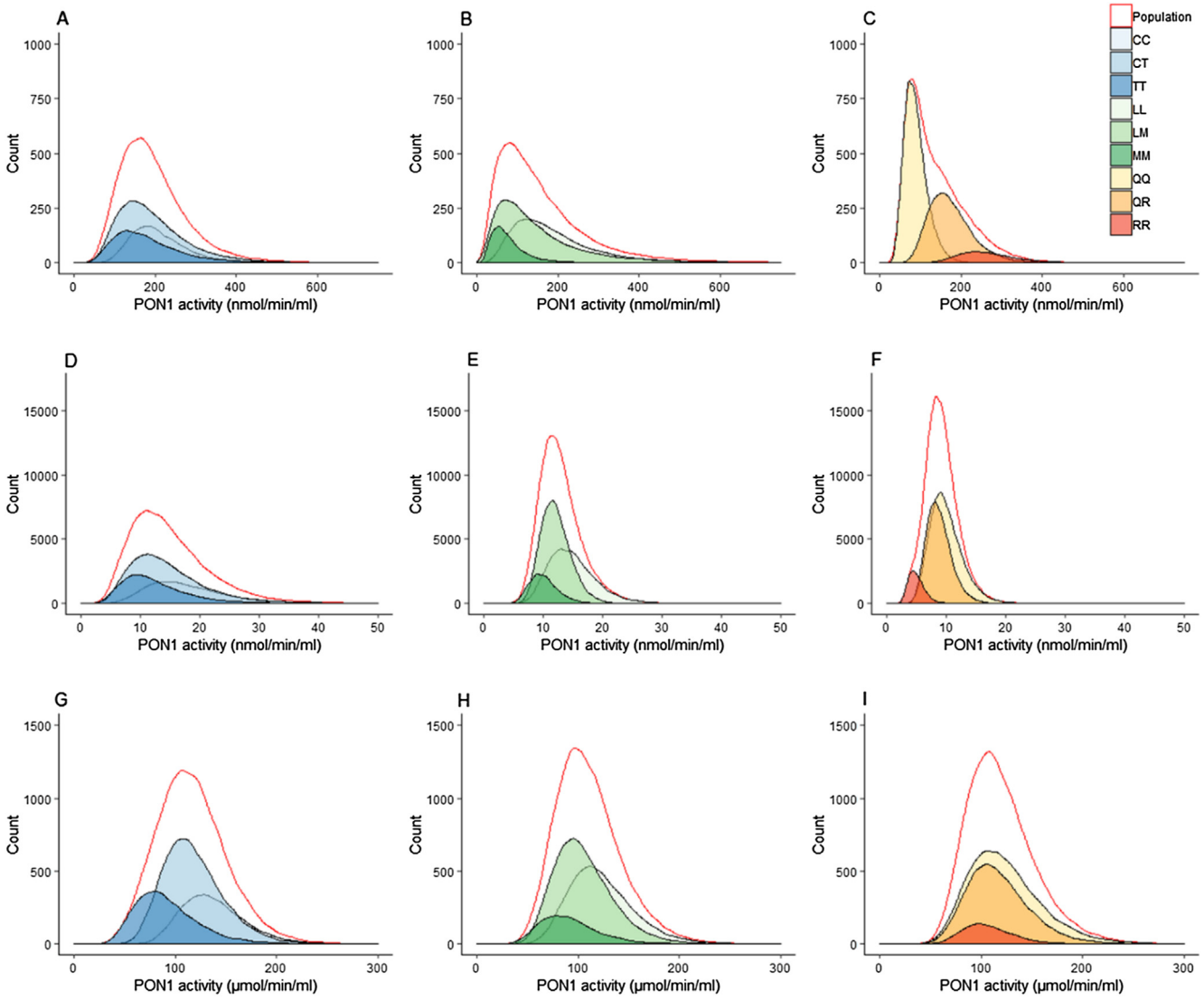

Fig. 5. An example of distribution of PON1 activity for Caucasian healthy adults (out of 18000). Simulations of PON1 activity according to different genotypic frequencies (-108 CC/CT/TT: 25/50/25%; 55 LL/LM/MM: 39/48/13%; 192 QQ/QR/RR: 53/39/8%). A, B and C: PON1 activity toward paraoxon, D, E and F: PON1 activity toward diazoxon, G, H and I: PON1 activity toward phenyl acetate.

been further demonstrated in previous analyses as a correlation between low PON1 activity and susceptibility to OP for a number of congeners (Costa et al., 2013). In contrast, PON1 activities for the R192Q SNP, using diazoxon as the probe substrate, did not conclude on an increase in susceptibility since the 192RR isoform displayed a lower activity toward diazoxon compared to that for the 192QQ SNP (Davies et al., 1996; Ginsberg et al., 2009). On the other hand, phenyl acetate hydrolysis was mostly influenced by C-108T polymorphism and to a lesser extent by L55M whereas Q192R polymorphism had almost no effect and confirms its relevance as a marker of PON1 activity in human serum (Dardiotis et al., 2019). It has been hypothesised that the observed differences in PON1 activity for various substrates may arise from differences in docking sites on the enzyme. Chlorpyrifos-oxon binds similar sites as paraoxon, where the 192R and 55 M alleles are the most active (Albers et al., 2010; Costa et al., 2013; Ellison et al., 2012; Ginsberg et al., 2009). On the other hand, diazoxon share the same docking sites as sarin and soman for which individuals expressing the 192Q allele are potentially more sensitive to their toxicity (Davies et al., 1996). Based on the available data, the genotype alone is not sufficient to determine individual susceptibility to OP toxicity for a range of congeners and inter-phenotypic differences together with substrate-specific information about the specific substrate would be most appropriate to characterise such susceptibility. It is foreseen that as compound specific docking information becomes readily available, PON1 variability distributions (or UF) can be integrated to characterise susceptibility to OP toxicity bearing in mind the limitation that PON1 crystal structure remains to be elucidated (Dardiotis et al., 2019).

Although exclusion criteria have been defined to limit possible bias in the meta-analysis due to technical aspects of the PON1 assay itself or to the lifestyle of the enrolled individuals, PON1 activities have been measured *ex vivo* and can be influenced by sources of variability other than genotypes (Ceron et al., 2014; del Carmen Xotlanihua-Gervacio et al., 2019; Ginsberg et al., 2009). Nonetheless, 65–92% of the variability in PON1 activities can be rationalised through inter-phenotypic differences, while lifestyle contributed only for 6% to such variability (Rainwater et al., 2009). In addition, *in vivo* studies suggest, that differences in serum PON1 phenotypes are relevant for predicting the sensitivity of high chlorpyrifos-oxon concentrations (Coombes et al., 2014; Li et al., 2000). However, at environmentally relevant concentrations, reported in the nanomolar range, no significant differences were found in the hydrolysis of chlorpyrifos-oxon between PON1 192 SNPs (Coombes et al., 2014).

In addition to PON1 polymorphisms, it is suspected that variability in Acetylcholinesterase (AChE) activity, breaking down esters of choline molecules, may influence OP toxicity as they are specific inhibitors of AChE (Lionetto et al., 2013). The AChE gene is well conserved in humans and has almost no loss of function via mutations; the most frequent AChE variant being His353Asn, resulting in a phenotype with normal activity (Lockridge et al., 2016). PON1 is closely located (5.5 Mb) to the AChE gene on chromosome 7 and it has been suggested that interactions between the AChE and PON1 occur and that the two genes are regulated on the same locus region. In addition, it has been shown that individuals with high PON1 activities had lower AChE activities whereas individuals with low PON1 activities had higher AChE activities. This has been explained for scenarios of low OP exposure under which AChE is inhibited in individuals with low PON1 levels, resulting in an upregulation of AChE. In individuals with high PON1 activity the degree of AChE inhibition will be minor with no consequence on upregulation of the enzyme, resulting in low plasma levels (Akgür et al., 1999; Bryk et al., 2005).

For Butyl Cholinesterase (BChE), more variants lead to lower BChE activity compared to the wildtype. However, it has been shown that OP inhibition of BChE by up to 85% did not result in any clinical signs and therefore it is unlikely that BChE (and genetic variants herein) contributes to OP toxicity (Lockridge et al., 2016; Nolan et al., 1984). Overall, the observed variability in the susceptibility to OP toxicity has been shown to be based mainly on inter-individual differences in PON1, cytochrome P450, and glutathione-s transferase activities so that variability in TK processes seem to be the driving variable to the toxicodynamics (TD) of OPs (Lockridge et al., 2016). It is proposed that future research would aim at unravelling human variability in AChE inhibition of after exposure to OPs, besides the variability in baseline activity. However, it is rather difficult to measure the TD contribution alone in *in vivo* studies, since TK variability is most often accounted for. Nevertheless, variability in the reactivation of AChE after exposure to OPs has been shown and has been used to parameterise physiologically based toxicokinetic-toxicodynamic models for chlorpyrifos and other OPs (Poet et al., 2017). Blood has been sampled and the inhibition and spontaneous reactivation of AChE has been measured *in vitro* together with variation in reactivation half-life (Mason et al., 2000). Data on TD and differences in AChE binding affinity to OPs are scarce, and more data should be generated to estimate inter-individual differences in this parameter.

The results of this meta-analysis provided inter-phenotypic and inter-individual differences distributions for PON1 activities and PON1-related UFs. Variability distributions can be implemented in generic physiologically based kinetic models to derive internal concentrations of chemicals. This would allow to model inter-individual differences in potential sensitivity to OP toxicity for chemical risk assessment purposes. Furthermore, variability distributions can provide inputs for the calibration of human quantitative *in vitro in vivo* extrapolation (QIVIVE) models. This approach has the advantage to integrate isoform-specific metabolism information and human variability distributions for chemical risk assessment. PON1-related UFs provides an intermediate option between CSAF and the default UF when chemical-specific data are not available (Bhat et al., 2017; Clewell et al., 2008). Overall, inter-phenotypic differences in PON1 activity are important for chemical risk assessment.

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CRediT authorship contribution statement

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

Declaration of Competing Interest

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

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105609.

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