An assessment of the impact of multi-route co-exposures on human variability in toxicokinetics: A case study with binary and quaternary mixtures of volatile drinking water contaminants

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RESEARCH ARTICLE

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An assessment of the impact of multi-route co-exposures on human variability in toxicokinetics: A case study with binary and quaternary mixtures of volatile drinking water contaminants

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Outline

- Background
- PBPK modeling
- Objective
- Methods
- Results
- Discussion/Conclusions

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Background

- **Guideline values (GV) are derived from single exposure data:**

$$GV = \frac{POD}{UF_H \times UF_A \times UF_{SC} \times UF_L}$$

- **Default factor for human variability**
  - $UF_H = 10 = 3.16\ (UF_{H\_TK}) \times 3.16\ (UF_{H\_TD})$
- **UF_{H_TK} can also be based on data**

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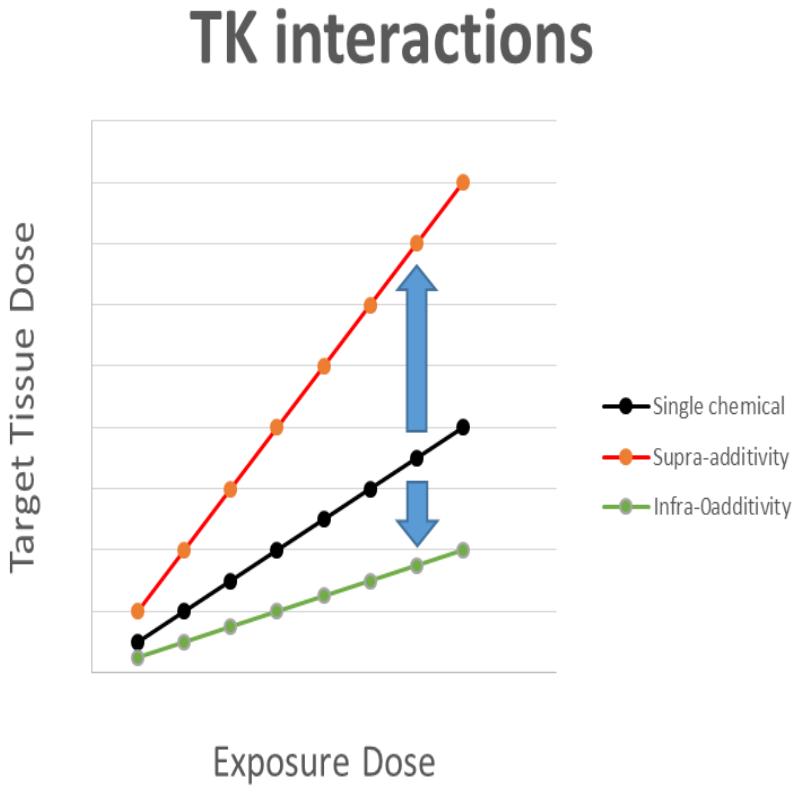
Background

- Exposures to VOCs in drinking water contaminants : Mixtures & Multiroute
  - Mixtures : Co-exposures can vary internal doses (interactions), mainly metabolic inhibitions for VOCs (CYP2E1 substrates):

⇒ assessable by PBPK modeling



PBPK: modeling of mixtures

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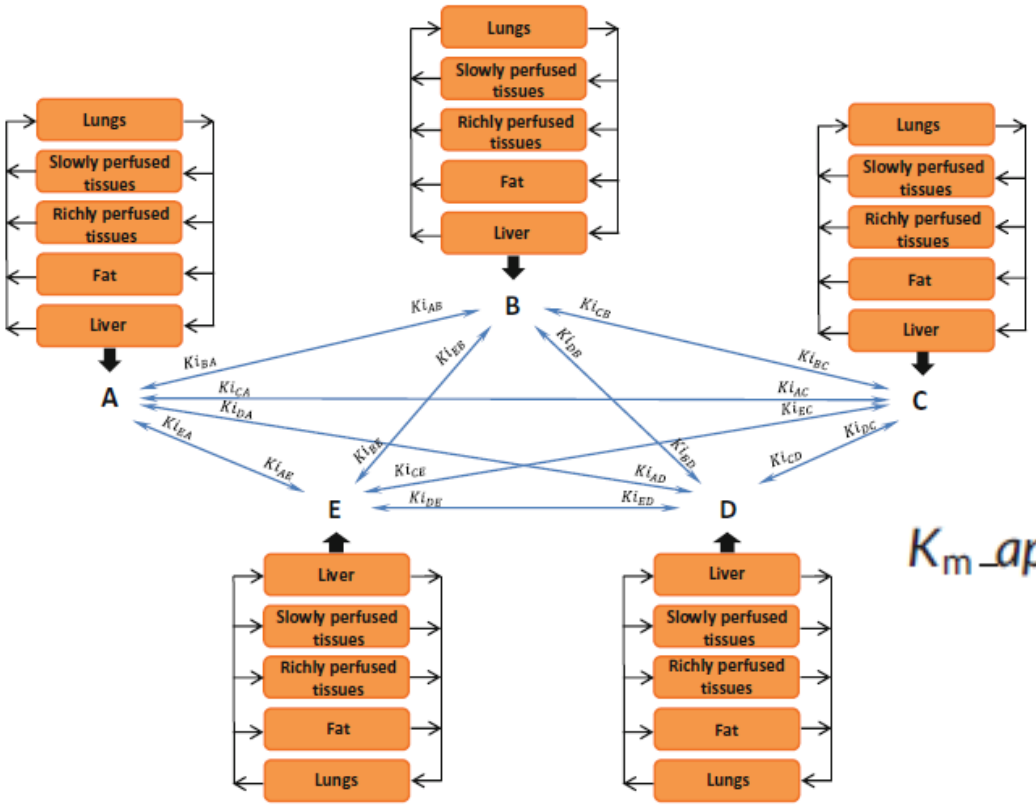
- **PBPK modeling of mixtures**



$$K_{m\_app} = K_m \left(1 + \sum_{i=1}^{n} \frac{[I]_i}{Ki_i}\right)$$

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PBPK: probabilistic modeling of mixture

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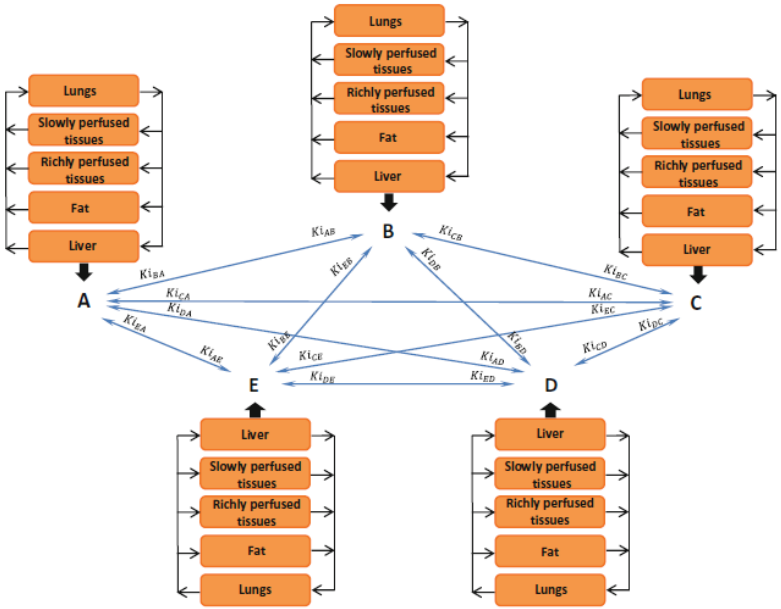
- Impact of VOCs co-exposures on variability previously investigated only for inhalation exposure (Valcke & Haddad, 2015)



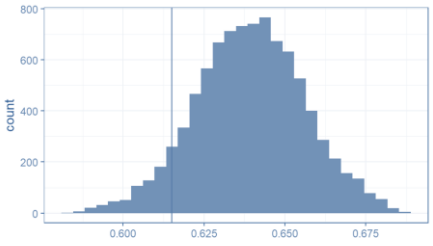
- **Variability**

Physiological

Physicochemical

Biochemical

Monte Carlo simulations



Concentrations

- Magnitude of impact depends on exposure levels, subpopulations and IDM.
- Additional routes (dermal and ingestion): impact on variability ? ⇒ **unknown**

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Objective

- **To assess multi-route co-exposure to chemicals on interindividual variability in toxicokinetics, for both ‘’high” and ‘’low” exposure levels**

  - **Binary mixture: TCE & vinyl chloride**
  - **Quaternary mixture: BTEX**

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Methods

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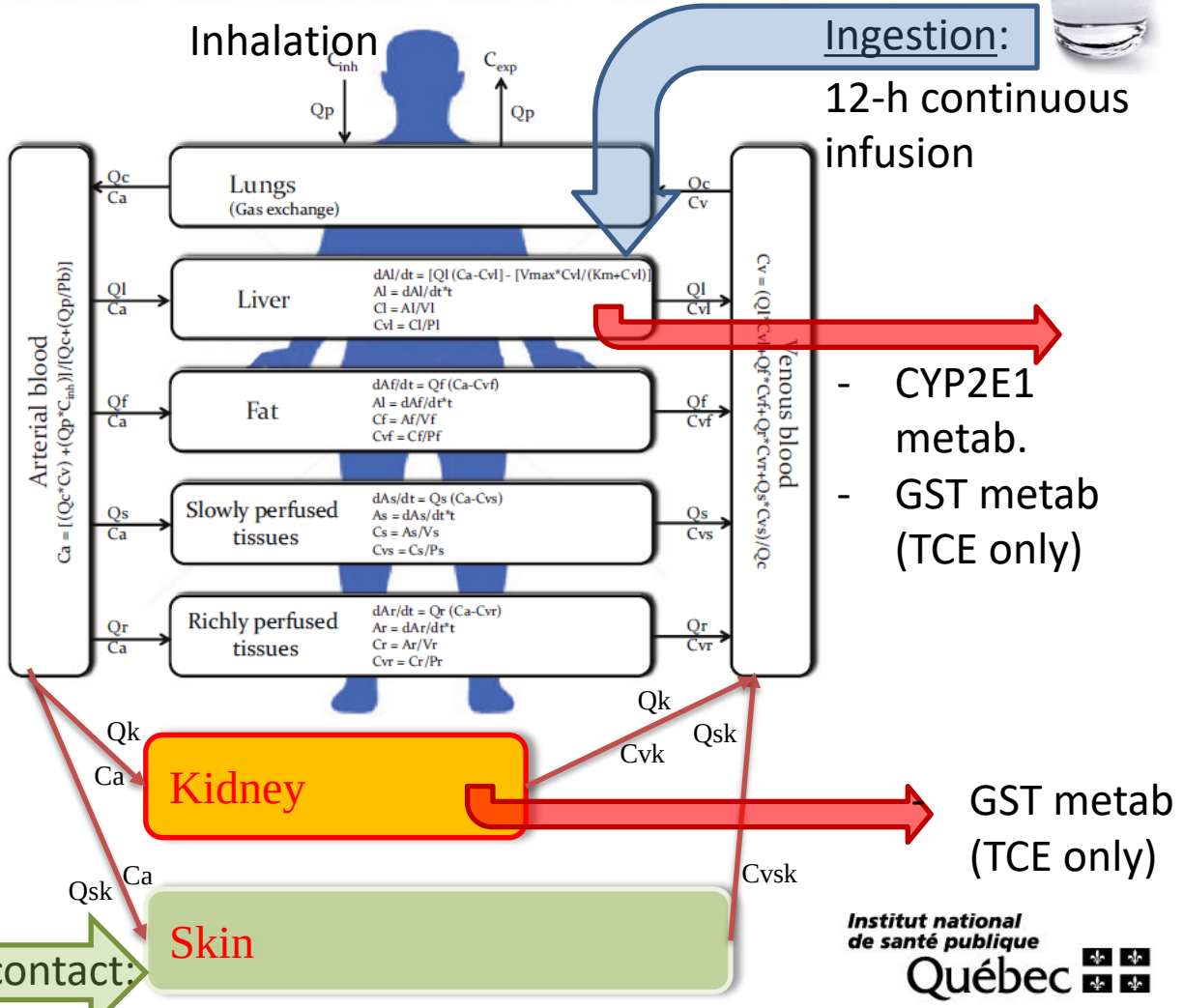
Methods: Exposure scenarios

Probabilistic PBPK multi-route interactions models

- Adults & subpopulations
  - 2-6 mo,
  - 7-24 mo
  - 2-10 yrs
  - 11-17 yrs



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Methods: model features

- **Physiological Parameters:**
  - Equations obtained from literature
- **Variability terms**
  - Q_c, Q_{alv}, Q_{fat}, Q_{liver} and V_{liver}
- **Adjustment of metabolic capacity:**

$$Vmax_{adj} = \frac{Vmax_C}{[CYP2E1]_{ad} \times Vl_{ad}} \times [CYP2E1]_{ind} \times Vl_{ind}$$

(Nong et al., TAP, 2006)

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Methods: model features

➢ Inter-group « physicochemical variability »

- ❖ Correction factors (*CF*) on tissue/air partition coefficients for subgroups (y) other than adults (a), based on tissue's volume and fraction of lipid (*FL*) and water (*FW*)
  - ✓ Adipose tissue and skin:

$$CF = \frac{K_{ow}.FLT_y + FWT_y}{K_{ow}.FLT_a + FWT_a}$$

  - ✓ Rest of the body (Pr):

$$P_{ry} = \frac{V_{heart} \cdot P_{ra} + V_{tongue} \cdot P_{ra} + V_{muscle} \cdot P_{ra} \cdot CF}{V_{ry}}$$

(Haddad et al., JTEH$_A$, 2006)

➢ Intra-group « physicochemical variability »

- ❖ Coefficients of variation for toluene (Tardif et al. (2002))

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Methods: physico-chemical parameters

Parameters	Contaminants					
	Bz	T	E	m-X	TCE	VC
Physicochemical parameters						
Molecular weight (g/mol)	78.11[a]	92.13[e]	106.17[g]	106.16[i]	131.39[j]	62.5[o]
Water/air partition coefficient	0.227[b]	0.272[b]	0.322[b]	0.271[b]	0.83[k]	1.14[b]
Transfer efficiency in the shower stall	0.498[c]	0.464[c]	0.437[c]	0.437[c]	0.61[l]	0.66[c]
Biochemical parameters						
V_{max}c (µg/min/kg 0.75)	35.17[d]	57.33[d]	106.5[d]	108.17[d]	166.67[k]	66.17[p]
K_m^s (µg/L)	100[d]	130[d]	1040.0[d]	450[d]	1500[k]	40[p]
K_i^s (µg/L)						
αB	–	140[d]	260[d]	220[d]	–	–
αT	220[d]	–	170[d]	330[d]	–	–
αE	630[d]	950[d]	–	1670[d]	–	–
αX	230[d]	360[d]	510[d]	–	–	–
αTCE	–	–	–	–	–	1500[q]
αVC	–	–	–	–	40[m]	–
V_{max}GSTI^s (µg/min)	–	–	–	–	1600[n]	–
K_mGSTI^s (µg/L)	–	–	–	–	2900[n]	–
V_{max}GSTk^s (µg/min)	–	–	–	–	2833[n]	–
K_mGSTk^s (µg/L)	–	–	–	–	2600[n]	–
Physiological parameters						
Fraction^s of metabolism in TCA	–	–	–	–	0.18[n]	–
Volume of distribution of TCA	–	–	–	–	(0.1 × BW)[k]	–
Dermal absorption constant^s (K_p, cm/min)	0.0013[a]	0.0002[f]	0.02[h]	0.004[i]	0.002[k]	0.00009[r]

Methods: exposure scenarios

Concentrations in drinking water (mg/L) and air (µg/m³)

McKone and Knevzovitch 1991

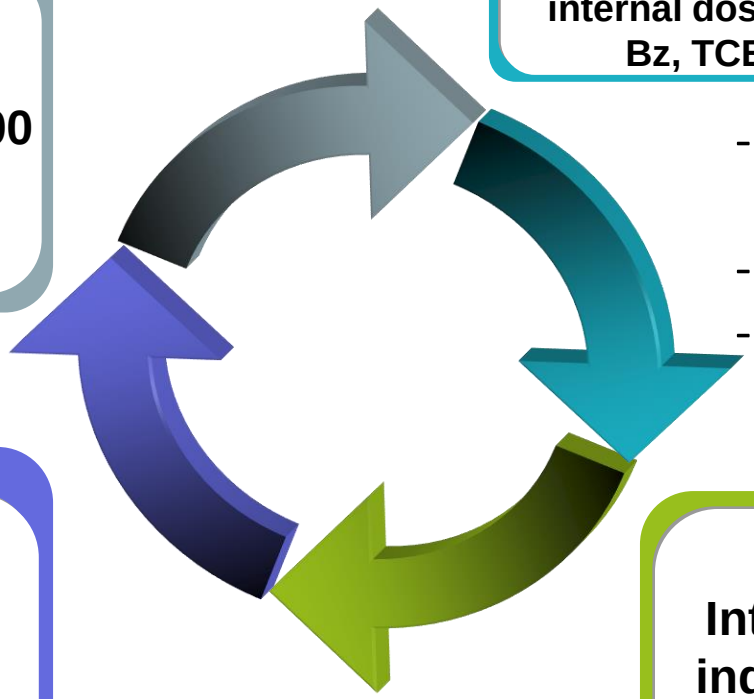
	Scenario	Quarternary exposure				Binary exposure	
		Bz	Tol	Eth-Bz	M-Xyl	TCE	VC
« LOW »	1	0.2; 17.3	0; 0	0; 0	0; 0	-	-
	2	0.2; 17.3	20; 3610	30; 228	40; 30	-	-
	3	-	-	-	-	0.2; 1.2	0; 0
	4	-	-	-	-	0; 0	3; 32
	5	-	-	-	-	0.2; 1.2	3; 32
« HIGH »	6	2; 173	0; 0	0; 0	0; 0	-	-
	7	2; 173	200; 36100	300 (2281)	400; 304	-	-
	8	-	-	-	-	2; 12	0; 0
	9	-	-	-	-	0; 0	30; 318
	10	-	-	-	-	2; 12	30; 318

Methods: simulation approach

(1)
PBPK models built combined with 10,000 Monte Carlo simulations

(2)
Distributions of relevant internal dose metrics for Bz, TCE and VC

- **AUC, parent compound**
- **$Amet_{CYP2E1}$**
- **$Amet_{GST}$ (TCE only) kidney + liver**



(3)
Inter-group variability indexes (VI) computed for the ''low'' (VI_L) and ''high'' (VI_H) exposure scenarios…

(4)
…as the ratio between the 95th percentile in each subpopulation over the median in adults

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Results

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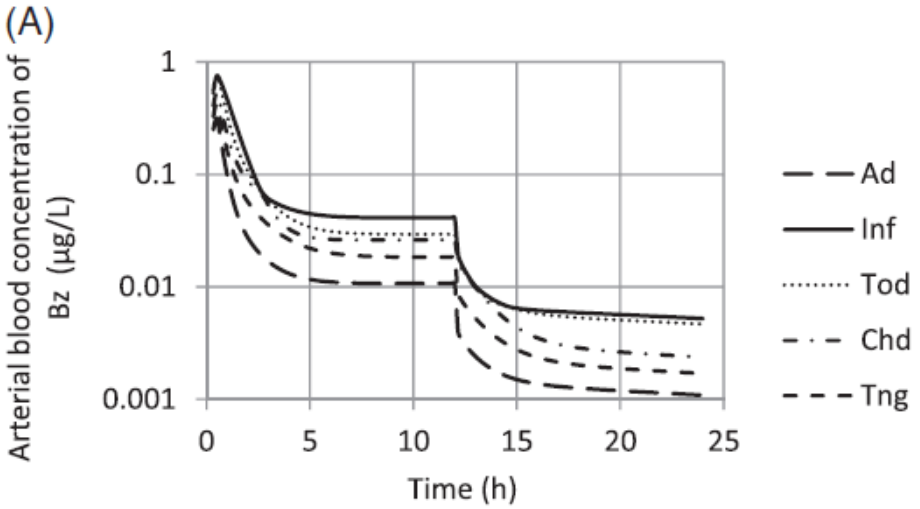
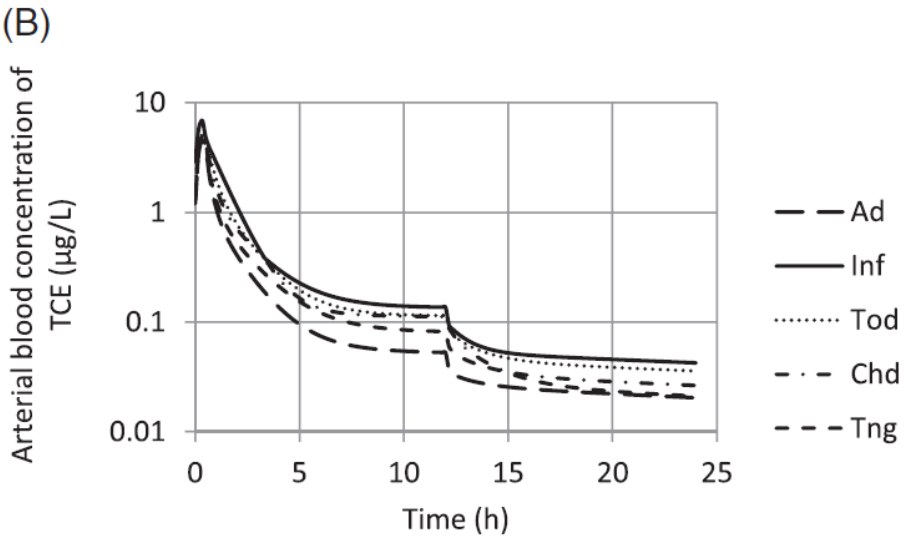
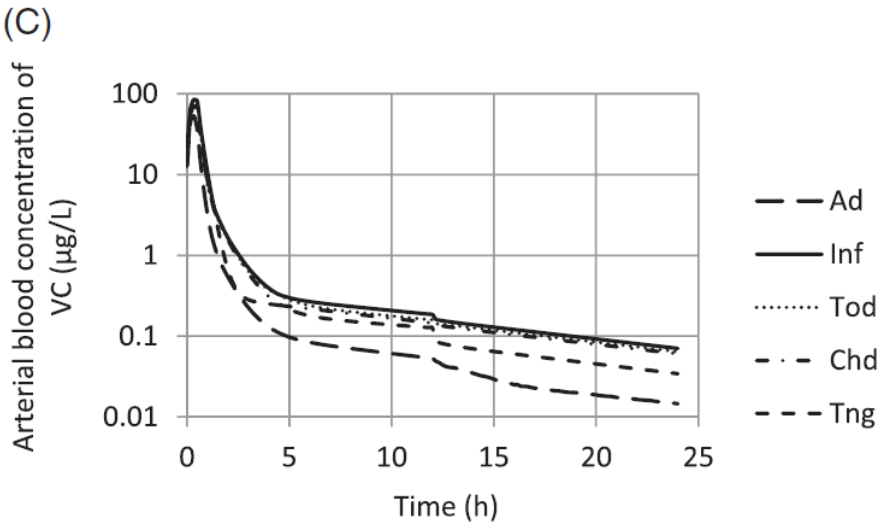
Results: simulation profiles

- « Low » exposure scenarios:

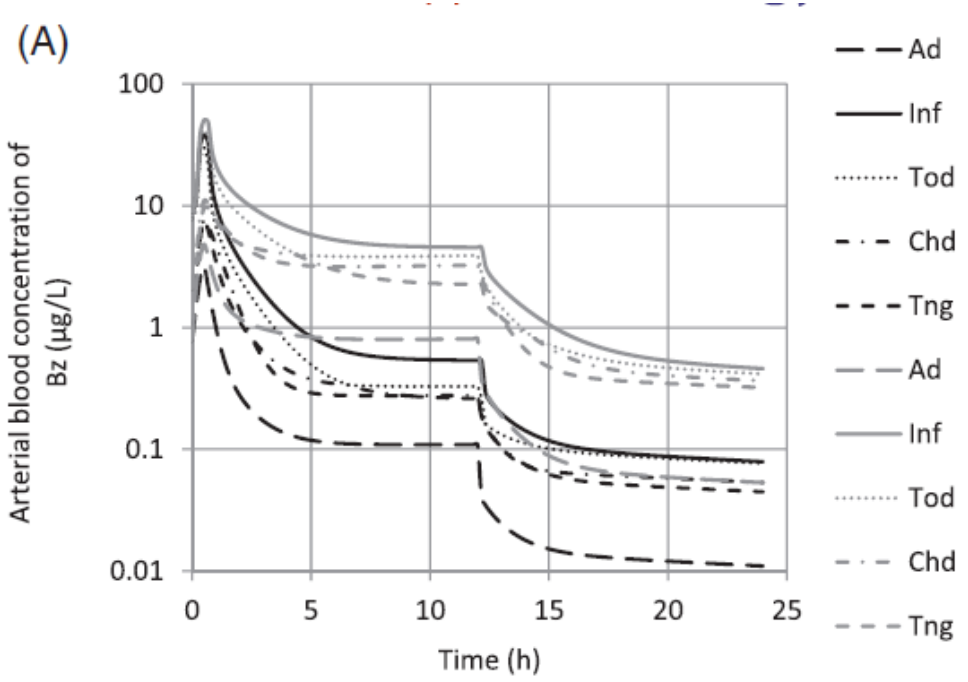


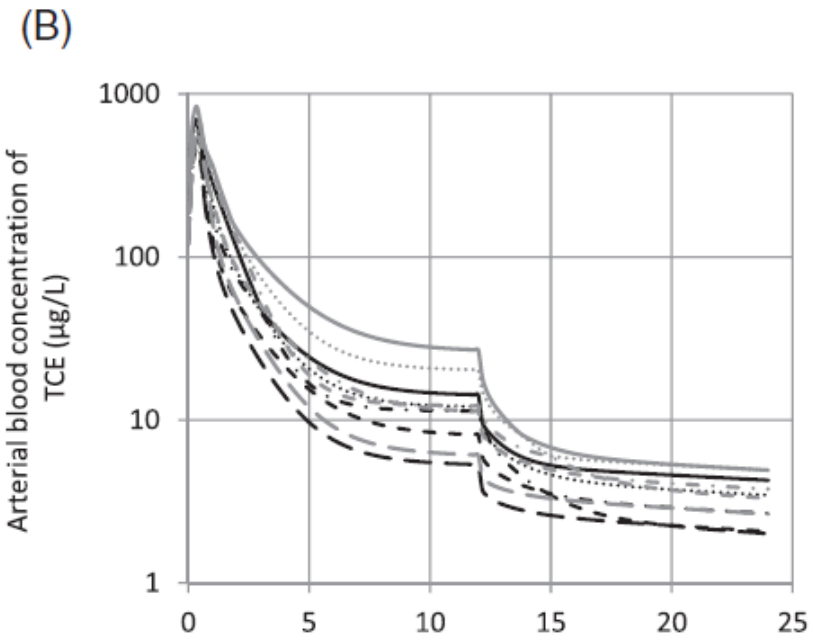


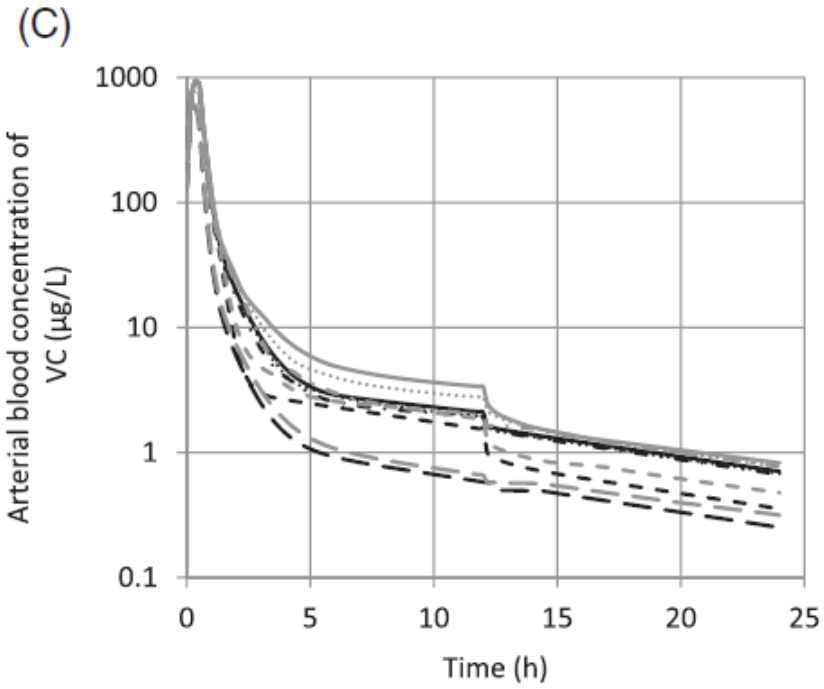


Results: simulation profiles

- « High » exposure scenarios:







Results: variability indices (VI)

Subgroup	Outcome	Benzene alone		Quaternary mixture (BTEX)		Vinyl chloride alone		Binary mixture (with TCE)	
		AUC µg.24h/L	Amet µg/24h.L_t	AUC µg.24h/L	Amet µg/24h.L_t	AUC µg.24h/L	Amet µg/24h.L_t	AUC µg.24h/L	Amet µg/24h.L_t
Adults (median IDM)	L_{IDM}	23	81	26	77	1925	1680	1925	1680
	H_{IDM}	230	1587	345	228	5854	3046	6319	2823
Infants	VI_L	2.8	2.1	3.1	1.9	2.2	1.4	2.2	1.4
	VI_H	**3.5**	2.4	**4.1**	1.6	2.3	1.5	2.5	1.3
Toddlers	VI_L	2.5	2.5	2.8	2.3	2.1	1.6	2.1	1.6
	VI_H	3.2	2.6	**3.7**	1.8	2.2	1.8	2.4	1.5
Children	VI_L	2.3	2.0	2.5	1.9	1.9	1.3	1.9	1.3
	VI_H	3.0	2.3	**3.5**	1.5	2	1.4	2.3	1.2
Teenagers	VI_L	1.7	1.6	1.9	1.5	1.6	1.1	1.6	1.1
	VI_H	2.5	2.1	2.9	1.3	1.8	1.3	2.1	1.1

Amet: amount metabolized by CYP2E1 per L of liver ; **AUC**, area under the curve; **H**, « high » exposure scenario; **IDM**, internal dose metric; **L**, « low » exposure scenario

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Results: changes in VI

Subgroup	Outcome	Quaternary mixture (BTEX) Benzene dose metrics		Binary mixture (VC with TCE) Vinyl chloride dose metrics	
		AUC µg.24h/L	Amet µg/24h.L_t	AUC µg.24h/L	Amet µg/24h.L_t
Infants	VI_L	+11%	-9.5%	≈	≈
	VI_H	+17%	-33%	+8.7%	-13%
Toddlers	VI_L	+12%	-8%	≈	≈
	VI_H	+16%	-31%	+9.1%	-17%
Children	VI_L	+8.7%	-5%	≈	≈
	VI_H	+17%	-35%	+15%	-14%
Teenagers	VI_L	+12%	-6.3%	≈	≈
	VI_H	+16%	-38%	+17%	-15%

Amet: amount metabolized by CYP2E1 per L of liver ; **AUC**, area under the curve; **H**, « high » exposure scenario; **IDM**, internal dose metric; **L**, « low » exposure scenario

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Results: variability indices (VI)

Subgroup	Outcome	TCE alone				TCE in binary mixture with VC (TCE dose metrics)			
		AUC µg.24h/L	Amet µg/24h.L_t	A_{GST_k} µg/24h.L	A_{GST_k+l} µg/24h.L_t	AUC µg.24h/L	Amet µg/24h.L_t	A_{GST_k} µg/24h.L_	A_{GST_k+l} µg/24h.L_t
Adults (median IDM)	L_{IDM}	371	81	26	77	1925	1680	1925	1680
	H_{IDM}	3780	1587	345	228	5854	3046	6319	2823
Infants	VI_L	1.8	1.6	1.5	1.5	1.8	1.6	1.5	1.5
	VI_H	2.0	1.7	1.6	1.6	2.3	1.5	1.8	1.8
Toddlers	VI_L	1.6	1.8	1.7	1.7	1.6	1.8	1.7	1.7
	VI_H	1.7	1.8	1.8	1.8	1.9	1.6	2.0	2.0
Children	VI_L	1.5	1.5	1.4	1.4	1.5	1.5	1.4	1.4
	VI_H	1.5	1.6	1.5	1.5	1.7	1.4	1.7	1.7
Teenagers	VI_L	1.2	1.3	1.2	1.2	1.2	1.3	1.2	1.2
	VI_H	1.3	1.5	1.3	1.3	1.5	1.2	1.5	1.5

A_{GST}, amount metabolized in kidney (k) or liver (l) by GST, per tissue volume**; Amet**, amount metabolized by CYP2E1 per volume of liver; **AUC**, area under the curve; **H**, « high » exposure scenario; **IDM**, internal dose metric; **L**, « low » exposure scenario

Results: changes in VI

Subgroup	Outcome	TCE in binary mixture witn VC (TCE dose metrics)			
		AUC µg.24h/L	Amet µg/24h.L_t	$Amet_{GST\_k}$ µg/24h.L_t	$Amet_{GST\_k+l}$ µg/24h.L_t
Infants	VI_L	≈	≈	≈	≈
	VI_H	+15%	-12%	+13%	+13%
Toddlers	VI_L	≈	≈	≈	≈
	VI_H	+18%	-11%	+11%	+11%
Children	VI_L	≈	≈	≈	≈
	VI_H	+13%	-13%	+13%	+13%
Teenagers	VI_L	≈	≈	≈	≈
	VI_H	+15%	-20%	+15%	+15%

A_{GST}, amount metabolized in kidney (k) or liver (l) by GST, per tissue volume**; Amet**, amount metabolized by CYP2E1 per volume of liver; **AUC**, area under the curve; **H**, « high » exposure scenario; **IDM**, internal dose metric; **L**, « low » exposure scenario

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Discussion and conclusion

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Discussion

- **First investigation of the impact of multi-route co-exposure on the magnitude of TK variability**
- **TK variability, for co-exposures:**
  - AUC, GST metabolism (A_{GST}) : increase
  - CYP2E1 metabolism (Amet): decrease

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Discussion

- **Threshold for metabolic interactions ? (c.f. Dobrev et al., 2001, 2002)**
  - Bz: both « low » and « high » exposure levels
  - VC and TCE: « high » exposure levels only
  - Are « high » exposure levels environmentaly-relevant?
- **Substance-specific consideration: Ki/Km ratio**
  - Bz: ≤ 6.3; VC: 37.5 ⇒ Bz potentialy « more susceptible » to competitive inhibition of CYP2E1 metabolism?
  - TCE: < 1, but compensatory secondary low affinity/high capacity pathway (GST)

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Discussion

- **Adjustment factors considerations: non-cancer risk**
  - « High » exposure levels:
    - AUC-based VI for Bz > 3.2 for infants
    - AUC-based VI for Bz going from ≤ 3.2 (Bz alone) to > 3.2 (quaternary mixture) in toddlers and children
  - Should **CSAF/DDEF**s be examined under the hypothesis of multiple exposures (environmental settings)?
  - But… multi-route exposure vs CSAF/DDEF?

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Discussion

➢ Adjustment factors considerations: cancer risk

- ❖ **Child-to-adult (ADAF)**: GST metabolites of TCE in kidney; CYP2E1 metabolites of VC in liver:

	Ratio (single exposure; mixture)			
	infant	toddlers	children	teenagers
TCE: $Amet_{GST\_kid}$				
Low exp.	1.3; 1.3	1.5; 1.6	1.2; 1.2	1; 1
High exp.	1.4; 1.6	1.6; 1.7	1.2; 1.4	1.1; 1.2
VC: $Amet_{CYP2E1}$				
Low exp.	1.3; 1.3	1.5; 1.5	1.2; 1.2	1;1
High exp.	1.4; 1.2	1.7; 1.4	1.3; 1.1	1.2; 1

Only an « inter-subpopulation » variability factor:

$$\frac{Median\_subgroup}{Median\_adult}$$

vs √10 = 3.16 **vs √3 = 1.73**

…as ADAF encompasses both TK and TD

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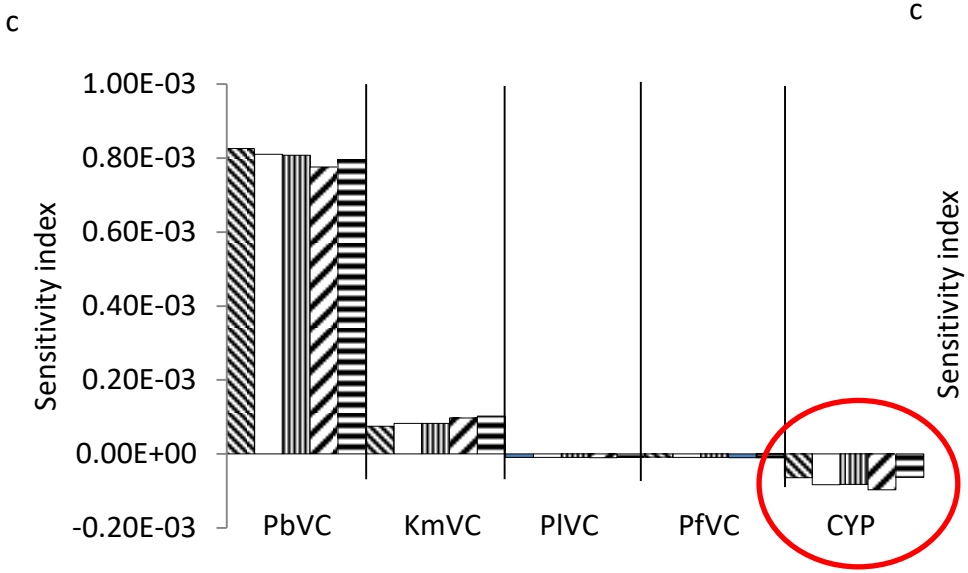
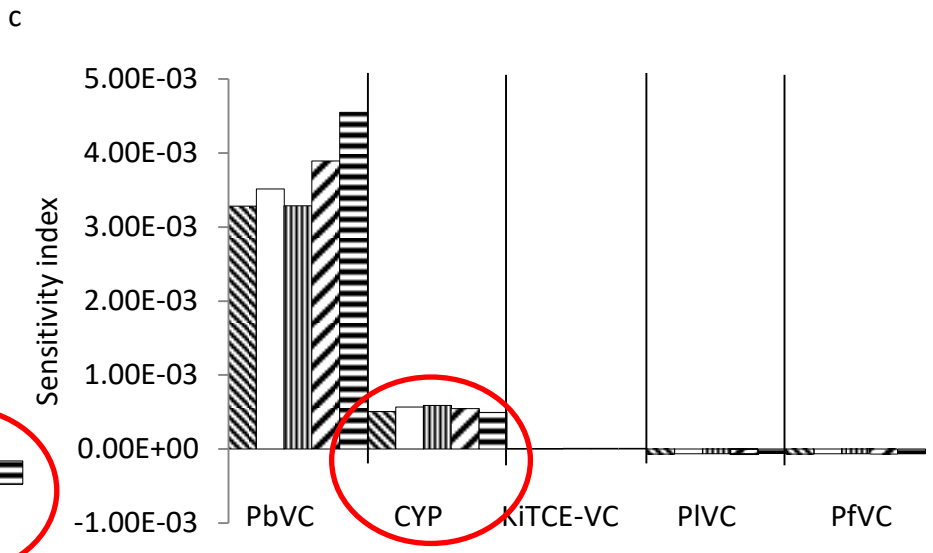
Discussion: local sensitivity analyses (ex.: vinyl chloride)

⇒ Important role of invariant Pb:a… and age-specific [CYP2E1]

- **AUC**



- **Amet**



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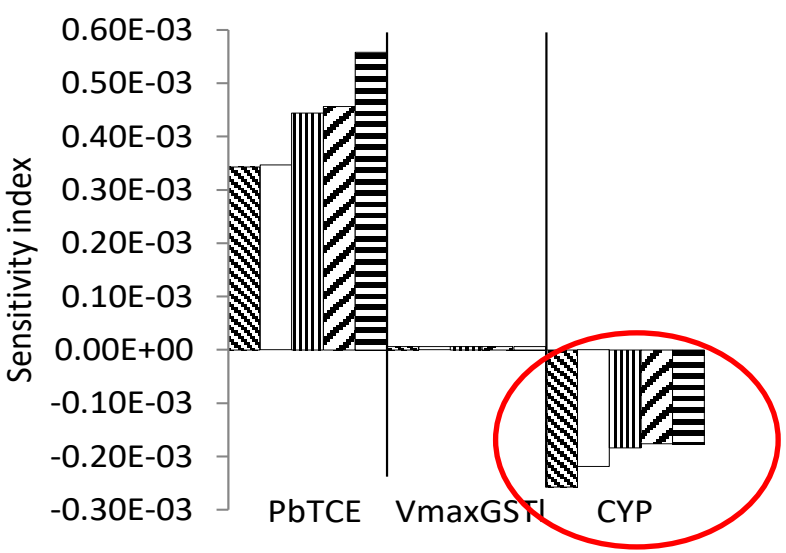
Discussion: local sensitivity analyses (TCE)

⇒ Important role of invariant Pb:a… and age-specific [CYP2E1]

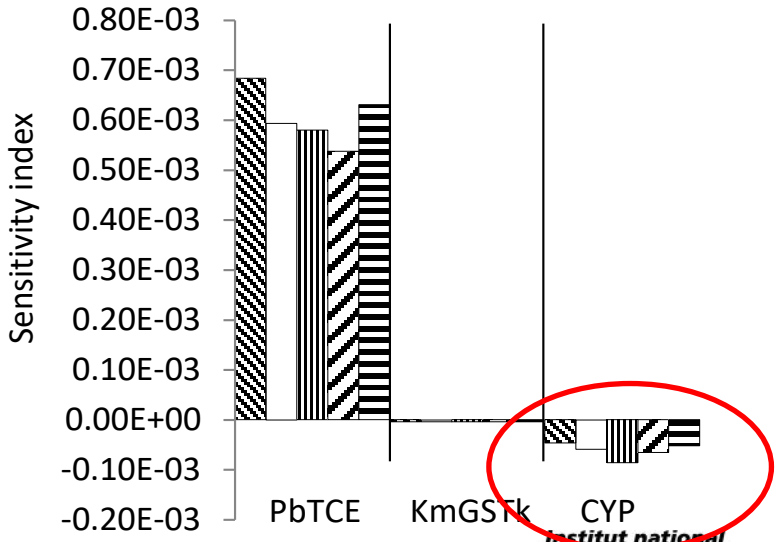
- $Amet_{GST}$(liver)

a



- $Amet_{GST}$ (kidney)

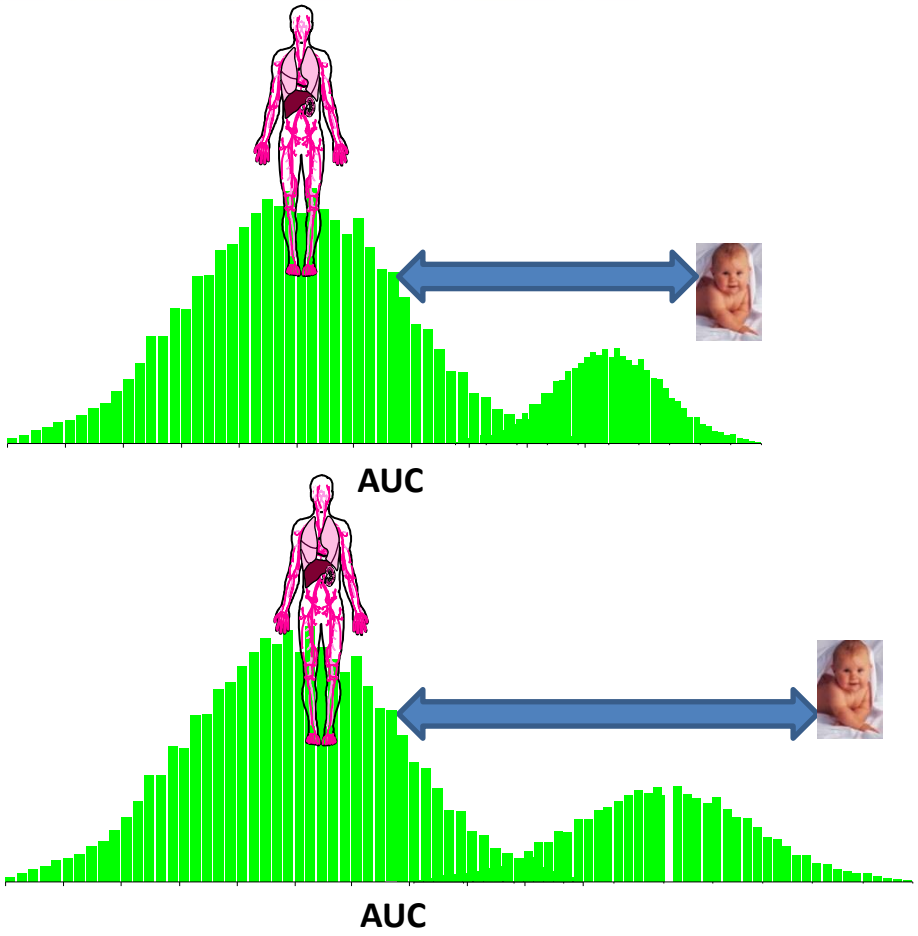
b



Discussion: hypotheses

- **Consideration of the subgroup-specific CYP2E1 metabolic capacity**
  - CYP2E1-depleted subgroups further affected by competitive inhibition ⇒ increased relative sensitivity

    ⇒ ↑ variability based on AUC



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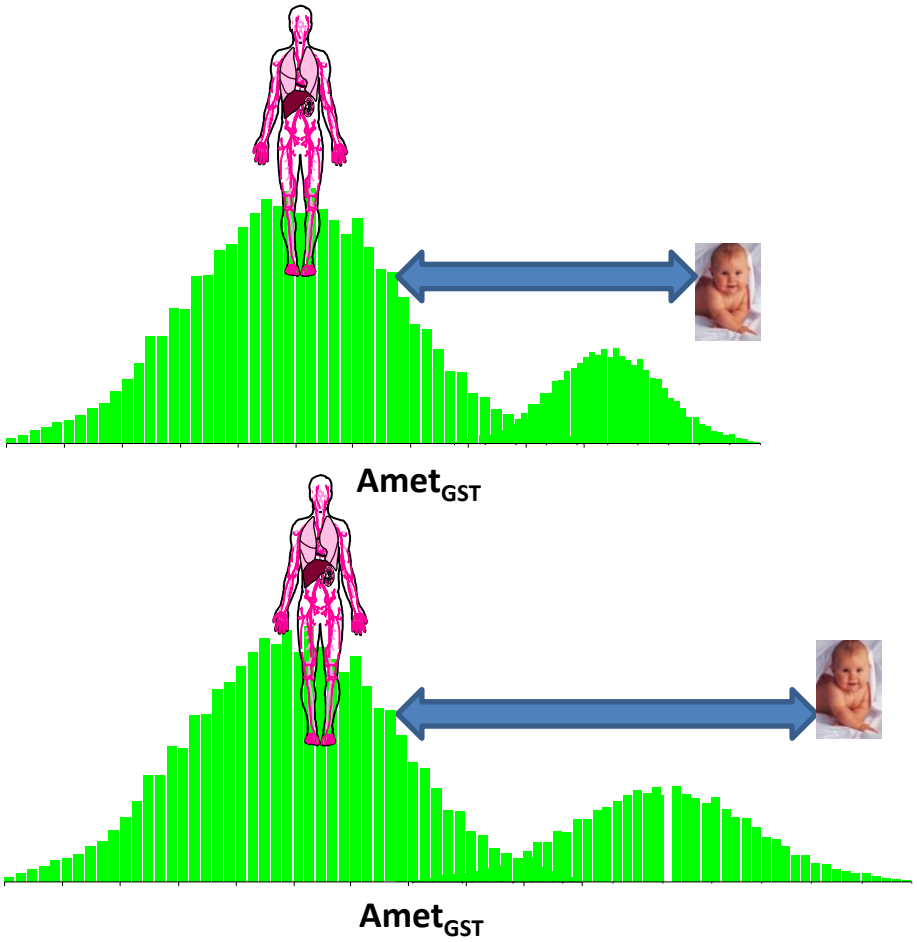
Discussion: hypotheses

- **Consideration of the subgroup-specific CYP2E1 metabolic capacity**
  - For TCE, the shift toward low affinity/high capacity GST metabolism is greater in CYP2E1-depleted subgroups :

    $\Rightarrow \uparrow$ variability based on $Amet_{GST}$



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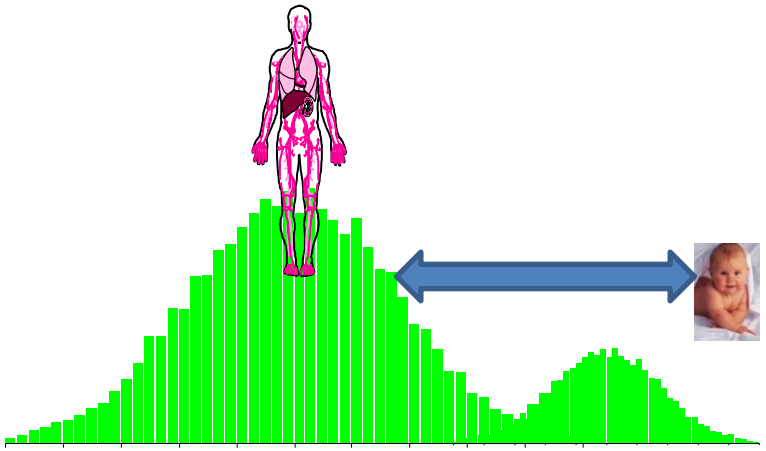
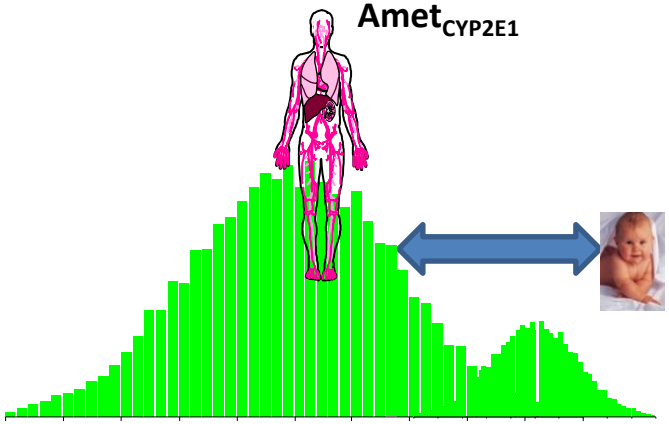
Discussion: hypotheses

- **Consideration of the subgroup-specific CYP2E1 metabolic capacity**
  - Opposite trend based on CYP2E1-mediated Amet, as even lesser metabolites are generated in CYP2E1-depleted subgroups.
  - But… no age-related trends in the % of variation on variability indices



$Amet_{CYP2E1}$



$Amet_{CYP2E1}$

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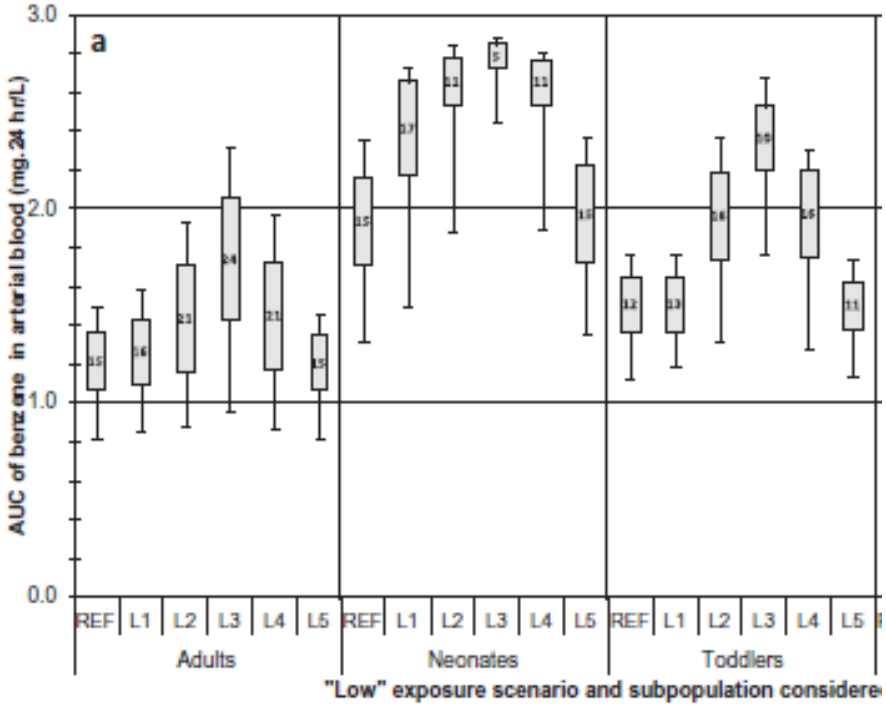
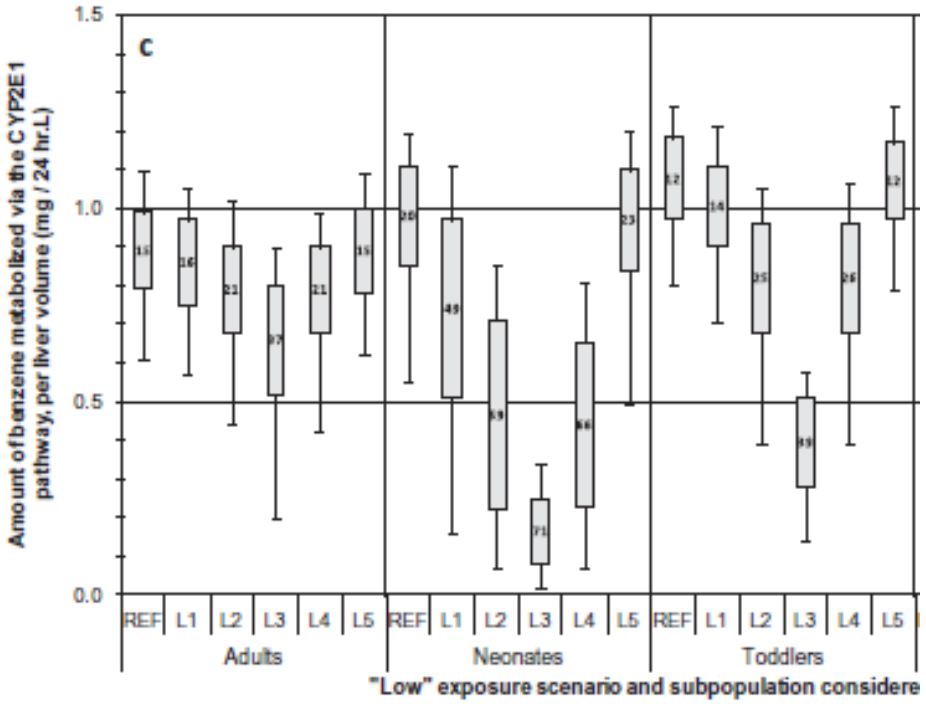
Discussion

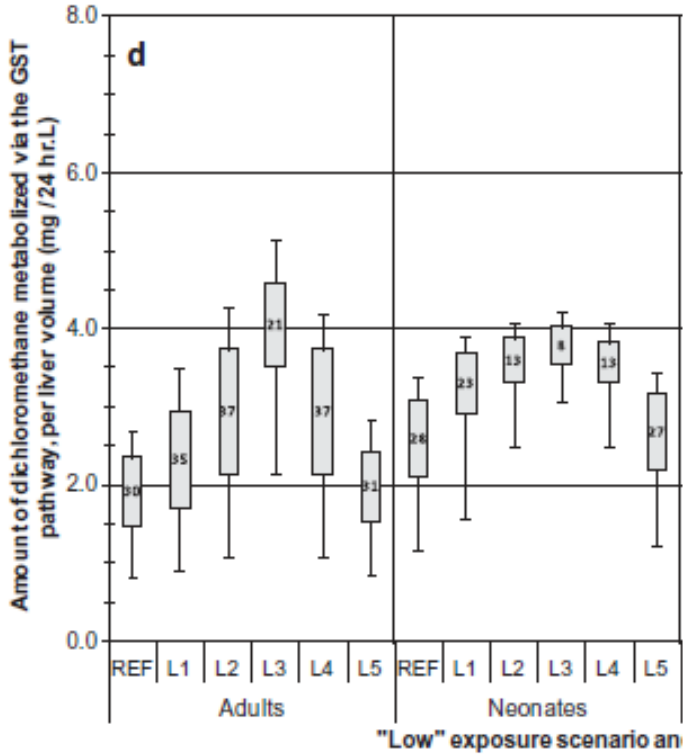
- **Inhalation only data, benzene in DBTEX mixture**
  (Valcke and Haddad, JTEH$_A$, 2015)

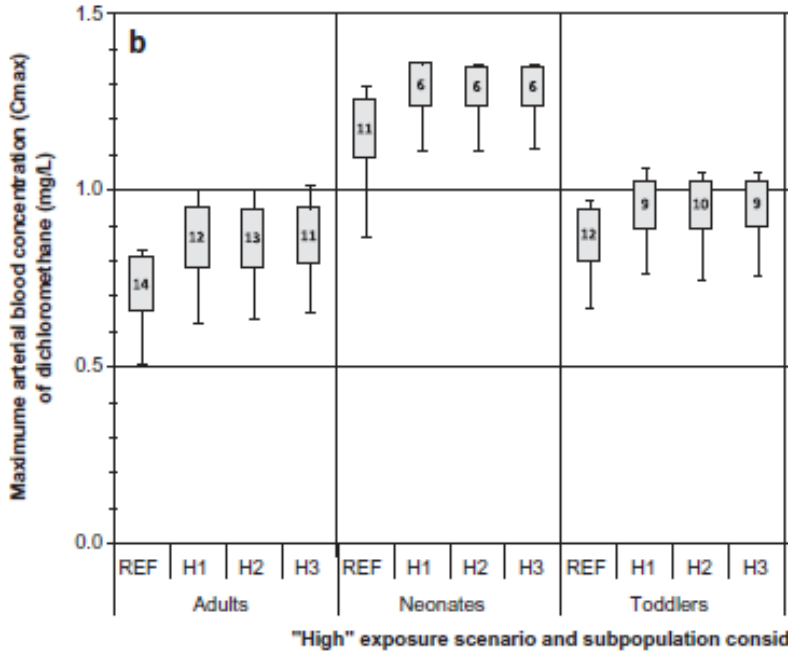


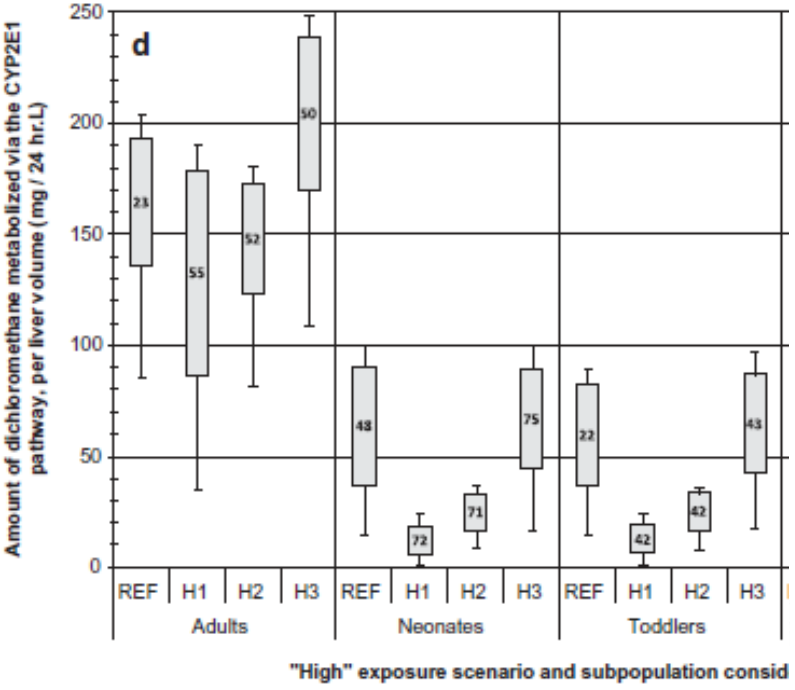


Discussion

- **Inhalation only data, DCM in DBTEX mixture**
  (Valcke and Haddad, JTEH$_A$, 2015)







Discussion: limitations

- Only healthy individuals considered
- Impact of polymorphism of GST not assessed
  - No age-related variations included in the model
- Impact of concomitant alcohol exposure (CYP2E1 inducer)??
- Only 3 inhibitors at the most. Mixtures of tens or hundreds of chemicals *vs* « low » exposure?
- Impact of co-exposures only assessed on metabolism. Absorption / transport & distribution?

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CONCLUSION

- **Multi-route co-exposure can have an impact on the TK variability of individual substances, as compared to single exposures.**
- **The extent of these impacts do not seem to challenge the default adjustment factors attributed for individual substances.**
- **The impact varies as a function of the internal dose metric, exposure level and subpopulation.**
- **Impact may not occur at environmental levels.**

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CONCLUSION

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- **To do:**
  - **Extend to other mixtures, > number of chemicals**
  - **Include other metabolic interactions, TD interactions?**
  - **Refine subpopulation-related differences in GST**

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Thanks!

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Time for questions, discussion?…

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