NEUROSOME

Exploring The Neurological Exposome

Integrative And Cumulative Health Risk From Xenobiotics Exposure

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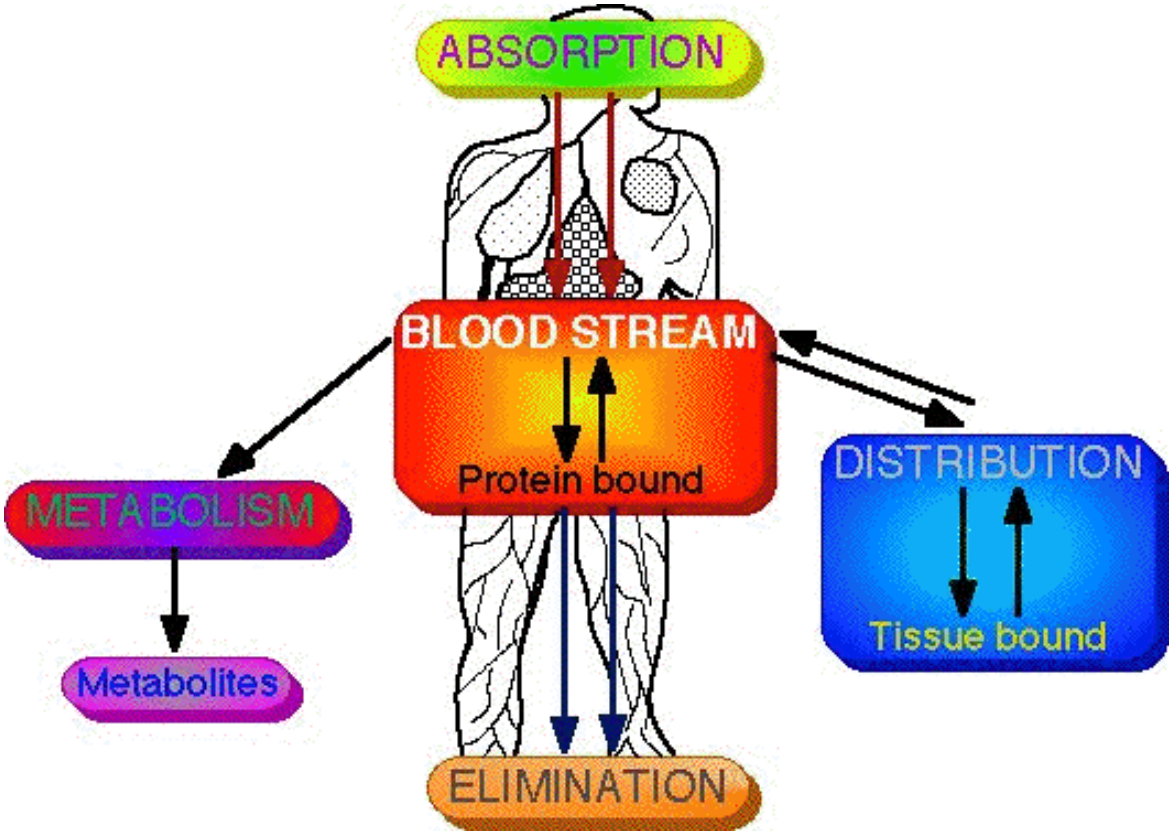
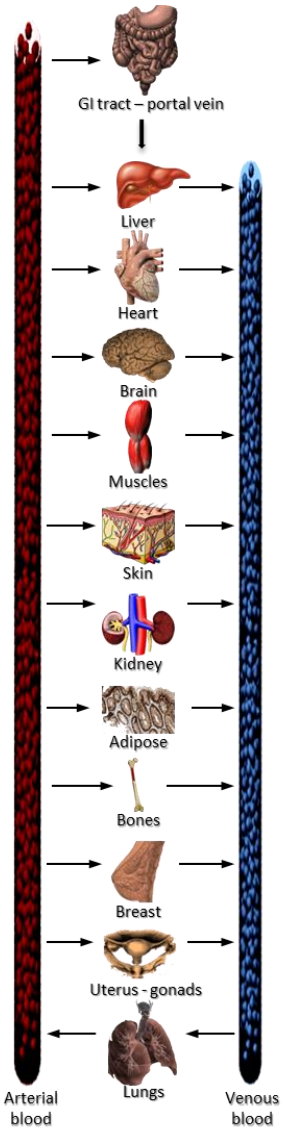


$$V_i \frac{dC_{ij}}{dt} = Q_i (CA_j - CV_{ij}) - Metab_{ij} - E\lim_{ij} + Absorp_{ij} - \Pr Binding_{ij}$$



- Current orientation in chemicals risk assessment is to tackle them as single substances affecting individual health endpoints.
- Human exposure occurs to mixtures of chemicals as they are present in the environment and consumer products.
- PBBK/PD model are able to consider interaction between chemicals for potential mechanisms of action
- Coupling PBPK/PD model with pathology models and hierarchical population modeling techniques [Markov Chain Monte Carlo], a quantitative estimate of health risk to the exposed population is estimated.

PBBK model for quaternary BTEX mixture

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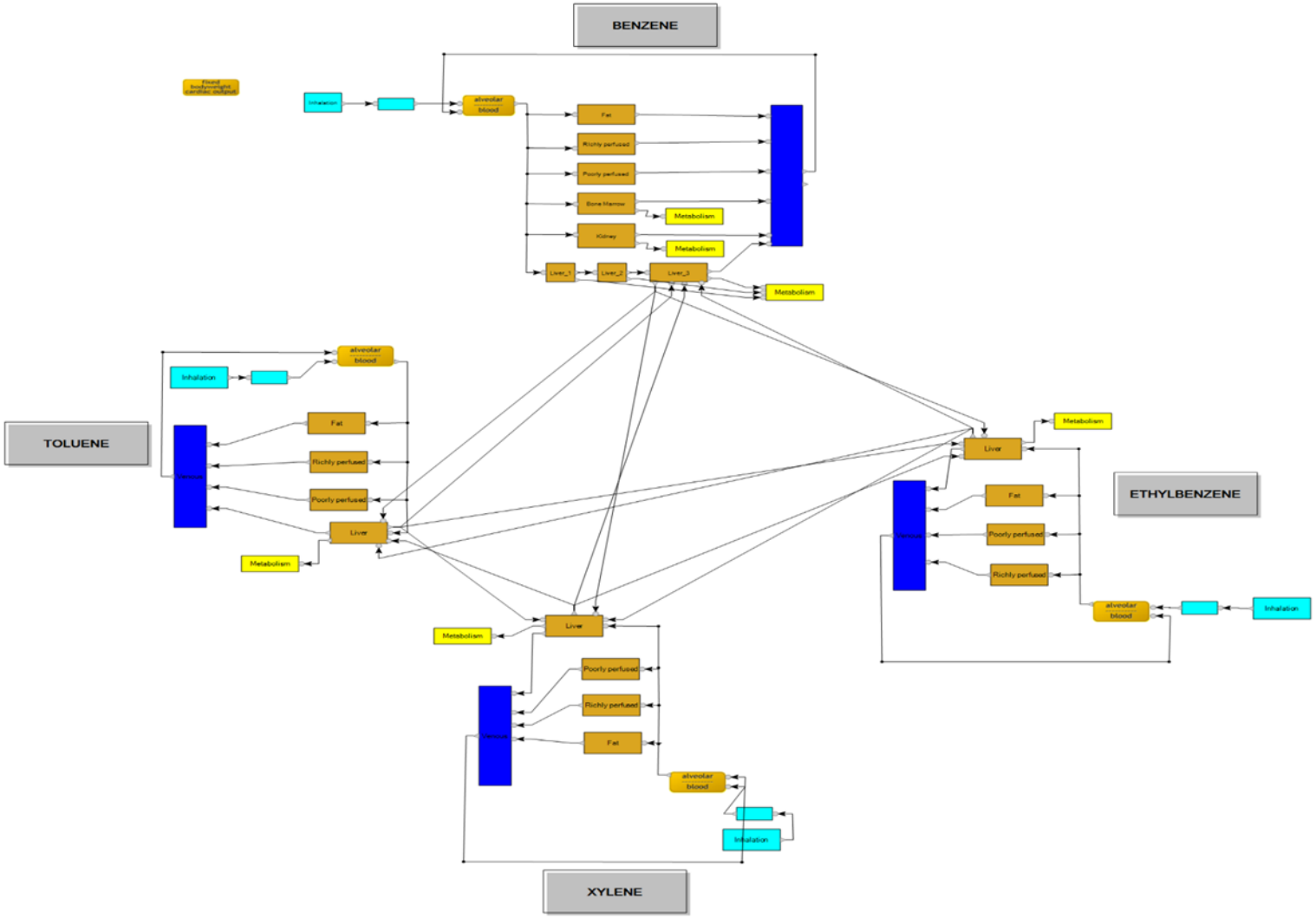
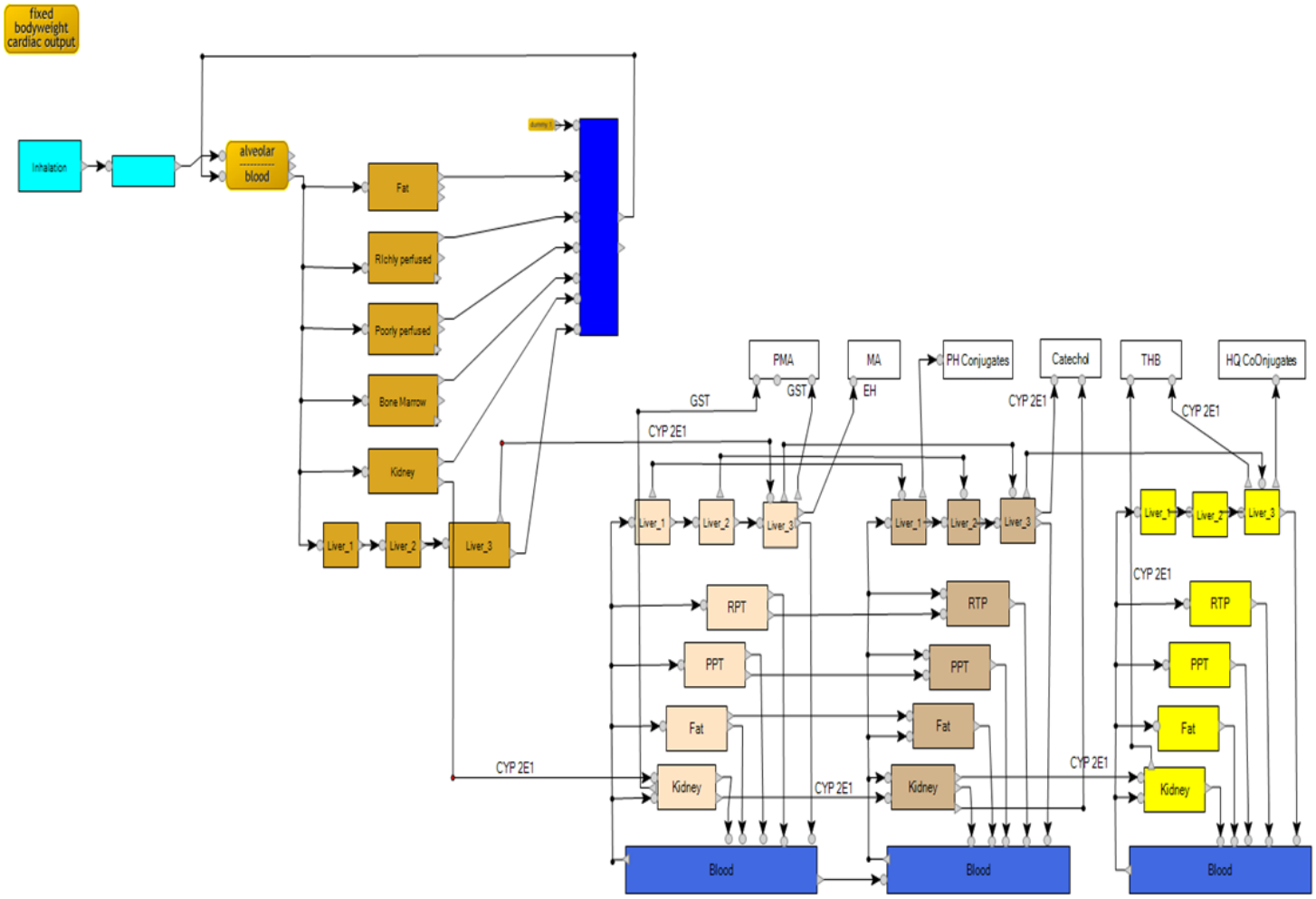
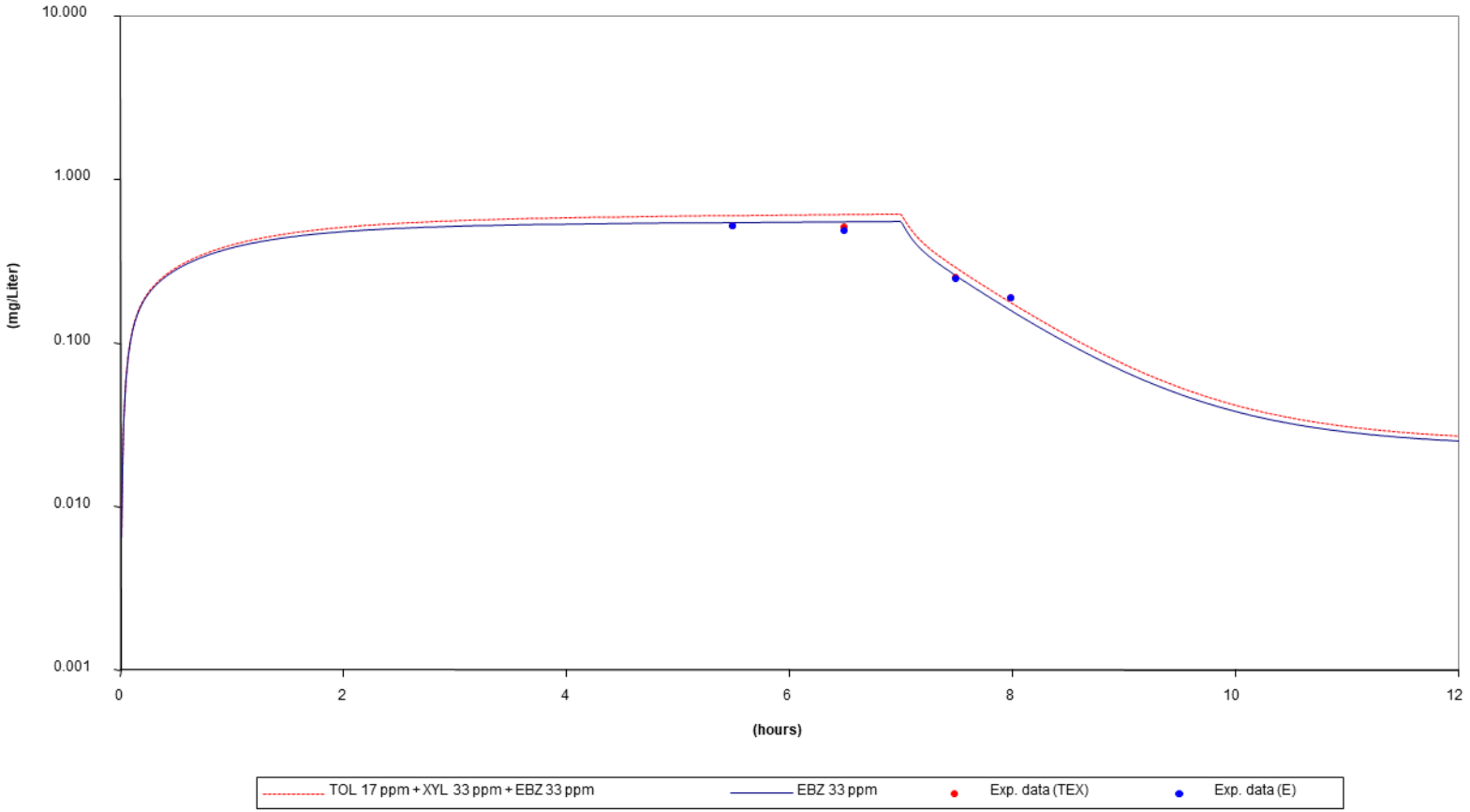



fixed bodyweight cardiac output
Inhalation
alveolar
blood
Fat
Richly perfused
Poorly perfused
Bone Marrow
Kidney
Liver_1
Liver_2
Liver_3
PMA
MA
PH Conjugates
Catechol
THB
HQ CoOnjugates
GST
EH
CYP 2E1
RPT
PPT
Fat
Kidney
Blood

Ethylbenzene concentration in Venous Blood



PBBK/PD model validation for benzene metabolites

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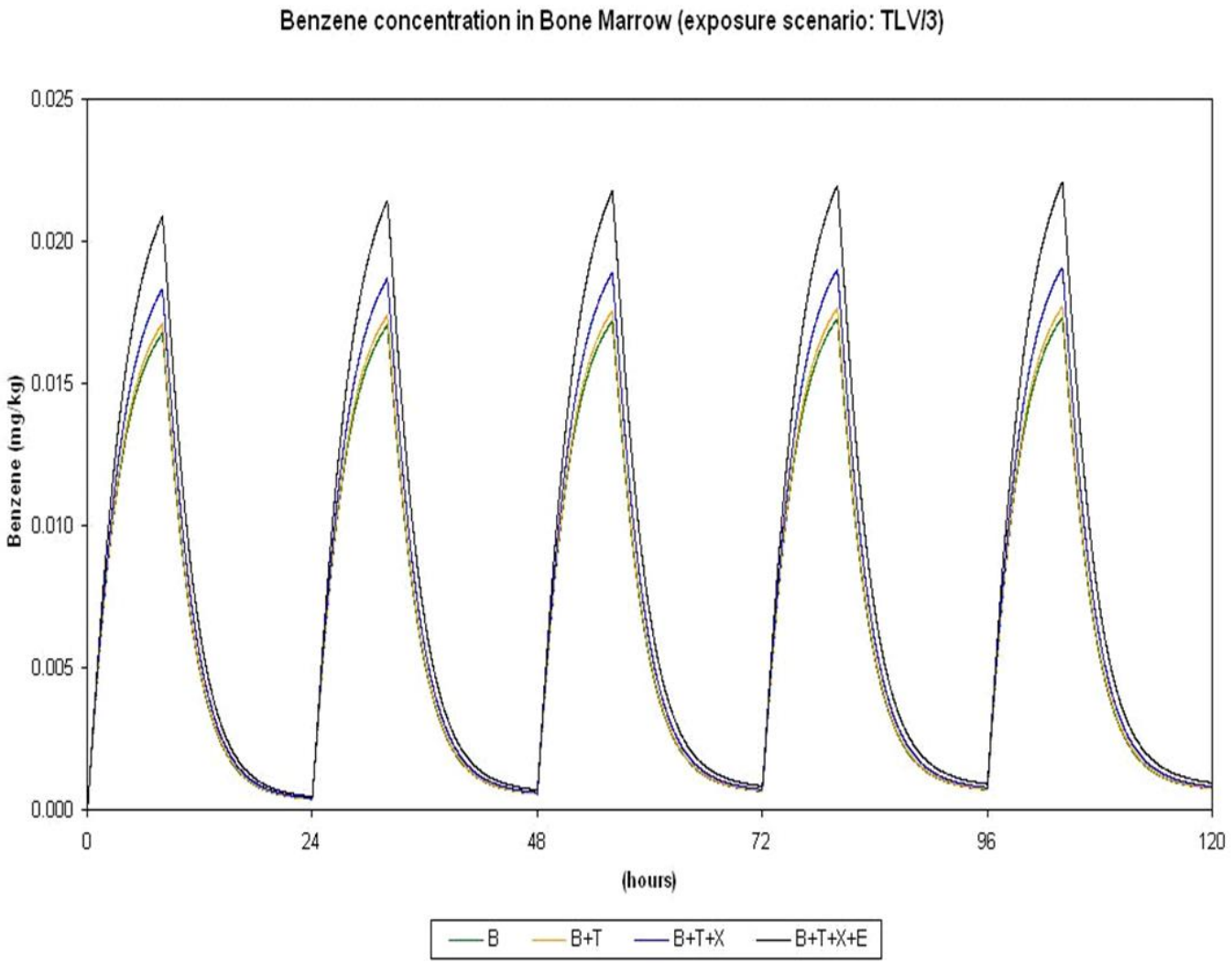
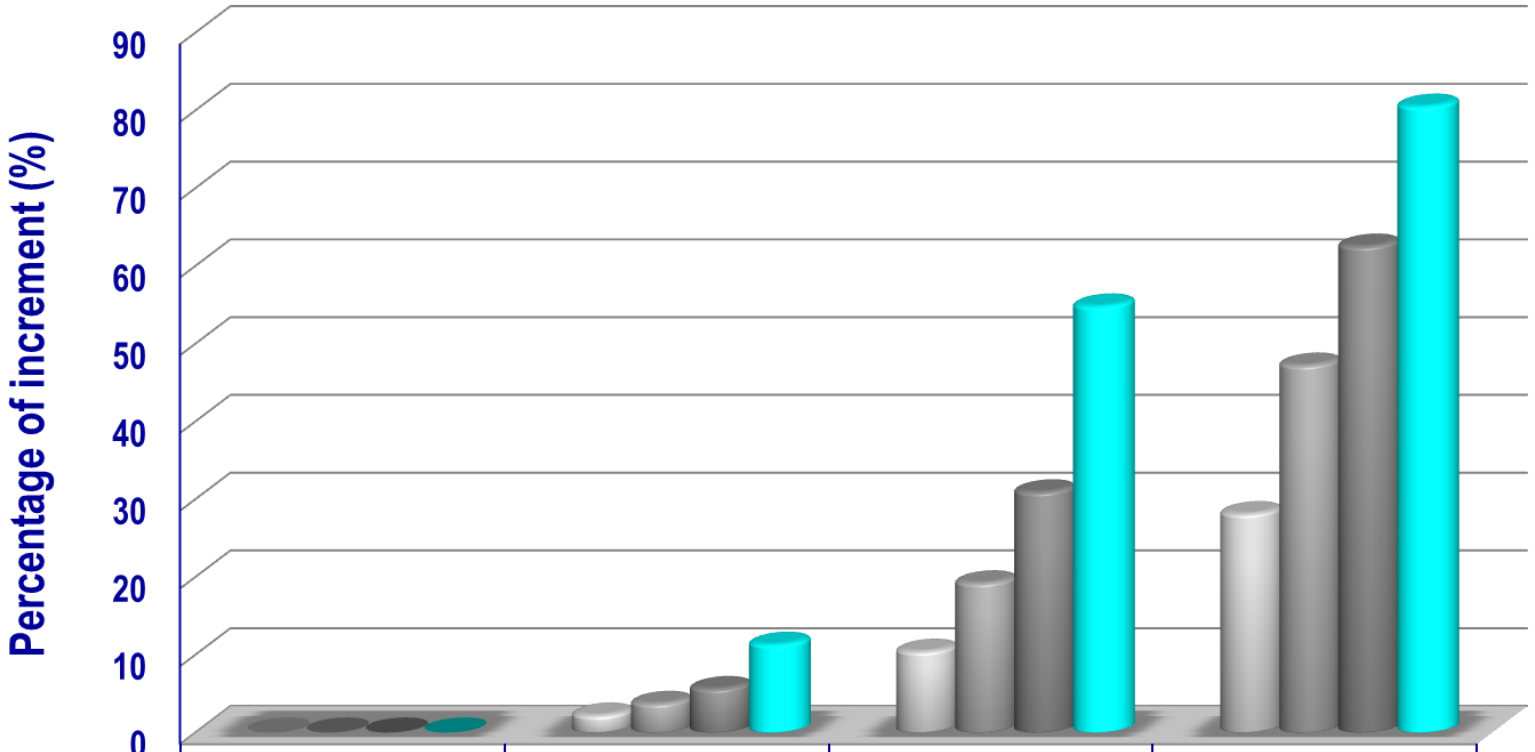
Benzene exposure: 92 ppm	**Metabolite**	**Urinary concentration (mg/L)* Median [min – max]**	**Urinary concentration from PBPK/PD model**
	PH	196 [27.1 - 374]	342.5
	CAT	40.3 [3.79 - 85.1]	71.9
	HQ	22.1 [3.3 - 50.6]	11.5
	S-PMA	7.69 [0.123 - 27.5]	6.2
	MA	41.2 [7.25 - 133]	32.6
Benzene exposure: 13.6 ppm	**Metabolite**	**Urinary concentration (mg/L)* Median [min – max]**	**Urinary concentration from PBPK/PD model**
	PH	18.2 [3.87 - 175]	86.2
	CAT	3.09 [0.673 - 23.8]	30.4
	HQ	3.97 [0.524 - 36.2]	4.5
	S-PMA	0.175 [0.050 - 5.89]	1.6
	MA	7.14 [1.14 - 77.8]	8.8

* Data from Waidyanatha et al. (2004)

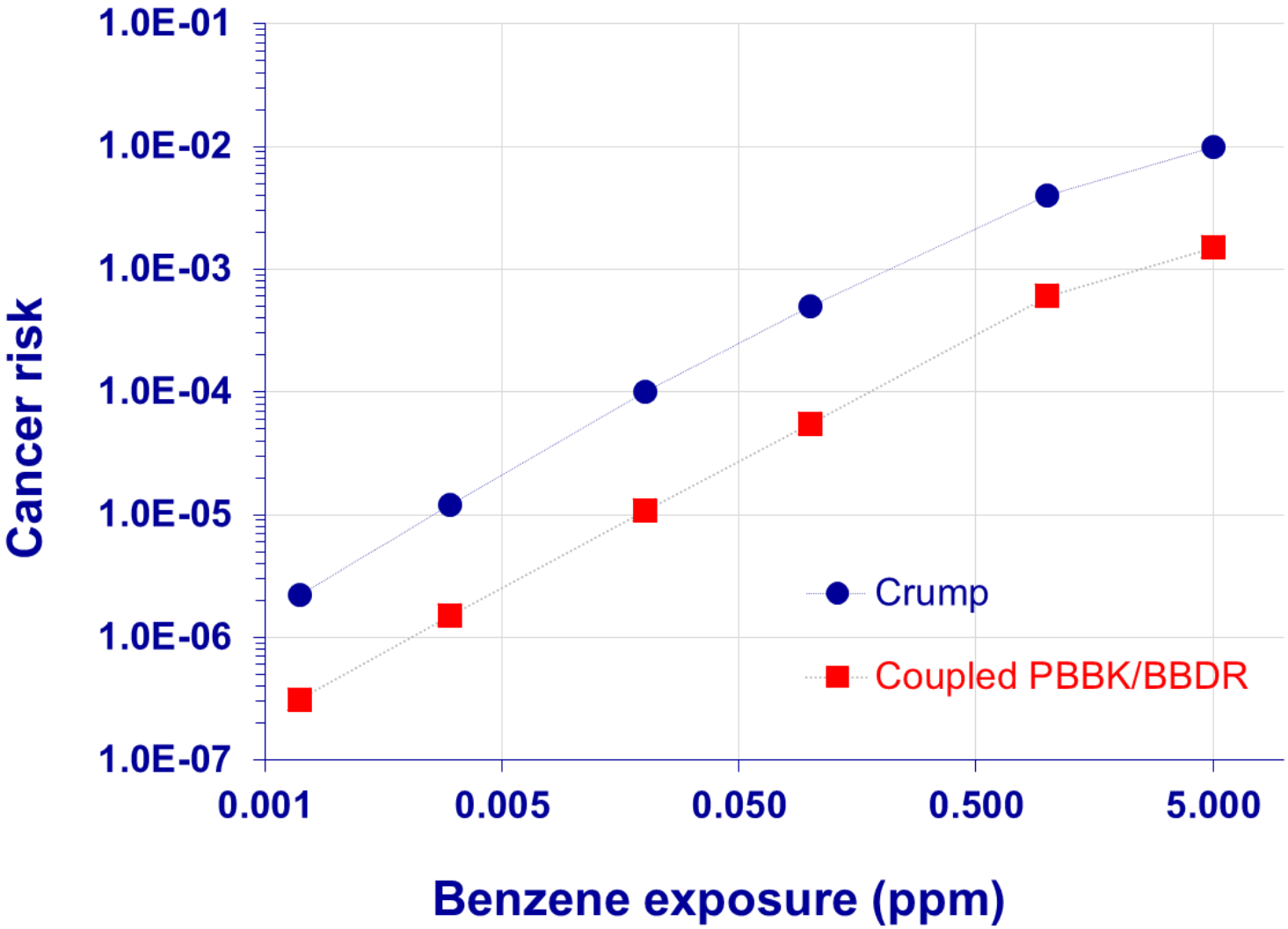

Benzene concentration in Bone Marrow (exposure scenario: TLV/3)
Benzene (mg/kg)
0.025
0.020
0.015
0.010
0.005
0.000
0
24
48
72
96
120
(hours)
B
B+T
B+T+X
B+T+X+E

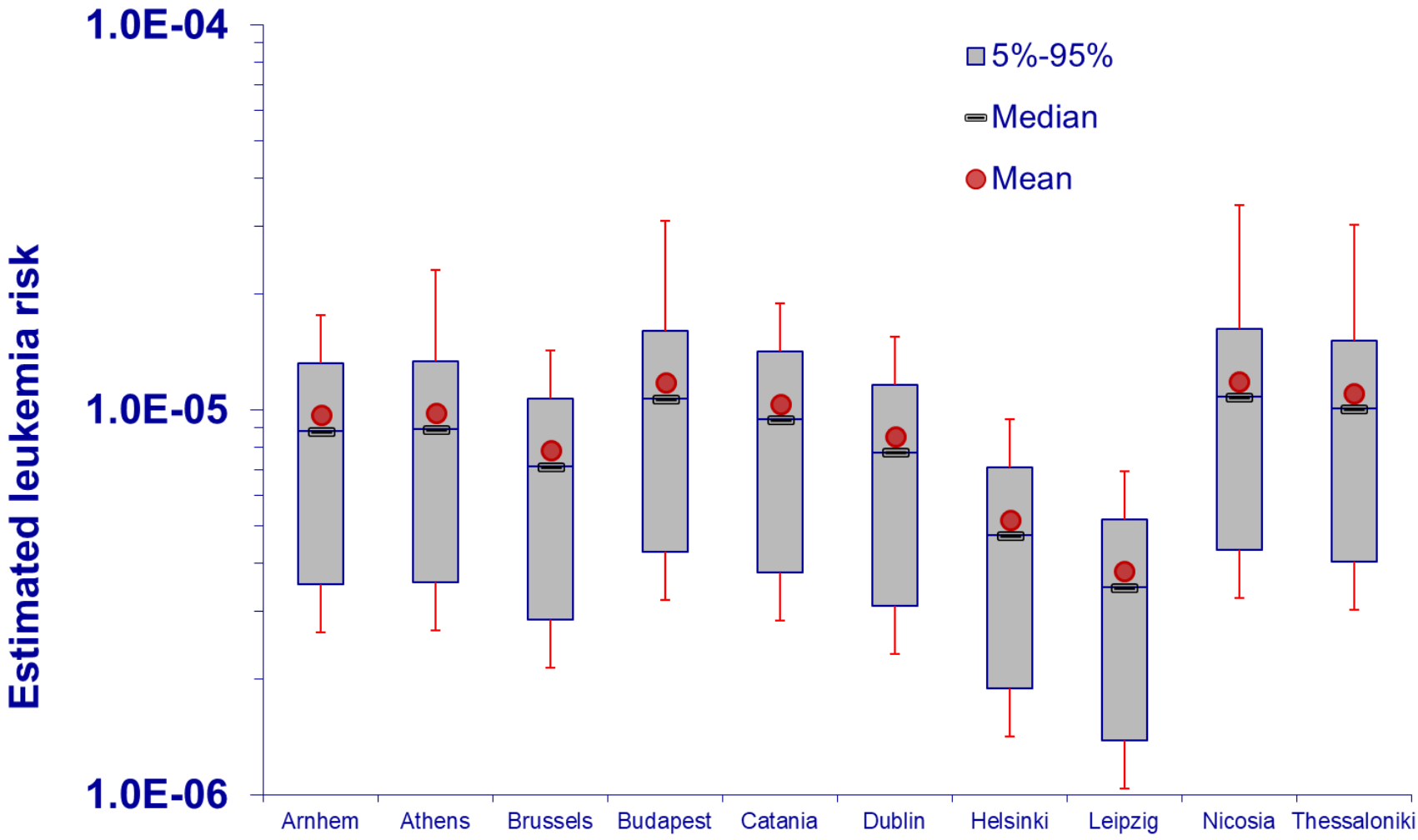
Increment in maximum bone marrow concentration of benzene from exposure to different mixtures of BTEX



	B	B+T	B+T+X	B+T+X+E
TLV/3	0	2.2	10.4	28.1
TLV/2	0	3.7	19.2	47.2
TLV(2/3)	0	5.6	30.9	62.5
TLV	0	11.3	54.8	80.5

Biology based dose response for benzene




1.0E-04
1.0E-05
1.0E-06
Estimated leukemia risk
5%-95%
Median
Mean
Arnhem
Athens
Brussels
Budapest
Catania
Dublin
Helsinki
Leipzig
Nicosia
Thessaloniki

- Biologically-based dose-response models can provide more reliable population health risk estimates for environmental exposure to VOC mixtures than linear dose-response models based on high dose extrapolations
- Biochemical interactions of VOCs in the body result in beyond-than-additive effects (in the case of BTEX, competitive inhibition of metabolism)
- INTEGRA-pathology model is a reliable tool for estimating the lifelong exposure to such xenobiotic mixtures in the occupational environment
- Current health protection legislation should take into account exposure scenarios representing realistic conditions, namely account for the interaction effect of chemical mixture components in the environment, in the workplace and in consumer products

Thank you for your attention!