**TOXICOKINETIC INTERACTIONS OF INDUSTRIAL CHEMICAL MIXTURES AS INTERNAL EXPOSURE MODIFIERS**

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**ABSTRACT**

Humans are generally exposed to chemical mixtures resulting in a combined effect on human health. Interactions can result in synergistic or antagonistic effects beyond simple additivity of the mixture components. Overall, PBTK models offer the advantage of calculating the effect of the interactions among the mixture compounds at the level of metabolism. For this study two relevant mixtures of chemicals were investigated. The first one is the bisphenols’ mixtures consisting of bisphenol A, S and F and the second one is the phthalates’ mixture consisting of DEHP, BBzP, DnBP and DiNP. Generic PBPK models were defined as mathematical models that simulate the concentration of a chemical over time in tissues and blood, by taking into account the rate of the chemical’s absorption into the body, distribution in tissues, metabolism and excretion and were parameterised using literature as well as quantitative structure-activity relationship (QSAR) delivered parameterization data. In order to evaluate the inhibitory effect on the metabolism as a result of co-exposure, a broad range of mean daily intake levels (bodyweight normalised) have been tested for bisphenols and phthalates, starting from 0.01 up to 100,000 μg/kg bw/day. From the results of the co-exposure interaction, it was clearly shown that under environmentally relevant exposure levels and even at the level of EFSA’s temporary tolerable daily intake (tTDI) of 4 μg/kg bw/d for bisphenol A and 50 μg/kg\_bw/d for DEHP, the effect of interaction on the internal dose (expressed as increase of the Area Under Curve, AUC) is negligible (below 1%). However, as expected, the interaction effect is higher when the daily intake level increases. The interaction is significant for intake levels above 10,000 μg/kg bw/d, which might be relevant only for occupational settings. From all the case studies, it is evident that co-exposure to chemicals that are subjected to interaction at the level of metabolism, is crucial at high exposure levels, that are mostly met in occupational settings. Thus, the internal exposure modification as a result of the co-exposure to bisphenols and phthalates should not be a concern for susceptible population groups such as neonates, infants or pregnant mothers and the developing fetus.

**KEYWORDS:** Industrial chemical mixtures, internal exposure, toxicokinetic interactions, human health