Short Communication

Internal Exposure of Children by Simulated Acute Inhalation of Volatile Organic Compounds: The Influence of Chemical Properties on the Child/Adult Concentration Ratio

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Accidental release of industrial chemicals may lead to an airborne exposure over a wide range of concentrations, and therefore is a special scenario with implications on risk assessment. In this context, children may be at higher risk compared to adults due to possible higher external exposure and different kinetics (behaviour, physiology), both leading to higher internal exposure. In addition, possible differences in the concentration-effect relationship (dynamics) have to be considered. The scope of this paper is the quantification of the age-dependent differences in the internal exposure of children occurring during acute inhalation of volatile organic compounds.

A physiologically-based pharmacokinetic model (Ramsey & Andersen 1984) with seven compartments (brain, liver, kidney, adipose tissue, muscle/skin, vessel rich organs, and skeleton) was used. Anatomical and physiological data were derived from the literature for the ages 0 (newborn), 1, 5, 10, and 15 years as well as for the middle-aged male adult ('reference man'). To include the 'immature' metabolism at the age of 0 and 1 year, 14% and 50% of adult CYP2E1 activity per liver volume were assumed, respectively (Abraham *et al.* 2005). Model simulations were made for styrene which has a high rate of alveolar absorption (low water solubility and reactivity, high partition coefficient blood:air). Data on partition coefficients (blood:air and tissue:blood) and metabolism (V_{max}, k_m) were taken from the literature. Simulations (using the *Matlab* software) were made for the arterial concentrations in the different age groups, taking into consideration a concentration range of 1 to 1000 ppm in ambient air and an exposure period of up to 8 hr (US-AEGL scenario). From these values, concentration ratios (child/adult) were calculated. In a second step, V_{max}, k_m and the different partition coefficients were varied in order to explore the influence of the chemical's properties on the calculated ratios of the arterial concentrations (new-

born/adult). Using the properties of styrene as basis, each of these parameters was varied (0.25-, 0.5-, 2- and 4-fold) for separate simulations of the concentration ratio.

Arterial concentrations increase continuously when exposure is simulated for 8 hr with concentrations of 1, 10, 100, and 1000 ppm in ambient air. Among all age groups, the levels are highest in the newborn. With increasing age of the child, concentrations more and more resemble those in the middle-aged adult (data not shown). The calculated ratios of arterial concentrations (child/adult) reveal a dose-dependent phenomenon (table 1, maximum values at about 100 ppm in ambient air). The highest ratio is observed in the newborn. This is explained by its relatively high ventilation rate and by saturation of metabolism at a lower external concentration than in older children and the adult. The latter is due to the lower level of CYP2E1 enzyme relevant for the metabolism of styrene. At very high exposure concentrations, the metabolism becomes saturated in all age groups resulting in a lower child/adult ratio for the very young.

To explore the influence of the chemical's properties on the calculated ratios of the arterial concentrations (newborn/adult), the substance-specific model parameters (V_{max}, k_m and the partition coefficients) were separately varied (0.25- to 4 times). These simulations were made for external styrene concentrations between 1 and 1000 ppm and an ex-

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Table 1.

Ratio of arterial concentrations (child/adult) for different age groups resulting from an 8 hr exposure to different styrene concentrations in ambient air.

Styrene exposure (8 hr)	1 ppm	10 ppm	100 ppm	1000 ppm
Newborn	2.25	2.49	3.77	1.69
1 year	1.31	1.34	1.83	1.28
5 years	1.17	1.18	1.34	1.37
10 years	1.15	1.16	1.30	1.28
15 years	1.10	1.11	1.16	1.20
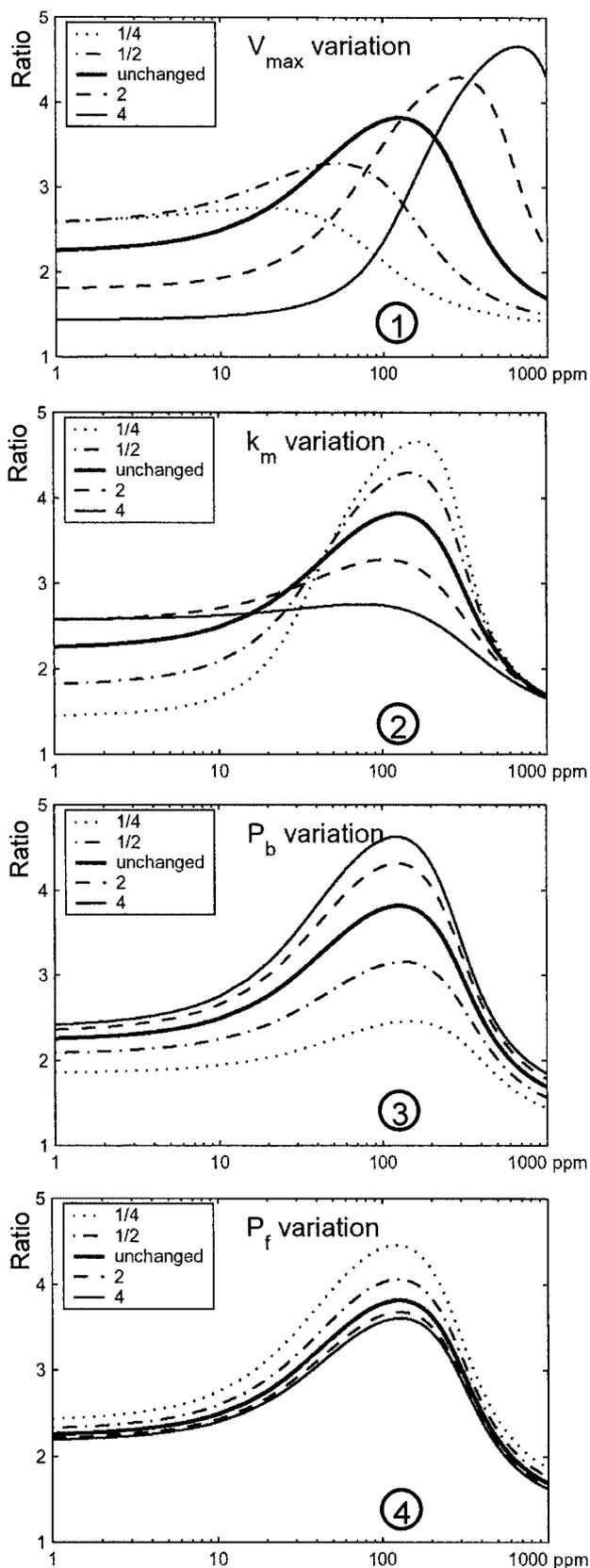
posure duration of 8 hr, computing the newborn/adult ratio only. As shown in fig. 1, with higher V_{max} (amount of enzyme) the ratio increases as compared to the genuine styrene situation (bold line in all figures). The external concentration at which the maximum ratio occurs increases with increasing amount of enzyme protein. A higher k_m (lower binding affinity) leads to a lower maximum at roughly the same external concentrations (fig. 2). A higher coefficient blood:air leads to a general increase of the ratios at all concentrations (fig. 3). Opposite (but less pronounced) changes are observed with a higher partition coefficient adipose tissue:blood (fig. 4). A higher partition coefficient liver:blood and a lower k_m have comparable effects. Lower values of all these parameters lead to corresponding changes in the opposite direction. Changes of other partition coefficients only have minor effect on the ratios.

For the kinetics of styrene we conclude that at the same external exposure the newborn experiences the highest internal exposure compared to older children and adults. The ratios of arterial concentration (child/adult) were found to be dose- and duration-dependent. They also depend on the properties of the chemical in a complex manner, with highest impact of V_{max}, k_m, and the partition coefficients blood:air, liver:blood and adipose tissue:blood. For risk assessment of systemic effects (due to the parent substance) resulting from inhalation of volatile organic compounds, these ratios can be used to establish data-derived kinetic assessment factors in order to include the newborn as sensitive subpopulation.

References

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Fig. 1–4. Ratio of arterial concentrations (newborn/adult) at the end of an 8 hr exposure to airborne styrene (concentrations 1 to 1000 ppm, logarithmic scale). The bold line represents the unchanged properties of styrene and is the same in all the figures. The other lines are the result of separate variations (0.25- to 4-fold) of V_{max} (fig. 1), k_m (fig. 2), and the partition coefficients blood:air (P_b, fig. 3) and adipose tissue:blood (P_f, fig. 4).