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ELEVATED INTERNAL EXPOSURE OF CHILDREN IN SIMULATED ACUTE INHALATION OF VOLATILE ORGANIC COMPOUNDS: DEPENDENCY ON PROPERTIES OF THE CHEMICAL

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Introduction

A specific exposure scenario, namely the accidental release of industrial chemicals leading to an airborne exposure over a wide range of concentrations, requires special consideration in the risk assessment including that of sensitive subpopulations. In this context, children may be at higher risk compared to adults due to possible higher external exposure (behaviour, physiology), different kinetics (both leading to higher internal exposure) and different dynamics. The scope of this paper is the quantification of the age-dependent differences in the kinetics of children occurring during inhalation of volatile organic compounds (VOCs).

Methods

A PBPK model (e.g. 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 (for details see: Abraham *et al.* 2004). Model simulations were made for styrene which has a high rate of alveolar absorption (low water solubility and reactivity). 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 between 1 and 1000 ppm in ambient air and an exposure period of up to 8 hours (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 (newborn/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.

Results and Discussion

During a simulated 8-hour exposure period with concentrations of 1, 10, 100 and 1000 ppm in ambient air, arterial concentrations continuously increase. Compared to the five other age groups, the levels are highest in the newborn. With increasing age, concentrations more and more resemble those in the middle-aged adult (data not shown). The calculated ratios of arterial concentrations (child/adult) are shown in the Table for the different age-groups and the different concentrations in ambient air (8-hour exposure).

Insert the Table here

These data reveal a dose-dependent phenomenon. For a concentration of about 100 ppm styrene, the concentration ratios (child/adult) reach a maximum which is pronounced in the newborn. This mainly results from the relatively high alveolar ventilation and the immature metabolism which gets saturated at lower concentration compared to older children and adults. With very high exposure concentrations, the metabolism gets saturated in all age groups. The phenomenon described also depends on the duration of exposure (pronounced with longer periods of exposure, data not shown).

Further simulations of the complex relationships were made for external styrene concentrations ranging between 1 and 1000 ppm and a duration of exposure of 8 hours, computing the newborn/adult ratio only. The highest value of this ratio occurs at an ambient air concentration of 130 ppm styrene, as can be seen in Figures 1-4 (bold line).

Insert Figures 1 – 4 here

To explore the influence of the chemical's properties on the calculated ratios of the arterial concentrations (newborn/adult), V_{max} , k_m and the partition coefficients were varied in separate runs using the properties of styrene as basis. As shown in Figure 1, a higher V_{max} leads to higher maximum ratios occurring at high external concentrations, but lower ratios at low external concentrations. A higher k_m (as well as a lower partition coefficient liver/blood, data not shown) leads to a lower maximum at roughly the same external concentrations (Figure 2). A higher coefficient blood/air leads to a general increase of the ratios at all concentrations (Figure 3). Opposite (but less pronounced) changes are observed with a higher partition coefficient adipose tissue/blood (Figure 4). 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.

Summary and Conclusion

1. 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. This phenomenon is pronounced in the newborn, mainly due to the relatively high ventilation rate (corresponding to the high metabolic rate), and the 'immature' metabolic capacity which gets saturated at lower concentrations (compared to older children and adults).
2. The ratios of concentrations (child/adult) 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.

3. For risk assessment of systemic effects resulting from inhalation of VOCs, these ratios can be used to establish data-derived kinetic safety factors in order to include the newborn as sensitive subpopulation. The simulations presented are of particular importance for the risk assessment in context of the AEGL concept: whereas other programs are aimed at setting 'safe' levels (which by definition are levels below the no adverse effect level), acute exposure guideline levels (AEGLs) are concentrations which are related to varying degrees of health impairment. Therefore, a broad range of concentrations has to be covered, including those leading to saturated metabolism.

References

- Abraham, K., H. Mielke, W. Huisinga & U. Gundert-Remy: Elevated internal exposure of children in simulated acute inhalation of volatile organic compounds: effects of concentration and duration (2004, submitted)
- Ramsey, J.C. & M.E. Andersen: A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. *Toxicol. Appl. Pharmacol.* 1984, **73**, 159-175.

Table

Ratio of arterial concentrations (child/adult) for different age groups and the middle-aged male adult resulting from an 8-hour exposure to different styrene concentrations in ambient air.

Styrene exposure (8 h)	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

Figures 1 - 4

Ratio of arterial concentrations (newborn/adult) depending on the external styrene concentration (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} (Figure 1), k_m (Figure 2), and the partition coefficients blood/air (P_b , Figure 3) and adipose tissue/blood (P_f , Figure 4).

