



**Karolinska
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Institutet för Miljömedicin

**Improved Scientific Basis for Human Health
Risk Assessment Factors by
Toxicokinetic Population Modeling**

AKADEMISK AVHANDLING

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ABSTRACT

Exposure limits or guidelines are derived to protect humans from adverse effects caused by exposure to chemical substances in the environment or at the workplace. The internal dose of a chemical is determined by toxicokinetic (TK) processes such as uptake, distribution and elimination, and is closely related to the risk of adversity. The internal dose varies among individuals due to differences in age, genetics, physical activity, health status and life-style. Thus, it is important to address population variability for the exposure limits to be protective. TK variability is typically accounted for by the use of a default assessment factor of 3.16. However, the scientific basis of the exposure limits may be improved by replacing the default value with a chemical specific adjustment factor ($CSAF_{HK}$), derived from experimental data. By doing so, more appropriate exposure limits are achieved, and large costs for society associated with both too high and too low exposure limits may be avoided.

Substitution of the default value is often obstructed by the lack of suitable experimental data. In this thesis, this limitation was addressed by the development of a probabilistic framework using physiologically based pharmacokinetic (PBPK) modeling. It was used to derive $CSAF_{HK}$ for four commonly used organic solvents; acetone, toluene, styrene and methyl chloride.

PBPK models based on information on anatomical, physiological and biochemical parameters were used to calculate the internal doses following inhalation exposure to the four chemicals. A description of washin-washout in the respiratory tract was evolved for polar solvents such as acetone. Additional information on the model parameters contained in human experimental toxicokinetic data was taken advantage of by Bayesian analysis. Meanwhile, the methodology was explored with respect to prior assumptions. $CSAF_{HK}$ were derived from population distributions of internal dose obtained by Monte Carlo (MC) simulation from distributions of the model parameters. The influence of age and gender on the internal dose was slight. Thus, the factors obtained for all substances were below 2.5. However, the effects of fluctuations in exposure level and workload increased the $CSAF_{HK}$ up to 6.1, indicating that workplace exposure may need specific attention. Given the diverse properties of acetone, toluene, styrene and methyl chloride, the results can probably be generalized to most organic solvents and similar chemicals.

The $CSAF_{HK}$ presented in this thesis are derived from extensive information on intraspecies toxicokinetic differences and cover the effects of common toxicokinetic modifiers. Thus, they are well suited to replace the default value. The population framework may be further extended to include other chemicals, as well as additional experimental data on population variability when such becomes available.