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Evaluation of semi-generic PBTK modeling for emergency risk assessment after acute inhalation exposure to volatile hazardous chemicals

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HIGHLIGHTS

- Simpler, user-friendlier PBTK models can equal complex ones.
- 8 out of 9 chemicals tested were calculated adequately.
- Simple PBTK-models could be applicable in acute risk assessment.

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ABSTRACT

Background: Physiologically Based Toxicokinetic Models (PBTK) may facilitate emergency risk assessment after chemical incidents with inhalation exposure, but they are rarely used due to their relative complexity and skill requirements. We aimed to tackle this problem by evaluating a semi-generic PBTK model built in MS Excel for nine chemicals that are widely-used and often released in a chemical incident. *Material & methods:* The semi-generic PBTK model was used to predict blood concentration–time curves using inhalation exposure scenarios from human volunteer studies, case reports and hypothetical exposures at Emergency Response Planning Guideline, Level 3 (ERPG-3) levels.[2] Predictions using this model were compared with measured blood concentrations from volunteer studies or case reports, as well as blood concentrations predicted by chemical-specific models. The performances of the semi-generic model were evaluated on biological rationale, accuracy, and ease of use and range of application. *Results:* Our results indicate that the semi-generic model can be easily used to predict blood levels for eight out of nine parent chemicals (dichloromethane, benzene, xylene, styrene, toluene, isopropanol trichloroethylene and tetrachloroethylene). However, for methanol, 2-propanol and dichloromethane the semi-generic model could

Abbreviations: 2-P, Isopropanol; AEGL, Acute Exposure Guideline Level; BNZ, Benzene; DCM, Dichloromethane (Methylene Chloride); ERPG-3, Emergency Response Planning Guideline, Level 3; MeOH, Methanol; PBTK Model, Physiologically Based Toxicokinetic Model; PCE, Tetrachloroethylene (Perchloroethylene); STY, Styrene; TCE, Trichloroethylene; TOL, Toluene; XYL, Xylene.

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[2] The maximum airborne concentration below which it is believed almost all individuals could be exposed to, for up to 1 h, without experiencing or developing life-threatening side effects.

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not cope with the endogenous production of methanol and of acetone (being a metabolite of 2-propanol) nor could it simulate the formation of HbCO, which is one of the toxic end-points of dichloromethane. The model is easy and intuitive to use by people who are not so familiar with toxicokinetic models. *Conclusion:* A semi-generic PBTK modeling approach can be used as a 'quick-and-dirty' method to get a crude estimate of the exposure dose.

1. Introduction

Risk assessment following acute exposure of humans to hazardous chemicals is not straightforward. In general, risk assessment consists of characterizing the nature and probability of adverse effects on people who have been exposed to one or more chemicals. The nature and probability are very much dependent on chemical blood-levels that can be reached. Various exposure situations are possible e.g., environmental exposure (low), occupational exposure (low to medium level) and acute chemical incidents (medium to high level). Risk assessment is a four-step process including hazard identification, dose–response assessment, exposure assessment, and risk characterization (WHO, 2009). Hazard characteristics (hazard identification + dose–response assessment) are generally well-known for those chemicals that are often encountered in acute situations. However, proper estimation of the external and internal exposure dose is crucial but, simultaneously, most challenging to obtain.[3]

Exposure assessment can be based on the evaluation of external inhaled exposure concentrations. In the case of acute incidents with hazardous chemicals, health professionals have guidelines such as the Acute Exposure Guideline Levels (AEGLs) and Minimal Risk Levels (MRLs) at their disposal. These levels roughly indicate at which exposure concentrations and durations clinical effects begin to appear in sensitive individuals. Using these guidelines requires reliable information on airborne levels. Unfortunately, however, reliable air level measurements are challenging to obtain because, after a release, chemicals rapidly dissolve into the atmosphere, soil and water (De Vocht et al., 2013).

An alternative to monitoring air and water is measuring the concentration of the involved hazardous chemical or its metabolite(s) in biological material (mainly blood and urine). Physiologically Based Toxicokinetic (PBTK) modeling in the 'reverse dosimetry' mode can help estimate the external exposure over time after exposure to chemicals. PBTK models are mathematical models that quantitatively describe the absorption, distribution, metabolism and excretion (ADME) of chemicals into the body using anatomical, physiological, biochemical and physicochemical parameters. Some recent publications have advocated in favour of the use of PBTK modeling in specific situations of human risk assessment (Scheepers, 2010; Mumtaz et al., 2012; Hunault et al., 2014). Examples of situations in which the use of PBTK models could be helpful are intoxications with delayed serious effects, repeated exposure, reverse dosimetry calculation of exposure doses in forensic cases, or interpretation of biomonitoring data. Many PBTK models are available to health professionals, but most are developed specifically for one compound, and/or solved using commercial software such as acsl, acslX, Berkeley-Madonna or MATLAB. Health professionals rarely use them in human risk assessment following acute exposure to hazardous chemicals, as they have a limited availability.

[3] Exposure dose is defined here as a description of exposure in two dimensions, i.e. level and duration.

Lately, a 'semi-generic' model has been developed to estimate blood and urine concentrations of multiple chemicals (Jongeneelen and Ten Berge, 2011) (http://cefic-lri.org/lri_toolbox/induschemfate/). A 'generic model' is defined as a PBTK model that does not need chemical-specific parameters that describe the ADME of the chemical. Physicochemical parameters such as MW, vapor pressure, $\log K_{ow}$ and water solubility of a compound are sufficient to use for model predictions. The built-in QSARs (quantitative structure–activity relationships) will automatically predict properties such as absorption upon inhalation (diffusion from air to blood) or diffusion from blood into the tissues. Completely generic PBTK models are scarce as it is difficult to predict metabolism pathways and rates by QSARs. By 'semi-generic', we mean a model including at least some metabolic clearance parameters, such as the maximum rate of metabolism (Vmax) and the Michaelis constant (e.g., km). The Jongeneelen semi-generic model (IndusChemFate) operates in MS Excel and its accuracy has been evaluated for several compounds, (e.g. pyrene, N-methyl-pyrrolidone, methyl-tert-buthylether, heptane, 2-butoxyethanol and ethanol) (Jongeneelen and Ten Berge, 2011).

At the start of the work described here, it was hypothesized that such a semi-generic PBTK model could be helpful to health professionals in charge of victims acutely exposed to volatile hazardous chemicals, in a context of emergency. It could be used, for instance, to reversely calculate the actual exposure dose, which would help in emergency decision making. Such a model could be used as a 'quick-and-dirty' method by health professionals not so familiar with toxicokinetic models. Therefore, we aimed to evaluate the model's accuracy and practicability for this purpose.

2. Material and methods

2.1. Models

2.1.1. Semi-generic Jongeneelen model

The semi-generic Jongeneelen model (Jongeneelen and Ten Berge, 2011) can be used to predict blood and urine concentrations of hazardous chemicals in humans, following a specific exposure scenario. This model divides the body into compartments (Fig. 1) and uses mathematical equations to describe the kinetic processes between them. The equations incorporate human physiological parameters, human xenobiotic metabolism parameters, and physicochemical characteristics to calculate the tissue concentrations and the total amount of substance present in the human body.

All these equations are written in Visual Basic, a system for writing programs for the Windows operating systems, which allows the model to run in MS Excel. The calculation of the internal dose based on blood concentration–time curves is possible for different routes of exposure: inhalation, dermal and oral. Dermal exposure following exposure to vapors is also a possible route of absorption in this model but inhalation was the main route of interest in this paper. Exposures can last from a few minutes to several weeks and periodical exposures are possible (for example, daily exposure in an occupational setting). Michaelis–Menten metabolism can be simulated in all compartments.