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Uncertainty and variability in the exposure reconstruction of chemical incidents – the case of acrylonitrile

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HIGHLIGHTS

- Exposure to acrylonitrile during a chemical incident was reconstructed.
- Variation in predicted concentrations was characterized by separating uncertainty and variability.
- Uncertainty can be reduced by collecting human biomonitoring data as soon as possible.
- Individual physiological information may further reduce variation by 5 to 20%

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ABSTRACT

The application of human physiologically based pharmacokinetic (PBPK) modeling combined with measured biomonitoring data, has a great potential to backtrack external exposure to chemicals during chemical incidents. So far, an important shortcoming of 'reversed dosimetry' is that uncertainty and variability in the model predictions are often neglected. The aim of this paper is to characterize the variation in predicted environmental air concentrations by means of reversed dosimetry as a result of uncertainty in chemical-specific input data and variability in physiological parameters. Human biomonitoring data (*N*-2-cyanoethylvaline in blood) from a chemical incident with acrylonitrile (ACN) combined with the BioNormtox PBPK model are used as a case to reconstruct the air concentration and uncertainty thereof at the time of the incident. The influence of uncertainty in chemical-specific properties and exposure duration, and interindividual variability in physiological parameters on the reconstructed air exposure concentrations were quantified via nested Monte Carlo simulation. The range in the reconstructed air concentrations of ACN during the incident was within a factor of 3. Uncertainty in the exact exposure duration directly after the chemical accident was found to have a dominant influence on the model outcomes. It was also shown that uncertainty can be further reduced by collecting human biomonitoring data as soon as possible after the incident. Finally, the collection of specific information about individual physiological parameters from the victims, such as body weight, may further reduce the variation by 5 to 20% in our case study. Future research should include the comparison of reversed dosimetry model outcomes with measured air and biological concentrations to further increase the confidence in the model approach and its implementation in practice.

1. Introduction

Assessing human exposure to uncontrolled emissions of hazardous substances after incidents is an increasingly important subject of research (Bongers et al., 2008; Hunault et al., 2014; Scheepers et al., 2011). During or in the aftermath of such incidents large amounts of information are collected within a short timeframe, primarily aimed at the identification of the population

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at risk, the quantification of these (acute) risks and decisions to be made regarding direct measures, such as evacuation (Bongers et al., 2008). As time is usually a limiting factor, measured (air) exposure levels during and directly after incidents are scarce.

In this context, human biomonitoring data may help to backtrack external exposure at the time of the incident, since this technique allows the collection of biological samples afterwards. Depending on the lifespan of biomarkers in the human body, the moment of data collection may vary from days to weeks, and sometimes even months after the incident (Scheepers et al., 2011). Several methods for external exposure reconstruction have been described, some of which have been readily applied in the context of chemical incidents (Bader and Wrbitzky, 2006; Liao et al., 2007; Lyons et al., 2008). As these methods generally make use of exposure prediction models that are applied backwards (or: in the reverse direction) in comparison with their original use, this application is also referred to as 'reversed dosimetry' (Clewell et al., 2008).

For a successful reconstruction of external exposure to chemicals during incidents based on biological samples from exposed individuals, the following issues should be considered. First, large variation in measured concentrations in biological media under relatively similar exposure conditions can be expected. This is illustrated by Spaan et al. (2010) who found that differences in biomarker half-life and concentrations within and between people are substantial in homogeneous exposure groups, based on the analysis of about 7000 observations from more than 40 biological monitoring studies with over 200 volunteers and various types of chemicals. Furthermore, the dynamics of exposure are likely to be different in incident exposure settings compared to exposure settings in occupational and public health studies: incidents usually result in a relatively short period (minutes to hours) of relatively high exposure levels, whereas occupational and public health scenarios generally deal with chronic exposure (starting from a single working day) to relatively low or moderate concentrations. Depending on the availability of contextual information of the incident, it may also be more difficult to define the exact moment and duration of the exposure.

Uncertainty about the relevant exposure scenario of the incident and variation in the collected biomonitoring data, may hinder the reconstruction of reliable estimates of the external exposure of individuals at the time of the incident. Therefore, it is important that the applied reconstruction method for the calculation of the (external) exposure at the time of the incident based on measured internal biomonitoring data, is able to take into account uncertainty and variability of the relevant parameters. So far, most of these methods neglect variation in the model predictions due to inter-individual differences (variability) and uncertainty (in measured parameter values). However, insight in the influence of interindividual variability and uncertainty is essential to assess the reliability and usefulness of reconstructed exposure estimates after incidents.

The aim of this paper was to quantify the variation in predicted environmental air concentrations by means of reversed dosimetry modeling after a chemical incident as a result of uncertainty in chemical-specific input data and variability in physiological parameters. As an example, human biomonitoring data from a chemical incident with acrylonitrile were used to identify the main sources of variability and uncertainty on the reconstructed air concentration at the time of the incident.

2. Material and methods

2.1. BioNormtox model

The human PBPK model BioNormtox was used to simulate concentrations of acrylonitrile (ACN) and its metabolites after a chemical incident. The model is briefly described here (see also Fig. 1), while a more detailed model description can be found in Huizer et al. (2012) and Huizer et al. (2014). BioNormtox model contains 10 biological compartments. Tissue:water partitioning is predicted with a Quantitative Structure-Activity Relationship (QSAR) as derived by Hendriks et al. (2005). The prediction of chemical absorption in the respiratory tract follows Mork and Johanson (2006) and Mork et al., (2009) to account for the so-called washin–washout effect of polar chemicals. Biotransformation follows Michaelis–Menten kinetics with the parameters V_{max} (maximum velocity of metabolism) and K_m (Michaelis–Menten constant).

Variation in the model output can be quantified as interindividual variability and uncertainty separately, based on the assigned parameter distributions. Interindividual variability for both resting conditions and light work was defined by literature-based distributions for human physiological parameters (Table SI-A). Continuous physiological parameters, such as body weight and cardiac output, were considered to follow a lognormal distribution (Gaddum, 1945; Slob, 1994; Wayne, 1990). Fractions, such as tissue composition (water, proteins and fat fractions), were described by Beta distributions or in case limited data were available by betaPERT disctributions (Van Hauwermeiren and Vose, 2009).

Uncertainty in physico-chemical and metabolic parameters was quantified with a lognormal distribution, except for the affinity exponents and intercepts of the QSAR that were described by

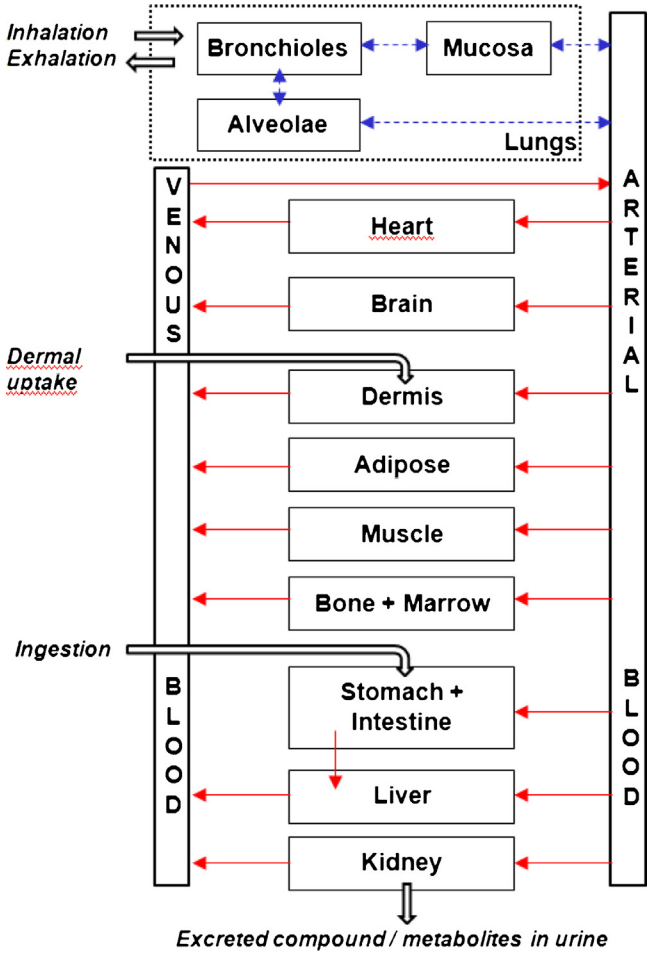

Fig. 1. Structure of the BioNormtox model. The continuous lines (red) represent blood flows between tissues, whereas the dashed lines (blue) represent the exchange of the parent compound or metabolites between the respiratory tract and the arterial blood.