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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.

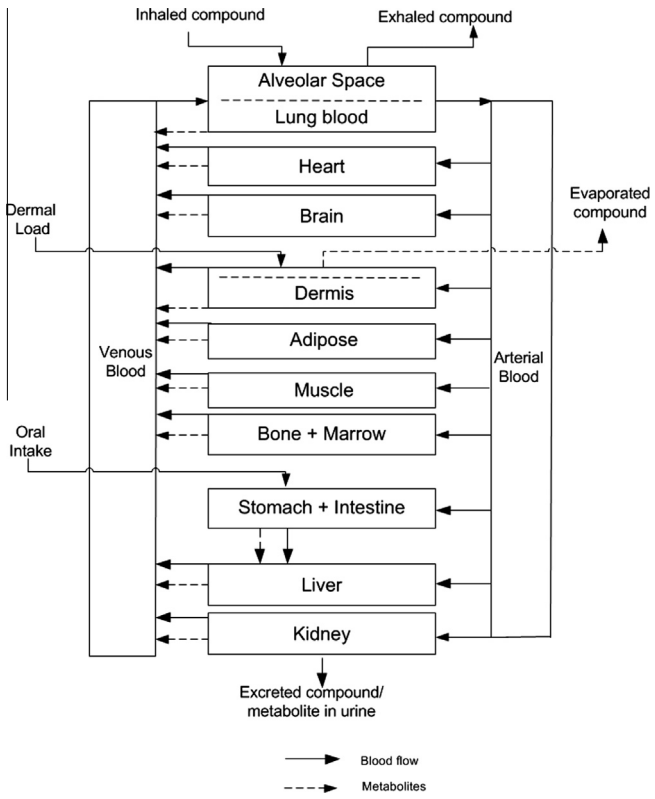

Fig. 1. A schematic of the IndusChemFate model developed by Jongeneelen et al. Source: CEFIC-LRI website

The semi-generic Jongeneelen IndusChemFate v2.00 model is freely available from the CEFIC-LRI-website and this version already includes necessary input values for 14 chemicals (http://cefic-lri.org/lri_toolbox/induschemfate/).

This semi-generic model is claimed to be suitable for first-tier risk assessment on chemicals (Jongeneelen and Ten Berge, 2011).

Its main advantage is the relatively low number of parameters needed to predict the internal dose of chemicals and/or metabolites; tissue partition coefficients are calculated by the QSARs in the model, based on the physicochemical characteristics of the investigated substance. This minimizes the need for tissue partitioning data obtained from animal studies. The model provides the opportunity to deal with a parent compound and up to 4 successive metabolites. If not yet available in the database linked to the Jongeneelen model, only metabolic clearance parameters specific for that particular parent chemical are needed.

2.1.2. Models used for comparison

Specific models developed for a particular parent chemical were used to evaluate the accuracy of the Jongeneelen model. Table 1 of Supplementary Data summarizes the references of the chemical-specific models used in this study.

2.2. Chemicals

The 9 chemicals selected for investigation are: dichloromethane (DCM), benzene (BNZ), xylene (XYL), toluene (TOL), styrene (STY), 2-propanol (2-P), methanol (MeOH), trichloroethylene (TCE), and tetrachloroethylene (PCE). The selection of these chemicals was primarily based on a review of acute incidents with hazardous chemicals in the Netherlands (Hunault et al., 2014) revealing that VOCs represent about 23% of all acute releases. Another reason for selecting these nine chemicals was their frequent use as industrial solvents.

Exposure scenario for semi-generic PBTK modelling	Data used for comparison to IndusChemFate modelling
Volunteer studies	Experimental data
Case reports	Incidental data Chemical-specific PBTK modelling
ERPG-3 levels	Chemical-specific PBTK modelling

Fig. 2. Schematic of the steps in the evaluation of the Jongeneelen semi-generic model.

2.3. Simulations

We assessed the predictive performance of the semi-generic model by carrying out simulations.

2.3.1. Input information

In order to calculate the internal dose after an exposure to a chemical, the semi-generic Jongeneelen model requires information about the physicochemical characteristics and the metabolic parameters of the considered compound (Table 2 of Supplementary Data). The origin of these data and the values that were used in performing the calculations are described in the Supplementary Data.

2.3.2. Human data

Human studies were selected to collect observed human data on chemical concentrations in blood after acute exposure. Studies were identified from scientific literature researched by two investigators, who followed the same procedure, which is described in the Supplementary Data.

When studies reported inhaled concentrations in parts per million (ppm), we converted them into milligram per cubic meter, using the following formula (CCOHS, 2013):

$$\text{concentration } [\text{mg m}^{-3}] = \text{concentration } [\text{ppm}] \times \text{MW } [\text{grams}]/24.45$$

Three categories of simulations were performed: one to simulate concentration–time profiles found in controlled volunteer studies (low exposure dose), one to simulate accidental exposures (case reports, medium to high exposure dose) and lastly, one to simulate exposure at ERPG-3 levels (high exposure dose, see Fig. 2). In the first category, human experimental measurements were used to assess the semi-generic predictions. In the second category, case reports data and predictions made with the chemical-specific models were available for the assessment of the semi-generic model. In the third category of ERPG-3 levels simulations, we could only compare the semi-generic model and the model that was specifically set up for that chemical. ERPG-3 levels are used in practice by health professionals not so familiar with PBTK models and in charge of victims acutely exposed to chemicals.

2.3.3. Software

Simulations of the semi-generic Jongeneelen model v2.00 were run in MS Excel version 2004 on Windows XP Service pack 3. The specific models were run either in acslX version 11.8 or in Berkeley-Madonna software version 8.3.11 on Windows XP Service pack 3.

2.4. Evaluation criteria

We evaluated the Jongeneelen model using the report of the International Program on Chemical Safety, part of the Global Harmonization Project of the WHO (IPCS, 2010). This document describes good practice in the evaluation of PBTK models.

The following evaluation criteria were used to evaluate the possible usefulness of the Jongeneelen semi-generic model for health professionals:

1. The mathematical description by the model of absorption, distribution, metabolism and elimination processes (ADME) should be consistent with what is known about the compound's kinetics in humans.
2. The shape of the blood time-concentration curve should resemble the shape of the observed data or the shape simulated by the chemical-specific model when no 'real-life' human measurements are available.
3. Blood concentrations predictions should, on average, be within a factor of 2 of experimental data or chemical-specific model

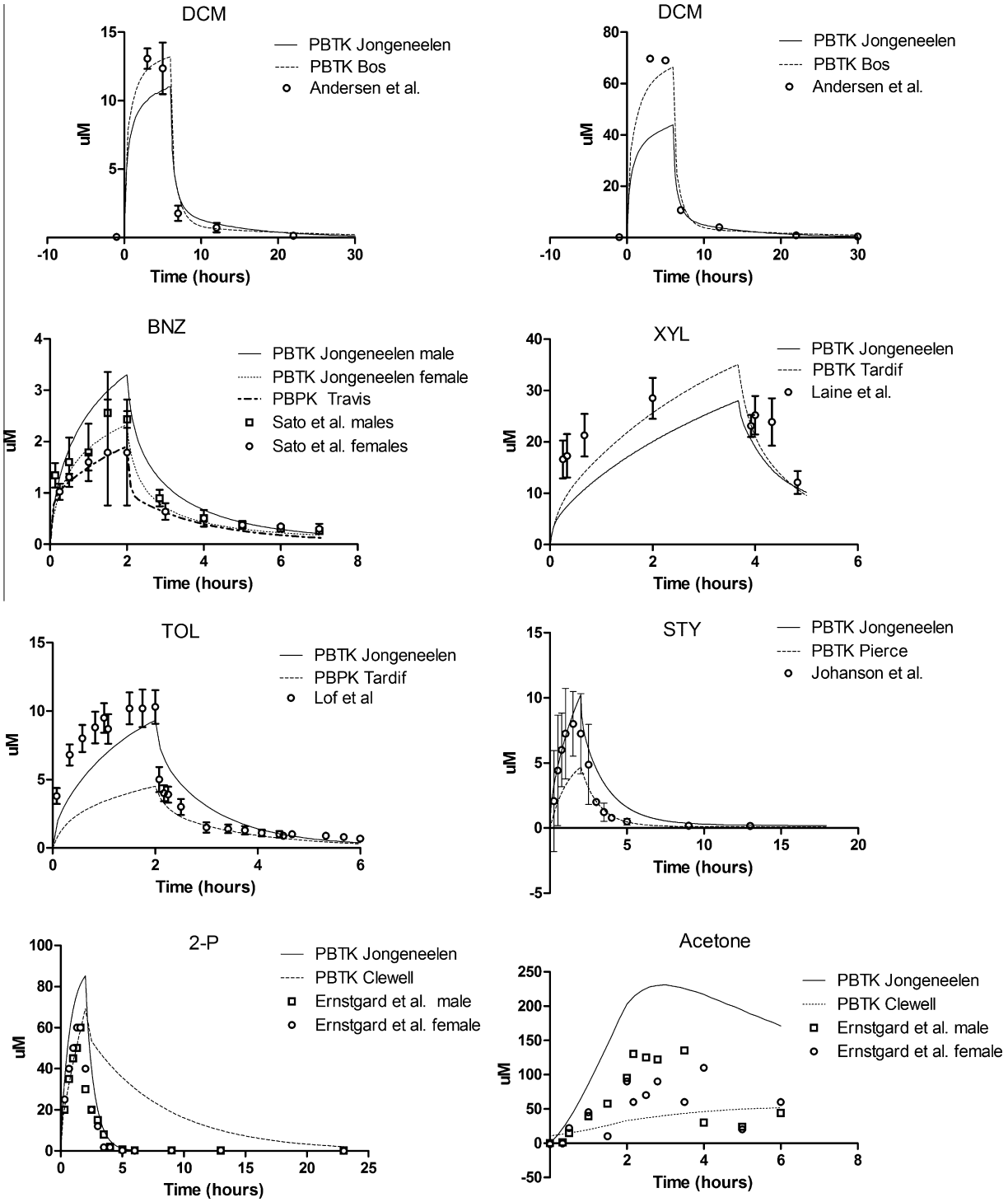

Fig. 3. Experimental and calculated data on exposures from volunteer studies for dichloromethane (347 or 1215 mg m^{-3}), benzene (80 mg m^{-3}), xylene (870 mg m^{-3}), toluene (200 mg m^{-3}), styrene (213 mg m^{-3}), isopropanol and acetone (350 mg m^{-3}).

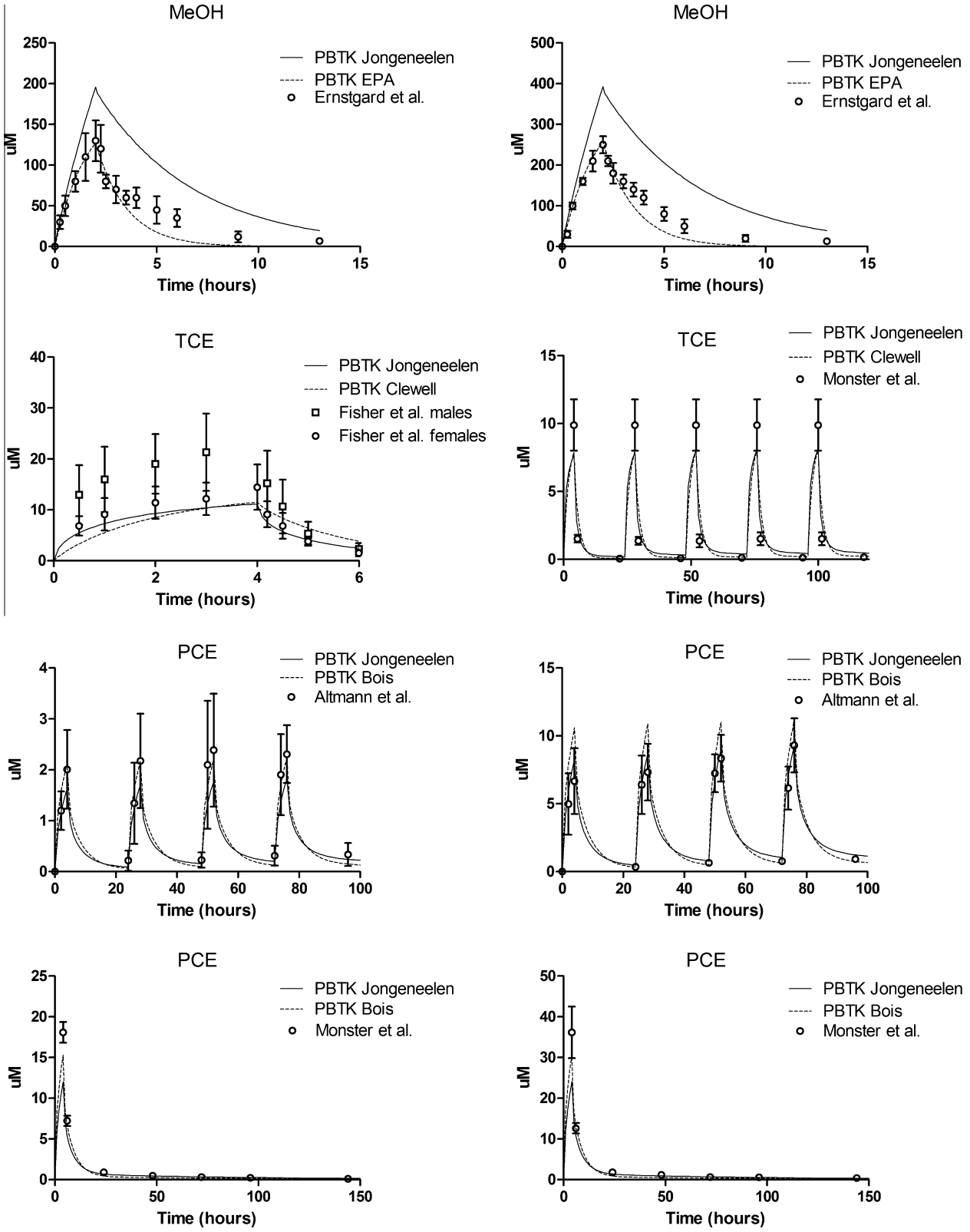

Fig. 4. Experimental and calculated data on exposures from volunteer studies for methanol (131 or 262 mg m^{-3}), trichloroethylene (537 mg m^{-3} or 376 mg m^{-3} for 5 days) and tetrachloroethylene (68 or 339 mg m^{-3} for 4 days, 488 or 977 mg m^{-3} for 4 h).

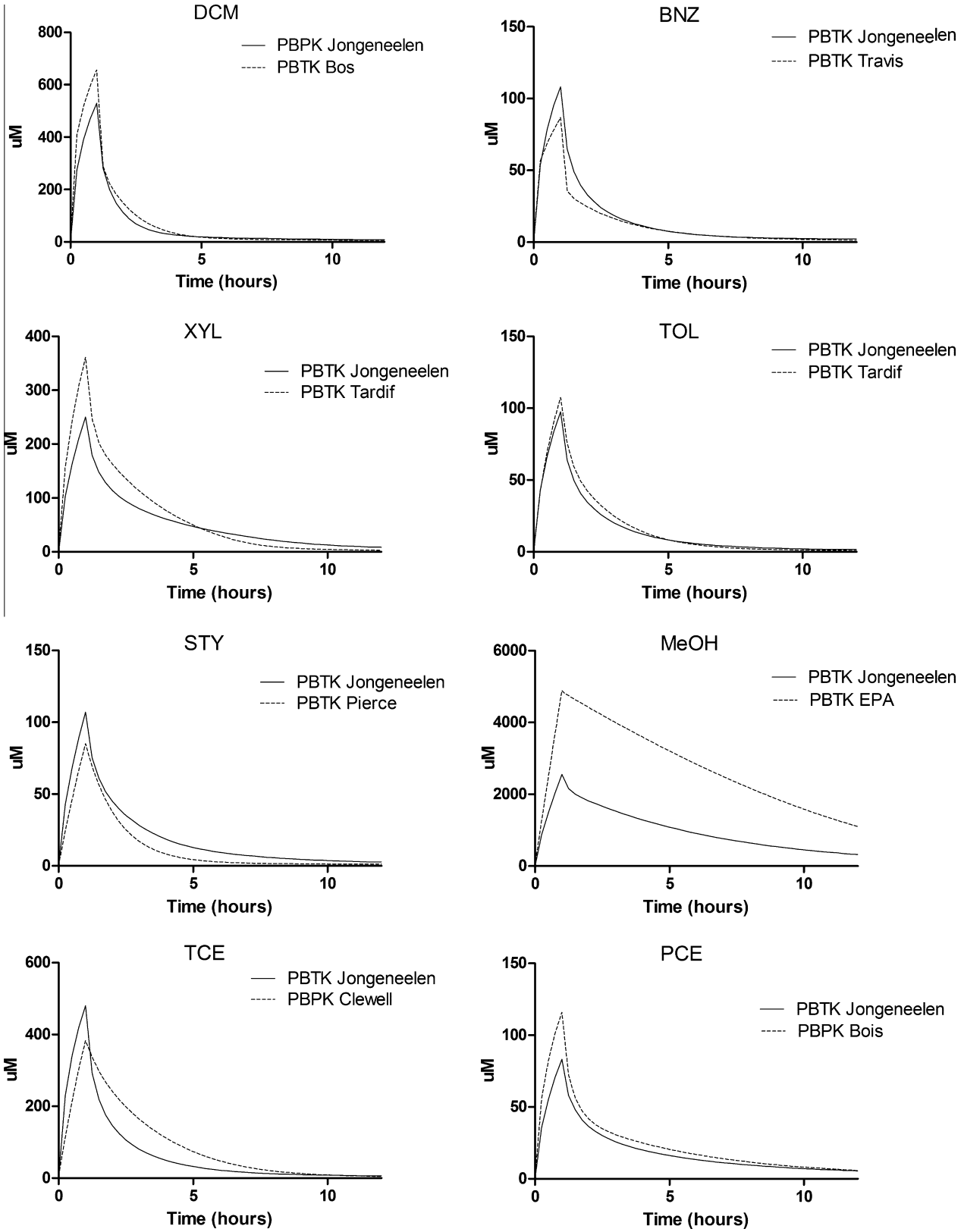

Fig. 5. Simulations by the chemical-specific models and the semi-generic Jongeneelen model of ERPG-3 levels for DCM (4000 ppm), BNZ (1000 ppm), XYL (2500 ppm), TOL (1000 ppm), STY (1000 ppm), MeOH (5000 ppm), TCE (5000 ppm) and PCE (1000 ppm).

predictions when no 'real-life' human measurements are available. This value of '2' is mentioned in the WHO document (IPCS, 2010).

3. Results

3.1. Mathematical description of ADME by the semi-generic Jongeneelen's model

For most chemicals, the semi-generic model was able to simulate the different ADME processes. However, two types of problems arose: a) simulating the formation of carboxy-hemoglobin (HbCO, an endogenous complex formed following the endogenous production of CO) in the case of DCM and b) taking into account the endogenous production of a chemical or a metabolite: MeOH and acetone (metabolite of 2-P).

3.1.1. DCM

The production of HbCO that follows DCM exposure could not be modeled because its formation does not follow Michaelis–Menten kinetics. Partial transformation of DCM by glutathione-S-transferase enzymes, followed by chemical degradation of reactive intermediates is difficult to model with saturable Michaelis–Menten kinetics. Despite this shortcoming, calculations for the parent compound were satisfactory.

3.1.2. Methanol & acetone

The semi-generic model was not able to handle the endogenous production of certain chemicals, namely MeOH and acetone (metabolite of 2-P). The 'background' levels of these compounds in the human body vary over time, depending on factors such as food intake and physical activity. Therefore, baseline data were needed to correct the calculated internal dose for the endogenous production of MeOH and acetone.

3.2. Volunteer studies simulations (low exposure dose)

3.2.1. Data used for exposure input

We used papers reporting on eleven volunteer studies with data on the nine chemicals under study to simulate different exposure scenarios (Table 3 of Supplementary Data).

3.2.2. Comparison of the semi-generic model predictions to human volunteer data

Figs. 3 and 4 show the simulations of the Jongeneelen model and the experimental data. The shapes of the simulated curves were comparable to those of the blood profiles measured in the volunteer studies. The Jongeneelen model could predict kinetic profiles in the blood following exposures within a factor 2 for all chemicals except MeOH, which was within a factor 3.

3.3. Case reports simulations (medium to high exposure dose)

3.3.1. Data used for exposure input

Table 4 of Supplementary Data summarizes the data used for the case report simulations. Case reports mentioning high dose exposures could be found for eight out of the nine chemicals (but not for benzene). Case reports on DCM, XYL, TOL and STY, concerned inhalation exposure. Case reports on 2-P, MeOH, TCE and PCE concerned ingestion.

The absorption rate constant for 2-P was set to 10/h instead of the value of 3/h which is the general default value in the Jongeneelen semi-generic model, based on the fact that absorption of 2-P is generally considered to be very rapid. We based this value on the absorption rate constant used in the 2-P-specific model (Clewell et al., 2001). The absorption rate constant for MeOH was set to 0.1/h, given that it is considered to be rate-limited. Therefore, high doses would have a very slow (0.1) absorption relative to the absolute amount of MeOH ingested (EPA, 2011). The cases with XYL and STY exposure did not report any blood levels. Consequently, the corresponding chemical-specific models were used as a gold standard to assess the performance of the semi-generic model.

Table 1
Evaluation of the semi-generic model.

	Structure[a]	Curve Shape comparable[b]			Predicted values within factor 2[c]		
		Vol.	Cases	ERPG-3	Vol.	Cases	ERPG-3
DCM	–	+	NA	+	+	+	+
BNZ	+	+	NA	+	+	NA	+
XYL	+	+	NA	+	+	+	+
TOL	+	+	NA	+	+	+	+
STY	+	+	NA	+	+	+	–
2-P	–	+	NA	NA	+	+	+
MeOH	–	+	NA	+	–	–	–
TCE	+	+	NA	+	+	+	+
PCE	+	+	NA	+	+	–	+

"+" = well, "–" = not, "NA" = not possible to judge.
[a] Implies that the PBTK model can produce calculations concerning kinetics of known acute toxic end points.
[b] Implies that the curve resembles the gold standard in absorption phase, distribution phase, elimination phase.
[c] Predicted values should roughly be within a factor 2 of the gold standard.

3.3.2. Comparison of the semi-generic model predictions to case-reports data and chemical-specific modeling

Fig. 1 of Supplementary Data shows that the curve shapes predicted by the semi-generic model are comparable with those generated by the chemical-specific models. The C_{max} and the elimination phases predicted by the Jongeneelen model and chemical-specific models were also comparable. However, the predicted shapes of the semi-generic model curves and the shapes of the chemical-specific models curves were less similar in the simulations following ingestion of 2-P, MeOH, TCE and PCE. These predictions ranged between a factor of 3–5 at some points, rather than a factor of 2 at all times. Comparison of the semi-generic model predictions to blood data from the case reports was tedious, as the information from case reports was limited to one-time measurement.

3.4. ERPG-3 (high exposure dose)

3.4.1. Data used for exposure input

Table 5 of Supplementary Data summarizes the data used for the ERPG-3 simulations. For 2-P, no AEGL or ERPG-3 values exist.

3.4.2. Comparison of the semi-generic model predictions to chemical-specific modeling

Just as in the volunteer studies and case reports with inhalation exposures, the Jongeneelen and chemical-specific models showed a high degree of concordance in curve shapes (Fig. 5).

The performance of the semi-generic model was good when compared with the chemical-specific models, except in the case of MeOH. The semi-generic model predictions for MeOH did not range within a factor of 2 at some points, but within a factor 3–5.

3.5. Summary of the results

Table 1 summarizes the assessment of the semi-generic model. The table specifies how the model performed for each compound and each type of data used, according to the three assessment

criteria (structure, curve shape and calculated values). The semi-generic PBTK model performed correctly (shape and calculated values) for eight out of nine parent chemicals (not for MeOH). For DCM, 2-P and MeOH, its structure was considered as non-adequate as the model could not simulate the formation of HbCO, which is one of the toxic end-points of dichloromethane nor could it cope with the endogenous production of acetone (being a metabolite of 2-propanol) and of methanol.

4. Discussion

This study evaluates whether a semi-generic PBTK model, the Jongeneelen model, is accurate enough to be used by health professionals in risk assessment after acute exposure to particular VOCs. We aimed to see whether this model could be used in acute risk assessment as a 'quick-and-dirty' method to get a crude estimation of the exposure dose. As it is impossible to evaluate the Jongeneelen model performance for a high number of chemical compounds, we limited ourselves to nine VOCs frequently encountered in acute chemical incidents in the Netherlands between 2008 and 2010 (Hunault et al., 2014). The results of this study show that the Jongeneelen model can readily be used in risk assessment for six out of the nine evaluated chemicals: (1) benzene (BNZ); (2) xylene (XYL); (3) styrene (STY); (4) toluene (TOL); (5) trichloroethylene (TCE); and (6) tetrachloroethylene (PCE). For dichloromethane (DCM) and isopropanol (2-P), the model has produced accurate calculations for the parent compounds but not for their acutely toxic metabolites. In the case of methanol (MeOH), the model was not accurate. For more accurate and detailed calculations, outside an emergency situation, and for volatile organic compounds that linked to endogenous metabolites, a chemical-specific PBTK modeling approach remains preferable.

The comparison of the semi-generic model predictions with reference data was generally satisfactory for both shape and levels. However, our study also establishes two major limits of the semi-generic model. Firstly, the formation of HbCO (an important toxicity end-point upon high level DCM exposure) was impossible to implement because this reaction does not follow Michaelis–Menten kinetics. Secondly, concentration predictions for compounds that are also endogenously produced was not satisfactory, as seen in the examples of MeOH and 2-P intoxications. Acetone, which is the metabolite of 2-P, and MeOH are endogenously produced in quantities that vary between individuals, but the semi-generic PBTK model does not adjust for this. We therefore do not recommend using the Jongeneelen semi-generic model in the case of intoxication with chemicals that are known with complex follow up kinetics (not following Michaelis–Menten mechanisms) and intoxications with chemicals that are also endogenous metabolites or are known to be metabolized to endogenous metabolites. Further, Jongeneelen's model uses algorithms that fix the partition coefficient values to 0.1 when $\log K_{ow}$ is below 0.4. This had undesirable consequences for the calculations of concentrations of MeOH, as this compound has a very low $\log K_{ow}$ (−0.7). Predictions for MeOH deviated more than a factor 2 in low as well as high doses.

In this study, we used available human data present in the international literature. Human experimental data could be found only for relatively low exposure doses, but data are lacking for high exposure doses. Comparison of the simulations obtained by the semi-generic model with data from high exposure doses in case reports studies was difficult because they often reported only one concentration measurement. As the next best alternative, we chose to use the chemical-specific PBTK models as reference points for evaluation, since these were all validated using animal studies with doses.

Chemical-specific PBTK models are more elaborate than the semi-generic model. These specific models are usually developed and validated using data from animal studies. If a species has a similar metabolism to humans, then, a specific animal PBTK model can first be developed for this species and subsequently adapted to humans. The same PBTK principles remain in both species. Therefore, if there are no kinetic differences across a range of exposure doses, it is assumed here that the human model is valid for high exposure doses if the corresponding specific PBTK animal model has been successfully validated with high exposure doses. These validated animal models are subsequently adapted to humans by changing organ blood flows and volumes, which usually differ between animals and humans. Partition coefficients are also replaced when possible; however, this data is often lacking. Between humans, differences related to absorption and distribution across a range of exposure doses are unlikely because absorption and distribution of VOCs are based on diffusion. Further, the saturable nature of VOC metabolism is integrated into the semi-generic model. Therefore, based on the above, we only cannot rule out a potential difference between the investigated species and humans in the elimination kinetics of VOCs. A possible mechanism could be a difference in levels at which kidney failure occurs. If such an occurrence would happen, the semi-generic model can readily be set to accommodate such a change.

For practical purposes, a PBTK model should be easy to use by non-specialists in PBTK modeling. The Jongeneelen IndusChemFate model still requires a basic level of experience and kinetic knowledge although it is much easier than the chemical-specific models using e.g., acslX. It is strongly advised to read the manual but this requires some time investment. Health professionals (e.g. clinical toxicologists, or Public Health Advisors on Hazardous Materials) might, then, use information derived from such a model, to assist their decision making when people are acutely exposed to chemical compounds. The major advantage of the Jongeneelen semi-generic PBTK model is its implementation in Excel, which makes it easy and intuitive to use. Few inputs are required to perform simulations, which can be performed for different types of subjects (men, women, obese, and active people), inhalation exposure and different chemical compounds. In addition, the model is freely available on the website of the European Chemical Industry Council (CEFIC). The only constraints prior to performing predictions with the Jongeneelen semi-generic model are to search for both physicochemical properties of a compound and kinetic parameters relevant to describe the human condition.

Table 2
Predicted maximum blood levels by Jongeneelen's semi-generic PBTK model using AEGLs for toluene. When C_{max} is determined through biomonitoring, these values can be used to assess whether the population at risk has probably been exposed to levels exceeding AEGLs.[a]

TOL Interim AEGLs						
Time	AEGL 1		AEGL 2		AEGL 3	
	Air levels (ppm)	C_{max} (μM)	Air levels (ppm)	C_{max} (μM)	Air levels (ppm)	C_{max} (μM)
10 min	200	6.02 (1.9)	3100	106.2 (33.61)	13000	441.63 (139.76)
30 min	200	10.9 (3.45)	1600	108.6 (34.37)	6100	425.56 (134.67)
60 min	200	15.8 (5)	1200	118.2 (37.41)	4500	458.56 (145.11)
4 h	200	29.96 (9.48)	790	143.72 (45.48)	3000	571.68 (180.91)
8 h	200	37.4 (11.84)	650	145.43 (46.02)	2500	474.85 (150.27)

[a] An assessment factor of 3.16 was used to account for interindividual variability in toxicokinetics (in brackets).

Such kinetic parameters might be drawn from in vitro data, animal studies or studies involving human material or even subjects. It can happen that such data is absent. In that case, parameter estimation is the next best solution, which requires information on the fate of the chemical throughout time in relevant biological materials. A total absence of metabolism constants may limit the applicability of the "semi-generic" method in the emergency case. This study has collected physicochemical data and human kinetic parameters in a structured way for eight additional chemicals compared to the current version (v2.0) of the Jongeneelen model on the CEFIC site, and thus further facilitates the use of this model.

The semi-generic Jongeneelen model can be used to determine whether or not it is worthwhile to conduct a biomonitoring study. Biomonitoring is defined as a method for assessing human exposure to chemicals by measuring the parent compound or its metabolites in human tissues or specimens, such as blood or urine (CDC, 2005). The shapes of the concentration–time curves of the semi-generic model were similar to the ones of the chemical-specific models for all chemical compounds. The semi-generic Jongeneelen model could therefore help determine the time-frame in which to sensibly collect samples, so as to evaluate the internal dose following exposure.

PBTK models can also be used for reverse dosimetry, which is using a PBTK model to estimate in reverse the external exposure dose based on chemical or metabolite concentrations measured in blood or urine samples of exposed people (Tan et al., 2007). The estimated external exposure is subsequently compared with toxicity values (MCL, etc.). As an example, Table 2 shows ranges of toluene peak blood levels calculated in reverse from interim AEGL values. We have assumed that the peak blood levels can vary by a factor 3.16 (square root of 10) between individuals (ECETOC, 2003).

PBTK models are also used to improve risk assessments after chemical exposure concerning occupational health. In occupational medicine, exposure to chemicals can consist of several short exposure periods within one day. The Jongeneelen model does not have any alternatives for multiple short-term exposures, different exposures varying in dose or physical activity, within a day. So far, exposure simulations are sometimes over-simplified in order to suit semi-generic modeling in the absence of other possibilities.

One limitation of our study is that the inter-individual variability has not been extensively studied for the Jongeneelen model. For example, variability due to gender has been evaluated for only two chemical compounds (BNZ and TCE). The ability of the semi-generic model to simulate the inter-individual variability is limited as genetic inter-individual differences of CYP enzymes, responsible for the majority of metabolism of xenobiotics, cannot be simulated. Furthermore, a subject's weight cannot be changed. Standardly, the semi-generic Jongeneelen model calculates with the average weight of an adult of 70 kg, and the average weight of an 'obese' adult of 80 kg (as mentioned in the PBTK Jongeneelen model user manual, version 2.00, 2011).

A second limitation is that we have not quantified the uncertainty within simulations of the Jongeneelen model. Uncertainty can be related to parameters used in the model, in particular the biochemical and physicochemical ones. Physicochemical data are reliable and not controversial, whereas metabolic rates and absorption constants can vary from individual to individual. To overcome this problem, we used parameters from validated specific models. Therefore, we think that little uncertainty was introduced.

In conclusion, the Jongeneelen semi-generic model performs surprisingly well, despite its simplicity. The model can readily be used in risk assessment for six chemicals: benzene (BNZ), xylene (XYL), styrene (STY), toluene (TOL), trichloroethylene (TCE) and tetrachloroethylene (PCE). This model is easier to use than the existing specific models. We do not recommend using the Jongeneelen model in risk assessment for methanol (MeOH). In the case of dichloromethane (DCM) and isopropanol (2-P), accurate predictions of the *parent* chemical are possible but the toxic metabolite cannot be reliably calculated. For more accurate and detailed calculations, outside an emergency situation, and for volatile organic compounds that linked to endogenous metabolites, a chemical-specific PBTK modeling approach remains preferable.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.chemosphere.2015.02.048.

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