Tomicic, C. M ; Vernez, D. **Sex differences in urinary levels of several biological indicators of exposure: a simulation study using a compartmental-based toxicokinetic model.** Journal of Occupational and Environmental Hygiene, 11(6):377-387, 2014.

Postprint version	Final draft post-refereeing
Journal website	www.tandfonline.com/loi/uoeh
Pubmed link	http://www.ncbi.nlm.nih.gov/pubmed/24372376
DOI	DOI:10.1080/15459624.2013.875180

Sex differences in urinary levels of several biological indicators of exposure: a simulation study using a compartmental based toxicokinetic model.

Catherine Tomicic[1], David Vernez[1]
[1] Institute for Work and Health, University of Lausanne, Lausanne, Switzerland

Correspondence to: Catherine Tomicic ; e-mail: Catherine.Tomicic@hospvd.ch

Key words toxicokinetic modeling, human biomonitoring, sex differences, organic solvents

Exposition word count 3354

ABSTRACT

Toxicokinetic modeling is a useful tool to describe or predict the behavior of a chemical agent in the human or animal organism. A general model based on four compartments was developed in a previous study in order to quantify the effect of human variability on a wide range of biological exposure indicators.

The aim of this study was to adapt this existing general toxicokinetic model to three organic solvents, which were methyl ethyl ketone, 1-methoxy-2-propanol and 1,1,1,-trichloroethane, and to take into account sex differences. We assessed in a previous human volunteer study the impact of sex on different biomarkers of exposure corresponding to the three organic solvents mentioned above. Results from that study suggested that not only physiological differences between men and women but also differences due to sex hormones levels could influence the toxicokinetics of the solvents. In fact the use of hormonal contraceptive had an effect on the urinary levels of several biomarkers, suggesting that exogenous sex hormones could influence CYP2E1 enzyme activity. These experimental data were used to calibrate the toxicokinetic models developed in this study.

Our results showed that it was possible to use an existing general toxicokinetic model for other compounds. In fact, most of the simulation results showed good agreement with the experimental data obtained for the studied solvents, with a percentage of model predictions that lies within the 95% confidence interval varying from 44.4 to 90 %. Results pointed out that for same exposure conditions, men and women can show important differences in urinary levels of biological indicators of exposure. Moreover, when running the models by simulating industrial working conditions, these differences could even be more pronounced.

In conclusion, a general and simple toxicokinetic model, adapted for three well known organic solvents, allowed us to show that metabolic parameters can have an important impact on the urinary levels of the corresponding biomarkers. These observations give evidence of an

interindividual variablity, an aspect that should have its place in the approaches for setting limits of occupational exposure.

INTRODUCTION

Toxicokinetic (TK) modeling is a useful tool to describe or predict the behavior of a chemical agent in the human or animal organism. Interest in it arose from the need to relate internal concentrations of active compounds with the external exposure conditions.[1] Data-based pharmacokinetic models were first developed in the 1920's and several disciplines like inhalation anesthesia, chemical engineering, toxicology or computer sciences, contributed to their maturation throughout the last decades.[2] Fiserova-Bergerova for example contributed intensively to the development of toxicokinetic models for inhaled organic solvents in humans.[3-5]

Depending on the substance, the complexity of the kinetics and the literature data available, two types of models can be used.[6] Classical pharmacokinetic/toxicokinetic (PK/TK) models, represented by compartments within which the chemical is assumed to be homogeneously distributed, are suitable when limited toxicological data is available. Various data-dependent parameters, as for example the volume of distribution or the half-life, can be derived from the analysis of classical compartments models. They are limited from a structural point of view but can be used to make generalizations. Physiologically-based toxicokinetic (PBTK) models, which rely on the anatomical and physiological structure of the body, are preferred when the purpose is to know the substance's concentration in different tissues or organs. They are more informative and usually allow for a better extrapolation

processes but they require a more intensive input data, which can raise more complex statistical issues.

Several authors investigated the quantification of biological variability through TK/PBTK modeling. Droz et al.[7], for example, developed a PBTK model for different workers under variable industrial environments while Pierrehumbert et al.[8] tried to develop a general compartmental based TK model. The variability extent index and the main parameters affecting biological indicators were investigated by Truchon et al.[9] while the impact of environmental variability was quantified by Berthet et al.[10]. Clewell et al.[11] have described the contribution of age and sex to biological variability by developing a physiologically based pharmacokinetic model model to determine the tissue concentration as a function of time of some xenobiotics.

The influence of sex on toxicokinetics may involve female-male differences in physical constitution (body water space, muscle mass, body fat, and blood flow), physiology (menopause and menstruation cycle), hormones (contraceptive pill) as well as metabolising enzymes (Löf et al., 1998).[12] Although we can establish a list of contributing factors, as shown in a framework for sex differences by Gochfeld[13], their relative importance is unknown for different chemicals of occupational interest.

The aim of this study was to adapt an existing general toxicokinetic model to three organic solvents, which were methyl ethyl ketone (MEK), 1-methoxy-2-propanol (1M2P) and 1,1,1,-trichloroethane (111TCE), and to take into account sex differences. The influence of sex on different biological indicators values had been evaluated in a previous human volunteer study[14] by exposing volunteers to the three organic solvents mentioned above. Experimental data from that study was used to calibrate the present models.

MATERIAL AND METHODS

Model description

Pierrehumbert et al.[8] have developed a compartmental based toxicokinetic model in order to quantify the effect of human variability on a wide range of biological exposure indicators. By applying it to four chemicals (toluene, phenol, lead and mercury), they showed its potential to be used for further substances. We actually underline this potential of the model by adapting it to three other compounds which are MEK, 1M2P and 111TCE.

The general compartmentally based toxicokinetic model developed by Pierrehumbert et al.[8] consists of four compartments and takes into account only absorption by inhalation. The mass rate of chemical absorption into the central compartment from inhaled air is equal to the product of the chemical's mass concentration in air, the alveolar ventilation rate scaled to body weight, and the fraction of the chemical absorbed by the lungs (pulmonary retention). The chemical is distributed between the central compartment and the peripheral one, or storage compartment. These compartments can be illustrated by different tissues, depending on the chemical. The distribution can be either flow or diffusion limited and includes the permeability and affinity of the tissue for the chemical. For transfer between central and peripheral compartments, mass rates are expressed as a function of blood flow, affinity and permeability. The metabolism, described with Michaelis–Menten kinetics, can give one or more metabolites, and can occur by serial or parallel metabolism. Elimination is represented by excretion in expired air, feces and urine, or by metabolism. For excretion, estimated mass rates are based either on the half-life of the chemical/metabolite, or on its clearance (e.g. bile flow for feces, urine flow for urine, alveolar ventilation for expired air) and volume of distribution. Mathematical equations describing the general model can be found in Pierrehumbert et al.[8].

This general model was adapted to MEK, 1M2P and 111TCE using toxicokinetic data available in literature.[15-21] The simulation software used for the development of the TK models was Berkeley Madonna (version 8.0.1.), developed by Robert Macey and George Oster of the University of California at Berkeley (USA).

Model parameters

The group arithmetic means for weight, height and body fat were used in the model. Values for general physiological parameters like alveolar ventilation, cardiac output or organ blood flows corresponded to the values of a reference man. These were scaled in function of body weight. Otherwise, values were taken from literature, like partition coefficients or metabolic parameters.

Sensitivity analysis

Sensitivity analysis was performed in the same way as did Pierrehumbert et al.[8] for determining the potential parameters with an important impact on the studied biological determinants. Changes in the model output values were calculated after increasing each initial toxicokinetic parameter value by 10 % for a given time. In this study, calculations were done for one time of interest, which was at the end of exposure (t=6).

Likewise, the simulation software Berkeley Madonna also allowed to carry out a sensitivity analysis of a toxicokinetic model. Thus, this tool option was used in order to identify parameters of interest in the model during other time phases as for example during the elimination phase.

Model analyses

The toxicokinetic models obtained for MEK, 1M2P and 111TCE were first calibrated with the experimental data obtained for these three solvents in a previous human volunteer study[14].

Briefly, in this previous study, controlled human exposures were carried out in a 12 m^3 exposure chamber for each solvent separately, during six hours and at half of the threshold limit value (TLV). The human volunteers groups were composed of ten young men and fifteen young women. The latter were separated into two sub-groups by taking into account the use or not of hormonal contraceptive. Following biological indicators of exposure were determined: urinary MEK, urinary 1M2P (conjugated and total), 111TCE in blood and in expired air, metabolites of 111TCE (trichloroethanol (TCOH) and trichloroacetic acid (TCA)) in urine. The corresponding biological exposure indices (BEIs) are summarized in Table I.

Curve fitting has been performed with the software Berkeley Madonna, which can automatically find the values of one or more parameters in the model by minimizing the root-mean-square between simulated and experimental data. The sensitivity analysis allowed the identification of the main parameters that could potentially influence the urinary concentrations of the studied biomarkers of exposure. These parameters were fitted to the experimental data obtained form the previous human volunteer study[14].

From these models, it is also possible to predict the concentration of the studied substances in other biological matrices, as for example in blood which corresponds to the concentration in the central compartment of the model.

In a second step, calibrated models were used to evaluate their predictive ability, by simulating the concentration of the studied substances in other biological matrices, as for example in blood, or by changing the exposure conditions. Simulations were performed to mimic an occupational exposure at the TLV (8 h per day, 5 days per week, physical activity of 50 W for 12 h per day and at rest for the remaining 12 hours).

Statistics

A goodness-of-fit between experimental data and simulated data was assessed by calculating the percentage of model predictions that lie within the 95% confidence interval of each corresponding data point for each model and by linear regression analysis assuming that the slope yields the value of 1 in the case of perfect agreement.

RESULTS

Toxicokinetic models for MEK, 1M2P and 111TCE

In most occupational exposure settings, the primary intake route for the three studied solvents is inhalation. The different compartmental TK models for the studied solvents, all metabolized via the cytochrome P450 mixed-function oxidase system, are illustrated on Figure 1.

MEK is metabolized to 2,3-butanediol, 2-butanol and 3-hydroxy-2-butanone (major metabolite), all excreted in urine. A low fraction of unchanged solvent is excreted in the exhaled air. The urinary concentration of MEK at the end of the shift has been recommended as the most appropriate biological exposure indicator. MEK is nearly equally distributed between water and fat containing tissues.[22] Thus the model is composed by a central compartment representing the total body water (TBW) and a peripheral compartment for the fatty tissues.

1M2P belongs to the family of the propylene glycol ethers (PGE) which exists under the form of two isomers, alpha-isomer and beta-isomer. The latter one, considered as an impurity in commercial use, is first transformed into 2-alkoxy acetaldehydes by alcohol

dehydrogenases, and then into alkoxyacetic acids by aldehyde dehydrogenases, a toxic metabolite. Alpha-PGE are primarily metabolized to propylene glycol, carbon dioxide and glucuronide as well as sulfate conjugates of the parent compound. The urinary 1M2P concentration at the end of the shift is an appropriate biomarker. A central compartment equivalent to TBW and a second compartment illustrating the conjugation of 1M2P constitute the TK model for 1M2P.

111TCE is metabolized to TCOH and TCA, both excreted in urine. Other minor metabolites (carbon dioxide, acetylene) are excreted in the exhaled air. The corresponding biological exposure indices are the urinary concentration of both metabolites and the blood concentrations of the parent compound and TCOH. The 111TCE concentration in the exhaled air can also be considered as a biomarker of exposure because the majority is excreted unchanged in the expired air and it can be measured several days after exposure due to its long half life in expired air. As the exposure scenarios were carried out during one day, urinary TCOH is the most appropriate biomarker for the model calibration with the experimental data. TCA concentrations are very low due to its long half life. Accumulation is possible during the week and thus, it is not an appropriate biomarker for reflecting a daily exposure. Measurements of the indicators of exposure in blood or in expired air would be more suitable in the case of a chronic exposure to the chlorinated solvent. Consequently the TK model includes a central compartment equivalent to TBW, a peripheral one constituting the fatty tissues because of its high liposolubility, and a third compartment for the considered metabolite.

The general physiological parameters used in the simulations are presented in Table II whereas the chemical specific parameters for each TK model are represented in Table III.

Sensitivity analysis

The results of the sensitivity analysis, obtained after increasing each initial toxicokinetic parameter value by 10 % for a given time and summarized in Figure 2, showed that for the MEK model, urinary MEK concentration is especially sensitive to the metabolic parameters, the cardiac output and the liver blood flow. For the 1M2P model, the metabolic parameters and the cardiac output were identified to influence most the urinary 1M2P concentrations. Urinary metabolites values for 111TCE were mainly influenced by the metabolic parameters, the different partition coefficients and the TCOH urinary excretion rate.

The sensitivity analysis carried out by the simulation software Berkeley Madonna indicated that for the MEK model, the partition coefficient between the central compartment and blood (at the beginning of the exposure as during the elimination phase) and the Michaelis-Menten maximum rate seemed to be relevant parameters. For the 1M2P model both Michaelis-Menten maximum rates, and for the 111TCE model the partition coefficient between the central compartment and air and the Michaelis-Menten maximum rate were influential. The exact values of the fitted parameters that have been identified by the sensitivity analysis are presented in Table III.

Experimental data *vs* simulated data

The percentage of model predictions that lies within the 95% confidence interval of each corresponding data point varies from 44.4 % to 87.5 % for the MEK model (44.4, 55.6 and 87.5 % for the model fitted to the data obtained for men, for women with hormonal contraceptive and for women without hormonal contraceptive respectively), from 50 % to 90 % for the 1M2P model (66.7, 80 and 50 % for the model fitted to the urinary free 1M2P data and 90, 72.7 and 55.6 % for the model fitted to the urinary total 1M2P obtained for men, for women with hormonal contraceptive and for women without hormonal contraceptive

respectively), and from 72.7 % to 88.9 % for the 111TCE model (80, 72.7 and 88.9 % for the model fitted to the data obtained for men, for women with hormonal contraceptive and for women without hormonal contraceptive respectively).

Table IV summarizes the experimental data obtained at the end of exposure in the human volunteer study[14] on one hand and the simulated values obtained at the end of exposure within the TK models on the other hand, for the considered biological determinants. Figures 3 to 6 illustrate the comparison of experimental data with simulated data for the different urinary indicators of exposure considered. Data points on Figures 3 to 6 are arithmetic mean values ± SD (standard deviation).

Regarding the goodness-of-fit between experimental data and simulated data, it can be assessed by linear regression analysis assuming that the slope yields the value of 1 in the case of perfect agreement. Thus a scatterplot of the predicted data *versus* the observed ones (see Figure 7) suggests that the toxicokinetic models seem adequate for the three studied substances, at least for the values obtained during exposure.

The predictive ability of the model showed that in the case of 111TCE for example, the maximal blood concentration in each group of volunteers was equal to 0.28 mg/l, showing no differences between them. This observation can in fact be confirmed by the experimental data obtained in the previous human volunteer study[14], where end-exposure values obtained for men, women with and without hormonal contraceptive, respectively were 362.97 (± 91.05), 306.53 (± 152.27) and 371.13 (± 240.64) µg/l, with no statistically significant differences between the different groups.

Predictive calculations were also done for estimating the urinary levels of the different biological biomarkers when workers were exposed during 8 hours per day, 5 days per week, at a 50 W work load, to the threshold limit value of each solvent studied. Results are illustrated in Figure 8 for each solvent and for each studied human volunteer group.

DISCUSSION

Our results showed that it was possible to use an existing generic toxicokinetic model for other compounds by adapting it to three organic solvents. In fact, most of the simulation results showed good agreement with the experimental data obtained in a previous human volunteer study[14]..

Regarding parameters that have been fitted in the three models, values indicate that differences between men and women can be explained by changes in metabolism, as suggested by a previous human volunteer study[14]. But the main conclusion of the latter one was that the differences observed between the human volunteers groups were due to an effect on the CYP2E1 activity by exogenous hormones. An analysis of variance in this study mainly showed an effect among women due to the use of hormonal contraceptive on the urinary levels of several biomarkers of exposure, with an increase of more than 50% in metabolites concentrations and a decrease of up to 50% in unchanged substances concentrations, suggesting an increase in their metabolism rate. This hypothesis can actually be confirmed with the obtained values when fitting the Michaelis-Menten maximum rates in the different models. The VM_1 value for the group of women with hormonal contraceptive is 2.1, 2.3 and 1.4 fold higher than the one for the group of women without hormonal contraceptive, in the MEK model, the 1M2P model and the 111TCE model respectively (see Table III notes).

Concerning phase II metabolism, Miners et al.[31] showed that glucuronidation was induced in women using oral contraceptives. In the previous human volunteer study[14], women on hormonal contraceptives appeared to excrete a higher fraction as conjugate than those not taking hormonal contraception, indicating also that sex hormones levels may influence the enzyme activity of phase II reactions but differences were not statistically significant due to a

high variability. The VM_2 value for the group of women with hormonal contraceptive is 2.5 fold higher than the one for the group of women without hormonal contraceptive (see Table III notes).

Physiological parameters are expressed in function of body weight and thus take into account possible male/female differences in pulmonary ventilation, cardiac output and organ blood flows, generally due to body size. Moreover the fact that differences are observed between women underlines Gochfeld's hypothesis[13] that toxicokinetic differences mainly involve metabolism. The author also stated that there is still a tendency to believe that most sex differences relate to morphology and body size. He pointed out that the differences in susceptibility between men and women need to be incorporated in risk assessments, as most toxicological studies still focus on only one sex.

The predictive simulations done over a week within working conditions indicated that exposure for women without hormonal contraceptive can be overestimated in the case of MEK and 1M2P but underestimated in the case of 111TCE. For the latter, Truchon et al.[9] have estimated the extent of the variability for its biomarkers, indicating that TCOH urinary levels can vary from 11 to 80 mg/l due to biological variability, without taking into account differences due to sex and age. Urinary TCOH concentrations measured in the previous human volunteer study[14] are even lower, meaning that in this case, sex differences could contribute to enlarge the extent of the variability for the considered biological indicator.

Moreover, the urinary levels in biomarkers predicted with our TK models were compared to the existing BEIs. Interestingly, urinary levels following TLV exposures to MEK and 1M2P were found to be higher than the current BEI (see Figure 8), suggesting that work load can have a significant impact on biological exposure indicators.[35]

The poorest fit of the model to data occurred in the elimination phases of the urinary biomarkers of exposure, mainly for urinary MEK and urinary 1M2P (free and total). In fact

agreement between observed and predicted values is weaker and this can lead to an over- or underestimation of the corresponding exposure level. In the case of MEK, an explanation could be the metabolic saturation, as in humans it begins at relatively low levels of exposure[18], and greater amounts of MEK would be expected to be excreted via the kidney. For 1M2P, the high variability in glucuronidation observed in the previous human volunteer study[14] could explain the differences observed between experimental and simulated data. These observations give rise to some limitations of our general model. First equations describing Michaelis-Menten kinetics were simplified by assuming that saturation would not occur for the selected biomarkers of exposure in Pierrehumbert et al.[8]. Another limitation of the model is the fact that it takes into account only the absorption of the chemicals by inhalation. Skin absorption could be relevant for some solvents when exposed to the liquid form or to aerosols but less when exposed to the vapours.

In conclusion, a general and simple toxicokinetic model, adapted for three well known organic solvents, allowed us to show that metabolic parameters can have an important impact on the urinary levels of the corresponding biomarkers. Indeed, experimental data from a previous study pointed out that for same exposure conditions, men and women can show a difference of 50 % among the urinary biological indicators levels. Moreover, when running the models by simulating industrial working conditions, these differences could be even more pronounced. These observations give evidence of an interindividual variability, an aspect that should have its place in the approaches for setting limits of occupational exposure.

ACKNOWLEDGMENTS

The present work was supported by the National Research Fund (FNR) in Luxembourg, the French Agency of Environmental and Occupational Health Safety (Anses) and the Swiss Federal Office of Public Health (FOPH). We thank first above all the late Dr Pierre-Olivier

Droz for his support and supervision of the project. We express our thanks to the group of Professor Gunnar Johanson from the Karolinska Institute (Stockholm, Sweden), particularly Ms Anna-Karin Mörk, for their support. We also want to thank Professor Thierry Buclin from the Division of Clinical Pharmacology and Toxicology (University Hospital, Lausanne, Switzerland) for the insightful discussions.

REFERENCES

1. **Andersen, M.E., R.S.H. Yang, H.J. Clewell III, and M.B. Reddy:** *Physiologically Based Pharmacokinetic Modeling. Science and Applications.* New York: Wiley-Interscience, 2005.

2. **Andersen, M.E.:** Toxicokinetic modeling and its applications in chemical risk assessment. *Toxicol. Lett.* 138:9-27 (2003).

3. **Fiserova-Bergerova, V.:** Mathematical modelling of inhalation exposure. *J. Combustion Toxicol.* 3:201-210 (1976).

4. **Fiserova-Bergerova, V., J. Vlach, and J.C. Cassady:** Predictable "individual differences" in uptake and excretion of gases and lipid soluble vapours simulation study. *Br. J. Ind. Med.* 37:42-49 (1980).

5. **Fiserova-Bergerova, V.:** Toxicokinetics of organic solvents. *Scand. J. Work Environ. Health* 11(1):7-21 (1985).

6. **Bernillon, P., and F.Y. Bois:** Statistical issues in toxicokinetic modeling: a Bayesian perspective. *Environ. Health Persp.* 108(5):883-893 (2000).

7. **Droz, P.-O., M.M. Wu, and W.G. Cumberland:** Variability in biological monitoring of solvent exposure. I. Development of a population physiological model. *Br. J. Ind. Med.* 46:447-460 (1989).

8. **Pierrehumbert, G., P.-O. Droz, R. Tardif, G. Charest-Tardif, and G. Truchon:** Impact of human variability on the biological monitoring of exposure to toluene, phenol, lead, and mercury. II. Compartimental based toxicokinetic modelling. *Toxicol. Lett.* 134:165-173 (2002).

9. **Truchon, G., R. Tardif, P.-O. Droz, G. Charest-Tardif, and G. Pierrehumbert:** Biological exposure indicators: quantification of biological variability using toxicokinetic modeling. *J. Occup. Environ. Hyg.* 3(3):137-143 (2006).

10. **Berthet, A., A. de Batz, R. Tardif, G. Charest-Tardif, G. Truchon, D. Vernez, and P.-O. Droz:** Impact of biological and environmental variabilities on biological monitoring--an approach using toxicokinetic models. *J. Occup. Environ. Hyg.* 7(3):177-184 (2010).

11. **Clewell, H.J., P.R. Gentry, T.R. Covington, R. Sarangapani, and J.G. Teeguarden:** Evaluation of the potential impact of age- and sex-specific pharmacokinetic differences on tissue dosimetry. *Toxicol. Sci.* 79:381-393 (2004).

12. **Löf, A., and G. Johanson:** Toxicokinetics of organic solvents: a review of modifying factors. *Crit. Rev. Toxicol.* 28(6):571-650 (1998).

13. **Gochfeld, M.:** Framework for gender differences in human and animal toxicology. *Environ. Res.* 104(1):4-21 (2007).

14. **Tomicic, C., M. Berode, A. Oppliger, V. Castella, F. Leyvraz, S.M. Praz-Christinaz, and B. Danuser:** Sex differences in urinary levels of several biological indicators of exposure: a human volunteer study. *Toxicol. Lett.* (2010).

15. **Reitz, R.H., J.N. McDougal, M.W. Himmelstein, R.J. Nola, and A.M. Schumann:** Physiologically based pharmacokinetic modeling with methylchloroform: implications for interspecies, high dose/low dose, and dose route extrapolations. *Toxicol. Appl. Pharm.* 95 (2):185-199 (1988).

16. **Bogen, K.T., and L.C. Hall:** Pharmacokinetics for regulatory risk analysis: The case of 1,1,1-trichloroethane (methyl chloroform). *Regul. Toxicol. Pharm.* 10(1):26-50 (1989).

17. **Liira, J., V. Riihimäki, and K. Engström:** Effects of ethanol on the kinetics of methyl ethyl ketone in man. *Br. J. Ind. Med.* 47(5):325–330 (1990a).

18. **Liira, J., G. Johanson, and V. Riihimaki:** Dose-dependent kinetics of inhaled methylethylketone in man. *Toxicol. Lett.* 50(2-3):195-201 (1990b).

19. **Thrall, K.D., J.J. Soelberg, K.K. Weitz, and A.D. Woodstock:** Development of a physiologically based pharmacokinetic model for methyl ethyl ketone in F344 rats. *J. Toxicol. Env. Health* 65(13):881-896 (2002).

20. **Corley, R.A., R.A. Gies, H. Wu, and K.K. Weitz:** Development of a physiologically based pharmacokinetic model for propylene glycol monomethyl ether and its acetate in rats and humans. *Toxicol. Lett.* 156:193-213 (2005).

21. **Kirman, C.R., L.M. Sweeney, R. Corley, and M.L. Gargas:** Using physiologically-based pharmacokinetic modeling to address nonlinear kinetics and changes in rodent physiology and metabolism due to aging and adaptation in deriving reference values for propylene glycol methyl ether and propylene glycol methyl ether acetate. *Risk Anal.* 25(2):271-284 (2005).

22. **Liira, J., V. Riihimaki, and P. Pfaffli:** Kinetics of methyl ethyl ketone in man: absorption, distribution and elimination in inhalation exposure. *Int. Arch. Occup. Environ. Health* 60(3):195-200 (1988).

23. **Fiserova-Bergerova, V.:** Extrapolation of physiological parameters for physiologically based simulation models. *Toxicol. Lett.* 79:77-86 (1995).

24. **Thomas, R.S., P.L. Bigelow, T.J. Keefe, and R.S.H. Yang:** Variability in biological exposure indices using physiologically based pharmacokinetic modeling and Monte Carlo simulation. *Am. Ind. Hyg. Assoc. J.* 57(1):23-32 (1996).

25. **Laparé, S., R. Tardif, and J. Brodeur:** Effect of various exposure scenarios on the biological monitoring of organic solvents in alveolar air II. 1-1-1-trichloroethane and trichloroethylene. *Int. Arch. Occup. Environ. Health* 67:375-394 (1995).

26. **Devanthéry, A.:** Toxico-cinétique et surveillance biologique du propylène glycol monométhyl éther. Etude sur des volontaires. Unpublished PhD thesis. Federal Polytechnic School of Lausanne, Switzerland (2003).

27. **Johanson, G., and B. Dynésius:** Liquid/air partition coefficients of six commonly used glycol ethers. *Br. J. Ind. Med.* 45(8):561–564 (1988).

28. **Nolan, R.J., N.L. Freshour, D.L. Rich, L.P. McCarty, and J.H. Saunders:** Kinetics and metabolism of inhaled methyl chloroform (1,1,1-trichloroethane) in male volunteers. *Fundam. appl. Toxicol.* 4:654-662 (1984).

29. **Tardif, R., G. Charest-Tardif, J. Brodeur, and K. Krishnan:** Physiologically based pharmacokinetic modeling of a ternary mixture alkyl benzenes in rats and humans. *Toxicol. Appl. Pharm.* 144(1):120-134 (1997).

30. **Caperos, J.R., P.-O. Droz, C.L. Hake, B.E. Humbert, and A. Jacot-Guillarmod:** 1,1,1-Trichloroethane exposure, biologic monitoring by breath and urine analyses. *Int. Arch. Occup. Environ. Health* 49(3-4):293-303 (1982).

31. **Miners, J.O., J. Attwood, D.J. Birkett:** Influence of sex and oral contraceptive steroids on paracetamol metabolism. *Br. J. Clin. Pharmacol.* 16(5):503–509 (1983).

32. **Devanthéry, A., M. Berode, P.-O. Droz:** Propylene glycol monomethyl ether occupational exposure. 3. Exposure of human volunteers. *Int. Arch. Occup. Environ. Health* 75(4):203-208 (2002).

33. **Lu, Y., S. Rieth, M. Lohitnavy, J. Dennison, H. El-Masri, H.A. Barton, J. Bruckner, and R.S.H. Yang:** Application of PBPK modeling in support of the derivation of toxicity reference values for 1,1,1-trichloroethane. *Regul. Toxicol. Pharm.* 50(2):249-260 (2008).

34. **Monster, A.C., G. Boersma, and H. Steenweg:** Kinetics of 1,1,1-trichloroethane in volunteers; influence of exposure concentration and work load. *Int. Arch. Occup. Environ. Health* 42: 293–301 (1979).

35. **Sari-Minodier, I., G. Truchon, G. Charest-Tardif, A. Bérubé, and R. Tardif:** The Effect of Workload on Biological Monitoring of Occupational Exposure to Toluene and N-Hexane: Contribution of Physiologically Based Toxicokinetic Modeling. *J. Occup. Environ. Hyg.* 6(7):415-432 (2009).

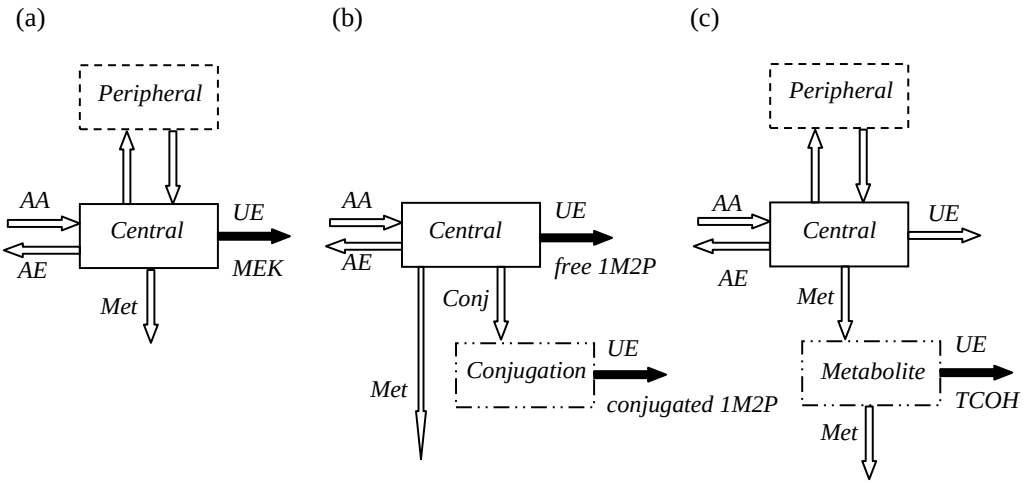


FIGURE 1. Illustration of the different compartmental based TK models for (a) MEK, (b) 1M2P and (c) 111TCE, with the black arrows indicating the biological determinants considered in this study, and with following flow rates air absorption (AA), air excretion (AE), urinary excretion (UE), metabolism (Met) and conjugation (Conj) expressed as [mg/h].

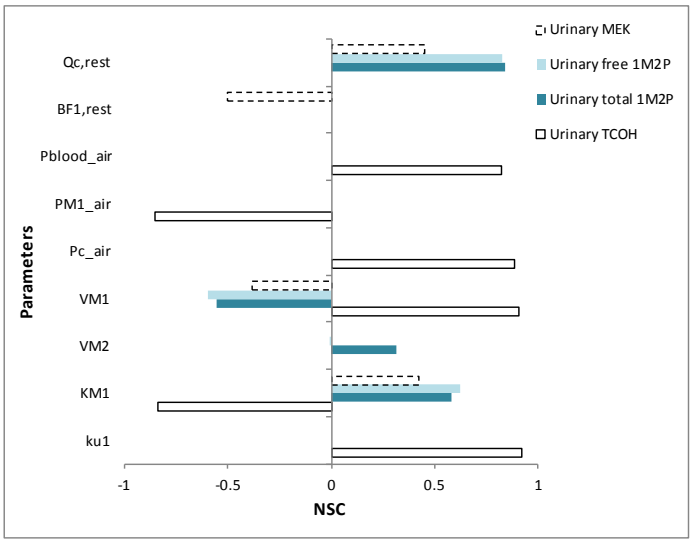


FIGURE 2: Normalized sensitivity coefficients (NSC) for the various parameters used in the TK models

(a) (b)

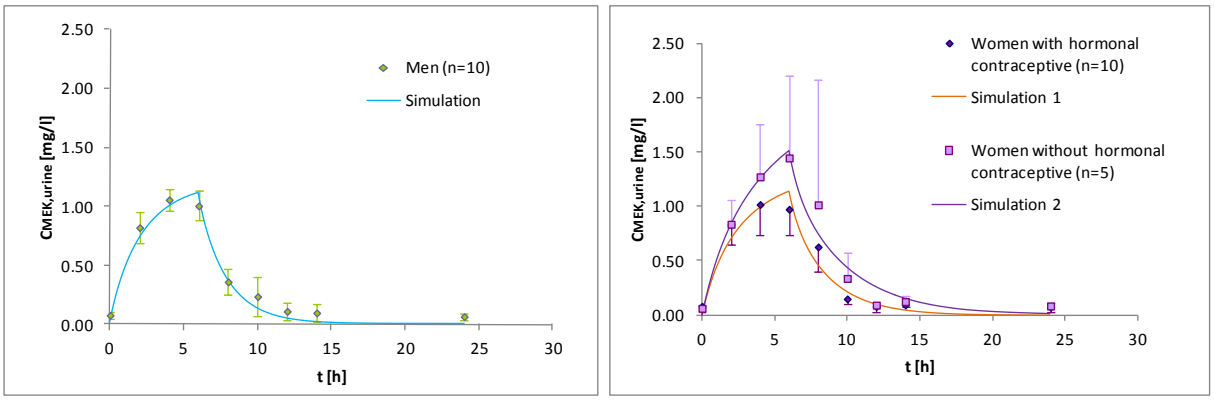


FIGURE 3. Comparison of experimental data with simulated data for urinary MEK obtained (a) in men and (b) in women. Urinary MEK concentrations as function of time were obtained after 6 hours of exposure to 99.15 (± 5.29) ppm MEK. Data points are arithmetic mean values ± SD (standard deviation); n = number of volunteers.

(a) (b)

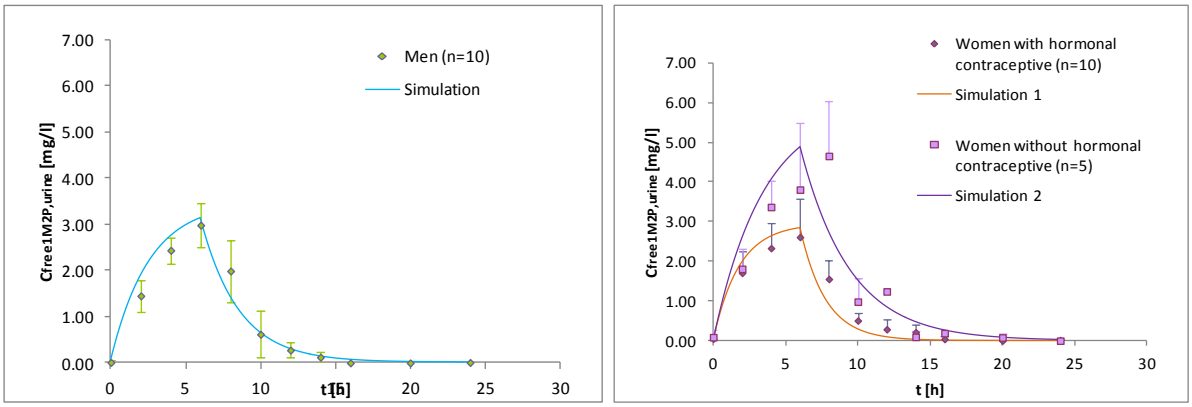


FIGURE 4. Comparison of experimental data with simulated data for urinary free 1M2P obtained (a) in men and (b) in women. Urinary free 1M2P concentrations as function of time were obtained after 6 hours of exposure to 53.22 (± 3.04) ppm of 1M2P. Data points are arithmetic mean values ± SD (standard deviation); n = number of volunteers.

(a) (b)

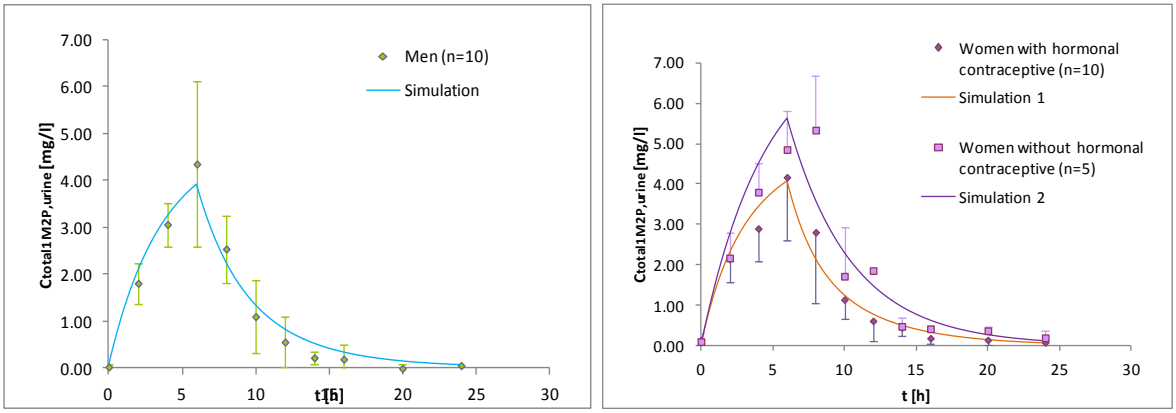


FIGURE 5. Comparison of experimental data with simulated data for urinary total 1M2P obtained (a) in men and (b) in women. Urinary total 1M2P concentrations as function of time were obtained after 6 hours of exposure to 53.22 (± 3.04) ppm of 1M2P. Data points are arithmetic mean values ± SD (standard deviation); n = number of volunteers.

(a) (b)

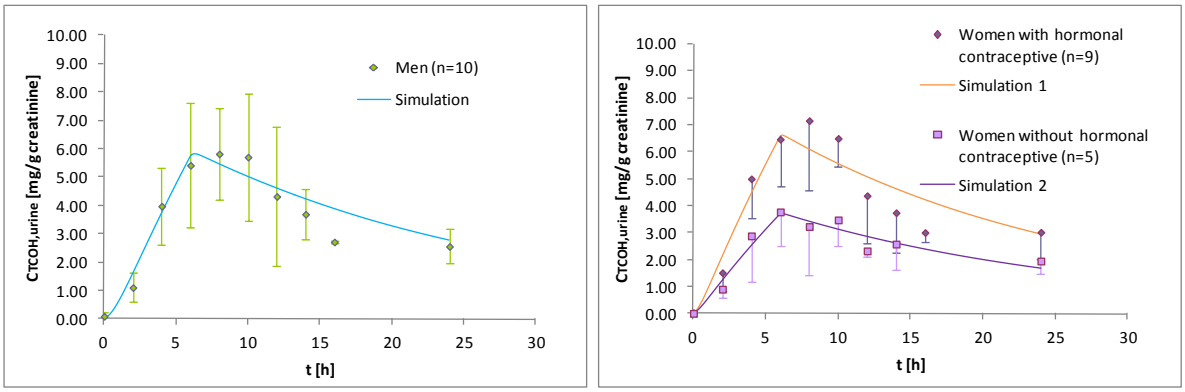


FIGURE 6. Comparison of experimental data with simulated data for urinary TCOH obtained (a) in men and (b) in women. Urinary TCOH concentrations as function of time were obtained after 6 hours of exposure to 102.55 (± 3.19) ppm of 111TCE. Data points are arithmetic mean values ± SD (standard deviation); n = number of volunteers.

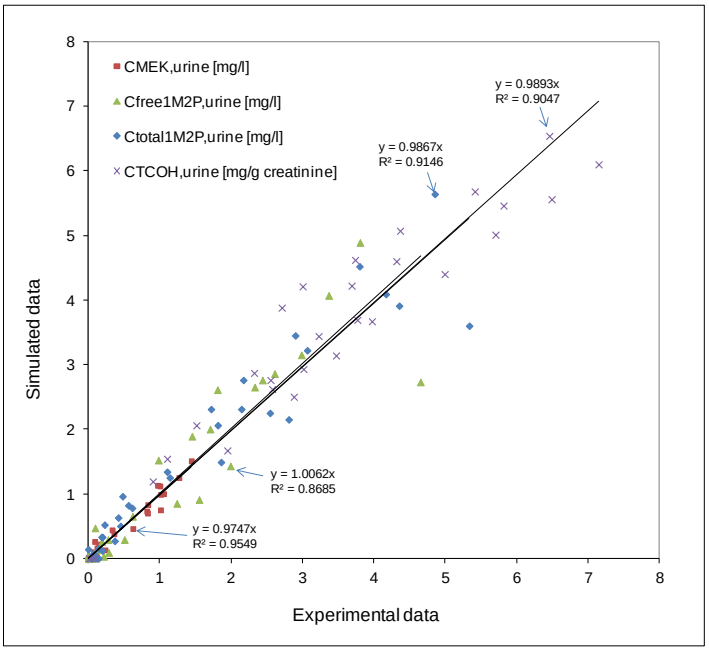
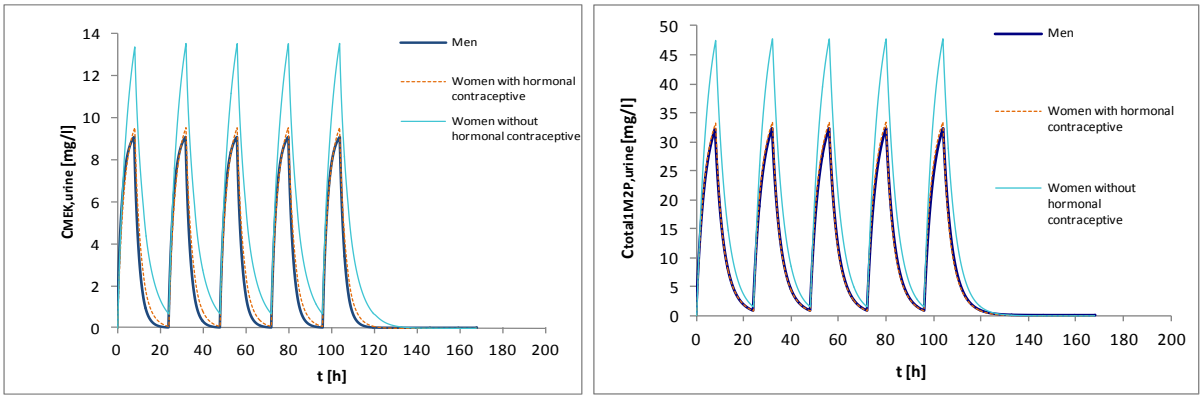


FIGURE 7. Predicted data versus experimental data for the studied urinary biomarkers of exposure. Linear regression has been done for data obtained during the whole exposure scenario for each solvent.

(a) (b)



(c)

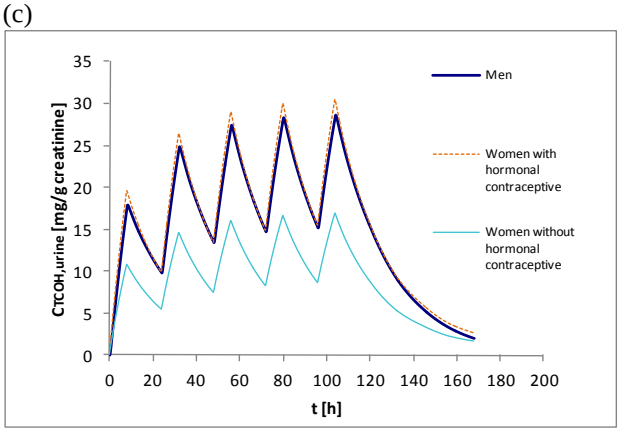


FIGURE 8. Simulation of mean urinary levels of biological indicators of exposure in workers (by considering men, women with and without hormonal contraceptive) exposed during 8 hours per day, 5 days per week, at a 50 W work load, to the threshold limit value of (a) MEK*, (b) 1M2P* and (c) 111TCE

* The curve for men and the one for women with hormonal contraceptive are nearly overlapping.

TABLE I. Summary of the selected organic solvents and their corresponding urinary biomarkers of exposure, with the existing occupational exposure limit values and biological exposure indices for different countries (USA, Germany, Switzerland)

Biological determinant	**TLV*/MAK**/VME*** (ppm)	**BEI*/BAT**/VBT*** urine (mg/l)	blood (μg/l)	expired air (ppm)
Methyl ethyl ketone (MEK)	200/200/200	2[a]/5[a]/5[a]		
1-Methoxy-2-propanol (1M2P)	100/100/100	-/15[a]/20[a]		
1,1,1-Trichloroethane (111TCE)	350/200/200	-	-/550[b,c]/550[b,c]	40[b,c]/-/-
Trichloroethanol (TCOH)		30[a,b]/-/-	1000[a,b]/-/-	
Trichloroacetic acid (TCA)		10[b]/-/-		

* The American Conference of Industrial Hygienists (ACGIH) sets threshold limit values (TLV) and biological exposure indices (BEI).

** The German Research Foundation (Deutsche Forschungsgemeinschaft - DFG) sets "Maximale Arbeitsplatz-Konzentrationen" (MAK) and "Biologische Arbeitsstoff-Toleranzen" (BAT).

*** The Swiss National Accident Insurance Fund (Schweizerische Unfallversicherungsanstalt - Caisse nationale suisse d'assurance en cas d'accidents - Istituto nazionale svizzero di assicurazione contro gli infortuni – (SUVA) sets "valeurs (limites) moyennes d'exposition" (VME) and "valeurs biologiques tolérables" (VBT).

[a] ES: end of shift [b] EW: end of week [c] PS: prior to shift

TABLE II. General physiological parameters used for the TK models. Arithmetic mean values (±SD: standard deviation) are indicated for body weight, body height and body fat; n = number of volunteers.

Parameters	**Symbol**	**At rest/50 W**
Body weight [kg]	BW	70.7 ± 10.3 for men (n=10)
		60.1 ± 7.2 for women with hormonal contraceptive (n=10)
		65.6 ± 11.2 for women without hormonal contraceptive (n=5)
Body height [cm]	BH	177.5 ± 3.2 for men (n=10)
		167 ± 3.8 for women with hormonal contraceptive (n=10)
		163.4 ± 2.3 for women without hormonal contraceptive (n=5)
Body fat [% of BW]	bf	11.3 ± 5.2 for men (n=10)
		19.8 ± 4.6 for women with hormonal contraceptive (n=10)
		26.6 ± 8.9 for women without hormonal contraceptive (n=5)
Lean body mass [kg]	LBM	LBM = BW – BF[a]with BF = bf * BW/100For a man : -12.86 + 0.1757 * BH + 0.3331 * BW [a]
Total body water [kg]	TBW	For a woman : -2.097 + 0.1069 * BH + 0.2466 * BW[a]
Cardiac output [l/(h*kg$^{0.7}$)]	Q_c	18.0[b] at rest/30.8[b] at 50 W
Alveolar ventilation [l/(h*kg$^{0.7}$)]	V_{alv}	18.0[b] at rest/2.1951*Q_c[b] at 50 W
Urinary excretion rate [ml/(h*kg$^{0.82}$)]	k_{ur}	1.848[c]
Creatinine excretion rate [µmol/(h*kg$^{0.9}$)]	k_{cr}	12.06[c]

[a] Fiserova-Bergerova[23]
[b] Thomas et al.[24]
[c] Laparé et al.[25]

TABLE III. Chemical specific parameters used for the TK models

Parameters	**Symbol**	**At rest/50 W**
MEK		
Threshold limit value [mg/m^3]	TLV	590
Molecular weight [g/mol]	MW	72
Exposure concentration [mg/m^3]	C_{exp}	282.9
Pulmonary retention [-]	R_{pulm}	0.558[a]
Volume of the central compartment expressed as a fraction of BW [-]	FV_c	1*TBW/BW
Volume of the peripheral compartment expressed as a fraction of BW [-]	FV_p	1*BF/BW
Fraction of cardiac output in the peripheral compartment [-]	BF_p	0.06[b]/0.05[b]
Fraction of cardiac output in metabolism [-]	BF_1	0.26[b]/0.16[b]
Blood/air partition coefficient [-]	P_{blood_air}	125[a]
Central/blood partition coefficient* [-]	P_{c_blood}	0.856[a]
Peripheral/central partition coefficient [-]	P_{p_c}	1.296[a]
Metabolism		
Michaelis-Menten maximum rate* [mg/(h*kg$^{0.75}$)]	VM_1	5.44[c]
Michaelis-Menten constant [mg/l]	KM_1	0.63[c]

1M2P		
Threshold limit value [mg/m^3]	TLV	360
Molecular weight [g/mol]	MW	90.12
Exposure concentration [mg/m^3]	C_{exp}	177.1
Pulmonary retention [-]	R_{pulm}	0.9[d]
Volume of the central compartment expressed as a fraction of BW [-]	FV_c	1*TBW/BW
Fraction of cardiac output in metabolism [-]	BF_1	0.26[b]/0.16[b]
Blood/air partition coefficient [-]	P_{blood_air}	12383[e]
Central/blood partition coefficient [-]	P_{c_blood}	12280[e]
Metabolism		
Michaelis-Menten maximum rate** [mg/(h*kg$^{0.75}$)]	VM_1	22[f]
Michaelis-Menten constant* [mg/l]	KM_1	45[f]
Conjugation		
Michaelis-Menten maximum rate** [mg/(h*kg$^{0.75}$)]	VM_2	0.2[f]
Michaelis-Menten constant [mg/l]	KM_2	80[f]
Urinary excretion rate for conjugated 1M2P [h^{-1}]	k_{conj}	0.2[d]
111TCE		
Threshold limit value [mg/m^3]	TLV	1080
Molecular weight [g/mol]	MW	133.40
Molecular weight of metabolite [g/mol]	MW_1	149.40
Molecular weight of creatinine [g/mol]	MW_{cr}	113.12
Exposure concentration [mg/l]	C_{exp}	545.6
Pulmonary retention [-]	R_{pulm}	0.25[g]
Volume of the central compartment expressed as a fraction of BW [-]	FV_c	1*TBW/BW
Volume of the peripheral compartment expressed as a fraction of BW [-]	FV_p	1*BF/BW
Volume of the metabolite compartment expressed as a fraction of BW [-]	FV_1	0.026[h]
Fraction of cardiac output in peripheral compartment [-]	BF_p	0.06[b]/0.05[b]
Fraction of cardiac output in metabolite compartment [-]	BF_1	0.26[b]/0.16[b]
Blood/air partition coefficient [-]	P_{blood_air}	2.53[i]
Central/air partition coefficient*** [-]	P_{c_air}	2.53[i]
Peripheral/air partition coefficient [-]	P_{p_air}	263[i]
Metabolite/air partition coefficient [-]	P_{M1_air}	8.6[i]
Metabolism		
Michaelis-Menten maximum rate*** [mg/(h*kg$^{0.75}$)]	VM_1	0.42[i]
Michaelis-Menten constant [mg/l]	KM_1	5.75[i]
Metabolic rate TCOH $\rightarrow$ TCA [1/(h*kg$^{-0.3}$)]	k_{M1_M2}	0.069[j]
Excretion		
TCOH urinary excretion rate [1/(h*kg$^{-0.3}$)]	k_{u1}	0.093[j]

[a] Liira et al.[22]
[b] Thomas et al.[24]
[c] Thrall et al.[19]
[d] Devanthéry[26]
[e] Johanson et al.[27]
[f] Corley et al.[20]

g Nolan et al.[28]

h Tardif et al.[29]

i Reitz et al.[15]

j Caperos et al.[30]

* For the MEK model, fitted parameters with their corresponding values are following:

- P_{c_blood} = 2.106, 2.817 and 2.662 for men, women with hormonal contraceptive and women without hormonal contraceptive respectively ;
- VM_1 = 2.13, 1.80 and 0.86 mg/l for men, women with hormonal contraceptive and women without hormonal contraceptive respectively.

** For the 1M2P model, fitted parameters with their corresponding values are following:

- VM_1 = 35.94, 44.56 and 19.37 mg/(h*kg$^{0.75}$) for men, women with hormonal contraceptive and women without hormonal contraceptive respectively ;
- VM_2 = 0.09, 0.15 and 0.06 mg/(h*kg$^{0.75}$) for men, women with hormonal contraceptive and women without hormonal contraceptive respectively.

*** For the 111TCE model, fitted parameters with their corresponding values are following:

- P_{c_air} = 7.28, 4.74 and 4.00 for men, women with hormonal contraceptive and women without hormonal contraceptive respectively ;
- VM_1 = 0.13, 0.24 and 0.17 mg/(h*kg$^{0.75}$) for men, women with hormonal contraceptive and women without hormonal contraceptive respectively.

TABLE IV. Summary of the different biomarkers values (experimental and simulated) obtained at the end of exposure. Arithmetic mean values (± SD: standard deviation) are indicated for experimental data.

	Biological indicators levels at the end of exposure			
	$C_{MEK,urine}$ [mg/l]	**$C_{free1M2P,urine}$ [mg/l]**	**$C_{total1M2P,urine}$ [mg/l]**	**$C_{TCOH,urine}$ [mg/g creatinine]**
Men				
Experiment	1.00 ± 0.13	2.99 ± 0.49	4.36 ± 1.76	5.42 ± 2.19
Simulation	1.12	3.15	3.91	5.68
Women with hormonal contraceptive				
Experiment	0.97 ± 0.23	2.61 ± 0.96	4.17 ± 1.58	6.46 ± 1.73
Simulation	1.13	2.86	4.09	6.54
Women without hormonal contraceptive				
Experiment	1.44 ± 0.76	3.81 ± 1.68	4.85 ± 0.97	3.77 ± 1.24
Simulation	1.51	4.89	5.64	3.69