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Using population physiologically based pharmacokinetic modeling to determine optimal sampling times and to interpret biological exposure markers: The example of occupational exposure to styrene

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HIGHLIGHTS

- We put forward a framework to optimize biomonitoring using population PBPK modeling.
- The optimal time to measure styrene in venous blood is at the end of shift.
- Styrene in exhaled air should be measured 15 min after the end of shift.
- Our results support the BEI® of 0.2 mg/l in venous blood at the end of shift.
- We propose a BLV of 0.3 ppm in exhaled air 15 min after the end of shift.

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ABSTRACT

Background: Biomonitoring of chemicals in the workplace provides an integrated characterization of exposure that accounts for uptake through multiple pathways and physiological parameters influencing the toxicokinetics.
Objectives: We used the case of styrene to (i) determine the best times to sample venous blood and end-exhaled air, (ii) characterize the inter-individual variability in biological levels following occupational exposure and (iii) propose biological limit values using a population physiologically based pharmacokinetic (PBPK) model.
Methods: We performed Monte Carlo simulations with various physiological, exposure and workload scenarios. Optimal sampling times were identified through regression analyses between levels in biological samples and 24-h area under the arterial blood concentration vs. time curve. We characterized the variability in levels of styrene in biological samples for exposures to a time weighted average (TWA) of 20 ppm.
Results: Simulations suggest that the best times to sample venous blood are at the end of shift in poorly ventilated workplaces and 15 min after the shift in highly ventilated workplaces. Exhaled air samples are most informative 15 min after the shift. For a light workload, simulated styrene levels have a median (5th–95th percentiles) of 0.4 mg/l (0.2–0.6) in venous blood at the end of shift and 0.5 ppm (0.3–0.8) in exhaled air 15 min after the end of shift.
Conclusion: This study supports the current BEI® of the ACGIH of 0.2 mg/l of styrene in venous blood at the end of shift and indicates a biological limit value of 0.3 ppm in end-exhaled air 15 min after the end of shift.

1. Introduction

Assessing the risk associated with exposure to chemicals in the occupational setting entails comparing exposure levels with guidelines derived from experimental or epidemiological studies. In the case of volatile compounds, regulations are usually expressed in terms of time weighted average (TWA) air levels to be monitored over different periods of a working day. However, concerns have been raised regarding air monitoring as the sole basis for exposure assessment as these measures cannot capture uptake through

Abbreviations: AC, autocorrelation coefficient; ACGIH, American Conference of Governmental Industrial Hygienists; AUC, area under the blood concentration vs. time curve; BEI®, Biological Exposure Indices; BLV, biological limit value; PBPK, physiologically based pharmacokinetic; TWA, time weighted average.

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multiple pathways and they do not account for inter-individual variability in physiological parameters that can influence internal levels for a given external exposure (e.g., physical exertion, metabolism). One way to circumvent these limitations is to rely on levels of parent compounds or metabolites in biological samples such as urine, blood or exhaled air which relate more closely to the levels at the target site or organ (Hays et al., 2007). Biological limit values (BLVs), such as the Biological Exposure Indices (BEI®) proposed by the American Conference of Industrial Hygienists (ACGIH), have been suggested for various contaminants found in the workplace. While these guidelines may be more appropriate than air levels, certain gaps have yet to be filled with regards to which are the best times to sample biological samples and what is the inter-individual variability in levels within the population. Furthermore, BLVs are only available for a limited number of compounds and biological matrices.

BLVs can be determined based on levels in biological samples following occupational/controlled exposures or simulated levels using pharmacokinetic modeling. Samples drawn in occupational and controlled environments generate precise measures of exposures but the number of subjects is often too small to ascertain variability across age groups and physiological profiles. On the other hand, population physiologically based pharmacokinetic (PBPK) modeling is particularly well suited to derive BLVs as it allows the estimation of complete blood level profiles under various physiological profiles, exposure regimens and workloads. These mathematical models simulate the toxicokinetics of xenobiotics based on the various physiologic processes governing absorption, distribution, metabolism and excretion. Once validated against data from controlled, occupational or environmental exposures, these models can accommodate a multitude of exposure scenarios (e.g., dose, duration, pathways) and physiological parameters (e.g., ventilation rates, body weight) to derive profiles of tissue and blood levels during and after exposure periods with a known precision. The inter-individual variability in the toxicokinetics of a contaminant can also be assessed through iterative Monte Carlo simulations in which model parameter values are sampled from population-derived distributions or, when available, posterior distributions obtained by Bayesian calibration of the model with experimental data.

In this study, we chose styrene as a model compound to address the issues of sampling times and inter-individual variability in biological samples. Styrene is a volatile chemical monomer used in the production of several materials including polystyrene, acrylonitrile-butadiene styrene and unsaturated polyester resin (fiberglass). It is classified as a possible human carcinogen by the International Agency for Research on Cancer (IARC, 2006). At levels below those of concern for styrene-induced carcinogenesis, exposure led to adverse effects on the nervous system such as increased choice reaction time (Benignus et al., 2005) and color vision loss (Kishi et al., 2000) in workers. Several PBPK models have been developed to describe the kinetics of styrene in humans (e.g., Csanady et al., 1994; Droz and Guillemin, 1983; Johanson and Naslund, 1988; Ramsey and Andersen, 1984). Based on available data on venous blood, arterial blood, end-exhaled air and fat levels from 24 individuals during and after controlled exposures, Jonsson and Johanson (2002) performed Markov Chain Monte Carlo (MCMC) analyses to validate their PBPK model and estimate model parameter distributions.

We conducted this study to (i) determine the times when venous blood and end-exhaled air samples are the most representative of daily internal exposure, (ii) characterize the inter-individual variability in venous blood and exhaled air levels following occupational exposure to air concentration guidelines and (iii) propose a BLV for exhaled air levels based on Monte Carlo simulations using the PBPK model presented in Jonsson and Johanson (2002).

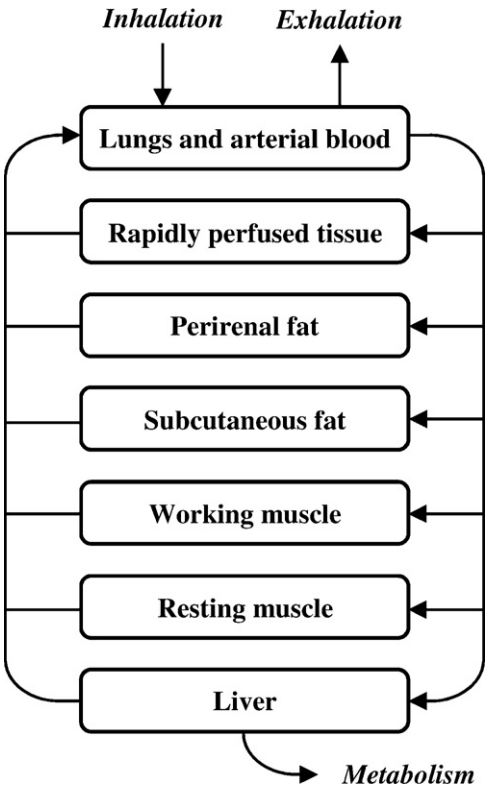

Fig. 1. Conceptual representation of the PBPK model.

2. Materials and methods

2.1. Physiologically-based pharmacokinetic (PBPK) model

We used the PBPK model described in Jonsson and Johanson (2002) to simulate styrene toxicokinetics in workers. Briefly, this model consisted of seven compartments: lungs and arterial blood, rapidly perfused tissues, perirenal fat, subcutaneous fat, working muscle, resting muscle and liver (Fig. 1). Organ volumes and blood flow were scaled according to gender, body weight and height. Because exposure guidelines in the occupational setting are defined in terms of air concentrations, only the inhalation pathway was considered. Inhalatory uptake was corrected for the washin–washout process that takes place in the airways. Distribution of styrene in the compartments was described by mass-balance differential equations. Metabolism was limited to the liver compartment and followed Michaelis–Menten kinetics. The model was re-coded in acslX language (Aegis Technologies Group, Inc., Huntsville, AL, USA) and is available in the Supplementary Data.

2.2. Simulations

Population blood level profiles during and following exposure were simulated by iterative Monte Carlo runs. Physiologic parameter values were sampled from the posterior distributions presented in Jonsson and Johanson (2002). In addition, body weight and height values were randomly sampled from normal distributions defined based on data published by the Center for Disease Control and Prevention (McDowell et al., 2008). Because no standard deviations were presented in this report, they were estimated from z-scores calculated based on mean and 5th percentile values. Weight distributions had mean ± SD (kg) values of 74.7 ± 14.7 for females and 88 ± 15.9 for males. Height distributions had mean ± SD (cm) values of 162.2 ± 7.0 for females and 176.3 ± 12.7 for males.

For each Monte Carlo iteration, exposure and workload levels were allowed to change every 7.5 min during the exposure period. This time interval was adopted to simulate exposure conditions comparable to those reported in Kumagai et al. (1993). Air styrene concentration during each interval was the result of random sampling from a lognormal distribution with a mean of 20 ppm, the Threshold Limit Value set by the ACGIH, and a standard deviation of 15 ppm (generating a coefficient of variation comparable to that calculated from monitored values published in Sato et al. (2009)). To account for different ventilation rates in work areas (i.e., how much levels of styrene in the air change from one interval to another), we used autocorrelation coefficients (AC) of 0.9 and 0.1 for air styrene levels during contiguous 7.5-min intervals to emulate exposures in poorly and highly ventilated work areas, respectively (Mork and Johanson, 2010). In addition, we ran the Monte Carlo simulations with an autocorrelation coefficient of 0.73 (for 7.5-min intervals) as documented in a study

on repeated measurements of styrene in a manufacture of fiber-reinforced plastics (Kumagai et al., 1993). The air level at a given interval was calculated as follows:

$$\text{Air level} = \text{AC} \times \text{Air level}_{\text{last interval}} + (1 - \text{AC}) \times \text{Air level}_{\text{sampled from the logmormal distribution}} \quad (1)$$

Similarly, workloads during each 7.5 min interval were calculated based on lognormal distributions and an autocorrelation coefficient. Two lognormal distributions were defined to represent moderate and light workloads: (1) mean of 50 W and a standard deviation of 25 W and (2) mean of 10 W and a standard deviation of 5. The autocorrelation coefficient was set to 0.5.

Ventilation rates (l/min) and excess oxygen uptake above rest (l/min) were calculated from workloads (W) by linear regression based on data from Carlsson (1982) study published in Jonsson and Johanson (2001):

$$\text{Ventilation rate} = 0.3 \times \text{Workload} + 6.8 \quad (2)$$

$$\text{Excess oxygen uptake above rest} = 0.0135 \times \text{Workload} \quad (3)$$

Although exposure levels and workload may be correlated in the workplace, we assumed these values to be independent due to the lack of supporting data.

For each combination of workload level (light or moderate) and autocorrelation coefficients (0.10, 0.73 or 0.90), simulations were performed for 1000 individuals, 30 exposure scenarios each. Antecubital venous blood and end-exhaled air levels were abstracted from toxicokinetic profiles every 15 min during and after exposures.

2.3. Determination of the best time to sample blood or end-exhaled air

Because it is impossible to obtain measures of neurotoxicants directly at the site where they exert their toxicity, i.e., the brain, investigators must rely on samples that can be used as proxies of internal exposure (e.g., end-exhaled air, blood, urine). Samples should be collected at a time when they best translate relevant internal exposures, for example, peak exposure in the case of acute toxicity, overall exposure in the case of chronic toxicity, or amount metabolized if bioactivation is involved. In the case of styrene, 24-h area under the arterial blood styrene concentration vs. time curve (AUC) was selected as the best metric of internal exposure because studies suggest that the effects of styrene on the nervous system depend not only on air levels, but also on the duration of exposure (Benignus et al., 2005). The optimal times to draw blood or end-exhaled air samples were determined by comparing simulated biological levels across the day to 24-h AUC through regression analyses. Optimal times to sample were defined as the times when biological levels were the most predictive of 24-h AUC, i.e., times with the highest coefficient of determination (R^2). Regressions were only calculated for moderate workload scenarios.

3. Results

We performed Monte Carlo simulations to generate toxicokinetic profiles of styrene during and following a variety of occupational exposure scenarios. Fig. 2 depicts an example of venous blood and end-exhaled air level profiles generated for a given physiological scenario and varying workloads and air concentrations.

3.1. Optimal time to sample venous blood and end-exhaled air

The most informative times to collect biological samples were identified using regression analyses between biological levels and 24-h AUC: the sampling times generating the strongest regressions (i.e., highest R^2 values) were assumed to be the most representative of the overall exposure. Coefficients of determination (R^2s) obtained for antecubital venous blood and end-exhaled air over the course of the day are plotted in Fig. 3. The simulations suggest that venous blood is a better proxy of internal exposure than end-exhaled air with R^2 values reaching 0.60 at the end of the morning shift and 0.65 at the end of the afternoon shift in poorly ventilated workplaces. Regressions observed for highly ventilated workplace scenarios were higher shortly after exposure than at the end of shift. The strongest regressions with end-exhaled air were obtained shortly after the work shifts. Fifteen minutes after the morning and afternoon work shifts, the regressions between end-exhaled air and 24-h AUC had R^2 values of 0.33 and 0.36. Biological levels derived from poorly ventilated workplaces consistently predicted 24-h internal exposure with a greater accuracy than those generated for highly ventilated areas for most of the day. This finding

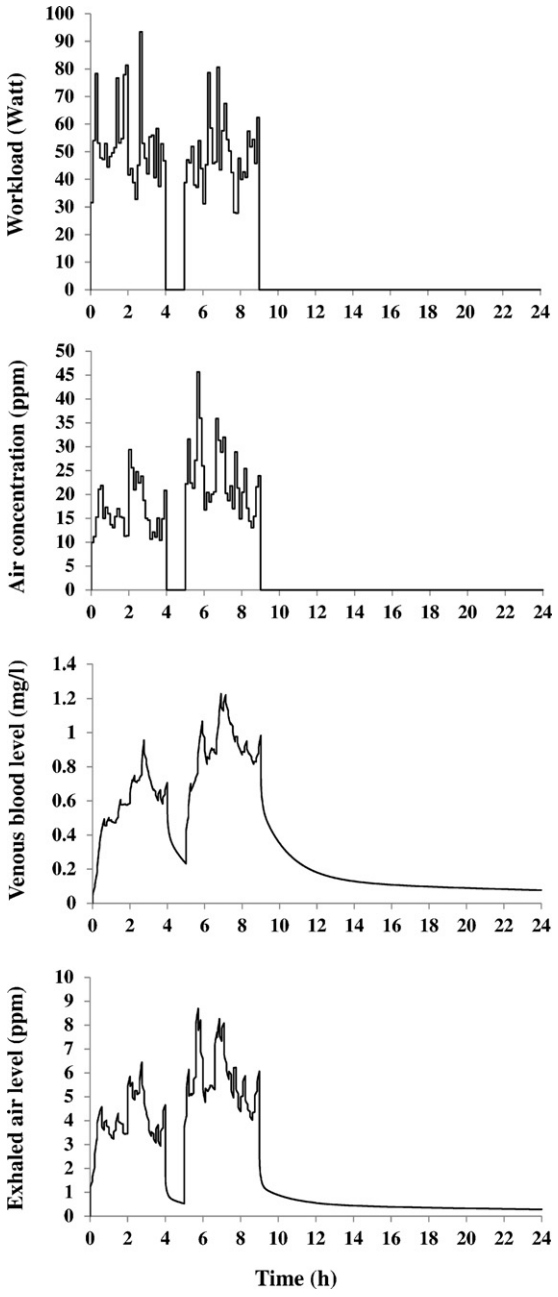

Fig. 2. Example of antecubital venous blood (mg/l) and end-exhaled air (ppm) styrene level profiles for a scenario of workloads (W) and air concentrations (ppm) with an exposure to a 8-h TWA of 20 ppm and an autocorrelation coefficient of 0.73.

was expected as styrene levels in the air during contiguous time intervals are autocorrelated to a greater extent in poorly ventilated areas (i.e., exposure is more stable).

3.2. Venous blood and end-exhaled air levels for exposures to TWA of 20 ppm

We characterized population distributions of antecubital venous blood and end-exhaled air styrene levels during and after TWA exposures of 20 ppm in the workplace by running Monte Carlo simulations based on posterior parameter distributions from a previous Markov Chain Monte Carlo exercise. Levels at the times of sampling that proved to be the most representative of 24-h internal exposures are shown in Table 1. The median venous blood at the end of working shift (light workload) was approximately 0.4 mg/l

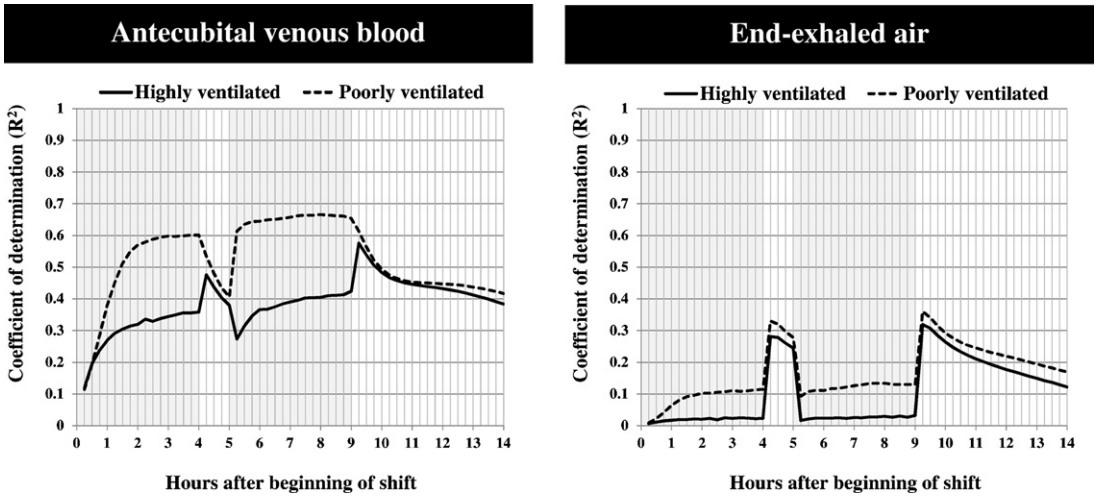

Fig. 3. Coefficients of determination (R^2s) between 24-h area under the arterial blood concentration vs. time curve and venous blood or end-exhaled air levels during and after exposures. The regression analyses were carried out for both highly and poorly ventilated workplaces with autocorrelation coefficients of 0.9 and 0.1, respectively (for 7.5-min intervals). The shaded areas represent the periods of exposure.

regardless of the autocorrelation in air levels, a value slightly above the BEI® guideline of 0.2 mg/l adopted by the ACGIH. At the end of shift, styrene levels in venous blood obtained for moderate workload scenarios (50 W) were on average twice as high as those observed for light workloads (10 W). Similarly, median exhaled air levels at the end of shift were 1.5-fold higher in moderate workloads scenarios when compared to lighter workload scenarios. The complete profiles of antecubital venous blood and end-exhaled air for 20 ppm time weighted average exposures are displayed in chart format in Fig. 4.

4. Discussion

Assessing exposure to contaminants in the workplace is a critical step in risk assessment. Whereas most guidelines are based on air levels, exposure estimates based on such measures disregard other exposure pathways as well as important toxicokinetic processes that may significantly modulate internal levels following exposure to a given air concentration. For example, increased ventilation during exercise, interindividual variability in metabolic rates and co-exposure to other contaminants or pharmaceuticals are among the parameters that could lead to increased blood and tissue concentrations. Biological levels of the parent compound or its metabolites circumvent these limitations by integrating relevant processes and thus providing a measure which relates more closely to target organ exposure. For this reason, increased use of biomonitoring is foreseen in the workplace. In this study, we used a physiologically based pharmacokinetic model to identify the best times to sample venous blood and exhaled air, and to estimate the variability in biological levels following occupational exposures to styrene at a guideline level of 20 ppm.

Results from this study suggest that venous blood should be sampled at the end of the working shifts in poorly ventilated workplaces for which autocorrelation in air levels is similar to that reported by Kumagai et al. (1993). This supports the time of sampling put forward by the ACGIH for the evaluation of exposure to styrene. However, the rapid loss of predictability after exposure suggests that blood samples should be taken at the end of exposure rather than at the end of shift as there may be a time gap between the two. As for end-exhaled air, samples should be drawn shortly after exposure. The delay between the end of shift and the sampling time reduces the influence of the latest exposure levels as exhaled air concentration is partially related to inhaled air concentration. Because levels decline rapidly after exposure, one should also make sure that levels measured after the period of exposure are well above the limit of detection to avoid introducing too much noise in analytical measurements. Simulated end-exhaled air levels until the beginning of the next day shift were mostly above 10 ppb whereas limits of detection and linearity in the quantification of volatile organic compounds including styrene was established down to the order of parts per trillion (ppt) (Poli et al., 2005). Hence, analytical precision does not preclude from sampling end-exhaled air long after the exposure has stopped.

Monte Carlo simulations generated distributions of venous blood and end-exhaled air levels for 8-h exposures to a time

Table 1
Distribution of end-exhaled air levels (ppm) and antecubital venous blood levels (mg/l) for 8 h exposures to styrene in the workplace at a time weighted average of 20 ppm and varying workloads.

Monte Carlo method	AC[a]	End-exhaled air (ppm)				Venous blood (mg/l)	
		End of shift		15 min after end of shift		End of shift	
		Median	5th–95th percentiles	Median	5th–95th percentiles	Median	5th–95th percentiles
Workload: 50 W	0.10	3.9	2.1–8.3	0.98	0.60–1.62	0.78	0.49–1.35
(SD = 25)	0.73	4.2	2.8–6.6	1.00	0.62–1.64	0.81	0.54–1.28
	0.90	4.3	3.0–6.2	1.00	0.62–1.64	0.82	0.54–1.27
Workload: 10 W	0.10	2.6	1.3–5.9	0.44	0.27–0.73	0.36	0.22–0.62
(SD = 5)	0.73	2.9	1.9–4.5	0.46	0.28–0.76	0.37	0.24–0.59
	0.90	2.9	2.2–4.0	0.44	0.28–0.72	0.37	0.24–0.56

[a] Autocorrelation coefficient for air styrene concentration during 7.5-min intervals.

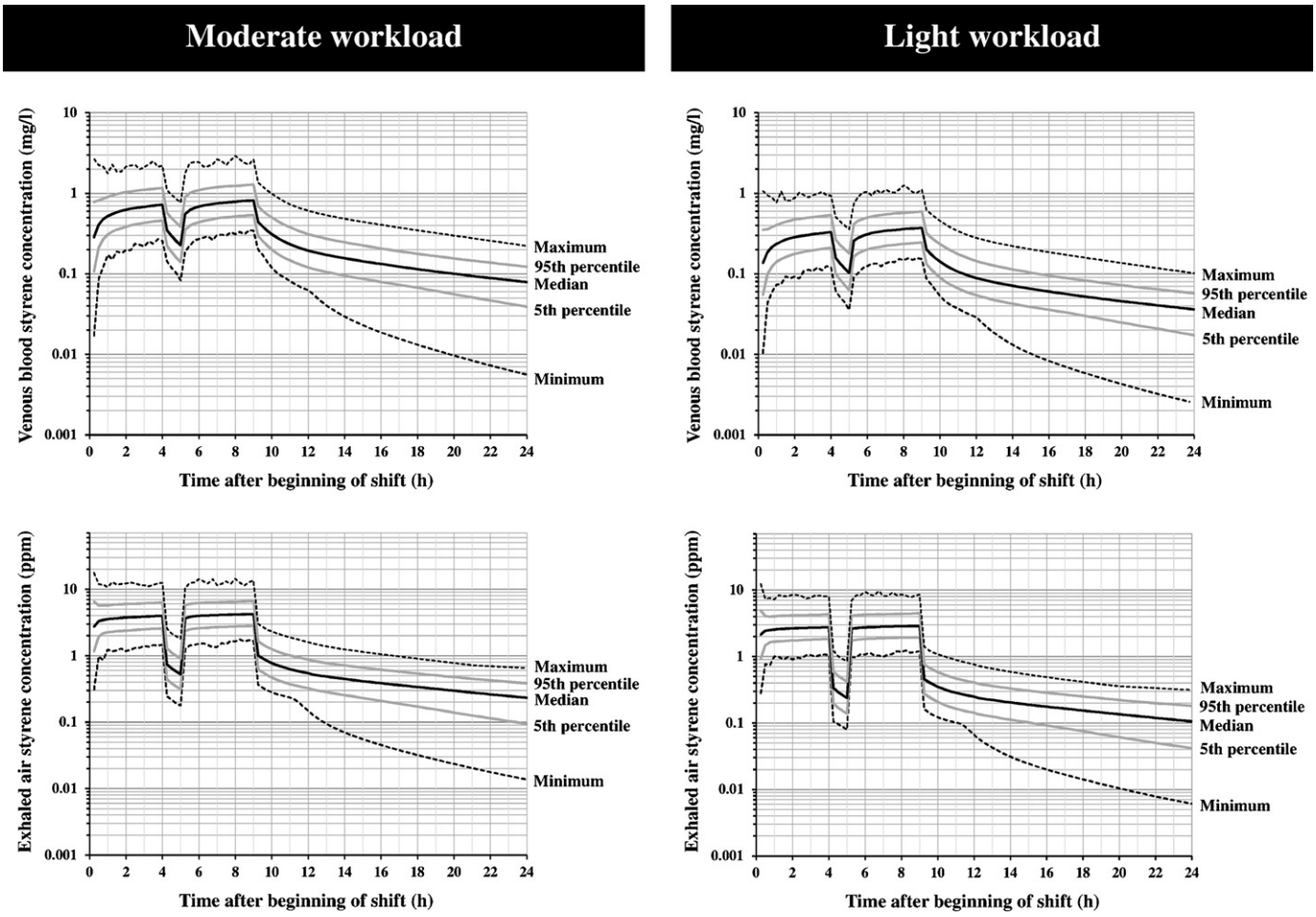

Fig. 4. Distribution of venous blood and exhaled air styrene concentrations during and following exposures to a TWA of 20 ppm and a standard deviation of 15 ppm. Only simulations using an autocorrelation coefficient of 0.73 (7.5-min intervals) are presented.

weighted average of 20 ppm. End of shift median venous blood levels were approximately 0.4 mg/l and 0.8 mg/l for light and moderate workloads, respectively. These levels are above the mean blood levels of around 0.1–0.2 mg/l measured in two groups of workers exposed to an 8-h time weighted averages of 22–24 ppm (Brodkin et al., 2001). It is difficult to compare controlled exposure studies with field studies, as the latter may be influenced by factors that are difficult to control such as workload, time of sampling in relation to end of exposure and dermal exposure. Yet, the Brodkin et al. (2001) study shows lower blood styrene levels than our model. A likely explanation for this discrepancy is that some time had elapsed between exposure and sampling in the field study. This stresses the need to keep track of when exposure ends. Still, the BEI® value of 0.2 mg/l put forward by the ACGIH compares well with the 5th percentile of simulated venous blood levels at the end of shift for a light workload, supporting the adequacy of the current BEI®. Simulated end-exhaled air concentrations were slightly higher than those reported by Truchon et al. (2009) for a constant exposure to 20 ppm. In the Truchon et al. (2009) study, levels in alveolar air at the end of exposure were 1.9 ppm at rest and 3.3 ppm at a time weighted average workload of 54 W compared to 2.9 ppm at light workload and 4.3 ppm at 50 W in this study. These measured exhaled air levels were, however, contained within the 5th–95th percentile interval. Based on the results of this study, an exhaled air concentration of 0.3 ppm 15 min after the end of shift (5th percentile) is proposed as a biological limit value. Should it be impossible to sample blood or exhaled air at the recommended times, investigators could refer to the charts in Fig. 4 to obtain distributions at any time during or after exposure.

While simulations were performed at a time weighted average of 20 ppm, the results could be extrapolated to a variety of exposure guidelines. A controlled exposure study conducted by Lof and Johanson (1993) in which volunteers were exposed to styrene levels ranging from 26 to 386 ppm suggested that metabolic saturation only occurs above 100 ppm. Below this level, the toxicokinetics of styrene in human are linear. Therefore, BLVs reported herein could be scaled to other guideline levels. For example, the Swedish Occupational Exposure Limit (OEL) was recently established to 10 ppm (SWEA, 2011). The BLVs for this OEL could be obtained by dividing those derived for 20 ppm exposures by a factor of two.

In this study, we chose venous blood and end-exhaled styrene levels over urinary metabolite levels as biomarkers of exposure for various reasons. When assessing exposure using biological samples, the compound to be analyzed should be specific to the exposure of interest (Hays et al., 2008). The two principal styrene metabolites found in urine, mandelic acid and phenylglyoxylic acid, are non-specific and could result from the biotransformation of other compounds such as ethylbenzene (Engstrom et al., 1984) for which co-exposure with styrene in the workplace is possible. The analyte to be measured should also be relevant to the mode of action. Because exposure guidelines are based on effects of the parent compound on the nervous system, internal levels of styrene are more closely related to the mechanism of toxicity than its metabolites in urine. Finally, the PBPK model used herein has not

been designed, calibrated nor validated for the estimation of urinary excretion of metabolites and would have required structural modifications and additional calibration.

Certain limitations of this study ought to be mentioned. Exposure scenarios assumed that air levels were either weakly or strongly autocorrelated across the working day with no specific patterns. This approach would not cover certain possible exposure patterns leading to a TWA of 20 ppm such as an exposure to 160 ppm for an hour at the beginning of the 8-h work shift. For this reason, thorough assessment of exposure patterns should be performed prior to sampling procedures. Another issue in this study relates to the Monte Carlo simulations that were based on posterior distributions obtained during a previous Bayesian calibration of the PBPK model. Because the calibration was performed on a relatively small sample size ($n = 24$), it is quite possible that the posterior distributions do not cover the full range of possible physiological values. On the other hand, no correlation was considered between physiological parameter values that were sampled from these distributions. This may have led to unlikely sets of physiological parameters that can, in turn, inflate distributions of venous blood and exhaled air levels. In spite of these limitations, our simulations compare relatively well with levels measured in other studies and allowed the evaluation of variability in biological levels for a wide range of physiological, workload and exposure scenarios that would have been impossible to cover in experimental or occupational settings.

The population PBPK modeling approach employed in this study is unique in that it relies on best available estimates on population toxicokinetic variability to identify the times when samples of venous blood and exhaled air are the most informative for biomonitoring purposes. Moreover, this approach allowed us to characterize the population variability in biological levels during and following exposures to volatile organic compounds, a major improvement on single BLV values which may not be conservative enough for a wide spectrum of physiological characteristics, energy expenditures and exposure. Results from this study support the current BEI® value of 0.2 mg/l in venous blood and suggest a BLV of 0.3 ppm in exhaled air 15 min after the end of shift. The framework provided in this paper is equally applicable to other volatile organic compounds and can be used to establish BLVs for other contaminants in the workplace.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.toxlet.2012.05.024.

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