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Predictions of Blood Ethanol Levels Resulting From Occupational Use of Hydro Alcoholic Solutions and Ethanol-Based Varnishes

Josée Dumas-Campagna, Sami Haddad, Ginette Charest-Tardif and Robert Tardif*

Department of Environmental and Occupational Health, School of Public Health (ESPUM), University of Montréal, P.O. Box 6128, Main station, Montreal, Québec, Canada

Abstract

The purpose of this study was to produce data on the ethanol concentrations in ambient air that result from hand rubbings with hydroalcoholic solutions (HAS) or the use of ethanol-based varnishes, and then to predict the blood ethanol levels (BELs) that result from these procedures. The concentration of ethanol in air at the volunteer's nose after the application of HAS on hands was measured with five volunteers who performed five tests in two different environments: 1) in an inhalation chamber (air change rate ~18 h-1), and 2) in a closed office (poorly ventilated) with two different amounts (1.5 and 3 g) of HAS. In the case of varnish, 125 ml were applied on a 1-m^2 wood surface placed in the middle of an inhalation chamber (n=4). The ethanol concentration was measured 20 cm and 40 cm from the center of the board for the next 60 minutes. As for HAS we noted a large intra- and inter-individual variability in ethanol levels in inhaled air. As expected the highest concentration in the inhalation chamber (~1250 ppm) was lower than in the office (~2352 ppm). For the application of the varnish, the ethanol concentrations greatly exceeded 1000 ppm for a short duration (< 4 min). Physiologically-based pharmacokinetic (PBPK) modeling of ethanol concentrations based on ethanol levels measured in inhaled air predicted the following maximum BELs in women (men): 0.39 and 0.37 mg/L (0.37 and 0.35 mg/L) in the office, and 0.26 and 0.42 mg/L (0.25 and 0.40 mg/L) in the inhalation chamber for 1.5 g and 3 g, respectively. The total dose of ethanol absorbed estimated for a working day involving 42 hand rubbings with 1.5 or 3 g of HAS averaged 0.20 g. For the varnish, the predicted highest BELs for men and women were 0.77 and 0.79 mg/L, respectively. In all cases, the BELs remained below 1 mg/L. The results of this study should make it easier to assess the risk related to chronic inhalation of low levels of ethanol in the general population and among workers associated with these practices.

Keywords: Ethanol; Inhalation; PBPK modeling; Human exposure; Hydroalcoholic solution; Varnish

Introduction

The advent of H1N1 influenza caused an increase in the use of hydroalcoholic solutions (HAS) containing ethanol among both professionals and the general population to reduce and limit the transmission of the virus, following the recommendation of international medical authorities. The efficiency of the mode of action of ethanol depends on the concentration of the latter in the HAS. Ethanol's effectiveness decreases when the concentration in the product is less than 70% and increases when the concentration is greater than 75% [1]. Nevertheless, the concentration found in the various HAS that are classified as effective and safe is 60% to 95% for use on hands [1,2].

Ethanol is known to increase the risk of being affected by various chronic diseases when ingested: i) mental, psychiatric and neurological disorders, and ii) cardiovascular, pancreatic and liver diseases [3,4]. In addition, ethanol in alcoholic beverages is also recognized by the International Agency for Research on Cancer as a Group 1 carcinogen for exposure through the oral route [4].

Ethanol present in HAS is a highly volatile substance that evaporates in the ambient air [5-8]. Several studies have shown that the use of HAS result in pulmonary absorption of ethanol that is evidenced by the presence of metabolites in urine such as ethyl glucuronide [9] and of ethanol in expired air [6].

Consequently, absorption ethanol through respiratory tract should be investigated [10]. Since exposure related to HAS or varnish use could possibly cause adverse effects (e.g., irritation) and contribute to increase the health risks associated with alcohol consumption. The dermal route was dismissed due to the very low absorption of ethanol through the skin [1,4-6,8]. On the other hand, only a few studies have assessed the absorption and kinetics of ethanol vapors via the respiratory tract in humans [11,12].

Exposure to ethanol is not limited to HAS use. Indeed, this alcohol is also found in many other products such as gasoline, disinfectants, paints, inks, varnishes, cosmetics, perfumes, and solvents, which could result in occupational exposure. And since these products can also be used or be present in the home, exposure of the general population to ethanol is also likely [13,14]. The usual permissible level (8-h) for ethanol in many countries is 1000 ppm (1880 mg/m^3). However in 2009, the American Conference of Governmental Industrial Hygienists (ACGIH) recommended that this value of 1000 ppm instead be used as a TLV-STEL (Short-term exposure level).

This study was aimed at estimating human exposure to ethanol following the use of HAS and ethanol-based varnishes. First, we measured the ambient levels of ethanol associated with the use of hydroalcoholic solutions (HAS) for hand disinfection as well as from the use of ethanol-based varnishes. Second, we estimated, using a PBPK modeling approach, the BELs and total dose that result from exposure to HAS and varnish.

Material and Methods

Hydroalcoholic Solutions (HAS)

The concentrations of ethanol in air resulting from HAS use were measured with an infrared spectrophotometer (Miran Series 205B SapphIRe) equipped with a 1.4-cm diameter tube. The instrument was previously calibrated with standards prepared in air using Tedlar®bags (373–2243 ppm). The measurements were made

***Corresponding author:** Robert Tardif, Department of Environmental and Occupational Health, School of Public Health (ESPUM), University of Montréal, P.O. Box 6128, Main station, Montreal, Québec, Canada, Tel: 514-343-6111 ext: 1515; E-mail: robert.tardif@umontreal.ca

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according to the manufacturer's specifications for real-time analysis (up to one measurement/second).

The tests were performed in two environments: 1) in an 18-m^3 inhalation chamber with an air change rate of approximately 18 per hour ($18h^{-1}$), and 2) in a typical 32-m^3 closed office without any particular fresh air input. Two quantities of HAS were tested:1.5 g and 3 g of the commercial product Purell® with an ethanol content of 70% (v/v).

The volunteers (3 men and 2 women) were asked to rub their hands for one minute, after which they put their arms next to their bodies until the end of the sampling period (3 minutes). Air sampling was done at a height of 30 cm above the subjects' hands (Figure 1). Between hand rubbings, the subjects rinsed their hands with tap water. Each volunteer performed 5 tests spaced at 15-minute intervals, in both environments.

Ethanol-based varnish

A volume of 125 ml of ethanol varnish (100%) was applied to a 1-m^2 wood surface located in the center of the inhalation chamber. The varnish was prepared by dissolving shellac (Les produits Waxine inc., Longueuil, Canada) in ethyl alcohol (anhydrous, 100%) (Commercial Alcohols Inc., Chatham, Canada). The experiment was repeated four times. The approximate average time required to apply the varnish on the entire surface of the work piece was 3.5 min. The experimental setup is described in Figure 2. Ethanol in air was measured 20 cm and 40 cm above the center of the board with the infrared spectrophotometer described above. The distance between the sampling point (worker's breathing zone) and the varnished board was chosen arbitrarily. The concentration in the inhalation chamber was also recorded and the measurements were done for an entire 60-minute period.

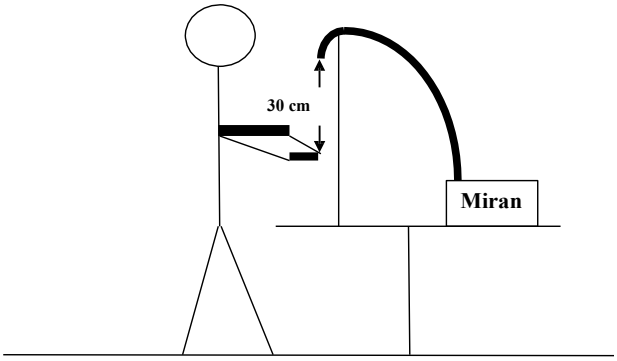

Figure 1: Experimental setup for studying the ambient levels of ethanol associated with the use of HAS.

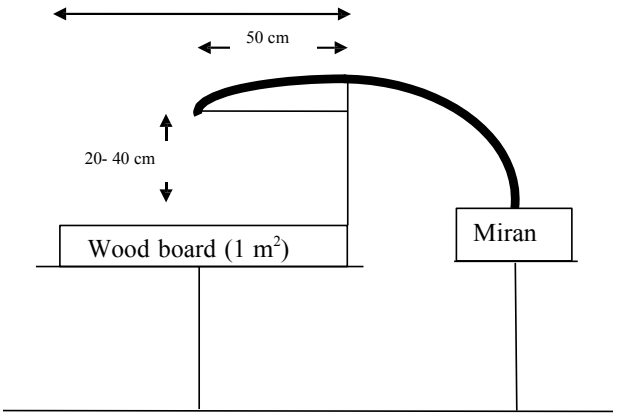

Figure 2: Experimental setup for studying the ambient levels of ethanol associated with the application of ethanol-based varnish on a wood surface placed in the center of the inhalation chamber.

Statistical analysis

The nonparametric Mann-Whitney test was used to determine whether there was a significant difference between the ethanol concentration in the air following the use of 1.5 g or 3 g of Purell® in the inhalation chamber or in the office or between the two environments. These tests were performed using SPSS statistical analysis software (version 17.0). The level of significance was set at $P < 0.05$.

Modeling and simulations of exposure to hydroalcoholic solutions and varnish containing ethanol, and blood ethanol predictions

The details pertaining to the PBPK model used for predicting BELs after exposure to ethanol vapors from either HAS or ethanol-based varnish are described in a previous paper [12]. This model was calibrated/validated using blood levels of ethanol collected from volunteers (men and women) exposed to various concentrations of ethanol (125–1000 ppm × 4 hours) under controlled conditions [12]. Briefly, the model consists of five compartments: brain, liver, richly perfused tissues (kidney, heart), poorly perfused tissues (muscle, skin), and adipose tissues. It allows the kinetics of ethanol in the human body to be described, taking into account the anatomical and physiological characteristics of a typical man (70 Kg) or woman (55 Kg) and the affinity of ethanol for the various body tissues and organs.

The scenario tested for the use of HAS was based on a working day (8 hours) divided into two periods of 3.5 hours interrupted by a break of one hour without exposure (ANSES, 2010) [13]. The duration of exposure to ethanol for every rubbing was three minutes. The first minute of these exposures represents the concentrations of ethanol in the air at the time of hand rubbing with the HAS, and the last two represent the air concentrations resulting from this friction. Frictions were spaced 10-min apart in order to reveal any potential increase in blood ethanol level during a workday (e.g., health professionals) during which a total of 42 hand rubbings were performed (21 in the morning and 21 in the afternoon) (ANSES, 2010) [13]. Average ethanol levels measured in air (office and inhalation chamber) were used to predict BELs (Table 1). In the case of varnish, the air ethanol concentrations used were those that were measured at a distance of 40 cm from the center of the board for the first five minutes after varnish application and those measured in the inhalation chamber during the

	Office				Inhalation chamber			
	1.5g		3.0g		1.5g		3.0g	
Time (min)	Average (ppm)	SD	Average (ppm)	SD	Average (ppm)	SD	Average (ppm)	SD
0.5	389.2	302.0	227.4	136.4	340.3	173.8	383.3	84.9
1.0	779.8	303.8	761.8	480.2	460.3	114.9	844.5	90.6
1.5	164.9	195.9	415.9	239.7	115.6	74.1	285.7	76.1
2.0	49.2	72.6	92.9	55.0	25.4	4.8	51.3	9.9
2.5	28.4	30.7	46.8	22.6	21.2	1.6	40.8	3.1
3.0	22.5	19.0	32.6	7.6	19.2	1.3	38.8	4.3

Table 1: Average values of concentrations in ambient air (inhaled air) measured at 30-second intervals for 3 minutes of hand rubbing. Experiment was repeated 4 times.

following 60 minutes. This scenario was chosen to best represent the concentrations encountered in the breathing zone of a typical worker during and after the application of the varnish on a wood board in a well-ventilated working place. The simulations were performed using the ethanol PBPK model described in a previous paper [12] which was transcribed into an MS Excel® spreadsheet [15].

Results

Hydroalcoholic solutions

Overall, the concentration of ethanol resulting from the evaporation of ethanol during hand rubbing with HAS (Purell® 70%) showed a high variability both intra- and inter-individually (Table 1). However, these variations appear attenuated in an environment where the airflow is stable and the air renewal is high (inhalation chamber) compared to an environment where there is no air change (office). Hand rubbings result in peak exposure that is characterized by a rapid increase of ethanol concentrations that decreased rapidly during the following minutes. The highest concentrations (peak level) were lower in the inhalation chamber but significantly lower only for the 1.5 g (p-value = 0.028). Values (Mean ± SD) for the 1.5 g and 3 g of HAS were 858 ± 258 ppm and 1134 ± 122 ppm, respectively for the inhalation chamber, compared to 1467 ± 883 ppm and 1243 ± 594 ppm, respectively for the office. Table 1 present the average of concentration measured in each 30 second intervals. Highest concentrations were measured 1 minute after the onset of hand rubbing.

Interestingly, the highest concentrations for each subject associated with the use of 3 grams were not necessarily higher than those measured with 1.5 g. In contrast, however, for four of the five subjects, the area under the curve (AUC) for ambient concentrations versus time corresponding to the three minutes of HAS exposure was significantly higher (p-value = 0.009) for the quantity of 3 g but only in the inhalation chamber which is indicative of an extended time of exposure in that case.

Ethanol-based varnish

The concentrations resulting from the application of 125 ml of ethanol-based varnish are shown in Table 2. Under the conditions tested, the ethanol concentrations can greatly exceed 1000 ppm for a short period of time. Indeed, this excedance was short (< 4 minutes) and the levels decreased rapidly; levels were below 100 ppm after 20 minutes. We also observed a slight decrease as a function of the distance from varnish application. The mean levels measured 20 cm and 40 cm from the center of the board and the mean ethanol concentration level in the inhalation chamber corresponding to the first 30 minutes post application were 331 ± 15.1 ppm, 318 ± 24.4 ppm, and 264 ± 5.5 ppm (mean ± SD), respectively.

Time (min)	20 cm		40 cm		Inhalation chamber	
	Average (ppm)	SD	Average (ppm)	SD	Average (ppm)	SD
5	917.0	54.4	841.7*	123.8	579.9	13.2
10	637.7	38.6	618.4	34.4	585.5*	15.3
15	278.1	13.6	280.9	11.8	344.1*	8.9
20	136.9	11.9	138.9	7.3	234.2*	7.4
25	79.6	11.1	79.1	5.1	112.5*	6.0
Last 35	34.6	7.2	34.2	3.8	17.5*	3.4

*Concentration used for PBPK modeling of BELs

Table 2: Average values of concentrations measured at 5-minute intervals for 60 minutes following varnish application in the inhalation chamber. Experiment was repeated 4 times.

Modeling of exposure to hydroalcoholic solutions and ethanol-based varnish

The results of the model simulations for men and women for repeated exposure to HAS are presented in Table 3, and Figures 3 and 4 for men only. The highest BEL predicted (0.42 mg/L in women and 0.40 mg/L in men) involved the use of 3 g of HAS. As shown in Figures 3 and 4, BELs do not return to the initial levels between frictions with HAS, even during the lunch break (i.e., 1 h without exposure). In fact, the model predicts that BELs would return to initial levels only 5 hours after the last hand rubbing. The predictions of the PBPK model give a higher blood AUC (15 hours) for the use of 3 g of HAS compared to 1.5 g in both environments (for men, 1.06-fold in the office and 1.36-fold in the inhalation chamber) (Table 4). The total doses of ethanol that result from the pulmonary exposure to ethanol from HAS averaged 0.2 g (Table 5).

Finally, for men and women, the highest BELs associated with varnish application were 0.76mg/L and 0.79 mg/L, respectively.

Discussion

The main purpose of this study was to facilitate the evaluation of the health risks for the general population and the workers associated with ethanol exposure by inhalation. First, we report the concentrations in the ambient air following the use of HAS and the application of a typical ethanol-based varnish. Second, these concentrations were used to predict the resulting BELs using a PBPK modeling approach.

Hydroalcoholic solutions

The ethanol concentrations in the ambient air resulting from the evaporation of HAS varied considerably depending on i) the amount used, ii) the way the volunteers rubbed their hands, and iii) the environment (room size and ventilation). The maximum concentrations measured in each subject were highly variable and as expected were higher in the office (closed room) than in the inhalation chamber (highly ventilated). The large variability that characterized the ethanol concentrations measured in the office can be explained in part by air convection and the air flow behavior in a room with no ventilation rate [16].

ANSES (2010) [13] reported that the highest ethanol concentration measured during a test performed by a nurse, in a poorly ventilated room, with 3 ml of an HAS of 80%, for one minute, reached 2222 ppm. This level is moderately higher than our values of 1243 ± 594 ppm (office) and 1467 ± 883 ppm (inhalation chamber) with 3 g (~3 ml) of HAS (70% v/v), and not surprisingly given their quite different experimental setups in both studies. Indeed, in this experiment hands as well as forearms were rubbed, which corresponds to a larger evaporation surface. Increasing the surface of evaporation amplifies

		Office		Inhalation chamber	
		1.5 g	3 g	1.5 g	3 g
Women	AM	0.39	0.37	0.26	0.42
	PM	0.39	0.37	0.26	0.42
Men	AM	0.37	0.35	0.25	0.40
	PM	0.37	0.35	0.25	0.40

*Predictions based on ethanol levels presented in Table 1.

Table 3: Highest BELs ($mg.L^{-1}$) predicted by the PBPK model during hand rubbing with HAS for a typical 8-h working day (total of 42 hand rubbings)

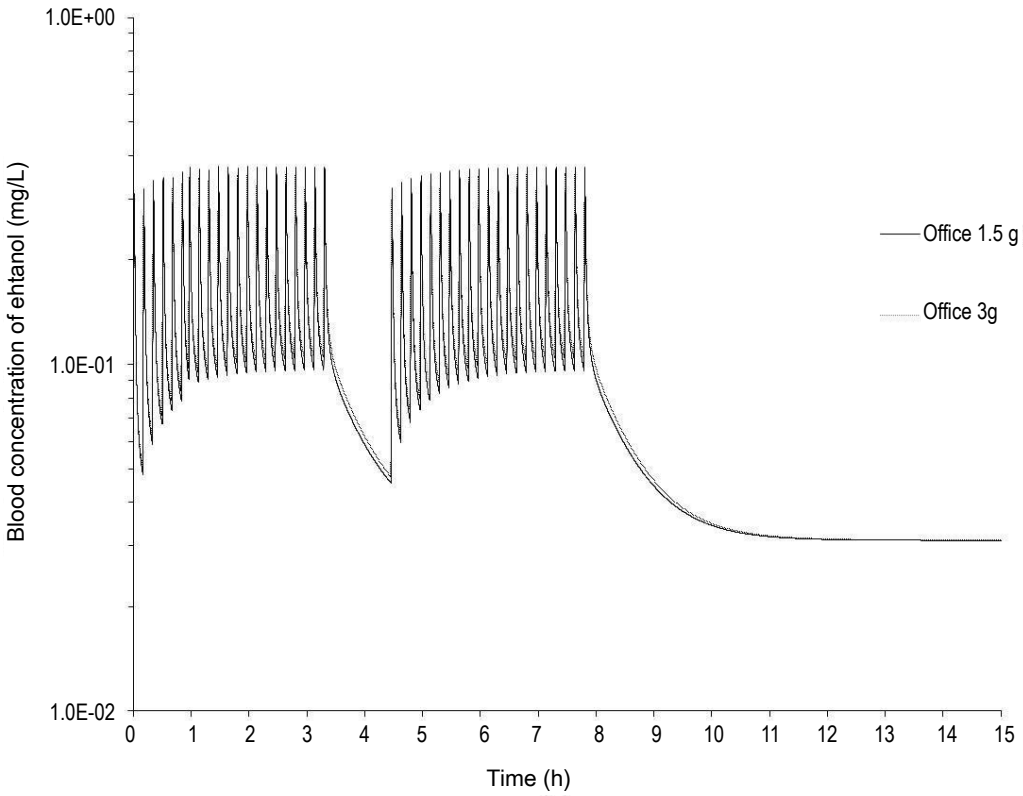

Figure 3: PBPK model simulation of BEL in a man (70 kg): hand rubbing with HAS (1.5 or 3 g) in a non-ventilated office was repeated every 10 minutes for a total of 42 during a typical 8-h working day.

	Office		Inhalation chamber	
	1.5 g	**3 g**	**1.5 g**	**3 g**
Women	51.0	56.1	34.4	58.7
Men	50.5	55.6	34.2	58.2

Table 4: Area under the curve of the BEL versus time [(mg/L)× min] predicted during hand rubbing with HAS for a typical 8-h working day (total of 42 hand rubbings).

			Office		Inhalation chamber	
			1.5g	3g	1.5g	3g
Women	42 push	Dose (gr)	0.17	0.21	119	200
	1 push		0.004	0.005	0.003	0.004
Men	42 push	Dose (gr)	0.21	0.23	0.14	0.24
	1 push		0.005	0.005	0.004	0.006

Table 5: PBPK predictions of the total dose of ethanol absorbed following 1 or 42 hand rubbings during a typical 8-h working day.

the evaporation rate, and as a result, the ethanol concentration in air [17]. Triolet and Benoît (2009) [17], in the same study, using a hemispherical exposure model, predicted that the average maximum concentration of ethanol in air for one rubbing (1 minute) with 3 ml of HAS (65-85%) with hands was 1633 ppm (ANSES, 2011). This value differs by only 10% (1.5 g) and 24% (3 g) from our values. Interestingly, the difference between the prediction of the hemispherical model and our results is smaller than the inter-individual variability of 10% to 56% observed in the present study, depending on the exposure scenario.

More recently, Bessonneau and Thomas [18] conducted an experimental laboratory simulation with commercial HAS (Aniosgel 85 NPC) containing 70% ethanol (v/v). The authors reported that the ethanol concentration reached in air was as high as 7590 ppm for a rubbing lasting 30 seconds with 3 ml of HAS. This value is much higher (about 3.2 times) than the highest concentration obtained with one of our volunteers (2352 ppm). Again, this difference can be explained in part by the use of a different experimental setup and a lower air change rate of 12 ± 1 h^{-1} in the room where the experiment was conducted. Hautemanière et al. [7] who investigated several scenarios involving single or repeated hand rubbings with 3 ml of a HAS (70% v/v) reported average ambient levels that ranged from 73 to 350 ppm with peak levels achieving 2000 ppm and more. They also estimated that the total dose of ethanol absorbed by health workers during their work life (24 hand rubbings/day × 217 days/year × 31 years) would range between 1.8 and 3.0 kg. Using the same exposure parameters the total dose estimated from the present study range between 1.3 and 1.6 kg (42 hand rubbings/day). In another experiment, Hautemanière et al. [7] reported that ethanol was not detected in the blood of health care workers who used HAS during a 4-hr workshift. However, the authors did not mention what was the profile of ethanol levels in inhaled air that was associated with hand rubbing (e.g., peak levels × time of peak…) in their study. They only mentioned that the average level measured during the 4-hr workshifts was 46.2 ± 34.8 mg/m^3 (approximately 25 ppm) and that the amount of HAS used during the 4 hr averaged 33 g that corresponds to 11.5 hand rubs (with 3 mL of HAS for each hand rub). Since that hand rubbing with HAS result in peak exposure characterised by high level of ethanol for only short

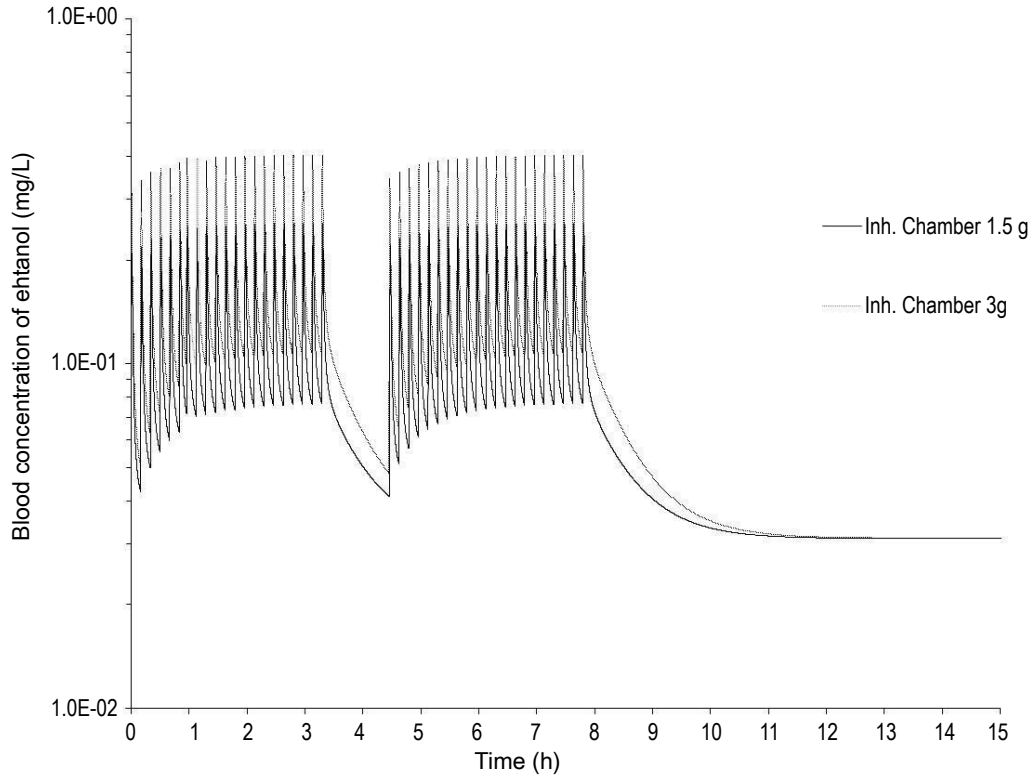

Figure 4: PBPK model simulation of BEL in a man (70 kg): hand rubbing with HAS (1.5 or 3 g) in the inhalation chamber (well-ventilated) was repeated every 10 minutes for a total of 42 during a typical 8-h working day.

durations of time and that ethanol clearance from blood is quite fast, the time between blood sampling and the end of exposure is critical for exposure assessment. In a recent study with human volunteers [12] we showed that exposure to 126 ppm of ethanol vapors during 4 hours under controlled conditions in an inhalation chamber produced the following blood levels after 1- and 4-hr exposure (end of exposure): in women 0.167 ± 0.042 mg/L and 0.196 ± 0.050 mg/L, respectively; in men, 0.163 ± 0.027 mg/L and 0.184 ± 0.034 mg/L, respectively. Within 30 minutes following the end exposure blood levels rapidly decreased to approximately 20% of end of exposure values.

The PBPK modeling exercise shows that the highest BELs associated with the use of HAS (3 g) and the application of varnish are 0.42 mg/L and 0.79 mg/L, respectively. Using a comparable modeling approach, ANSES (2010) [13] reported a value of 1.28 mg/L, which is approximately 3 times higher than the highest BEL estimated in the present study for HAS. Two reasons may explain this difference: first, the ethanol concentrations in air used by ANSES (2010) [13] in their scenario were obtained with models that predicted higher levels (2.9-fold) compared to those measured experimentally in the present study; second, we used a modified PBPK model to predict BELs that involves not only hepatic metabolism (high capacity and low affinity) but also extra-hepatic metabolism (low capacity and high affinity). This modification produces lower BELs, and allows the kinetics (elimination) of ethanol in blood to be more appropriately described when exposure levels are below 1000 ppm [12].

Ethanol-based varnish

For the varnish, the highest ethanol concentrations measured above the surface where the varnish was applied (1 m^2) reached rather high peak ethanol levels (> 1000 ppm) even though the tests were conducted in a well-ventilated room. However, the level decreased rapidly, and after 30 minutes, the concentration was less than 100 ppm. Nevertheless, one might expect that the levels would be higher in a less-ventilated room.

Recently, results of simulation exposures to ethanol vapors from varnish application have been reported (ANSES, 2011) [14]. Two models were compared. The main parameters of the simulations for both models were the following: volume of varnish (0.5 L), ethanol content of 80% (v/v), application time (3 hours), volume of the room (50 m^3), application surface (2 m^2), and 3 different air changes (0.25 h^{-1}, 0.5 h^{-1} and 1 h^{-1}). While the peak levels (1082 ppm) were quite similar to ours, the mean levels predicted were much higher than those measured in our study. For instance, at an air renewal rate of 1 h^{-1}, the mean levels for 3 hours predicted by the MOD model and the CONSEXPO RIVM model were 771 ppm and 755 ppm, respectively (ANSES, 2011), compared to a value of 264 ppm for 30 minutes in the present study.

For varnish application, the BELs reported by ANSES (2011) [14] were 9.6 mg/L (1327 ppm) and 5.3 mg/L (770 ppm). These results, which are respectively 12 times and 6.6 times higher than those predicted in our study, may be explained by the different experimental conditions, described above which would correspond to a worst-case scenario compared to our conditions [20,21].

Conclusion

In conclusion, this study confirms the results reported in previous publications that the use of HAS for sanitizing hands may result in short-term exposure to high levels of ethanol that are likely to result in absorption of ethanol into the blood circulation. However the level of ethanol in blood remains low (< 1 mg/L) and the total dose absorbed estimated for a working day involving 42 hand rubbing is approximately 0.2 gr which, for instance, is far less that the amount contained in a standard drink (approximately 14 gr).

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Declaration of Interest

The authors report no existing potential conflicts of interest.

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