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In vitro and *in vivo* evaluation of propylene glycol ethers metabolism in humans

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ABSTRACT

Propylene glycol ethers (PGEs) consist of a major α-isomer (secondary alcohol group) and a minor β-isomer (primary alcohol group). Animal studies have reported toxic effects of the β-isomer metabolites, but human metabolism of PGEs remains poorly understood. We aimed to characterize the metabolism of two common PGEs in humans. Nine participants were exposed under controlled conditions (4 h) to propylene glycol ethyl ether (PGEE) or propylene glycol propyl ether (PGPE) (<35 ppm). Blood and urine samples were collected, and the respective β-isomers metabolites; 2-ethoxypropanoic acid (2-EPA) and 2-propoxypropanoic acid (2-PPA) were quantified. The 2-PPA blood absorption rate was 0.0005 ± 0.0002 μg/mL/h*ppm followed by rapid urinary elimination (half-life: 2 h) and slower secondary elimination (half-life: 10 h). No dose-response was observed for 2-EPA; therefore, β-PGEE metabolism was investigated *in vitro* using human liver S9 fractions. We provide 2-EPA hepatic kinetic and enzyme kinetic parameters. We recommend using of 2-PPA as a biomarker for PGPE exposures.

1. Introduction

Glycol ethers are a family of organic solvents with a widespread use in household and professional products. There are two major subgroups of glycol ethers: ethylene and propylene glycol ethers. Commercial products containing technical grade propylene glycol ethers are usually a mixture of two different isomers: the major α isomer (> 95 %) with a secondary alcohol group and the minor β isomer (< 5 %) with a primary alcohol group (Miller et al., 1986). According to previously published rat studies, each isomer follows a different metabolic pathway (Kemper et al., 2008; Werner et al., 2025). The α isomers of propylene glycol ethers are mostly metabolized into propylene glycol, which in turn is metabolized to CO_2 and eliminated in exhaled air. A fraction of α isomers is also eliminated through urine in unchanged or conjugated form of the parent molecule (Miller et al., 1983; Multigner et al., 2005). The β isomers are mostly metabolized in a secondary metabolite specific to their respective parent propylene glycol ether (Miller, 1987; Miller et al., 1983, 1984, 1986). Their metabolism pathway is similar to the more

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known ethylene glycol ethers having in common an alcohol group in the primary position on their alkyl chain (Multigner et al., 2005). This alcohol group is metabolized by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) to produce the corresponding acid (Werner et al., 2024). Alkoxypropionic acids in case of propylene glycol ether metabolism (Multigner et al., 2005) and alkoxyacetic acids for ethylene glycol ethers are both eliminated through urine. Experimental *in vivo* studies associated developmental toxicity, hemolysis, and testicular atrophy in animals with the presence of alkoxyacetic acids (European Centre for Ecotoxicology and Toxicology of Chemicals, 2005). Propylene glycol ethers are considered a safer alternative to the ethylene glycol ethers. However, limited evidence suggests that β-isomer-derived alkoxypropionic acids may be associated with reproductive toxicity in animal studies (Lemazurier et al., 2005). Many propylene glycol ethers remain unexplored with respect to their metabolism and internal dosimetry in humans (Multigner et al., 2005).

One of the most common propylene glycol ethers are propylene glycol ethyl ether (1-ethoxy-2-propanol, PGEE) and propylene glycol propyl ether (1-propoxypropan-2-ol, PGPE). More than 2000 products contain these chemicals in Switzerland with a great proportion (80 %) for professional use (OFSP, 2022). Thus, over 100,000 workers are potentially exposed every day including painters, cleaners, and printers in Switzerland (OFS, 2024). Occupational exposure limits are set only for a few propylene glycol ethers, and in Switzerland, this limit is set at 50 ppm for PGEE, but none exist for PGPE. Several studies have assessed glycol ether exposures by measuring urinary alkoxy acid concentrations in the European population (Fromme et al., 2013; Garlantézec et al., 2012; Multigner et al., 2007), but these focused mostly on ethylene glycol ethers. Despite the widespread use of products containing PGEE and PGPE, especially among a large professional population, no studies have evaluated metabolism of β-PGEE and β-PGPE and internal dose of their metabolites after human exposure. We hypothesized that β-PGEE and β-PGPE follow the same toxicokinetic metabolism pathways as the known β isomer of propylene glycol methyl ether (1-methoxypropan-2-ol, PGME) (Miller et al., 1986). Consequently, β-PGEE could result in 2-ethoxypropionic acid (2-EPA) and β-PGPE would result in 2-propoxypropionic acid (2-PPA) (Fig. 1).

The purpose of this study was to evaluate the metabolism of the β isomers of PGEE and PGPE in humans. We studied the toxicokinetic of 2-EPA and 2-PPA *in vivo* in healthy participants exposed for four hours under controlled conditions to either PGEE or PGPE vapor. We quantified the 2-EPA, and 2-PPA concentrations in urine and blood to construct the toxicokinetic curves for each participant over time. Furthermore, we studied the metabolism of β-PGEE *in vitro* using human liver subcellular fraction (S9) containing all Phase I and II enzymes including ADH and ALDH. S9 is commonly used to investigate mammalian metabolism *in vitro*.

2. Methods

This study is part of a larger project combining *in vitro*, *in silico* and *in vivo* studies to assess toxicokinetic, metabolism and neurotoxicity of propylene glycol ethers (Hopf et al., 2024). The experimental design, population, and sampling were previously described (De Luca et al., 2025). Briefly, the selected exposure concentrations for PGEE (25, 30, 35 ppm) were chosen to remain below the Swiss OEL of 50 ppm while enabling resolution of a dose-response relationship for metabolite formation. For PGPE, no toxicological data are available; therefore, concentrations (15, 20, 25 ppm) were selected based on prior pilot testing for odor tolerance and participant comfort, ensuring safety while allowing assessment of internal dose and metabolism. Nine healthy participants were exposed at rest for four hours to the three different air concentrations of PGEE or PGPE in an exposure chamber under controlled conditions. PGEE and PGPE vapors were a mixture of α- and β-isomers representative of products content available on the market. We were unable to determine the exact concentrations of the α- and β-isomers in the PGEE and PGPE test materials, as we did not have an analytical method to distinguish between the isomers, and the manufacturer did not provide this information. Blood samples were collected during exposure and two hours post-exposure. Participants recorded the total volume of each urine void during the 24-hour period following exposure. For each void, a portion of the urine was retained in the collection cup and returned to our laboratory for chemical analysis. The respective metabolites of β-PGEE and β-PGPE were quantified in urine and blood samples.

2.1. Chemicals and S9 fractions

Propylene glycol ethyl ether (CAS no. 1569–02–4, >95 %) and propylene glycol propyl ether (CAS no. 1569–01–3, >99 %) were purchased

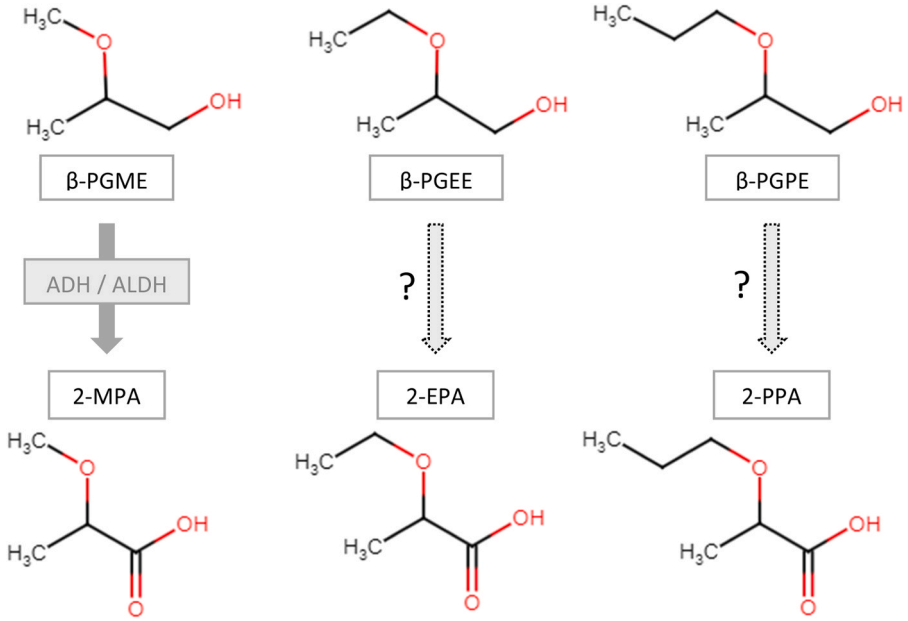

Fig. 1. Hypothetical secondary metabolites formation for β-PGEE and β-PGPE based on β-PGME metabolism reported in Miller et al. (1986). Formation of 2-EPA and 2-PPA following metabolism by alcohol (ADH) and aldehyde dehydrogenases (ALDH) of β-PGEE and β-PGPE respectively.

by Chemie Brunschwig AG (Basel, Switzerland) for inhalation exposure sessions. For metabolite quantification in blood and urine samples, standard for 2-ethoxypropionic acid (2-EPA, CAS no. 53103–75–6, 95 %) was obtained from Alfa-Chemistry (Holbrook, USA), and from ChemBridge (California, USA) for 2-propoxypropionic acid (2-PPA, CAS no. 56674–67–0). Methanol (MeOH) was purchased from Thommen-Furler AG (Rüti bei Büren, Switzerland), hydrochloric acid (HCl) from Sigma Aldrich (St. Louis, MO, USA), and acetic acid and ammonium from Merck (Buchs, Switzerland). 2-EPA and β-PGEE for the *in vitro* experiments were purchased from Sigma-Aldrich (St. Louis, MO, USA). Ultrapure water was obtained from a purification system (Milipore Milli-Q Plus, Beford, MA, USA). Phosphate buffer was prepared in-house, adjusted to pH 7.4, and stored at 4 °C. All other chemicals and reagents were of analytical grade and purchased from commercial sources. Pooled adult mixed gender human liver subcellular fraction (S9) was purchased from Thermo Fisher Scientific (Reinach, Switzerland; HMS9PL).

2.2. Assessment of Michaelis-Menten-kinetics

The incubation mixtures contained S9 fraction at a protein concentration of 2 mg/mL, 100 mM potassium phosphate buffer (pH 7.4), 3 mM MgCl2, 1 mM NAD+ (Sigma; NAD100-RO), 1 mM NADPH (Sigma; NADPH-RO), and the respective substrate concentrations (Table 1). After 5 min of preincubation, the reaction was initiated with the addition of NAD+ and NADPH, and incubations conducted (45 min, 300 rpm, 37 °C) on a Thermomixer (Eppendorf, Hamburg, Germany). Incubations without NAD+ and NADPH were included as a control. Reactions were stopped by the addition of ice-cold acetonitrile (ACN; Sigma; 439134–1 L) at defined time-points (Table 1). Samples were then vortexed and centrifuged (15 min, 2500 × *g*, 4 °C). The reaction rates were linear with respect to time of incubation and the protein concentrations. Michaelis-Menten-Kinetic parameters (V_{max} and K_m) were obtained by nonlinear regression using GraphPad Prism applying the Michaelis-Menten-equation. The *in vitro* intrinsic clearance (CL_{int}) was calculated according to the equations described in 2.4.

2.3. Chemical analysis

2.3.1. Analytical methods in blood and urine

Blood samples were diluted 1000 times and urine samples 10 times with ultra-pure water (MilliQ, Merck Millipore, France) for the quantification of metabolites. Free metabolites were analyzed directly, while conjugated metabolites required deconjugation prior to analysis. Samples were incubated with an acid (HCl, 4 N) (2-EPA: 20 μL and 2-PPA: 50 μL) for two hours at room temperature before being neutralized with 25 % aqueous NH_3 (2-EPA: 76 μL and 2-PPA: 40 μL). In blood and urine samples, 2-EPA was quantified directly, whereas quantification of 2-PPA required pre-analytical step consisting of a solid phase extraction (Chromoband HR-XA, Macherey-Nagel, Germany). The solid phase extraction (SPE) was conditioned with MeOH (2 mL) and 1 % aqueous NH_3 (2 mL). Diluted samples were loaded onto the SPE columns, washed twice (first with 1 % aqueous NH_3 (3 mL) and then with H2O:MeOH (3:1) 1 % NH_3 (3 mL)), and eluted with 1 % MeOH in acetic acid (3 mL). The samples were evaporated dry with nitrogen (N_2, 52°C, 3 psi, 30 min, TurboVAP, Caliper Lifesciences, Hopkinton, USA) and transferred into glass vials containing 1 mL ammonium acetate (15 mM). Blood and urine samples were injected (50 μL) into a liquid chromatography (LC) (Ultimate 3000, Thermo Scientific, Waltham, USA) equipped with a column (Waters Acquity HSS T3 150*2.1, 1.8 μm, Milford, USA) coupled with tandem mass spectrometry (MS/MS) (Quantiva, Thermo Scientific, Waltham, USA). The internal standard was 2-PPA for 2-EPA and vice versa (100 ng/mL, 20 μL). The limit of quantification (LOQ) in blood was 2000 ng/mL and 2 ng/mL for 2-EPA and 2-PPA respectively. In urine, the LOQ was 50 ng/mL for both metabolites.

Table 1
Parameters for the assessment of Michaelis-Menten-kinetics and metabolite formation of β-PGEE using S9 fractions.

Parameters	Michaelis-Menten kinetics assessment	Metabolite formation assessment
Incubation mixture volumes (μL)	200	400
Substrate concentrations for β-PGEE (mM)	0.1, 0.3, 0.4, 0.6, 0.8, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 4.5, 5.0, 5.5	0.27
Reaction end time (added volume)	45 min (+ 400 μL ACN)	1, 12, 23, 34, and 45 min (+ 80 μL ACN)

2.3.2. Analytical methods after incubation with S9

2-EPA was quantified with a high-performance liquid chromatography (1200 Series Gradient HPLC system, Agilent, Santa Clara, CA, USA) equipped with a C18 column (InfinityLab Poroshell 120 CS-C18 column (2.1 × 50 mm, 2.7 μm), Agilent, Santa Clara, USA) and a MS (Triple Quadrupole 6475 mass spectrometer, Agilent, Santa Clara, USA). The system run in electrospray ionization mode (AJS ESI, G1958–65638) operated by a data acquisition software (MassHunter Quantitative Analysis 10.1, Agilent, Santa Clara, USA). Data evaluation was performed using Agilent MassHunter Quantitative Analysis 10.1 (Agilent). Samples (1 μL) were injected at an oven temperature of 50 °C. MilliQ-water containing 0.2 mM ammonium fluoride was used as mobile Phase A (A), whereas 100 % methanol was used as mobile Phase B (B). The flow rate was 0.4 mL/min and the following gradient was applied: 96 % A / 4 % B for 1 min, followed by 90 % A / 10 % B 3 min, ramp up to 5 % A / 95 % B in 0.5 min and keep for 1 min. The source parameters multiplier voltage, gas temperature, gas flow, nebulizer, sheath gas temperature, and sheath gas flow were set at −300, 250 °C, 8 L/min, 60 psi, 375 °C, and 11 L/min, respectively. The capillary spray voltage was set to 3'000 V Positive and Negative, and the nozzle voltage to 500 V Positive and Negative. The Dwell time was set for 35 ms. A 15-point external calibration curve was with $R^2 > 0.99$ was built for each analytical run in the range of approximately 0.03 – 30.0 ng/μL, thus covering the concentration ranges of the samples. The LOQ was defined based on the values corresponding to a signal-to-noise ratio (S/N) of 10 and is reported as 0.22 ng/μL.

β-PGEE was quantified with a gas chromatography (GC) (Agilent; 6890 N, Santa Clara, USA) equipped with a capillary column (Rxi-624Sil, 60 m, 0.25 mm ID, 1.4 μm, Restek, Bad Soden, Germany) coupled to a 5973 Network mass selective detector (Agilent, Santa Clara, USA) with a data acquisition software (Agilent MassHunter Quantitative Analysis 10.0, Santa Clara, USA). Data evaluation was performed using Agilent MassHunter Quantitative Analysis 10.0. Samples (1 μL) were injected in splitless mode (200 °C, 8.4 psi) using a PAL auto sampler system. Column conditions were pressure at 8.4 psi, 1.1 mL/min flow rate. GC conditions were carrier gas helium, 60 °C for 1 min, 10 °C/min up to 200 °C and hold 3.5 min, then 40 °C/min up to 250 °C and hold 1.25 min with a total run of 21 min. MS conditions were positive ion polarity, ion source 230 °C. The total Dwell time was set for 300 ms. A 6-point external calibration curve using cyclohexanol as internal standard (IS) with $R^2 > 0.99$ was built in the range of approximately 1–100 ng/μL covering the concentration ranges of the samples. Thus, samples were diluted with an IS solution before analysis. The LOQ was defined based on the values corresponding to a signal-to-noise ratio (S/N) of 10 and can be expected as < 1 ng/μL.

2.4. Calculation of the in vitro clearance and processing to the hepatic organ clearance

The *in vitro* CL_{int} for the remaining parent compound and the metabolite formation was determined according to Eq. 1 (Obach et al., 1997):

$$CL_{\text{int},in\ vitro}\quad[\mu L/min/mg] = \frac{\pm k\quad[1/min] \times volume[\mu L]}{S9protein[mg]} \tag{1}$$

where the elimination constant (-k) was derived from the slope of the linear regression from the ln-transformed % of solvent remaining versus the incubation time, and the formation constant (+k) was derived from the ln-transformed metabolite concentration versus the incubation time.

The *in vitro* CL_{int} for the S9 incubations was calculated as following:

$$CL_{\text{int},in\ vitro}\quad[\mu L/min/mg] = \frac{V_{max}\quad[nmol/min/mg]}{K_m\quad[\mu M]} \qquad \text{Eq. 2}$$

where V_{max} is the maximum velocity and K_m the Michaelis-Menten-Constant (substrate concentration at half maximal velocity), both predicted from GraphPad Prism.

The *in vivo* hepatic intrinsic clearance ($CL_{int,\ in\ vivo}$) was calculated using physiological scaling factors for hepatocellularity (Barter et al., 2007; Musther et al., 2017), for the protein (Houston and Galetin, 2008), and liver weight (Davies and Morris, 1993) according to Eq. 3:

$$CL_{\text{int},in\ vivo}\quad[mL/min/kg] = CL_{\text{int},in\ vitro} \times 121\quad\frac{mgS9protein}{gliver} \times 25.7\quad\frac{gliver}{kg\ bodyweight} \tag{3}$$

The hepatic organ clearance (CL_h) was predicted using the well-stirred liver model, which reflects the physiological reality that hepatic clearance is influenced by both hepatic blood flow (Q_H; 20.7 mL/min/kg) (Riley et al., 2005) and hepatic intrinsic clearance ($CL_{int,\ in\ vivo}$), as shown in Eq. 4 (Pang and Rowland, 1977) where the numerator is a product of three terms: hepatic blood flow, hepatic intrinsic clearance, and the binding ratio, and the denominator is a sum of two terms: hepatic blood flow plus the product of hepatic intrinsic clearance and binding ratio:

$$CL_h\quad[mL/min/kg] = \frac{Q_H\quad[mL/min/kg] \times CL_{\text{int},in\ vivo}\quad[\mu L/min/kg] \times \frac{f_{u,\ b}}{f_{u,inc}}}{Q_H\quad[mL/min/kg] + CL_{\text{int},in\ vivo}\quad[\mu L/min/kg] \times \frac{f_{u,\ b}}{f_{u,inc}}} \tag{4}$$

Incubational binding for the test system ($f_{u,inc}$) and plasma binding ($f_{u,b}$) were predicted using an QIVIVE platform (qivivetools.wur.nl) taking into account the physicochemical properties of β-PGEE. The used S9 protein concentration (2 mg/mL) was considered, and the Hallifax and Houston method applied (Hallifax and Houston, 2006).

2.5. Statistical analysis

Regarding *in vivo* experiments, the maximal concentration (Cmax) of propylene glycol ether metabolites as well as the time this maximal concentration was reached (Tmax) within each session were computed for each participant for blood and urine. The absorption of propylene glycol ether metabolites in both biological samples was modelled using a linear mixed model from t_0 until Cmax. The fixed independent variables were the cumulative dose computed as the time exposed multiplied by the airborne concentration with subject-specific random effects as well as subject-specific random slopes. The excretion of propylene glycol ether metabolites in both biological samples was modelled using a linear mixed effect model of the log-transformed concentration from Tmax (or the end of exposure whichever was earlier) to the last measurement. The independent variables were the time (in minutes) since Tmax and with subject-specific random effect as well as subject-specific random slope. The half-life of excretion was computed as log(2)/excretion slope with the corresponding confidence interval computed from the confidence interval of the slope.

Regarding *in vitro* experiments, data representation and data analyses were performed using Microsoft Excel (Microsoft, Redmond, WA) and GraphPad Prism (GraphPad Software, San Diego, CA, USA; Version 10.0.2). Data is expressed as mean values ± SD.

3. Results

The majority (> 90 %) of metabolites quantified was not conjugated, so we considered only the results of free metabolites for analysis of *in vivo* human exposure.

3.1. Toxicokinetic profiles for 2-PPA

The geometric means of 2-PPA blood concentrations over time are presented in Fig. 2. Blood concentrations of 2-PPA were below the LOQ for all participants before exposure. Its Cmax in blood was reached 15 min after participants left the exposure chamber, *i.e.*, 15 min after the end of exposure, and increases with air concentrations. Thus, Cmax was 0.03, 0.05 and 0.06 μg/mL in blood following 15, 20 and 25 ppm of exposure respectively (Fig. 2). Metabolite concentrations followed a linear absorption and an exponential elimination rate in blood. The absorption and elimination rate were similar whatever the air concentrations of exposure. The 2-PPA metabolite in blood was below the LOQ for all participants the day after the exposure session.

Fig. 3 represents the geometric means of creatinine adjusted urinary 2-PPA concentrations over time. The Cmax of 2-PPA in urine was reached two hours post-exposure, *i.e.*, 120 min after participants left the exposure chamber. Urinary 2-PPA Cmax increased with air concentrations, *i.e.*, 84.7, 112.6 and 190.9 μg/g creatine following 15, 20 and 25 ppm of exposure respectively (Fig. 3). Urinary concentrations did not follow a linear increase (Table 2). We observed two phases of urinary elimination for 2-PPA (Fig. 3). The first apparent urinary elimination half-life of 2-PPA was nearly two hours (Fig. 3: between Cmax and t_{600}). The second apparent urinary elimination half-life of 2-PPA was close to ten hours (Fig. 3: between t_{600} and t_{1700}). The concentration of 2-PPA in urine did not return to baseline for any participants the day after the exposure session.

Blood and urinary kinetic parameters are described in Table 2 including the geometric means, standard deviations and 95 % confidence intervals of area under the curve (AUC), Cmax, absorption and elimination rates in blood as well as in urine.

3.2. Toxicokinetic profiles for 2-EPA

We investigated the 2-EPA metabolite following PGEE vapors exposure. Fig. 4 shows the geometric means (± standard deviations) of 2-EPA measured in blood in μg/mL and urine in μg/g creatinine of all participants (N = 4) over time. Blood concentrations of 2-EPA before exposure were above the LOQ and remained similar irrespective of exposure (Fig. 4.A). As in blood, urinary concentrations of 2-EPA before the exposure were above the LOQ. We observed an increase of metabolite concentrations over time until Cmax, which was two hours after leaving the exposure chamber for most of the participants. The urinary concentrations decreased slowly returning to baseline the day after the exposure (Fig. 4.B). No toxicokinetic parameters, such as absorption or elimination rates, could be estimated with these data.

3.3. Assessment of β-PGEE hepatic metabolism in S9 incubations

Fig. 5.A illustrates the β-PGEE concentrations versus reaction velocity (V). The K_m value was 1130 ± 245 μM and V_{max} 1.37 ± 0.12 nmol/min/mg for the β-PGEE to 2-EPA reaction. The calculated *in vitro* CL_{int} was 1.23 ± 0.18 μL/min/mg (c.f. Eq. 2). The results for metabolite formation and β-PGEE depletion are presented in Fig. 5.B and illustrate a linear progression over 45 min. A remaining parent compound of 13.8 % was determined. Fig. 5.C represents the calculated natural logarithm of the percentage of remaining β-PGEE and formed 2-EPA concentration versus time plots. Based on these, the *in vitro* CL_{int} for the remaining parent compound was determined as 3.28 ± 0.11 μL/min/

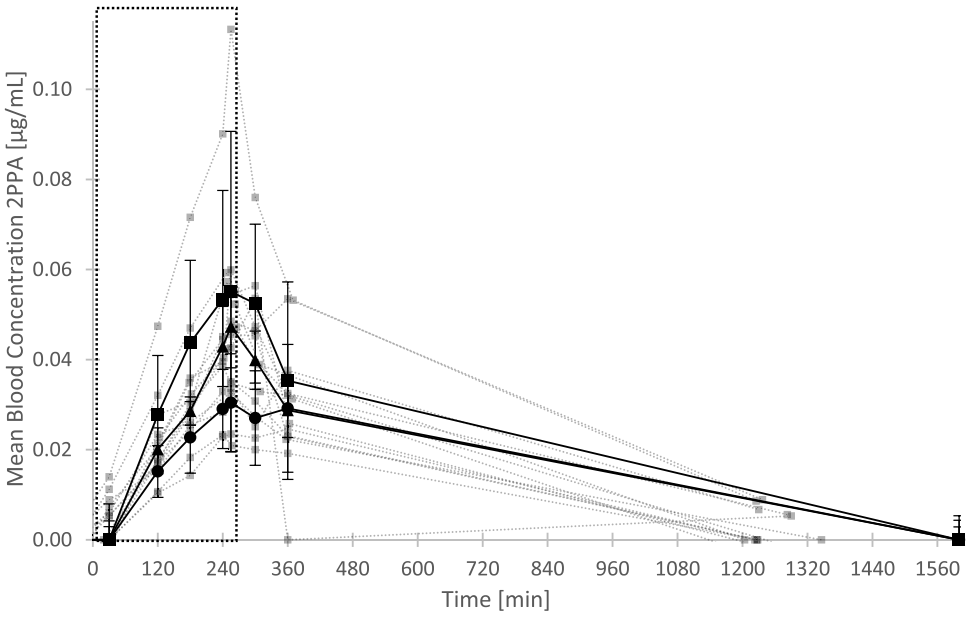

Fig. 2. Concentration of 2-PPA in blood (µg/mL) over time (minutes). Each grey curve is the result from one participant. The large square represents the time in the exposure chamber (4 h). Geometric means (± standard deviations) of 2-PPA blood concentrations for all participants (n = 5) as a function of time for a 15 (●), 20 (▲) and a 25 (■) ppm exposure to PGPE vapors.

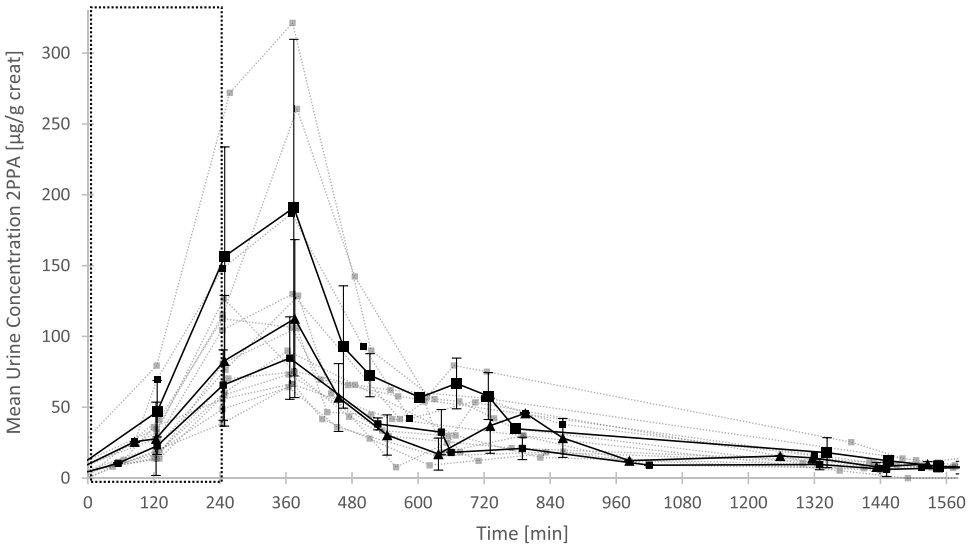

Fig. 3. Urinary concentration of 2-PPA (µg/g creatinine) over time (minutes). Each grey curve is the result from one participant. The large square represents the time in the exposure chamber (4 h). (A) Geometric means (± standard deviations) of 2-PPA urinary concentrations for all participants (n = 5) as a function of time for a 15 (●), 20 (▲) and a 25 (■) ppm exposure to PGPE vapors.

Table 2
Human 2-PPA toxicokinetic parameters following PGPE vapors exposure in blood and urine adjusted with creatinine. Geometric means (± standard deviations) of all concentration of exposure for all participants (n = 5) and 95 % confidence intervals of area under the curve (AUC), maximum concentration (Cmax), absorption and elimination rate, and half-life (between Cmax and t_{600}).

Parameters	Concentration of 2PPA							
	BLOOD				URINE			
AUC [mg*min/mL]	0.023	±	0.01	[0.02, 0.03]	64.03	±	33.61	[46.42, 81.63]
Cmax [ug/mL]	0.05	±	0.03	[0.04, 0.07]	129.11	±	77.50	[88.51, 169.71]
Absorption [ug/mL/h*ppm]	0.0005	±	0.0002	[0.0004, 0.0006]	na			na
Elimination [ug/mL/h*ppm]	−0.10	±	0.02	[−0.12, −0.07]	−0.17	±	0.05	[−0.21, −0.13]
Half-life [h]	3.1			[2.4,4.4]	1.7			[1.4,2.3]

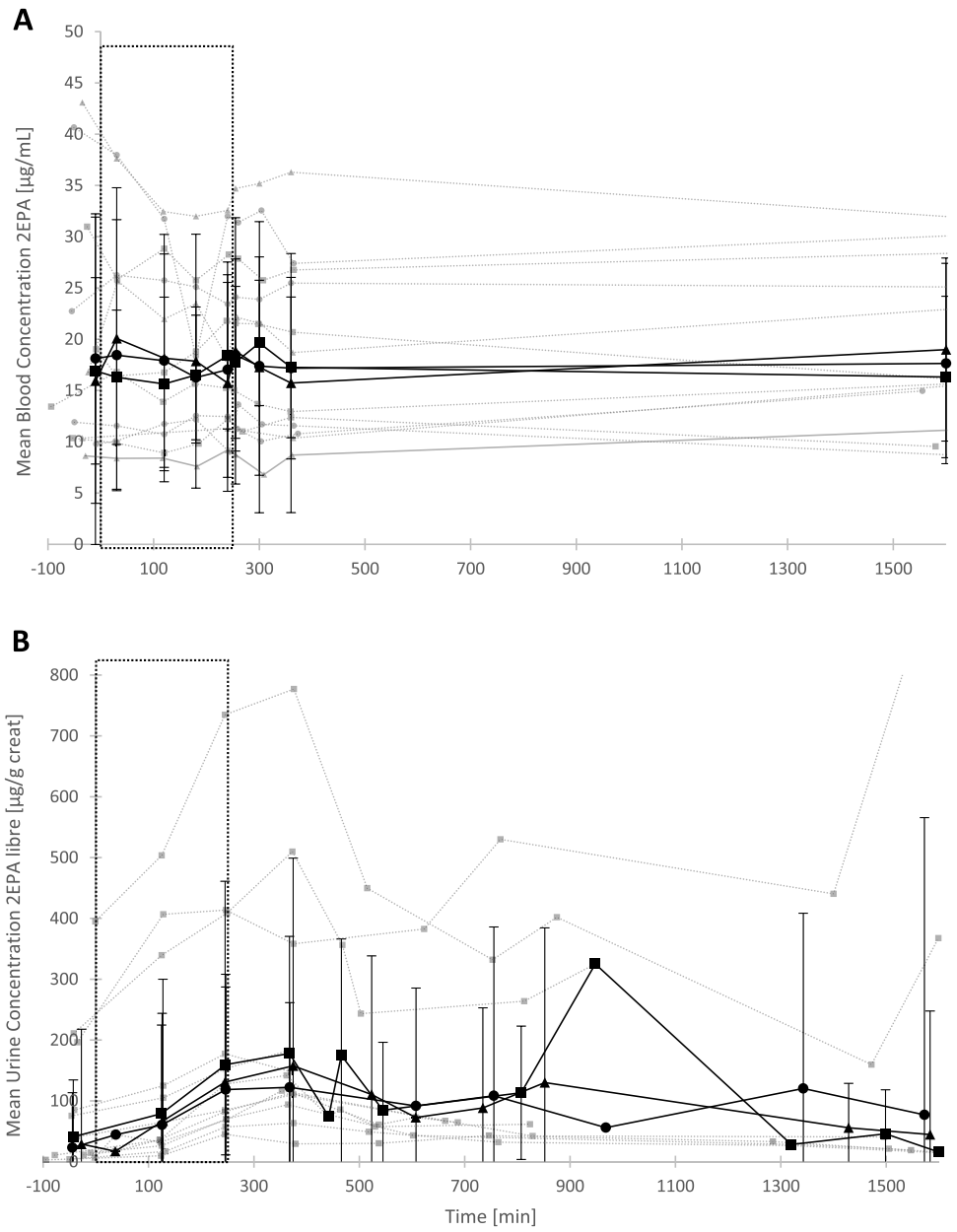

Fig. 4. 2-EPA concentrations as a function of time (minutes) for a 25 (●), 30 (▲) and 35 (■) ppm exposure to PGEE vapors. The large square represents the time in the exposure chamber (4 h). Each grey curve is the result from one participant. (A) Geometric means (± standard deviations) of 2-EPA blood concentrations (µg/mL) over time. (B) Geometric means (± standard deviations) of 2-EPA urinary concentrations (µg/g creatinine) over time.

mg, while the *in vitro* CL_{int} for the metabolite formation was determined as 29.1 ± 6.33 µL/min/mg, which is approximately nine times higher.

Table 3 summarizes the predicted hepatic organ clearance (CL_h) through *in vitro-in vivo* extrapolation (IVIVE) based on the *in vitro* CL_{int} obtained from the performed measurements as well as the *in vitro* CL_{int} calculated from K_m and V_{max}. The *in vitro* predicted CL_h values were within a three-fold deviation (measured metabolite formation: 16.1 ± 0.9 mL/min/kg; measured remaining parent compound: 5.99 ± 0.14 mL/min/kg). Besides, the *in vitro* predicted CL_h based on V_{max}/K_m was 2.74 ± 0.35 mL/min/kg, which was close to the measured value for the remaining parent compound (Table 3).

4. Discussion

Healthy participants exposed to PGPE vapors eliminated the metabolite 2-PPA in urine with a short half-life, *i.e.*, less than 10 h. The formation of alkoxy propionic acids from human metabolism of β-PGPE through ADH and ALDH activity follows the same pathway as previously described for other propylene glycol ethers in animal studies (Miller, 1987; Miller et al., 1986). Concentrations of 2-PPA increased proportionally with PGPE air concentrations and peak systemic concentrations (Cmax in blood) occurred 15 min after participants exited the exposure chamber as observed in Fig. 2. The blood concentration-time profiles suggest a linear absorption phase followed by exponential elimination and this time-course overlaps with urinary elimination. Therefore, it may be misleading to label this phase solely as the "absorption rate". PGPE reached steady-state concentrations in blood after approximately three hours of continuous exposure (De Luca et al., 2025), indicating that absorption and distribution had stabilized. In contrast, 2-PPA did not reach steady-state during the same period, with blood concentrations continuing to rise throughout the 4-hour exposure. This suggests that the formation of 2-PPA may be slower than PGPE absorption, and

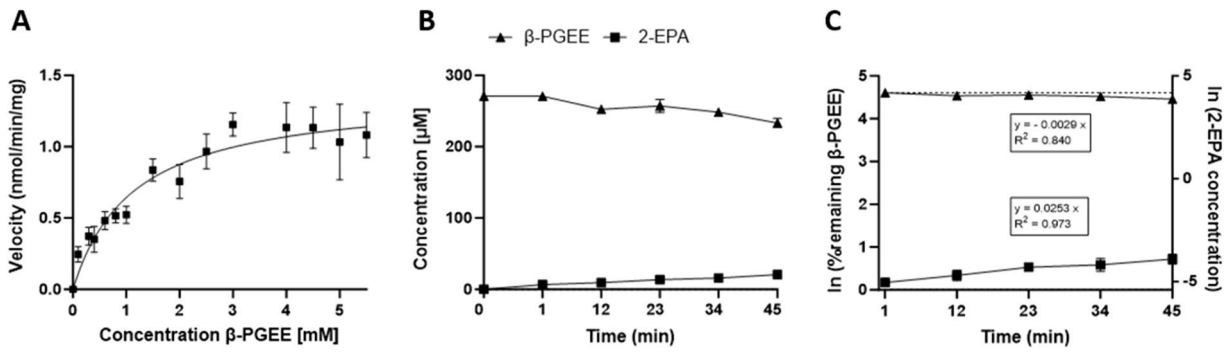

Fig. 5. (A) Velocity against substrate (β-PGEE) concentration plot for Michaelis-Menten kinetics in S9 incubations. 2-EPA (■) was quantified using HPLC-MS/MS. The Michaelis-Menten curve was fitted to the data using Graphpad Prism, and K_m and V_{max} predicted. Data points represent means ± SD of N = 3 independent incubations with 2 technical replicates. (B) Parent compound remaining-time profile (▲) and metabolite formation (■) in S9 incubations. Data points represent means ± SD of N = 3 independent incubations with 2 technical replicates. (C) Ln of % remaining parent (▲) and ln of metabolite concentration (■) versus time profile in S9 incubations. The in vitro CL_{int} was calculated from the slope. Data points represent means ± SD of N = 3 independent incubations summarizing calculated slopes derived from each single graph. The dotted line represents the parent value at time-point 1 min.

Table 3
Obtained Michaelis-Menten-Kinetic parameters (V_{max}, K_m), in vitro hepatic intrinsic clearance ($CL_{int,\ in\ vitro}$) calculated on V_{max}/K_m and measured from human liver subcellular fraction (S9) incubations, predicted in vivo hepatic intrinsic clearance ($CL_{int,\ in\ vivo}$) and predicted hepatic organ clearance (CL_h). Data represents mean values ± SD. (a) Incubational binding for the test system ($f_{u,inc}$) and plasma binding ($f_{u,b}$) derived from QIVIVE.

β-PGEE → 2-EPA	**S9 incubations**		
V_{max} [nmol/min/mg]	1.37 ± 0.12		
K_m [µM]	1130 ± 245		
	Calculated (V_{max}/K_m)	**Measured** Remaining parent compound	**Measured** Metabolite formation
$f_{u,inc}^a$	0.86	0.86	0.86
$f_{u,b}^a$	0.71	0.71	0.71
$CL_{int,\ in\ vitro}$ [µL/min/mg]	1.23 ± 0.18	3.28 ± 0.11	29.1 ± 6.33
Predicted $CL_{int,\ in\ vivo}$ [mL/min/kg]	3.83 ± 0.55	10.2 ± 0.34	90.5 ± 19.7
Predicted CL_h [mL/min/kg]	2.74 ± 0.35	5.99 ± 0.14	16.1 ± 0.90

that metabolic conversion and/or elimination could be rate-limiting steps. The observation that 2-PPA Cmax occurred at the end of exposure supports this interpretation. Additionally, the urinary Cmax of 2-PPA was observed two hours after the end of exposure. While this delay could reflect slower renal elimination, it may also be influenced by the urine sampling schedule (every 2 h), and by redistribution of 2-PPA from peripheral tissues back into the central compartment prior to excretion. These tissues may act as a temporary reservoir, contributing to prolonged elimination and sustained systemic exposure, which could be relevant for toxicological outcomes.

Unlike blood concentrations, urinary levels did not follow a linear increase, and two distinct elimination phases were observed, which further supports the hypothesis of peripheral distribution as a temporary reservoir. The first phase, with a half-life of approximately two hours, occurred between Cmax and timepoint 600 (i.e., t600), while the second phase, with a half-life of approximately ten hours, extended from t600 to t1700. Our study is in line with another published study assessing the formation and elimination profile of 2-methoxypropanoic acid (2-MPA) following PGME inhalation exposure in volunteers (Devanthery et al., 2003). In that study (Devanthery et al., 2003), volunteers exposed to 50 ppm PGME showed a maximum urinary concentration of 2-MPA two hours post-exposure, which is similar to our observations for 2-PPA at 15, 20, and 25 ppm. We exposed our volunteers to PGPE concentrations (15, 20, and 25 ppm) representing only 16–50 % of the exposure concentrations used by Devanthery and colleagues. However, when Devanthery and colleagues exposed their volunteers to 50 ppm PGME, the maximum urinary concentration of 2-MPA occurred two hours post-exposure, which is similar to our observations for 2-PPA. Furthermore, 2-MPA was still detectable in urine 16 h post-exposure at 95 ppm, whereas concentrations returned to levels before the exposure session the day after exposure at 50 ppm. The half-life and Cmax for 2-MPA reported by Devanthery and collaborators are in the same concentration range as for 2-PPA calculated in our study. Although, the half-life of 2-PPA was short (hours), the metabolite was still quantified in urine from the participants the day after exposure for all air concentrations of exposure. This suggests that the slow metabolism increases the retention time in the body.

This persistence was not observed for the parent compounds (De Luca et al., 2025). Physical and chemical as well as structural properties may help predict persistence (Burnison, 1998). It can be estimated with the logarithmic form of n-octanol/water partition coefficient (Log K_{ow}) (Burnison, 1998; PubChem, 2024a, 2024b). We observed that an increase of solvent air concentrations (inhalation exposure) resulted in an increase of metabolite's Cmax in both blood and urine. Consequently, at higher exposure concentrations, more time is needed to eliminate completely the substance. The persistence of 2-PPA in blood and urine observed in our study suggests peripheral distribution rather than bioaccumulation in tissues, and may reflect delayed metabolism and/or renal clearance. While metabolites were still detectable in urine the day after exposure, 2-PPA was no longer present in blood five hours post-exposure. This pattern indicates that although the compound is eliminated gradually, it does not accumulate in tissues over time. This observation has been observed for EGME. Ahmed et al. (1994) administrated oral doses of deuterated EGME to mice to evaluate the organ distribution of the compound. They observed elevated level of deuterated substance in the liver, lungs, heart, and urinary bladder, which is expected but also in testis, brain, spinal cord, and bone marrow, demonstrating a transient distribution rather than long-term storage, (Ahmed et al., 1994). We conclude that metabolites appear to be stored in the body before they are gradually eliminated, but animal studies are necessary to understand in which organs PGPE would accumulate.

2-EPA was quantified in blood and urine of all participants. However, 2-EPA blood concentration did not vary according to PGEE exposure (Fig. 4.A), raising questions about its metabolic origin. Therefore, 2-EPA blood concentration is not specific to PGEE and therefore not a good biomarker of exposure. These results suggest that 2-EPA or a molecule very close chemically is an endogenous metabolite in humans. Currently, no data in the published scientific literature can corroborate this hypothesis. These results suggest also that our participants were likely exposed to PGEE or to another chemical having the same

metabolite outside the experimental setting (*e.g.* at home). In fact, PGEE is present in various common products, such as fragrances, floor and window cleaners, and inks (European Chemical Agency, 2022). Urinary concentrations of β-PGEE metabolite can be explained by this hypothesis, as urinary 2-EPA concentrations were above the LOQ in samples obtained from the participants before the exposure session. However, unlike blood results, we observed a small increase of urinary 2-EPA concentrations suggesting that the compound was metabolized by the liver *in vivo* and thus, 2-EPA is a metabolite of β-PGEE (Fig. 4.B). To investigate this, we conducted in vitro experiments using human liver subcellular fractions, which confirmed the formation of 2-EPA and demonstrated the involvement of ADH and ALDH in its metabolism. The affinity of β-PGEE to these enzymes is similar to the V_{max} and K_m of other ethylene glycol ethers reported in the literature (Aasmoe et al., 1998; Louisse et al., 2010). According to our results, the predicted hepatic organ clearance (CL_h) derived from V_{max}/K_m, metabolite formation and remaining parent compound parameters are in the low/intermediate range of values. Intermediate clearance compounds have a clearance between 15 and 45 mL/min/kg (Hultman et al., 2016; Sloczynska et al., 2019). Slowly metabolized compounds remain in the body for a longer period, thus, inducing a higher probability of persisting or accumulating in tissues. This can also explain the high concentrations of 2-EPA (1000 times more than for 2-PPA) quantified in blood samples of the participants (Fig. 2 and 4B). Due to financial constraints, we were unable to perform analogous *in vitro* studies for PGPE. Nonetheless, the *in vivo* data strongly support the metabolic conversion of PGPE to 2-PPA.

Although glycol ethers are widely present in common commercial products, our findings revealed distinct differences in background exposure between PGEE and PGPE. 2-EPA was consistently detected in participants' samples, independent of exposure concentrations, suggesting an alternative origin, potentially environmental or endogenous in nature. In contrast to 2-PPA, we observed no exposure-response relationship for 2-EPA following controlled exposure to PGEE vapors. This discrepancy between the confirmed *in vitro* metabolic pathway and the absence of a dose-response relationship *in vivo* is unexpected, given the generally straightforward nature of glycol ether metabolism, and highlights the limitations of extrapolating in vitro findings to human exposure scenarios. Therefore, we do not recommend using 2-EPA as a biomarker for PGEE exposure and instead suggest quantifying the parent compound in biomonitoring studies.

In contrast, no background exposure to PGPE was detected in our study; specifically, 2 PPA was not quantified in urine samples collected prior to experimental exposure. A previous study similarly reported no detection of PGPE in urine samples collected the day after exposure (De Luca et al., 2025), supporting the conclusion that environmental exposure to PGPE was negligible among participants. However, 2-PPA remained detectable in urine the day after exposure, indicating that repeated daily exposure may lead to metabolite accumulation, a consideration relevant for occupational settings where PGPE is used regularly. A key study by Bader et al. (1996) represents one of the earliest investigations into human metabolism of PGPE, providing biomonitoring data from occupationally exposed workers (N = 16) working as technicians on color rotogravure machines. In their study, urinary 2-PPA concentrations ranged from 3 to 38 mg/L, with a median of 22 mg/L, following workplace air exposures to PGPE with a median concentration of 1.87 mg/m^3 . Bader and colleagues observed a stronger correlation between external exposure and 2-PPA than with the parent compound, suggesting that 2-PPA is a more reliable biomarker for PGPE exposure. We plotted our data and Bader et al.'s values assuming a creatinine value of 1 and this yielded a strong correlation ($R^2 = 0.97$) with the regression equation $y = 6.8003x - 5.4236$. This consistency reinforces the relevance of our findings. We extrapolated our measured metabolite concentrations to the Swiss occupational exposure limit of 50 ppm, assuming a linear relationship between air concentration and internal dose. At 50 ppm, the estimated blood concentration of 2-PPA is 0.12 μg/mL, and the estimated urinary concentration is 331.8 μg/g creatinine.

One of the limitations of our study was that the exposure we chose for the participants was barely above background exposures, and thus, we could not elucidate 2-EPA toxicokinetics. The ideal situation would be to expose human participants to radiolabeled compounds to eliminate the background exposure from the experimental exposure. Unfortunately, PGEE and PGPE were not commercially available in deuterated or radiolabeled form at the time of the study. We chose to set the air concentrations below the Swiss OEL for PGEE but could potentially have elucidated the toxicokinetics at OEL concentration. This is not, however, of interest, as we want to have a sensitive and specific exposure biomarker to monitor human exposures. Despite these limitations, the study offers several strengths. The controlled exposure design and biological monitoring enabled accurate characterization of metabolite kinetics. Although the sample size was limited (n = 9) and the exposure duration short (4 h), the use of multiple exposure levels and complementary in vitro hepatic metabolism data strengthened the mechanistic interpretation. The exposure concentrations were environmentally relevant, and the consistency of metabolite detection across participants supports the robustness of the findings. However, the lack of chronic exposure data and the inability to fully separate background from experimental exposure remain limitations. The detection of metabolites beyond the exposure period suggests potential for accumulation, warranting further investigation in occupational settings.

5. Conclusion

Here, we provide evidence that humans metabolize β-PGEE and β-PGPE following the same metabolic pathway as other PGEs producing the corresponding alkoxypropionic acid metabolites. Even if β-isomers of the compounds are present in small amounts in commercially available products, 2-EPA and 2-PPA, metabolites formed via the well-established AH and ALDH pathway, were present in blood and urine of participants exposed to PGEE and PGPE, respectively. The extent of metabolite formation reflects the β-isomer content in the technical grade product, which is not regulated for PGEE and PGPE. In contrast to PGME, which has a stipulated maximum β-isomer content of 5 %, the lack of such specifications for other PGEs likely explains the higher metabolite levels observed in our study compared to previously published data for PGME. However, the lack of correlation between PGEE exposure and 2-EPA blood or urine concentrations indicates that further investigation is needed to clarify its toxicokinetics. Metabolites of ethylene glycol ethers are suspected to induce developmental toxicity, hemolysis, and testicular atrophy, but currently, there are no studies assessing possible PGEs acid metabolite toxicities. This study provides important data for the establishment of reference or occupational exposure limit values to protect human populations from possible health effects due to propylene glycol ether exposures. Based on extrapolation to the Swiss occupational exposure limit of 50 ppm, the estimated blood concentration of 2-PPA is 0.12 μg/mL, and the estimated urinary concentration is 331.8 μg/g creatinine, providing a useful benchmark for future risk assessments.

CRediT authorship contribution statement

Sophie Werner: Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Pascal Wild:** Writing – review & editing, Formal analysis, Data curation. **Hélène P. De Luca:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Myriam Borgatta:** Writing – review & editing, Supervision, Methodology, Investigation. **Laura Suter-Dick:** Writing – review & editing, Data curation. **Nancy B. Hopf:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Sylvain Le Gludic:** Writing – review & editing, Formal analysis.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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