Providing context for phosphatidylethanol as a biomarker of alcohol consumption with a pharmacokinetic model

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ABSTRACT

Phosphatidylethanol (PEth) is increasingly used as a biomarker of heavy drinking. Many different forms of PEth can form in red blood cell membranes from the action of the enzyme phospholipase D. PEth has a very long duration in blood because, in contrast to other tissues, RBCs lack the enzymes that degrade PEth. Because this biomarker is relatively new, interpretations of the analytical measurements of PEth may be misinterpreted and the resulting predictions of actual alcohol consumption inaccurate. Hence, a simple pharmacokinetic model of PEth was developed to provide a means of contextualizing these analytical results. A number of alcohol consumption scenarios and current clinical screening levels were examined with the model.

1. Introduction

Phosphatidylethanol (PEth) is increasingly being recognized as a potential biomarker of chronic alcohol consumption for forensic use (Isaksson et al., 2011). A number of homologues of phosphatidylethanol are formed in the membranes of erythrocytes when alcohol is present. The reaction between ethanol and phosphatidylcholine is catalyzed by phospholipase D (PLD). This enzyme is ubiquitous in mammals; for many years, the function of this enzyme remained unknown; recent knowledge indicates PLD and its normal product, phosphatidic acid, play a role in signaling pathways related to inflammation, cancer pathogenesis and neurodegenerative disorders. Phosphatidyl alcohols have varied effects on downstream targets but physiological changes due to altered PLD signaling appear relatively insignificant (Brown et al., 2017).

A large number of distinct homologues of PEth form in blood exposed to alcohol. The two most abundant are PEth 16:0/18:1 and PEth 16:0/18:2. The homologue generally analyzed by testing laboratories in the US is PEth 16:0/18:1 (Gnann et al., 2010).

Estimates of the half-life of PEth 16:0/18:1 and other homologues range from 1 to 13 days and the half-life varies greatly between individuals (Javors et al., 2016). A recent meta-analysis demonstrates good clinical efficiency of PEth for detecting chronic heavy drinking (Viel et al., 2012). The variability in the pharmacokinetics of PEth, however, restricts the ability of this biomarker to predict alcohol consumption with any certainty. The choice of a cut-off value is complicated by the lack of any quantitative pharmacokinetics to date (Dasgupta, 2015).

PEth was first used as a marker of alcohol consumption in the late 1990s; the analytical method was high-performance liquid chromatography with evaporative light scattering detection (HPLC-ELSD); this method could not separate PEth homologues and had a detection limit of almost 600 ng/ml (Hansson et al., 1997; Gunnarsson et al., 1998; Gnann et al., 2009; Varga et al., 1998). In 2009, a method was introduced with a much lower detection limit utilizing LC-ESI-MS/MS following miniaturized organic solvent extraction and reversed phase chromatography (Gnann et al., 2009, 2010). Schröck et al. (2014) provide a useful description of analytical methods and a table of detection and quantitation limits for the various methods.

Differing choices of PEth homologues as alcohol biomarkers as well as the change in analytical methodology with a tenfold lowering of detection limits has created uncertainty regarding the interpretation of PEth results. Weinmann et al. (2016) note: "According to an agreement between Swedish laboratories, the limits of decision for excessive alcohol consumption has been defined at $\geq 0.3\,\mu mol/l$" or 215 ng/ml and these authors refer to the original work in Swedish (Helander and Hansson, 2013). A number of other cutoffs representing varying degrees of potentially excessive alcohol consumption have been suggested. Recent cutoff values are summarized in Table 1 and the range of these cutoffs reflects the varying comparison endpoints, i.e. abstinence vs. moderate drinking vs. drunk driving. The recent interest in developing new cutoffs likely stems from advances in PEth analysis and the comparative advantages of this biomarker (Winkler et al., 2013).

Here, an empirically-derived pharmacokinetic model for PEth 16:0/18:1 pharmacokinetics is developed and then used to provide context and credible ranges for PEth analytical results corresponding to varying

Table 1

Suggested cut-points for PEth 16:0/18:1. Abbreviations: DUI: driving under the influence; DBS: dried blood spot; AUDIT: Alcohol Use Disorder Identification Test; ROCC: receiver-operator characteristic curve; Sn: sensitivity; Sp: specificity.

Cut-point value	Population	Sample method	Statistical methods	Source
≥700 ng/ml	Blood samples from 142 Swiss drivers stopped for DUI; BAC separated as BAC > 0.016 g% or < 0.016 g%	Whole blood	ROCC: Sn = 0.659, Sp = 0.684	Schröck et al., 2016
≥400 ng/ml for severe misuse	Mixed population from medical ICUs, alcohol detoxification units and healthy volunteers (AUDIT)	DBS	ROCC: Sn = 0.778, Sp = 0.931	Afshar et al., 2017
≥250 ng/ml any alcohol misuse;	Mixed population from medical ICUs, alcohol detoxification units and healthy volunteers (AUDIT)	DBS	ROCC: Sn = 0.873, Sp = 0.879	
≥221 ng/ml for chronic and excessive consumption	Inpatients in an alcohol detoxification unit (n = 50) and control non-alcoholic volunteers (n = 18)	Whole blood and DBS	ROCC: Sn = 0.86, Sp = 1.0	Kummer et al., 2016
≥80 for 4 drinks/d	222 patients with chronic liver disease self-reporting alcohol use with ethylglucuronide in urine and hair also tested	Whole blood	ROCC: Sn = 0.91, Sp = 0.77	Stewart et al., 2014
≥6.3 ng/ml indicating any drinking	46 healthy Danish volunteers randomized to either abstinence or 1.3 drinks/d for women and 2.7 drinks/d for men for 3 months	DBS	ROCC: Sn = 0.84, Sp = 0.83	Kechagias et al., 2015

Table 2

Model Parameters. Abbreviations: BMI: body mass index; BW: body weight.

Parameter	Distribution	Parameters	Dependencies	Source
Anthropometric parameters				
Gender	Binomial	1, 0.5	NA	NA
Body weight (M)	Lognormal	$\mu = 4.4626$ $\sigma = 0.2112$	BMI: $\rho = 0.86$	Portier et al. (2007); Revicki and Israel (1986)
Body weight (F)	Lognormal	$\mu = 4.2979$ $\sigma = 0.2502$	BMI: $\rho = 0.86$	
BMI (M)	Lognormal	$\mu = 3.3620$ $\sigma = 0.1889$	BW: $\rho = 0.86$	McDowell et al. (2008)
BMI (F)	Lognormal	$\mu = 3.3312$ $\sigma = 0.2381$	BW: $\rho = 0.86$	
Height (m)	Calculated as sqrt(BW/BMI)			
Widmark Model parameters				
Widmark factor r (M)	Normal	M = avg. of methods; CV = 9.2%	BMI: $\rho = 0.6748$	Posey and Mozayani (2007); Maudens et al. (2014); Gullberg (2007)
Widmark factor r (F)	Normal	M = avg. of methods; CV = 9.2%	BMI: $\rho = 0.7755$	
Absorption rate constant	Johnson SB	$\gamma = 1.5$ $\delta = 0.61$ $\epsilon = 0.5$ $\lambda = 29.5$	Varies with food intake (not modeled)	Fig. 2 of Uemura et al. (2005); Flynn (2004, 2006)
Elimination (M)	Johnson SB	$\gamma = 1.28$ $\delta = 1.44$ $\epsilon = 0.01$ $\lambda = 0.03$	None	Fit to data in Table 1 of Pavlic et al. (2006); Flynn (2004, 2006)
Elimination (F)	Johnson SB	$\gamma = 0.552$ $\delta = 1.121$ $\epsilon = 0.01$ $\lambda = 0.03$	None	
PEth model parameters				
Bmax	Lognormal	$\mu = 0.4600$ $\sigma = 0.2086$	Kd: $\rho = 0.7342$	Developed here from Gnann et al. (2012), Javors et al. (2016) and Schröck et al. (2017)
Kd	Lognormal	$\mu = -4.640$ $\sigma = 0.5103$	Bmax: $\rho = 0.7342$	
Elimination	Lognormal	$\mu = -5.80$ $\sigma = 0.4856$	None	

daily consumption of alcohol. The Widmark model for blood alcohol concentrations (BAC) has proved useful in both legal and clinical settings for many years. The simple model presented here serves to characterize a long-term biomarker of alcohol consumption. The inter-individual variability in PEth results adds difficulty to the interpretation of cutoffs; however, a reduction in PEth concentration over time suggests an individual is reducing consumption or is abstinent. Hence, a recommendation is made to obtain at least two samples with at least one week between them, consistent with a recent clinical study

(McDonell et al., 2017).

2. Theory/Calculation

Modeling was performed in MS-Excel using Monte Carlo simulation with the Yasai add-in (http://www.yasai.rutgers.edu/). The time step for modeling was 0.25 h or 15 min and time-dependent parameters were expressed on an hourly basis. Model parameters are provided in Table 2 and described below. Dependencies in the model were achieved
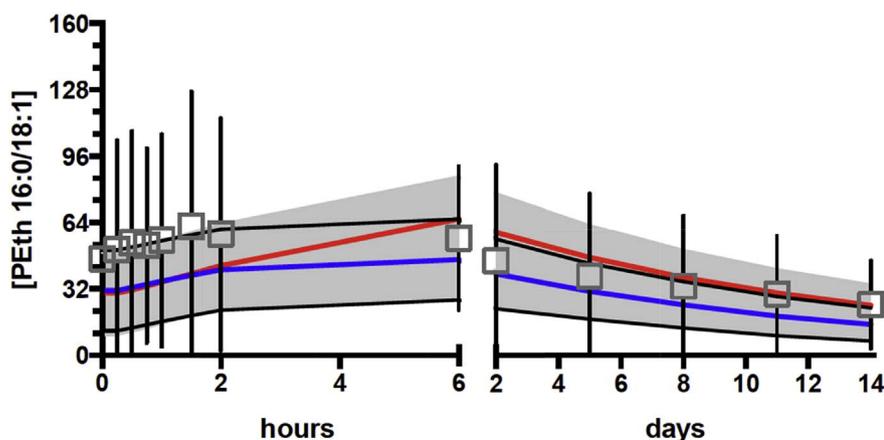
Fig. 1. Comparison of modeled PEth 16:0/18:1 concentrations in blood with measured concentrations in blood of volunteers from Javors et al. (2016). The blue line shows modeled volunteers receiving 0.25 g/kg alcohol; the red line shows modeled volunteers receiving 0.5 g/kg alcohol. The gray shaded area shows the overlapping two-sided 90% CI for modeled results of both doses. The gray unfilled squares with error bars show the median value and 90% two-sided CI extracted from Fig. 4 in Javors et al. (2016). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

using Spearman correlation coefficients with normal copulas. The model is provided in Supplementary Content and the Yasai add-in is free of charge.

2.1. Blood alcohol concentration

Blood alcohol concentration (BAC) was modeled with the Widmark equation and distributions for the parameters (Posey and Mozayani, 2007; Gullberg, 2007; Cowan et al., 2016). The version of the Widmark equation used is shown in Eq. (1).

$$BAC = \frac{A_{ingested}(1 - e^{-kt})}{rW} - \beta t \tag{1}$$

where

Aingested = amount of alcohol ingested
k = absorption rate constant for ingested alcohol
W = body mass
r = Widmark constant
β = elimination rate constant for BAC

BAC is commonly presented in g/dL or g% and that convention is followed here.

2.2. Formation of PEth

Measurements of BAC and PEth 16:0/18:1 every hour for 8 h following consumption of 1 g/kg of alcohol in 5 different individuals were obtained by digital extraction from Fig. 3 in Gnann et al. (2012). The average hourly BAC and the hourly increase in PEth 16:0/18:1 were used to develop an empirical model of PEth formation. These values were fit to a Michaelis-Menten type equation as a starting point for developing and parameterizing the model (Table 1; Eq. (2)). The form of the model was chosen to reflect basic Michaelis-Menten kinetics.

$$\log_{10}\left(\frac{d[PEth]}{dt}\right) = \frac{B_{max} \, BAC}{K_d + BAC} \tag{2}$$

where

[PEth] = PEth 16:0/18:1 concentration (ng/ml)
Bmax = maximum rate of increase in [PEth]
BAC = average BAC over time
Kd = BAC at half-maximal formation of [PEth]

The model was optimized to each of the individual data presented in the supplement to Gnann et al. (2012) and also that extracted from Fig. 2 in Schröck et al. (2017). Distributions for model parameters B_{max} and K_d (Eq. (2)) were fit to the optimized results. Fit was judged by

inspection of the plots in Supplemental Fig. 1–4. Considerable variability exists in the formation rates of PEth in human blood and the distributions of B_{max} and K_d represent an attempt to capture this variability (Aradóttir et al., 2004; Hahn et al., 2016; Weinmann et al., 2016). Formation of PEth likely occurs with greater complexity in its kinetics and dependence on BAC than are included in this relatively simple empirical model (Brown et al., 2017; Ganesan et al., 2015; Hahn et al., 2016).

2.3. Elimination of PEth

Slow elimination and persistence of PEth in the blood are the hallmarks of a chronic biomarker. Elimination of PEth was modeled as a single exponential decline. The assumption of a single mechanism of elimination is likely an oversimplification; individual data reveal, in many cases, two elimination phases (Supplemental Fig. S1 –S4). In animal studies, considerable differences between PEth elimination rates have been observed in different tissues (Brühl et al., 2003). In humans, PEth elimination rates appear to vary considerably (Hahn et al., 2016).

2.4. Monte Carlo considerations

Results from Monte Carlo simulation bear greater uncertainty in their tails (Roelofs and Kennedy, 2011). Using Monte Carlo simulation with the Widmark model parameters from the literature (Table 1) often produced extreme BAC values, greater than 0.4 g% and often associated with death (Li et al., 2017). Known model dependencies are provided in Table 1. Because PEth formation is dependent on BAC, PEth results are presented as median and inter-quartile range (IQR), i.e., from the 25th to 75th percentiles, rather than the two-sided 90% CI from the 5th to 95th percentiles, to avoid spurious values in the tails. The model was executed for 3000 iterations and results reported as median and IQR unless otherwise noted. In the figures, modeled IQRs or other ranges are shown as a blue or pink envelope for men and women respectively.

2.5. Alcohol consumption scenarios

The model was used to examine the potential range of PEth 16:0/18:1 results in a hypothetical population in four alcohol consumption scenarios. Here, a drink is defined as 14 g of alcohol (https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink). These scenarios are defined for these specific scenarios as follows:

- Light drinker – 1 drink each day consumed between 5:00pm to 7:00pm;
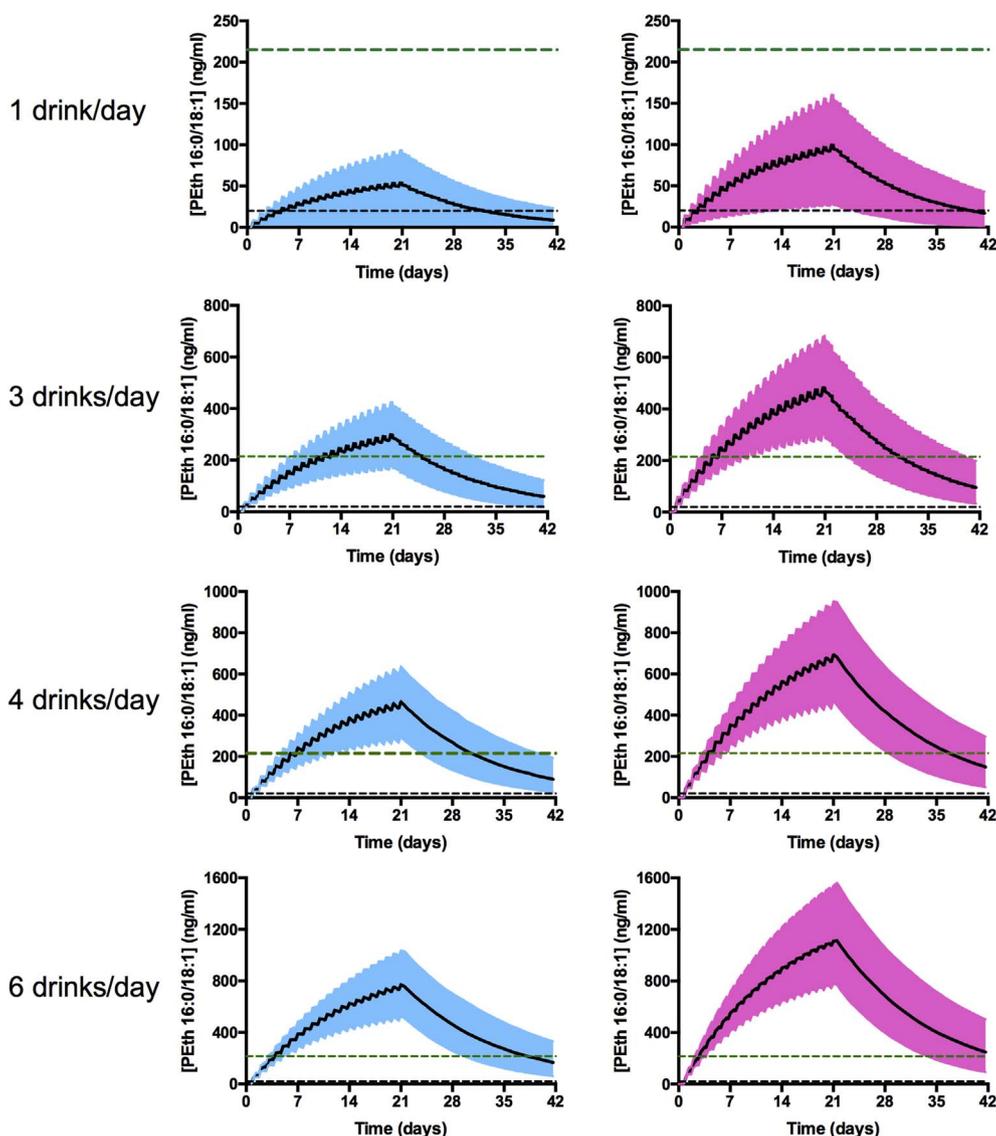- Moderate drinker #1–3 drinks per day from 5:00pm to 7:00pm each day;

Fig. 2. Concentrations of PEth 16:0/18:1 in men and women consuming 1, 3, 4 or 6 drinks per day. The solid black lines show the median modeled value and the blue or pink envelopes show the IQR. The black dashed line is the commonly used LOQ of 20 ng/ml. The green dashed line shows the Swedish cutoff of 215 ng/ml (Weinmann et al., 2016; Helander and Hansson, 2013). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

- Moderate drinker #2–4 drinks per day from 5:00pm to 7:00pm; and
- Heavy drinker – 6 drinks per day from 5:00pm to 8:00pm; and,

In each scenario, drinking occurred for 21 days follows by 21 days of abstinence. Several other scenarios were considered with the model in which drinking days were followed by one or more abstinence days. Scenarios corresponding to the specific definitions of "binge" drinking and "heavy" drinking from the to the National Institute of Alcoholism and Alcohol Abuse (NIAAA) were also considered.

3. Results

3.1. Model evaluation

Fig. 1 shows a visual comparison with the PEth 16:0/18:1 results from Javors et al. (2016). Volunteers consumed either 0.25 or 0.5 g/kg of alcohol and average results are reported. The blue line shows the median modeled re-creation of the 0.25 g/kg dose and the red line shows the model results for the 0.5 g/kg dose. Visually, the model results seem generally consistent with the data of Javors et al. (2016), although the model in Eq. (2) seems to underestimate formation of

PEth.

Supplementary Figs. 1–4 show the comparison of the model with individual results from Gnann et al. (2012) and Schröck et al. (2017). In almost all individuals, the modeled PEth results are similar in both magnitude and timecourse to the observed data. The exception is the formation of PEth, which, similar to the observation from Fig. 1, often exceeds the modeled results.

3.2. Comparison levels for PEth 16:0/18:1

In the US, the limit of quantitation reported by testing laboratories using LC/MS is 20 ng/ml for PEth 16:0/18:1 and this value may often be used, albeit incorrectly, to identify excessive drinking. The corresponding value in Sweden for low or no alcohol consumption is 35 ng/ml. The LOQ for some LC/MS methods can be as low at 1 ng/ml (Schröck et al., 2014). Testing labs in Sweden reached an agreement for a cutoff level of 0.3 μmol/L or 210 ng/ml above which, excessive alcohol consumption is assumed (Viel et al., 2012; Weinmann et al., 2016). These comparison levels are shown on many of the plots to provide some additional context.
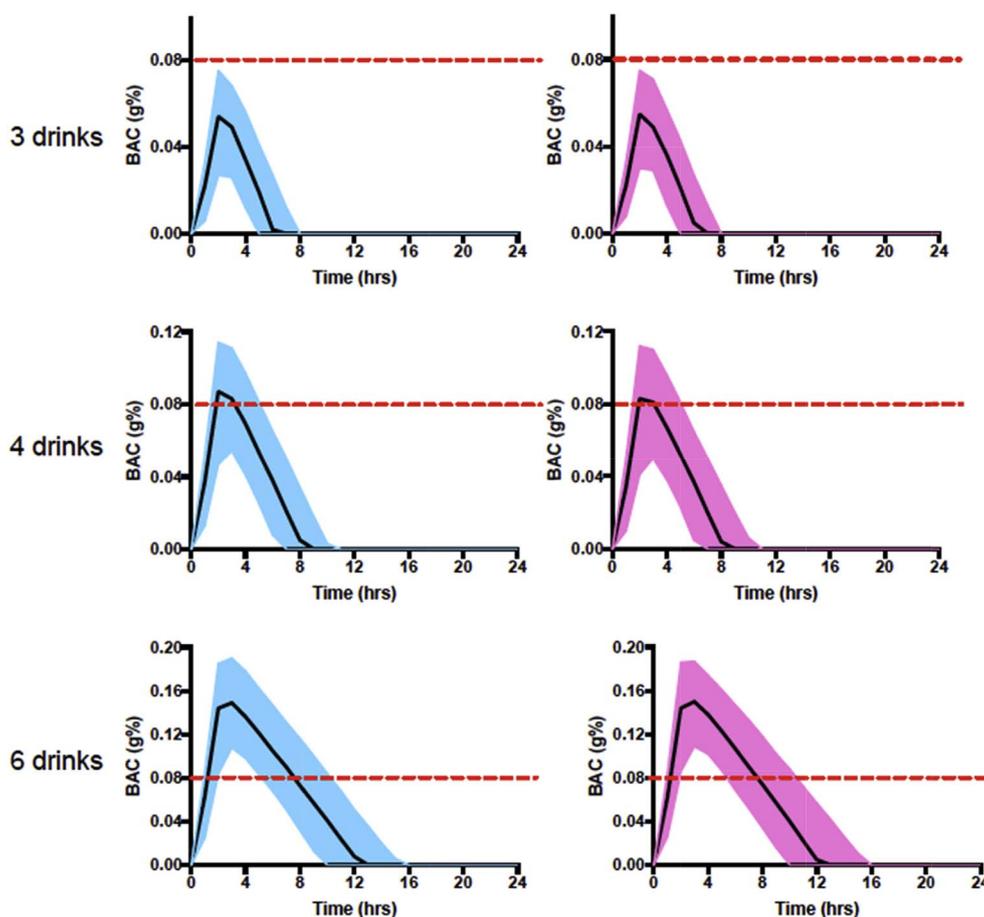
Fig. 3. Modeled BAC for men and women for consumption of three, four, or six drinks with a comparison to the legal limit for intoxication. The blue and pink shaded areas show the IQR and the legal limit of 0.08 g% is shown as a red dashed line. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. PEth and the amount of alcohol consumed

As noted, the model was exercised to obtain a median and IQR for modeled PEth concentrations in men and women consuming either 1, 3, 4, or 6 drinks per day for 21 days followed by 21 days of abstinence (Fig. 2). Peth concentrations are roughly proportional to the amount of alcohol consumed.

For those consuming 4 drinks per day, an amount sufficient to produce intoxication in about half of both men and women (Fig. 3), the median maximum PEth concentrations in men after 21 days of drinking are about 415 ng/ml with an IQR of about 250–550 ng/ml; the similar concentration range in women has a median of 610 ng/ml with an IQR of 420–820 ng/ml.

To provide context regarding PEth concentrations and intoxication, Fig. 3 shows the median and IQR for BAC over 24 h in men and women consuming 3, 4 or 6 drinks over a 2 h period. When consuming three drinks, the chance of having a BAC greater than the legal limit for intoxication is less than 25% (based on the IQR). Consuming 4 drinks would produce legal intoxication (BAC > 0.08 g%) about 50% of the time in both men and women for a period of 3–5 h. Consuming 6 drinks will produce intoxication for periods of about 7–14 h.

Based on these results, specifically those for 3 drinks/day in Figs. 2 and 3 drinks in Fig. 3, one can be very confident that men with PEth levels less than about 400 ng/ml have not been drinking past the level of intoxication. Almost half the modeled population of women drinking 4 drinks per day would not reach a BAC of greater than 0.08 g% and thus be legally intoxicated; but from about day 3 to day 35, however, more than 75% of the modeled female population could have a PEth level greater than the Swedish cutoff of 215 ng/ml.

3.4. PEth and abstinence duration

The effect of abstinence time on modeled PEth concentrations based on consuming 3 drinks at varying intervals over a 21-day period is shown in Fig. 4.

The peak PEth concentrations are proportionately reduced from drinking every day. The majority of men drinking every other day will remain below the Swedish consensus value of 215 ng/ml for low or no alcohol consumption; not so the women—during days 19, 20 and 21, more than half are above this value. Drinking less frequently, every third or every firth day produce considerably lower levels of PEth over the 21 days.

3.5. Comparison with NIAAA guidelines

In Appendix 9 of *Dietary Guidelines for Americans, 2015–2020* (https://health.gov/dietaryguidelines/2015/guidelines/appendix-9/), the NIAAA alcohol guidelines are described as follows:

- Binge drinking – 4 drinks within 2 h for women, 5 drinks within 2 h for men;
- Heavy drinking – 8 or more drinks per week for women, 15 or more drinks per week for men.

The model allowed the testing of the LOQ of 20 ng/ml and the Swedish cutoff of 215 ng/ml to determine if these levels are appropriate with these definitions of drinking behavior. (Fig. 5).

A single episode of binge drinking would raise PEth 16:0/18:1 to between 40 and 80 ng/ml in both men and women (considering the
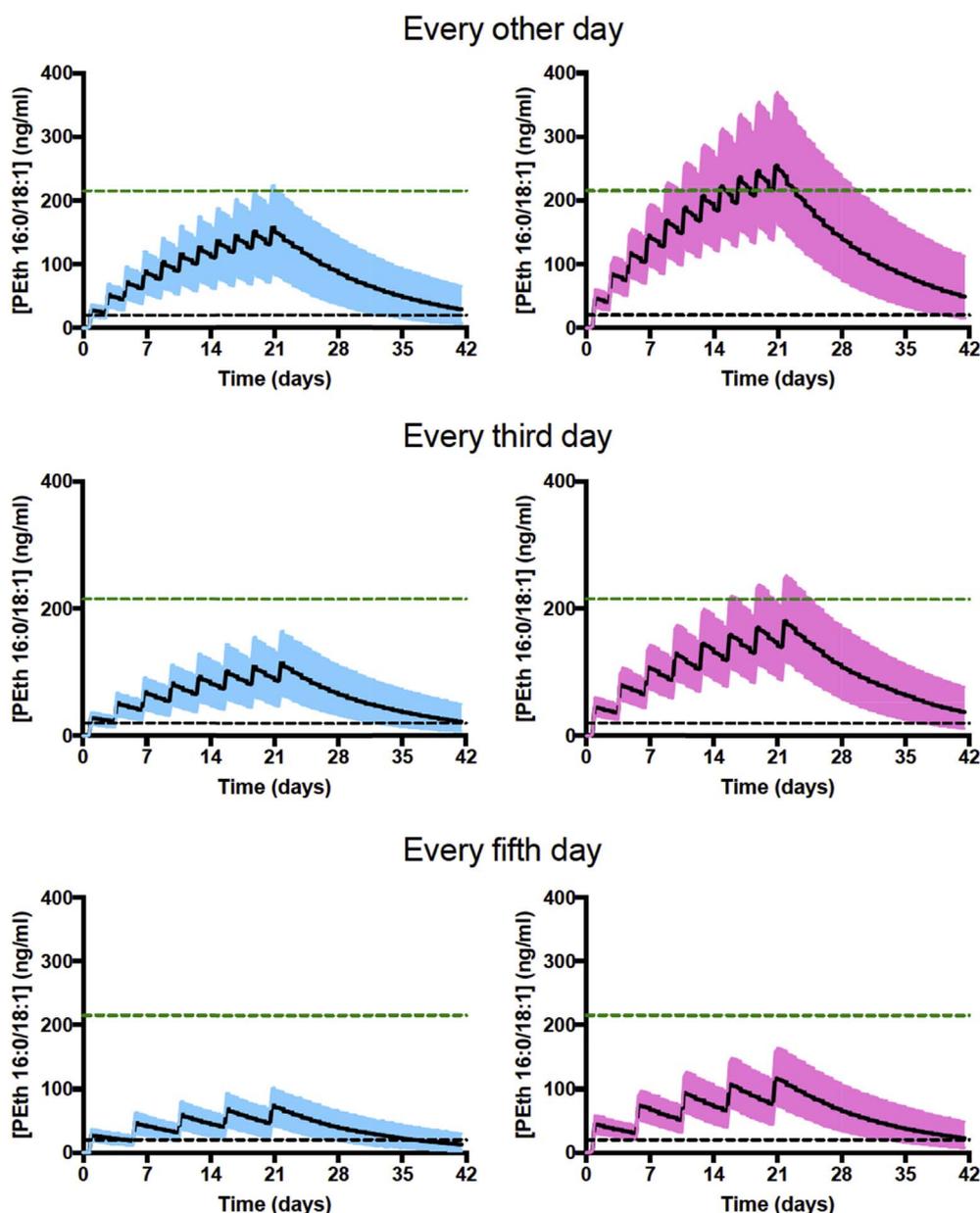
Fig. 4. The Effective of Abstinence Periods on modeled PEth concentrations. The modeled populations of men (left column) and women (right column) consumed 3 drinks over a 2-h period every other day, every third day and every fifth day.

IQRs), not even half the Swedish cutoff value (Fig. 5).

A cutoff level of 20 ng/ml would identify 75% of male binge drinkers for about 8 days and this proportion would fall to 25% in 3 weeks. This same cutoff level would identify 75% of female binge drinkers for about 18 days and the proportion in women falls to about 30% in 3 weeks (Fig. 5). However, a look back at Fig. 2 suggests that a single measurement at this cutoff will also identify almost all individuals consuming only a single drink a day.

The definition of heavy drinking is considerably different in men and women in terms of the weekly amount of alcohol consumed—210 g for men and 120 g for women—and accounts for the difference in the plots. The Swedish cutoff of 215 ng/ml for low alcohol use would, however, identify about 30–40% of males engaged in "heavy" drinking, as defined by NIAAA; this cutoff would not identify any women who drank 8 drinks per week as excessive consumers in contrast to the NIAAA identification of this level of consumption as "heavy" drinking.

4. Discussion

This model is a preliminary one and fills an immediate need—PEth results are being used as forensic evidence without consideration of an appropriate cutoff level for considering an individual a chronic drinker or an alcoholic. One recent review paper indicates that consumption of 50 g of alcohol or more for several weeks is required to produce detectable levels of PEth (Dasgupta, 2015). This unfortunate statement is based on an early study that used HPLC-ELSD as the analytical method with a detection limit of 600 ng/ml and no discrimination between the various PEth homologues (Varga et al., 1998).

4.1. Comparison of the model with additional data

The understanding of the formation of PEth is currently insufficient to develop a biologically based model. Two different isoforms of PLD exist in humans and both isoforms function in the formation of PEth in red blood cell membranes. PLD2 is constitutively active in RBCs; both
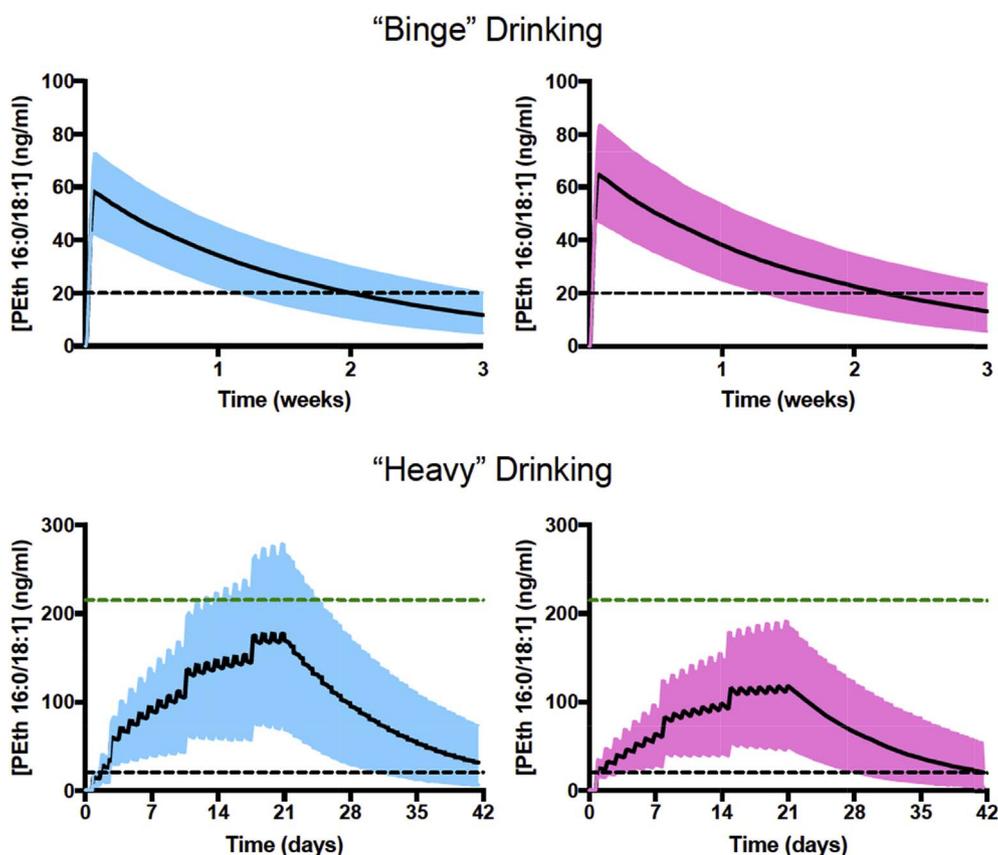
"Binge" Drinking

"Heavy" Drinking

Fig. 5. Model results for "binge drinking" and "heavy drinking" scenarios in men and women as defined by the National Institute on Alcohol Abuse and Alcoholism. Top panel: Modeled PEth 16:0/18:1 concentrations following a single episode of binge drinking. The dashed horizontal line shows the laboratory cutoff of 20 ng/ml. Bottom panel: Modeled PEth 16:0/18:1 concentrations during three weeks of heavy drinking by men and women. The green dashed line shows the Swedish cutoff of 215 ng/ml. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

PLD1 and PLD2 can be activated by protein kinase C and a variety of G-proteins. The role of PLD in cell signaling has yet to be completely understood, although this ubiquitous enzyme family appears to play a significant role in health and disease (Brown et al., 2017; Frohman, 2015; Ganesan et al., 2015; McHarg et al., 2008; Nelson and Frohman, 2015; O'Reilly et al., 2014). The involvement of PLD in a number of cellular processes suggests a considerable variability in humans of the efficacy of these enzymes in producing PEth following alcohol consumption.

Walther et al. (2015) measured PEth 16:0/18:1 in whole blood in 115 participants in a clinical trial of varenicline along with self-reported alcohol consumption. At the start of the trial, the median daily alcohol consumption of men was 78 g, between 5 and 6 drinks, and the same value for women was 65 g, between 4 and 5 drinks. The median PEth concentration in the 76 men was 464 ng/ml and in the women 406 ng/ml, consistent with model results shown here.

After 6 weeks of the trial, the median daily consumption for men was 52 g, almost 4 drinks and for women 42 g, exactly 3 drinks. The PEth values at that time were 326 ng/ml and 290 ng/ml respectively, well within the IQRs developed by the model (Fig. 2).

Kechagias et al. (2015) monitored daily consumption of red wine over 3 months in 7 men and 21 women volunteers without a history of overconsumption of alcohol. The median and range of PEth values at the end of the study ranged from 5 to 123 ng/ml, similar to the modeled results for 1 drink per day (Fig. 2). The authors developed receiver operator characteristic curves to distinguish abstention from use with cutoff values of 6.3, 4.2 and 2.8 ng/ml. These cut-off values are clearly not useful for distinguishing alcoholism from problem drinking from moderate drinking.

4.2. Cutoff levels and determination of drinking patterns

From Fig. 5, if one were to use PEth concentrations to discover so called "heavy" drinkers, a different cutoff for men and women would be needed based on the NIAAA definitions. The use of on-site portable alcohol breath measurements to obtain a BAC provide a routine and rapid means of identifying intoxicated individuals. In contrast, the actual meaning of PEth concentrations to estimate the level and time frame of recent alcohol consumption remains to be fully determined.

Another ongoing issue is the use of dried blood spots. This technique may be preferred because less blood is required—a finger stick rather than a tube. Because PEth can form *in vitro*, care must be taken by testing personnel not to use alcohol swabs or alcohol-containing products such hand sanitizers (Varga and Alling, 2002). The same caution has been noted for those conducting breath alcohol measurements (Ali et al., 2013).

4.3. Conclusions and recommendations for interpreting PEth analyses

Recently, McDonell et al. (2017) used measurements of the sum of PEth 16:0/18:1 and PEth 16:0/18:2 obtained weekly as part of a study on contingency management intervention as a treatment for alcohol use disorder. These authors observed a 56% reduction in PEth levels in those individuals who reported no drinking the previous week and concluded that weekly reduction in PEth concentrations was a more accurate means of assessing abstinence than a specific cutoff. Further, these authors suggested that multiple weekly PEth measurements along with the measurement of another alcohol biomarker, e.g. ethyl glucuronide, may provide the most accurate method for assessing abstinence.

In terms of cutoffs representing the NIAA definitions of heavy drinking, obtaining at least two PEth measurements is advisable; if both measurements are greater than 500–600 ng/ml in men and 700–800 ng/ml in women, then the individual in question likely consumes alcohol to excess, i.e. "heavy" drinking, with daily intoxication as the result.

The model predicts generally higher PEth concentrations in women than in men; for a given amount of alcohol consumed, women will

Table 3
Percent reduction in PEth 16:0/18:1 concentrations with either abstinence or reduced drinking in both men and women following 3 weeks of drinking 6 drinks per day. The values are the median percent reduction and the IQR in parentheses for the change in drinking behavior and the time between analyses.

Reduction in daily consumption	Time between analyses		
	7 days	10 days	20 days
Abstinence	41%	53%	77%
(6/d → 0/d)	(31–52)	(42–65)	(67–87)
83% reduction	37%	48%	69%
(6/d → 1/d)	(26–49)	(36–62)	(54–83)
67% reduction	29%	37%	54%
(6/d → 2/d)	(17–42)	(22–53)	(32–74)
50% reduction	20%	26%	39%
(6/d → 3/d)	(7–35)	(8–45)	(10–66)

likely have a higher BAC than men because of their generally smaller body size. This generalization should be considered, however, in the light of the considerable variability in PEth formation and elimination rates.

The model also provides a means for monitoring reduction in alcohol use, either lower consumption or abstinence using two PEth analyses a week or more apart. For both men and women consuming six drinks per day and then reducing intake following the first of two PEth analyses, median and IQR values in the percent reduction in PEth are provided at 5 days, 7 days, 10 days and 20 days between the two analyses (Table 3). These values were based on exercising the model for men and women consuming 6 drinks per day and then either abstaining or reducing their alcohol consumption.

With a reduction in PEth 16:0/18:1 at 7 days of 40% or more, the individual in question was more likely than not abstinent. With a 50% reduction in PEth 16:0/18:1 concentrations at 7 days, one can be 75% confident that abstinence was maintained. At ten days between analyses, one could likely distinguish abstinence from reducing consumption by 50% but not from the 83% or 6-fold reduction (6 drinks/day to 1 drink/day). Table 3 also suggests that an increased amount of time between analyses may help distinguish abstinence from reduced alcohol consumption.

The model includes only a single exponential decline in PEth 16:0/18:1 with a median half-life of 9.5 days (calculated from Table 2) and resulting in a weekly median decline of 40% with abstinence. In contrast, McDonell et al. (2017) observed a 56% reduction in the sum of concentrations of PEth 16:0/18:1 and PEth 16:0/18:2 over 1 week of abstinence. The observed faster rate of reduction suggests a lower capacity more rapid elimination component, consistent with the two phases observed in Supplementary Figures 1–4, and for simplicity's sake, not included in the model.

Currently, PEth measurements are being used in civil matters, such as child custody determinations, and thus can significantly affect peoples' lives. The fact that a meta-analysis of 58 studies exists suggests that sufficient data are available to identify a cutoff appropriate for the legal rather than the clinical setting. Although the focus of Viel et al. (2012) is clinical, they highlight the difficulties of identifying problematic drinking behavior. The model presented here is preliminary but with the explicit incorporation of variability can potentially provide a useful tool in providing much needed context for these measurements. Notwithstanding this additional context, a number of different analytical methods are used for PEth and caution is warranted when drawing conclusions from any analytical results.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.yrtph.2018.01.029.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.yrtph.2018.01.029.

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