(REVIEW ARTICLE)

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# Phosphatidylethanol (PEth) in practice: A specific and proportional marker of alcohol consumption

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## Abstract

Alcohol abuse causes more than three million deaths a year, or one in twenty, more than three-quarters of them men. Alcohol abuse accounts for over 5% of the global burden of disease. In this context, objective clinical and biochemical tests are essential to characterize drinking patterns, quantify the amount of ethanol ingested daily and enable effective management of these patients. We recently investigated the feasibility and benefits of measuring phosphatidylethanol (PEth) in daily medical practice for the management of alcohol dependence in the outpatient setting.

We report the results of a quantification of palmitoyl-2-oleoyl-glycero-3-phosphoethanol (PEth 16:0/18:1) in comparison with biological indicators (SGOT, SGPT GGT) on a group of volunteers followed as outpatients for alcohol problems.

**Methods**: In this prospective study, a total population of 57 volunteers consulting a private addictology practice was recruited for PEth tests, 21 of which were complemented by biological tests including SGOT, SGPT GGT assays. A file was completed specifying the methods of alcohol use, the quantities consumed (AU) and the Alcohol Use Disorders Identification Test (AUDIT) score. Blood samples are collected in a 10 µL drop, using a medical device (VAMS from Neoteryx, USA), air-dried. The dry samples are extracted and reconstituted with methanol. The analyzes carried out by high pressure liquid chromatography coupled with high resolution mass spectrometry.

**Results and discussion**: 57 volunteers (19 F and 38 M) aged between 20 and 70 were included. These volunteers had the Quantities consumed (AU/d) at 6.7 (0-20) and the Alcohol Use Disorders Identification Test (AUDIT) score at 17.8 (0-30).

A strong positive correlation of 0.88 (n=57) was observed between PEth concentrations and levels of daily alcohol consumption. The usual biology, the "hepatic assessment" provides little or no information on the risks associated with alcohol consumption with correlation coefficient estimated at 0.28 for GGT, 0.09 for SGOT and 0.00 for SGPT. PEth degradation was 13% for samples stored at room temperature, compared with those stored at +4°C and -80°C.

**Conclusion**: PEth is a specific and proportional marker of alcohol consumption. Measuring PEth enables us to accurately gauge the reality of alcohol consumption and adapt it to care and prevention contexts. This measurement of phosphatidylethanol (PEth) can be carried out as part of a consultation, at a distance from the analysis centers.

Finally, the PEth, along with the interpretation tools described in this article, is an important help in the management of alcohol dependence.

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## 1. Introduction

According to a report published by the World Health Organization (WHO), alcohol abuse led to more than three million deaths in 2016, or one in twenty, more than three-quarters of which were men (1). Alcohol abuse accounts for more than 5% of the global burden of disease (1). In this context, objective clinical and biochemical tests are essential to characterize alcohol consumption patterns, quantify the amount of ethanol ingested daily and enable effective management of these patients. The investigation of suspected alcohol dependence or abuse includes symptoms, medical history, self-report forms, special questionnaires, clinical examination and biochemical analyses (2).

The limited diagnostic efficacy of self-reports and the difficulty of objectively assessing drinking behavior have led to an intensive search for reliable biomarkers of chronic heavy drinking. These markers can be divided into two categories: direct and indirect (2-6):

- Indirect biomarkers detect alcohol-related toxic effects, particularly on the red blood cell or liver, such as mean corpuscular volume (MCV), aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT) and gamma-glutamyltransferase (GGT).
- Direct markers include blood ethanol itself, as well as its derivatives such as acetaldehyde, acetic acid, fatty acid ethyl esters (FAEE), ethylglucuronide (EtG), ethyl sulfate (EtS) and phosphatidylethanol (PEth).

Phosphatidylethanol (PEth) was discovered in 1983: "An abnormal acidic phospholipid was found in large quantities in the organs of rats subjected to an alcoholic diet (7). Phosphatidylethanols are lipids (acids) with long unsaturated chains. Depending on the position of the double bonds ; 48 different forms of phosphatidylethanols have been identified. Their kinetics are different. PEth 16:0/18:1 (palmitoyl-2-oleoyl-glycero-3-phosphoethanol) has become the reference measure (figure 1); it is the most abundant (48%), it has the longest lifespan (8-10).

Due to PLD's greater affinity for short-chain alcohols than for water, phosphatidylethanols are formed within seconds of contact with ethanol and slowly disappear over the following weeks.

The mechanism of PEth catabolism has not yet to be fully elucidated and, to date, there is still no evidence of the involvement of phospholipases in PEth degradation in vivo. Therefore, PEths accumulate, in the same way, in all cells (11-13). The PEth can be recovered after two months of abstinence (14).

Phosphatidylethanol is measured by high pressure chromatography coupled with mass spectrometry (LC-MS). These techniques are available in toxicology laboratories. Specific, quantified, comparable measurements are possible with commercially available standards.

Dried blood retains some of its properties at room temperature without time limit. This mode of sampling allows many assays (15).

Dry membrane lipids, therefore, phosphatidylethanol, are perfectly preserved at room temperature. Dried samples, properly wrapped, circulate by post. Dry biological samples present very little risk of contamination. The samples can be taken remotely, in the care structures and sent to the specialized laboratory at little cost (16).

We have recently begun research on the feasibility and benefits of measuring phosphatidylethanol in everyday medical practice, with non-invasive sampling from capillary blood after a finger prick on a medical device suitable for transport to the biomedical laboratory without special precautions. In this article, we report the results of a quantification of palmitoyl-2-oleoyl-glycero-3-phosphoethanol (PEth 16:0/18:1) in comparison with biological indicators (GGT, SGOTand SGPT) on a group of volunteers followed as outpatients for alcohol problems.

## 2. Material and method

In this prospective study, a total population of 57 volunteers consulting a private addictology practice was recruited for PEth tests, 21 of which were complemented by biological tests including SGOT, SGPT , GGT. All patients were informed and agreed to participate in the study. A file was completed specifying the methods of alcohol use, the quantities consumed (AU) and the Alcohol Use Disorders Identification Test (AUDIT) score. These elements are collected with

respect and confidence in the statements made. For estimation of the alcohol consumption alcohol unit absorbed (UA): 1 glass= 10 g alcohol= 1AU (alcohol unit).

Blood samples are collected in a 10 μL drop, using a medical device (VAMS from Neoteryx, USA), air-dried. This device resembles a "cotton bud", with a stem at one end made of a neutral (hard) material that absorbs by capillary action the drop of capillary blood formed after a prick on the fingertip (or elsewhere). A box protects the sample and allows it to dry quickly. This box, placed in an envelope, can be returned to the laboratory.

The dry samples are extracted and reconstituted with methanol. The analyzes carried out by high pressure liquid chromatography coupled with high resolution mass spectrometry (Figure 1). The LC and MS parameters are shown at table 1.

**Table 1** LC and MS parameters for PEth analysis

| Parameter (LC 1290, TQ 6740 Agilent USA) | Set at |
|---|---|
| Drying Gas flow | 11 L/min |
| Drying Gas Temperature | 325 °C |
| Nebulizer pressure | 35 psi |
| Capillary Voltage | Negative 3500 V |
| Sheath Gaz Flow | 11 L/min |
| Sheath Gaz Temperature | 350 °C |
| Nozzle Voltage | 500 V |
| Column Temperature | 50 °C |
| Flow rate) Isocratic mobile phase | 0.7 mL/min Acetonitrile/ 5 mmol/l Ammonium acetate and 0.1% acetic acid (80/20 V/V). |
| Column | Acquity uplc BEH C18 1.7 μm 2.1 x 50 mm (Waters, USA) |
| Quantification transition Qualification transition | 701.5→281.2 701.5→255.1 |
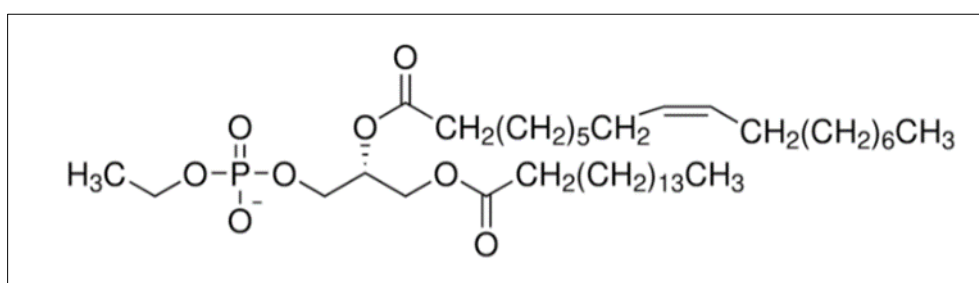


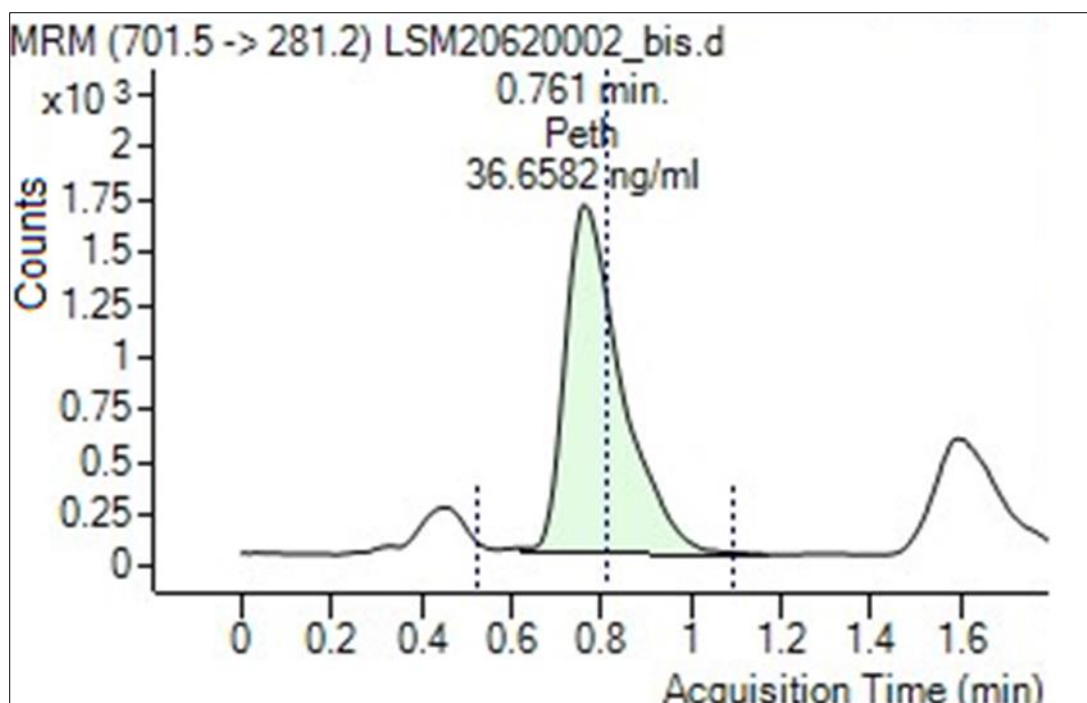**Figure 1** PEth 16:0/18:1 (palmitoyl-2-oleoyl-glycero-3-phosphoethanol)

**Figure 2** PEth quantification of human sample using LC-MS LC–MS technique

For samples stability study, storage and stability checks were carried out on 10 dry samples taken from the VAMS. They were stored for 5 months at room temperature, without any special precautions and stored at +4°C and -80°C.

## 3. Results

In this prospective study 57 volunteers (19 F and 38 M) aged between 20 and 70 were included. These volunteers had The quantities consumed (AU) at 6.7 UA/d (0-20) and the Alcohol Use Disorders Identification Test (AUDIT) score at 17.8 (0-30) (Table 2).

Table 3 shows that there is a significant difference between moderate consumption of less than 4 AU/d and more than 4 AU/d (60.54±39.42ng/ml for AU/d<4 versus and 383.74±283.7442ng/ml for AU/d>4). Although there is a tendency for PEth levels to increase as a function of AU/d between 4 and 8, this increase is not significant, but becomes highly significant between AU/d<8 and AU/d > 10.

PEth levels are not quantifiable (PEth ≈0ng/ml) in non-users, even in the presence of hepatic and peritoneal metastases and under chemotherapy in case #5. The PEth level is 126 ng/ml in the presence of active hepatitis in case #8, who consumes 4 UA/d (Table 4).

**Table 2** Epidemiological characteristics

| Gender | Age (Years) | PEth (ng /ml) | UA/Day | AUDIT Score |
|--------|-------------|---------------|--------|-------------|
| F (n=19) | 50 (25-67) | 639 (36-2566) | 6 (2-10) | 19.5 (7-30) |
| M (n=38) | 43 (20-70) | 539 (0-2432) | 7 (0-20) | 17 (0-28) |
| F+M (n=57) | 45 (20-70) | 572 (0-2566) | 6.7 (0-20) | 17.8 (0-30) |

**Table 3** PEth concentrations and daily alcohol consumption levels

| UA/day | 2-3 | 4-6 | 7-8 | >10 |
|---|---|---|---|---|
| | N=11 | N=27 | N=9 | N=10 |
| PEth (ng/ml) | 60.54±39.42 | 383.74±283.74 | 625.01±218.28 | 1603,10±498.52 |
| t. test | p<0.05 | | | |
| | | p=0.37 no significant | | |
| | | | p<0.001 | |

**Table 4** Comparison of alcohol consummation and levels of SGPT, SGOT, GGT and PEth.

| Subject | UA/Day | Audit | SGPT (IU/L) | SGOT (IU/L) | GGT (U/L) | PEth (ng/ml) |
|---|---|---|---|---|---|---|
| #1* | 0 | 0 | 30 | - | 32 | 210 |
| #2* | 0 | 0 | 26 | - | 33 | 340 |
| #3 | 0 | 0 | 9 | 14 | 28 | 0 |
| #4 | 0 | 0 | 9 | 14 | 25 | 0 |
| #5* | 0 | 0 | 300 | 250 | 450 | 0 |
| #6 | 1 | 6 | 9 | 14 | 21 | 29 |
| #7 | 2 | 7 | 9 | 14 | 21 | 30.45 |
| #8* | 4 | 13 | 48 | 60 | 90 | 126 |
| #9 | 5 | 10 | 9 | 14 | 25.2 | 37.7 |
| #10 | 5 | 12 | 9 | 14 | 25.2 | 87 |
| #11 | 6 | 15 | 18 | 28 | 29.4 | 116 |
| #12 | 6 | 16 | 27 | 28 | 33.6 | 174 |
| #13 | 6 | 18 | 27 | 28 | 37.8 | 615.84 |
| #14 | 6 | 22 | 27 | 28 | 46.2 | 821.12 |
| #15 | 6 | 24 | 27 | 28 | 46.2 | 872.44 |
| #16 | 6 | 24 | 27 | 28 | 50.4 | 923.76 |
| #17 | 8 | 25 | 31.5 | 37.3 | 52.08 | 1334.32 |
| #18 | 10 | 26 | 36 | 43.9 | 54.6 | 1519.072 |
| #19 | 10 | 28 | 45 | 53.2 | 60.48 | 2360.72 |
| #20 | 20 | 29 | 54 | 61.6 | 92.4 | 2463.36 |
| #21 | 25 | 29 | 67 | 89 | 298 | 2566 |
| Moyenne | 6 | 14.48 | 40.21 | 44.58 | 73.88 | 696.51 |
| Min-Max | 0-25 | 0-29 | 9-300 | 14-250 | 21-450 | 0-2566 |

*Patient #1, #2 behavior disorder, patient #8 : chronic active hepatitis C, patient #5: liver and peritoneum metastases

**Table 5** Correlation coefficient between alcohol consumption and biological parameters

|             | UA   | Audit score | GGT  | SGOT  | SGPT  | PEth |
|-------------|------|-------------|------|-------|-------|------|
| UA          | -    | 0.81        | 0.28 | 0.09  | 0.00  | 0.88 |
| Audit score | 0.81 | -           | 0.01 | -0.10 | -0.13 | 0.82 |
| GGT         | 0.28 | 0.01        | -    | 0.95  | 0.91  | 0.22 |
| SGOT        | 0.09 | -0.10       | 0.95 | -     | 0.99  | 0.12 |
| SGPT        | 0.00 | -0.13       | 0.91 | 0.99  | -     | 0.03 |
| PEth        | 0.88 | 0.82        | 0.22 | 0.12  | 0.03  | -    |

Table 5 describes the relationships between consumption and biological parameters:

- There is a positive correlation of 0.88 between alcohol consumption and PEth concentration
- There is a positive correlation of 0,82 between PEth concentration and Audit score
- There is a week positive correlation (Correlation Coefficient<0,22) between PEth and biological parameters (GGT, SGOT, SGPT)

Figure 3 shows the PEth profile of three people who abstained from alcohol over a two-month period:

- Patient # 1, Mr Z, 40 years old, totally abstinent for two months after having consumed about 15 UA per day for several years.
- Patient #2, Mr Y, 38, occasional heavy drinker (2 times a year, drunkenness accompanied by major behavioral problems) sample 0 taken one week after an episode. Between these major episodes, he consumes from 0 to 6 UA per week. PEth follows these fluctuations.
- Patient #3, Mr. W, 18 years old, average consumption 6 UA/day, seen again after a long hospitalization for alcohol withdrawal and resumption of consumption of 3 UA/d for one week.
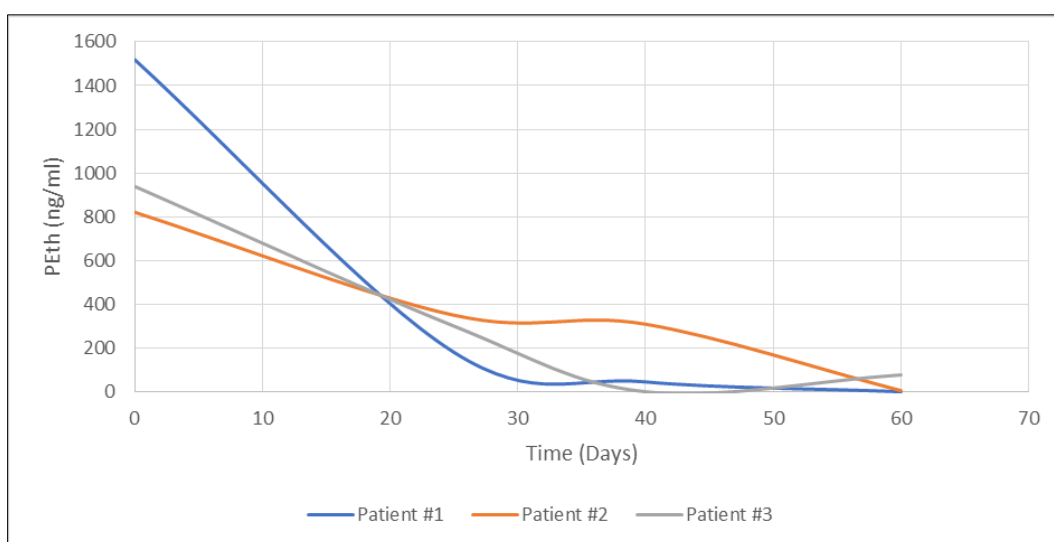


**Figure 3** PEth profile of three people who abstained from alcohol over a two-month period

Furthermore, a 13+5% difference in PEth concentration was observed when samples were stored at room temperature compared with those stored at +4°C and -80°C.

## 4. Discussion

Alcohol abuse and dependence has harmful consequences on health, social life and emotional life. In France, an estimated 1.5 million people are alcohol-dependent, and 2.5 million have risky drinking habits. Alcohol addiction is more common in men: 14% of men versus 5% of women. Depending on the source, excessive alcohol consumption is responsible for between 33,000 and 49,000 deaths a year in France (17). In this context, objective clinical and biochemical tests are essential to characterize alcohol consumption patterns, quantify the amount of ethanol ingested daily and enable effective management of these patients. The investigation of suspected alcohol dependence or abuse includes symptoms, medical history, self-report forms, special questionnaires, clinical examination, and biochemical analyses.

In this prospective study, 57 volunteers (19 F and 38 M) aged between 20 and 70 were included. A strong positive correlation of 0.88 (n=55) was observed between PEth concentrations and levels of daily alcohol consumption. As shown in figure 4, PEth concentration is a function of UA: [PEth]ng/ml=100 (UA/day)- 94.
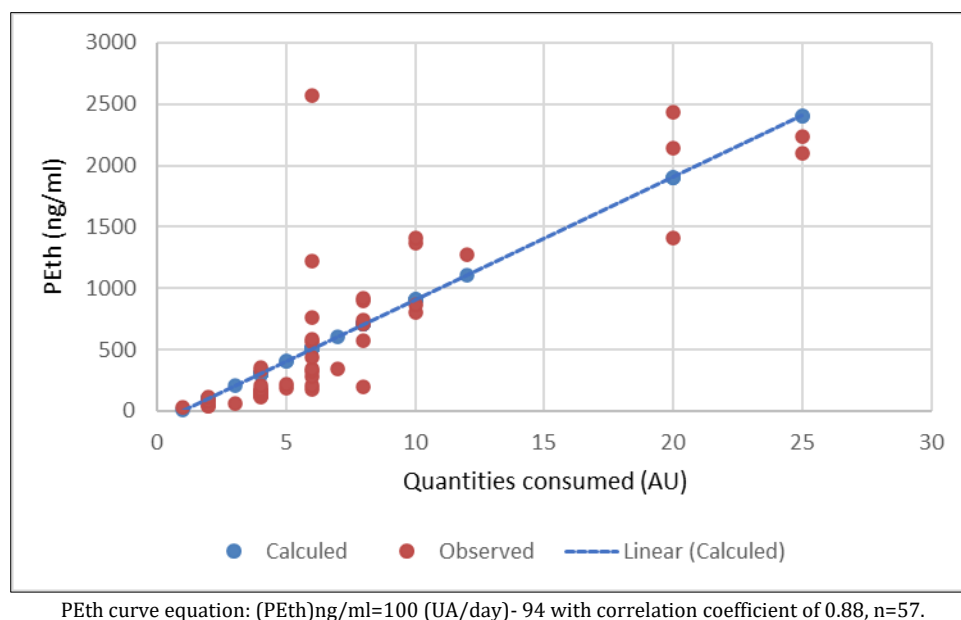


PEth curve equation: (PEth)ng/ml=100 (UA/day)- 94 with correlation coefficient of 0.88, n=57.

**Figure 4** Modelling curve of PEth concentration as a function of alcohol consumption

More precisely Table 3 shows that there is a significant difference of PEth levels between moderate consumption of less than 4 AU/d and more than 4 AU/d (for AU/d<4: 60.54±39.42ng/ml vs. and 383.74±283.74 ng/ml for AU/d>4). Although there is a tendency for PEth levels to increase as a function of AU/d between 4 and 8, this increase is not significant, but becomes highly significant between AU<8 and AU/d > 10.

- Case #5: In a situation of peritoneal carcinomatosis, undergoing chemotherapy with severely disturbed liver function tests, the enzymes SGOT, SGPT, GGT, are 10 times higher than normal, but PEth is negative, and this in the absence of declared consumption for months.
- Case #8: In a situation of hepatitis C infection, elevated and variable liver enzymes (2 to 4 times the normal value), and reported consumption of 3 to 4 UA/day, the PEth concentration is 126 ng/ml. This level lies within the confidence interval (IC 95%) of PEth (383.74±283.74ng/ml) for a consumption of 4-6 UA/d (Table 1).

The average PEth level is 20% higher in women than in men. This difference corresponds to a higher level of severity among women who accepted the test, in terms of the level and duration of alcohol misuse.

The usual biology, the "hepatic assessment" provides little or no information on the risks associated with alcohol consumption with correlation coefficient estimated at 0.28 for GGT, 0.09 for SGOT and 0.00 for SGPT (Table 5).

Our results confirm the conclusions of several authors, indeed in occupational risk situations, PEth is the only positive specific marker of alcoholism compared to biological parameters (GGT, VGM) which provide little information" (18-19).

## 4.1. PEth in withdrawal situations

In the present study, during total abstinence in an alcohol-dependent patient with a consumption of 15 UA/d, the decay kinetics of PEth blood concentration is single-phase exponential, corresponding to a single-compartment kinetic model of the following formulation $C_t = C_{initial} \times Exp(-0.09*t)$, with an estimated half-life in case #1 of about 7.7 days (Figure 4-5). PEth concentration falls below 1% after 52 days (table 6). Wurst et al. described the degradation kinetics on 57 alcohol-dependent subjects following a detoxification program [20]. The PEth decreased over time, with a half-life of around 3-5 days, and was detectable in 64.3% of cases after 28 days of sobriety [21]. Varga reports that in his study of 15 alcoholics undergoing a detoxification program, the mean half-life of blood PEth was 4.0 ± 0.7 days, with a range of 3.0 to 5.3 days [22]. Furthermore, it has been shown that sex, gender, age, and body mass index do not influence the rate of PEth normalization [20].
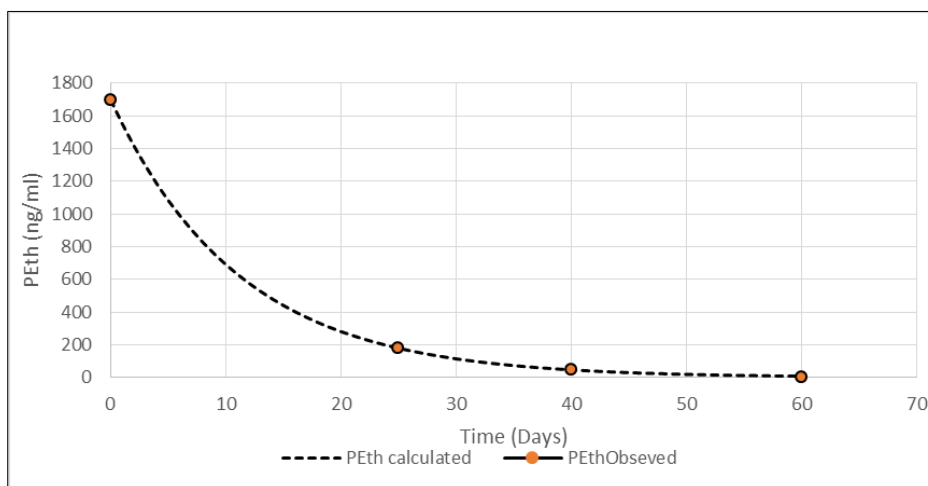


**Figure 5** Evolution of PEth concentration in case 1 after total abstinence

**Table 6** Estimation of PEth concentration as a function of time during abstinence*

| Day | % (Ct/Ci) | Day | % (Ct/Ci) | Day | % (Ct/Ci) | Day | % (Ct/Ci) |
|-----|-----------|-----|-----------|-----|-----------|-----|-----------|
| 0 | 100.00% | 14 | 28.37% | 28 | 8.05% | 42 | 2.28% |
| 1 | 91.39% | 15 | 25.92% | 29 | 7.35% | 43 | 2.09% |
| 2 | 83.53% | 16 | 23.69% | 30 | 6.72% | 44 | 1.91% |
| 3 | 76.34% | 17 | 21.65% | 31 | 6.14% | 45 | 1.74% |
| 4 | 69.77% | 18 | 19.79% | 32 | 5.61% | 46 | 1.59% |
| 5 | 63.76% | 19 | 18.09% | 33 | 5.13% | 47 | 1.46% |
| 6 | 58.27% | 20 | 16.53% | 34 | 4.69% | 48 | 1.33% |
| 7 | 53.26% | 21 | 15.11% | 35 | 4.29% | 49 | 1.22% |
| 8 | 48.68% | 22 | 13.81% | 36 | 3.92% | 50 | 1.11% |
| 9 | 44.49% | 23 | 12.62% | 37 | 3.58% | 51 | 1.02% |
| 10 | 40.66% | 24 | 11.53% | 38 | 3.27% | 52 | 0.93% |
| 11 | 37.16% | 25 | 10.54% | 39 | 2.99% | 53 | 0.85% |
| 12 | 33.96% | 26 | 9.63% | 40 | 2.73% | 54 | 0.78% |
| 13 | 31.04% | 27 | 8.80% | 41 | 2.50% | 55 | 0.71% |

*According to equation: $C_t = C_{initial} \times Exp(-0.09*t)$ ; When Ci : initial concentration of PEth and Ct : concentration of PEth On a given test day;
Example: Initial PEth concentration Ci= 1700ng/ml, Estimated PEth concentration on day 25 ($Ct_{25}$) is 10.54% corresponding to 179 ng/ml.

In a situation of withdrawal, the PEth, UA and AUDIT curves are roughly parallel. For the highest doses of PEth, the drop in declared consumption is plausible. These are older people, with long histories of consumption. Monitoring should be based on PEth 's exponential decay kinetics, which must be single-phase (Figure 6) and whose rates are shown in Table 6.
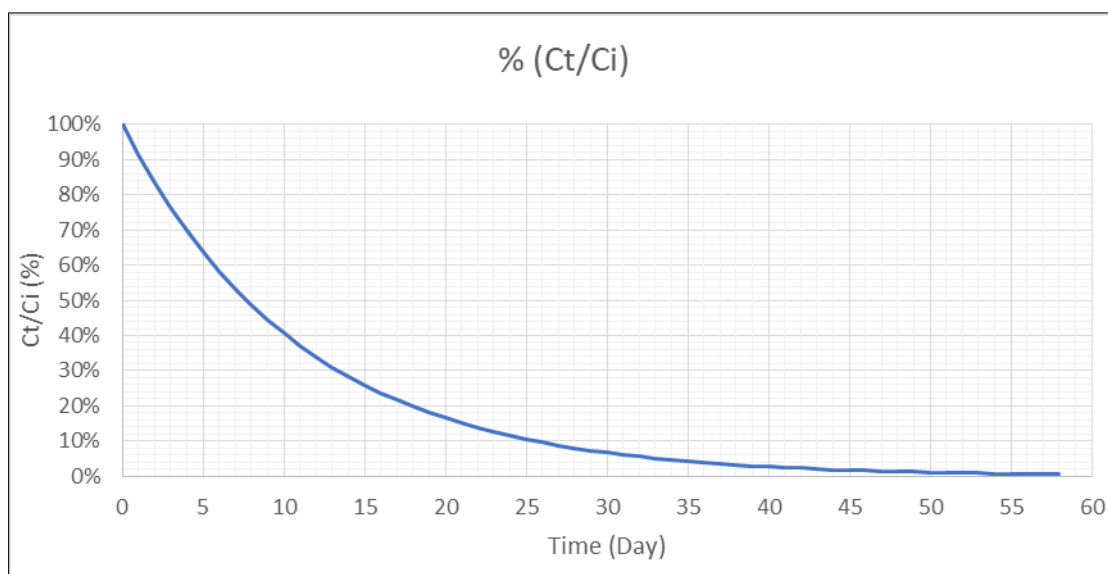


**Figure 6** Modelling curve of PEth decay after total abstinence ($C_t = C_{initial} \times Exp\ (-0.09*t)$)

The PEth assay in whole blood offers a high level of sensitivity and specificity as an alcohol biomarker, and provides clear answers in forensic situations where alcohol consumption is problematic. It appears to be a useful tool for prevention in all professions where vigilance is essential, and where alcohol is a risk (23-26).

### 4.2. PEth in forensic situations

In legal situations, it can be used as strong evidence:

Cases #1 and #2: In a forensic situation, according to the court certificates that described behavioral disorder, episode of violence under alcohol with denial by the patients. They acknowledge some consumption, in the evening after confrontation with the high PEth results of 210 and 340 for case #1 and case #2 respectively.

### 4.3. Stability of samples PEth

In our preliminary experiment, the average difference in PEth between two samples, measured at D4±3 days and 5 months apart, was 30%. PEth degradation was 13% for samples stored at room temperature, compared with those stored at +4°C and -80°C. This difference does not significantly alter the results of PEth measurements in practice (27). This work provides access to phosphatidylethanol (PEth) for consultation purposes, at a distance from the analysis centers. The technologies described enable a simple drop of blood to be taken and sent by post to the expert laboratory.

## 5. Conclusion

PEth is a specific and proportional marker of alcohol consumption. PEth has a long shelf life, from 4 to 8 weeks, depending on the quantities consumed. Measuring PEth enables us to accurately gauge the reality of alcohol consumption and adapt it to care and prevention contexts. This measurement of phosphatidylethanol (PEth) can be carried out as part of a consultation, at a distance from the analysis centers. The method described simply involves taking a drop of blood and sending it by post to the expert laboratory.

Finally, the PEth, along with the interpretation tools described in this article, is an important help in the management of alcohol dependence. In forensic situations, it can be used as solid evidence.

## Compliance with ethical standards

*Disclosure of conflict of interest*

No conflict of interest to be disclosed

*Statement of ethical approval*

This observational study on ex vivo analyses does not contain any studies carried out directly on animals/humans by either of the authors.

*Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

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