Toxicology

How can alcohol biomarkers be used in practice?

In Germany, around 6.7 million people between the ages of 18 and 64 consume alcohol (ethanol, ethyl alcohol, EtOH) in a way that is dangerous to their health.[1] Approximately 1.6 million people in this age group are considered to be alcohol dependent.[1-3] Alcohol abuse is a major risk factor for numerous chronic diseases (e.g. cancer, liver disease, cardiovascular disease)[4] and traffic accidents. Therefore, in forensic contexts, the influence of ethanol in particular is an important consideration when it comes to determining road safety[5] and criminal liability. It also plays a role in legal family disputes (custody rights, right of access) and in suitability issues (fitness to drive, labor inspections, probation requirements).

The prevailing opinion in our society is non-critical and accepting towards alcohol. Although there may have been a slight decline in alcohol consumption compared to previous years, in Germany, an average of ten liters of pure ethanol is consumed per capita every year.[1] On a global scale, this figure sees Germany remain within the upper decile. This costs the economy around 57 billion euro per year (according to *Jahrbuch Sucht 2021*, an annual review on drug abuse published by the German Center for the Control of Drug Abuse).[6]

The thresholds between low-risk and high-risk alcohol consumption[2] are different for men and women. The limit is 24 g EtOH/d for healthy adult men and 12 g EtOH/d for healthy adult women. Chronic excessive drinking is defined by the WHO as an average daily consumption of at least 60 g of ethanol over the course of several months.

80 to 90% of the consumed ethanol is absorbed in the intestine, 94 to 98% of which is broken down in the liver. Here, the ethanol is metabolized by alcohol dehydrogenase to produce acetaldehyde, which in turn is metabolized into acetic acid by aldehyde dehydrogenase. The final products are CO_2 and H_2O. Ethanol can also be metabolized in the liver by the inducible cytochrome P450 (CYP2E1). Further metabolism (0.1 to 0.2%) into ethyl glucuronide, phosphatidylethanol or fatty acid ethyl ester, for example, is due to non-oxidative causes.

Various methods are used to determine levels of alcohol in the body.[3] Breath alcohol tests are only used as a rough initial assessment, as the process is not accurate enough. Another disadvantage of this method is that it is not possible to carry out follow-up tests for drugs or medications or any concomitant analyses for other alcohols (methanol, acetone, isopropanol, n-propanol).[7]

Alcohol biomarkers[8] are substances that are altered or newly produced in the body when alcohol is consumed. Biomarkers play a particularly important role in addiction treatment in that they enable us to objectivize alcohol abstinence or to detect harmful alcohol consumption. In Germany, the costs for most biomarker analyses are charged in accordance with the German medical fee schedule and are covered by health insurance providers.

Common **indirect** biomarkers include gamma-glutamyl transferase (**γ-GT**), mean corpuscular volume (**MCV**) and carbohydrate-deficient transferrin (**CDT**). They react not only to alcohol consumption itself but also to other influencing factors, so they offer low specificity. Another disadvantage of this method is that common indirect biomarkers only increase after a sustained high level of alcohol consumption.

Determining **direct** alcohol biomarkers is therefore the gold standard. These direct alcohol biomarkers are compounds that are formed after ethanol is absorbed by conjugating with alcohol in the body. Enzymes metabolize small amounts of the absorbed alcohol into phosphatidylethanol (**PEth**), fatty acid ethyl esters (**FSEE**), ethyl glucuronide (**EtG**) and ethyl sulfate (**EtS**). Direct alcohol biomarkers can be detected in blood and urine for much longer than ethanol itself and are sometimes also stored in hair.

PEth and FSEE are suited to detecting more frequent alcohol consumption, while EtG and EtS indicate even short-term absorption of smaller amounts of alcohol. The detection time period of EtG depends on the dose. The detection time of EtG in urine is approximately 21 to 184 hours (median 92 hours, cut-off 100 ng/mL). In whole blood, the detection time is approximately 22 to 179 hours (median 111 hours, cut-off 1 ng/mL).[9] The detection of EtG in hair is used for a long-term, retrospective diagnosis of alcohol consumption but is dependent on individual drinking behavior, the location of hair sampling and other external factors.

The direct biomarker PEth (phosphatidylethanol) can be detected shortly after the start of consumption, irrespective of pharmacokinetic factors. PEth is therefore suitable for both the detection of current consumption and as a proof of abstinence.

PEth levels are determined by a whole blood test, which means that any tampering with the sample before analysis can usually be ruled out. In the context of moderate and dangerous drinking behavior over a long period of time, as well as in the context of relapses, the informative value of PEth is higher than that of CDT and EtG because PEth can be detected after both one-time and long-term consumption, and an estimation of consumption behavior can be made based on concentration levels.

Combining PEth concentration with EtG concentration may also provide an indication of the patient's drinking behavior from a single test. An EtG concentration of >100 ng/mL in combination with PEth >0.3 µmol/L may indicate continuous alcohol consumption, or that a high amount of alcohol has been consumed very recently.[10]

In cases of chronic excessive consumption, PEth accumulates in the blood and can therefore be detected even after a few weeks of abstinence. It is possible to distinguish between low, moderate and excessive consumption. PEth is often used as a biomarker of abstinence since, unlike CDT, it also reveals acute relapses and drinking episodes. It allows differentiation between drinking behaviors ("abstinence," "social drinking," "riskful drinking").

PEth alcohol tests have become a part of addiction treatment and are the preferred tests for motivating contingency treatment and to prevent relapse. In addiction treatment in particular, concepts and approaches have changed since the 1990s. Alcoholism used to be regarded as misconduct and was branded as a disease; nowadays, we are seeing a shift toward acceptance and risk minimization, whereby drinking is more closely monitored by means of a drinking diary, PEth checks and feedback sessions.

Under the motto "objectivity instead of confrontation" an improvement in the patient-doctor relationship is expected by empowering patients to monitor and reflect on their alcohol use in collaboration with their doctors with virtual support by the app "Checkpoint-S". This app is available on Android in the Google Playstore and allows patients to record various addiction values (ethanol, nicotine, drugs, opiates, etc.).[11]

PEth tests have proven useful on many fronts. The sampling of capillary plasma is simple and can be carried out anywhere; and with weekly tests, PEth levels are reliable proof of abstinence, or proof of an increase or decrease in ethanol consumption, which can then be used as a self-help aid (self-monitoring).

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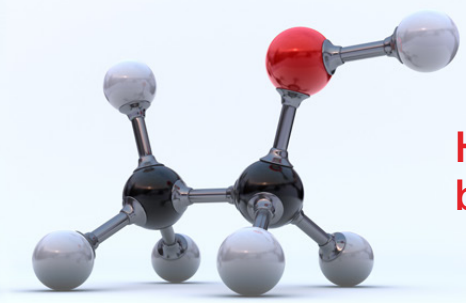

How can alcohol biomarkers be used in practice?

- **What is the use of alcohol markers from the point of view of an established addiction doctor?**
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  East German Working Group on Addiction Medicine e.V. (OGAS), Halle, Germany
- **Blood alcohol from a forensic and clinical perspective**
  Private lecturer Hilke Andresen-Streichert
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- **Importance of alcohol consumption markers in forensic-toxicological questions**
  Professor Frank Musshof
  Forensic-Toxicological Center GmbH, Munich, Germany
- **Diagnostic importance of PEth and EtG**
  Dr. Michael Boettcher
  MVZ Medical Laboratories Dessau-Kassel GmbH, Dessau, Germany

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