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Food-Induced Lowering of Blood-Ethanol Profiles and Increased Rate of Elimination Immediately After a Meal

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ABSTRACT: In a two-part crossover study, ten healthy men drank a moderate dose of ethanol (0.80 g/kg) in the morning after an overnight fast or immediately after breakfast. The breakfast consisted of orange juice (150 mL), fruit yogurt (250 mL), two cheese sandwiches, one boiled egg, and one cup of coffee with milk and sugar. Ethanol was determined in venous blood at various times after the start of drinking by headspace gas chromatography. All subjects felt less intoxicated when alcohol was ingested after breakfast compared with drinking on an empty stomach. The peak BAC (± SD) was 67 ± 9.5 mg/dL (ethanol + food) compared with 104 ± 16.5 mg/dL when the drinking occurred after an overnight fast ($P < 0.001$). The mean area under the alcohol concentration-time profile (0→6h) was 398 ± 56 mg/dL × h in the fasting state compared with 241 ± 34 mg/dL × h when subjects drank alcohol after the meal ($P < 0.001$). The time required to metabolize the dose of ethanol was approximately two hours shorter after the subjects had eaten breakfast. These results suggest that food in the stomach before drinking not only leads to a lowering of the peak BAC and diminishes the feelings of intoxication, but also boosts the rate of ethanol metabolism. A food-induced increase in the rate of disposal of ethanol was also confirmed when subjects ate a meal 5 h after drinking, that is, when the postabsorptive phase of ethanol metabolism was well established. The mean rate of disappearance of alcohol from blood was increased by between 36 and 50%.

KEYWORDS: toxicology, alcohol, ethanol, metabolism, food

Estimating a person's blood-alcohol concentration (BAC) on the basis of a declared drinking scenario requires a careful consideration of how alcohol is absorbed, distributed and metabolized by the body [*1,2*]. Factors influencing the maximum BAC reached after drinking, and the time needed to eliminate alcohol from the body are questions that often arise during drink-driving litigation [*3,4*]. Many earlier studies have shown that the peak BAC is less when alcohol is ingested after a meal compared with the same dose taken on an empty stomach [*5–7*]. However, the timing of the meal relative to the ingestion of ethanol and the quantity and nature of the food eaten, whether in the form of liquid or

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solid and the relative proportions of macro-nutrients (fat, protein, and carbohydrate) seems to play a role in modulating the pharmacokinetics of ethanol [*8–10*].

This article presents the results of controlled experiments designed to assess the effect of a standardized meal on the pharmacokinetics of a moderate dose of ethanol. The alcohol was ingested in the morning either after an overnight fast or immediately after volunteers had eaten breakfast. We also report the results from studies when the volunteer subjects received a substantial meal 5 h after drinking ethanol, that is, when the absorption and distribution processes were already complete.

Materials and Methods

Subjects and Conditions

Ten healthy men with a mean age 31 y (SD 8.1, range 22 to 43) and mean body weight 71 kg (SD 6.9, range 62 to 87) participated in this study as paid volunteers. Each subject served in two experiments at least one week apart. On arrival at the laboratory, a catheter was inserted into a cubital vein to facilitate obtaining samples of blood at frequent intervals. The subjects drank 0.80 g ethanol/kg body weight starting at about 8:00 a.m. in exactly 30 minutes either on an empty stomach (10 h fast) or immediately after breakfast. This drink was prepared from 95% v/v ethanol solvent which was diluted with sugar-free orange juice to make a 20 to 25% v/v cocktail. Breakfast consisted of fresh orange juice (150 mL), fruit yogurt (250 mL), two cheese sandwiches served on hard wheat bread, one boiled egg, and one cup of coffee with milk and sugar. The breakfast was eaten in exactly 15 min and a lunch was served 240 min after the start of drinking.

Another series of experiments, which have been described in more detail elsewhere [*11*], dealt with the pharmacokinetics of ethanol in the fasting state. We evaluate here the blood ethanol profiles in a new way. Healthy male volunteers drank a moderate dose of alcohol (0.51, 0.68, or 0.85 g/kg) as neat whiskey (N = 16 subjects/dose) after an overnight fast. A substantial meal was served exactly 5 h after the drinking started. This experimental design was exploited to test the influence of a meal on the rate of disappearance of ethanol from blood when the absorption and distribution stages of ethanol metabolism were complete.

Blood Sampling and Determination of Ethanol

Samples of venous blood were obtained through an indwelling catheter before ingestion of alcohol and then at exactly 10, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, and 420 min, timed from the start of drinking. Blood was drawn into 5 mL Vacutainer tubes (Becton Dickinson Ltd.) containing NaF (20 mg) and heparin (143 units) as preservatives. The catheter tubing was flushed with a few drops of heparin-saline solution to prevent coagulation between taking successive blood samples. The blood-alcohol concentration was determined in duplicate by headspace gas chromatography as described in detail elsewhere [*12*]. In brief, aliquots of venous whole blood (100 μL) were diluted 11-fold with n-propanol (8 mg/dL) as an internal standard. The diluted blood specimens were ejected directly into headspace vials (22 mL) that were made air-tight with rubber stoppers and crimped-on aluminum caps. The chromatographic column was made of glass (2 m × 3 mm i.d.) packed with Carbopack C (0.2% Carbowax 1500 on Carbopak) as the stationary phase. The precision of this method of analysis was 0.8 mg/dL at a mean BAC of 100 mg/dL corresponding to a coefficient of variation of less than 1% and therefore indicating a high analytical precision [*12*].

In our previous studies, ethanol was determined in capillary (fingertip) blood samples obtained at 0, 30, 60, 90, 120, 180, 240, 300, 360, 420, and 480 min timed from start of drinking. An automated enzymatic (ADH) method was used for the quantitative analysis

of ethanol as described in detail elsewhere [*13*]. The standard deviation of this method of alcohol analysis was 1.7 mg/dL at a mean concentration of 53 mg/dL.

Evaluation of Results

Blood-ethanol profiles were plotted for each subject in both the fed and fasted conditions of drinking. These individual traces were evaluated by defining a set of summary measures to depict the time course of ethanol in the body [*14,15*]. The rate of disappearance of alcohol from the blood stream (ß) was derived from the pseudolinear elimination part of the curves after reaching the peak concentration in blood [*16*]. The apparent volume of distribution of ethanol (V_d) was calculated as the dose (0.8 g/kg) divided by the concentration of alcohol in blood at time zero (C_o). This C_o parameter is provided by the y-intercept of the concentration-time regression equation. The highest BAC reached (C_{max}), the time required to reach the peak (T_{max}), and the time needed to eliminate the dose of alcohol from the body ($time_o$) were also calculated and compared for the fed and fasting conditions. The overall rate of ethanol disposal was expressed as g/kg/h and this was derived from the ratio of dose/$time_o$. The area under the concentration-time profiles (AUC) were calculated by the trapezoidal rule [*17*]. The rate of absorption of alcohol (mg/dL/h) was derived by dividing the C_{max} for each subject by the corresponding T_{max} measured from the start of drinking.

The rate of disappearance of ethanol from the blood was also calculated from the hourly decrease in BAC starting at least 2 hours after drinking began or $1^1/_2$ h after the end of drinking. The mean disappearance rate of alcohol (mg/dL/h) was calculated and compared for each subject for the time period before and after they ate a substantial meal at exactly 5 h after the drinking began.

Results

Concentration-Time Profiles with and Without Breakfast

Figure 1 shows the blood-alcohol profiles obtained for each subject in the fed and fasting drinking conditions. Without exception, when alcohol was ingested after breakfast the curves followed a lower course with a lower C_{max}, a later T_{max} and a smaller area under the curve. More importantly, the time needed to eliminate alcohol from the body ($time_o$) was considerably shorter when alcohol was taken after the meal.

Figure 2 gives a closer look at the absorption profiles of ethanol after drinking on an empty stomach compared with intake after breakfast. Large inter-individual differences in the rate of absorption and the time of reaching the peak BAC were evident regardless of whether alcohol was ingested on an empty stomach or after a meal. However, variability was more pronounced in the fed-state. The average absorption profiles for the two drinking situations are shown as an insert in Fig. 2. The C_{max} was reached on average 45 min later when the alcohol was ingested after eating breakfast compared with the fasting state. This meant that the rate of absorption of alcohol was about 3 times faster when volunteers drank on an empty stomach (Table 1).

Blood-Alcohol Parameters

Table 1 shows the mean blood-alcohol parameters for the fed and fasting conditions. The mean intra-subject differences were evaluated by Student's t-test. The peak BAC was 36% lower ($P < 0.001$) when alcohol was ingested after breakfast compared with intake after an overnight fast whereas the parameter C_o was lowered by 5.2% ($P < 0.01$). The time required to eliminate alcohol from the body was shortened by 2 hours (24%) when alcohol was taken after food compared with drinking on an empty stomach ($P < 0.001$).

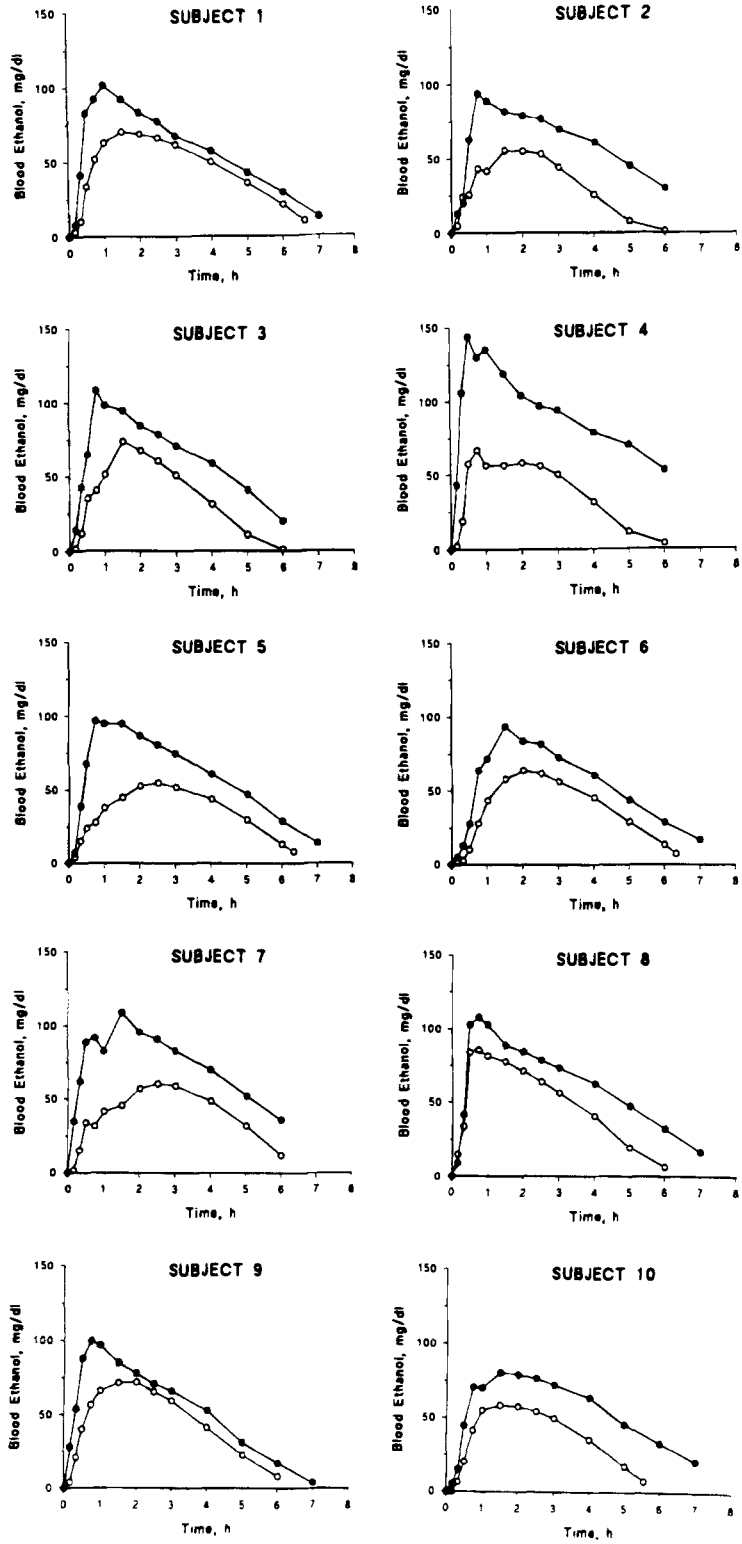

FIG. 1—*Blood-ethanol profiles in 10 healthy men after they drank 0.80 g ethanol/kg body weight in 30 min either after an overnight (10 h) fast (•) or immediately after breakfast (○).*

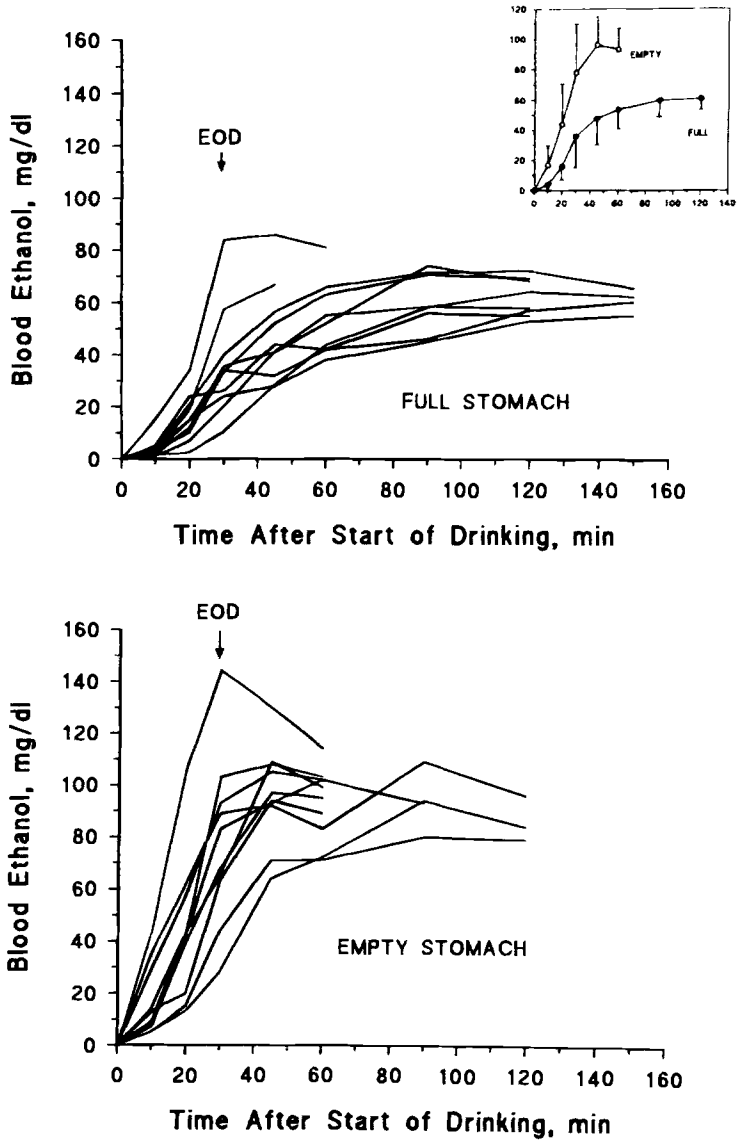

FIG. 2—*Comparison of the absorption profiles of ethanol in 10 healthy men who drank 0.80 g ethanol/kg body weight on an empty stomach (lower plot) or after a meal (upper plot). The insert* (top right) *shows the mean absorption profiles for these drinking conditions.*

This corresponds to a 36% faster rate of disposal of alcohol in the fed state. The mean area under the concentration time profile was reduced by 39% when alcohol was taken immediately after breakfast ($P < 0.001$). The rate of disappearance of alcohol from blood (ß) was faster in the fed state and showed an increase by 23% on average ($P < 0.01$).

Ingestion of Food During the Post-absorptive Phase of Ethanol Kinetics

Table 2 presents the successive hourly decrease in BAC before and after subjects ate a substantial meal. The first estimate of the rate of disappearance of ethanol from blood

TABLE 1—*Blood alcohol parameters in healthy mean (N = 10) after they drank 0.8 g ethanol/kg body weight either on an empty stomach (overnight fast) or immediately after breakfast.*

Blood alcohol parameter	With breakfast mean ± SD	Empty stomach mean ± SD
Peak BAC, mg/dL	67 ± 9.5	104 ± 16.5[a]
Time to peak[c] (min)	90 (45–150)	45 (30–90)[d]
Absorption rate[c] (mg/dL/h)	38 (22–114)	127 (54–288)[d]
C_0 (mg/dL)	109 ± 7	115 ± 7[b]
$Time_0$ (h)	6.3 ± 0.64	8.3 ± 0.78[a]
ß-slope (mg/dL/h)	17.4 ± 1.6	14.2 ± 1.5[a]
V_d (L/kg)	0.74 ± 0.047	0.68 ± 0.052[b]
Disposal rate (g/kg/h)	0.128 ± 0.013	0.097 ± 0.009[a]
Disposal rate from body (g/h)	9.1 ± 1.56	6.7 ± 0.82[a]
Area Under Curve (mg/dL × h)	241 ± 34	398 ± 56[a]

[a] $P < 0.001$.
[b] $P < 0.01$ compared with fed state.
[c] Median and range from the start of drinking which lasted 30 min.
[d] Significantly different ($P < 0.01$) by nonparametric Wilcoxen signed rank test.

shown in Table 2 was made between 2 to 3 hours after the start of drinking. After the meal, a faster rate of removal of alcohol from blood, as reflected in a steeper ß-slope, was clearly evident for the 3 doses of alcohol administered. The mean rates of disappearance of ethanol increased by 40%, 36%, and 50% for the ethanol doses of 0.51, 0.68, and 0.85 g/kg respectively. All the increases in ß-slope after the meal were statistically highly significant ($P < 0.001$).

Discussion

The systemic availability of ethanol is appreciably less if the drinking takes place together with or after a meal. This reduced bioavailability is reflected in a lowering in the peak BAC, a smaller AUC, a shortening of the time required to eliminate alcohol from the body as well as diminished feelings of intoxication. However, these observations are not new and the influence of food on blood-alcohol concentration was reported during the first decades of this century by Mellanby [*18*] and Widmark [*16*]. Widmark suggested that part of the dose of alcohol "disappeared" when taken together with a meal [*16*]. On the basis of making a quantitative evaluation of blood-ethanol profiles for the same individual under fed and fasting conditions, Widmark estimated that between 10 and 12 g of alcohol could

TABLE 2—*Disappearance rates of alcohol from blood (ß-slopes, mg/dL/h) before and after healthy men (N = 16) drank 0.51, 0.68 or 0.85 g ethanol/kg body weight after an overnight fast. Five hours after the drinking started the subjects ate a substantial meal.*

Time interval after drinking	Ethanol dose 0.51 g/kg	Ethanol dose 0.68 g/kg	Ethanol dose 0.85 g/kg
2–3 hours	11 ± 2.2	10 ± 2.8	13 ± 2.8
3–4 hours	11 ± 1.8	11 ± 2.6	12 ± 3.2
4–5 hours	10 ± 1.4	11 ± 2.4	12 ± 2.0
5–6 hours	14 ± 2.4[a]	15 ± 1.9[a]	18 ± 2.7[a]
6–7 hours	BAC at Zero	15 ± 2.8[a]	18 ± 2.2[a]
7–8 hours	BAC at Zero	BAC at Zero	17 ± 2.8[a]

[a] $P < 0.001$ compared with all estimates of ß-slope before the intake of food.

not be accounted for. He speculated that the alcohol molecules might have become bound to various constituents of the food, particularly the amino acids, and thereby escaping absorption into the portal blood. However no direct experimental evidence was provided to support this notion.

Later investigators offered other explanations for the food-induced lowering of blood-ethanol profiles. A more effective hepatic oxidation of ethanol was thought to occur when the absorption from the gut was slow and more prolonged [*19,20*]. This explanation fitted with the generally accepted Michaelis-Menten kinetics of ethanol [*21*]. The saturable nature of the enzyme system implies a more effective clearance at low substrate concentrations and therefore when the transport of ethanol to the hepatic metabolizing enzymes is slowed down in some way [*20*].

More recently, considerable interest has focused on the possibility of first-pass oxidation of ethanol occurring in the stomach. The existence of alcohol dehydrogenase (ADH) in the mucous membranes of the stomach is very well documented by methods that are difficult to fault [*22*]. Gastric ADH represents a new form of the enzyme (class 1V) having an appreciably higher K_m for ethanol compared with hepatic class 1 ADH [*23*]. However, the quantitative significance of gastric-ADH in the overall metabolism of ethanol has been challenged by some investigators who have presented convincing arguments supporting the liver as the primary site for first-pass metabolism of ethanol if there is any [*24*]. The activity of gastric ADH is modulated by age, gender, alcohol drinking habits, and whether the subjects are fed or fasted prior to drinking [*25,26*]. It appears that the metabolism of ethanol in the stomach is more pronounced when small doses (0.15–0.30 g/kg) are ingested about 1 hour after breakfast.

The method most widely used in forensic alcohol research to calculate the rate of disappearance of ethanol from the bloodstream considers all relevant post-peak BAC measurements. Accordingly, the slope of the best fitting straight line furnishes an average rate of alcohol elimination for a particular dose of alcohol and other relevant experimental conditions. However, another way to estimate the ß-slope is to look at changes in BAC between two successive time points when the post-absorptive stage of ethanol metabolism has become definitely established. For this method to yield reliable results, the entire post-absorptive phase of ethanol metabolism must be carefully mapped-out. Moreover, values of the ß-slope derived in this way reflect not only the elimination rate of alcohol from the bloodstream but also any redistribution between the blood and tissue compartments during the sampling interval. The results presented in Table 2 demonstrate that eating a meal seemingly boosts the rate of disappearance of ethanol from blood by 36 to 50% on average. This increase in the elimination rate of ethanol was seen after three different doses of alcohol. Other workers reported similar observations when subjects received a meal during the postabsorptive portion of the blood-alcohol profile [*27*].

Gastric-ADH cannot account for this faster rate of disposal of ethanol when the postabsorptive phase of metabolism has already become well established because negligible amounts of alcohol remain in the stomach at 5 hours post-drinking. Instead, this finding probably reflects a more effective hepatic oxidation of ethanol by one or more possible mechanisms. We know that food increases the hepatic blood flow and thereby enhances the exposure of ethanol to the oxidizing enzymes mainly located in the liver [*28,29*]. Although ethanol is generally not considered a high-extraction drug, hepatic blood flow will become an increasingly important determinant of clearance rate as the BAC approaches the V_{max} of ADH isozymes [*19*]. Five hours after drinking the two smaller doses of ethanol (0.51 and 0.68 g/kg) the BAC is probably approaching the V_{max} for class I ADH isozymes. Animal studies have shown a marked lowering in activity of hepatic ADH after food deprivation compared with a well nourished organism [*30*]. This reduced enzyme activity might also contribute to the slower oxidation of ethanol seen when the subjects drank alcohol after an overnight fast. Interestingly, feeding a low protein diet brought about a

marked decrease in the rate of disappearance of ethanol from blood in humans [*31*]. Whether changes in posture and the increased muscular activity associated with eating the meal have any influences on the rate of clearance of ethanol from blood has not been elucidated in our experimental design.

The lower AUC after ethanol + food compared with the same dose when ingested on an empty stomach might also be explained by the "two pool" alcohol absorption hypothesis first advocated by Schultz et al. [*32*] on the basis of extensive experiments with rats. These investigators suggested that when alcohol was given together with food, part of the dose becomes physically entrapped by food particles in the stomach. This bound pool is therefore prevented from making contact with the absorption surfaces in the stomach. However, there is also a free-pool of alcohol available, which accounts for the initial rapid rise in BAC observed even when ethanol is taken together with food. The relative pool sizes might depend on whether solid or liquid food was taken and the proportions of macro-nutrients. Factors influencing stomach emptying might also influence the relative pool sizes and the rate of absorption of alcohol and therefore the resulting C_{max} [*33*]. Cortot et al. [*34*] showed that when alcohol was taken with food, 73% of the dose was absorbed through the stomach and only 24% was taken up through the duodenum. Indeed, some of the alcohol was retained in the stomach for as long as 6 h after drinking. It seems likely that the bound pool of alcohol might be released so slowly that it becomes oxidized at the same rate as it reaches the liver via the portal circulation. This part of the dose of alcohol is therefore prevented from reaching the systemic circulation and will not contribute to the concentration reached in the peripheral blood.

The experiments reported here add another dimension to our knowledge of food-ethanol interactions but we can still only speculate about the underlying mechanisms involved. But whatever the mechanism, the results have ramifications in forensic science practice when expert statements are made concerning driving under the influence of alcohol. For instance, if a person has been drinking together with or after a meal the dose of alcohol entering into theoretical calculations of the person's BAC should be decreased by about 15 g. This means that the C_{max} as well as the time required to reach an alcohol-free state needs to be adjusted accordingly. For a man with a body weight of 70 kg, 15 g of ethanol when fully absorbed and distributed in all body fluids would correspond to a BAC of about 30 mg/dL (± 20%). Furthermore the time needed to reach zero BAC will be shortened by about 2 hours when alcohol is taken together with or after a meal.

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