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OVERVIEW

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Alcohol, its absorption, distribution, metabolism, and excretion in the body and pharmacokinetic calculations

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Abstract

The ethanol contained in alcoholic beverages is rapidly absorbed from the gastrointestinal tract and the maximum blood-alcohol concentration (BAC) is usually reached between 10 and 60 min postdosing. Once in the bloodstream, ethanol is distributed into the total body water (TBW) compartment, which comprises ~55–60% of body weight in nonobese males and ~50–55% in females. The volume of distribution (V_d) of ethanol depends on a person's age, gender, and degree of adiposity (ratio of fat to lean tissue). Studies have shown that the average V_d for healthy men and women are ~0.70 and ~0.60 L/kg, respectively. Elimination of ethanol from the body occurs primarily through metabolism (92–98% of dose) by hepatic alcohol dehydrogenase (ADH), an enzyme located in the liver cytosol and a microsomal enzyme, denoted CYP2E1. A small fraction (0.1–0.2%) of the dose of ethanol ingested undergoes nonoxidative metabolism by phase II conjugation reactions leading to formation of ethyl glucuronide and ethyl sulfate. Only between 2 and 10% of the dose of ethanol is excreted unchanged in urine, breath, and in sweat/perspiration. Ethanol exhibits dose-dependent pharmacokinetics, because the hepatic ADH enzyme is saturated with substrate at BAC above 15–20 mg/100 mL (15–20 mg%). Zero-order kinetics operate for most of the postabsorptive elimination phase and the BAC decreases at a constant rate per unit time ranging from 10 to 35 mg% per hour (average 15 mg% per hour for moderate drinkers). Examples of various pharmacokinetic calculations are presented because these are often necessary in forensic science and legal medicine casework.

This article is categorized under:

Toxicology > Alcohol
Toxicology > Analytical Toxicology
Toxicology > Drug-Impaired Driving

KEYWORDS

ADME, ethanol, forensic toxicology, pharmacokinetics, Widmark calculations

1 | INTRODUCTION

The disposition and fate of drugs and other chemical substances in the body began to attract scientific interest and research during the second half of the 19th century coinciding with advances in pharmacy and pharmacology, such as the isolation of

drugs from natural products. This also marked the birth of forensic toxicology and the development of chemical methods to identify poisonous substances in biological specimens, such as in connection with the investigation of sudden, unnatural and/or suspicious deaths (Coley, 1998).

In Victorian Britain, excessive drinking and drunkenness had developed into a major problem for public health and the medical profession was baffled about what happened to alcohol in the body; was it a food, a medicinal drug or a poison? This question was answered in experiments done by Dr. Francis Anstie (1833–1874), who showed that only a small fraction (<10%) of the amount of ethanol ingested (the dose) was excreted unchanged in breath, urine and sweat (Anstie, 1874). It appeared that the bulk of the dose of ethanol was "burnt up" and utilized in the body in the same way as ordinary foodstuffs. Later work by other scientists verified that oxidative metabolism of ethanol produced 7.1 kcal of energy per gram combusted (Lieber, 1994a).

By the 1920s, methods became available for the quantitative analysis of ethanol in small volumes of fingertip blood (~50–100 μL), which permitted making more detailed studies of the absorption, distribution, metabolism, and excretion (ADME) of ethanol in the human body (Widmark, 1922). The physiological laws governing ADME of ethanol were formulated in the 1930s along with the basic principles of ethanol pharmacokinetics (Widmark, 1932).

The blood-alcohol concentration (BAC) reached after a person drinks an alcoholic beverage depends on many factors, including the dose ingested, the type of beverage consumed, the fed-fasted state, the speed of drinking, and the person's body weight, age, and sex (Jones, 2016). Variability in the ADME of ethanol has a profound effect on how a person reacts to the drug, including behavioral and impairment effects (Norberg, Jones, Hahn, & Gabrielsson, 2003). Once absorbed into the bloodstream, ethanol easily passes the blood–brain barrier (BBB) and acts as a depressant of the central nervous system (CNS). The ethanol-induced impairment of body functioning depends on the BAC reached and an important task for forensic practitioners is to interpret analytical results in relation to the observed signs and symptoms of intoxication and drunkenness.

This chapter describes the ADME of ethanol and the many factors influencing the disposition and fate of ethanol in the body. Examples are also given of various pharmacokinetic calculations that might be required in forensic science and legal medicine, such as forward or backward extrapolation of a person's BAC or when alcohol intoxication deaths are investigated.

2 | FORENSIC ASPECTS OF ALCOHOL

The quantitative analysis of ethanol in blood and other biological specimens ranks high among the routine duties of forensic scientists and toxicologists, because abuse of alcohol and drunkenness are underlying factors in many types of crime (Dingwall, 2013). Accurate and precise determination of a person's BAC is relatively simple compared with interpreting the BAC in relation to the quantity of ethanol consumed and the effects on body functioning, including risk of toxicity and poisoning death (Jones, 1991).

Without any doubt, a person's BAC or breath-alcohol concentration (BrAC) is the most important evidence in drink-driving cases, because statutory concentration limits exist in most countries. The alcohol limits currently enforced in England and Wales are 80 mg/100 mL (80 mg%) in blood and 35 μg/100 mL (35 μg%) in breath, whereas in Ireland and Scotland the corresponding limits are 50 mg% BAC and 22 μg% BrAC. The BAC or BrAC give a point estimate of the amount of alcohol in the body at time of sampling, although the police often want to know what the person's BAC was at some earlier time, such as the time of driving or when a crime was committed, such as alleged sexual assault. This requires making a back calculation of a person's BAC, which is often referred to as retrograde extrapolation, and requires knowledge of the ADME of ethanol and the factors influencing these processes (Al-Lanqawi et al., 1992; Jackson, Tucker, & Woods, 1991; Montgomery & Reasor, 1992).

BAC calculations are done in slightly different ways depending on the scientific background and training of the expert witness or forensic practitioner and a lot might be gained if these procedures were more standardized (Labay & Logan, 2018). Although there is not yet any international agreement reached, certain guidelines are available, such as those promulgated by the United Kingdom and Ireland Association of Forensic Toxicologists (UKIAFT). This organization has produced a document entitled "alcohol technical defenses," and this is available on-line via the website (http://www.ukiaft.co.uk/publications.html). A lot will depend on the standard of proof necessary, whether beyond a reasonable doubt or the balance of probabilities. Nevertheless, it is crucial that any assumptions made when BAC calculations are done should be fully explained in a deposition or affidavit or during oral testimony in court and therefore subjected to direct and cross-examination (Mason, 1986).

Ethanol is an unusual psychoactive substance in as much that massive amounts must be ingested to bring about its pharmacological effects compared with other recreational drugs. The principal reason for this is that ingested ethanol becomes diluted

with the TBW, which represents 50–60% of body weight. Unlike many other drugs, ethanol does not bind to plasma proteins or other biomolecules, and easily crosses the BBB to cause impairment.

The degree of impairment is dose-dependent; after drinking small doses of ethanol to reach BAC of about 30–50 mg% people become more talkative, they feel less inhibited and experience a mild euphoria. When higher BACs are reached, such as 80–120 mg% the outward signs of impairment are more obvious; reaction times are slower, information processing is more difficult, motor coordination is impaired, and a slurred speech and staggering gait might be seen. Drinking ethanol in the amount necessary to reach BAC of 200 mg% or more is associated with gross intoxication and incapacitation. At BAC- > 300 mg% most people would be unresponsive and comatose with risk of dying from paralysis of respiratory centers in the brain stem (Morley, Smith, & Johnson, 2014). Another mechanism of death is asphyxia from inhalation of vomit, which usually occurs at considerably lower BAC than 300 mg%.

Figure 1 shows a schematic diagram illustrating the fate of ethanol in the body resulting in a BAC profile, passage through the BBB, and eliciting pharmacological effects. In the CNS, ethanol molecules interact with cell membranes and receptor proteins, primarily acting as an agonist at the GABA-A receptor and GABAergic neurons are inhibitory, although other receptor sites and mechanisms are involved (Lobo & Harris, 2008). On reaching the CNS, ethanol triggers a cascade of physiological responses depending on the drug dosage, the speed of drinking, and the BAC reached.

3 | BLOOD-ALCOHOL CONCENTRATION

A quantitative dose-effect relationship exists between a person's BAC and the pharmacological effects produced, as reflected in behavioral changes and reduced cognition and impairment of psychomotor performance (Kalant, 1996). The route of administration of ethanol in forensic casework is usually by mouth (peroral), although aqueous solutions can also be given intravenously or rectally leading to inebriation and drunkenness. After rapid drinking on an empty stomach, the BAC is higher and occurs earlier compared with drinking the same dose more slowly over longer times or after eating a meal (Jones & Jonsson, 1994b; Jones, Jonsson, & Neri, 1991).

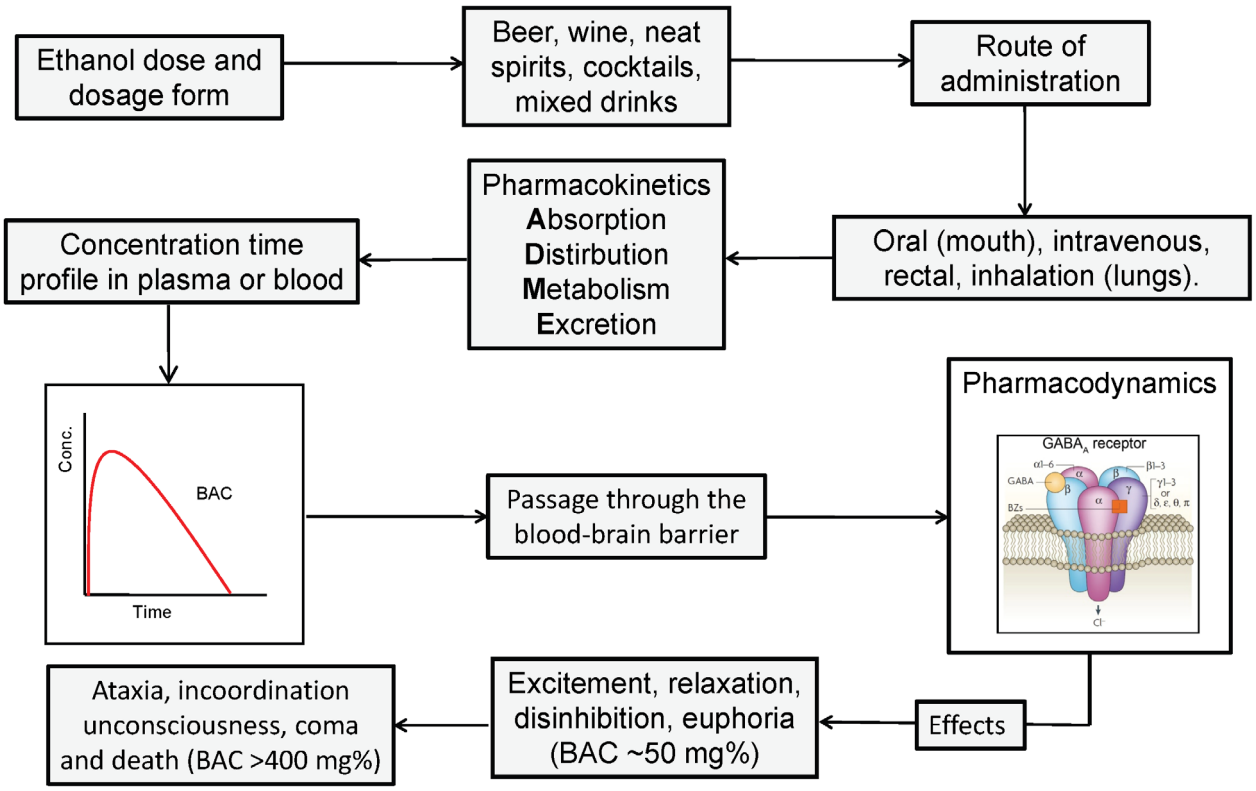

FIGURE 1 Schematic block diagram depicting the disposition and fate of ethanol in the body, resulting in a BAC profile and impacting on cerebral functions causing impairment

3.1 | Endogenous ethanol

Trace amounts of ethanol are produced naturally in the body, by fermentation of carbohydrates in the gut or as a result of biochemical reactions associated with intermediary metabolism, often involving acetaldehyde as a precursor (Ostrovsky, 1986). Sensitive analytical methods reveal that the concentrations of endogenous ethanol in peripheral blood are normally very low of the order of 1 mg/L or 0.001 g/L (0.1 mg%) (Sprung, Bonte, Rudell, Domke, & Frauenrath, 1981; Walker & Curry, 1966). The concentrations of endogenous ethanol in blood are not much different in people with metabolic disturbances, such as Type I diabetes mellitus (Simic, Ajdukovic, Veselinovic, Mitrovic, & Djurendic-Brenesel, 2012).

In people suffering from yeast infections in the gastrointestinal tract, such as a proliferation of *Candida albicans*, the concentrations of endogenous ethanol in portal venous blood might be higher than expected, especially after eating carbohydrate-rich meals (Kaji et al., 1984; Logan & Jones, 2000). However, the portal blood has to flow through the liver before reaching the systemic circulation and hepatic alcohol dehydrogenase (ADH) enzymes are effective in clearing low concentrations of ethanol by first-pass metabolism (FPM) (Ammon, Schafer, Hofmann, & Klotz, 1996).

Ethanol is produced endogenously via reduction of acetaldehyde, generated from pyruvate during microbiological and fermentation processes. Many people of Asian descent, such as Chinese and Japanese, lack an effective hepatic low *Km* mitochondrial aldehyde dehydrogenase (ALDH) enzyme, owing to enzyme polymorphism (Agarwal, 2001). Accordingly, these individuals have a deficit capacity to metabolize the acetaldehyde formed during hepatic oxidation of ethanol and concentrations of the toxic metabolite in blood are higher than normal causing adverse effects (Mizoi et al., 1989).

Accordingly, people of Asian decent are more prone to acetaldehyde toxicity than Caucasians and tend to flush in the face after a single drink, they experience nausea, tachycardia, and other unpleasant sensations depending on their ability to metabolize acetaldehyde (Agarwal & Goedde, 1986). This phenomenon is not unlike the reaction caused when a person treated with the alcohol-sensitizing drug disulfiram (Antabuse) drinks alcohol, which works by blocking the action of hepatic ALDH (Kitson, 1977; Koppaka et al., 2012).

4 | ALCOHOLIC BEVERAGES

The three main alcoholic beverages are beers, wines, and spirits, and these differ in the amount of ethanol they contain, which is reflected in their % v/v or % alcohol by volume (ABV). This differs by a factor of about 10 with liquor drinks being 35–45% ABV, table wines 8–12% ABV and beers 3–9% ABV. When forensic BAC calculations are made the % ABV needs to be expressed as % w/v (g/100 mL) so that the number of grams of ethanol consumed and the dose in g/kg body weight can be calculated. Ethanol content in % ABV is converted into percent by weight by multiplying % ABV with the density of ethanol, which is 0.789 g/mL at 20°C.

Table 1 shows the amounts of ethanol contained in beers, wines, and spirits as % ABV and g/100 mL. The number of grams of ethanol consumed will depend on the volume the drink and this might differ between drinking establishments depending on the country (Wansink & van Ittersum, 2005). The notion of a "standard drink" is often discussed but this also differs between countries and in the United States corresponds to 14 g ethanol, whereas in the United Kingdom one unit of alcohol contains 8 g ethanol (Ferner & Chambers, 2001). The last column of Table 1 contains the number of grams of ethanol in one bottle of beer (330 mL), table wine (750 mL), or bottle of liquor (750 mL).

A simple calculation shows that if a person drinks two bottles of 5% ABV beer (2 × 330 mL) and one bottle of 12% ABV table wine (750 mL), this corresponds to an intake of (2 × 13 g) or 26 g ethanol from beer and 71 g from wine. This amounts to 97 g of pure ethanol or a dose of 1.21 g/kg for a man weighing 80 kg, which is important information when BAC calculations are made.

5 | FATE OF ALCOHOL IN THE BODY

The BAC reached after drinking an alcoholic beverage depends on an interplay between a number of biochemical and physiological processes, which are discussed in more detail below (see Boxes 1 and 2). Ethanol is one of the few drugs that gets absorbed into the blood through the gastric mucosa, although its rate of uptake into the portal venous blood occurs faster when the stomach contents empty into the duodenum and jejunum.

Factors influencing gastric emptying are therefore important considerations when the rate of absorption and time of reaching peak BAC are considered. In pharmacokinetics, the highest BAC for a given dose is denoted C_{max} and the time of its occurrence as t_{max} and these parameters determine the intensity of the pharmacological effects of ethanol ingested. The speed

TABLE 1 Relationships between the alcohol content of different beverages (% v/v or % ABV) and the corresponding weight percent (g/100 mL or % w/v) and the amount of ethanol contained in a typical serving of the drink and in one normal size bottle of the same beverage

Beverage type	Ethanol conc. % ABV[a]	Ethanol conc. in % w/v[b]	Volume (mL) of typical drink[c]	Ethanol (g) per drink	Ethanol (g) in one bottle[d]
Beers	3	2.4	500[b]	12.0	7.9
	4	3.2		16.0	10.6
	5	4.0		20.0	13.2
	6	4.7		23.5	15.6
Table wines	9	7.1	150	10.6	53.3
	10	7.9		11.9	59.2
	12	9.5		14.2	77.3
Fortified wines (sherry, port)	16	12.6	100	12.6	94.5
	18	14.2		14.2	106.5
	20	15.8		15.8	118.5
Spirits (whisky, gin, vodka, brandy)	35	27.6	25	6.9	201.0
	40	31.6		7.9	231.0
	45	35.6		8.9	267.0

[a]% ABV = percentage alcohol by volume.
[b]% v/v x 0.79 (density of ethanol) = g% (w/v).
[c]In the United Kingdom, one pint of beer = 568 mL.
[d]Beer (330 mL), wine (750 mL), spirits (750 mL).

BOX 1 The pathway of drugs in the body

Absorption. This refers to the uptake of alcohol or other drugs into the bloodstream by different routes of administration, although in forensic casework people drink alcohol, hence absorption takes place from the gastrointestinal tract.
Distribution. Transport of absorbed ethanol with the blood throughout the all body fluids and tissues in proportion to their water content. Rate of equilibration depends on ratio of blood flow to mass of the tissue concerned. Ethanol does not bind to plasma proteins or other biomolecules and easily crosses the blood–brain barrier to cause impairment of brain functioning.
Metabolism. This refers to the breakdown or biotransformation of ethanol into its metabolites (acetaldehyde and acetic acid), by oxidative enzymes mainly located in the liver. Between 90 and 98% of the dose of ethanol ingested is metabolism and the remainder excreted unchanged.
Excretion. The main routes of ethanol excretion are in breath, sweat, and urine, although altogether this amounts of less than 10% of the dose ingested.
Bioavailability. Is defined as the fraction (F) of dose of the drug, often expressed in percent, that reaches the systemic circulation in unchanged form. Bioavailability is 100% when administered by intravenous infusion.
First-pass metabolism. This refers to disposal (metabolism) of some fraction of the dose of an administered drug before it reaches the systemic circulation. For an orally administered drug, this presystemic metabolism occurs by enzymes located in the gut and/or liver.

of drinking and the nature of the drink, such as its ethanol and carbohydrate content, also impact on rate of absorption of ethanol into the bloodstream (Mitchell Jr., Teigen, & Ramchandani, 2014).

During the time ethanol is being consumed and for some time afterwards, absorption is the dominant physiological process and BAC rises until a maximum concentration in blood is reached (C_{max}). The results from many controlled drinking experiments show that C_{max} usually occurs between 10 and 60 min after the end of drinking. But in any individual case t_{max} might

BOX 2 Important elements of drug disposition

Pharmacokinetics. A word derived by combining two Greek words *pharmacon* (drug or poison) and *kinesis* (movement), which entails an evaluation of the concentration-time (C-T) profile of a drug in blood or plasma in mathematical terms.

Pharmacodynamics. Derived from the Greek words *pharmacon* (drug or poison) and *dynamikos* (force or power), and which is concerned with the actions or therapeutic effects of drugs on the body in relation to the dose and route of administration.

Pharmacogenetics. From the Greek word for drug (*pharmacon)* and genetics (origin), a subject that deals role of person's genes and inheritance on drug response. Pharmacogenetics entails studies of racial, ethnic, and genetic factors and how these influence the therapeutic action of drugs including variability in pharmacokinetic and pharmacodynamics response.

Zero-order kinetics. Zero-order kinetics implies that a constant amount of a drug, such as ethanol, is eliminated from the blood (g/L/h) or entire body (g/kg/h) per unit time. The blood-concentration time profile during the elimination phase is linear.

First-order kinetics. For drugs that follow a first-order kinetics, a constant proportion is eliminated from the blood or the entire body per unit time. The higher the concentration (or amount) of drug present the faster is the rate of elimination.

Volume of distribution. Usually denoted V_d refers to a theoretical volume of fluid in which the drug is distributed to give the same concentration as in a reference compartment, usually blood, plasma, or serum. V_d is calculated as ratio of the amount of drug in the body (the dose in g/kg) to the concentration in blood (g/L). V_d is expressed in liters (L) of fluid or L/kg, although these do not correspond to any particular anatomical space in the body.

be as short as 10 min, if gastric emptying is rapid, or as long as 120 min when absorption is slow, such as after a pyloric spasm (Jones, 1991).

Absorption rate of ethanol is a first-order kinetic process, which means its rate is proportional to the concentration or amount of ethanol in the stomach. As the concentration in gastric contents decreases, the rate of absorption slows down and eventually becomes equal to the rate of ethanol metabolism (~10–30 mg% per hour). At this point, the BAC reaches a maximum point and at later times a declining phase starts or there might be a BAC plateau for some time afterwards. Provided no additional ethanol is consumed, the BAC will start to decrease as ethanol is eliminated from the body. Under some circumstances, such as when alcohol is consumed with food, the BAC remains more or less constant (a plateau) for several hours (Jones & Neri, 1991). This signifies that absorption of residual alcohol into the bloodstream is occurring at the same rate as ethanol is being metabolized in the liver, with the result that the BAC remains more or less constant.

When BAC exceeds 15–20 mg%, the oxidative enzyme mainly responsible for metabolism of ethanol, ADH, is saturated with substrate and is working at its full capacity, hence existence of zero-order kinetics (Wilkinson, 1980). This contrasts with the metabolism and pharmacokinetics of most other drugs, which are eliminated by first-order kinetics. For zero-order processes, the concentration of a substance in blood decreases by a constant amount per unit time, whereas in first-order processes, the rate of decline is proportional to concentration and a constant percentage is eliminated per unit time (Rowland & Tozer, 1995).

Figure 2 illustrates the disposition and fate of ethanol in the body, the relative amounts metabolized, excreted unchanged, and pathways of non-oxidative metabolism.

5.1 | Absorption

Absorption is the process by which a drug passes from the site of administration into the blood stream for transport throughout all body fluids and tissues. Alcohol (ethanol) is a small uncharged molecule that easily crosses biological membranes by passive diffusion process, depending on the concentration gradient (Berggren & Goldberg, 1940). Small amounts of ethanol can be absorbed into the blood through the mucous surfaces of the oral cavity if an alcoholic drink is held in the mouth for sufficiently long time without swallowing any.

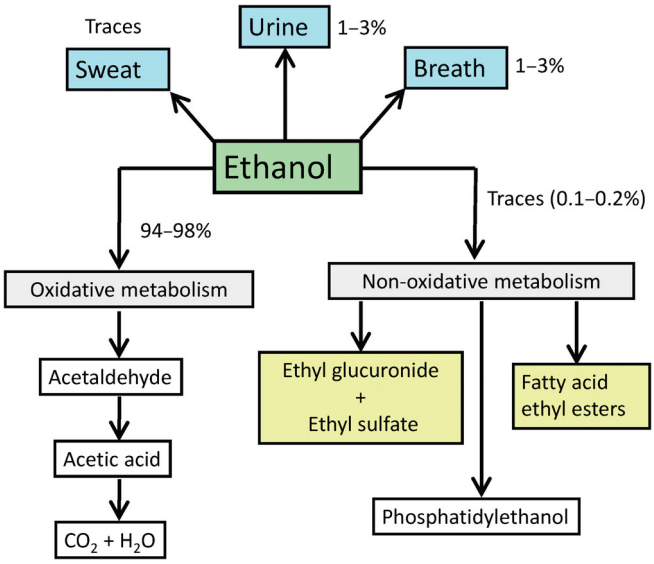

FIGURE 2 The metabolism and excretion of ethanol in the body showing the approximate amount eliminated by oxidative and nonoxidative pathways and in the exhaled breath, urine, and sweat

The rate of absorption of ethanol is faster when contents of the stomach enter the duodenum and jejunum, owing to the larger absorption surface area provided by the villi and microvilli of the small intestines. Emptying of the stomach is controlled by the pyloric sphincter, which normally is almost totally closed, owing to tonic contraction of the pyloric muscle. Drinking alcohol together with or after a meal delays gastric emptying and absorption into the blood is slower leading to a lower C_{max} and a later occurring t_{max} compared with drinking on an empty stomach (Jones & Jonsson, 1994b). In this connection, the amount of food ingested is seemingly more important than its composition in terms of fat, protein, or carbohydrate content (Jones, Jonsson, & Kechagias, 1997).

In any given individual case, the rate of absorption of ethanol is unpredictable, which makes it difficult to make a definite statement about the C_{max} and t_{max} reached after drinking a defined amount of alcohol. However, based on results from hundreds of controlled drinking experiments and evaluation of blood-alcohol curves, some general guidelines can be given as shown in Table 2.

TABLE 2 Some factors influencing the blood-alcohol concentration (BAC) or C_{max} reached after consumption of a given dose of ethanol and possible mechanism/explanation

Variable or drinking conditions	Possible mechanism and/or explanation	Anticipated effect on the person's BAC
People with low body weight	Less body water	Higher BAC
Appreciable adiposity, high BMI[a]	More fat and less body water	Higher BAC
Female gender	Lower V_d and less body water	Higher BAC
Rapid drinking versus slower ingestion	Faster absorption	Higher BAC
Drinking on empty stomach	Rapid gastric emptying	Higher BAC
Drinking together with or after a meal	Delayed gastric emptying	Lower BAC
High ethanol content in the drinks consumed, for example, spirits versus beer	Faster absorption	Higher BAC
Low or restricted liver blood flow	Slower metabolism	Higher BAC
Smoking cigarettes	Delayed gastric emptying	Lower BAC
Drugs that active pyloric sphincter	Rapid gastric emptying, absorption	Higher BAC
Drugs that delay gastric emptying	Slower absorption	Lower BAC
Gastric bypass surgery	Faster absorption	Higher BAC

[a]BMI = body mass index kg/m^2.

5.2 | Distribution

After its absorption into the portal venous blood, ethanol reaches the liver and passes through the hepatic vein on to the heart, before entering the lungs, passing back to the heart and then being pumped throughout the entire systemic circulation and intra- and extracellular fluids.

The equilibration of ethanol between blood and the extravascular fluids and tissue depends on the cross-sectional area of the local capillary bed and the blood flow per gram of tissue (Kalant, 1996). Organs and tissues with a high rate of blood flow per gram tissue, such as brain, liver, and kidney rapidly equilibrate with the concentration of ethanol in the arterial blood. This contrasts with the bulky skeletal muscles, which take a longer time to equilibrate and during the absorption phase concentrations of ethanol in arterial blood are higher than in venous blood and the difference is especially marked when a bolus dose is ingested on an empty stomach (Jones, Lindberg, & Olsson, 2004).

Ethanol distributes into the total body water (TBW) compartment, which represents between 50 and 60% of body weight or 43–51 L for a person weighing 85 kg (Endres & Gruner, 1994). After ethanol is completely equilibrated in all body fluids and tissues, the concentrations are higher in biofluids with most water, which means sweat, saliva, and urine contain higher concentrations than blood, serum, or plasma (Jones, Hahn, & Stalberg, 1992). Evidence that ethanol distributes into the water compartment of the body comes from experiments in which TBW was determined by isotope dilution using $^{2}H_2O$ and $^{3}H_2O$ and H_2O^{16} as tracers in comparison with ethanol dilution (Endres & Gruner, 1994).

Leaner individuals with heavier body weights have more water to dilute ingested ethanol and therefore they reach a lower BAC compared with lighter individuals after the same dose/kg of ethanol is administered. During aging, especially in men, muscle mass decreases and fatty tissue increases resulting in less TBW per kg of body weight. Accordingly, elderly men >60 years have less TBW to dilute ingested ethanol, which explains why they reach higher BAC for the same ethanol dose per kg ingested compared with younger men (Jones & Neri, 1985).

There are statistically significant differences between men and women in regard to their TBW. Women are generally smaller than men, they are shorter and have lower body weight, and also more fatty tissue. For a water soluble drug like ethanol, its distribution volume (V_d) is influenced by a person's age and gender, with lower values observed in women and in elderly men. Table 3 makes a comparison of ethanol V_d determined for healthy male and female subjects in controlled drinking experiments (Maskell et al., 2019). The average V_d was 0.69 L/kg for men compared with 0.60 L/kg for women, which suggests that after drinking the same dose/kg of ethanol females achieve a roughly 15% higher peak BAC than males.

5.3 | Metabolism

The metabolism of ethanol and other drugs occurs primarily in the liver by the action of various biochemical processes and enzymatic activity (Zakhari, 2006). Unlike other psychoactive drugs, during the metabolism of ethanol energy is produced, actually 7.1 kcal per gram, which is more than that from proteins and carbohydrates (4 kcal/g), but less than from fat catabolism (9 kcal/g) (Lieber, 1991b).

The principal metabolizing enzyme is alcohol dehydrogenase (Class I ADH), which is located in the cytosol fraction of liver cells (hepatocytes) and converts ethanol into acetaldehyde, which is more toxic than the parent drug. Luckily, acetaldehyde is rapidly oxidized further to acetic acid by low k_m ALDH, located in the mitochondria. The acetate produced during the metabolism of ethanol leaves the liver and enters the Krebs cycle and gets converted into CO_2 and H_2O in peripheral organs and tissues (Lieber, 1991a).

During ethanol oxidation by ADH, the coenzyme nicotinamide adenine dinucleotide (NAD^+) is reduced to NADH, which raises the NADH/NAD^+ ratio in hepatocytes. This altered redox state of the liver disturbs other NAD-dependent metabolic reactions. Accordingly, the lactate/pyruvate ratio increases causing a lactic acidosis, which indirectly is responsible for the clinical condition of gout (Lieber, 1997).

TABLE 3 The mean and range of ethanol distribution volumes (Widmark rho-factors) for healthy men and women derived from controlled drinking experiments (Maskell, Jones, Savage, & Scott-Ham, 2019). The mean ± *SD* for V_d L/kg and age, body weight, and height of the subjects are shown

Gender	*N*	Age, years	Weight, kg	Height, cm	Mean V_d or rho-factor, L/kg	Min and max values of V_d or rho-factor
Males	173	33 ± 10.8	75 ± 11.6	177 ± 7.1	0.69 ± 0.086	0.43–0.94
Females	63	35 ± 14.1	64 ± 14.9	164 ± 6.7	0.60 ± 0.100	0.39–0.86

The K_m of the class I isozymes of ADH is only 5–10 mg% for ethanol as substrate, which means that it is saturated at all BAC >15–20 mg% ($2 \times k_m$), hence zero-order kinetics. Another form of the ADH enzyme (class IV) is located in the gastric mucosa and is thought to contribute to first-pass metabolism (FPM) of ethanol causing a reduced bioavailability of the dose (Parlesak, Billinger, Bode, & Bode, 2002). However, there are differences of opinion whether FPM of ethanol is predominantly gastric or hepatic and this question has not been fully resolved (Ramchandani, Bosron, & Li, 2001).

Another hepatic enzyme involved in ethanol metabolism is located in smooth endoplasmic reticulum, particularly the microsomal fraction. Microsomal enzymes constitute a large family of proteins, known as cytochrome P450 monooxygenases, which are responsible for the metabolism of many drugs and xenobiotics, including industrial solvents and pharmaceutical agents (Guengerich, 2006).

The particular form of the P450 enzyme involved in ethanol metabolism to acetaldehyde is denoted CYP2E1, which has a Michaelis constant (K_m) of 60–80 mg/100 mL, being appreciably higher than the K_m of Class I ADH (Tanaka, Terada, & Misawa, 2000). Accordingly, CYP2E1 plays a more important role in the oxidation and clearance of ethanol from the body after heavy drinking when high BACs are reached.

$$CH_3CH_2OH + NADPH + H^+ + O_2 \xrightarrow{CYP2E1} CH_3CHO + NADP^+ + 2H_2O.$$

Another property of CYP2E1, besides its higher K_m is the fact that after heavy binge drinking (for weeks or months) enzyme activity increases, making it more effective in oxidative metabolism of ethanol (Tsutsumi, Lasker, Takahashi, & Lieber, 1993). This enzyme induction is the mechanism proposed to explain faster clearance of ethanol from blood in heavy drinkers and alcoholics. However, their enhanced capacity to metabolize ethanol disappears when they stop drinking and remain abstinent for several days (Keiding et al., 1983).

CYP2E1 is also responsible for some undesirable drug-alcohol interactions (Lieber, 1994b), such as with the antipyretic paracetamol (acetaminophen or Tylenol®). This medication is mainly metabolized by conjugation reactions, but a small amount is oxidized by CYP2E1 to highly reactive intermediates. This becomes a clinical problem if and when alcoholics and heavy drinkers have an induced CYP2E1 activity and medicate with paracetamol, which increases the risk for hepatoxicity and tissue necrosis (Prescott, 2000).

A third liver enzyme system, catalase located within the peroxisomes might theoretically oxidize ethanol at least under in vitro conditions. However, its role in vivo is questionable, because of the lack of hydrogen peroxide necessary for the reaction to proceed. For all practical purposes, ADH and CYP2E1 are the oxidative enzymes responsible for hepatic metabolism of ethanol in man (Zakhari, 2006).

Figure 3 depicts the oxidative metabolism of ethanol and methanol, which involves the same two hepatic enzymes ADH and ALDH (Roe, 1982). These two aliphatic alcohols compete for binding sites on ADH, which has a higher affinity for ethanol as substrate. Accordingly, at elevated BAC oxidation of methanol is blocked and formation of its toxic metabolites prevented. The first-aid treatment of patients poisoned with methanol is to administer ethanol solutions intravenously to reach

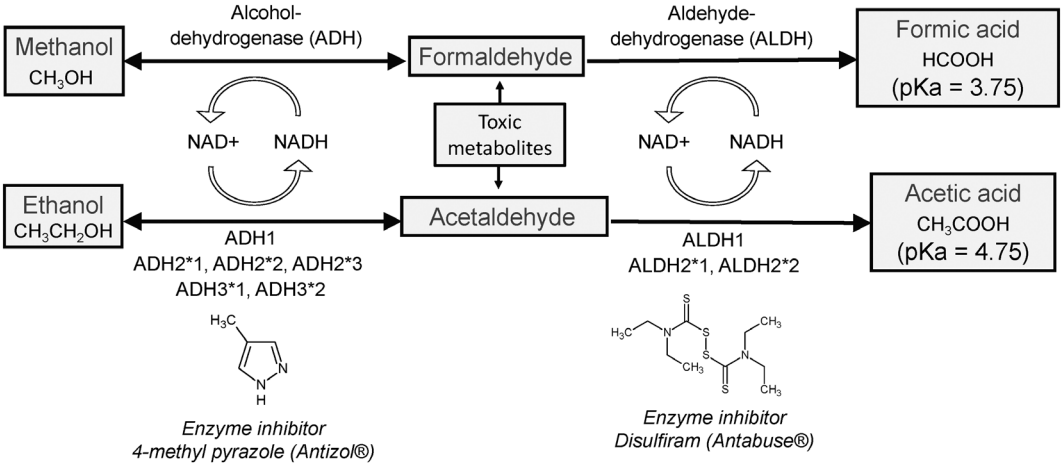

FIGURE 3 Comparison of the metabolism of ethanol and methanol in the liver by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) enzymes into more toxic metabolites, acetaldehyde and formaldehyde. Also shown are the chemical structures of the enzyme inhibitors 4-methyl pyrazole (ADH) and disulfiram (ALDH)

BAC of 100–120 mg% (McMartin, Jacobsen, & Hovda, 2016). After blocking the oxidation by competitive enzyme inhibition, methanol and its toxic metabolites can be removed from the bloodstream by dialysis.

Also shown in Figure 2 are the chemical structure of two enzyme inhibitors, 4-methyl pyrazole (fomepizole or Antizol®) in the case of ADH and disulfiram (Antabuse®) in the case of ALDH. A metabolic interaction between ethanol and various H_2-antagonist drugs such as cimetidine and ranitidine was suggested when it was found that these substances blocked the activity of ADH located in the gastric mucosa (Lim Jr. et al., 1993). If this happened FPM would be prevented leading to higher BAC than expected after an oral dose, perhaps with clinical and forensic implications. However, research on this topic became highly controversial with proponents for and against there being a significant FPM of ethanol by gastric ADH (Crabb, 1997; Levitt, 1993). Much seemed to depend on the fed-fasted sate of the individual and the dose of ethanol ingested, with FPM being more significant after small doses (0.15–0.30 g/kg) and in the postprandial state after breakfast (Oneta et al., 1998). The literature dealing with FPM of ethanol caused by H_2-receptor antagonists was recently reviewed and called for further studies (Moody, 2018).

5.4 | Excretion

Most of the ethanol a person drinks (95–98%) is removed from the body by oxidative metabolism and less than 10% is eliminated unchanged by excretion via the lungs, the kidneys, and skin. After moderate drinking, 2–5% of the dose of ethanol can be recovered by analysis of urine, exhaled air, and sweat. These body fluids are often analyzed in forensic toxicology as proof a person has consumed alcohol in situations when, for some reason, they are required to remain abstinent (Marques & McKnight, 2009). When subjects drank 0.54, 0.68, or 0.85 g/kg as neat whisky, urine samples collected during 7 hr contained 0.70, 0.80, and 1.55% of the dose administered (Jones, 1990). In these experiments, the maximum BAC reached was 120 mg %, so these percentages of the dose excreted are expected to be higher on reaching higher BAC as expected for first-order urinary excretion of ethanol.

5.5 | Nonoxidative metabolites

A small fraction (<0.2%) of the dose of ethanol a person drinks undergoes conjugation reactions in the liver to produce ethyl glucuronide (EtG) and ethyl sulfate (EtS), which are the major nonoxidative metabolites (Palmer, 2009). The pharmacokinetic profiles of EtG and ethanol in blood are different in several respects (Halter, Dresen, Auwaerter, Wurst, & Weinmann, 2008). For example, the EtG curve in blood rises more slowly than the BAC and reaches a peak concentration in blood 1–2 hr later than the ethanol peak. The EtG and ethanol curves are shifted in time and the EtG concentration in blood is about 1,000 times lower than the concentration of ethanol. EtG is also eliminated from the body more slowly and is detectable in blood and urine for several hours longer than ethanol, which means that analysis of EtG is useful to disclose recent drinking in different clinical and forensic situations (Hoiseth et al., 2007).

After gas chromatography-mass spectrometry methods were introduced for analysis of EtG and EtS in blood, urine, and hair strands, a number of forensic applications have emerged (Schmitt, Aderjan, Keller, & Wu, 1995). These metabolites are used as biomarkers for recent drinking and to control abstinence in people expected to refrain from drinking, because of their employment (safety-sensitive work) or participation in treatment programs for alcohol abuse (Walsham & Sherwood, 2012).

In postmortem (PM) toxicology, the analysis of EtG in blood and urine can help in differentiation between ethanol that might be produced after death from antemortem ingestion (Hoiseth et al., 2007). In this connection, there appears to be some advantages of analyzing EtS metabolite as a biomarker of recent drinking and whether postmortem synthesis of ethanol has occurred (Helander & Beck, 2005; Krabseth, Morland, & Hoiseth, 2014). Another method to test the origin of PM ethanol is to determine the ratio of two metabolites of serotonin, the 5-HTOL/5-HIAA ratio as described elsewhere (Helander, Beck, & Jones, 1995).

Other nonoxidative metabolites of ethanol include various fatty acid ethyl esters (FAEE) and phosphatidylethanol (PEth), both of which have found applications in clinical medicine as biomarkers of heavy drinking (Staufer & Yegles, 2016).

6 | PHARMACOKINETIC CALCULATIONS

The two most important pharmacokinetic parameters of ethanol are (a) rate of disappearance from the blood (β-slope) and (b) distribution volume in the body (V_d). The latter is often referred to as the Widmark rho-factor, a term first coined by Erik MP Widmark a pioneer in the development of ethanol pharmacokinetics in the 1930s (Andreasson & Jones, 1996). The rate of

ethanol elimination from blood is derived from the slope of the linear declining phase of the BAC curve in the postabsorptive state when zero-order kinetics operate.

From the results of hundreds of controlled alcohol dosing studies in healthy subjects, average values for the rho-factor or V_d were 0.69 L/kg for men and 0.60 L/kg for women (Maskell et al., 2019). An evidenced-based review of rates of ethanol elimination from blood, showed a range from 10 to 35 mg% per hour (Jones, 2010) with highest rates observed in alcoholics during detoxification and also in some drunken drivers, owing to enzyme induction and contribution of the CYP2E1 pathway.

6.1 | Blood alcohol curves

The fate of ethanol in the body is usually depicted by a graph plotting BAC on the y-axis and time of blood sampling on the x-axis (see Figures 4 and 5). These BAC profiles are evaluated in a quantitative way by defining a set of pharmacokinetic parameters including the β-slope and the volume of distribution (V_d) or rho-factor.

Hundreds of controlled drinking experiments have been published providing a wealth of information about the pharmacokinetics of ethanol and the factors influencing ADME processes (Jones, 2011). The ethanol dose administered in laboratory studies is usually limited to about 1.0 g/kg when this is ingested as a bolus dose on an empty stomach. The consumption of larger doses in a short time on an empty stomach leads to nausea and vomiting.

Administering small doses of ethanol <0.30 g/kg is not recommended because of the relative short duration of the post-absorptive phase. This makes it difficult to calculate the slope of the declining part of the C-T profile in a reliable way.

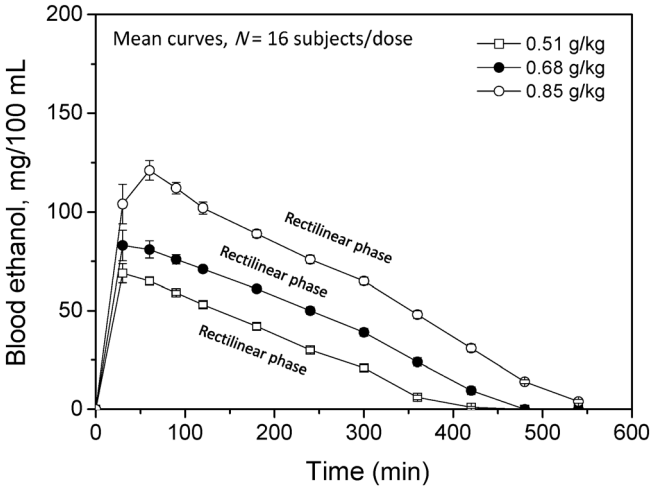

FIGURE 4 Concentration-time profiles of ethanol in blood after three doses of ethanol were consumed on an empty stomach in 15–25 min. Average curves are shown for $N = 16$ subjects ingesting each dose of ethanol. The rectilinear descending phase is marked for each dose of ethanol

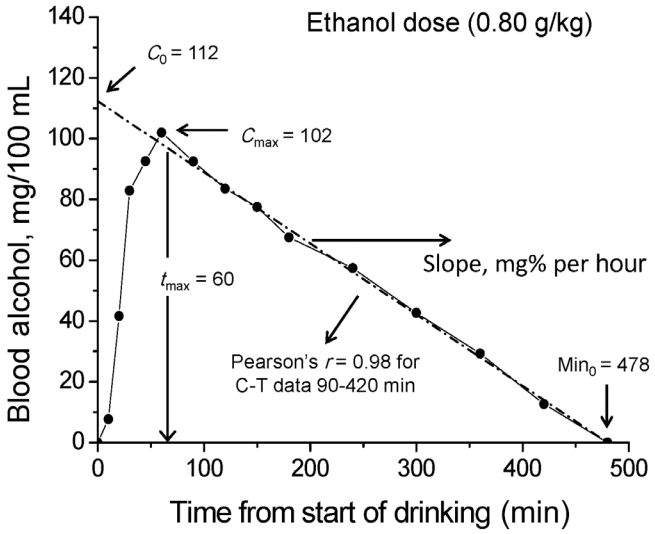

FIGURE 5 Concentration-time profile of ethanol in blood for one subject who drank 0.80 g/kg body weight in 30 min after an overnight fast. The method used to derive the β-slope or zero-order elimination rate is shown as the gradient of the rectilinear descending phase

Furthermore after drinking such low doses of ethanol, the maximum BAC is insufficient to ensure that ethanol metabolizing enzymes (ADH) are saturated with substrate.

Examples of mean BAC profiles generated in experiments with $N = 16$ subjects after they drank 0.54, 0.68, and 0.85 g/kg ethanol on an empty stomach are shown in Figure 4. Ethanol was consumed as neat whisky in a drinking time of 15–25 min (Jones, 2011). These drinking conditions favor rapid gastric empting and faster absorption of ethanol into the bloodstream. The rectilinear elimination portions are indicated on the graph and the slopes of these declining phase of the BAC curves represent the rate of elimination from blood.

The C-T profiles shown in Figure 4 share certain characteristics. They begin with a rapid rising portion (absorption) eventually reaching a C_{max} before this changes to a steady declining phase which shows BAC decreasing at a constant rate per unit time (zero-order kinetics). A linear elimination phase is evident for the three doses of ethanol and this persists for longer after the higher doses of ethanol were consumed.

6.2 | Zero-order kinetics

Figure 5 shows a typical BAC profile from a controlled drinking experiment with a male subject who consumed a dose of 0.80 g/kg ethanol on an empty stomach in 30 min. This C-T plot can be evaluated in a quantitative way by defining certain parameters or summary measures that defines and delineates the shape of the curve (Jones, 1984).

The starting point is to select blood samples on the postabsorptive declining part of the curve and then draw the best fitting straight line through these points. This line is then extrapolated back to intersect the y-axis and forward to intersect the x-axis as shown in Figure 5. The y-intercept corresponds to the parameter C_0 which is the theoretically expected BAC if the dose of ethanol had been absorbed and distributed in all body fluids and tissues without any metabolism occurring. The x-intercept is the time necessary to eliminate alcohol from the bloodstream neglecting the curvilinear part of the curve starting at very low BAC (<5–10 mg%).

The slope of the rectilinear declining phase is calculated as $C_0/\min_0$ or by linear regression analysis of C-T data points to give the rate of elimination of ethanol from blood, which is usually multiplied by 60 to express this rate of decrease in BAC per hour.

The distribution volume (V_d) of ethanol is calculated as the ratio of dose (g/kg) divided by the y-intercept (C_0) shown in Figure 5. The units of V_d are L/kg if BAC is expressed as w/v units (g/L or mg%), otherwise V_d is a dimensionless ratio if mass/mass units (g/kg) are used to report BAC.

Because ethanol absorption occurs from both the stomach and intestine, but at different rates, this makes the mathematical modeling of C-T points on the rising portion of the BAC curve impractical in most cases. A more pragmatic way to determine rate of absorption is simply to divide C_{max} by the time needed to reach C_{max} which is usually denoted as t_{max} expressed in units of mg% per hour. A limitation with this simple method is that blood samples in PK studies are usually taken every 15–30 min so if the peak BAC (C_{max}) happened to be reached between two sampling times, neither the actual peak value nor its time of occurrence are known with certainty.

Ethanol is cleared from the body at a constant rate per unit time independent of the prevailing BAC as expected for zero-order kinetics ($-dC/dt = k_0$) where k_0 is the zero-order rate constant. This contrasts with the pharmacokinetics of most other drugs, which obey first-order kinetics ($-dC/dt = k_1C$), and the elimination rate is directly proportional to drug concentration. A constant percentage of the drug is eliminated from the blood per unit time and this is best characterized by its half-life, time necessary to lower the concentration by 50% (Rowland & Tozer, 1995).

6.3 | Applications of the Widmark equation

The zero-order kinetics model for ethanol is appropriate for most of the questions arising in forensic science and legal medicine, although below a BAC of 5–10 mg% the metabolizing enzymes are no longer saturated with substrate and first-order kinetics apply. The shape of the entire postabsorptive phase of the BAC curve therefore looks more like a hockey stick rather than a straight line (see later). In forensic casework, it is rarely necessary to consider BAC under 20 mg% ($2 \times K_m$) when analytical results are interpreted, making it safe to assume zero-order kinetics (Zhang, Wu, & Wan, 2017).

In BAC calculations requested in forensic casework, realistic values for the distribution volume V_d and the rate of elimination rate from blood (β-slope or k_0) are necessary. The person's body weight is given in kg and the amount of ethanol consumed in grams (A), where A/kg is the dose of ethanol and BAC is the concentration in blood in mass/volume units (g/L).

A mathematical equation representing the declining part of the postabsorptive phase of the BAC curve is given by Equation (1):

$$\mathrm{BAC}_t = \mathrm{BAC}_0 - \beta \times t, \tag{1}$$

where BAC_t is the concentration in blood at time t somewhere on the linear declining phase of the curve and BAC_0 is the theoretical concentration in blood extrapolated back to the time of starting to drink (C_0). The linear declining phase has a slope denoted as β or sometimes written as k_0 where the subscript zero indicates zero-order kinetics.

Equation (2) can be rearranged to estimate the BAC existing at an earlier time provided both samples of blood were taken on the postabsorptive portion of the curve:

$$\mathrm{BAC}_1 = \mathrm{BAC}_2 + \beta \times (t_2 - t_1). \tag{2}$$

Similarly, an equation can be derived to calculate how long it takes for a measured BAC to drop below some threshold value, such as 50 mg% as shown in Equation (3).

$$\mathrm{Time\ (hours)} = [\mathrm{BAC}_t - 50]/\beta, \tag{3}$$

where BAC_t is the measured BAC at time t and β is the elimination rate of ethanol from blood per hour for that person, such as 15 mg% per hour.

The rho-factor or distribution volume of ethanol (V_d) is the concentration of ethanol in the body expressed in relation to some reference compartment, such the bloodstream and is derived from Equations (4a) and (4b) where C_0 is the theoretical BAC extrapolated back to the time of starting to drink, kg is the person's body weight, A is grams of ethanol in all body fluids and [A/kg] is the dose.

$$V_d = (\text{ethanol conc.in body})/(\text{ethanol conc.in blood}), \tag{4a}$$

$$V_d = \mathrm{dose}\ (A/\mathrm{kg})/C_0 = A/(\mathrm{kg} \times C_0). \tag{4b}$$

Rearrangement of the above equation gives:

$$A\ (\mathrm{g}) = C_0\ (\mathrm{BAC\ g/L}) \times \mathrm{body\ weight\ (kg)} \times V_d\ (\mathrm{L/kg}). \tag{5}$$

Equation (5) is often referred to as the Widmark equation and forms the basis of many of the BAC calculations required in forensic casework. Note that if the blood sample was taken too soon after the end of drinking when some of the ingested ethanol was unabsorbed in the stomach, use of Equation (5) would underestimate the amount of ethanol absorbed and distributed in all body fluids.

Equations (1) and (5) are the two basic Widmark equations, and these can be combined in various ways to answer questions arising in forensic science and legal medicine. For example, it might be relevant to calculate a person's BAC a certain number of hours after they started to drink and this can be done using Equation (6).

$$\mathrm{BAC}_t = [A/\mathrm{kg} \times V_d] - (\beta \times t). \tag{6}$$

Here [A/(kg × V_d)] is the same as C_0 or the maximum BAC expected for the amount of ethanol consumed and from this is subtracted the ethanol eliminated by metabolism over t hours at a rate of β (mg% per hour or g/L per hour).

This calculation assumes that the entire dose of ethanol (A/kg) reaches the systemic circulation and that FPM is negligible (100% bioavailability). This assumption is tenuous when people consume alcohol in real-world situations, sometimes with a meal and over longer drinking times. If the dose of alcohol was consumed with or after a meal or over several hours, the bioavailability of ethanol might be appreciably less than 100% (Jones & Jonsson, 1994b; Jones, Wigmore, & House, 2006).

If a blood sample is taken on the postabsorptive phase of the BAC curve (BAC > 15–20 mg%), the result can be used to calculate the total amount of ethanol consumed provided that the time when drinking started is known (Equation (7)). The

oxidative metabolism of ethanol commences immediately after drinking starts, even during the absorption phase. The BAC lost through metabolism is given by the product of $\beta \times t$ where β is the zero-order elimination rate from blood per hour for t hours since drinking started. This amount of ethanol is lost through metabolism and needs to be added to the amount in the body at the time blood was sampled (Equation (7)).

$$\text{Ethanol ingested } A\,(\text{gram}) = \text{kg} \times V_d \times (\text{BAC} + \beta \times t). \tag{7}$$

A slight modification to Equation (7) makes it possible to calculate how much ethanol a person would need to drink to reach a certain BAC (e.g., 0.80 g/L or 80 mg%), for example, 5 hr after the start of drinking (Equation (8)).

$$A\,(\text{gram}) = \text{kg} \times V_d \times (0.8 + \beta \times 5). \tag{8}$$

The V_d or rho-factor for ethanol depends on the person's age, gender, and degree of adiposity (ratio fat to lean tissue). A simple clinical measure of obesity is given by the person's body mass index (BMI); ratio of weight to height squared (kg/m^2). The Widmark-rho-factor and the person's BMI are negatively correlated as shown in a drinking study in people with widely different BMI (Maudens et al., 2014). A recent evidence-based survey of the distribution volumes of ethanol reported average values of 0.69 L/kg for men and 0.60 L/kg for women as shown in Table 3 (Maskell et al., 2019). In any individual case, the rho-factor might vary by a factor of two in the population of drinkers.

During social drinking, it appears that an appreciable amount of ingested ethanol is oxidized in the gastric mucosa or the liver and does not reach the systemic circulation, owing to a FPM (Jones et al., 2006). FPM is also enhanced if small doses of ethanol (<0.3 g/kg) are ingested in the form of beer (Holford, 1997) or when eating and drinking at the same time, such as during a dinner party or dining out with friends (Jones & Neri, 1991).

6.4 | Ethanol elimination in blood from drunken drivers

The elimination rate of ethanol from blood in apprehended drivers has not been determined in an unequivocal with multiple blood samples taken over several hours on the postabsorptive phase of the BAC curve. However, another approach is to take two consecutive blood samples about 60 min apart and calculate the rate of change in BAC per hour. In this calculation, one needs to assume that zero-order kinetics operate and that the person was in the postabsorptive phase at the time that the first blood sample was taken.

$$\text{Elimination rate} = (\text{BAC}_1 - \text{BAC}_2)/\text{time difference}. \tag{9}$$

Figure 6 shows a frequency distribution of elimination rates of ethanol from blood determined in more than 1,000 apprehended drivers using two consecutive blood samples (Jones & Andersson, 1996). The frequency distribution of β-slopes is a good fit to a Gaussian curve with mean and standard deviation (*SD*) of 19 ± 5 mg% per hour and median and 95% range

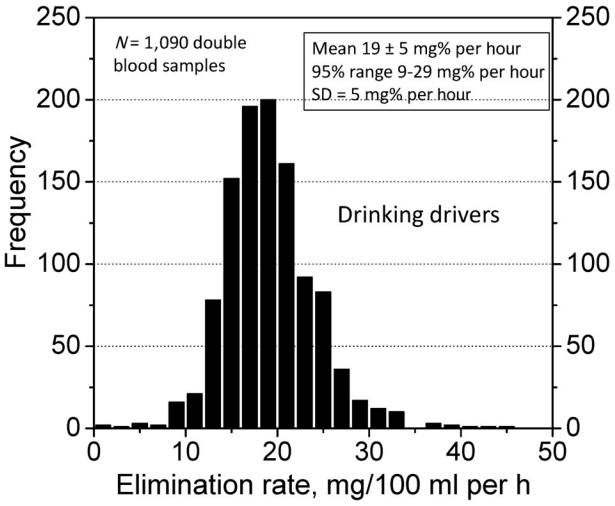

FIGURE 6 Frequency distribution of the rates of ethanol elimination from blood in apprehended drunken drivers in Sweden. These results were derived from the change in BAC between two blood samples taken about 60 min apart. Values under 10 mg% per hour probably reflect those drivers who were not on the post-peak phase when the first blood sample was taken

of 19 mg% per hour and 11 and 31 mg% per hour, respectively. Values less than 10 mg% per hour are unrealistic and probably represent cases where the suspect had consumed alcohol fairly recently and was not in the postabsorption phase when the first blood sample was taken (Neuteboom & Jones, 1990).

Table 4 shows results from an evidence-based survey of ethanol elimination rates from blood based on a review of hundreds of published studies available in the literature (Jones, 2010). These articles were selected if they met certain criteria with regard to experimental design, such as rapid drinking on an empty stomach, moderate ethanol dose, and adequate number of blood samples taken on the postabsorptive phase to allow pharmacokinetic evaluation. The values of the β-factor in Table 4 can be considered representative for the general population of healthy individuals. Also shown are the amounts of ethanol cleared from the whole body for a man with rho-factor 0.70 L/kg and a body weight 70 kg. The experimental conditions or circumstances that might explain the various rates of ethanol elimination are considered.

In apprehended drivers (Figure 6), the average elimination rate of ethanol from blood was 19 mg% per hour, which is slightly higher than 15 mg% per hour observed in moderate drinkers (Hoiseth, Wiik, Kristoffersen, & Morland, 2016). The difference stems from an over-representation of heavy drinkers and alcoholics in the population of drunken drivers, the latter being individuals with an enhanced capacity to metabolize alcohol, via the CYP2E1 pathway (Keiding et al., 1983).

Racial and ethnic differences in rates of ethanol elimination are small compared with many other factors, although there is evidence that people of Asian descent, owing to a polymorphism in the Class I hepatic ADH enzyme, have a slightly faster rate of metabolism (Mizoi et al., 1989). The slope of the declining phase of the BAC curve was slightly steeper in Japanese subjects after drinking the same dose as Caucasians (Mizoi et al., 1987). Enzyme polymorphism of Class I ADH explains why East Asians have a more active β-2 ADH isoenzyme and a higher V_{max} for ethanol as its substrate (Crabb, Bosron, & Li, 1987). Nevertheless, there is a considerable overlap in the elimination rates in Asians, Caucasians and African Americans, so the racial differences lack any forensic significance (Li et al., 2000).

6.5 | Updating the Widmark equation

In 1981, investigators from New Zealand published a paper calling for an update of the Widmark equation, especially the rho-factor or volume of distribution (Watson, Watson, & Batt, 1981). They felt that because Widmark's pharmacokinetic studies were done in the 1930s, in only 20 men and 10 womenan an update was warranted considering the lasting importance of the work. They further pointed out that body composition had changed a lot since the 1930s, with much more obesity evident in today's society (Yanovski & Yanovski, 2002).

Watson et al. (1981) advocated that it would be better to calculate an individual rho-factor based on anthropometric data, such as age, height, weight, and degree of adiposity for that particular individual. They presented multiple regression equations with TBW as the dependent variable and age (year), weight (kg) the height (cm) as the independent variables. These

TABLE 4 Physiological range of elimination rates of ethanol from blood (mg% per hour) in healthy subjects according to an evidence-based review of the literature (Jones, 2010). Also shown are elimination rates from whole body (g/hr) along with circumstances or conditions under which these might be obtained

Elimination rate from blood, mg% per hour	Elimination rate from whole body, g/hr[a]	Conditions, treatment, or the special circumstances when such elimination rates are encountered
8–10	4–5	People with liver dysfunction (e.g., owing to cirrhosis or carcinoma) or who might be malnourished or eat low-protein diets. Treatment with enzyme inhibitor of alcohol dehydrogenase, fomepizole (4-methyl pyrazole).
10–12	5–6	Consumption of moderate doses of alcohol by healthy individuals after an overnight (10 hr) fast.
12–16	6–8	Consumption of moderate doses of ethanol under nonfasting conditions.
16–25	8–12	Healthy individuals who consumed alcohol to reach intoxicating BAC (>120 mg%) such as is the case with drunken drivers
25–35	12–17	Alcoholics during detoxification or periods of heavy drinking for days or weeks to reach high BAC (>200 mg%). People having a genetic predisposition for rapid disposal of ethanol. Factors leading to a hypermetabolic state (e.g., after burn trauma or hyperthyroidism or certain medicinal drugs).

[a]This calculation assumes a nonobese male person with body weight 70 kg and volume of distribution (rho-factor) of ethanol of 0.70 L/kg.

Equations (10) and (11) were derived from TBW measurements in liters (L) determined by isotope dilution experiments in hundreds of people.

$$\begin{aligned}&\text{TBW Liters (men)} = 2.447 - 0.09516\,\text{age (year)} + 0.1074\,\text{height (cm)} + 0.3362\,\text{weight (kg)}\\&\text{Residual standard deviation} = 3.78\,\text{L}\end{aligned} \tag{10}$$

$$\begin{aligned}&\text{TBW Liters (women)} = -2.097 + 0.1069\,\text{height (cm)} + 0.2466\,\text{weight (kg)}\\&\text{Residual standard deviation} = 3.60\,\text{L}\end{aligned} \tag{11}$$

Once TBW is calculated from Equations (10) or (11), the rho-factor is obtained as the ratio of the percentage of water in body (L/kg) and percentage of water in the blood in g/100 mL.

$$\text{Rho} - \text{factor} = \text{water in body (L/kg)}/\text{water in blood (g/100 mL)}. \tag{12}$$

The water content of blood is fairly constant in healthy individuals (78–82% w/w), although the values are slightly higher in females, owing to their lower hematocrit and thus a greater plasma fraction per unit volume (Lenter, 1981). Accurate determination of the water content of biological specimens is done by desiccation (de Jong et al., 1987). A multicenter study in Germany determined the water content of blood from 682 men and 141 women. The water content was 78.2% w/w (range 74.8–83.3) for men and 79.4% w/w (range 76.3–82.5) for women, a small but statistically significant gender difference (Iffland, West, Bilzer, & Schuff, 1999). Note that these percentages are weight/weight, because the aliquots of blood and serum were weighed before desiccation. Because density of whole blood is 1.055 g/mL (Lenter, 1981) percentages of water in blood on the basis of weight/volume are 82.5% w/v for men and 83.8% w/v for women (% w/w × 1.055).

Use of Equation (10) assuming a 45-year-old man with a body weight of 85 kg and height 184 cm gives a TBW value of 46.5 L or 54.7% of body weight. If the water content of whole blood is taken as 83 g/100 mL, the ratio of TBW (%) to blood water (%) is 0.66 L/kg (54.7%/83% = 0.66 L/g), which is a rho-factor tailored for this individual.

The residual *SD* in the above equations reveals the uncertainty in calculating TBW; 95% of individuals fall within ±2 × *SD*, which is 40 ± 7.6 L (18.9%) for a man with TBW of 40 L.

Another approach to updating the Widmark equation, that received certain currency, was suggested by Forrest (1986). His method for estimating V_d or rho-factor depended on calculating the person's BMI as ratio of weight (kg) to height in meters squared (kg/m^2) and considering the percentage fat-free body mass (Barbour, 2001).

6.6 | Saturation kinetics

If the C-T profile of ethanol in the postabsorptive state is followed from high to low BAC, its shape is more like a hockey stick as depicted in Figure 7 (left graph). Accordingly, when BAC is about twice the K_m of ADH, the enzymatic reaction works at its maximum velocity (V_{max}). In the case of ethanol, the postabsorptive elimination phase is linear down to a BAC of 15–20 mg% but thereafter starts to tail off and under 10 mg% follows an exponential function (Holford, 1987). Making a logarithmic transformation of the BAC data produces the curve shown in Figure 7 (right part). The transformed data (semi-log plot) indicates that first-order kinetics operates at BAC of <15 mg% and that clearance of ethanol can be described by its elimination half-life of about 15–20 min (Ludden, 1991).

In mathematical terms, the BAC extending from high to low concentration can be fitted to the Michaelis–Menten Equation (13), which was developed many years ago to characterize the rate of enzymatic reactions (Lundquist & Wolthers, 1958; Wagner, 1973).

$$(-\mathrm{d}C/\mathrm{dt}) = (V_{\max} \times \text{BAC})/(K_m + \text{BAC}). \tag{13}$$

The two important kinetic parameters are K_m, which is the Michaelis constant denoting the binding power of the enzyme to its substrate and the other is V_{max} which is the maximum velocity of the biochemical reaction.

With reference to Equation (13), when the BAC (substrate concentration) is considerably higher than K_m (0.05–0.1 g/L of ADH), the equation simplifies to Equation (14), which conforms to a zero-order rate constant (V_{max}) (Wagner, Wilkinson, & Ganes, 1989).

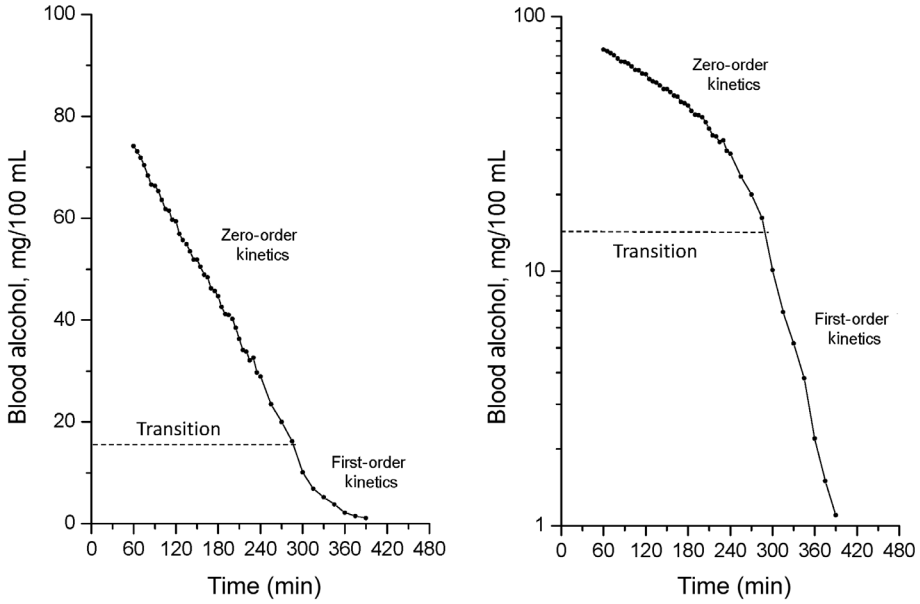

FIGURE 7 Concentration-time profiles of ethanol in blood with samples taken at 5 min intervals from high to low ethanol concentrations. The left plot on Cartesian coordinates shows the hockey stick shape characteristic of drugs with saturation kinetics. The right plot shows a logarithmic transformation of the BAC measurements and existence of zero-order kinetics (BAC > 20 mg%) and first-order kinetics (BAC <15–20 mg %)

$$(-\mathrm{d}C/\mathrm{dt}) = V_{\max} = k_{0.} \tag{14}$$

On the other hand when the BAC is much less than K_m, Equation (13) simplifies to Equation (15), which is the formula for a first-order kinetic reaction, with a rate in direct proportion to the substrate concentration (BAC). The first-order rate constant (k_1) is given by the ratio $V_{\max}/K_m$ in Equation (16).

$$(-\mathrm{d}C/\mathrm{dt}) = (V_{\max}/K_m) \times \mathrm{BAC}, \tag{15}$$

$$(-\mathrm{d}C/\mathrm{dt}) = k_1 \times \mathrm{BAC}. \tag{16}$$

Figure 7 (right part) shows a logarithmic transformation of the same C-T data for ethanol elimination and one notices that at concentrations 15 mg%, a straight line is evident and can be used to derive the half-life ($t½$) from the first-order rate constant (k_1) as $\mathrm{Ln}2/k_1$ or $t½ = 0.693/k_1$. This half-life was determined to be 15-20 min, so after five half-lives or 75-100 min, the BAC would have decreased to reach the endogenous levels.

7 | FORENSIC APPLICATIONS

There are numerous applications of the Widmark equation in forensic casework when alcohol-related crimes, such as drunken driving, are investigated (Gullberg, 2007). Such calculations are done somewhat differently depending on the traditions and case law existing in various countries and whether metric units or imperial units are used in the calculations for things like body weight, height, volume of drink, and concentration units for reporting BAC (Gullberg, 2007). Much can be said for trying to standardize the way various BAC calculations are made, including retrograde extrapolation (Brick, 2006; LaBay & Logan, 2018).

7.1 | Amount of alcohol in body

The average BAC in apprehended drunken drivers in most countries is between 1.5 and 1.8 g/L (150–180 mg/100 mL) and this is easy to convert into the amount of ethanol absorbed and distributed in all body fluids at time of sampling blood. For a male subject with body weight 80 kg, volume of distribution 0.7 L/kg and BAC of 150 or 180 mg% (1.5 or 1.8 g/L), there are 84 g or 100.8 g of ethanol equilibrated throughout all body fluids and tissues. Table 5 presents further examples of this calculation based on BACs from 50 to 450 mg% for men with body weights of 60, 80, or 100 kg.

The amount of ethanol in grams is easy to convert into volumes of different alcoholic drinks based on the information contained in Table 1. For example, 100.8 g ethanol is contained in 325 mL of whisky or vodka (40% v/v). If there was any

alcohol remaining unabsorbed in the stomach when blood was sampled, this would not be reflected in the amount of alcohol in the body calculated from the BAC.

7.2 | Total amount of alcohol consumed

The metabolism of ethanol starts as soon as alcohol reaches the stomach and passes though the liver so some part of the amount ingested has been disposed of by the time a blood sample is taken in forensic casework (Wagner, Wilkinson, & Ganes, 1990). If the number of hours elapsed between start of drinking and the time of sampling blood is known then it is easy to calculate the total amount of ethanol consumed. This calculation can be done in two ways (a) assuming an average elimination rate from blood (β) of 0.15 g L^{-1} hr^{-1} (15 mg% per hour) or elimination from the whole body at a rate of 0.10 g kg^{-1} hr^{-1}, the latter being the product of $\beta \times$ rho.

Equation (17) uses the elimination rate from blood along with average values of β and rho-factors and the BAC at t hours from start of drinking.

TABLE 5 Relationship between blood alcohol concentration (BAC) and amount of ethanol consumed

Blood alcohol conc. mg%	Body weight, kg[a]	Ethanol (g) in whole body	Metabolism (g) over time of 1 hr[b]	Amount of ethanol consumed (g)[c]
50	60	21.1	6	27.1
	80	28.2	8	36.2
	100	35.2	10	45.2
80	60	33.8	6	39.8
	80	45.0	8	53.0
	100	56.3	10	63.3
100	60	42.2	6	48.2
	80	56.3	8	64.3
	100	70.4	10	80.4
150	60	63.4	6	69.4
	80	84.5	8	92.5
	100	105.6	10	115.6
200	60	84.5	6	90.5
	80	112.6	8	120.6
	100	140.8	10	150.8
250	60	105.6	6	111.6
	80	140.8	8	148.8
	100	176.0	10	186.0
350	60	126.2	6	132.2
	80	169.0	8	177.0
	100	246.4	10	256.4
450	60	190.1	6	196.1
	80	253.5	8	261.8
	100	316.9	10	326.9

Note: The calculations assume body weights of 60, 80, or 100 kg and a time of 1 hr from start of drinking to time of sampling blood. The elimination rate of ethanol from whole blood is assumed to be 0.10 g kg^{-1} hr^{-1}.

[a]The calculations assumed a healthy male subject with Widmark rho-factor (V_d) of 0.70 L/kg.
[b]Ethanol is metabolized at a rate of 0.1 g ethanol per kg body weight per hour from the start of drinking.
[c]The sum of alcohol in body and the amount metabolized over 1 hr.

$$\text{Total amount consumed (g)} = [\text{kg} \times \text{rho}\,(\text{BAC}_t + \beta \times t)]. \quad (17)$$

From the results of hundreds of controlled drinking experiments, it has been shown that the elimination rate of ethanol from the whole body is approximately 0.1 g ethanol per kg body weight per hour or 7 g/hr for a 70 kg person and 9 g/hr for a person weighing 90 kg. Equation (18) shows an alternative way of calculating the total amount of alcohol a person has consumed from the measured BAC and when *t* hours have elapsed since the start of drinking.

$$\text{Total amount consumed (g)} = [(\text{BAC} \times \text{kg} \times \text{rho}) + (0.1 \times \text{kg} \times t)]. \quad (18)$$

Consider a man with a body weight of 80 kg, a rho-factor of 0.70 L/Kg and BAC determined 5 hr after the start of drinking or 2 hr after end of drinking. Use of Equation (17) and assuming a BAC of 100 mg% (1.0 g/L) shows that the total amount of ethanol consumed was 98 g ethanol whereas use of Equation (18) gives a result of 96 g ethanol. The blood sample was taken 2 hr after the end of drinking, which makes it safe to assume that absorption and distribution of ethanol in all body fluids was complete.

7.3 | Alcohol poisoning death

Deaths attributed to acute alcohol poisoning are often encountered during forensic investigations (Darke, Duflou, Torok, & Prolov, 2013; Jones, Kugelberg, Holmgren, & Ahlner, 2011). A recent report from the UK National Health Service reported that there were 5,507 alcohol-specific deaths in 2016, being up by 4% compared with 2015 and 11% up compared with 2006 (NHS_UK, 2018). Assuming that the autopsy BAC is the same as it was in the body at the time of death, the result can be used to calculate the amount of alcohol the deceased had consumed prior to death.

In this calculation, consider that a man (body weight 73 kg) was found dead at his home and the autopsy BAC was reported as 389 mg% (femoral blood), which is consistent with an acute poisoning death. Because this was a sudden and unexpected death an inquest was held in the coroner's court and the question arose about how much alcohol the deceased had consumed?

From interviews with friends, it emerged that the day prior to death the man started drinking at a pub at 12 noon and continued the whole day. Time of death, according to the pathologists report, was 2:00 a.m., the following morning. Accordingly, 14 hr elapsed from time of starting to drink alcohol and the time of death, when metabolism of ethanol ceases. Over these 14 hr, the man eliminates ~102 g ethanol from the body (14 × 7.3 = 102 g) through metabolism. The autopsy BAC of 389 mg% corresponds to there being 198 g ethanol absorbed and distributed in all body fluids at time of death (assuming a rho-factor 0.70 L/kg).

The deceased had therefore consumed 300 g ethanol (102 g + 198 g = 300 g) some time before death, which is roughly the amount contained in 4.2 bottles (750 mL each) of wine (12% ABV) or 949 mL spirits (40% ABV) or 7.6 L of beer (5% ABV), by any standards a heavy drinking binge (Jones & Holmgren, 2009).

7.4 | Retrograde extrapolation

The concentration of ethanol determined in blood gives useful information about the amount of alcohol in the body and the degree of impairment at the time blood was sampled. However, the police are often more interested in knowing what the person's BAC was at an earlier time, such as the time an alcohol-related crime was committed (Jackson et al., 1991; Lewis, 1987).

Typically, a person might be involved in a traffic crash and rushed to hospital for medical treatment so blood for toxicology was taken several hours after the time of the traffic incident. Accordingly, the result of analysis is not a reliable indication of the driver's BAC at the time of the crash (Lewis, 1986).

Because ethanol is eliminated from the blood at a constant rate per unit time (zero-order kinetics), making a forward or backward calculation of the BAC is valid provided the postabsorptive phase existed at the material times (Stowell & Stowell, 1998). Another necessary assumption is that there was no consumption of alcohol after the time of driving and before the blood was taken for toxicological analysis. Most people eliminate alcohol from the blood at a rate of 10–20 mg% per hour with a mean of 15 mg% per hour for moderate drinkers. The mean elimination rate in people arrested for drunken driving is slightly higher closer to 19 mg% per hour, because there are many heavy drinkers in this population (Jones & Andersson, 1996).

Examples of back calculating BAC starting from 20 mg% to times of 2–8 hr before the blood sample was taken are shown in Table 6. The mean (range) of ethanol elimination rates were 15 mg% per hour (10–20 mg% per hour), which are appropriate for most healthy people with normal liver function. Performing a back calculation of BAC in drink-driving cases is a contentious issue, because a person might be below a statutory limit initially but above the limit after the back-calculation was done (Lewis, 1987). To avoid having to perform back calculation routinely, the law in some jurisdictions presumes that if blood was sampled within 2 hr of driving, the analytical result would be considered not less than the BAC existing at the time of driving. In other jurisdiction, no time restrictions apply and the prosecution BAC is that which was determined at the time of sampling.

When sexual assault crimes are investigated, the victims might not report an offense until many hours afterwards. Blood samples for determination of ethanol are obtained when the victims are eventually examined by medical professionals. Under these circumstances, the BAC and state of inebriation are different than they were when the alleged crime took place (Jones, Kugelberg, Holmgren, & Ahlner, 2008). If a victim of date rape had zero, BAC detected a back calculation is not possible, but if the analytical result is >15–20 mg%, then such a calculation is certainly possible.

In sexual assault cases, there is no need to consider a threshold BAC, such as the statutory alcohol limit for driving. So in a back-calculation it is better to use an average elimination rate of ethanol from blood for that particular individual. If a young lady with little or no experience of drinking alcohol was sexually assaulted, then 15 mg% per hour is a good rate of elimination to use. Assuming the measured BAC was 120 mg% at the time of sampling blood and the crime occurred 6 hr earlier, with reasonable scientific certainty the victim's was ~210 mg% [120 + (6 × 15) = 210 mg%].

If the subject in the above example was accustomed to drinking alcohol, a more appropriate elimination rate would be 19 mg% per hour, which was the median value in drinking drivers (Jones & Andersson, 1996). The estimated BAC would then be closer to 234 mg% [120 + (6 × 19) = 234 mg%]. In such cases, a perpetrator often maintains that sexual activity was consensual, and a key question that arises in litigation and expert witness testimony is whether the victim, because of drink, drugs, or a medical condition, was so incapacitated that they could not possibly have consented to sex (Gunby, Carline, Bellis, & Beynon, 2012).

7.5 | Forward extrapolation

In some forensic cases, a blood sample might be unavailable, but the suspect or witnesses provided information about the amount of alcohol consumed. This information along with the person's age, body weight, and gender can be used to calculate the BAC expected. Assume a man with body weight 80 kg (rho-factor of 0.70 g/L) who drank five bottles of 5% ABV beer (360 mL per bottle) in 1 hr. The expert witness might be asked to calculate the likely BAC 2 hr after the end of drinking or 3 hr after start of drinking.

TABLE 6 Blood-alcohol concentrations calculated at the time of an offense derived from a BAC of 20 mg% at the time of sampling, which was assumed to be 2–8 hr later. The calculation assumes zero-order kinetics and mean and range of ethanol elimination rates 15 mg% (10 to 20 mg % per hour)

Hours elapsed after the traffic offence[a]	Estimated BAC at time of offense (mean value)[b]	Spread of estimated BAC		
		Lowest	Highest	Highest minus lowest BAC
2	50	40	60	20
3	65	50	80	30
4	80	60	100	40
5	95	70	120	50
6	110	80	140	60
7	125	90	160	70
8	140	100	180	80

[a]Assumes an analytical result of 20 mg% BAC after making a deduction for uncertainty.

[b]The calculation assumes that the suspect had reached the postpeak phase of the BAC curve at time of offense and that no further alcohol was consumed before blood was taken for toxicology.

One bottle of beer contains 14.2 g ethanol, so five bottles contain 71.1 g. According to Equation (5), the maximum BAC for this amount of ethanol is 127 mg% if absorption and distribution in all body fluids occurred instantaneously. During the 1 hr drinking and 2 hr postdrinking, the BAC can drop by ~45 mg% (3 × 15 mg% per hour) through metabolism, so the BAC 2 hr after drinking ends is likely to be about 82 mg% (127–45 = 82). This calculation assumes that bioavailability of the dose of ethanol in the five beers was 100% so 82 mg% is the highest possible result. After drinking beer as described in this example, bioavailability of ethanol is less than 100%, owing to carbohydrate content of the beer, dilution factors, time elements, and FPM (Holford, 1997).

In UK law, it is an offense for a person to be in charge of a motor vehicle with a BAC above the statutory limit of 80 mg %. Sometimes a person is found asleep in the vehicle but claims they had no intention of driving until the next morning when the BAC would be below the statutory limit for driving. If the BAC at the time of arrest is known, this allows calculating the time necessary for the concentration to decrease below a certain threshold value, such as 20 mg% as shown in Table 7.

In the calculation, the starting BAC was assumed to range from 50 to 300 mg% and the mean and (range) of ethanol elimination rates from blood were taken as 15 mg% per hour (10–20 mg% per hour) assuming zero-order kinetics above 20 mg% BAC. In reality, it is virtually impossible for a person to know what their BAC was a certain time after drinking, without making an analytical determination. Neither does a person know their rate of ethanol metabolism, which varies as much between as within the same individual on different occasions (Jones & Jonsson, 1994a).

Furthermore, after a few hours of sleep, the subjective feelings of intoxication are less evident, because the brain has adapted to the ethanol environment, a phenomenon known as acute tolerance (Kalant, 1998). This apparent sobering-up effect and greater impairment observed on the rising limb of the BAC curve compared with the postabsorptive phase have been demonstrated experimentally and were recently reviewed (Holland & Ferner, 2017; Martin & Moss, 1993).

Another need to make a forward projection of BAC arises when a driver is arrested for driving under the influence of alcohol and after obtaining a blood sample for forensic analysis the person is released from custody. Five hours later the same person was seen by the police driving again, but on this second occasion, blood was not available for analysis of alcohol. The prosecution might wonder what the suspect's BAC was on this second occasion, so that this information could be made part of the prosecution case. Table 7 can help to answer this question and the example assumes a statutory BAC limit for driving of 20 mg%.

A good rule of thumb for ethanol elimination rate from the whole body is 0.10 g/kg body weight per hour or 9 g ethanol per hour for man weighing 90 kg. Accordingly, if this person drank a whole bottle of 12% ABV wine (750 mL), this would correspond to 71.1 g ethanol and would require a time of ~7.9 hr (71.1/9 = 7.9 hr) to be disposed of by the body. If instead the person weighed only 60 kg, it would require 11.9 hr to become alcohol-free (71.1/6 = 11.9 hr).

8 | CONCLUDING REMARKS

Interpreting the concentration of ethanol and/or other drugs in biological specimens is an important duty for forensic practitioners, such as when alcohol-related crimes are investigated, including drinking and driving, drug-facilitated sexual assault, and violent behavior in general (Jones, 2017). Alcohol is the psychoactive substance most often encountered in forensic casework, because heavy drinking and drunkenness are tightly linked to deviant behavior and criminal activity (Fairbairn et al., 2017).

TABLE 7 Estimated times necessary for a measured blood-alcohol concentration (BAC) to decrease below 20 mg/100 mL assuming that zero-order kinetics of ethanol operate

Starting BAC, mg%	Mean time (hours) to 20 mg% BAC[a]	Range of times (hours) to 20 mg% BAC[b]
50	2.0	1.2–3.0
100	5.3	3.2–8.0
150	8.7	5.2–13.0
200	12.0	7.2–18.0
300	18.7	11.2–28.0

[a]Based on an average elimination rate from blood of 15 mg/100 mL per hour.
[b]Based on minimum and maximum elimination rates from blood of 10–25 mg/100 mL per hour.

The BACs reached after drinking depend on the dose administered and interaction between the various ADME processes (Jones & Jonsson, 1994a). People react differently to the same dose of alcohol, which is coupled to individual, genetic and environmental factors, and intersubject variations in ADME. Also important is the development of tolerance to ethanol's impairment effects as well as cultural and/or social norms that determine a person's drinking habits. It is the concentration of ethanol in arterial blood reaching the brain that causes impairment of body functions. However, in forensic science practice venous blood is the specimen submitted for toxicological analysis. The concentration of ethanol in breath follows more closely the arterial BAC, which suggests that BrAC is a better indicator of brain exposure to alcohol than venous BAC as demonstrated in a controlled alcohol dosing study (Lindberg et al., 2007). The magnitude of arterio–venous differences in ethanol concentration is more pronounced on the absorption phase of the BAC curve compared with the postabsorptive declining phase (Jones et al., 2004).

Overconsumption of alcohol and drunkenness is responsible for many unnatural deaths, including suicides, accidental drownings, acute poisonings, and damage to body organ and tissue after years of heavy drinking (Jones & Holmgren, 2003; Koski, Ojanpera, & Vuori, 2002). The BAC determined at autopsy can be converted into the amount of ethanol in the body at the time of death. Death form acute ethanol poisoning might occur with a BAC in the range from 300 to 400 mg%, although there are many exceptions. The mechanism of death from acute alcohol poisoning is by paralysis of the respiratory centers in the brain stem—hence a type of drug-induced asphyxia (Heatley & Crane, 1990). The frequency distribution of BAC in acute poisoning deaths overlaps with the BAC observed in people arrested for drunken driving (Jones & Holmgren, 2003). However, the mean BAC in fatalities is ~200 mg% higher than in drunken drivers, which are in the range 150–180 mg% in most countries indicating many binge drinkers among these traffic delinquents.

The present article has reviewed key aspects of ethanol's ADME and gives examples of various pharmacokinetic calculations that might be required in forensic science casework, such as drink-driving prosecutions. The evidence for prosecution of traffic offenders in most countries is nowadays obtained by analysis of ethanol in expired air with various types of evidential breath-alcohol analyzer (Dubowski, 1991). Scores of studies show that BAC and BrAC are highly correlated over a wide range of concentrations so it is perfectly feasible that pharmacokinetic calculations are done using BrAC measures and the resulting breath-ethanol profiles (Jones, 2011). One study showed that the V_d of ethanol derived from analysis of breath alcohol curves in male and female subjects, assuming a 2,100:1 blood-breath ratio, agreed well with values expected from analysis of blood samples (Cowan Jr., Weathermon, McCutcheon, & Oliver, 1996). However, more studies are needed in which ADME of ethanol was characterized from BrAC profiles and pharmacokinetic parameters derived and compared with conventional BAC analysis (Dettling, Witte, Skopp, Graw, & Haffner, 2009).

Forensic alcohol research is broadly multidisciplinary and the relevant scientific literature is spread throughout many different scientific journals, book chapters, and review articles (Jones, 2008, 2011). The scientific basis of the various BAC calculations has high validity, because hundreds of human ethanol dosing studies have been done since the 1930s (Holford, 1987; Widmark, 1932). The relevant pharmacokinetic parameters of ethanol, such as V_d and rate of elimination from blood (β-slope), are well-defined in men and women including magnitude of inter- and intrasubject variations (Jones, 2010; Maskell et al., 2019).

Hopefully, this review will serve as a primer for use by forensic scientists and others when they are required to interpret BAC measurements in alcohol-related cases, write expert statements or appear in court and testify as expert witnesses.

CONFLICT OF INTEREST

The author has declared no conflicts of interest in publishing this article.

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