Getting Drunk and Sober Again

André Heck (heck@science.uva.nl), AMSTEL Institute, University of Amsterdam, Netherlands

Abstract

Students can be provided insight into processes of enzyme kinetics and physiology via compartmental models. Graphical modeling software supports this. In this paper we will discuss various models that students could implement and use to investigate blood alcohol concentration after consumption of one or more alcoholic drinks. Results from these computer models are compared with measured data that were obtained with breath analysis equipment. The broad range of models for intake and clearance of alcohol in the human body ensures that students have great opportunity to practice evaluation and revision of their models. They can develop the critical attitude that is necessary for successful modeling of biological, chemical or physical phenomena. All models presented, ranging from the simplest linear elimination model to a sophisticated physiologically based 5-compartmental model, are used in pharmacokinetic studies. This implies that the students' investigation work is not only fun to do, but also resembles professional research practice.

Introduction

Alcohol is widely used by secondary school pupils. Some facts about Dutch pupils (NDM, 2004; NDM, 2006; Monshouwer et al, 2003; Pol & Duijser, 2003): 90% of fifteen-year-old pupils have ever drunk alcohol, 52% is doing this on a weekly basis, 63% of them have got drunk once (33% every month), and two-third of the children of this age who are out socializing prefer to drink alcoholic drinks (especially breezers and beer) instead of long drinks. 50% of fifteen-year-old pupils consume every week. 6% of juveniles (male and female) of age between 12 and 17 can be considered heavy drinkers, i.e., persons who consume six or more glasses of alcohol on one or more days per week. Binge drinking under adolescents is not unusual anymore, especially during school holidays (in a recent survey at youth camp sites boys are reported to drink on average 17 glasses per day). It is difficult to prevent teenagers from experimenting with alcohol; most pupils consume their first alcoholic drink between the age of 11 and 14. The number of children who go into a coma because of severe alcohol abuse and who are taken into hospital is growing fast in the Netherlands. Pediatricians gave the alarm about this disturbing trend and warned that it will not take long before children will get killed. The Dutch current affairs program NOVA on the 19th of April 2006 drew people's attention to this subject. The pediatrician Nico van der Lely of the Reinier de Graaf Gasthuis in Delft said in the television program: "Annually between five hundred and one thousand children are taken into a Dutch hospital because of alcoholic poisoning." Since 1999 he has noticed in his hospital that the number of hospitalizations has been multiplied by sixteen. It involves particularly girls of age between 12 and 14, who consume in short time a huge amount of alcoholic drinks, especially mixed drinks. Van der Lely: "You must think of one to one and a half liter of alcoholic drinks within two hours." The situation of alcohol usage among secondary school pupils in the Netherlands is not unique: data from other Western European counties, Australia and the United States of America give the same picture of alcohol consumption under adolescents. But compared to many countries, alcohol consumption among schoolgoers in the Netherlands is high and frequent. Only for the measure 'drunkenness', they score less highly.

Alcohol poisoning occurs when the blood alcohol concentration and hence the alcohol concentration in the brains becomes so high that you can get senseless or even can go into coma. A person can get alcohol poisoned at a blood alcohol level of 4‰, i.e., after more than twenty alcoholic drinks in a few hours time. There is a good chance that the drunken person gets unconscious and is in danger of losing his or her life. At a blood alcohol level of 5‰ a person runs the

risk of getting into a coma. Eventually the nervous system is stunned to such an extent that the respiratory system gets paralyzed and the person dies. Teenagers, but also their parents seem to realize insufficiently that alcohol is a poisonous substance that can be damaging. One quarter of the young drinkers of alcohol are of opinion that it takes at least 10 glasses to get drunk (boys: 39%; girls: 15%). Only 11% thinks that four drinks or less suffice. If teenagers (and their parents) would realize how easily one gets drunk and how long it takes before alcohol is removed from the human body, they might think twice before turning to alcohol abuse and they might be more careful in participating to traffic after consumption of alcoholic beverages.

In this paper we will discuss various mathematical models that secondary school pupils could implement and use to investigate blood alcohol concentration (BAC) after consumption of one or more alcoholic drinks. BAC must be understood as the total amount of alcohol (in gram) in the body divided by the total amount of body water (in liter). All models originate from professional research on alcohol metabolism and are in mathematical terms compartmental models, which can be studied on a computer for instance by using a graphical modeling environment. With computer models, pupils could investigate various scenarios of alcohol consumption: Does it matter in the long term whether you drink fast or slowly? Does it matter whether you consume drinks after a meal or not? Do there exist ways to speed up the clearance of alcohol from your body? Are there gender differences in alcohol intake and clearance? And so on. This type of work gives the pupils a broad idea of alcohol pharmacokinetics and it provides them with examples of compartmental models that can also be applied in investigations of other biological, chemical, and physical processes.

But not only mathematical models serve this purpose: conclusions could also be drawn and would make stronger impressions on pupils from data collected with breath analyzing equipment. Such data are anyway useful in discussions of the various mathematical models, not in the least to remind pupils of the fact that not understanding of the mathematical models is important, but understanding of the phenomenon under investigation, even under circumstances that measurements of the biological processes in the human body are complicated. Our own test data were collected with the Dräger Alcotest 6510, which has an accuracy of 0.017‰ within the range of measurements (Dräger Safety, 2006). Breath alcohol measurement can be used as a reliable estimate of blood alcohol concentrations since the 1970s and the accuracy of the equipment used means that it can be reliably applied in clinical studies. However, a recent technical design project (Killian & Kerkstra, 2003) shows that pupils could build their own breath analyzer from a suitable, low cost gas sensor and use the professional equipment to evaluate or calibrate their own alcohol tester. Finally, this paper gives an impression of the possibilities of graphical modeling, and in particular the modeling environment of Coach 6 (Mioduszewska & Ellermeijer, 2001).

Mathematical Models of Alcohol Metabolism

First we will give a review of mathematical models found in the research literature that discusses what happens after alcohol consumption. The range of models give a good view on issues that concern researchers who try to model clearance of alcohol from the human body [see (Lands, 1998), (Weathermoon & Crab, 1999), and (Swift, 2003)].

Widmark model

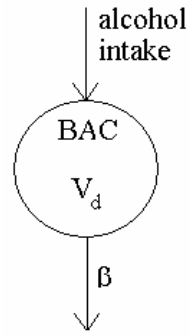
Widmark (1932) developed the first model that predicts the blood alcohol concentration after consuming alcohol. It is still much used in forensic research because it works well with real data for a large range of values. This model is in fact an open 1-compartment model with a zero-order elimination process: it is assumed that the alcohol after consumption is quickly taken into the body and spread over the total body water, i.e., is distributed rapidly into the bloodstream from the stomach and small intestine, and further into the watery fluids in and around somatic cells. Alcohol does not dissolve into body fat. Hereafter, the alcohol in the human body is assumed to be eliminated at a constant rate. The whole process is schematically drawn in Figure 1.

After absorption of alcohol, the blood alcohol level is represented in the Widmark model by the formula

$$\mathrm{BAC} = \frac{D}{r \cdot W} - \beta \cdot t \,,$$

where D is the amount of alcohol consumed (in gram), r is the so-called Widmark factor, W is the body weight (in kg), β is the rate of metabolism (clearance rate in g/l/h), and t is the time (in hours) after consuming alcohol. The rate of alcohol metabolism is individual (for example different for occasional drinkers and alcoholics, men and women, and age dependent), it depends on circumstances (for example before or after a meal) and it varies from 0.10 to 0.20 g/l/h. The Widmark factor is also individual and depends mainly on body composition. Mean values are 0.68 for men with standard deviation 0.085 and 0.55 for women with standard deviation 0.055 (the lower value for women is explained because the female body contains in general a higher percentage of body fat and therefore less body water than the male body). The product $r \cdot W$ is equal to the volume of distribution V_d, i.e., the theoretical volume of the total body water compartment into which the alcohol is distributed. It is considered in most pharmacokinetic models equal to the total body water. Various methods can be found in the research literature to estimate the Widmark factor or the volume of distribution from variables such as height, weight and age. For example, Seidl et al (2000) gave the following formulas:

Fig. 1. Widmark model.



$$r(\text{men}) = 0.3161 - 0.004821 \cdot W + 0.004632 \cdot H$$

$$r(\text{women}) = 0.3122 - 0.006446 \cdot W + 0.004466 \cdot H$$

where H is the body height (in cm). Assuming a percentage of 80% water in blood, Watson et al (1980) determined various linear regression formulas. Two of these formulas, in which *AGE* is in years, are:

$$0.8 \cdot V_d(\text{men}) = 0.3626 \cdot W - 0.1183 \cdot AGE + 20.03$$

$$0.8 \cdot V_d(\text{women}) = 0.2549 \cdot W + 14.46$$

Hybrid, open 1-compartment model with zero-order elimination

In reality it takes some time before consumed alcohol get distributed in the total body water compartment. You can deal with this explicitly in the formula of the Widmark model: for example, $\mathrm{BAC} = D/(r \cdot W) - \beta \cdot (t - 0.5)$ expresses a time difference of half an hour between consumption and absorption of alcohol. A more reliable method is the following (Lotsof, 2003): Assume that alcohol intake is a first order absorption process and that clearance is linear in time, just as in the Widmark model, then the blood alcohol concentration is given as:

$$C_0 + \alpha \cdot \left(1 - H(t - t_0) \cdot e^{-k_a (t - t_0)}\right) - \beta \cdot t \,,$$

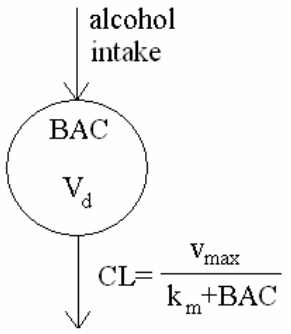
where C_0 is the BAC at time $t = 0$, α is a constant proportional to the amount of alcohol consumed at time $t = 0$, k_a is the absorption coefficient, t_0 is the retardation time for absorption, and H is the Heaviside function. This formula can be rewritten for $t \geq t_0$ as:

$$\mathrm{BAC} = B \cdot e^{-k_a \cdot t} + A - \beta \cdot t \,,$$

where k_a is estimated (Hahn et al, 1997) at 0.08 min^{-1} with standard deviation 0.03, which corresponds with a half-time of 8.7 min, for drinking with an empty stomach. t_0 is estimated at 1.6 minutes with standard deviation 0.5. A third way of dealing with delayed absorption of consumed alcohol in the body in a mathematical model is to assume that absorption of a dose D takes a certain amount of time T_0 (say 30 minutes) and that alcohol distribution in the total body water compartment during this time interval happens at constant speed D/T_0.

Wagner model

Fig. 2. Wagner model.

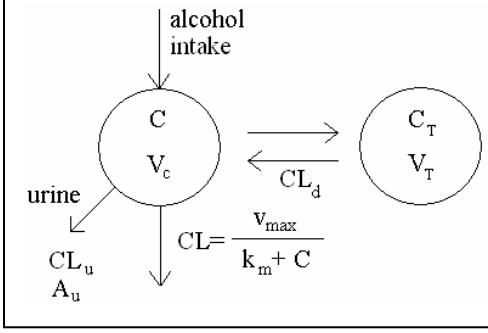


The third model that predicts the blood alcohol consumptions comes from Wagner (1972). Like the Widmark model it is an open 1-compartment, with the only difference that the clearance of alcohol is now described by Michaelis-Menten kinetics (see Figure 2). This means that after absorption of alcohol, the rate of change in blood alcohol concentration is given by the following formula:

$$V_d \cdot \frac{\mathrm{d}}{\mathrm{dt}}\mathrm{BAC} = -\frac{v_{\max} \cdot \mathrm{BAC}}{k_m + \mathrm{BAC}},$$

where V_d is the volume of distribution of the total body water compartment (the total amount of body water), k_m is the Michaelis-Menten constant, and $v_{\max}$ is the maximum disappearance rate. In Figure 2 we use the clearance factor CL that is associated with Michaelis-Menten kinetics. For a high value of BAC we have that the value of the clearance rate CL is almost equal to the maximum removal rate $v_{\max}$ (≈140 mg/min) and the graph of BAC vs. time looks like a straight line. Curvature in the graph becomes noticeable when BAC reaches half of the maximum removal rate. At this point BAC = k_m and this value is mostly taken between 5 and 50 mg/l.

Fig. 3. Norberg 2-compartment model.



Norberg 2-compartment model

Norberg et al (2000) used a 2-compartment model consisting of the central compartment, which is in this case the plasma and the tissues that are in rapid equilibrium with it (liver and kidney), and the peripheral compartment, which contains the rest of the body fluids in other tissues. From the central compartment there is parallel alcohol clearance through the liver following Michaelis-Menten kinetics and through the kidneys (unmodified alcohol in urine) following a linear first-order kinetic process. By the way, only a small portion of the consumed alcohol (2-5%) is excreted in breath, sweat and urine. We denote the alcohol concentration and the volume of the central and peripheral compartment by C, V_C and by C_T, V_T, respectively. The increase in the amount A_u of unmodified alcohol in the urine is determined by the elimination constant CL_d. The distribution of alcohol over the two compartments is determined by the intercompartmental distribution parameter CL_d. The relation

$$CL = v_{\max} / (k_m + C)$$

corresponds with Michaelis-Menten kinetics. So in this pharmacokinetic model, the following equations hold after absorption of alcohol in the central compartment:

$$V_C \cdot \frac{dC}{dt} = -CL \cdot C - CL_d \cdot C + CL_d \cdot C_T - CL_u \cdot C$$

$$V_w \cdot \frac{dC_T}{dt} = CL_d \cdot C - CL_d \cdot C_T$$

$$\frac{dA_u}{dt} = CL_u \cdot C$$

Norberg and colleagues came to the following parameter values in clinical trials with intravenous infusion of alcohol and via analysis of blood samples at various times:

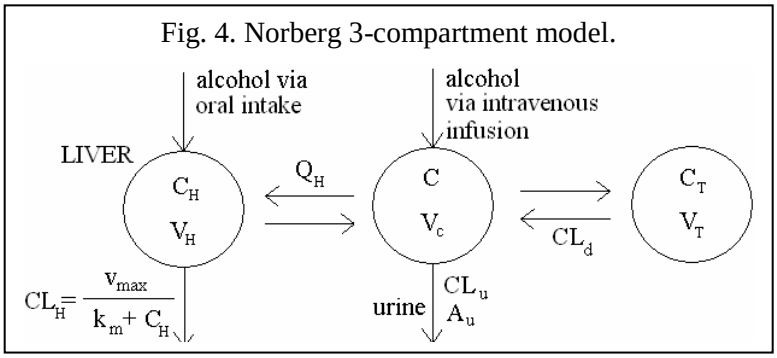
$v_{\max} = 95.0 \pm 25.1\,(\mathrm{mg/min})$, $k_m = 27.0 \pm 18.9\,(\mathrm{mg/l})$, $CL_d = 809 \pm 232\,(\mathrm{ml/min})$,

$V_C = 14.5 \pm 4.3\,(\mathrm{l})$, $V_T = 21.2 \pm 4.4\,(\mathrm{l})$, $\mathrm{CL_u} = 3.65 \pm 2.04\,(\mathrm{ml/min})$.

Norberg 3-compartment model

Norberg (2001) extended the 2-compartment model to a semi physiological 3-compartment model consisting of the central compartment, from which alcohol is eliminated via urine, the liver, in which alcohol is metabolized following Michaelis-Menten kinetics, and the peripheral compartment (see Figure 4).

Fig. 4. Norberg 3-compartment model.



This model takes into account that alcohol can distribute directly through the hepatic portal vein from the gastrointestinal tract into the liver so that a portion of the consumed alcohol can be eliminated before the alcohol is distributed via the blood stream to other fluid parts of the body. By the way, this so-called 'first-pass metabolism' is not undisputed. Some researchers [see (NIAAA, 1997), (Lim et al, 1993), and (Ammon et al., 1996)] are of the opinion that enzymes in the stomach play an important role, while others [see (Levitt, 1996) and (Levitt et al, 1997)] are of the opinion that the liver is the most important place in the first-pass metabolism. In all research work is concluded that under normal drinking behavior first-pass metabolism contributed only for a small portion to the total clearance of alcohol.

In the Norberg 3-compartment model we have the following equations after intravenous administration of alcohol:

$$V_c \cdot \frac{dC}{dt} = \frac{D_{\inf}}{T_{\inf}} - Q_H \cdot C + Q_H \cdot C_H - CL_d \cdot C + CL_d \cdot C_T - CL_u \cdot C$$

$$V_H \cdot \frac{dC_H}{dt} = Q_H \cdot C - Q_H \cdot C_H - CL_H \cdot C_H$$

$$V_T \cdot \frac{dC_T}{dt} = CL_d \cdot C - CL_d \cdot C_T$$

$$\frac{dA_u}{dt} = CL_u \cdot C$$

Here, $D_{\inf}$ is the given amount of alcohol, $T_{\inf}$ is the infusion time, and the term $D_{\inf}$ / $T_{\inf}$ in the first equation is set to zero 0 for t > $T_{\inf}$. C_H is the concentration in the liver compartment, V_H is the liver water volume, and Q_H is the liver blood water flow rate. is The liver clearance rate is given by Michaelis-Menten kinetics:

$$CL_H = v_{\max} / (k_m + C_H).$$

The following parameter values can be taken (Norberg et al, 2003):

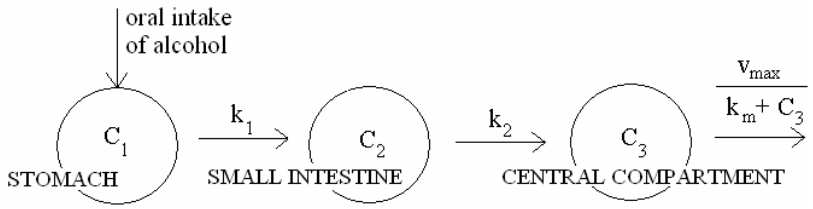
$$v_{\max} = 89 \pm 18\,(\text{mg/min}), \quad k_m = 2.9 \pm 5.1\,(\text{mg/l}), \quad Q_l = 1100\,(\text{ml/min}), \quad V_l = 1.1(\text{l}).$$

It follows that the value of $v_{\max}$ is close to the value in the 2-compartment model, but that the parameter k_m strongly depends on the model choice. This parameter value turns out to depend much on the value of Q_H.

Pieters 3-compartment model

Pieters et al (1990) also modeled alcohol clearance with a 3-compartment model. However, their model considers the central compartment, in which alcohol is metabolized following Michaelis-Menten kinetics, the stomach and the small intestine. The alcohol goes into the stomach first, hereafter into the small intestine, and finally from there it is absorbed into the bloodstream and rapidly distributed over the central compartment. Figure 5 illustrates the model, in which the volumes of distribution of the compartments are not specified, but hidden in the parameters.

Fig. 5. Pieters 3-compartment model.



The model equations are:

$$\frac{dC_1}{dt} = -\frac{k_1}{1 + a \cdot C_1^{\,2}} \cdot C_1, \qquad \frac{dC_2}{dt} = \frac{k_1}{1 + a \cdot C_1^{\,2}} \cdot C_1 - k_2 \cdot C_2, \qquad \frac{dC_3}{dt} = k_2 \cdot C_2 - \frac{v_{\max}}{k_m + C_3} \cdot C_3,$$

with initial conditions

$$[C_1(0), C_2(0), C_3(0)] = [C_0, 0, 0],$$

where $C_0 = D_0 / V$, the initial amount of alcohol D_0, divided by the volume of distribution V of the central compartment, and where C_1, C_2, and C_3 are the alcohol concentrations in the stomach, small intestine and central compartment, respectively, related to the volume of distribution of the third compartment. Tabulated parameter values are (Pieter et al, 1990):

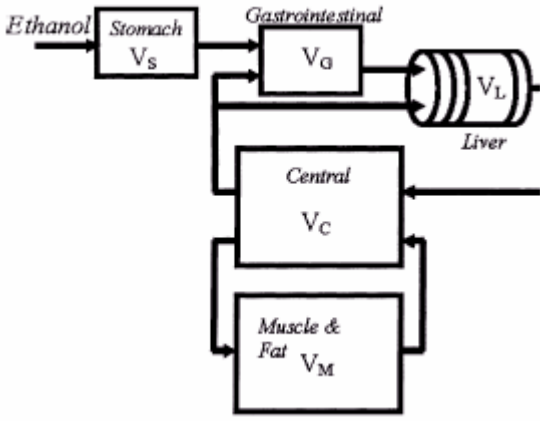
Table 1. Parameter values for the Pieters model.

		Mean Values	
Parameter	Dimension	Men	Women
$v_{\max}$	$g \cdot l^{-1} \cdot h^{-1}$	0.470	0.480
k_m	$g \cdot l^{-1}$	0.380	0.405
C_0	$g \cdot l^{-1}$	0.455	0.703
k_1	h^{-1}	5.55	4.96
k_2	h^{-1}	7.05	4.96
a	$l^2 \cdot g^{-2}$	0.42	0.75

The first differential equation in the Pieters model, which models emptying of the stomach, does not represent a simple first-order process, but a feedback control is built-in that depends on the instantaneous concentration in the stomach, $C_1(t)$. The parameter a in the quadratic term of the denominator determines whether gastric emptying is faster (negative a) or slower (positive a) than the first order rate k_1 under normal conditions. So, the effect of an empty or full stomach on alcohol clearance can be taken into account mathematically (Wedel et al, 1991). By the way, food promotes alcohol clearance, even when alcohol intake takes place via an intravenous infusion (Hahn et al, 1994). The Pieters model cannot explain this.

Physiologically based modeling

Fig. 6. Umulis 5-compartment model.



Umulis et al (2005) described a model of five organ compartments that exchange material. The compartments are the central compartment, stomach, gastrointestinal tract, liver, and muscle. The scheme in Figure 6, taken from the original paper, describes the exchange of alcohol between the compartments. All compartments, except the liver, are modeled as stirred reactors; the liver is modeled as a tubular flow reactor. The stomach in this model contains zero tissue water volume and only the volume of liquid contents V_S (alcoholic beverage), which is absorbed into the gastrointestinal tract in accordance with a first-order process of which rate constant k_S depends nonlinearly of the amount D of alcohol consumed. The delayed absorption of alcohol is described by the constant k_d, which is equal to 0 for $t > T_0$ for a given time interval T_0 (the term $k_d \cdot T_0$ is usually chosen smaller than the dose D). The equation is:

$$\frac{dV_S}{dt} = -k_S \cdot V_S + k_d ,$$

where

$$k_S = {k_{\mathrm{Smax}}} \Big/ \left(1 + a \cdot D^2\right).$$

The gastrointestinal compartment accounts for the tissue water volume of the intestines and the stomach where alcohol is first absorbed. The stomach and intestines water volumes are grouped into one compartment because they are connected directly to the liver via the hepatic portal vein and because they are the sites of oral alcohol absorption. The blood flow rate in the hepatic portal vein is about 2/3 of the total blood flow rate v_L in the lever. Let C_{Cet} and C_{Get} denote the ethanol concentration in the central compartment and the gastrointestinal compartment, respectively. Let V_G be the volume of distribution of the gastrointestinal compartment and let C_{S0} be the initial concentration of ethanol in the stomach. A mass balance on the gastrointestinal compartment gives the following differential equation:

$$V_G \cdot \frac{dC_{Get}}{dt} = \frac{2}{3} v_L \cdot \left(C_{Cet} - C_{Get}\right) + k_S \cdot V_S \cdot C_{S0}.$$

After entering the liver, ethanol is converted into acetaldehyde by the enzyme alcohol dehydrogenase (ADH) and cytochroom P450 (CYP). This substance is poisonous, but it is converted into acetate by enzyme aldehyde dehydrogenase (ALDH). These coupled chemical reactions, of which the first one in reversible and the second not, play an important role model of enzyme kinetics (see Fogler, 2005). The rate of disappearance r_{et} with which ethanol is eliminated is a function of the ethanol and acetaldehyde concentrations C_{et} and C_{ac} (other symbols are reactions constants), and it is given by the following formula:

$$-r_{et}(C_{et}, C_{ac}) = \frac{v_{\max_{ADH}} \cdot C_{et} - v_{\mathrm{rev}_{ADH}} \cdot C_{ac}}{k_{m_{ADH}} + C_{et} + k_{\mathrm{rev}_{ADH}} \cdot C_{ac}} .$$

The rate of disappearance r_{ac} of acetaldehyde elimination is given as a function of the concentration C_{ac} (other symbols are reactions constants) by

$$-r_{ac}(C_{ac}) = \frac{v_{\max_{ALDH}} \cdot C_{ac}}{k_{m_{ALDH}} + C_{ac}} .$$

We will use both formulas in the modeling of alcohol metabolism in the liver. Let C_{Cac} and C_{Gac} be the acetaldehyde concentration in the central compartment and in the small intestine. The change of acetaldehyde concentration in the gastrointestinal tract is given by the equation

$$V_G \cdot \frac{dC_{Gac}}{dt} = \frac{2}{3} v_L \cdot (C_{Cac} - C_{Gac}).$$

The liver is modeled as a tubular flow reactor partitioned into N subcompartments that each contribute to alcohol clearance. Let the total volume of distribution in the lever be V_L and let the distribution volume for each part be ΔV_L (thus: $\Delta V_L = V_L / N$). Let C_{Let1} and C_{Lac1} be the ethanol and acetaldehyde concentration, respectively, in subcompartment 1 of the lever, and so on. We get the following equations:

Subcompartment 1:

$$\Delta V_L \cdot \frac{dC_{Let1}}{dt} = v_L \cdot \left(\frac{1}{3} C_{Cet} + \frac{2}{3} \cdot C_{Get} - C_{Let1} \right) + r_{et}(C_{Let1}, C_{Lac1}) \cdot \Delta V_L$$

$$\Delta V_L \cdot \frac{dC_{Lac1}}{dt} = v_L \cdot \left(\frac{1}{3} C_{Cac} + \frac{2}{3} \cdot C_{Gac} - C_{Lac1} \right) - r_{et}(C_{Let1}, C_{Lac1}) \cdot \Delta V_L + r_{ac}(C_{Lac1}) \cdot \Delta V_L$$

Subcompartment 2:

$$\Delta V_L \cdot \frac{dC_{Let2}}{dt} = v_L \cdot (C_{Let1} - C_{Let2}) + r_{et}(C_{Let2}, C_{Lac2}) \cdot \Delta V_L$$

$$\Delta V_L \cdot \frac{dC_{Lac2}}{dt} = v_L \cdot (C_{Lac1} - C_{Lac2}) - r_{et}(C_{Let2}, C_{Lac2}) \cdot \Delta V_L + r_{ac}(C_{Lac2}) \cdot \Delta V_L$$

$$\vdots$$

Subcompartment N:

$$\Delta V_L \cdot \frac{dC_{Let(N)}}{dt} = v_L \cdot \left(C_{Let(N-1)} - C_{Let(N)} \right) + r_{et}\left(C_{Let(N)}, C_{Lac(N)} \right) \cdot \Delta V_L$$

$$\Delta V_L \cdot \frac{dC_{Lac(N)}}{dt} = v_L \cdot \left(C_{Lac(N-1)} - C_{Lac(N)} \right) - r_{et}\left(C_{Let(N-1)}, C_{Lac(N)} \right) \cdot \Delta V_L + r_{ac}(C_{Lac(N)}) \cdot \Delta V_L$$

Finally we describe the exchange of material between the central compartment and the muscle and fat compartment. Some notations: v_M is the blood flow rate to the muscle and fat compartment, V_C and V_M are the volume of distribution in the central compartment and in the muscle and fat compartment, respectively, and C_{Met} and C_{Mac} are the ethanol and acetaldehyde concentration in the muscle system, respectively. The following equations hold:

$$V_C \cdot \frac{dC_{Cet}}{dt} = -v_L \cdot \left(C_{Cet} - C_{Let(N)} \right) - v_M \cdot (C_{Cet} - C_{Met})$$

$$V_C \cdot \frac{dC_{Cac}}{dt} = -v_L \cdot \left(C_{Cac} - C_{Lac(N)} \right) - v_M \cdot (C_{Cac} - C_{Mac})$$

$$V_M \cdot \frac{dC_{Met}}{dt} = v_M \cdot (C_{Cet} - C_{Met})$$

$$V_M \cdot \frac{dC_{Mac}}{dt} = v_M \cdot (C_{Cac} - C_{Mac})$$

For the ‘standard man’ with weight of 69.4 kg you may choose the following parameter values (Umulus et al, 2005):

$V_G = 2.4\,(\text{l}),\ V_L = 1.1\,(\text{l}),\ V_C = 11.6\,(\text{l}),\ V_M = 25.8\,(\text{l}),\ v_L = 1.35\,(\text{l/min}),\ v_M = 0.75\,(\text{l/min}),$

$v_{\max_{ADH}} = 101\,(\text{mg/min/[kg liver]}),\quad k_{m_{ADH}} = 18.4\,(\text{mg/l}),$

$v_{\text{rev}_{ADH}} = 32.6\,(\text{mmol/min/[kg liver]}),\quad k_{\text{rev}_{ADH}} = 1,$

$v_{\max_{ALDH}} = 124.5\,(\text{mg/min/[kg liver]}),\quad k_{m_{ALDH}} = 0.055\,(\text{mg/l}).$

Graphical computer models of alcohol metabolism

All mathematical models that were described in the previous section can be converted into computer models. In general, the computer implementation of a mathematical model consists roughly of two phases: specification of the mathematical model and simulation of the model. Starting with the description of the first phase, Coach 6 has a graphical interface to describe a model qualitatively (see the screen shots in the examples below). In the graphical model you specify which quantities in the mathematical model play a role (distinguishing parameters and state variables), how they depend on each other, which formulas for quantities are used and which values parameters have. The graphical model is automatically translated into a system of equations that is used in a computer simulation, i.e., in running the model. We will look at some examples of alcohol clearance from the human body. We will assume that a 'standard glass' in the catering industry contains 10 grams of alcohol, regardless of the type of beverage. Parameter values are estimated on the basis of the reported literature values.

Widmark computer model

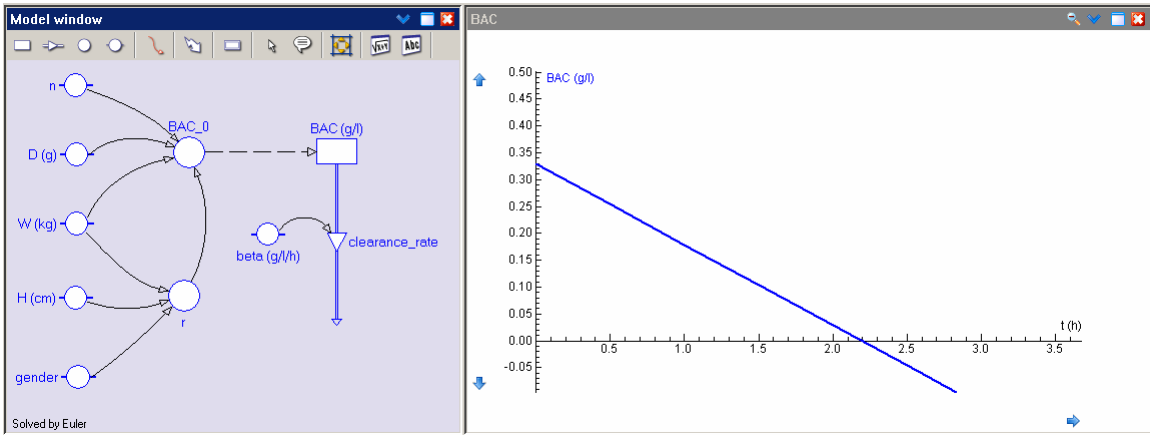
We start with the Widmark model, in which we work with the formulas of Seidl et al (2000) for the Widmark factor. Thus, after immediate consumption of *n* drinks holds:

$$\frac{d\ \mathrm{BAC}}{dt} = -\beta \cdot t, \quad \mathrm{BAC}(0) = \frac{n \cdot D}{r \cdot W}, \quad r(\text{men}) = 0.3161 - 0.004821 \cdot W + 0.004632 \cdot H,$$

$$r(\text{women}) = 0.3122 - 0.006446 \cdot W + 0.004466 \cdot H.$$

The screen shot below (Fig. 7) shows the graphical model and a run for the average German man who has consumed two drinks. The graph illustrates that there is a weakness in the computer model: the computed BAC becomes negative after about two hours. In reality this is not possible of course. But having a critical look at the quality of a (computer) model is actually something that pupils have to learn or that has to become second nature.

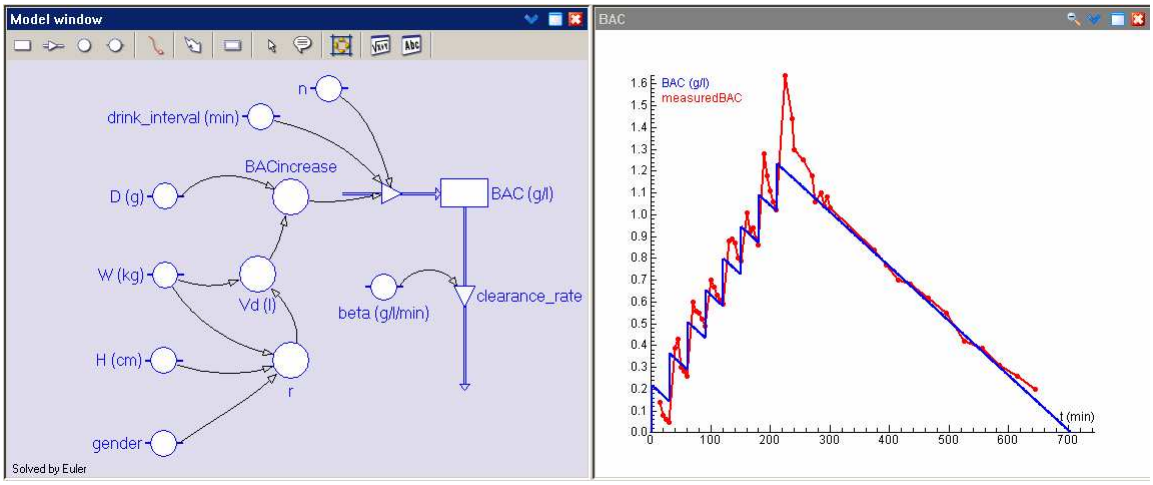
Fig. 7. Screen shot of the simple Widmark computer model after two alcoholic drinks.



We can already make the Widmark computer model somewhat more realistic by choosing minutes as time unit instead of hours, and choosing BAC < 0 as stop condition. Furthermore, we will assume that not all drinks are consumed at once, but at regular intervals, say of 30 minutes. This means that we assume that every 30 minutes the blood alcohol concentration increases instantaneously with $D / (r \cdot W)$. In the screen shot below (Fig. 8) you see the graphical model, the graph of computed blood alcohol concentration against time, and a measured BAC curve of the author drinking eight glasses of red whine at regular time intervals. Ignoring the apparent overshoot of BAC shortly after each drink, the accordance between model and measurement is good for a clearance rate β of 0.0025 g/l/min. By the way, the alcohol consumption has been specified as a

repeated pulse of height D / V_d every 'drink_interval', but it could also have been specified by drawing a sketch of the drinking behavior or by implementing a repetition loop by means of 'events'. From the computed BAC curve you could draw the conclusion that BAC after consumption of two glasses has come above the legal limit of 0.2‰ for persons under age of 24. Another conclusion is that this particular person must wait more than seven hours after his final drink before the blood alcohol concentration is again below 0.2‰.

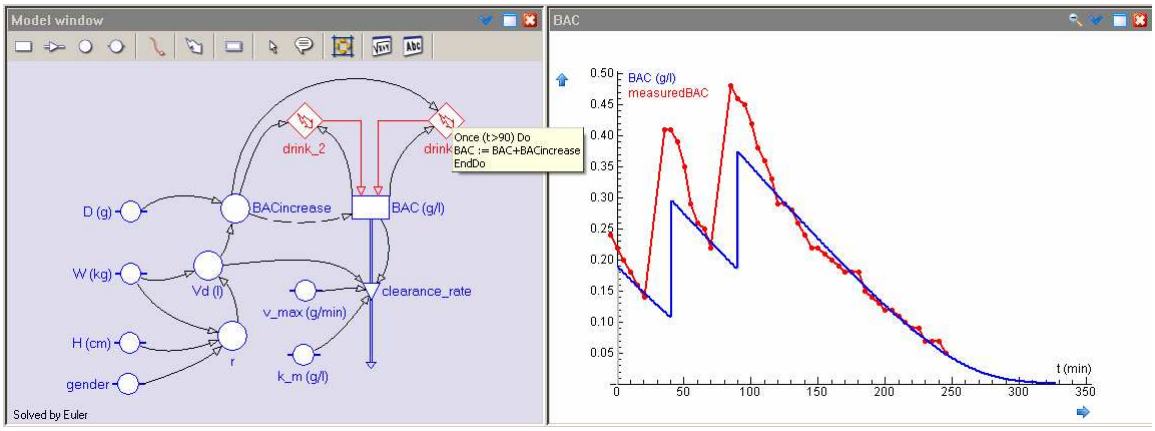
Fig. 8. Screen shot of the Widmark computer model for regular consumption of 8 standard units.



Wagner computer model

In the screen shot below (Fig. 9) we assume an alcohol consumption of drinking three glasses 'ad fundum' on an empty stomach: one at the start of the experiment, one after 40 minutes, and another drink 50 minutes later. In the computer model we have specified the 2nd and 3rd intake of alcohol by means of 'events' (represented graphically by an icon with a thunderbolt). Coach is a actually hybrid modeling environment for continuous-time and discrete-event dynamic modeling. With events one can take actions when a certain condition is met; see the yellow page in the screen shot for the event of consuming the third drink. The first alcoholic drink is just the initial condition (BAC(0) = BACincrease). Alternatively, the intake can be specified by means of mathematical formulas (e.g., with the Pulse function) or by drawing a sketch of the drinking behavior.

Fig. 9. Screen shot of the Wagner computer model for regular consumption of 3 standard units.



In the comparison of the computer model and the measured data we assume a time delay of half an hour for absorption of the consumed alcohol into the total body water: for this reason we have translated the graph of the measured BAC 30 minutes to the left. Alcohol clearance follows in the Wagner model Michaelis-Menten kinetics. The parameters v_{max} = 170 mg/min and k_m = 45 mg/l have been chosen such that a reasonable match between the measured data and the computer model exists, at least if one ignores overshoot of blood alcohol concentration. But obtaining good values for parameter appears to be quite tricky in practice: for instance, the values v_{max} = 340 mg/min and k_m = 290 mg/l are almost as good.

Norberg 2-compartment computer model

Comparing a mathematical model with real data is essential for judging the quality of a model. We use in this paper data collected by ourselves with a breath analyzer as well as data from research literature. We will use in our model of intake and clearance of alcohol data collected for subjects no. 19 and no. 22 in the clinical study described in the SWOV-report R-2001-19 (Mathijssen & Twisk, 2001). Subject no. 22 (female, 54 kg, 40 years, drinking daily) consumed, just like most of the participants, on two different days 72 grams of pure alcohol, in three equal portions of 24 gram. For each alcohol portion was available a drinking time of 25 minutes. A quarter of an hour later began measurements by means of breath analysis. Subject no. 19 (female, 66 kg, 20, drinking weekly) consumed only one portion of 24 grams of alcohol. Using the hybrid Widmark formula and using the formulas of Watson et al (1980) for the volume of distribution, the blood alcohol concentration could be predicted as

$$\text{BAC} = \frac{D}{18.075 + 0.3186 \cdot G} - \beta \cdot (t - 0.5),$$

where D is the amount of alcohol consumed (in gram), β is the clearance rate (in g/l/h), and t is the amount of time (in hours) passed since alcohol consumption. The measured data and the predicted values for the two participants are listed in Table 2 below.

Table 2. BAC data of subjects no. 19 and no. 22 in the SWOV-report (Mathijssen & Twisk, 2001)

Development of BAC after consumption of 72 g pure alcohol by subject no. 22						
Time of measurement (after start, in minutes)	40	80	120	150	180	210
Amount of alcohol consumed	24	48	72	72	72	72
BAC measurement 1	0.55	0.97	1.45	1.38	1.27	1.10
BAC measurement 2	0.55	1.15	1.47	1.47	1.31	1.22
Predicted value (β=0.175)	0.52	1.09	1.65	1.56	1.48	1.39

Development of BAC after consumption of 24 g pure alcohol by subject no. 19						
Time of measurement (after start, in minutes)	40	70	100	130		
Amount of alcohol consumed	24	24	24	24		
BAC measurement	0.46	0.32	0.21	0.16		
Predicted value (β=0.2)	0.44	0.34	0.24	0.14		

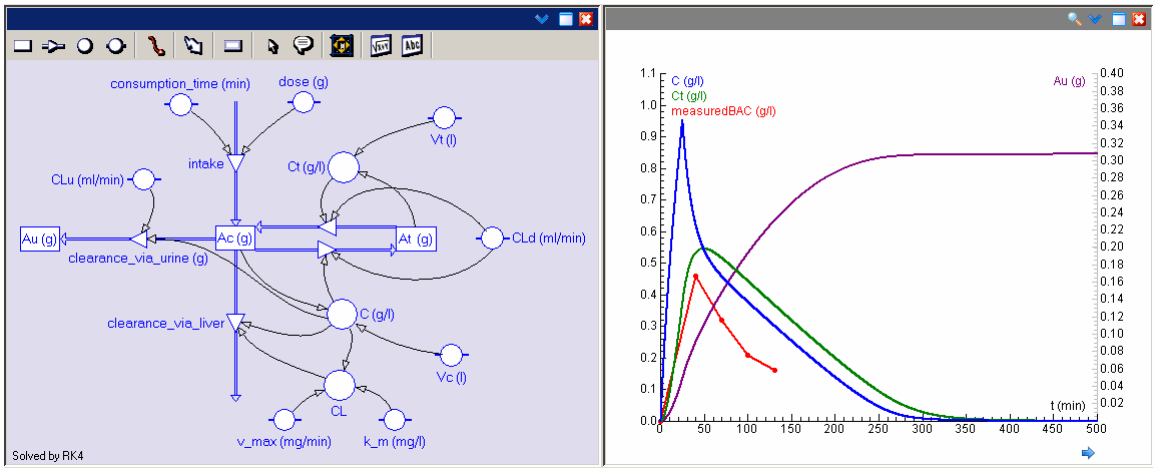
The screen shot below (Fig. 10) illustrates that the Norberg 2-compartment model does not give a good match between measurements and model for subject 19, whereas the hybrid Widmark model worked reasonably. In the computer model we have used a rate of intake of alcohol equal to 24/25 = 0.96 g/l/min for time between 0 and 25 minutes, and 0 elsewhere. Such a function can be specified in Coach by means of the Pulse function: Pulse(t;0;25;24/25). Thus, we obtain the following system of differential equations in the 2-compartment model:

$$\frac{dA_C}{dt} = \text{Pulse}(t;0;24;24/25) - CL \cdot C - CL_d \cdot C + CL_d \cdot C_T - CL_u \cdot C,$$

$$\frac{dA_T}{dt} = CL_d \cdot C - CL_d \cdot C_T, \qquad \frac{dA_u}{dt} = CL_u \cdot C,$$

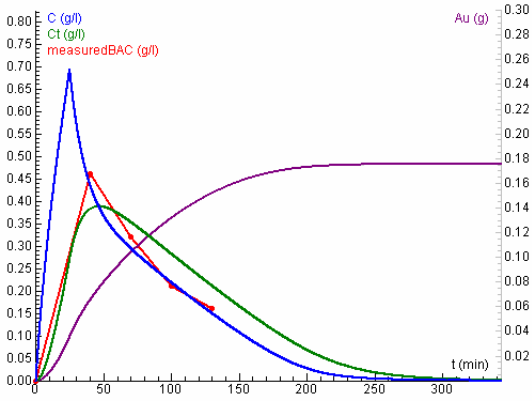
where A_C, A_T, and A_u, are the amounts of alcohol in the central compartment, in the peripheral compartment, and in the urine, respectively.

Fig. 10. Screen shot of the Norberg 2-compartment computer model with data of subject no. 19.



A number of things catch the eye in the computed BAC curve: there exists a fast increase of BAC in the central compartment and after the peak value the alcohol concentration falls rapidly down under the values of the peripheral compartment. For some time there is a decline in alcohol concentration in both compartments that is almost linear. The amount of alcohol that leaves the body via urine is in the computer model about 1% of the total amount consumed. It cannot be denied that the match between measurements and computer model is not good. The main reason for this is that we applied a mathematical model for intake of alcohol via intravenous infusion under completely different circumstances, viz., oral intake of alcohol. Of course the blood alcohol concentration raises rapidly when it is injected directly into the bloodstream. Our graphs are indeed consistent with graphs found in the scientific literature about clinical trials in which alcohol is supplied by intravenous infusion. The 2-compartment model is not really made for oral intake of alcohol. Such a critical look at circumstances under which experiments take place is something that we want to achieve with our pupils: a critical look at the applicability of methods should be second nature.

Fig. 11. Norberg 2-compartment computer model with data of subject no. 19 using an 'effective dose'.



For a better match between the measurements and the Norberg 2-compartment model we must use a better model for the intake of alcohol. One solution is to use a smaller dose in the computation, as if just part of the alcohol consumption really matter. Figure 11 shows the computed graphs when we use an 'effective dose' of 18 grams of alcohol in 25 minutes. Then we achieve a nice match, but in an artificial way. More promising is it to use the Norberg 3-compartment model because in this model intravenous and oral intake have been separated.

Norberg 3-compartment computer model

In the Norberg 3-compartment model the so-called first-pass metabolism is taken into account: in the screen shot below (Fig. 12), which is a computer run for subject no. 19, you can see that the peak value of BAC in the central compartment is smaller than in the 2-compartment model. For the rest there is no great improvement in the match between experiment and computer model. With a suitable choice of 'effective oral dose', just like we did in the 2-compartment model, the conformity between experiment and model can be improved much. The volumes of distribution are theoretical volumes anyway. Henceforth we will use in the computer models the notation A_C, A_T, A_l, and A_u for the amount of alcohol in the central compartment, the peripheral compartment, the liver and the urine, respectively.

Fig. 12. Screen shot of the Norberg 3-compartment computer model with data of subject no. 19.

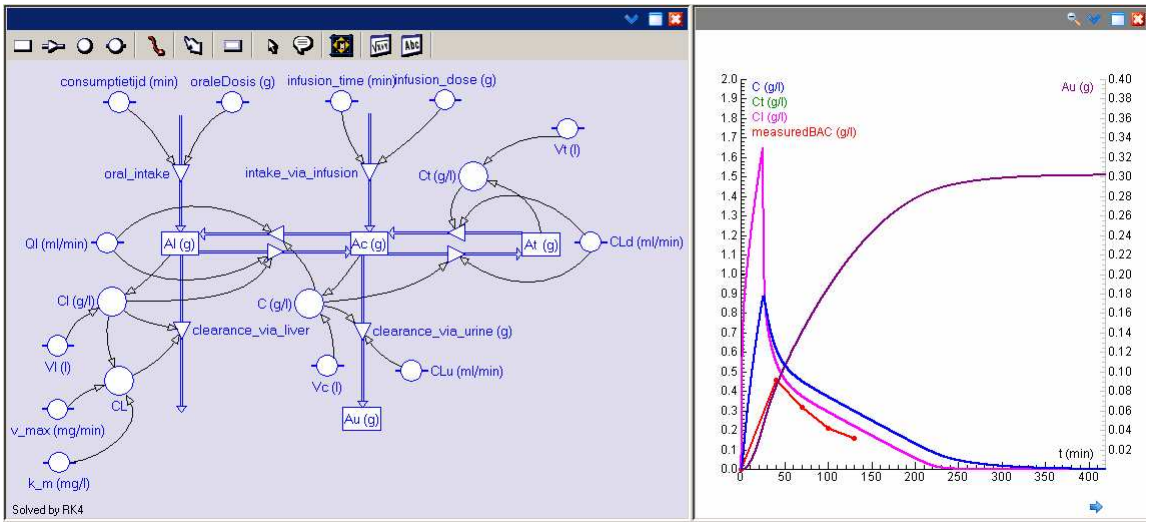
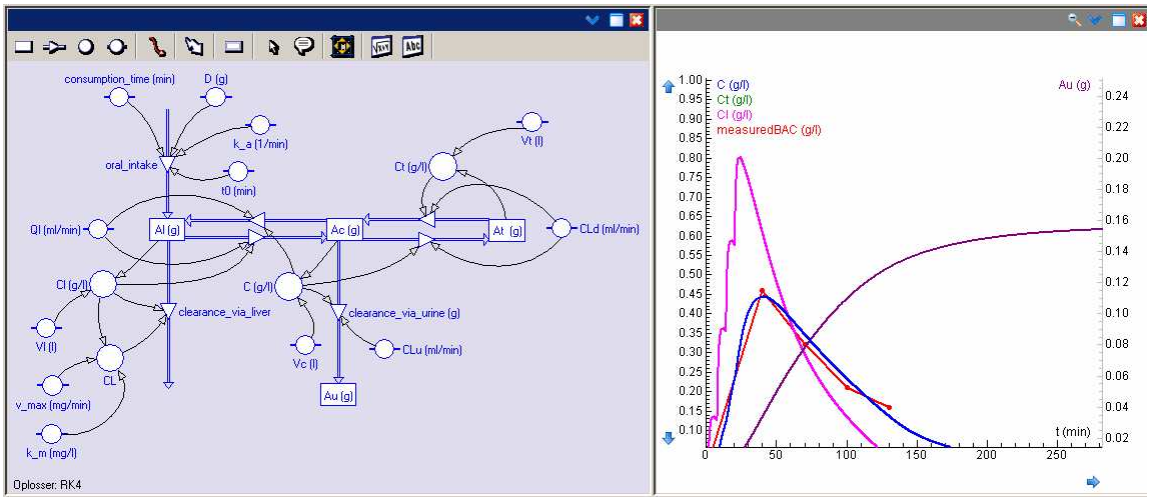


Fig. 13. Screen shot of the Norberg 3-compartment computer model with data of subject no. 19. and with improved modeling of intake of alcohol.



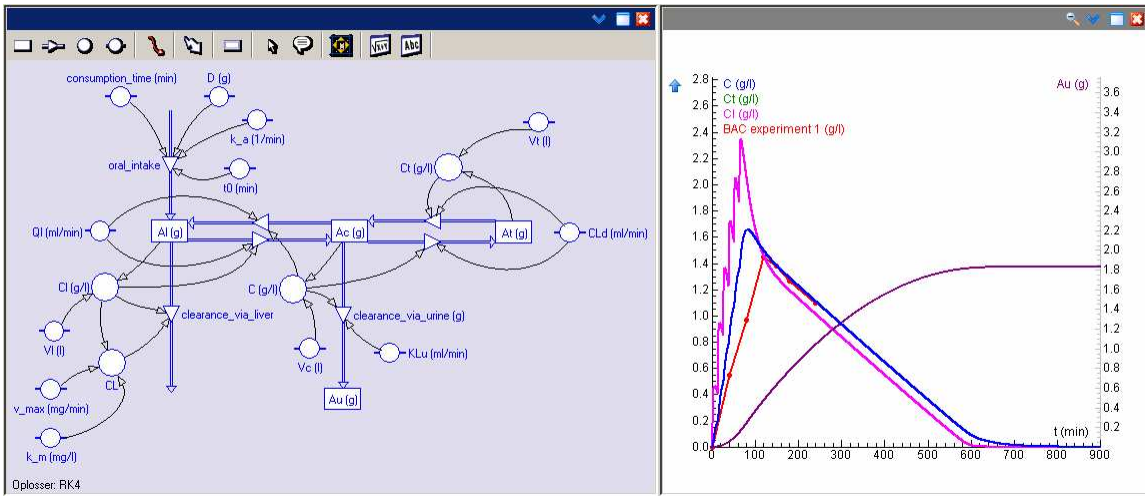
Another description of oral intake of alcohol leads to a better, but still not perfect match between experiment and model: a delayed absorption following fist-order kinetics, like we have described before in the hybrid Widmark model. This means that we assume:

$$\text{rate of intake} = \begin{cases} 0 & \text{if } t < t_0 \\ D \cdot k_a \cdot e^{-k_a \cdot (t - t_0)} & \text{if } t \geq t_0 \end{cases}$$

where D is the alcohol dose, k_a is the absorption coefficient, and t_0 is the time of delay. The screen shot above (Fig. 13) shows that the alcohol concentrations in the liver and the central compartment take less extreme values than before and that a good result can be obtained for suitable choices of parameter values. By the way, we have divided the intake of alcohol during consumption time into four equal parts in order to get a more realistic consumption pattern (here we use again the Pulse function). We have not included the intake via intravenous infusion anymore because the dose will be taken zero in all examples.

For a more adequate model we need a mathematical model that uses more organs. In the Pieters 3-compartment model and in the physiologically based 5-compartment model of Umulis et al this is the case. But before we do this, also have a look at the nice result shown in figure 14, in which measurement 1 of subject no. 22 is compared for suitable parameter vales with the result obtained with the Norberg 3-compartment model.

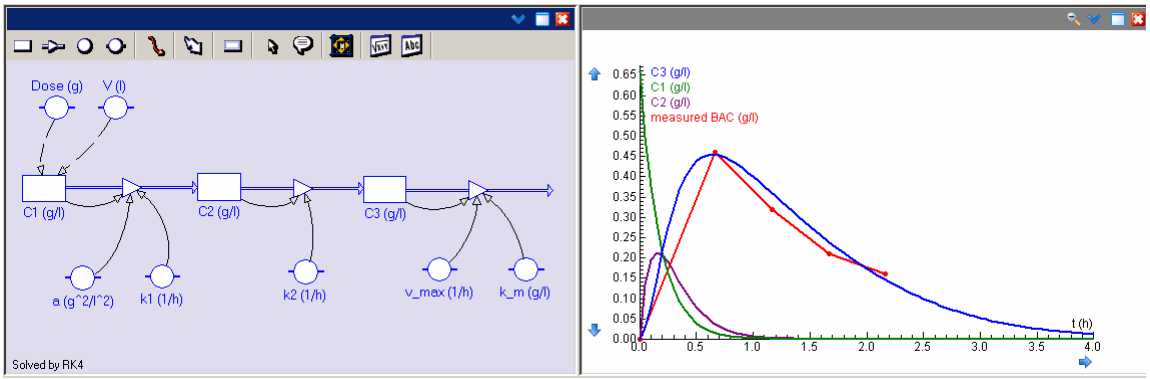
Fig. 14. Screen shot of the Norberg 3-compartment computer model with data of subject no. 22.



Pieters 3-compartment computer model

Figure 15 shows a graphical implementation of the Pieters model that compares well for suitable parameter values with the measurement of subject 19.

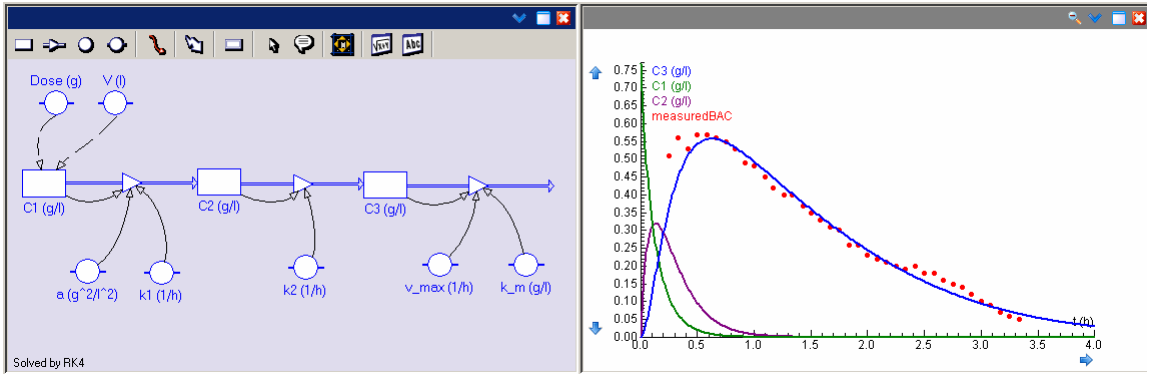
Fig. 15. Screen shot of the Pieters 3-compartment computer model with data of subject no. 19.



For the initial concentration in the first compartment (the stomach) we have chosen the alcohol concentration that would hold in the human body in case the alcohol had been able to distribute immediately over the total body water in an estimated volume of distribution *V*.

Disadvantage of the data set in the previous example is that so small. In Figure 16 we present the measured data of the author drinking 3 glasses of red whine at once on an empty stomach early in the morning. The Pieters model matches for suitable parameter values the recorded blood alcohol concentration very well. In the computer model we have chosen for the feedback parameter a negative value (a = –0.6 l^2/g^2) to get an accelerated intake of alcohol because drinking happened after fasting. Other parameter values have also been chosen within ranges reported in the literature for the Pieters model.

Fig. 16. Screen shot of the Pieters 3-compartment computer model after drinking 3 standard units.



A physiologically based 5-compartment computer model

Most detailed is the physiologically based 5-compartment model of Umulis et al (2005). This model is typically not implemented by pupils themselves, but it serves as an example for them of how modeling is done in modern pharmacokinetic research (Rowland et al, 2004).

Fig. 17. Screen shot of the Umulis 5-compartment computer model.

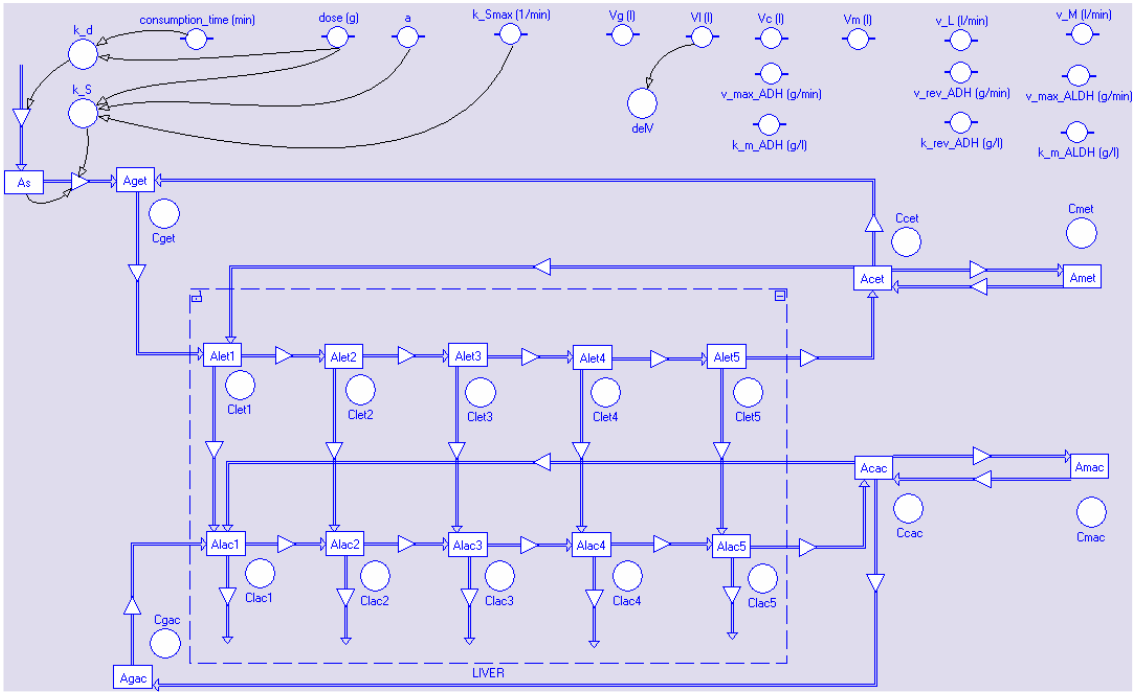
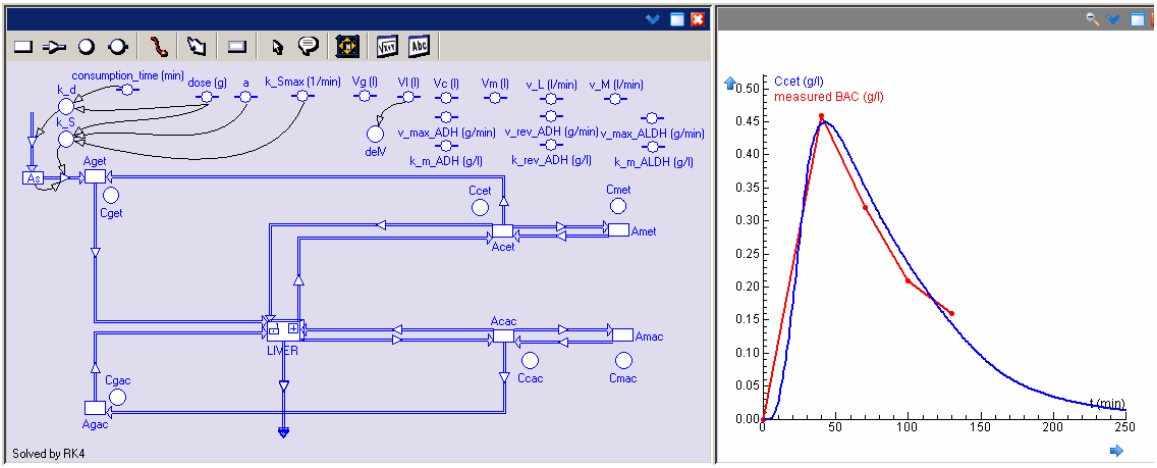


Figure 17 illustrates the complexity of the model. In our implementation of the liver as a tubular flow reactor we have divided the organ into five subcompartments. Not all relation arrows between parameters and other variables have been drawn in the graphical model for the sake of clarity of the picture. The dotted lines in the graphical model indicate that we would like to see the liver as one unit and that the details can be taken out of sight of the user of the computer model; Figure 18 show this looks like. Using this presentation of the computer model teacher and pupils can discuss the model more easily. The match between model and data measured for subject no. 19 is good. However, since we are dealing with a stiff system of differential equations, the time step in the ODE solver must be chosen very small (0.001 min) to avoid numerical problems. This means that the computation takes long.

Fig. 18. Screen shot of the Umulis 5-compartment computer model with data of subject no. 19.



For those who still have doubts about the usefulness of the physiologically based model we give Figure 19 that is a screen shot of the graphs of alcohol concentration in the small intestine and the central compartment of a sober person with a personal weight of 80 kg after consumption of 24 grams of alcohol in 20 minutes. The background graph belongs to measured data from a clinical trial (Di Padova et al, 1987). It is easy to see that it takes about is two hours after consumption of this amount of alcohol before the concentrations in the two compartments are equal. At that moment, most of the consumed alcohol has been taken into the total body water.

Fig. 19. Umulis 5-compartment computer model of alcohol consumption in a clinical trial with an empty stomach.

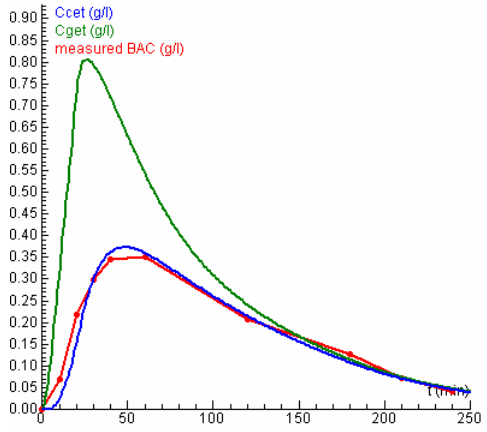
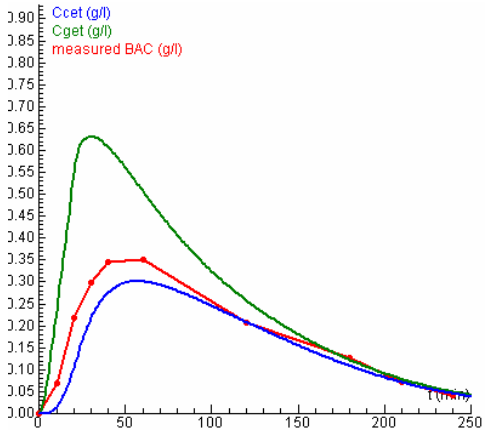


Fig. 20. Umulis 5-compartment computer model of alcohol consumption with a full stomach.



In the computer model of Figure 19 we have chosen for the feedback parameter a negative value ($a = -0.0003$) to get an accelerated intake of alcohol because the subject in the clinical trial had fasted before the experiment. Choosing a positive value can simulate the effect of a meal. Figure 20 has been obtained by choosing a equal to +0.0003. It is evident that the peak value of BAC for alcohol consumption with a full stomach is less high than with an empty stomach. The effect is after some time gone.

Conclusion

The last example in the previous section illustrates in particular the power of mathematical modeling: After one has successfully constructed a mathematical model and a corresponding computer model that describe reality adequately for well-chosen parameter values, one can investigate the influence of various factors in the model by varying the parameter values. We have already seen that the physiologically based 5-compartment model predicts that someone gets drunk faster if he or she consumes alcohol with an empty stomach than a person who drinks after or during a meal. With this computer model, but also with the less complicated models described in this paper, a pupil can investigate whether a person who drinks 3 glasses of beer at once may drive a car earlier than a person who consumes the same amount of alcohol, but at a slower speed and with time intervals in between. A pupil can also find clues that explain why women in general get drunk earlier than men when they consume the same amount of alcohol. A pupil could investigate what happens when drugs inhibit the conversion of acetaldehyde into acetate. Anyway, the amount of acetaldehyde would accumulate under these circumstances. This chemical substance has physiological side effects like sickness, decrease of blood pressure, flushing, and qualms. These aversive sensations in people are actually used in treatments of alcoholics.

The diversity of the models of alcohol intake and clearance in humans that have been discussed in this paper give a good idea of the common method of working in mathematical modeling: first one simplifies the situation to such an extent that a simple (computer) model can be constructed. Hereafter one evaluates this model, preferably by comparing it with experimental data, and one adapts the model if necessary. In the process of evaluation, parameter estimation plays an important role as well. The complexity of finding suitable parameter values must not be underestimated. Adaptation of the model normally means that one makes the model more complicated by taking more factors that cannot really be neglected into account or by undoing some earlier simplifications. In this way one comes into the process of simplifying first and then adding step-by-step more details to the model, with the purpose of matching the model better with reality.

This progressive aspect of graphical modeling is also a pointer to a suitable manner to introduce it to pupils: it seems best not to let them construct out of the blue some well-functioning model, but to let them first improve an existing model by changing or adding details. Here it is important that pupils can compare the results of the computer model with real data, preferably collected in an earlier measurement activity. For the modeling of alcohol intake and clearance breath analysis equipment of sufficient quality is available for the price of 125 euro; professional equipment, which researchers use in clinical trials and which the police uses for traffic control is more expensive (about 700 euros), but it can be rented and sometimes borrowed. A third alternative is to build yourself analysis equipment by means of a rather cheap gas sensor (about 20 euros). Anyway, measurement of intake and clearance of alcohol in humans are feasible as practical work for pupils at school. Confrontation of a model with reality turns graphical modeling not only into a fun way of learning, but it also makes it exciting, challenging, and concrete work for pupils. Experience is that this is practicable (TdB, 2003) and that pupils can actually use the same theoretical framework, methods and techniques as practicing professionals.

Acknowledgments

The author would like to thank his colleague Cor de Beurs for the financial support in the framework of outreach activities of the Faculty of Science, University of Amsterdam, that allowed purchase of the breath analysis equipment.

List of references

Ammon E., et al. (1996). Disposition and first-pass metabolism of ethanol in humans: Is it gastric or hepatic and does it depend on gender? *Clin Pharmacol Ther* **59**, 503-5133.

Di Padova, C., Worner, T.M., Julkunen, R.J.K., Lieber, C.S. (1987). *Gastroenterology* **92**, 1169-1173.

Dräger Safety (2006). www.draeger.com/ST/internet/pdf/Master/En/gt/Alcodrug/9044868_Alcotest6510_e.pdf

Fogler, H.S. (2005). *Elements of Chemical Reaction Engineering* (3rd Ed.). Upper Saddle River, NJ: Prentice Hall. See also: www.engin.umich.edu/~cre/

Hahn, R.G., Norberg, Å., Jones, A.W. (1997) 'Overshoot'of ethanol in the blood after drinking on an empty stomach. *Alcohol & Alcoholism* **32** (4) 501-507.

Hahn RG, et al. (1994). Eating a meal increases the clearance of ethanol given by intravenous infusion. *Alcohol Alcohol* **29**, 673-677.

Killian, F., Kerkstra, A. (2003). Een alcohol-blaastest: technisch ontwerpen als praktische opdract voor 6-vwo (A Breathalyzer: Technical Design as Practical Work for 6-vwo). NVOX 5 (mei 2003), 218-221.

Lands, W.E.M. (1998). A Review of Alcohol Clearance in Humans. *Alcohol* **15**, 147-160.

Levitt M.D. (1996). Agonist: the case against first-pass metabolism of ethanol in the stomach. *J. Lab. Clin. Med.*, Vol 123, 1996, pp. 28-31.

Levitt M.D., et al. (1997). Use of measurements of ethanol absorption from stomach and intestine to assess human ethanol metabolism. *Am J Physiol* **273** (*Gastrointest. Liver Physiol* 36): G951- G957.

Lim R.T., et al. (1993). First-pass metabolism of ethanol is predominantly gastric. *Alcoholism: Clin Expr Res* **17**, 1337-1344.

Lotsof, J. (2003). A Revised Pharmacokinetic Model for Alcohol. *Clin Pharmacokinet* **42** (6) 585-587.

Mathijssen, M.P.M, Twisk, D.A.M. (2001). *Opname en afbraak van alcohol in het menselijk lichaam* (Intake and clearance of alcohol in the human body). SWOV rapport r-2001-19. www.swov.nl/rapport/r-2001-19.pdf

Mioduszewska, E., Ellermeijer, T. (2001). An Authoring Environment for Multimedia Lessons. In: R. Pinto, S. Rusinach (eds.) *Physics Teacher Education Beyond*, Elsevier: Paris, pp. 689-690.

Monshouwer, K., et al (2003). *Jeugd en riskant gedrag. Kerngegevens uit het Peilstationonderzoek 2003* (Youth and Risky Behavior: Key Figures from the Peilstation Survey 2003) Utrecht: Trimbos-instituut.

NDM (2004) *Nationale Drugs Monitor 2003* (National Drugs Monitor. Annual report 2003). Utrecht: Bureau NDM, Trimbos-instituut.

NDM (2006) *Nationale Drugs Monitor 2005* (National Drugs Monitor. Annual report 2003). Utrecht: Bureau NDM, Trimbos-instituut.

NIAAA (1997). National Institute on Alcohol Abuse and Alcoholism: Alcohol Metabolism. *Alcohol Alert*, **35**. http://pubs.niaaa.nih.gov/publications/aa35.htm

Norberg, Å., Gabrielsson, J., Jones, A.W., Hahn, R.G. (2000). Within- and between subject variations in pharmacokinetic parameters of ethanol by analysis of breath, venous blood and urine. *Br J Clin Pharmacol* **49**, 399-408.

Norberg, Å (2001). Clinical Pharmacokinetics of Intravenous Ethanol: Relationship Between the Ethanol Space and Total Body Water. PhD thesis. Karorlinska University: Stockholm, Sweden. http://diss.kib.ki.se/2001/91-7349-053-9/thesis.pdf

Norberg, Å., Jones, A.W., Hahn, R.G., Gabrielsson, J. (2003). Role of Variability in Explaining Ethanol Pharmacokinetics. *Clin Pharmacokinet* **42** (1) 1-31.

Pieters, J.E., Wedel, M., Schaafsma, G.J (1990). Parameter estimation in a three-compartment model for blood alcohol curves. *Alcohol & Alcoholism* **25** (1) 17-24.

Pol, M. van de, Duijser, E. (2003). *Meting alcoholgebruik jongeren. Onderzoek onder Nederlandse jongeren 10 t/m 15 jaar* (Measuring Alcohol Usage amongst Young People: Research amongst Dutch young people of age between 10 and 15). Amsterdam: NIPO.

Rowland, M., Balant, L., Peck, C. (2004). Physiologically Based Pharmacokinetics in Drug Development and Regulatory Science: A Workshop Report (Georgetown University, Washington DC, May 29-30, 2002). *AAPS PharmSci* **6** (1) article 6. www.aapspharmsci.org.

Seidl, S., Jensen, U. en Alt, A. (2000). The calculation of blood ethanol concentrations in males and females. *Int J Legal Med* **114**, 71-77.

Swift, R. (2003). Direct measurement of alcohol and its metabolites. *Addiction* **98** (Suppl. 2) 73-80.

Tdβ (2003). Special issue on modeling. *Tijdschrift voor Didactiek der β-wetenschappen* **20** (2003), nr. 1.

Umulis, D.M, Gürmen, N.M., Sing, P., Fogler,H.S. (2005). A physiologically based model for ethanol and acetaldehyde metabolism in human beings. *Alcohol* **35**, 3-12.

Wagner, J.G., Patel, J.A. (1972). Variations in absorption and elimination rates of ethyl alcohol in a single subject. *Res Commun Chem Pathol Pharmacol* **4**, 61-76.

Watson, P.E, Watson, I.D. en Batt, R.D. (1980). Total body water volumes for adult males and females estimated from simple anthropometric measurements *Am J Clin Nutr* **33** (1) 27-39.

Weathermon R., Crab D.W. (1999) Alcohol and Medication Interactions. *Alcohol Research & Health* **23** (1) 40-54.

Wedel, M., Pieters, J.E., Pikaar, N.A., Ockhuizen, Th. (1991). Application of a three-compartment model to a study of the effects of sex, alcohol dose and concentration, exercise and food consumption on the pharmacokinetics of ethanl in healthy volunteers. *Alcohol & Alcoholism* **26** (3) 329-336.

Widmark, E.M.P (1932) Die theoretischen Grundlagen und die praktische Verwendbarkeit der gerichtlich-medizinischen Alkoholbestimmung. Urba & Schwarzenberg: Berlin.