INVESTIGATING PHARMACOKINETICS BY DETERMINING THE IMPACT OF GENDER ON RATE OF ALCOHOL METABOLISM IN THE HUMAN BODY USING EULER'S METHOD

BACKGROUND AND THEORY

The idea for this investigation came about when I was thinking about my family. My mom, who rarely ever drinks, always talks about how women and men breakdown alcohol differently, causing them to be high for longer or shorter periods of time. Because she is female, she claimed that drinking alcohol is worse for her than for my dad because she feels "high" longer. In addition, in the future, I want to be an anesthesiologist—a doctor that administers anesthesia before surgery. Compelled by my curiosity into anesthesiology and my wishes to see if my mom's beliefs have basis in truth, my math group decided to do research into the math behind the relationship between drugs and the body and the differences between men and women.

In the United States, alcohol ranks as the most abused drug, with more than 17,600,000 people—or 14% of all adults aged 18+—suffering from alcohol addiction or abuse. In fact, according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), "more than 100,000 Americans die from alcohol-related causes, making it the third leading cause of death behind cancer and heart disease" ("Alcohol Abuse and Death"). Moreover, under-age drinking is a serious problem amongst today's youth. At Skyline High School, we are surrounded by peers who drink alcohol regardless of the detrimental effects of alcohol on their abilities to concentrate. In Washington State, over 40% of teenagers aged 15-19 have consumed alcohol in the past month. Additionally, over 20% of teenagers have admitted to drinking and driving ("What is alcohol awareness and why is it important?"). It is quite evident from the data that teenage drunk driving is a prominent issue in our country. Given the high mortality rates due to alcohol, the dangers of alcohol abuse, and its prevalence at my school, the aim of this study is to use mathematics to investigate the differences in rates of alcohol metabolism between men and women.

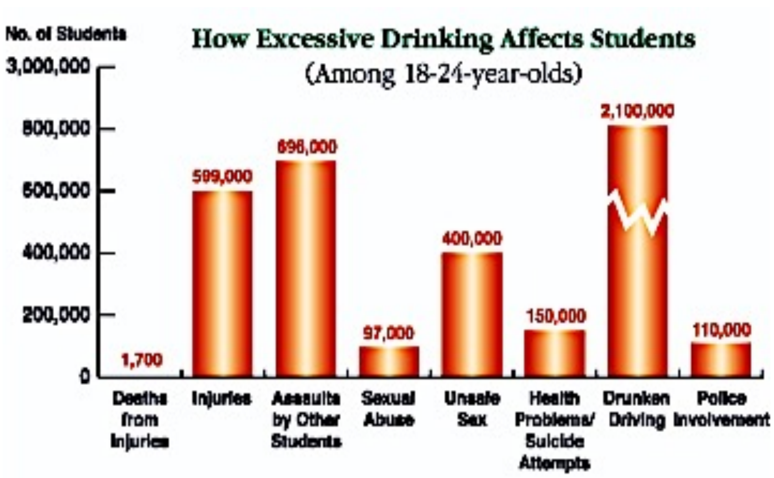

Fig.1. Illustration of the harmful effects of drinking on students and deaths associated with drinking. It is clear that alcohol is a huge problem in today's society, especially amongst young adults.

A procedure was developed using pharmacokinetics. According to Bourne et al., Pharmacokinetics is defined as "the mathematics behind what happens to a drug from the time it is administered throughout its circulation within the body to the moment it is ultimately eliminated" (Bourne et al., 2010). After administration, the concentration of any drug in the body decreases over time as the body metabolizes it.

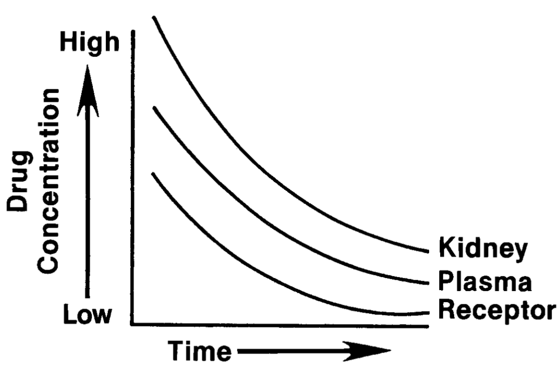

Fig.2. The general trend for drug concentration in the body over time. At first, the drug is metabolized faster due to a higher concentration in the bloodstream, but soon, the rate slows. Eventually, the amount of the drug in the body becomes negligible.

In order to model the metabolization of alcohol using mathematics, blood alcohol concentration (BAC) must be calculated as a relation to time. However, because the behavior of drugs in the body is complex and thousands of processes factor into drug concentrations in different tissues and fluids, simplifications of body processes are necessary. One way to make these simplifications is to separate the processes into different groups. This approach to pharmacokinetics is known as the "compartmental model" (Dipiro et al., 2010). In this model, tissues and organs that interact with that drug similarly are grouped together in a single "compartment".

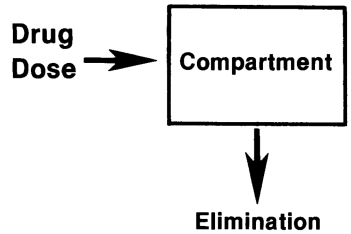

Fig.3. The simplest, version of the compartment model: the single compartment model. The only "compartment" in this model contains the organs involved in drug elimination for the body.

In order to more accurately model alcohol metabolism, our model will be slightly more complicated than in figure 3. It will contain two compartments—drug absorption and drug elimination:

1. ***Compartment 1:*** *Absorption*
   Absorption is defined as the "irreversible transfer process in which the drug is transferred from its site of administration to the systemic circulation" ("Absorption"). Most drug absorption takes place in the gastrointestinal tract. In the case of this study, after being ingested, alcohol is channeled down to the stomach. There, it is broken apart and disperses into the gastric lumen. It then permeates the membrane of the small intestine into blood stream where it travels to other organs such as the brain and heart. Overall, absorption is dependent on the amount of drug taken, amount that can be absorbed by the body, and an individual's absorption rate constant. Due to all of these factors, absorption in the body can be modeled by the following equation:

$$\mathbf{1}/_{\boldsymbol{V_D}}\,(\boldsymbol{K_A} \times \boldsymbol{F} \times \boldsymbol{D} \times \boldsymbol{e^{-0.5t}})$$

   a. $\boldsymbol{K_A}$ is defined as the *absorption rate constant*
      -In the gastrointestinal tract, drugs are absorbed at a constant rate. Thus, absorption rate constant is a characteristic of the patient based on his/her physical characteristics and genetics ("Absorption"). The average absorption rate constant is 0.077 in women aged 20-45 and 0.044 in men aged 20-45 (Avdeef et al., 2003).
   b. $\boldsymbol{F}$ is defined as *bioavailability*, or fraction of the dose that has been absorbed into the bloodstream
      - Bioavailability is defined as "the proportion of drug or other substance that enters the bloodstream when introduced into the body" ("Drug Absorption and Elimination: Pharmacokinetics"). Because each individual has varying based on genetics and lifestyle, the amount of drug absorbed though the gastrointestinal tract varies from person to person. The average bioavailability in women aged 20-45 is 66% or 0.66, and the average bioavailability in men aged 20-45 is 73%, or 0.73 (Baraona et al., 1994).
   c. $\boldsymbol{V_D}$ is defined as the *volume of distribution*
      -Volume of distribution is the "ratio of the dose present in the body (*X*) and its plasma concentration (*P*)" (Dipiro et al., 2010).

$$\boldsymbol{V_D} = \boldsymbol{X}/_{\boldsymbol{P}}$$

      V_D is not a real "volume" of substance. Instead, it indicates the amount of body fluids that is necessary for the drug to be distributed evenly in the body. Hence, drug concentrations depend greatly on the physicochemical properties of the drug. Consequently, V_D is a characteristic property of the drug and is not impacted much by an individual's physical features (Cowan et al., 1996). For ethyl alcohol, the volume of distribution is 0.63 in women aged 20-45 and 0.72 in men aged 20-45 (Cowan et al., 1996).
   d. $\boldsymbol{D}$ is defined as the *drug dose*
      -In this study, drug dose is defined as 120 mL of ethyl alcohol in any amount of wine, spirit, beer, vodka, or other alcoholic drink. This value was chosen because this is the minimum amount of alcohol that can lead to death via alcohol poisoning in humans. The value was also chosen out of our own group's own curiosity.
   e. $\boldsymbol{e^{-0.5t}}$ represents the *absorption half-life* of the drug in the body.

-The value *"-0.5t"* is a reflection of the time it takes to absorb half of the circulating drug. *"t"* is time in minutes.

2. ***Compartment 2:*** *Elimination*

Elimination is defined as the "irreversible removal of drug from the body by all routes of elimination" ("Chapter 6. Drug Elimination and Clearance"). The kidney is responsible for the majority of the excretion of alcohol from the body through urine. Trace amounts are also secreted via saliva, exhaled air, bile, or sweat. The elimination dynamic is dependent directly on an individual's elimination rate constant, the amount the substance distributes itself in the body, and the concentration of the drug left in the body after a certain period of time. Due to all of these factors, elimination in the body can be modeled by the following equation:

$$\boldsymbol{K_E \times V_D \times C}$$

a. $\boldsymbol{K_E}$ is defined as the *elimination rate constant*

-In the human body, drugs are eliminated at a constant rate through urine, sweat, and other methods. Thus, elimination rate constant is a characteristic of the individual rather than the drug. The average elimination rate constant is 0.004 in women aged 20-45 and 0.0037 in men aged 20-45 (Avdeef et al., 2003).

b. $\boldsymbol{V_D}$ is defined as the *volume of distribution*

-V_D for elimination is the same as in the absorption compartment.

c. $\boldsymbol{C}$ is defined as *concentration in the bloodstream* (in %mg)

- This is what we are trying to determine over time in men vs women using our pharmacokinetic equation. It will tell us the BAC over time.

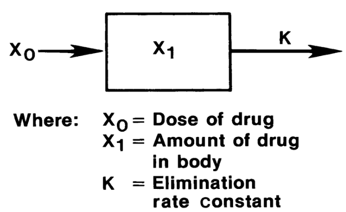

Fig.4. An illustration of how absorption and elimination correlate in the body. X_1 is the amount of drug absorbed from after the original dose of drug, X_0. K, the elimination rate constant, is the amount of drug leaving the body over time after absorption.

Using the two above equations, a third equation can be derived. According to the laws of pharmacokinetics, we can subtract the elimination compartment from the absorption compartment. This is based on the idea that absorption into the bloodstream increases the amount of a drug in the bloodstream and elimination decreases it. The complete relationship is described in the following differential equation:

$$\boldsymbol{\frac{dC}{dt} = \frac{1}{V_D}\left(K_A\, F D e^{-0.5t}\right) - K_E\, V_D C}$$

Using this equation, our group can now model the metabolization of alcohol in the body by substituting researched values for the variables in males and females. The created two equations will demonstrate values for a 160 lb female and a 180 lb male from ages 20-45. These ages were chosen because the age range from 20-45 has the highest proportion of its population that has reported drinking in the past 12 months—64.5% ("Alcohol Abuse and Death"). Ages 20-45 are also in the peak range of adulthood for a human being. In addition, 160 lbs was chosen for females and 180 lbs for males because the average weight for women in the US is 166.2 lbs, and the average weight for men is 195.5 lbs. Research will be conducted to find the appropriate constants to fit into the equations. These constants will be the averages for the defined population and will come from credible sources like governmentally funded research and universities. After the differential equations are created, Euler's method can be used to generate data from these equations that outline the decline in BAC (in %mg) over time in both gender groups. Data will be rounded to 3 significant figures because data is in the triple digits and additional accuracy would not make a significant difference in our end result. The step size for our data will be 30 min starting at 0 min for a total of 20 steps. Data can be used to demonstrate general trends in how fast BAC declines in men versus women. This data can be graphed in a line graph in excel and values compared to real life data to evaluate how accurate our trends are and whether they reflect reality.

This investigation can further my knowledge on the use of Euler's method in real world applications such as in anesthesiology with pharmacokinetics. Complex pharmacokinetical testing can determine levels of drugs in the body during surgery and toxic chemicals during chemotherapy (Eason et al., 1990). However, this investigation proposes to look into a more every-day application of the pharmacokinetics equations with BAC, an application that has not been looked into in my mathematics class. My personal objective is to gain a deeper understanding of how I can use Euler's method to investigate pharmacokinetics.

RESEARCH QUESTIONS

1. In what ways does gender impact the rate of metabolism of alcohol in the body?
2. Do males or females metabolize alcohol faster?
3. How long does it take for alcohol to leave the bloodstream in men vs women?

HYPOTHESIS

If the rates of absorption and elimination of alcohol in males and females are compared, then females will absorb alcohol faster and eliminate from their bodies slower.

SOLVING FOR EQUATIONS AND DETERMINING TRENDS

1. *Determining values for the equation's variables for women and men in the age range 20-45*

   The following values were accumulated from internet research:

VARIABLE	SOURCE	VALUE	HOW DATA WAS DETERMINED
V_D	Cowman et al., 1996	• Women: 0.63 • Men: 0.72	Six men (age 20-43) and four women (age 25-35) were given ethanol alcohol at 0.9 mg per kilogram of body weight. After inoculation, breath alcohol measurements were recorded every 20 min until each subject's BAC returned to zero. The average volume of distribution (V_D) was calculated as an average percentage. For the women, the mean was 0.63 (range, 0.54-0.71). For the men, the mean was 0.72 (range 0.63-0.77).
K_A	Avdeef et al., 2003	• Women: 0.077 • Men: 0.044	Using conditional constants and conducting ion-pair absorption of ionized drugs using liposome chromatography, Avdeef et al. determined a constant for an average absorption rate in drugs for both men to women (age 20-30) and men (age 20-30). In women, the average absorption rate constant was 0.077 while in men it was 0.044.
K_E	Avdeef et al., 2003	• Women: 0.004 • Men: 0.0037	Using conditional constants and conducting ion-pair absorption of ionized drugs using liposome chromatography, Avdeef et al. determined a constant for an average elimination rate in drugs for both men to women (age 20-30) and men (age 20-30). In women, the average absorption rate constant was 0.004 while in men it was 0.0037.
D		120 mL of pure ethanol alcohol in any amount of liquid	Drug dose was set at 120 mL of ethyl alcohol in any amount of wine, spirit, beer, vodka, or other alcoholic drink. This value was chosen because this is the minimum amount of alcohol that can lead to death via alcohol poisoning in humans. The value was also chosen out of our own group's own curiosity.
F	Baraona et al., 1994	• Women: 0.66 • Men: 0.73	Baraona et al., conducted an experiment on the role of gastric metabolism in different individuals with different characteristics, such as gender, on bioavailability. She gave women (age 23-37) and men (age 35-43) 20 mL of ethanol alcohol in the form of 40 g/L shots. She determined that women have a higher average bioavailability for alcohol, at 0.66 (66%), in comparison to men, at 0.73 (73%).

2. *Replacing the variables in the pharmacokinetics equation with values and simplifying*

   a) The pharmacokinetics equation derived for this study is: $\boldsymbol{\frac{dC}{dt} = \frac{1}{V_D}\left(K_A FDe^{-0.5t}\right) - K_E V_D C}$

   b) If we plug in the researched values for the variables and simplify:

   MEN:

   i. $\frac{dC}{dt} = \frac{1}{0.72}(0.044 \times 0.73 \times 120 \times e^{-0.5t}) - (0.0037 \times 0.72 \times C)$

   ii. $= \frac{1}{0.72}(3.8544\, e^{-0.5t}) - (0.002664\, C)$

   iii. $= \mathbf{5.3533\, e^{-0.5t} - 0.002664\, C}$

   WOMEN:

   i. $\frac{dC}{dt} = \frac{1}{0.63}(0.077 \times 0.66 \times 120 \times e^{-0.5t}) - (0.004 \times 0.63 \times C)$

   ii. $= \frac{1}{0.63}(6.0984\, e^{-0.5t}) - (0.00252\, C)$

   iii. $= \mathbf{9.68\, e^{-0.5t} - 0.00252\, C}$

3. *Creating the equation for Euler's Method*

a) Euler's method is to find an approximation to a particular solution by numerical analysis. The general equation is:

$$y_{n+1} = y_n + y' dx$$

b) If we plug in our own data and equation from step 2 in addition to our step size at 30 minutes, we get:

MEN: $\mathbf{C_{n+1} = C_n + 30(5.3533\, e^{-0.5t} - 0.002664\, C)}$

WOMEN: $\mathbf{C_{n+1} = C_n + 30(9.68\, e^{-0.5t} - 0.00252\, C)}$

4. *Solving the equation*

MEN:

n	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
x (min)	0	30	60	90	120	150	180	210	240	270	300
Y (BAC in mg %)	0	161	148	136	125	115	105	97.4	89.6	82.5	75.8
n	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
x (min)	330	360	390	420	450	480	510	540	570	600	
Y (BAC in mg %)	69.8	64.2	59.1	54.4	50.1	46.1	42.4	38.9	35.8	32.9	

Sample Calculations:

i. $C_{n+1} = C_n + 30(5.3533\, e^{-0.5t} - 0.002664\, C)$

ii. $C_{0+1} = 0 + 30[5.3533\, e^{-0.5(0)} - 0.002664\,(0)]$

iii. $= \mathbf{160.599}$

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iv. $C_{1+1} = 161 + 30[5.3533\, e^{-0.5(30)} - 0.002664\,(161)]$

v. $=$**148.133**

*Rest of values were calculated using Microsoft excel

WOMEN:

n	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
x (min)	0	30	60	90	120	150	180	210	240	270	300
Y (BAC in mg %)	0	290	268	248	229	212	196	181	167	154	143
n	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
x (min)	330	360	390	420	450	480	510	540	570	600	
Y (BAC in mg %)	132	122	113	104	96.6	89.3	82.6	76.3	70.5	65.2	

Sample Calculations:

i. $C_{n+1} = C_n + 30(9.68\, e^{-0.5t} - 0.00252\, C)$

ii. $C_{0+1} = 0 + 30[9.68\, e^{-0.5(0)} - 0.00252\,(0)]$

iii. $= \mathbf{290.4}$

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iv. $C_{1+1} = 290 + 30[9.68\, e^{-0.5(30)} - 0.00252\,(290)]$

v. $= \mathbf{268.076}$

*Rest of values were calculated using Microsoft excel

5. *Graph of data comparing men and women*

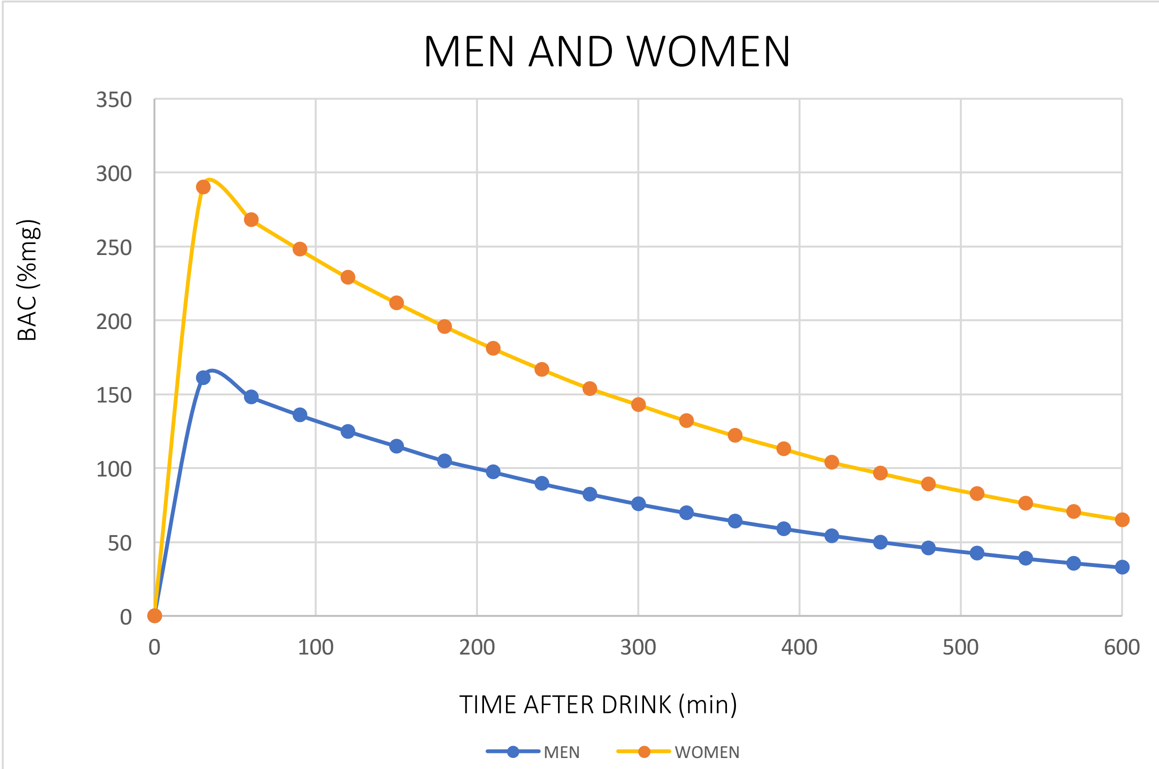

Fig.5. Illustration of the BAC over time in men vs women. Trends suggest that women absorb much more alcohol into their bloodstream than men do, but they eliminate the alcohol from their bloodstream much faster as well. This means that women get intoxicated with alcohol much easier than men.

<u>CONCLUSION</u>

Considering the dangers of alcohol consumption to the human body and the detrimental effects it has on an individual's concentration, the effects of gender on alcohol metabolism are important to understand. The goals of this investigation were to determine how alcohol is absorbed and eliminated differently in males and females. Our objective was to use the mathematics behind anesthesiology—pharmacokinetics—to create two differential equations that model alcohol metabolism. Then, using Euler's method, we were to evaluate the equation to create data that could be graphed to show the trends in the rates of male vs female metabolism. I had hypothesized that females would absorb a lot more alcohol than men and would also eliminate it from their bodies slower. Results from this study disproved my hypothesis. The main conclusions are the answers to the research questions stated earlier:

1. Females absorb alcohol at a higher rate than men do, making their BAC rise to a higher level
2. But, females also eliminate the alcohol from their bodies much faster than men do
3. However, because female absorption of alcohol is so much higher than that of a man, data suggests they will stay intoxicated longer

Findings from this study uphold the concept that females metabolize alcohol differently than men ("National Institute of Health"). According to the National Institute on Alcohol Abuse and Alcoholism, women have a lower percentage of water in their body than men that have a similar body weight. As a result, they accumulate higher concentrations of ethanol in their blood after drinking the same amount of alcohol. This lesser amount of body water in comparison causes women to become intoxicated much faster when drinking alcohol.

Likewise, findings from this study also substantiated the concept that women exhibit higher rates of elimination than males. In the words of Dr. Thomasson at the University of Rochester, men "exhibit higher alcoholic metabolic rates than males as a result of hormonal differences" (Thomasson et al., 1995). These hormonal differences include genetic factors, gastric elimination, and hepatic and gastric alcohol dehydrogenase. Thus, due to hormonal differences, BAC in women lowers at a faster rate than in men.

Finally, findings from this investigation also supported the idea that alcohol-induced liver diseases would develop more quickly in women than in men ("Casa Palmera"). Because results suggest that women absorb alcohol into their blood stream at a higher rate than men, it demonstrates that they have higher risks of diseases caused by alcohol such as heart disease, breast cancer, and liver damage than men who drink the same amount.

Essentially, this study demonstrated that although women eliminate alcohol faster than men do, they need to be more cautious because they are at higher risks for alcohol poisoning and become intoxicated at much slower rates. This trend can be applied to other drugs as well. Because absorption and elimination rate coefficients are characteristic of the individual and not based off the drug, it would make sense for women to have a greater absorption and elimination rate than men. This conclusion is supported by findings from the Leafly Cannabis Institute. According to Rough et al., women are more susceptible to impulsivity, stress, and learning and memory damage than men after smoking weed (Rough et al.). This data supports the idea that absorption and elimination vary greatly depending on an individual's physical characteristics. Hence, trends for differences between men and women can be translated to in other medicines and drugs for blood concentration.

REFLECTION AND EVALUATION OF LIMITATIONS

Values that were gotten from the investigation were values that I had expected to obtain. I had expected women to accumulate more alcohol in their bloodstream than men. I also expected the BAC to decrease over time in both men and women due to elimination. The results of this study follow the laws of pharmacokinetics, mathematics, chemistry, and physiology of the human body.

In addition, the trends demonstrated in our equations are similar to the trends demonstrated in real life data. Figure 6 demonstrates how the trends are similar. Corresponding patterns in real data illustrate that our data is reasonable.

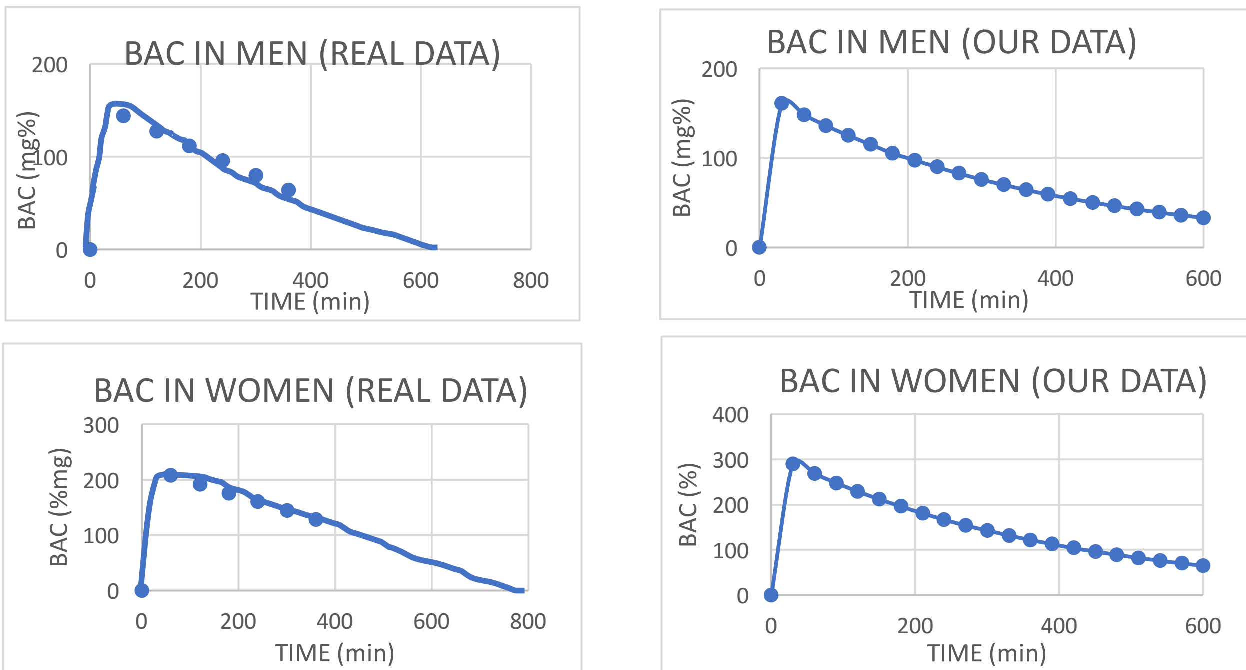

Fig.6. Illustration of the BAC over time in men and women in our equation in comparison to real data. The trends are extremely similar, and our trends match up with what is occurring in real life. In women, peak blood alcohol constant is higher, and they also eliminate alcohol faster than men (Miller et al., 1982).

In this investigation, our group utilized the "2-compartmental model" in combination with Euler's method. Although this method is useful for outlining the general trend, it simplifies the physiology of the human body. Thus, it has several limitations. Because tissues and organs that share similar characteristics when interacting with the drug are grouped into a single "compartment", the specific aspects of each organ are not taken into consideration. In addition, the compartment model considers elimination rate to be a constant. However, in real life, inter-individual variability exists due to one or more of these factors:

- Variations in drug absorption and drug distribution per individual
- Differences in an individual's ability to metabolize and eliminate the drug (e.g. genetics)
- Disease states (e.g. renal or hepatic insufficiency) or physiologic states (e.g. obesity or activity levels)
- Interactions with other drugs

As a result, our generated data was slightly inaccurate because it did not account for all aspects of the human body. However, these errors were not enough to completely change the overarching conclusions from this lab.

In the future, further investigation along this path can be pursued. It would be interesting to see the effects of age or weight on alcohol metabolism in the body and whether it plays a bigger or smaller role than gender. This would mean creating differential equations for different weight or age groups—maintaining a constant gender—and seeing how weight or age impacts the rates of absorption and elimination in the human body.

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