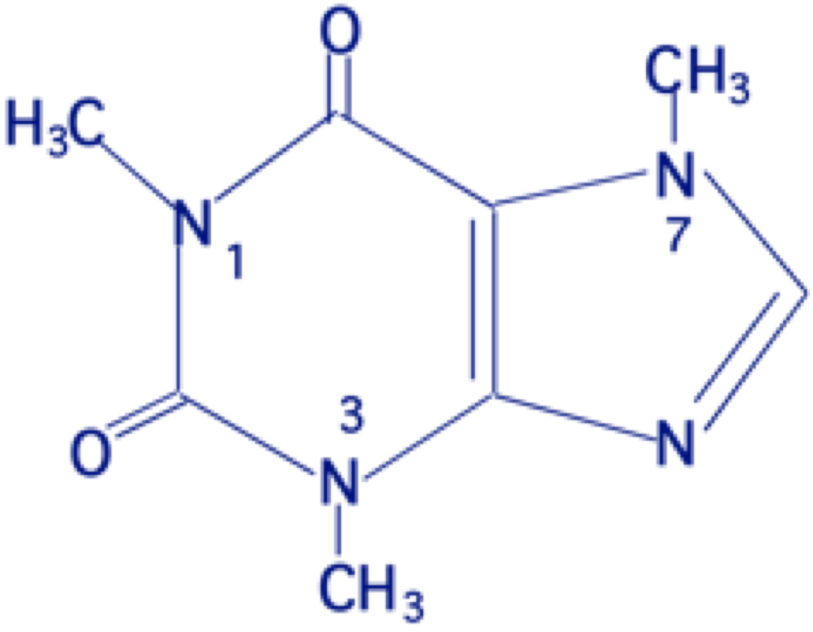
A Small Dose of Caffeine
Or
An Introduction to the Health Effects of Caffeine



Caffeine or 1,3,7-trimethylxanthine

Caffeine Industry
The coffee and cola industries owe their wealth to the physiological and pharmacological properties of the drug caffeine.
S.G. Gilbert (2001)

Dossier

Name: Caffeine (1,3,7-trimethylxanthine)
Use: most widely used stimulant in the world
Source: coffee, tea, cola and other soft drinks, chocolate, stimulant pills, some analgesics
Recommended daily intake: the U.S. Food and Drug Administration (FDA) advised pregnant women to "avoid caffeine-containing foods and drugs, if possible, or consume them only sparingly."
Absorption: rapid following oral consumption
Sensitive individuals: fetus, children, some adults
Toxicity/symptoms: high dose – agitation, tremors; withdrawal - headache
Regulatory facts: GRAS (Generally Recognized as Safe)
General facts: long history of use
Related xanthines – Theobromine (3,7-dimethylxanthine) and theophylline (1,3-dimethylxanthine)
Environmental: contaminates sewage discharge
Recommendations: be thoughtful about consumption

Coffee
Black as hell, strong as death, sweet as love.
Turkish proverb.

"Often coffee drinkers, finding the drug to be unpleasant, turn to other narcotics, of which opium and alcohol are most common."
Morphinism and Narcomanias from Other Drugs (1902) by T. D. Crothers, M.D.

Coffee, which makes the politician wise,
And see through all things with his half-shut eyes.
Alexander Pope (1688–1744), English satirical poet. *Rape of the Lock,* cto. 3 (1712).

The morning cup of coffee has an exhilaration about it which the cheering influence of the afternoon or evening cup of tea cannot be expected to reproduce.
Oliver Wendell Holmes Sr. (1809–94), U.S. writer, physician. *Over the Teacups,* ch. 1 (1891).

Tea
Is there no Latin word for Tea? Upon my soul, if I had known that I would have let the vulgar stuff alone.
Hilaire Belloc (1870–1953), British author. *On Nothing,*"On Tea" (1908).

It has been well said that tea is suggestive of a thousand wants, from which spring the decencies and luxuries of civilization.
Agnes Repplier (1858–1950), U.S. author, social critic. *To Think of Tea!* ch. 2 (1932).

Tea, though ridiculed by those who are naturally coarse in their nervous sensibilities will always be the favorite beverage of the intellectual.
Thomas De Quincey (1785–1859), English author. *Confessions of an English Opium-Eater,*"The Pleasures of Opium" (1822).

Case Studies

The Individual

With as commonly consumed and easily available a drug as caffeine, the very best case study is yourself, your family, or your friends. Ask the following questions and carefully consider the implications of these answers. Have you ever drunk too much caffeine? If so, how did you know you had too much? If the answer to the first question is yes, then you are on your way to becoming a toxicologist. If you have felt the jitters or agitation of too much caffeine, then you have experienced the nervous system effects that can be called a form of neurotoxicology and you are on your way to becoming a neurotoxicologists.

An additional question related to the nervous system effects of caffeine is what happens when you stop drinking caffeine? Do you get a headache? If the answer is yes then you are dependent on the drug caffeine. Some of your caffeine consumption is driven by a desire to avoid a caffeine-induced headache.

How many hours elapse before you reach for that second cup of coffee? Many of us have learned by practice that when our blood caffeine levels decline too far, we need to boost them back up with a second cup of coffee, tea or a can of soda.

The above factors make caffeine the most widely consumed stimulant drug in the world. The stimulant and other basic biological properties of caffeine make it an almost ideal drug for many large corporations and small businesses to make large amounts of money.

The Society

The study of caffeine is a window into our culture and society. Why do so many people consume caffeine and what does that say about our drug consumption? What are the basic biological properties that make caffeine the most widely consumed stimulant in the world and allow a number of international corporations to make vast sums of money?

Many people start consuming caffeine at an early age. It is not uncommon for schools to have soda machines and even coffee stands at and certainly near schools. Middle and high school students are well aware of the stimulant properties of caffeine. Is it appropriate to have soda machines in schools, which encourages caffeine consumption?

Introduction and History

> If Christianity is wine, and Islam coffee, Buddhism is most certainly tea. – Alan Watts, The Way of Zen, 1957

Caffeine, a naturally occurring chemical found in a number of plants, has a long and illustrious history and continues to have an enormous impact on our society. It has gone from being vilified and compared to alcohol and nicotine to become the most widely accepted and consumed neuroactive drug in the world. Caffeine is available in a wide range of products with no regulations on its sale or use. Caffeine, even more than alcohol and nicotine, demonstrates the human interest and capacity to consume drugs that affect our nervous system.

In this chapter, we will explore why we so readily consume caffeine. There are sound physiological and pharmacological reasons why so many companies make so much money from caffeine. The economics are staggering. Coffee alone is one of the largest cash crops in the world and produced all over the world. It is estimated that in 2019 coffee production was approximately that 10 million kilograms (more that 2.2 billion pounds – a huge amount), which would translate in to over a trillion cups of coffee and literally tons of caffeine. This does not even take into consideration the caffeine consumed from cola beverages, tea (approximately 6 million tones), and chocolate. Our brains and our wallets are hooked on caffeine.

Historically, caffeine has played an important role in trade and politics and even now the export of coffee is an extremely important part of world trade for many countries. The health effects of caffeine have been the subject of numerous scientific inquires, many scientific papers and conference, and many books and articles. Perhaps the best book to combine both historical and health aspects of caffeine is *The World of Caffeine – The Science and Culture of the World's Most Popular Drug* by Bennett Alan Weinberg and Bonnie K. Bealer, published in 2001. This book gives a wonderful account of the interaction of caffeine and society from its ancient roots to present times, as well as a look at the health effects. A book devoted almost entirely to the health effects of caffeine is *Caffeine and Health* by Jack E. James, published in 1991. There is no lack of information on caffeine.

Given the many plants that contain caffeine, some have speculated that even Stone Age humans chewed the leaves and fruit of caffeine-producing plants to enjoy its stimulant properties. Although this early consumption is speculative, it is clear that caffeine consumption has been with us for a long time.

Tea appears to be the most ancient of caffeine drinks. The first documented use is in China by its first great emperor, Shen Nung, in about 2700 B.C. Throughout Chinese history there are many references to tea and its many benefits. The earliest written record

of tea consumption is from a Chinese document from 350 B.C. Tea became popular with Buddhist monks to keep them awake during long hours of meditation. Despite the association of tea with China, some believe that tea was actually introduced into China from Northern India. In the 5th century, tea was an important aspect of trade on the Silk Road to China. About 800 A.D. tea was introduced to Japan. In Japan the consumption of tea, more specifically a green powdered tea, evolved into an elaborate ceremony that is still practiced today. The Dutch brought tea to Europe in 1610, and the Americans revolted over taxes on tea in 1773. A few years later, the England sent the first opium to China in payment for tea, which ultimately resulted in the Opium wars and England's control of Hong Kong. Tea bags were accidentally invented in 1908. In more recent times, we are treated to a great many fragrant varieties of tea from around the world.

Coffee's history is equally rich and savory. According to the legends in about 850 A.D., an Ethiopian goatherd (or shepherd depending on your source) noticed that his goats seemed more alert after consuming wild berries. Wishing to increase his own performance, he tried the berries himself, constituting the first occupational consumption of coffee. The cultivation of coffee trees and roasting of coffee beans was developed by 1100. Four hundred years later, Mecca, Cairo, and Constantinople were the sites of the first coffee shops. Coffee came to Europe in the 1600s and quickly spread to the Americas. By the 1700s there were coffee shops throughout Europe, and coffee was fast becoming part of the culture. Coffee trees were introduced into the Americas in 1723. The first espresso machines were made in France in the early 1800s, and the early 1900s saw the introduction of instant coffee. In 1971, the first Starbuck's coffee shop was opened in Seattle, Washington and now there are thousands of Starbucks around the world, as well as many other local coffee shops. In many parts of the world, coffee shops are an important gathering place for discussion and relaxation, an integral aspect of people's culture. In this respect, the United States is just catching up to the rest of the world.

Chocolate provides much less caffeine than tea or coffee but by people all over the world consume not so much for the caffeine but for the taste. Archeological evidence indicates that the Olmec people of Mexico harvested the cacao bean to make a drink in 400 B.C. or perhaps earlier. By 250 A.D., the Mayans of Mexico were cultivating the cacao tree. The Aztec people used the cacao bean as currency and equated it to a drink form the Gods. The scientific name for the cacao bean tree is *Theobroma cacao*. *Theobroma* is Greek for "Food of the Gods." Theobromine, the primary caffeine like compound, found in chocolate also derives it names from Theobroma. The Spanish explore Hernando Cortés brought cocoa to Spain in 1528, were it was kept secret from the rest Europe until 1600 when it quickly became very popular, so popular that the Pope had to declare that chocolate drink did not break a fast. The first English chocolate houses opened up in 1657. In 1828, shortly after the invention of the first espresso machine, the screw press for extracting cocoa butter from the beans was invented in Holland. Chocolate as a solid was invented in the 1840s and soon it was a staple of solders at war and just about everyone else.

A glance at the table 5.1 illiterates how caffeine cuts across society, trade, politics, and industry to become the drug of choice for billions of people. The amount caffeine in a particular product, as well as the amount consumed, can vary enormously. The amount of caffeine in a cup of coffee varies with the type of bean, the roasting, and the type of brewing method employed. The cup size adds another variable. Tea actually has a higher concentration of caffeine than coffee, but the extraction of the caffeine from coffee is more efficient than that of tea. If you want more caffeine in your tea, however, you only need to brew it for a longer period of time. By weight coca has the least amount of caffeine, but it also has the structurally similar compound theobromine. Caffeine is added to many cola and other soda-like beverages. Some are known for their high caffeine concentration. It is now possible to buy water-based drinks fortified with caffeine. Over the counter pills of caffeine are available, and many analgesic medications contain caffeine as well, in part to alleviate the headache due to lack of caffeine.

Table 5.1 Common products and caffeine concentration

Product	Caffeine	Size
Coffee	50-150 mg	Cup about 8 ounce or 225 ml
Tea	20-100 mg	Cup about 8 ounce or 225 ml
Cola drink	20-100	8 ounce or 225 ml
Energy Drinks	120-300	12 ounce
Chocolate (cocoa)	1-35 mg	Ounce or 28 grams

Table 5.2 History of Caffeine Consumption (T=Tea, Co=Coffee, Ch=Chocolate)

Date	Type	Event
3000 B.C.	T	Tea discovered in China or introduced form India
350 B.C.	T	First written description of Tea drinking in China.
400 B.C.	Ch	Olmec people of Mexico made chocolate drinks
250 A.D.	Ch	Mayans of Mexico were cultivating cocoa crops
450	T	Turkish traders bargain for Tea and the Silk road is born.
800	T	Tea introduced to Japan.
850 (about)	Co	Coffee beans discovered - The fable says that an Ethiopian goat or sheepherder noticed that the goats were more alter after eating the wild berries. He then sampled this new delicacy.
1100 (about)	Co	First coffee trees and roasting of coffee beans.
1450	T	Japanese Tea ceremony created and popularized
1475	Co	Constantinople – the world's first coffee house.
1528	Ch	Cocoa was brought to Spain by Hernando Cortés
1600s	Co	Coffee enters Europe and moves quickly to the Americas
1600s	Ch	Chocolate drinks introduced into Europe
1610	T	Dutch bring Tea to Europe

1657	Ch	First English chocolate houses open
1700s	Co	Coffee house open throughout Europe.
1723	Co	First coffee plants are introduced into the Americas.
1773	T	Boston Tea party, rebellion against England's tea tax
1776	T	England sends first Opium to China to help pay for tea.
1822	Co	First espresso machine is created in France.
1828	Ch	Screw press that extracted the cocoa butter from the beans invented in Holland
1835	T	First experimental tea plantations in Assam, India.
1840s	Ch	Chocolate as solid developed
1908	T	Tea bags invented in New York.
1938	Co	First instant coffee invented by the Nestlé company.
1971	Co	Starbucks opens its first location in Seattle, Washington's Pike Place Market.

Biological Properties

Caffeine is a naturally occurring chemical manufactured by a number of plants in either the fruit—as in coffee bean, cola nuts, and cocoa beans—or the leaves—as in tea. The common use of caffeine-bearing substances throughout the world at the start of the 19th century coincided with a period of great discovery in the physical and chemical sciences. Caffeine was isolated from coffee beans in 1819 by Friedlieb Ferdinand Runge, a young German physician and chemist. Caffeine derives its name from the German Kaffeine, which is in turn from Kaffee or coffee. In 1827, the active ingredient in tea was isolated and called "thein", but was later found to be identical to the caffeine of coffee.

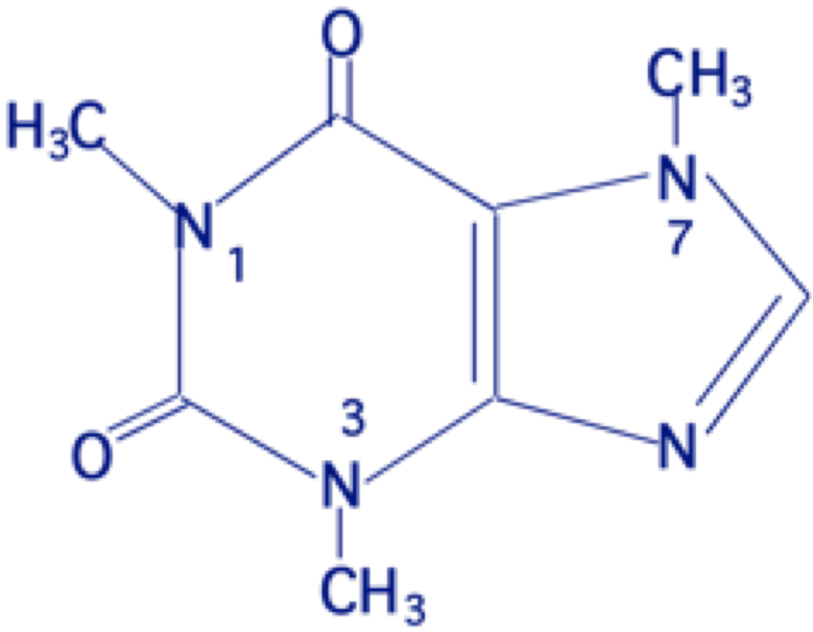


Figure 5.1 Caffeine or 1,3,7-trimethylxanthine

Purified, caffeine (Figure 5.1) is a white crystalline powder with a bitter taste. While caffeine is not particularly soluble in water, it is extracted from plant material with hot water. The longer the extraction period, the greater the amount of caffeine extracted. In plants, caffeine's purpose may be to discourage consumption by predators with its bitter taste and mild nervous system effects. From an insects perspective the caffeine family on chemicals are insecticides. But with humans it has clearly has the opposite effect of encouraging consumption of the plant.

The chemical name of caffeine is 1,3,7-trimethylxanthine, and it is part of the purine family derivatives of methylxanthines (Figure 5.2). Caffeine's basic chemical structure is similar to the purine structure found in DNA (see below). This similarity in structure generated speculation that caffeine may somehow cause cancer by interacting with DNA or RNA. Despite this similarity in structure, there is no indication that caffeine is mutagenic or causes cancer.

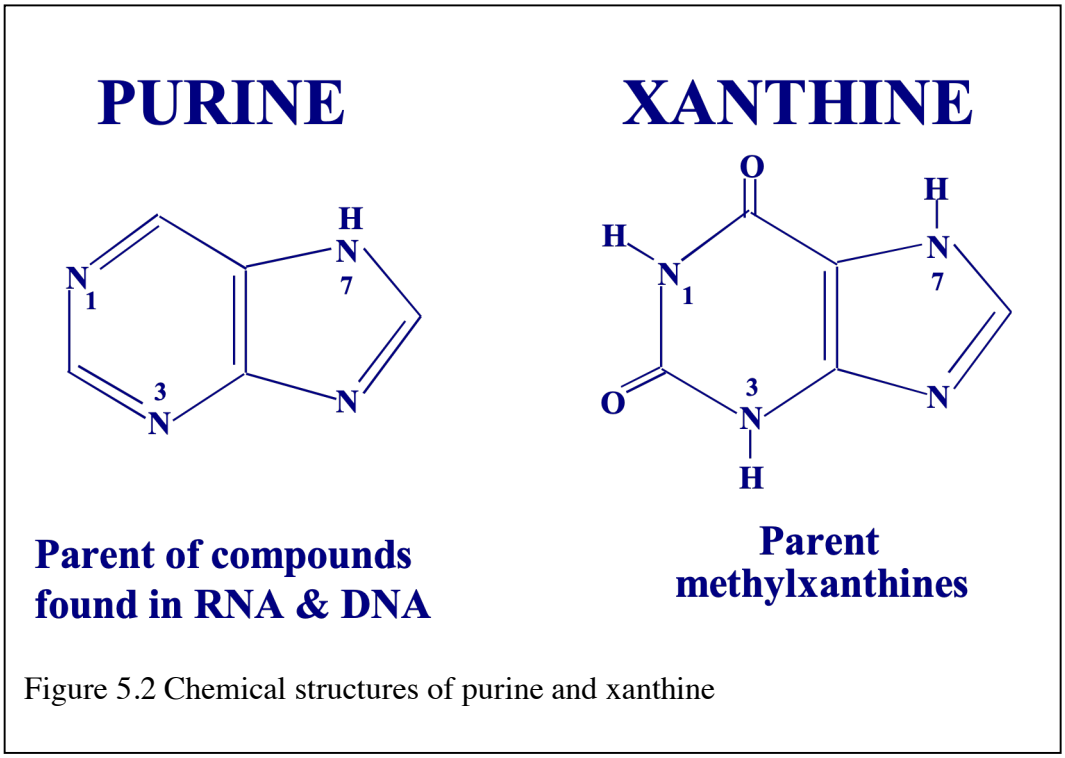


Figure 5.2 Chemical structures of purine and xanthine

Closely related methylxanthines include theophylline (1,3-dimethylxanthine), theobromine (3,7-dimethylxanthine) and paraxanthine (1,7-dimethylxanthine). Theobromine is found primarily in chocolate. These derivatives of caffeine are important because they are pharmacologically active and also are the common metabolites of caffeine.

Caffeine is readily and completely absorbed from the intestine following oral ingestion. It distributes throughout body water, so that blood, urine or breast milk will all have about the same concentration of caffeine. Metabolism varies between individuals, but on average he caffeine from a cup of coffee will produce peak blood caffeine levels in about 30 minutes. This peak level will drop by one half in 4-5 hours, the so-called half-life. If you are a smoker, you will metabolize caffeine more quickly, usually with a half-life of about three hours. During pregnancy, the half-life of caffeine increases to 8-10 hours. The newborn cannot metabolize caffeine and must rely solely on excretion of caffeine in the urine, which means the half-life of caffeine is measured in days not hours. Metabolism occurs primarily in the liver and starts with the removal of one or two of the methyl (CH3) groups to make di- or mon-methylxanthines, which are excreted in the urine. The relatively short half-life of caffeine is an important property of the drug and accounts for its for its repeated consumption. The half-life of theophylline is about twice that of caffeine.

Caffeine and the related dimethylxanthines have similar pharmacological or therapeutic effects and similar toxic effects. The primary actions include stimulation of the central nervous system, relaxation of bronchial muscles, mild cardiac muscle stimulation, and diuretic effects on the kidney.

There are a number of possible ways that caffeine can exert its effects, but the most probable action particularly at concentrations from common consumption is blockage of the adenosine receptor. Adenosine is a neurotransmitter that produces a calming effect. Caffeine blocks the receptors that are activated by adenosine, which results in stimulation (Figure 5.3). There is additional evidence that over time the cells of the nervous system respond to the blockage of adenosine receptors by increasing or up-regulating the number of adenosine receptors.

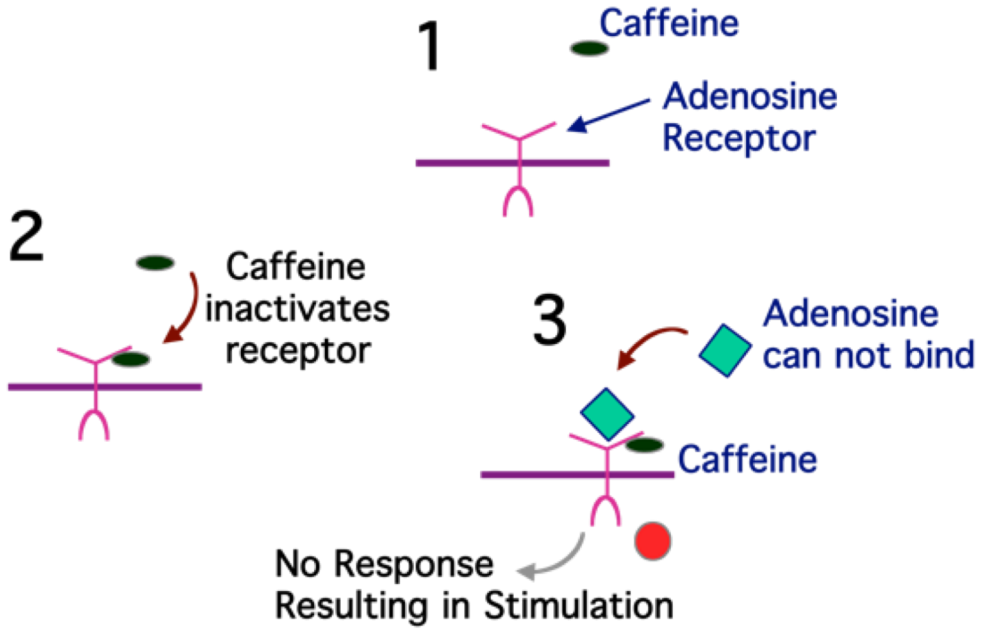


Figure 5.3 Mechanism of action of caffeine

Caffeine and theophylline are the most active on the central nervous system, while theobromine is much less active. Caffeine and theophylline also appear to stimulate the respiratory centers, making them useful in the treatment of infants that stop breathing for extend periods of time (sleep apnea), which can lead to sudden infant death.

Methylxanthines have a number of other effects, including effects on smooth muscles and the cardiovascular system. The most notable effect on smooth muscles is relaxing the bronchi of the lungs. Theophylline is prescribed to treat mild forms of asthma. While

both caffeine and theophylline will relax the bronchial smooth muscles, theophylline is used therapeutically because of its longer half-life. This allows the drug to stay in the therapeutic range longer.

The caffeine naïve individual may notice some changes in heart rate following consumption of a strong cup of coffee. Most caffeine users have developed a tolerance to the cardiovascular effects, but these effects may occur if there is elevated consumption.

Health Effects

Most people experience the stimulant effects of caffeine as an increase in alertness and energy and possibly an increase in concentration. What many like most is the ability to stay awake. Long-term consumption of caffeine does not seem to lessen the desirable effects of caffeine. In other words, long-term consumption of caffeine does not result in tolerance to the stimulatory effects. This is important for the caffeine industry because if we developed tolerance to this drug we would stop consuming because it lost its effectiveness.

Another important aspect of caffeine is that repeated consumption does not change the metabolism of caffeine. From individual to individual, the half-life of caffeine in the blood, how fast it is removed, does not change with repeated use. If the half-life of caffeine decreased and the metabolism were faster, we would have to drink even more caffeine to maintain our blood caffeine levels.

The adverse effects of caffeine are a common experience to most caffeine consumers. Too much caffeine results in uncomfortable to adverse central nervous system effects, or neurotoxicity. The effects include restlessness, tension, and mild tremor or the jitters and may progress to feelings of anxiety and even fear. Regular caffeine users soon learn how to manage their caffeine consumption to maintain blood caffeine levels at a desirable level that produces mild stimulation without the uncomfortable neurotoxic effects. Fortunately, the half-life of caffeine is short, so that any undesirable effects soon decline. Many people also experience insomnia from caffeine consumption. Caffeine's effect on sleep varies from individual to individual. Some people can consume caffeine late in the evening and sleep well, but for other people consumption of caffeine late in the day affects sleep. It is important to understand your own individual response to caffeine.

Many people experience undesirable withdrawal effects when they stop consuming caffeine. The most prominent undesirable effect is a headache. Additional effects may include feelings of fatigue and irritability. Relief from symptoms usually occurs with resumption of caffeine consumption, a classic sign of drug dependence. Awareness of your individual potential to suffer from withdrawal effects of caffeine is important. This knowledge can often explain the onset of a headache when there is a sudden or unexpected cessation of caffeine consumption.

Chocolate contains theobromine, which can be toxic to dogs.

Most of the overt toxicity of the methyl xanthines, caffeine, theophylline or theobromine is associated with the cardiovascular effects. Sensitive individuals may experience elevated or irregular heartbeats and elevated respiration. A good example of the cardiovascular effects of theobromine is evident when dogs consume chocolate. Milk chocolate contains about 45 mg/oz (150 mg/100 g) of theobromine and baking chocolate as about 400 mg/oz (1400 mg/100 g). The lethal effect of theobromine for dogs is 100-150 mg/kg. In addition, the half-life of theobromine for a dog is about 17 hours. For a small dog it does not take much to produce serous toxic effects from the accidental consumption of chocolate. For example, 1 ounce of baker's chocolate could be fatal for a dog weighing 22 pounds. For humans the lethal effects of caffeine are between 5 to 10 grams, which on a mg/kg basis is similar to the 100-150 mg/kg of theobromine for dogs.

In 1980, the U.S. Food and Drug Administration (FDA) advised pregnant women to "avoid caffeine-containing foods and drugs, if possible, or consume them only sparingly."

There are several good reasons to consider the potential for caffeine to affect the developing fetus. First, caffeine and its metabolites distribute throughout body water. This means that the fluid surrounding the fetus contains caffeine and its metabolites at levels similar to those in the mother's blood. The fetus is literally swimming in and breathing caffeine. Second, during the last two trimesters of pregnancy, maternal caffeine metabolism decreases. The half-life increases to about twice normal, or 8-10 hours. This means that after caffeine consumption the material blood caffeine levels and the infant's exposure will stay higher for a longer period of time. Third, caffeine clearly interacts with the nervous system by affecting the adenosine receptor. The consequences of having the fetal brain develop while being influenced by a drug that is blocking the adenosine receptor are not yet clear. There is, however, some human and animal data indicating that high levels of caffeine may adversely affect the infant. The U.S. FDA advises pregnant women avoid or limit caffeine consumption in an effort to address these concerns.

People who drink caffeine have learned from experience how much to consume and thus to avoid the adverse behavioral effects of *too much* caffeine. Excessive consumption of caffeine is an almost perfect example of the fundamental dose / response principle of toxicology. A sudden reduction in caffeine consumption by the regular consumer can lead to the onset of headaches. It can be argued that many people are dependent on their caffeine consumption to maintain their body in a comfortable pain-free state. There is not agreement about the mechanism responsible for the caffeine-induced headache. One possibility is that caffeine causes a small constriction of cerebral blood vessels. When

caffeine consumption is stopped for an extended period of time these vessels enlarge causing a headache.

Reducing Exposure

Many of us consume caffeine throughout our lives. Through experience we learn how much to consume to achieve the desired effects and avoid the undesirable ones. The first step in reducing exposure to any agent is being aware of the exposure and our response to it. It is simple to say that reducing exposure to caffeine only requires reduction in the consumption of caffeinated beverages. But in reality, it is more complicated. For example, should there be easily available caffeinated products in high schools? What the consequences of caffeine exposure to high school students?

Regulatory Standards

The U.S. Food and Drug Administration classifies caffeine Generally Recognized As Safe (GRAS). This designation means that there is sufficient data and history of use to indicate that caffeine is safe to consume in the amounts commonly found in foods and beverages. The FDA allows caffeine to be added to cola drinks.

Recommendation and Conclusions

Caffeine is the perfect moneymaking drug. First, it has very desirable stimulatory effects on the central nervous system. Second, you cannot consume too much at one time because the drug produce undesirable nervous system effects. Third, you cannot stop drinking it because you will get a headache. Fourth, the half-life of the drug is relatively short, so that you must go back for more. Fifth, you don't lose your craving for it. And finally, it is a naturally occurring substance with a long history of use that is recognized by the regulatory authorities as being safe. The coffee, tea, and cola industries benefit enormously from our desire for this drug.

Each of us should be aware of our dose / response to caffeine and limit our consumption accordingly. Over 200 foods, beverages, and over-the-counter medications contain caffeine, which means it is important to read the labels. If you are pregnant, think about whether you want your fetus swimming in caffeine and its metabolites.

More Information and References

Slide Presentation

- A Small Dose of Caffeine slide presentation material and references are online: Web site contains presentation material related to the health effects of caffeine.

European, Asian, and International Agencies

- International Food Information Council (IFIC) Foundation. Online: https://foodinsight.org (accessed: 07 March 2020).
  The International Food Information Council (IFIC) Foundation is dedicated to the mission of effectively communicating science-based information on health, nutrition and food safety for the public good. IFIC is supported primarily by the broad-based food, beverage and agricultural industries.

- England – The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) is an independent scientific committee that provides advice to the Food Standards Agency, the Department of Health and other Government Departments and Agencies on matters concerning the toxicity of chemicals.
  –Reproductive Effects of Caffeine 2008. Online: https://cot.food.gov.uk (accessed: 07 March 2020).
  Excellent report on the reproductive effects of caffeine.

North American Agencies

- U.S. MEDLINEplus Health Information. Online: <http://www.nlm.nih.gov/medlineplus/caffeine.html> (accessed: 07 March 2020).
  Medline has multiple references on caffeine, including a number of useful web based links.

- U.S. PubMed - https://pubmed.ncbi.nlm.nih.gov/?term=caffeine A search for recent research on caffeine. (accessed: 07 March 2020).

- U.S. Food and Drug Administration (FDA) Spilling the Beans: How Much Caffeine is Too Much?. Online: https://www.fda.gov/consumers/consumer-updates/spilling-beans-how-much-caffeine-too-much (accessed: 07 March 2020).
  This FDA wed site provides general information on caffeine.

Non-Government Organizations

- Center for Science in the Public Interest – Caffeine – The Good, the Bad, the Maybe (March 2008). Online: < https://cspinet.org/eating-healthy/ingredients-of-concern/caffeine-chart > (accessed: 09 March 2020).
  Chart of amount of caffeine in various drinks. General information on the health effects of caffeine is also available at this site. For example: Beware of These

Effects of Caffeine on the Body - https://cspinet.org/tip/beware-these-effects-caffeine-body . (accessed: 09 March 2020).

- March of Dimes – Caffeine in Pregnancy Fact Sheet. Online: https://www.marchofdimes.org/pregnancy/caffeine-in-pregnancy.aspx (accessed: 09 March 2020).
  March of Dimes has a number of fact sheets including this one on caffeine.

- In Pursuit of Tea. Online: <http://www.inpursuitoftea.com/> (accessed: 09 March 2020).
  Company web site dedicated to "Exploring remote regions of the world to supply the finest Teas".

- Caffeine – The Vaults of Erowid. Online: <http://www.erowid.org/chemicals/caffeine/caffeine.shtml> (accessed: 09 March 2020).
  The Erowid web site has a wide range of information on caffeine.

- Caffeine and Pregnancy. Organization of Teratology Information Specialists (OTIS) - MotherToBaby. Online: < https://mothertobaby.org/fact-sheets/caffeine-pregnancy/pdf/ > Numerous fact sheets on wide range of medicines. (accessed: 09 March 2020),
  Advices women to limit caffeine consumption during pregnancy.

References Books

There are many books on caffeine. I have picked just a few – see below. A quick scan through Amazon or Google search will provide you with lots of reading. To look into caffeine in further detail, I would recommend Wikipedia, which has an extensive and will referenced article on caffeine.

Caffeine: How Caffeine Created the Modern World Audible Audiobook – Original recording by: Michael Pollan Caffeine: How Caffeine Created the Modern World Audible Audiobook – Original recording

The Truth About Caffeine Audible Audiobook – Unabridged
Marina Kushner (Author), Timothy McKean (Narrator), SCR, LLC (Publisher). The book *The Truth About Caffeine* exposes caffeine's darker side that scientists know. New and updated third edition. ©2010 Al Kushner

The World of Caffeine – The Science and Culture of the World's Most Popular Drug. By: Bennett Alan Weinberg and Bonnie K. Bealer. Routledge, New York and London 2001. ISBN-13: 978-0415927239

Reference Papers

Caffeine is popular research subject. I have selected a small sampling some new some older. There is also a wide selection of animal studies that I did not reference.

Caffeine & Health. By Jack E. James. Academic Press – Harcourt Brace Jovanovish, Publishers. New York, 1991.

Robert L. Brent, Mildred S. Christian, and Robert M. Diener. (2011) Evaluation of the Reproductive and Developmental Risks of Caffeine. Birth Defects Res (Part B) 92:152–187, 2011. © 2011 Wiley-Liss, Inc.

Kolahdouzan, M., & Hamadeh, M. J. (2017). The neuroprotective effects of caffeine in neurodegenerative diseases. CNS neuroscience & therapeutics, 23(4), 272–290. https://doi.org/10.1111/cns.12684

Doepker, C., Franke, K., Myers, E., Goldberger, J. J., Lieberman, H. R., O'Brien, C., Peck, J., Tenenbein, M., Weaver, C., & Wikoff, D. (2018). Key Findings and Implications of a Recent Systematic Review of the Potential Adverse Effects of Caffeine Consumption in Healthy Adults, Pregnant Women, Adolescents, and Children. Nutrients, 10(10), 1536. https://doi.org/10.3390/nu10101536

dePaula, J. and Farah, A. (2019) Caffeine Consumption through Coffee: Content in the Beverage, Metabolism, Health Benefits and Risks. Beverages 2019, 5, 37; doi:10.3390/beverages5020037. www.mdpi.com/journal/beverages

Gaelle Gourmelon. (2017). What You Should Know About The Chocolate You're Eating. http://blogs.worldwatch.org/chocolate-ethical-sustainable/. Gaelle Gourmelon is the Director of Communications and Marketing at the Worldwatch Institute. Her work aims to connect people with their environment to empower them to make informed decisions.