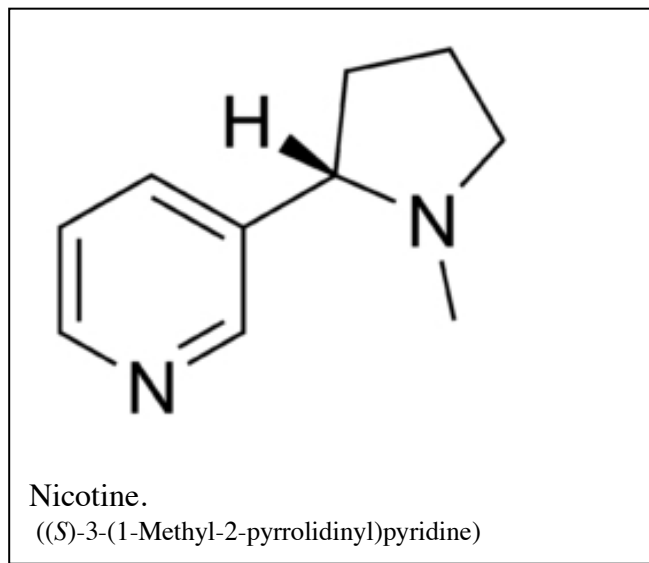


A Small Dose of Nicotine

Or

An Introduction to the Health Effects of Nicotine



Dossier

Name: Nicotine

Use: pesticide, drug in tobacco, chewing, smoking

Source: tobacco contains nicotine

Recommended daily intake: none (not essential)

Absorption: lung, skin, stomach (poor), intestine (better), (poor absorption in the stomach because nicotine is a strong base)

Sensitive individuals: fetus, children

Toxicity/symptoms: dependency producing, acute effects: nausea, vomiting, salivation, diarrhea, dizziness, mental confusion, weakness

Regulatory facts: RfD (none), LD50 10 mg/kg, not currently regulated but legislation is being considered to allow regulation by FDA. In 1964, the U.S. Surgeon General issued a report linking smoking with lung cancer and heart disease. In 1994 that the US FDA determined that nicotine was a dependency-producing drug.

General facts: long history of use; produces dependency in user

Environmental: growing demand for cigarettes in developing countries and vaping becomes popular

Recommendations: avoid

Case Studies

“The Divine Origin of Tobacco”

Tobacco was a powerful medicine for the first people of the Americas. The indigenous peoples in California tribal legend, trace the origins of tobacco to sacred immortals that they believed first inhabited the land. The immortal ancestors gave tobacco to the humans to heal and guide them from the ancient past to the present and beyond; tobacco was an important part of creation. Native medicine doctors and shaman relied upon tobacco for guidance, a source of strength, and part of the healing rituals. Tobacco was sacred, not to be rapidly consumed in the doorway of a back alley. As Native American author Julian Lang suggested, the warning on a pack of cigarettes should be “Use of this product should be restricted to prayerful or religious activity, or social activity which reflects aspects of the Creation”. (Lang, 1997)



1000 BC

Figure 6.1 Mayan priest with smoking tobacco
Ancient temple carvings depict Mayan priests in Central America smoking tobacco through a pipe. Tobacco leaves become widespread in medicine for use on wounds as a means of reducing pain. Later the Aztecs incorporate smoke inhalation into religious rituals.

Green Tobacco Sickness

Green tobacco sickness (GTS) afflicts workers harvesting tobacco when nicotine is absorbed through the skin from handling wet tobacco leaves. Workers report symptoms of nausea, vomiting, weakness, dizziness, headache, and, depending on the amount of exposure, decreases in heart rate and blood pressure. These are the classic signs of nicotine poisoning. This illness often lasts for several days, and some workers required hospital treatment. In the fields, the worker’s clothes became wet from moisture on the tobacco leaves, and most workers did not use gloves or protective clothing. Workers that used tobacco products were less likely to suffer from GTS because they developed a tolerance to the effects of nicotine. In addition, longer term workers are less likely to report GTS, possibly because younger workers who are sensitive to nicotine tend to drop out of the work force. Appropriate worker education about the absorption of nicotine through the skin and the use of protective clothing would reduce the incidence of GTS. For more information see Morbidity Mortality Weekly Report on GTS (reference below).

Second and Third Hand Smoke

First hand smoke is the particulate matter that is directly inhaled into a smokers lungs. Second hand smoke is particulate matter that is inhaled into a bystanders lungs. While

Third hand smoke refers to the toxicants that linger on the surfaces of material after the original smoke has cleared. Second hand smoke is particularly hazardous to children in a home environment but extends to all enclosed environments. In 2020 it is hard to imagine smoking on air planes or even in airports. The health effects of second hand smoke are essentially identical to first hand smoke such lung cancer, cardiovascular, other associated diseases. The acceptance of the health effects of second hand smoke was radically changed the regulatory rules that governed smoking. Smoking in the workplace ended as well as smoking in the public except in designated areas. Recognizing that rules governing second hand smoke would broadly reduce smoking the cigarette industry fought the science of the health effects of second and third hand smoke, fortunately industry lost several of the legal cases. The tobacco was made for excellent reading with nicotine at the heart of the story.

Facts on cigarettes

During 2017, about 249 billion cigarettes were sold in the United States—a 3.5% decrease from the 258 billion sold in 2016.

Four companies—Philip Morris USA, Reynolds American Inc., ITG Brands, and Liggett—accounted for about 92% of U.S. cigarette sales.

Introduction and History

Nicotine is a potent and addictive drug with a long history of use with enormous effects on our society. From a toxicology perspective, nicotine is a pesticide that naturally occurs in tobacco, and is a powerful drug with multiple nervous system effects. Thus, cigarettes or vaping devices are highly effective drug delivery devices.

Nicotine was isolated from tobacco leaves (*Nicotiana tabacum*) in 1828, but the powerful effects of nicotine were already well recognized. The tobacco plant is native to the Americas and its use as a medicine and stimulant goes back at least 2000 years and most likely many millennia before that. South American temple carvings show Mayan priests enjoying the benefits of this drug from smoking tobacco through a pipe. Tobacco appears to part of the healing arts and sacred rituals of many of the native peoples of the Americas.

There are various theories of how tobacco was introduced to Europe, but undoubtedly (see above box) Christopher Columbus and his crews sampled this native weed and succumbed to its spell. Once introduced into Europe at about 1528, tobacco for use in pipes and as cigars spread rapidly. Some thought it was powerful medicine and might even cure the Plague, while others saw it as an evil and nasty habit.

"We found a man in a canoe going from Santa Maria to Fernandia. He had with him...some dried leaves which are in high value among them, for a quantity of it was brought to me at San Salvador".

Christopher Columbus' Journal, 15 October 1492

The habit of tobacco use is directly related to the biological effects of nicotine. While people in the 1500s did not understand the mechanisms behind the complex physiological effects of nicotine, they certainly felt and appreciated its stimulating and relaxing properties. The desire to consume nicotine is encouraged not only by these seemingly pleasant effects, but also by the need to avoid the unpleasant effects of no longer having nicotine in your blood.

The societal effects of tobacco and nicotine started early and continues today. By the early 1600s tobacco farming had become an important cash crop for export to Europe by the new colonies in North America. Some historians believe the colonies would not have prospered without the money from this toxic crop along with slavery. Tobacco is a demanding crop to grow, and as tobacco farming spread south there was a growing demand for workers. In the 1700s tobacco plantation farmers began capturing African slaves to work the tobacco farms. Tobacco became important not only for local economies, but also for national governments as soon as it became apparent that one could tax the people's habit. The physiological effects of tobacco consumption, largely related to nicotine, helped it become a powerful habit that has influenced society in countless ways. It is only relatively recently that society has looked at the true cost of tobacco consumption.

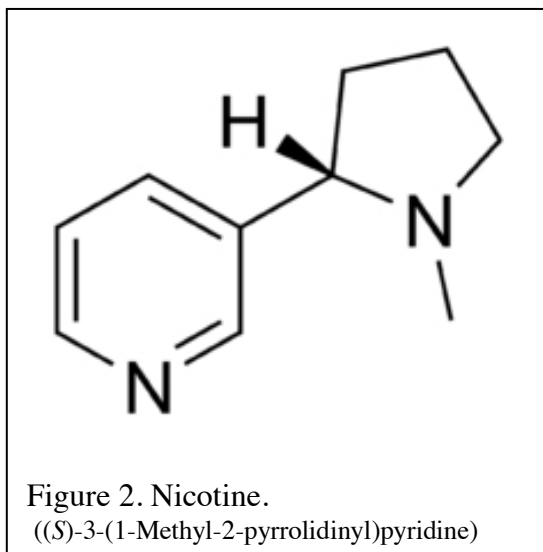
It took many years to refine and develop tobacco consumption as a means of drug delivery. Tobacco consumption was initially confined to chewing or smoking with a pipe or cigar. Cigarettes were invented in 1614 by beggars in Seville, Spain, who collected scraps of cigars and rolled the tobacco into small pieces of paper. Cigarette consumption grew gradually in popularity, but cigarettes were expensive to produce until 1880 when a machine to roll cigarettes was patented. This invention ushered in much cheaper cigarettes and major tobacco corporations. Sir Walter Raleigh popularized pipe smoking in England. He was beheaded on October 28, 1618, but before his head dropped he requested to smoke a final bowl full of tobacco.

The undesirable health effects of tobacco consumption were not entirely unrecognized. By 1890, 26 states had passed laws banning the sale of cigarettes to minors. Cigarette consumption increased steadily, spurred along by both world wars and relentless marketing by the tobacco companies. In 1964, the U.S. Surgeon General issued a report linking smoking with lung cancer and heart disease, which started a slow recognition among policy makers of the true cost of smoking and began efforts to reduce consumption. It was not until 1994 that the U.S. Food and Drug Administration officially determined that nicotine was a dependency-producing drug. The U.S. Supreme Court

subsequently ruled that the FDA could not regulate nicotine as a drug. However, all this attention did encourage legal action that resulted in the tobacco companies paying billions of dollars to cover health care costs of tobacco related diseases. While tobacco consumption is declining in North America and parts of Europe, it continues to increase in many parts of the world that have yet to recognize the costs both to the individual and ultimately to society.

The widespread personal consumption of nicotine is not its only role. In 1763 nicotine was first used as an insecticide. The potent nervous system effects of nicotine kill or deter insects; these are the same effects that attracted people to nicotine (see below). Nicotine is extracted from tobacco leaves by steam or solvent treatment and then sprayed on vegetation where it comes in contact with and is readily absorbed by insects.

Nicotine based insecticides were first developed by Henry Feuer, a chemist at Purdue University, in 1970. Shell chemists later refined and developed it as nithiazine postsynaptic acetylcholine receptor agonist. In 1985, Bayer patented imidacloprid as a neonicotinoid. This class of compounds called neonicotinoids were commercially very successful and by mid 2010 were generating over \$1 billion in revenue. Unfortunately, neonicotinoids were not powerful against



Nicotine based pesticides are no longer registered by the U.S. (EPA, 2008).

Biological Properties

Nicotine (Figure 2) has a range of physiological effects and has provided researchers with an opportunity to learn about nervous system function. It is readily absorbed through the skin and lungs, but because it is a strong base is not well absorbed in the acidic environment of the stomach. Nicotine travels from the lungs to the brain in about 7 seconds, thus each puff produces a reinforcing effect. The positive effects of nicotine are associated with a complex balance of stimulation and relaxation. For example, depending on the dose, it can increase or decrease the heart rate. One of the most prominent reactions of first time users is nausea and vomiting. This reaction is due to stimulation of both central and peripheral nervous systems that trigger a vomiting reaction. The

underlying mechanism of action is its effect on acetylcholine-like receptors, sometimes referred to as nicotinic receptors.

Nicotine is metabolized in the liver, lung, and kidney. It has a relatively short half-life of about 2 hours, which greatly contributes to the desire to have another exposure to nicotine (a smoke) in an effort to restore the blood nicotine levels. The primary metabolite of nicotine is cotinine, which has a much longer half-life than nicotine. Nicotine and its metabolites are readily excreted in the urine. Because of cotinine's longer half-life, insurance companies will typically test urine or blood samples for cotinine to determine if someone has been smoking. Nicotine is also excreted in the breast milk of nursing mothers, with heavy smokers having up to 0.5 mg of nicotine per liter of milk. Given the infant's small size, this can represent a significant dose of nicotine for the baby.

The skin absorption of nicotine and subsequent adverse effects make it an effective pesticide. Nicotine poisoning occurs primarily from children coming in contact with nicotine insecticides or tobacco products.

Health Effects

1604: "A Counterblaste to Tobacco"

"Smoking is a custom loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs, and in the black, stinking fume thereof nearest resembling the horrible Stygian smoke of the pit that is bottomless." -- James I of England, "A Counterblaste to Tobacco."

Nicotine is a highly toxic drug, with only 60 mg being lethal to an adult. The average cigarette contains 8 to 9 mg of nicotine; so one pack of cigarettes contains enough nicotine to kill the average adult, to say nothing of a child. Depending on smoking technique, a smoker receives about 1 mg of nicotine per cigarette. The effects of nicotine are complex but are similar to acetylcholine poisoning. Acute effects of nicotine poisoning include nausea, vomiting, salivation, diarrhea, dizziness, mental confusion, and weakness. At high levels of exposure, nicotine causes decreased blood pressure, difficulty breathing, irregular pulse, convulsions, respiratory failure and death.

Nicotine is probably the most addictive drug readily available to the average person. The nicotinic effects from smoking are highly reinforcing, with some users comparing the effects to cocaine or amphetamine. Regular smokers consume nicotine for stimulation but also to avoid the withdrawal effects. The withdrawal effects include irritability, anxiety, restlessness, impatience, increased appetite and weight gain. Nicotine patches take advantage of nicotine's ability to cross the skin barrier and are used to maintain a steady state blood level of nicotine and thus reduce the desire to smoke. Nicotine gum and now nicotine drinks are often used as an alternative to smoking.

Nicotine also affects the developing fetus. Adverse effects of chronic nicotine consumption during pregnancy include reduced infant birth weight, attention deficit disorders, and other cognitive problems. Nicotine receptors are expressed early during development, and it is not clear what effects nicotine exposure during development has on the fetus.

The health effects of nicotine cannot be entirely separated from the effects of cigarettes as a whole. Nicotine keeps people smoking, but the many other compounds found in cigarettes that are inhaled when smoking contribute to respiratory disease, cardiovascular disease and lung cancer.

Concerns over the hazards of second hand smoke are now widely accepted, which has resulted in increased restrictions on indoor smoking. Some states have laws limiting smoking outdoors near doorways and more recently have even limited smoking in cars when children are present.

E-cigarette (Electronic cigarette)

An e-cigarette (electronic cigarette) is a battery powered device that simulates tobacco smoking, often called vaping. It consists of a power source such as a battery, an atomizer and a container such as a cartridge or tank which contains a liquid. Instead of smoke, the user inhales vapor, thus called vaping. The liquid which becomes the vapor, varies in composition varies but is commonly made up of propylene glycol, glycerin, nicotine, flavors, and traces of toxicants, carcinogens, heavy metals, and metal nanoparticles. The toxicity of the inhaled vapor is unknown but is often considered to be less than regular tobacco smoking. In reality the vaping device is really just a drug, most often nicotine, delivery device along with a range of other toxic byproducts. Most importantly don't start, which according to some is already increasing independently of regular smoking,

Reducing Exposure

"To cease smoking is the easiest thing I ever did. I ought to know, I've done it a thousand times."
Mark Twain

Given the serious health effects associated with cigarette smoking, primarily maintained by the addictive properties of nicotine, the best advice is not to start. Unfortunately, despite the obvious health problems and cost to society, thousands of young people start smoking each year.

All nicotine containing products should be handled with care and kept out of the reach of children. Second hand smoke should be avoided, particularly for children, and laws limiting second hand smoke exposure encouraged.

Regulatory Standards

On March 21, 2000, the U.S. Supreme Court ruled that the U.S. Food and Drug Administration did not have the authority to regulate tobacco. New laws are being considered by the US congress that would give the FDA expanded authority to regulate nicotine and tobacco products. As of 2018, 169 states have signed the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC), which governs international tobacco control.

Recommendation and Conclusions

Nicotine is a very potent drug, highly addictive when regularly consumed, and its use should be avoided. Laws restricting or defining smoking areas that reduce second and third hand smoke exposure should be encouraged. Most importantly don't use a product the internally puts toxic particles in your lungs.

More Information and References

Slide Presentation

- A Small Dose of Nicotine presentation material and references online:
Power point slides contains presentation material related to the health effects of nicotine.

European, Asian, and International Agencies

- England – Department of Health - Health matters: smoking and quitting in England. Online: <https://www.gov.uk/government/publications/health-matters-smoking-and-quitting-in-england/smoking-and-quitting-in-england> (accessed: 15 March 2020).
- Society for Research on Nicotine and Tobacco. Online: <http://www.srnt.org/> (accessed: 15 March 2020).
“he Society for Research on Nicotine & Tobacco (SRNT) is the only professional association dedicated exclusively to the support of researchers, academics, treatment professionals, government employees, and the many others working across disciplines in the field of nicotine and tobacco research.”
- World Health Organization (WHO) Tobacco. Online: <https://www.who.int/health-topics/tobacco> (accessed: 15 March 2020).
Covers tobacco and international efforts to track and reduce use of tobacco.

- Global Information System on Tobacco Control (GISTOC) . Online. Available HTTP: https://www.who.int/tobacco/global_data/en/ (accessed: 15 March 2020). “Tobacco Free Initiative (TFI) is working to set up a global information system on tobacco control.”

North American Agencies

- Health Canada – Tobacco. Online: < <https://www.canada.ca/en/health-canada/services/health-concerns/tobacco.html> > (accessed: 15 March 2020). Health Canada information on the health effects of tobacco products.
- US Centers for Disease Control and Prevention (CDC). Online: <<http://www.cdc.gov/tobacco/>> (accessed: 15 March 2020). US CDC site has multiple listing on health, tobacco and nicotine.
- US National Institute on Drug Abuse (NIDA). Online: <https://www.drugabuse.gov/drugs-abuse/tobacconicotine-vaping> (accessed: 15 March 2020). US NIDA site has general information on Tobacco, Nicotine, and E-Cigarettes.
- US Medline plus – Smoking Tobacco. Online: <https://medlineplus.gov/smoking.html> (accessed: 15 March 2020). Site has many good reference on smoking tobacco.
- Odani S, Armour BS, Graffunder CM, Willis G, Hartman AM, Agaku IT. State-Specific Prevalence of Tobacco Product Use Among Adults — United States, 2014–2015. MMWR Morb Mortal Wkly Rep 2018;67:97–102. DOI: [http://dx.doi.org/10.15585/mmwr.mm6703a3external icon](http://dx.doi.org/10.15585/mmwr.mm6703a3external%20icon)

Non-Government Organizations

- Neuroscience for Kids – Nicotine. Online: <http://faculty.washington.edu/chudler/nic.html>. (accessed: 15 March 2020). Addresses the health effects of smoking tobacco and nicotine.
- Tobacco and Nicotine – The Vaults of Erowid. Online: <<http://www.erowid.org/plants/tobacco/tobacco.shtml>> (accessed: 15 March 2020).
• Site has a wide range of information on tobacco and nicotine.
- Tobacco Portal - <https://tobacco.publichealth.gsu.edu/resources/data> (accessed: 15 March 2020)
A resource center providing links to tobacco related data, reports, scientific information and publications.

- e-cigarettes. Wikipedia https://en.wikipedia.org/wiki/Electronic_cigarette - (accessed: 18 July, 2020).

References

History of tobacco – Wikipedia - https://en.wikipedia.org/wiki/History_of_tobacco

MMWR (1993). Green Tobacco Sickness in Tobacco Harvesters -- Kentucky, 1992. Vol 42, No 13;237 April 9, 1993. Online: <www.cdc.gov/mmwr/preview/mmwrhtml/00020119.htm> (accessed: 15 March, 2020).

Rabin, R.L., Sugarman, S.D. (eds) (2001). *Regulating Tobacco*. Oxford University Press, USA.

Barrington-Trimis JL, Urman R, Berhane K, et al. E-Cigarettes and Future Cigarette Use. *Pediatrics*. 2016; 138(1):e20160379

Odani, S, Armour, BS, Graffunder, CM, Willis, G, Anne M. Hartman, AM, Agaku, IT. State-Specific Prevalence of Tobacco Product Use Among Adults — United States, 2014–2015. *Weekly / January 26, 2018 / 67(3);97–102*<https://www.cdc.gov/mmwr/volumes/67/wr/mm6703a3.htm> or <http://dx.doi.org/10.15585/mmwr.mm6703a3>

David M. Homa, DM, Neff, LJ, King, BA Caraballo, RS, Bunnell, RE, Babb, SD, Garrett, BE, Sosnoff, CS, Lanqing W. Vital Signs: Disparities in Nonsmokers' Exposure to Secondhand Smoke — United States, 1999–2012. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6404a7.htm>. February 6, 2015 / 64(04);103-108. On February 3, 2015, this report was posted as an MMWR Early Release on the MMWR website (<http://www.cdc.gov/mmwr>).

Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, Cigarettes, and the Prevalence of Adolescent Tobacco Use. *Pediatrics*. 2016;138(2):e20153983

Jennifer E. Bruin, Hertzell C. Gerstein, and Alison C. Holloway. Long-Term Consequences of Fetal and Neonatal Nicotine Exposure: A Critical Review. *Toxicological Sciences*. 116(2), 364–374 (2010). doi:10.1093/toxsci/kfq103