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The E-Cigarette Controversy...

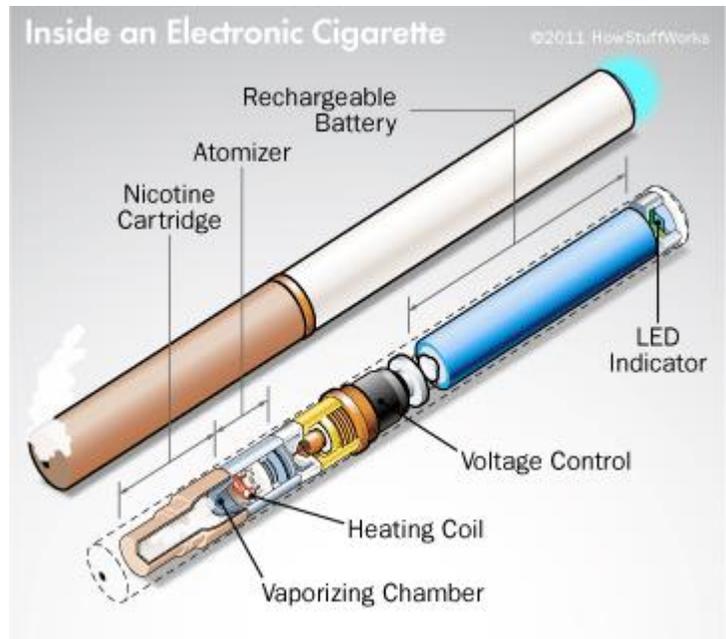
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An Addiction Catalyst or a Convenient Tool?

The idea for a smokeless cigarette is not a new one. A man named Herbert A. Gilbert filed the first patent for a smokeless cigarette in 1963, but big business and advertising for the tobacco industry quickly consumed the idea and the product was never manufactured. The E-Cigarette (electronic cigarette) of today, originally manufactured in 2003, has been in the United States since 2007, and quickly became an overnight sensation. The original manufacturer marketed them as a "SAFE smoking alternative". In the beginning, the China based company made no claims about using them as an aid for smoking cessation. After several years of deceptive marketing strategies, manufacturing secrets, and legal trickery to get them into the United States, there are still many unanswered questions. Even today, the United States government still cannot agree on how to classify the e-cigarette. Is it a drug delivery system or a tobacco product? Is it a smoking alternative, or an effective new tool? Wrapping up its first decade in the United States the controversy continues. Is it a clever and convenient new tool to aid in smoking cessation, or is the electronic-cigarette just another "wolf in sheep's clothing"?

The Current-Day E-Cigarette

The electronic cigarette, often referred to as an E-Cigarette, is an electronic device that looks, feels, and functions like a real cigarette. In some cases, it even “tastes” like a real cigarette. In reality, the E-Cigarette is a portable electronic cigarette simulator. It’s a micro atomizer contained in a device that looks and feels like a real cigarette. The user activates the device by putting it into his/her mouth and drawing on it as they would a real cigarette. The tiny atomizer heats up a liquid



solution that is drawn from a cartridge contained within the device. The liquid solution is heated in the atomizer, and converted into a vapor that looks a lot like cigarette smoke (The smoke-like effect is caused by certain ingredients). When inhaled it even tastes like cigarette smoke, and when the user exhales they blow out the smoke-like vapor. In the solution is a number of ingredients, flavorings, and nicotine. (There are 0mg nicotine cartridge alternatives available).

Some History

The idea for a smokeless cigarette is not a new one. The original idea was from a man named Herbert A. Gilbert, a Korean War veteran who lived and worked in Beaver Falls, PA. He actually filed for the first patent for his idea of the smokeless cigarette on April 17th, 1963 (<http://www.google.com/patents/US3200819>). Unfortunately, Mr. Gilbert was way ahead of his time, as was his version of the smokeless cigarette. The tobacco industry was booming, tobacco advertising was HUGE business, and tobacco smoking was commonplace, well accepted, and not yet regarded as harmful, despite occasional speculation. The unfortunate result of this triad was that Mr. Gilbert’s smokeless cigarette idea was quickly put to rest.

In 2003 a Chinese Pharmacist (and smoker) named Han Lik, age 52, developed a ‘modern-day version’ electronic cigarette with the backing of the company he worked for, which was named “Golden Dragon Holdings”. They were in full support and began to develop his product, eventually changing their name to “Ruyan,” which simply means “Like Smoke”.

Sales were so good that the electronic cigarette was then introduced to countries around the world. From mid-2006 – 2007 the e-cigarette was introduced to Europe and then the United States. Just as it happened in China, the e-cigarette exploded in popularity almost overnight.

The Arguments

Currently the electronic cigarette is a worldwide subject of discussion, but not necessarily a well-accepted one. There is a wealth of information on the electronic cigarette – much of it in favor of the device, and just as much is very much against it. This pro/con phenomenon is a worldwide one, with the device being banned from about as many countries as it has been accepted in. This is because there is still growing controversy on whether the electronic cigarette is actually a safer alternative to smoking conventional tobacco cigarettes, or simply just another nicotine delivery system, which some are calling a *drug addiction catalyst*. Some even question whether the device is safe at all. This fear appears to have been caused by the manufacturers' deceptive marketing strategy and the secrecy of ingredients in the solution when they first began to arrive in the United States.

While it's true that there is a lot of information available about the e-cig, very little of that information is from official or scientific sources. Much of the information in favor of the device can actually be traced back to an e-cigarette manufacturer or sales establishment. This could make it appear that much of the information found on the e-cig is biased, leaving a lot of room for doubt and raising many questions. Exactly what is true and what is not true about the electronic cigarette? Currently it is very difficult to tell, and the lack of scientific data seems to add to that difficulty. Data is lacking mainly because the electronic cigarette is too "young" in the United States for thorough research to have been completed. Slowly, very slowly, we are starting to see some data show up in the medical literature, and most of it so far is showing that the electronic cigarette does indeed have significant health risks. So now, the question becomes "does the benefit outweigh the risk"? Is the electronic cigarette in fact a safer alternative to smoking traditional tobacco cigarettes? That is not the same thing as asking; "is the electronic cigarette safe"? This is where many arguments come into play. Some users of the e-cigarette, however, are reporting decreased blood pressure, decreased need for blood pressure medications, weight loss, easier walking or exercise with less shortness of breath, etc. Still, we are lacking adequate scientific data, especially on the long-term use of the device – at least for now.

The Big Question

So, is the electronic cigarette safe? Probably not. Is the electronic cigarette safer than smoking traditional tobacco cigarettes? Probably yes ONLY if it is used as a 100% replacement of smoking traditional tobacco products. This is where behavior come into play. Smoking cessation is 100% effort dependent. Transitioning from cigarettes to electronic cigarettes is also 100% effort, or user, dependent. Those who are using both, e-cigarettes and tobacco cigarettes are dramatically increasing their intake of nicotine and almost doubling their health risk. Unfortunately, this is a very common practice. Only about 25% of smokers who transitioned to electronic cigarettes completely quit smoking traditional tobacco and replaced it 100% with electronic cigarettes. It appears that a lot of current smokers use the e-cigarette as a bridge so they can continue to get their “dose” of nicotine while at the workplace or at indoor establishments, where smoking tobacco is currently illegal in the United States, and several other countries. One of many reasons for the importance of strict regulation of nicotine delivery devices and products.

Unfortunately, the lack of regulation has made obtaining e-cigarettes extremely easy. They can be purchased from a seemingly never-ending list of on-line establishments, and a rapidly growing list of local retail stores. In the US there are still no federal regulations or age restriction being enforced when it comes to purchasing e-cigs, and although there are a few states that now have their own regulations there is no effective way to restrict the sale of e-cigs to minors who order them from on-line establishments. These two facts have made the device extremely popular with the younger adults, high school students, and even younger in some cases. Another argument for the need for strict regulation of ALL nicotine delivery devices and products.

What is Nicotine?

So what’s the big deal anyway? Well, let’s start with nicotine itself since that seems to be the main attraction of e-cigs. Nicotine ($C_{10}H_{14}N_2$) is a potent parasympathomimetic alkaloid, nicotinic acetylcholine receptor (*nAChR*) agonist, but an antagonist of *nAChR α 9* and *nAChR α 10*. It is a potent stimulant and is well known to be highly addictive. Studies show that nicotine is just as addictive, or even more addictive, than heroin and cocaine. Nicotine is also an antiherbivore and was widely used as an insecticide, especially in the farming industry, to

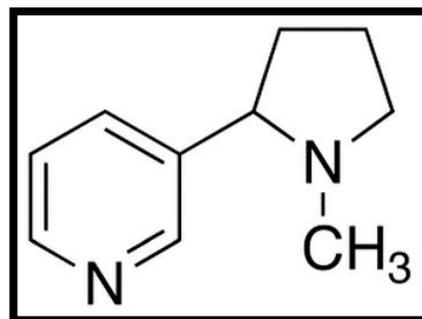


Figure 1: Chemical Structure of Nicotine ($C_{10}H_{14}N_2$)

protect crops from being destroyed by plant eating insects. Nicotine is equally as lethal as strychnine, and three times more lethal than arsenic.

The effect of nicotine changes from stimulant to sedative as the dose increases making it very unique in comparison to most other drugs. There is some research that suggests that smokers who want a more stimulating effect tend to take short quick puffs, while those who want a more relaxing effect take deeper slower puffs.

Nicotine causes an increased production of the hormone and neurotransmitter epinephrine (also known as adrenaline) by stimulating the adrenal glands. An increased level of epinephrine causes blood vessel constriction, tachycardia, and hypertension. Nicotine also causes increased levels of the neurotransmitter dopamine, which controls the brains pleasure center. It is believed that this action contributes to the addictive nature of nicotine. Nicotine itself also has a long list of potentially harmful adverse effects. Some of them are listed in Table-1 below.

When inhaled, nicotine reaches the brain within 7 to 10 seconds. The stimulating effect is the result of the release of epinephrine from the adrenal medulla, and the release glucose from the liver, also causing increased alertness, mental sharpness, and at the same time relaxation and calmness. Nicotine also reduces appetite and increases activity of the thyroid, speeding up metabolism, which frequently leads to weight loss. In rare cases, however, it can also cause uncontrollable restlessness and anxiety. Indirectly, several other chemical messengers are released including acetylcholine, arginine vasopressin, beta-endorphin, norepinephrine, and serotonin.

| | |
|---------------------------------------|---|
| Cardiovascular and Circulation | <ul style="list-style-type: none"> • Tachycardia • Hypertension • Cardiac arrhythmias • Increased potential for venous thromboembolism • Aortic Enlargement • Atherosclerosis |
| Central Nervous System | <ul style="list-style-type: none"> • Lightheadedness • Headache • Dizziness • Increased risk of stroke • Abnormal sleep pattern |
| Gastrointestinal | <ul style="list-style-type: none"> • Nausea/Vomiting • Dry mouth |

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|----------------------------------|--|
| | <ul style="list-style-type: none"> • Heartburn/Dyspepsia • Peptic ulcer • Diarrhea • Stomach or intestinal cancer |
| Pulmonary/Respiratory | <ul style="list-style-type: none"> • Bronchospasm • Increased risk of pulmonary embolism |
| Nicotine During Pregnancy | Risks to Child Later in Life: <ul style="list-style-type: none"> • Hypertension • Type-II Diabetes • Neurobehavioral Defects • Infertility • Respiratory Dysfunction • Obesity |
| Hormonal | <ul style="list-style-type: none"> • Insulin Resistance • Increased Insulin Production |

Table 1: Some Side Effects of Nicotine. When inhaled nicotine usually reaches the brain in less than 10 seconds and can cause quite a lengthy list of adverse effects.

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Acetylcholine

Acetylcholine (ACh) is the main neurotransmitter of the parasympathetic nervous system, part of the autonomic and peripheral nervous systems. It has numerous functions throughout many systems of the body. It is released by motor

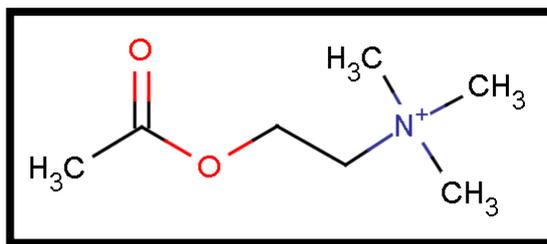


Figure 3: Chemical structure of acetylcholine

neurons and binds to post-synaptic acetylcholine receptors (AChR). In the peripheral nervous system, it is mainly responsible for allowing the contraction of skeletal muscle fibers. It does this by changing the permeability of the cell membrane and allowing sodium ions to flow into the cells of skeletal muscle fibers. Within the autonomic nervous system, it acts as a vasodilator, it decreases heart rate, decreases cardiac muscle contractility, increases gastric peristalsis and intestinal contractions / peristalsis.

Arginine Vasopressin

Arginine vasopressin (antidiuretic hormone), sometimes called argipressin or simply vasopressin, is a hormone that functions mainly to retain water in the body and constrict blood vessels.

Figure 2: Chemical Structure of Arginine Vasopressin

Beta-endorphin

Beta-endorphin is an endogenous opioid neuropeptide found in the neurons of the central and peripheral nervous systems. It is one of the 5 endorphins found in humans. The others are alpha-endorphin, alpha-neoendorphin, gamma-endorphin, and beta-neoendorphin.

Beta-endorphin mainly functions as a u-opioid receptor agonist. The u-opioid receptors are the same site of action as chemical opioid pain medications such as morphine and oxycodone. This action might also play an important role in the physical addiction of nicotine.

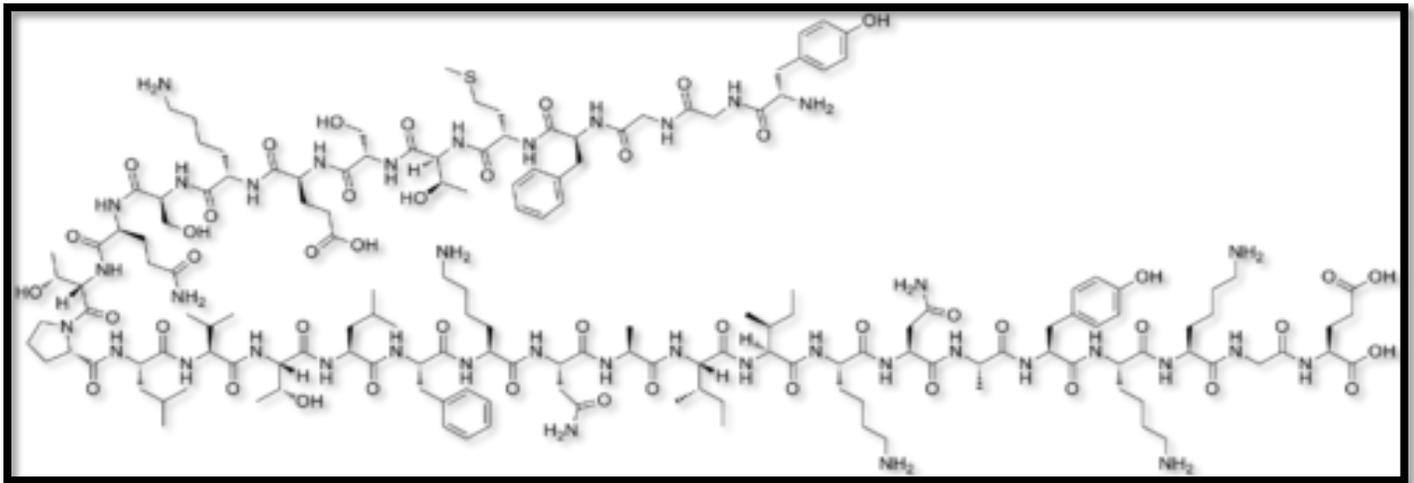


Figure 4: Chemical Structure of Beta-Endorphin

Epinephrine

Epinephrine is a hormone chemical messenger (neurotransmitter) produced naturally from the adrenal glands and some neurons. Its stimulating effect dilates the pupils, increases blood sugar, increases cardiac output and blood flow to the muscles. These actions are all secondary to the "fight-or-flight" response. As a nonspecific beta-agonist epinephrine also relaxes smooth airway muscle dilating the airways.

0 As a medication epinephrine (also known as the brand name Adrenalin) is often given either by IV or directly through an endotracheal tube to treat severe bronchospasm or allergic anaphylaxis. It is also used as an ACLS drug during cardiac arrest emergencies to attempt to reverse fatal heart rhythms such as ventricular fibrillation.

Norepinephrine

Norepinephrine is an organic catecholamine hormone and neurotransmitter that functions in the brain. The release of norepinephrine is lowest during sleep, is much higher while awake and increases dramatically during stressful situations as part of the fight-or-flight system. It also increases in response to the presence of certain other substances such as nicotine.

The effects of increased norepinephrine are similar to that of increased levels of epinephrine. It increases arousal, alertness, memory, and focuses attention. It also causes restlessness, anxiety, tachycardia, hypertension and hyperglycemia. In addition, it decreases blood flow to the GI system and promotes voiding of the bladder and large intestine.

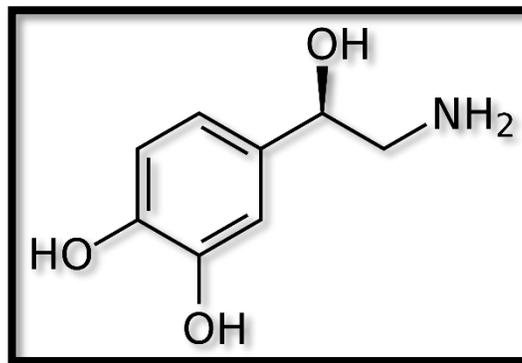


Figure 5: Chemical Structure of Norepinephrine

Serotonin

Serotonin is another neurotransmitter but it is a little different than the others. Serotonin is derived from tryptophan and is most abundant in the gastrointestinal tract. It is also found in the blood platelets and the central nervous system. It is believed that serotonin is responsible for feelings of wellbeing and happiness. Serotonin also increases gastrointestinal mobility, and it aids in hemostasis by increasing blood clotting and acting as a vasoconstrictor.

The presence of too much serotonin can lead to uncontrollable anxiety and agitation, tachycardia, hypertensive crisis, and when in combination with other substances can cause serotonin syndrome, which can be fatal.

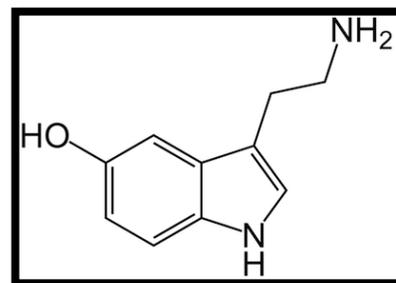


Figure 6: Chemical Structure of Serotonin

Other Ingredients

So, what else is in E-Cigarette cartridges? That's another question that has very few answers. There is a broad range of differences among manufacturers. In the beginning all e-cigarettes and cartridges were manufactured in China, but now some are also being manufactured in the United States and Europe. Here in the United States there are no federal regulations when it comes to E-Cigarettes and how they are manufactured. There is no agency to oversee quality or consistency of ingredients, and no agency to oversee safety. Manufacturers are basically free

to make the devices and the e-liquid solution any way they want. The list of ingredients on the cartridges may not be what is actually in them. No overseeing agency means manufacturers can disclose anything they want and not disclose what they don't want us to know about.

Here is what we do know (or what we *'think'* we know). The FDA's review of e-cig cartridges found vast differences in many of them. Some contained toxic chemicals and carcinogenic substances while others did not. An interesting detail is that nearly all cartridges that were labeled "No Nicotine" did in fact contain nicotine.

Flavorings

Numerous chemicals are used to create the hundreds of flavors that are available in the liquid of the e-cigarette cartridge, commonly known as e-juice. Many of these chemicals are also used to flavor the foods that we eat and the FDA has deemed them safe to consume. The problem is that we do not know what the risks are when we inhale these chemicals, nor do we know what chemical changes take place when the e-cig heats them up before we inhale them.

Propylene Glycol

Propylene glycol, a humectant, is a viscous, colorless, organic compound that has a slightly sweet taste and is nearly odorless. Its chemical formula is $C_3H_8O_2$. It is sometimes also called α -propylene glycol.

Propylene glycol is frequently used in theatrical fog makers and is partly responsible for creating the smoke like vapor of e-cigarettes. As a food additive it is used to maintain moistness of food products. As an additive to tobacco it prevents the tobacco from drying out, and as an additive in cosmetics and skincare products it aids in skin absorption and skin moisturizing. In the aviation industry it is used as a deicing solution to help remove or prevent ice from forming on the leading edges of aircraft wings, propellers, engine intakes, etc. It is also one of the main ingredients of many e-liquid solutions, making up for somewhere between 10 – 92% of the volume.

The FDA considers propylene glycol safe as a food and cosmetic additive. The effects of inhaled propylene glycol are unknown, as are the effects of propylene glycol when it is dissolved in the various e-liquid recipes' and vaporized with heat and inhaled.

Glycerin

Glycerin, also called glycerol, is a colorless, odorless viscous liquid compound. Its chemical formula is $C_3H_8O_3$. It is a non-toxic, sweet tasting simple sugar alcohol. It is derived naturally from the plants soybean or palm, and some animals. It can also be manufactured synthetically.

Glycerin is used in many applications. In the food industry it is most often used as a sweetener. It can also be a sugar substitute. It is a thickening agent for liqueurs. In medicine glycerin is a suppository laxative. It works by irritating the rectal mucosa causing it to secrete more water and other liquid agents. It was used in the automotive industry as an antifreeze agent but was replaced with propylene glycol which has a lower freezing point. In the e-liquid solution of e-cigarettes it is used to aid in the aerosol production of the smoke like vapor.

Glycerin is safe and non-toxic when ingested or used topically. Inhaled as a heated vapor the effects are unknown.

Diacetyl

Diacetyl occurs naturally as a byproduct of yeast fermentation. It is a yellowish/green liquid organic compound with a strong buttery flavor. Its chemical formula is $(CH_3CO)_2$ (molecular formula $C_4H_6O_2$)

Diacetyl is mainly used as a food additive to induce a buttery aroma and flavor. It is considered by the FDA to be safe as a food additive but currently there is question about the safety and health hazards of inhaling diacetyl, or diacetyl vapor. An increasing number of patients who work in food flavoring plants and microwave popcorn flavoring plants are being diagnosed with flavorings related bronchiolitis obliterans, a non-reversible mild to severe obstructive lung disease. Many of these diagnoses have been linked to the inhalation of food flavoring vapors, with diacetyl being the likely causative agent. More research is needed to see if other flavoring vapors also have an increased risk of developing flavorings related bronchiolitis obliterans.

Diacetyl is used in many flavors of e-liquid. The inhaled concentration of diacetyl when smoking e-cigarettes is suspected to be 100 times lower than the concentration inhaled when

smoking traditional tobacco cigarettes. More research is needed to fully understand the risks associated with inhaling vaporized diacetyl in e-liquid.

Acetylpyrazine

Used as a flavorant but very little information is known about this substance when it is used in food or when it is heated and inhaled.

Guaiacol

Guaiacol is an organic compound that occurs naturally in the gut of *Schistocerca gregaria*, (desert locusts). It is also derived from the guaiacum plant or creosote wood. It has the chemical formula of $C_6H_4(OH)(OCH_3)$.

Guaiacol is mostly used as a precursor to flavorants. (vanillin for example). Its derivatives are used in medicine as a local anesthetic, antiseptic, and expectorant. It also reacts to light and the presence of oxygen, changing color in chemical reactions that produce oxygen.

The US Food & Drug Administration considers guaiacol generally as safe for use in foods. More research is needed to understand the risks when guaiacol is heated and inhaled.

Myosmine

Myosmine is an alkaloid found in tobacco and is very closely related to nicotine.

Cotinine

Cotinine is an alkaloid found in tobacco, and is the primary metabolite of nicotine. Similar to nicotine, cotinine binds to nicotinic acetylcholine receptors, activating and desensitizing them. In animal studies cotinine has been shown to have antipsychotic effects, as well as decreased depression, anxiety, and fear. In humans' cotinine has had no such effects but little research has been done.

Cotinine has a 20-hour half-life on average. In drug testing cotinine is used as a biomarker for tobacco exposure and can be detected for up to 7 days. Much more research is needed to fully understand the effects of cotinine.

Citric acid

Citric acid is a relatively weak organic tribasic acid that occurs naturally in citrus fruits. It has the chemical formula of $C_6H_8O_7$. Lemons and limes have a particularly high concentration of citric acid, yielding approximately 47 grams per liter of juice. Citric acid accounts for approximately 8% of the dry weight of the fruit.

Worldwide approximately 1.6 million tons of citric acid was produced in 2007. That amount has slowly and steadily increased annually since, with more than 50% being produced in China.

50% of the citric acid produced is used as an acidity regulator in beverages, 20% on other foods, 20% is used in detergents, and 10% for pharmaceutical, cosmetic, and misc. chemical uses.

Citric acid is mildly caustic (as in mildly acidic) and can therefore be very irritating to the airways when inhaled. When inhaled deeply citric acid can damage small airway tissue and alveolar epithelial cells. This can lead to scarring and fibrosis, which is irreversible.

Chemicals Formed

Chemistry is full of activity in that most chemicals change under numerous conditions. In the subject of e-cigarettes, we know how some of the chemicals (ingredients) react when they are not only mixed with others, but also when they are heated up. Sometimes the results are the creation of other chemicals. Below is a partial list of some of the more prominent chemicals formed when the main ingredients of e-juice are mixed together and heated up to a vapor for the purpose of inhalation.

Formaldehyde

Also known as methanal, formaldehyde is a naturally occurring organic compound that has a chemical formula of CH_2O . It is similar in nature and closely related to formic acid.

Formaldehyde has many uses. It is used as a base or precursor in the creation of many other chemical compounds. Most of the environmental formaldehyde is formed in the upper atmosphere. Formaldehyde is also formed from a chemical reaction during combustion of many other carbon compounds, including tobacco smoke.

The US National Toxicology Program lists formaldehyde as a “known carcinogenic to humans”. Formaldehyde is formed in significant concentrations during the heating and vaporizing of e-juice.

Acetaldehyde

Acetaldehyde, closely related to formaldehyde, is another organic chemical compound that occurs naturally and is for industry on a large scale. Acetaldehyde has a chemical formula of CH_3CHO .

The International Agency for Research on Cancer lists acetaldehyde as a Group-1 carcinogen. It is one of the most abundant toxins found in the atmosphere, and has a cancer risk of approximately 1 in 1 million. During alcohol consumption, the liver the enzyme alcohol dehydrogenase oxidizes ethanol, which creates acetaldehyde. It is believed that acetaldehyde is a contributing factor in handovers.

Historically acetaldehyde was mostly used to create acetic acid, although this use is declining worldwide. It is also used as a precursor to some resins and polyvinyl.

Acetaldehyde is a known carcinogenic to humans. It is irritating to the skin, eyes, respiratory tract, and mucus membranes.

Acrolein

Acrolein is a simple unsaturated aldehyde, also known as propenal, with a molecular formula of $\text{C}_3\text{H}_4\text{O}$ (also expressed as $\text{CH}_2=\text{CHCHO}$). It is a colorless liquid that emits a piercing acrid odor that resembles burnt fat, as when cooking oil is heated to its smoking point. The odor is caused by the breaking down of glycerol into acrolein while superheating fat to its smoking point.

Acrolein is mainly used as a herbicide to control floating and submerged weeds and algae in irrigation canals and drilling waters.

Acrolein is a strong irritant to skin, eyes, and upper respiratory tract tissue. The World Health Organization labels Acrolein as toxic and suggests an occupational exposure of no greater than 7.5ug/kg of body weight per day.

Benzene

Benzene is an organic chemical compound with the chemical formula of C₆H₆, and is classified as an aromatic hydrocarbon. It is colorless, has a sweet smell, and is highly flammable.

Benzene is a byproduct of incomplete combustion of many other chemicals and materials. It is mainly used as a precursor to manufacturing many other chemicals, including gasoline, in which it is used to increase the octane rating and reduce engine knocks. Benzene is a known human carcinogen, and its non-industrial use is limited.

Ethylbenzene

Ethylbenzene, C₆H₅CH₂CH₃, is colorless, liquid organic compound that has an odor similar to that of gasoline. It is a monocyclic aromatic hydrocarbon, and plays an important role in the petrochemical industry – where it is used as a precursor plastics and many other chemical compounds. It is highly flammable and evaporates quickly.

Ethylbenzene is a gasoline additive, used to increase the octane rating and act as an anti-knock agent.

Acute toxicity of ethylbenzene is fairly low, and it appears that short term and long term exposure how little adverse effect. It is listed as a *possible carcinogen* by International Agency for Research on Cancer.

Toluene

Toluene is a colorless liquid with an odor similar to that of paint thinners. It is a water-insoluble aromatic hydrocarbon, mono-substituted benzene derivative. Its IUPAC systematic name is methylbenzene.

Toluene is a precursor to the production of many other chemicals. It is also used as a gasoline additive to increase octane ratings and prevent engine knocks. In the 1980's 86% toluene by volume fueled all of the turbo Formula-1 race cars.

Conclusions

The subject of e-electronic cigarettes continues to be quite dynamic and volatile. Even with all of the information we do have there are still many unanswered questions, and even a few new ones. Many of the answers remain just beyond our reach. Is the electronic cigarette a good thing, or a bad thing? Is it a drug delivery device, or a tobacco product? Is it a modern-day smoking cessation aid, or is the electronic cigarette just another wolf in sheep's clothing? The electronic cigarette controversy... Continues...

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Volatile