A Meta-Analysis to Elucidate the Link Between Tocopherol Acetate and Lung Illnesses of Vape Users

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Introduction

Vaping is the act of inhaling and exhaling the aerosol, often referred to as vapor, which is produced by an e-cigarette or similar device. The device is filled with vape liquid, it heats up, the liquid is aerosolized into millions of tiny droplets, and then inhaled. In this process the liquid in the electronic cigarette is being heated up and turned into vapor. The term is used because e-cigarettes do not produce tobacco smoke, but rather an aerosol (1), which is often mistaken for water vapor, that actually consists of fine particles. Many of these particles contain varying amounts of toxic chemicals, which have been linked to cancer, as well as respiratory and heart disease (2). E-liquid aerosols contain particulates, oxidizing agents, aldehydes, and nicotine. When inhaled, these aerosols most likely affect the heart and circulatory system. A 2018 report from the National Academies Press (NAP) found significant evidence that taking a puff from a nicotine e-cigarette triggers an increase in heart rate.There was also moderate evidence suggesting that taking a puff from an e-cigarette increases blood pressure. Both of these could affect heart health over the long term (3).

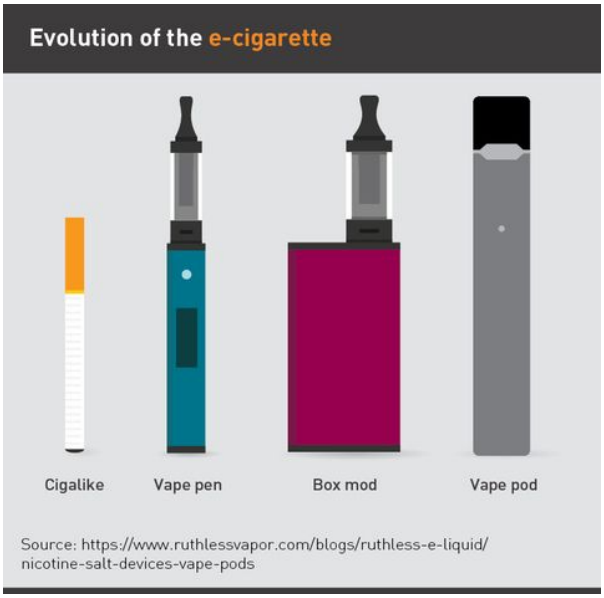

Figure 1: Evolution of the e-cigarette.
Vaping/smoking has changed over the course of many years. It has evolved over time and is now more technology-based. Older generations of e-cigarettes used a form of nicotine called free-base nicotine. The most recent generation of e-cigarettes on the market, which include pre-filled pod systems like JUUL use nicotine salts in the e-liquids. The nicotine salt formulas allow for much higher levels and efficient delivery of nicotine with less irritation compared to earlier generations of e-cigarettes. While using an e-cigarette is often called "vaping," the devices produce an aerosol, not a vapor. Unlike vapor, which is simply a substance in gas form, the aerosol from an e-cigarette contains tiny chemical particles from both the liquid solution and the device (e.g., metals from the heating coil).
(www.ruthlessvapor.com/blogs/ruthless-e-liquid/nicotine-salt-devices-vape-pods)

Figure 2: Juul Pod (www.juul.com/learn/pods#juulpods-ingredients)

Tocopheryl acetate, also known as Vitamin E Acetate, is an ester of acetic acid and α-tocopherol. It is a specific form of Vitamin E that is often found in skincare and dietary supplements which means that it is safe for human consumption. Vitamin E is known for its antioxidant properties. Antioxidants help to protect your body from damaging compounds called free radicals. Normally, free radicals form when your body converts food into energy (5). On the other hand, it does not seem to be safe for inhalation (6). Alpha-tocopherol is Vitamin E acts to protect cells against the effects of free radicals, which are potentially damaging by-products of the body's metabolism (10).

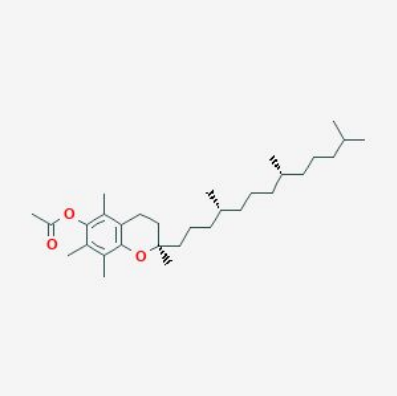

Figure 3: **Alpha tocopherol acetate**. Alpha-tocopherol is the first and most important form of vitamin E that is especially used by the human body to meet appropriate dietary requirements. Alpha-tocopherol acetate is subsequently most commonly indicated for dietary supplementation in individuals who may demonstrate a genuine deficiency in vitamin E.
https://www.drugbank.ca/drugs/DB14002
Source: "Alpha-Tocopherol Acetate." *National Center for Biotechnology Information. PubChem Compound Database*, U.S. National Library of Medicine, pubchem.ncbi.nlm.nih.gov/compound/alpha-Tocopherol-acetate.

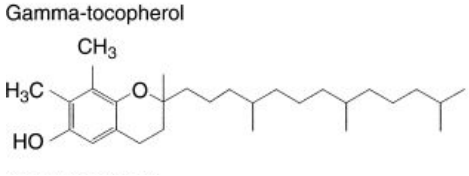

Figure 4: Gamma-tocopherol. Able to scavenge free radicals, thereby protecting against oxidative damage.

https://www.cancer.gov/publications/dictionaries/cancer-drug/def/gamma-tocopherol,
https://comptox.epa.gov/dashboard/dsstoxdb/mixture_search?cid=24075
Gamma-Tocopherol (γ-tocopherol) is needed in only small amounts and are available in the foods that you eat. /

Vitamin E prevents a chemical reaction called oxidation, which can sometimes result in harmful effects in your body. It is also important for the proper function of nerves and muscles (11). The problem with adding it to vaping liquids is that there is not enough data on the effects of inhalation and the toxicity associated with it. Research shows that lipids (oils) in the lungs are highly toxic and have been associated with lung injury. Tocopherols stick fast to the fluid in the lining of the lungs known as lung surfactant. Lung surfactant enables oxygen to transfer from air into your body (7). The Vitamin E acetate oil can become "like honey" and stick to the vaper's lungs (8). This substance facilitates the transfer of oxygen from air breathed into the lungs to the rest of the body. Tocopherols block this form of exchange and this results in the death of lung cells which causes damage that triggers an immune system response in the body that resembles lipoid pneumonia. With smoking this effect occurs.

Pneumocytes are a type of epithelial cell, lining the alveoli, the air sacs in the lungs. The alveoli are, in fact, lined with two types of pneumocyte cells, type I and type II.

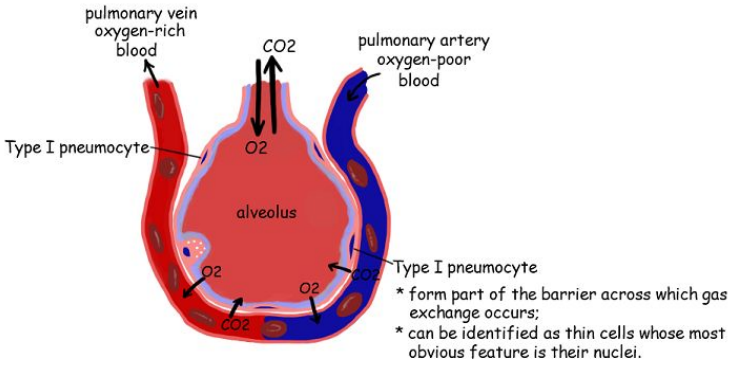

Figure 5: Gas exchange in the alveoli. Oxygen is going inside the alveoli and carbon dioxide is leaving the alveoli. http://ibbiologyhelp.com/HumanPhysiology/gasexchange.html

The cells cover 95% of the surface. Type I pneumocytes are responsible for the gas (oxygen and carbon dioxide) exchange that takes place in the alveoli. If one smokes they are covering theses

pneumocytes which decreases lung surfactant. Lung surfactant is a mixture of lipids and proteins which is secreted by the epithelial type II cells into the alveolar space. Its main function is to reduce the surface tension at the air/liquid interface in the lung. When smoking with Vitamin E acetate it covers your pneumocyte cells which causes your breathing rate to decrease and makes it harder to breathe. Vitamin E acetate affects the normal functioning of the lung. Similarly, cigarette smoking can induce alterations of the surfactant system, while surfactant homeostasis and function might be broken down through both direct and indirect mechanisms. Cigarette smoke injuries secretion of type II pneumocytes, resulting in the reduction of the total amount of lung surfactant (9).

Materials and Methods

A systematic review and meta-analysis will be conducted. Electronic databases will be searched using key search terms to identify relevant information and up-to-date findings. Studies performed on the ingredients found in vaping and physiological effects will be included in this analysis. Primary observational studies and studies with experimental designs will be included. Interviews and blogs may also be included.

Meta-analysis - online research
Pubmed.org
Google Scholar
News articles related to vaping, tocopheryl acetate
NIH - CDC

Null Hypothesis (H0) - Tocopheryl acetate is a chemical found in e-cigarettes; however, it has no physiological effects on the functioning of alveolar cells/tissues/.

Alternate Hypothesis (Ha) - Nicotine, although in a different form?, is in fact the major causative factor related to vaping illnesses.

Expected Outcome - Tocopheryl acetate adheres to the pneumocyte (lung surfactant) cells of the alveoli, inhibiting normal physiological function,

The goal and purpose of this meta-analysis is to make the many (young) adults currently vaping aware of the toxins they are putting into their bodies. Many are unaware of the effects of smoking on the lungs; also, you never know what chemicals you can be allergic to. For example, tocopheryl acetate seems to be giving most people who use vaping allergic reactions. Most teenagers are uneducated and unaware about this topic and have no clue on what can harm them. Thus, this project aims to address young adults - We can save lives if people just knew more about what there inhaling; so our mission is to prevent more kids from dying and to stop the children who use vape now.

The active ingredients of e-cigarettes

There are many ingredients that contribute to the effects of e-cigarettes. In e-cigarettes, scientists found propylene glycol, glycerin, nicotine, flavors, small amounts of toxicants, carcinogens, and heavy metals, as well as metal nanoparticles, and other substances. These substances can be found in vapes, e-cigarettes and juuls. These chemicals can be very dangerous when inhaled in vapor form.
The effects of the ingredients can lead to lung diseases and also possibly you can be allergic to the ingredients in e- cigarettes. These harmful chemicals are inhaled deep into the lungs (13).

What does tocopherol/Vitamin E Acetate have to do with vaping illnesses and deaths?

Even though there is no official confirmation that vitamin E acetate is the culprit in the development of vaping related lung diseases, researchers have found lots of evidence as to why it must be linked to vaping illnesses and deaths. Laboratory data has shown that vitamin E acetate which is an additive in some THC-containing e-cigarette, or vaping, products, is strongly linked to the EVALI outbreak. A recent study analyzed samples from 51 EVALI cases from 16 states and a comparison group of samples from 99 healthy people for vitamin E acetate. Vitamin E acetate was identified in bronchoalveolar lavage (BAL) fluid samples which are fluid samples collected from the lungs. These samples were collected from 48 of the 51 EVALI patients, but not in the BAL fluid from the healthy

comparison group. No other toxicants were found in BAL fluid from either group, except for coconut oil and limonene (4). Researchers believe it has an effect on lungs because cannabis-containing vape cartridges used by those who had fallen ill showed traces of vitamin E acetate when tested. Vitamin E acetate is oil soluble but not a true oil which means and Tocopherols stick fast and "like honey" to the fluid in the lining of the lungs known as lung surfactant. This substance facilitates the transfer of oxygen from air breathed into the lungs to the rest of the body. Tocopherols block this form of exchange and this results in the death of lung cells causing damage that triggers an immune system (5). A form of vitamin E has been identified as a "very strong culprit" in lung injuries related to vaping THC and It has killed 40 people and sickened 2,051. Many patients with the mysterious illness have wound up hospitalized in intensive care units, needing ventilators or even more desperate measures to help them breathe (6)

Physiological effects of e-cigarettes

Globally, people are suffering and dying from e-cigarettes. Vitamin E acetate was identified in bronchoalveolar lavage (BAL) scientist took fluid samples from 48 of the 51 EVALI patients. Doctors are finding tocopheryl acetate in the lungs of people hospitalized because of vaping. This is showing how vitamin E acetate is the culprit in the outbreak of vaping-related illnesses. As of January 14th 2020 a total of 2,668 hospitalized e-cigarette, or vaping, product use-associated lung injury (EVALI) cases or deaths have been reported to CDC from 50 different states, the District of Columbia, and two U.S. territories (Puerto Rico and U.S. Virgin Islands). Health officials have now found vitamin E acetate in the damaged lungs of 48 out of 51 patients who had fallen ill or died of lung injuries, said Anne Schuchat, principal deputy director at the Centers for Disease Control and Prevention. In comparison vitamin E acetate was not found in the lung fluids of any of 99 healthy individuals being tested; these people said they never smoked before. Researchers also found no evidence of other potential toxins in the healthy comparison group (4).

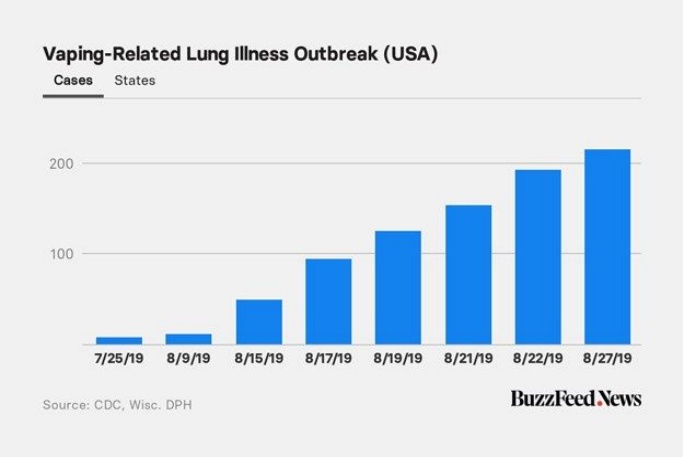

Figure 6: Vaping-Related Lung Illness Outbreak (USA). The amount of Vaping- Related Lung Illness Outbreaks in the USA are continuing to increase. The number of outbreaks quadrupled in a few weeks from July 25th to August 27th. As the days go by people are getting a negative effect from vaping and this it is getting worse over time. https://www.buzzfeednews.com/article/danvergano/vaping-illness-outbreak-spread, www.buzzfeednews.com/article/danvergano/vaping-illness-outbreak-spread.

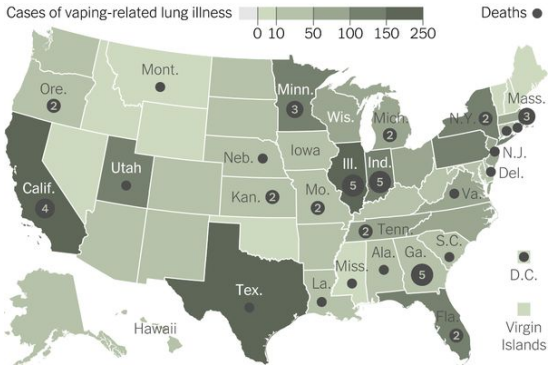

Figure 7: Vaping Illness Tracker: 2,506 Cases and 54 Deaths. Thousands of people have been sickened by lung illnesses linked to vaping, most by using THC products. www.nytimes.com/interactive/2019/health/vaping-illness-tracker.html.

Difference between Nicotine delivery via cigarettes versus e-cigarettes

E-cigarettes produce an aerosol by heating a liquid that usually contains nicotine—the addictive drug in regular cigarettes, cigars, and other tobacco products—flavorings, and other chemicals that help to

make the aerosol. Using an e-cigarette is sometimes called “vaping. Vitamin E acetate has killed 40 people and sickened 2,051 people (18).

Is vitamin E acetate a recently added component in THC-containing products?

To explore whether vitamin E acetate is a recently added component in THC-containing products Minnesota Department of Health (MDH) tested ten products seized by law enforcement in 2018. Before the EVALI which is the Centers for Disease Control and Prevention (CDC) to the dangerous, newly identified lung disease linked to vaping, outbreak 20 products were seized in 2019 during the outbreak. Twenty-four products obtained from 11 EVALI patients from 2019 contained vitamin E acetate and among the seized products tested by MDH, none seized in 2018 contained vitamin E acetate (12).

Discussion and Conclusions

There are scientist testing and trying to figure out the cause of people getting hospitalized and sick so they took samples from the lungs of the 29 patients, including two who died, “provided evidence of vitamin E acetate at the primary site of injury in the lungs. Tocopheryl acetate is the reason for the outbreak of a vaping-linked lung disease that has caused 380 cases of pulmonary distress and six deaths across the US. Tocopheryl acetate is being connected to a spate of serious lung problems caused by vaping. They have figured out that most people were hospitalized because of the tocopheryl acetate in vapes and juuls. Scientists came to the conclusion that the vitamin E acetate is what is harming the lungs the most. The factors in the vitamin E acetate are damaging the lining of the lungs. Tocopheryl acetate must be an allergen that some people have because not everyone who vapes is suffering from vaping related illnesses. If one is allergic to the Tocopheryl acetate it can cause many problems and may lead to hospitalization. It's very clear what the effects of Tocopheryl acetate has on lungs and people. Tocopheryl acetate has injured many people because of the harsh chemicals that people are smoking. Even young teenagers are vaping and it's terrible because the chemicals in e-cigarettes are too harsh for teenagers. We need to spread awareness and show how terrible it is to vape and how bad it is for your lungs. There are

many diseases that can occur from the e-cigarettes, juuls or anything that people can use to vape. It is a terrible addiction and is affecting many people of the younger generation now.

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