We need to talk about vaping. I feel beyond blessed and incredibly lucky to have only sampled a girl's vape a handful of times at most, and proudly have never owned one or even enjoyed trying it the very few times I have. (Every time without exception it led to a severe coughing attack, so it is no surprise that I will not dare try them again.) This goes to show how embedded in social culture these things have become. I know many health conscious individuals that have tried them at least once, usually while under the influence of alcohol (a vicious combination when it comes to acetaldehyde concentration and neurotoxicity).

Vapes, or 'electronic cigarettes' started off as a quitting aid for those addicted to cigarettes, which knowingly contain not just dozens but hundreds of carcinogenic, neurotoxic, genotoxic, endocrine disruptive, and teratogenic chemicals. However, they quickly appealed to youth as another unregulated, cheap and discrete 'legal high'.

We saw the rise and fall of 'JUUL' pods after serious legal troubles and acute adverse events leading to a global epidemic of vape-related hospitalizations. Instead of throwing the towel and admitting e-cigs were a terrible mistake, the industry quickly revamped ingredients and rebranded vapes. This doubling-down meant specifically marketing to teenagers with brands like Elfbar, Lost Mary, and Geekbar boasting colorful designs and tantalizing flavors, all designed to target the unsuspecting and naive young adult demographic. Social media influencers, music industry icons, and even YouTube personalities deeply blurred the lines between 'druggy/junky and popular/cool kid', leading to the recent bloom in teen vaping. "If they do it and they are famous/pretty/successful/nice/funny, etc. it must mean its not that bad." is the evident 'appeal to the people' fallacy.

This immature mentality among many young adults bars them from recognizing that adverse effects take years to follow suit, and for some the news comes like a freight train, as it is often too late to make a change. A lifetime addiction or worse (cancer, chronic lung injury, and permanent neurological or respiratory damage) eventually crept in.

What is it that makes vapes so dangerous as to cause permanent neurological, hepatic, respiratory, or other forms of biological and psychological harm?

For one, the form of nicotine in most vapes is ambiguous and often misleading. Some contain fully synthetic nicotine, whose breakdown combustion byproducts are extremely toxic and untested, let alone regulated. Others boasting natural nicotine are tainted with prevalent tobacco pesticides, which synergistically exacerbate harm alongside toxic solvents, leeched metallic & chemical fumes from the heating element/coil & sponge-wick mechanisms, and flavoring chemicals.

Vitamin E Acetate was used predominantly in cannabis vapes, which also contain coil & sponge-wick mechanisms which leech toxic chemicals and heavy metals and at times synthetic aromatic compounds like flavoring terpenes. It was quickly denounced toxic after a breakout of acute lung damage among users.

Nowadays the most popular solvents for both cannabis and nicotine vapes include polyethylene glycol, propylene glycol, and vegetable glycerin. Their long-term toxicokinetics are poorly understood, but it has been documented that acutely, vegetable glycerin produces the least amount of neurotoxic, carcinogenic, and endocrine disruptive chemical byproducts including formaldehyde, acetaldehyde, dioxins, acrolein, asbestos, and polycyclic aromatic hydrocarbons.

It all depends on what chemicals are present in conjunction, which given their varying chemical affinities, combustion breakdown byproducts, and capacity to form compounds that are concomitantly more toxic than they would be individually.

The studies compiled for this research (veritavitalis.com/vaping) demonstrate the toxicokinetics of solvents, flavoring chemicals, and other toxic factors regarding nicotine e-cigarettes. A thorough analysis of these studies will demonstrate that many factors overlap within the cannabis disposable vape industry, and warrant immediate regulatory action across the board for all products offering volatile-compound insufflation of any kind, even towards recently-promoted 'nicotine-free', 'natural' or 'essential-oil-based' vapes, which as you may guess are being pushed as a new 'vape-quitting aid'. The irony is deafening.

SOLVENT TOXICITY:

PEG (POLYETHELENE GLYCOL):

1] **Hypersensitivity to polyethylene glycol (PEG)**
https://pubmed.ncbi.nlm.nih.gov/35180202/
- Polyethylene glycol (PEG), widely used as an excipient in various vaccines, is considered the primary cause of allergic reactions associated with administration of Comirnaty (Pfizer/BioNTech) and Covid-19 Vaccine (Moderna) vaccines.
- Undoubtedly, the issue of hypersensitivity to PEG warrants further research, while patients with the diagnosis require individual diagnostic and therapeutic approach.

2] **Anaphylactic shock caused by ingestion of polyethylene glycol**
https://pubmed.ncbi.nlm.nih.gov/25691849/
- Polyethylene glycol (PEG) is most commonly utilized as a bowel preparation solution for colonoscopy.
- First case of anaphylactic shock following the ingestion of PEG solution in Korea.

3] **Polyethylene glycol acute and sub-lethal toxicity in neotropical Physalaemus cuvieri tadpoles (Anura, Leptodactylidae)**
https://pubmed.ncbi.nlm.nih.gov/33848902/
- Although many polymers are known by their toxicity, we know nothing about the impact of polyethylene glycol (PEG) on anurofauna.
- This finding suggests physiological changes altering REDOX homeostasis into oxidative stress. In addition, the increased activity of acetylcholinesterase and butyrylcholinesterase, and reduction in superficial neuromasts, confirmed PEG's neurotoxic potential.

4] **Retinal Toxicity of Intravitreal Polyethylene Glycol 400**
https://pubmed.ncbi.nlm.nih.gov/26540613/
- Ophthalmic examinations demonstrated diffuse signs of retinal degeneration and cataract formation in all 6 eyes injected with PEG-400.
- Histopathological and TEM analysis of eyes demonstrated both inner and outer retinal atrophy.

5] **Toxicity of topical polyethylene glycol**
https://pubmed.ncbi.nlm.nih.gov/7179288/

- This raises a concern about the potential presence of free phytosterols and beta-Sitosterol, which could have antiestrogenic, antiprogestational, gonadotrophic, antigonadotrophic, and antiandrogenic effects in PEG sterols.

6] **A cautionary note: Toxicity of polyethylene glycol 200 injected intraperitoneally into mice**
https://pubmed.ncbi.nlm.nih.gov/31526095/
- Mice injected intraperitoneally (i.p.) with PEG 200 at a dose of 8 mL/kg (i.e. 9 g/kg) did not tolerate PEG 200 well, and half of the animals had to be euthanized.

7] **Sub-lethal toxicity of chlorpyrifos alone and in combination with polyethylene glycol to common carp (Cyprinus carpio)**
https://pubmed.ncbi.nlm.nih.gov/30682763/
- Chlorpyrifos is a widely used pesticide commonly found in tobacco.
- Chlorpyrifos increased the toxicity of PEG.

8] **Toxicity of high-molecular-weight polyethylene glycols in Sprague Dawley rats**
https://pubmed.ncbi.nlm.nih.gov/35092809/
- PEG treatment led to a molecular-weight-related increase in PEG in plasma and a low level of PEG in cerebrospinal fluid.
- Subcutaneous and intravenous exposure to high-molecular-weight PEGs produces anti-PEG IgM antibody responses and tissue vacuolation.

9] **Safety assessment on polyethylene glycols (PEGs) and their derivatives as used in cosmetic products**
https://pubmed.ncbi.nlm.nih.gov/16011869/
- Manufacturers of PEGs and PEG derivatives must continue their efforts to remove impurities and by-products such as ethylene oxide and 1,4-dioxane.

10] **Polyethylene glycol intoxication in burn patients**
https://pubmed.ncbi.nlm.nih.gov/7172076/
- Unexplained increases in the anion gaps and serum osmolalities were observed in 3 burn patients who died following treatment with a polyethylene glycol-based burn cream.
- The cause of this high 'calcium gap' appeared to be binding of calcium by dicarboxylic acid metabolites of polyethylene glycol.

11] **Polyethylene glycol in suppositories: carcinogenic?**
https://pubmed.ncbi.nlm.nih.gov/7212494/

12] **E-cigarette exposure causes early pro-atherogenic changes in an inducible murine model of atherosclerosis**
https://pubmed.ncbi.nlm.nih.gov/38164438/
- Evidence suggests that e-cigarette use (vaping) increases cardiovascular disease risk.
- These data show that various parameters including weight, circulating lipoprotein/glucose levels, and splenic immune cells were significantly affected by exposure to PG/VG and/or nicotine-containing aerosols.

13] **Rapid Screening of Vaping Liquids by DART-MS**
https://pubmed.ncbi.nlm.nih.gov/36074975/
- E-cigarette, or vaping, product use-associated lung injury was reported in over 2800 cases from August 2019 to February 2020.

- This is a simple DART-MS method for screening vaping liquids for substances of concern in less than 2 min per sample.

14] **E-cigarette aerosol impairs male mouse skeletal muscle force development and prevents recovery from injury**
https://pubmed.ncbi.nlm.nih.gov/36250633/
- Inhalation of E-cigarette aerosol delivers high doses of nicotine, raises systemic cytokine levels, and compromises cardiopulmonary function.
- In male mice, nicotine-containing E-cigarette aerosol compromises muscle contractile function, regeneration from injury, and whole body running speeds. The vehicle used to deliver nicotine, propylene glycol, and vegetable glycerin, also reduces running speed and impairs the restoration of muscle function in injured muscle. However, the predominant effects of nicotine in this inhaled aerosol are evident in altered catecholamine levels, increased glycogen content, decreased running capacity, and impaired recovery of force following an overuse injury.

15] **Investigation of Vaping Fluids Recovered From New York State E-Cigarette or Vaping Product Use-Associated Lung Injury Patients**
https://pubmed.ncbi.nlm.nih.gov/34778204/
- E-cigarette or vaping product use-associated lung injury (EVALI) is a serious pulmonary condition that is associated with the extended use of certain vaping products.
- The safety of additional components and additives that are present in vaping fluids are likewise of concern.

PG (PROPYLENE GLYCOL) & VG (VEGETABLE GLYCERIN):

16] **Recognition, treatment, and prevention of propylene glycol toxicity**
https://pubmed.ncbi.nlm.nih.gov/17555487/
- Toxic effects include hyperosmolality, increased anion gap metabolic acidosis (due to lactic acidosis), acute kidney injury, and sepsis-like syndrome.

17] **Propylene glycol toxicity in children**
https://pubmed.ncbi.nlm.nih.gov/25762872/
- Reported adverse effects from PG include central nervous system (CNS) toxicity, hyperosmolarity, hemolysis, cardiac arrhythmia, seizures, agitation, and lactic acidosis.

18] **Toxicity of Propylene Glycol Extract of Propolis on Central Nervous System and Liver in Pregnant and Neonatal Rats**
https://pubmed.ncbi.nlm.nih.gov/36889342/
- Propylene glycol extract caused dilatation of blood vessels and apoptosis of neurons in brain tissue.

19] **Ethylene glycol and propylene glycol ethers - Reproductive and developmental toxicity**
https://pubmed.ncbi.nlm.nih.gov/26647990/
- Our particular attention was focused on the metabolism of some EGAEs and their organ-specific toxicities, apoptosis of spermatocytes associated with changes in the expression of various genes that code for oxidative stress factors, protein kinases and nuclear hormone receptors.

20] **Acute and subacute oral toxicity of propylene glycol enantiomers in mice and the underlying nephrotoxic mechanism**
https://pubmed.ncbi.nlm.nih.gov/34461418/
- The results show that the nephrotoxic effects of PG are induced by oxidative stress, and the activation of the inflammatory response is mediated by the NF-κB signaling pathway.

21] **Developmental toxicity and neurotoxicity assessment of R-, S-, and RS-propylene glycol enantiomers in zebrafish (Danio rerio) larvae**
https://pubmed.ncbi.nlm.nih.gov/35000155/
- R-, S-, and RS-PG enantiomers of high doses could potentially exhibit the neurotoxicity and ocular developmental toxicity in zebrafish larvae.

22] **Propylene glycol toxicity in an adolescent secondary to chronic cornstarch ingestion**
https://pubmed.ncbi.nlm.nih.gov/38756767/
- She was admitted to the intensive care unit (ICU) with multisystem organ failure due to propylene glycol toxicity.

23] **Propylene glycol-associated renal toxicity from lorazepam infusion**
https://pubmed.ncbi.nlm.nih.gov/14524641/
- The patients' increased serum creatinine concentrations are likely to have resulted from exposure to propylene glycol as a result of lorazepam infusion. Serum osmolality and osmol gap may be useful markers for propylene glycol toxicity.

24] **Propylene glycol toxicity: a severe iatrogenic illness in ICU patients receiving IV benzodiazepines: a case series and prospective, observational pilot study**
https://pubmed.ncbi.nlm.nih.gov/16162774/
- Propylene glycol toxicity is a potentially life-threatening iatrogenic complication that is common and preventable.

25] **Acute propylene glycol ingestion**
https://pubmed.ncbi.nlm.nih.gov/12217005/
- The propylene glycol elimination pattern, absence of significant acid-base disturbance, and minimal lactate elevation in this case are consistent with ethanol-related inhibition of propylene glycol metabolism.

26] **Toxicity of ethylene glycol, diethylene glycol, and propylene glycol to human cells in culture**
https://pubmed.ncbi.nlm.nih.gov/3814844/

27] **Propylene glycol, a component of electronic cigarette liquid, damages epithelial cells in human small airways**
https://pubmed.ncbi.nlm.nih.gov/35999544/
- PG damaged SAECs more than Gly. In addition, COPD-SAECs were more susceptible to PG than SAECs without COPD. Usage of e-cigarettes may be harmful to the respiratory system, especially in patients with COPD.

28] **Studies on toxicity and inflammatory reactions induced by e-cigarettes : In vitro exposure of human nasal mucosa cells to propylene glycol at the air-liquid interface**
https://pubmed.ncbi.nlm.nih.gov/33586050/
- Possibly repairable dose-dependent DNA fragmentation and profound DNA alterations at high concentrations of propylene glycol warrant enhanced genotoxicological studies.

29] **Comparative short-term inhalation toxicity of ethylene glycol monomethyl ether and propylene glycol monomethyl ether in rats and mouse**
https://pubmed.ncbi.nlm.nih.gov/7330878/

30] **Ethylene glycol monomethyl ether and propylene glycol monomethyl ether: metabolism, disposition, and subchronic inhalation toxicity studies**
https://pubmed.ncbi.nlm.nih.gov/6499808/
- Overexposure to PGME has been associated with increases in liver weight and central nervous system depression.

31] **Predicting human neurotoxicity of propylene glycol methyl ether (PGME) by implementing in vitro neurotoxicity results into toxicokinetic modeling**
https://pubmed.ncbi.nlm.nih.gov/37156387/
- All tested substances elicited a concentration-dependent increase in pro-inflammatory cytokine expressions.

32] **Two Fast GC-MS Methods for the Measurement of Nicotine, Propylene Glycol, Vegetable Glycol, Ethylmaltol, Diacetyl, and Acetylpropionyl in Refill Liquids for E-Cigarettes**
https://pubmed.ncbi.nlm.nih.gov/36838889/
- The use of e-cigarettes (ECs) has become increasingly popular worldwide, even though scientific results have not established their safety. Diacetyl (DA) and acetylpropionyl (AP), which can be present in ECs, are linked with lung diseases. Ethyl maltol (EM)-the most commonly used flavoring agent-can be present in toxic concentrations.

33] **Comparative study of lung toxicity of E-cigarette ingredients to investigate E-cigarette or vaping product associated lung injury**
https://pubmed.ncbi.nlm.nih.gov/37055947/
- Transcriptomic analysis revealed that PG exposure was associated with fibrotic lung injury via the AKT signaling pathway and M2 macrophage polarization, and VEA exposure was associated with asthmatic airway inflammation via the mitogen-activated protein kinase signaling pathway.

34] **Electronic cigarette liquid substances propylene glycol and vegetable glycerin induce an inflammatory response in gingival epithelial cells**
https://pubmed.ncbi.nlm.nih.gov/32729321/
- Stimulation with PG/VG mixtures reduced cell viability compared to nonexposed controls ($p < 0.05$). Adding PG/VG increased the levels of IL-6, IL-8, and MMP-9, and the amount of PG had more biological impact compared to the VG amount. The nicotine augmented this effect compared to its nicotine-free counterparts.

35] **An Unrecognized Hazard in E-Cigarette Vapor: Preliminary Quantification of Methylglyoxal Formation from Propylene Glycol in E-Cigarettes**
https://pubmed.ncbi.nlm.nih.gov/33419122/
- Diacetyl and methylglyoxal was detected in 100% of samples with median concentration (range) of 20 µg/m3 (less than limit of quantification: 54 µg/m3) and 4219 µg/m3 (677-15,342 µg/m3), respectively. We also detected acetaldehyde (median concentration: 341 µg/m3) and propionaldehyde (median concentration: 87 µg/m3) in all samples. The recent evidence that methylglyoxal is more cytotoxic to airway epithelial cells than diacetyl makes this an urgent public health concern.

36] **Formation of flavorant-propylene Glycol Adducts With Novel Toxicological Properties in Chemically Unstable E-Cigarette Liquids**
https://pubmed.ncbi.nlm.nih.gov/30335174/

- Flavor aldehydes including benzaldehyde, cinnamaldehyde, citral, ethylvanillin, and vanillin rapidly reacted with the e-liquid solvent propylene glycol (PG) after mixing, and upward of 40% of flavor aldehyde content was converted to flavor aldehyde PG acetals, which were also detected in commercial e-liquids. Vaping experiments showed carryover rates of 50%-80% of acetals to e-cigarette vapor.
- This study demonstrates that e-cigarette liquids can be chemically unstable, with reactions occurring between flavorant and solvent components immediately after mixing at room temperature. The resulting compounds have toxicological properties that differ from either the flavorants or solvent components.

37] **Quantification and cytotoxicity of degradation products (chloropropanols) in sucralose containing e-liquids with propylene glycol and glycerol as base**
https://pubmed.ncbi.nlm.nih.gov/34543670/

- The results of the chemical analysis, which was executed by employing GC-MS/GC-FID, demonstrated high amounts of various chloropropanols. The most abundant one is extremely toxic, namely 3-chloropropane-1,2-diol, which can be detected at concentrations ranging up to 10,000 mg/kg.

38] **Influence of the E-Cigarette Emission Profile by the Ratio of Glycerol to Propylene Glycol in E-Liquid Composition**
https://pubmed.ncbi.nlm.nih.gov/31460462/

- Analysis of the vapor phases of E-cig emissions detected toxicants such as acetaldehyde, acrolein, benzaldehyde, as well as benzene, toluene, ethylbenzene, and xylene (BTEX) compounds.
- In summary, users of E-cig are exposed to harmful chemicals even if the E-liquids contain only propylene glycol and glycerol without flavorings, nicotine, or impurities. Furthermore, this study shows that E-liquids containing higher percentages of glycerol will produce higher levels of toxicants compared to E-liquids with similar percentages of propylene glycol.

39] **Toxicity and pharmacology of propylene glycol**
https://pubmed.ncbi.nlm.nih.gov/13871629/

40] **Acute and chronic in vivo effects of exposure to nicotine and propylene glycol from an E-cigarette on mucociliary clearance in a murine model**
https://pubmed.ncbi.nlm.nih.gov/28651446/

- In this murine model, a chronic, daily, 20 min-exposure to N/PG, but not an acute exposure, slowed MCC, compared to exposure to PG alone and led to systemic absorption of nicotine.

41] **Ex vivo toxicity of E-cigarette constituents on human placental tissues**
https://pubmed.ncbi.nlm.nih.gov/36084357/

No effects on tissue viability were observed at PG/VG concentrations < 8 % (v/v), while viability significantly reduced at PG/VG concentrations ≥ 10 % (v/v); biomarker studies employed only non-cytotoxic doses. Exposure to PG/VG decreased levels of 8-IsoP, IL-6, and E2, and treatment with 2 % or 8 % PG/VG significantly reduced HO-1 levels, compared to non-treated controls. Exposure to nicotine alone at 2,500 nM and 5,000 nM reduced MTT activity by 20 % ($P = 0.04$) and 70 % ($P < 0.001$), respectively, and significantly increased ($P < 0.001$) levels of HO-1 and BDNF, compared to controls. Treatment with nicotine alone and in combination with PG/VG reduced IL-6 and E2 levels.

VAPING TOXICITY

42] **Vaping-Associated Lung Injury: A Review**
https://pubmed.ncbi.nlm.nih.gov/35334588/
- Since commercial development in 2003, the usage of modern electronic cigarette (e-cigarette) continues to increase amongst people who have never smoked, ex-smokers who have switched to e-cigarettes, and dual-users of both conventional cigarettes and e-cigarettes.
- With such an increase in use, knowledge of the irritative, toxic and potential carcinogenic effects on the lungs is increasing.

43] **Addiction to Tobacco Smoking and Vaping**
https://pubmed.ncbi.nlm.nih.gov/37441760/
- The tobacco epidemic has been one of the biggest public health threats, and smoking is one of the world's largest preventable causes of premature death. An estimated 15.4% of all deaths in the world are attributable to tobacco smoking.
- While the lax regulation may allow for the introduction of toxic compounds that can lead to acute or subacute toxicity, such as the e-cigarette- or vaping-associated lung injury that has been linked to vitamin E acetate. In addition, regular vapers and heated tobacco devices emit toxins, although at lower concentrations than burned tobacco.

44] **EVALI and the Pulmonary Toxicity of Electronic Cigarettes: A Review**
https://pubmed.ncbi.nlm.nih.gov/32246394/
- EVALI, or "electronic cigarette or vaping product use-associated lung injury," is a recently described entity at the forefront of current investigations.
- The presentation, diagnostic work-up, treatment, and pathophysiology of EVALI are herein described, as well as the general pulmonary toxicity profile of electronic cigarettes.

45] **Review of Health Consequences of Electronic Cigarettes and the Outbreak of Electronic Cigarette, or Vaping, Product Use-Associated Lung Injury**
https://pubmed.ncbi.nlm.nih.gov/32301069/
- Electronic cigarettes (e-cigarettes) are battery-operated devices to insufflate nicotine or other psychoactive e-liquid aerosols.
- Propylene glycol and glycerin are humectants (water-retaining excipients) that generate pulmonary irritants and carcinogenic carbonyl compounds (e.g., formaldehyde, acetaldehyde, and acrolein) when heated in e-cigarettes.
- Metals contained in heating coils and cartridge casings may leach metals such as aluminum, chromium, iron, lead, manganese, nickel, and tin.
- Flavoring agents are considered safe for ingestion but lack safety data for inhalational exposures. Diacetyl, a common buttery flavoring agent, has known pulmonary toxicity with inhalational exposures leading to bronchiolitis obliterans.
- Patients with EVALI present with a constellation of respiratory, gastrointestinal, and constitutional symptoms.

46] **E-cigarette vaping associated acute lung injury (EVALI): state of science and future research needs**
https://pubmed.ncbi.nlm.nih.gov/35822508/
- The main histopathologic pattern consisted of diffuse alveolar damage with bilateral ground-glass-opacities at chest radiograph/CT, and increased number of macrophages or neutrophils and foamy-macrophages in the bronchoalveolar lavage.

47] **A review of toxic effects of electronic cigarettes/vaping in adolescents and young adults**
https://pubmed.ncbi.nlm.nih.gov/32715837/
- Adolescents are vulnerable to the risks of e-cigarettes, as they are targeted as new consumers with advertisements and flavoring compounds, and are not utilizing them as a means to smoking cessation.
- Additionally, there have been more recent studies showing extrapulmonary effects including cardiovascular, immunologic and neuro-developmental effects.

48] **E-Cigarette Toxicology**
https://pubmed.ncbi.nlm.nih.gov/34555289/
- Adverse health effects related to e-cigarette aerosols are influenced by several factors, including e-liquid components, physical device factors, chemical changes related to heating, and health of the e-cigarette user.
- The evolving e-cigarette landscape continues to impede timely toxicological studies and hinder progress made toward our understanding of the long-term health consequence of e-cigarettes.

49] **Cardiovascular toxicity of nicotine: Implications for electronic cigarette use**
https://pubmed.ncbi.nlm.nih.gov/27079891/
- Nicotine exerts pharmacologic effects that could contribute to acute cardiovascular events and accelerated atherogenesis experienced by cigarette smokers.

50] **Vaping, Environmental Toxicants Exposure, and Lung Cancer Risk**
https://pubmed.ncbi.nlm.nih.gov/37760496/
- Lung cancer (LC) is the second-most prevalent tumor worldwide.
- EVPs consumption may increase the risk of LC because EVPs contain several proven carcinogenic compounds.
- E-cigarette contains nicotine derivatives (e.g., nitrosnornicotine, nitrosamine ketone), heavy metals (including organometal compounds), polycyclic aromatic hydrocarbons, and flavorings (aldehydes and complex organics).
- Proven and plausible environmental carcinogens could be physical (ionizing and non-ionizing radiation), chemicals (such as asbestos, formaldehyde, and dioxins), and heavy metals (such as cobalt, arsenic, cadmium, chromium, and nickel).
- Combined, both EVPs and toxic environmental exposures may demonstrate significant synergistic oncogenicity.

51] **An update on controversies in e-cigarettes**
https://pubmed.ncbi.nlm.nih.gov/33071065/
- These devices have been misleadingly marketed as "less harmful" alternatives to conventional smoking tobacco products.
- The e-liquid in e-cigarettes include nicotine, a humectant and other additives including flavourings, colourants, or adulterants such as bacterial and fungal products.
- We also describe what is known about the toxicity and mechanisms of EVALI (e-cigarette or vaping associated lung injury). This characterised by respiratory failure with an intense inflammatory response.
- E-cigarettes have a worse acute toxicity than tobacco and their long-term toxicity is unknown.

52] **RESPIRATORY IMPACT OF ELECTRONIC CIGARETTES AND "LOW-RISK" TOBACCO**
https://pubmed.ncbi.nlm.nih.gov/30810544/

- The aerosol's composition is determined by temperature, and by the substances contained in the heated liquid: glycerin, propylene glycol, nicotine in variable concentrations, flavoring agents, and other non-nicotine compounds.
- >80 compounds (including known toxics, e.g., formaldehyde, acetaldehyde, metallic nanoparticles, and acrolein) have been found in e-liquid and aerosols.
- Airway irritation, mucus hypersecretion, and inflammatory response, including systemic changes, have been observed after the exposure to e-cigarettes, leading to an increase in respiratory symptoms and changes in respiratory function and the host defense mechanisms.
- E-cigarette has been linked with an increase of symptoms in individuals with asthma, cystic fibrosis, and chronic obstructive pulmonary disease.

53] **Mechanisms of E-Cigarette Vape-Induced Epithelial Cell Damage**
https://pubmed.ncbi.nlm.nih.gov/37947630/
- E-cigarette use has been reported to affect cell viability, induce DNA damage, and modulate an inflammatory response resulting in negative health consequences.
- Most studies focus on oral and lung disease associated with e-cigarette use. However, tissue damage can be found in the cardio-vascular system and even the bladder.
- The toxicants generated by the heat of the vaping device may include probable human carcinogens. Furthermore, nicotine, although not a carcinogen, can be metabolized to nitrosamines. Nitrosamines are known carcinogens and have been shown to be present in the saliva of e-cig users.
- E-cig vape can induce DNA adducts, promoting oxidative stress and DNA damage and NF-kB-driven inflammation.
- This review considers different aspects of e-cigarette-induced cellular changes, including the generation of reactive oxygen species, DNA damage, DNA repair, inflammation, and the possible tumorigenic effects.

54] **Electronic cigarettes and health outcomes: umbrella and systematic review of the global evidence**
https://pubmed.ncbi.nlm.nih.gov/36939271/
- There is substantial evidence that nicotine e-cigarettes can cause dependence or addiction in non-smokers, and strong evidence that young non-smokers who use e-cigarettes are more likely than non-users to initiate smoking and to become regular smokers.
- E-cigarettes can be harmful to health, particularly for non-smokers and children, adolescents, and young adults.

55] **Cardiopulmonary Consequences of Vaping in Adolescents: A Scientific Statement From the American Heart Association**
https://pubmed.ncbi.nlm.nih.gov/35726609/
- Preclinical studies have been used to study the effects of naive e-cigarette use on various organ systems; however, almost all of these studies have used adult animals, which makes translation of health effects to adolescents problematic.

56] **The pulmonary toxicity of e-cigarette vaping exposure and the benefits of air cleaner application**
https://pubmed.ncbi.nlm.nih.gov/38186173/
- The results showed that, RNA sequencing assays suggested that the differential genes between the control and vaping exposure groups were significantly enriched in the oxidative stress (Fold Enrichment=3.18) and mitochondrial oxidative phosphorylation (OXPHOS) (Fold Enrichment=5.74) pathways.

57] **Vaping versus Smoking: A Quest for Efficacy and Safety of E-cigarette**

https://pubmed.ncbi.nlm.nih.gov/29485005/
- A total of 22 toxic substances apart from nicotine were reported in liquid of ECIG cartridges and its emissions.

58] **Vaping and Lung Inflammation and Injury**
https://pubmed.ncbi.nlm.nih.gov/34724436/
- The use of electronic (e)-cigarettes was initially considered a beneficial solution to conventional cigarette smoking cessation. However, paradoxically, e-cigarette use is rapidly growing among nonsmokers, including youth and young adults. In 2019, this rapid growth resulted in an epidemic of hospitalizations and deaths of e-cigarette users (vapers) due to acute lung injury; this novel disease was termed e-cigarette or vaping use-associated lung injury (EVALI).
- Furthermore, adverse effects of e-cigarette use have been linked to chronic lung diseases and systemic effects on multiple organs.

59] **The chemistry and toxicology of vaping**
https://pubmed.ncbi.nlm.nih.gov/33753133/
- Over the past decade, the vaping market has increased exponentially, raising health concerns over the number of people exposed and a nationwide outbreak of cases of severe, sometimes fatal, lung dysfunction that arose suddenly in otherwise healthy individuals.
- We examine the complex chemistry of vape carrier solvents, flavoring chemicals, and transformation products.

60] **Big Vape: The Incendiary Rise of JUUL, Geekbar, & Elfbar E-Cigarettes.**
https://books.google.com/books?id=P-cIEAAAQBAJ&printsec=frontcover#v=onepage&q&f=false

61] **Subculture wars: The struggle for the vape industry**
https://onlinelibrary.wiley.com/doi/full/10.1111/1468-4446.12981
- Studies with vapers have shown that they typically have strong views about the symbolic meaning of their own practice, whether this involves embracing or rejecting a vaper "identity".

62] **Up in smoke: Considerations for lithium-ion batteries in disposable e-cigarettes**
https://www.cell.com/joule/fulltext/S2542-4351(23)00482-8?uuid=uuid%3A5920cece-c780-459f-9882-51aae55eb11b
- Disposable e-cigarettes, powered by lithium-ion cells, have exploded in popularity in recent years. As the world moves toward electrification, lithium and other crucial materials used to make rechargeable batteries are in demand, yet the cells used in disposable e-cigarettes are sold as single-use.

63] **TOPIC: Vaping Amongst Young People: the Need for Repackaging of E-Cigarettes**
https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4925003
- Glaringly, these products which could be harmful to the human body are currently being targeted at young people due to their production style and forms thus, attracting teenagers and children.

64] **Marketing of "Tobacco-Free" and "Synthetic Nicotine" Products**
https://tobacco-img.stanford.edu/wp-content/uploads/2022/03/13161808/Synthetic-Nicotine-White-Paper-3-8-2022F.pdf
- Synthetic Nicotine (SYN): Nicotine produced via synthesis using chemical precursors derived from non-tobacco sources.

- Tobacco-Free Nicotine (TFN): A term loosely used by a number of emerging nicotine products, sometimes with ambiguous meaning. Technically, it should be a broad term encompassing synthetic nicotine and nicotine derived from other nightshade family plant sources such as tomato and eggplant.
- Some companies may be using this label inaccurately, describing their brands as “tobacco-free” but actually using a highly purified form of tobacco-derived nicotine or merely inaccurately labelling standard tobacco-derived nicotine. While “TFN” is the registered trademark of synthetic nicotine manufacturer Next Generation Labs, it is also used generically by many brands.

65] **Synthetic Nicotine: Science, Global Legal Landscape, and Regulatory Considerations**
https://pmc.ncbi.nlm.nih.gov/articles/PMC10516533/

- The rapid and poorly regulated introduction of synthetic nicotine products (electronic cigarettes, oral pouches, and other product categories) in the United States and other countries raises questions about product safety and potential differences in the addictive and reinforcing properties of synthetic nicotine.
- The starting material is myosmine, first converted to S-nornicotine using a recombinant enzyme.
- S-nornicotine is then converted to S-nicotine through methylation (Figure 1B). This product is currently marketed under the brand name “SyNic” (33). Hangsen International Group, a major manufacturer of vaping devices and e-liquids, applied for a Chinese and World Patent for a similar process, marketing synthetic S-nicotine under the brand name “Motivo”
- There are currently two forms of synthetic nicotine in marketed products, S-nicotine and racemic nicotine, the latter consisting of 50% S-nicotine and 50% R-nicotine.
- Nevertheless, even at this high degree of purity, trace amounts of other chemicals remaining from the chemical process might be present, deserving further attention.
- A tobacco industry-sponsored study on acetylcholinesterase, the enzyme that degrades the neurotransmitter acetylcholine in the synaptic cleft to terminate neurotransmission, revealed that R-nicotine is a more potent inhibitor of the enzyme than S-nicotine, binding to a different site on the enzyme protein.
- At higher concentrations, nicotine vapor causes nasal irritation, including stinging and burning sensations, mediated by the trigeminal nerve that transmits pain signals to the brain
- Current marketing claims for certain synthetic products may be misleading people who use those products by, for example, suggesting that they are safer than tobacco-derived nicotine products even though existing evidence does not support such a claim.
- Synthetic nicotine products—including nicotine pouches, e-liquids, disposable e-cigarettes, gums, toothpicks, and infused combustible products—are being marketed and sold throughout the world.
- Synthetic nicotine products are being sold with marketing claims (e.g., “tobacco-free”) that may suggest they are safer than products using tobacco-derived nicotine and some products are being sold with flavour concepts (e.g., “chocolate dream,” “pink lemonade”) that are likely to appeal to youth.
- Synthetic nicotine is added to marketed products in two forms—S-nicotine and R-nicotine. S-nicotine is the primary form of nicotine found in tobacco plants, but the pharmacological, metabolic, and toxicological effects of R-nicotine, and of mixtures and R- and S-nicotine, remain poorly understood.
- No standard methodologies for the chemical analysis of synthetic nicotine exist, and product adulteration with tobacco-derived nicotine is of concern.

66] **Electronic cigarette aerosol increases the risk of organ dysfunction by enhancing oxidative stress and inflammation**
https://pubmed.ncbi.nlm.nih.gov/34474637/

- The aerosol contains varying amounts of organic and inorganic toxicants as well as carcinogens, which might serve as the source of such deleterious events. In addition, the aerosol also contains nicotine, which is known to be addictive.

67] **An Approach to Flavor Chemical Thermal Degradation Analysis**
https://pubmed.ncbi.nlm.nih.gov/38250972/
- For each of 90 flavor chemicals, quantitative measurements of acetaldehyde, acrolein, and glycidol, in addition to semiquantitative non-targeted analysis tentatively identifying chemicals from thermal degradation, were obtained.

68] **E-Cigarette Chemistry and Analytical Detection**
https://pubmed.ncbi.nlm.nih.gov/30848928/
- The determination of aerosol levels of known toxins, as well as of molecules with unknown inhalation toxicity profiles, affords specific information for estimating the risks of e-cigarettes and for uncovering areas that should be prioritized for further investigation.

69] **Electronic Cigarette Toxicity**
https://pubmed.ncbi.nlm.nih.gov/27650036/
- This research letter reports the frequency of hazardous exposures to e-cigarettes and characterizes the reported adverse health effects associated with e-cigarette toxicity.

70] **E-cigarettes and their lone constituents induce cardiac arrhythmia and conduction defects in mice**
https://pubmed.ncbi.nlm.nih.gov/36284091/
- Exposure to e-cigarette aerosols from vegetable glycerin and its byproduct, acrolein, diminish heart rate and early repolarization.

71] **Formaldehyde in Electronic Cigarette Liquid (Aerosolized Liquid)**
https://pubmed.ncbi.nlm.nih.gov/34115663/
- The e-liquid products contain toxic chemicals not declared on product labels, as shown in this study with 25.0% of e-liquids containing formaldehyde. All positive e-liquids were within pods or disposable devices.

72] **Electronic Cigarettes: Their Constituents and Potential Links to Asthma**
https://pubmed.ncbi.nlm.nih.gov/28983782/
- Moreover, workplace inhalation exposures to the flavoring agent diacetyl have caused irreversible obstructive airway disease in healthy workers. Additionally, recent studies report that thermal decomposition of propylene glycol (PG) and vegetable glycerin (VG), the base constituents of e-liquids, produces reactive carbonyls, including acrolein, formaldehyde, and acetaldehyde, which have known respiratory toxicities.

73] **Toxicological and analytical assessment of e-cigarette refill components on airway epithelia**
https://pubmed.ncbi.nlm.nih.gov/28742478/
- The addition of flavours and aromas has also proven to be popular with younger generations. In this review, we survey the range of studies in the short timeframe since e-cigarettes reached the market to draw attention to the health associated risks and benefits of their introduction. We complement this review with a case study reporting on the composition of selected e-cigarette refills with particular emphasis on the toxicological activity of its components on lung cells.

74] **Rat bronchoalveolar lavage proteome changes following e-cigarette aerosol exposures**
https://pubmed.ncbi.nlm.nih.gov/36881561/
- In summary, global proteomics support e-cigarette aerosol exposures to PG/VG alone as having a significant biologic effect on the lung independent of nicotine or flavoring with increased markers of extracellular trap formation.

75] **Evaluation of e-liquid toxicity using an open-source high-throughput screening assay**
https://pubmed.ncbi.nlm.nih.gov/29584716/
- Furthermore, these data indicated that (i) the more chemicals contained in an e-liquid, the more toxic it was likely to be and (ii) the presence of vanillin was associated with higher toxicity values. Further analysis of common constituents by electron ionization revealed that the concentration of cinnamaldehyde and vanillin, but not triacetin, correlated with toxicity.

76] **Effects of electronic cigarette E-liquid and device wattage on vascular function**
https://pubmed.ncbi.nlm.nih.gov/37468077/
- These pre-clinical data provide evidence that chronic exposure to aerosol produced by either VG or PG, and regardless of the wattage used, leads to vascular dysfunction at multiple levels within the arterial system. For all exposures, we observed greater impairment of arterial reactivity in a resistance artery (i.e. MCA) compared with the aorta.

77] **E-cigarette vapor exposure in utero causes long-term pulmonary effects in offspring**
https://pubmed.ncbi.nlm.nih.gov/36218276/
- Lung histology revealed increased collagen deposition around the vessels/airways and in alveolar tissue in PV and PV + Nic groups. Furthermore, goblet hyperplasia was observed in PV male and PV/PV + Nic female mice. Our work shows that in utero exposure to e-cigarette vapor, regardless of nicotine presence, causes lung dysfunction and structural impairments that persist in the offspring to adulthood.

78] **Characteristics and toxicant emissions of JUUL electronic cigarettes**
https://pubmed.ncbi.nlm.nih.gov/30745326/
- JUUL emits a high-nicotine concentration aerosol predominantly in the protonated form. JUUL's nicotine-normalised formaldehyde and total aldehyde yields are lower than other previously studied ECIGs and combustible cigarettes.

79] **Electronic cigarette vaping with aged coils causes acute lung injury in mice**
https://pubmed.ncbi.nlm.nih.gov/36195745/
- In conclusion, we observed that the concentration of aldehydes (formaldehyde and acetaldehyde) increased with repeated and prolonged usage of e-cigarette coils. Exposure to high levels of aldehyde in vaping aerosol was associated with acute lung injury in mice. These findings show significant risk of lung injury associated with prolonged use of e-cigarette devices.

80] **Inhalation toxicity of thermal transformation products formed from e-cigarette vehicle liquid using an in vitro lung model exposed at the Air-Liquid Interface**
https://pubmed.ncbi.nlm.nih.gov/39377481/
- Thermochemical transformation of the solvent leads to the formation of both cytotoxic and genotoxic substances that may disrupt lung homeostasis. Toxicity is therefore not limited to the presence of additives, as most harmful volatiles originate from the solvent itself, ultimately related to the device power output.

81] **Nicotine, Humectants, and Tobacco-Specific Nitrosamines (TSNAs) in IQOS Heated Tobacco Products (HTPs): A Cross-Country Study**
https://pubmed.ncbi.nlm.nih.gov/38535913/
- As NNN and NNK are known human carcinogens, and as humectants like PG and VG can degrade into toxic carbonyl compounds upon heating, monitoring the concentration of these chemicals in HTPs is important for protecting users' health and ensuring compliance with regulations.

82] **A Public Health Crisis: Electronic Cigarettes, Vape, and JUUL**
https://pubmed.ncbi.nlm.nih.gov/31122947/
- We describe the vast array of e-cigarette devices and solutions, concern for nicotine addiction, and the scientific background on the known health harms. There are accompanying visual depictions to assist in identifying these products, including newer e-cigarette products and JUUL.

83] **Health effects and known pathology associated with the use of E-cigarettes**
https://pubmed.ncbi.nlm.nih.gov/36561957/
- In addition, e-cigarettes contain alarmingly high levels of carcinogens and toxicants that may have long-lasting effects on other organ systems, including the development of neurological manifestations, lung cancer, cardiovascular disorders, and tooth decay.

84] **Electronic cigarettes and cardiovascular disease: epidemiological and biological links**
https://pubmed.ncbi.nlm.nih.gov/38376568/
- The incidence and mortality of various types of cardiovascular disease, such as cardiac arrhythmia, hypertension, acute coronary syndromes, and heart failure, have a modest growth in vapers (users of e-cigarettes).

85] **Chemical and physiological interactions between e-liquid constituents: cause for concern?**
https://pubmed.ncbi.nlm.nih.gov/38658055/
- There is a significant current knowledge gap concerning how specific combinations of ENDS chemical ingredients result in synergistic or antagonistic interactions.

86] **Biological Toxicity of the Compositions in Electronic-Cigarette on Cardiovascular System**
https://pubmed.ncbi.nlm.nih.gov/32748205/
- The recent outbreak of e-cig vaping-related tragic deaths in youth and multiple hospitalized patients raised a question on the safety of e-cig use and led to an urgent need for the knowledge of the health risk of the e-cig compositions. Therefore, in the review, we summarized the latest findings from both human and animal studies on the potential cardiovascular toxicological effects of e-cig on the cardiovascular system in terms of the systemic physiological implications and the cellular and molecular mechanisms involved.

87] **Main and side stream effects of electronic cigarettes**
https://pubmed.ncbi.nlm.nih.gov/30836280/
- The levels of potentially toxic compounds (e.g. volatile organic compounds (VOCs), particulate matter (PM), metals, radicals, nitrosamines, etc.) emitted from vaping appear to be lower compared to that of tobacco smoking (from combustible cigarettes). Nevertheless, measurable toxic elements and VOCs are still released (e.g. acetaldehyde, formaldehyde, acrolein, benzene, etc.) along with other volatiles associated with e-liquid flavoring and device variability with PG and VG. The wide range of available flavors at various purities along with the heating temperature are important parameters affecting the evolution of VOCs and aerosols.

88] **Benzene formation in electronic cigarettes**
https://pubmed.ncbi.nlm.nih.gov/28273096/
- In the two tank systems benzene was found to form from propylene glycol (PG) and glycerol (GL), and from the additives benzoic acid and benzaldehyde, especially at high power settings. With 50:50 PG+GL, for tank device 1 at 6W and 13W, the formed benzene concentrations were 1.9 and 750 µg/m3. For tank device 2, at 6W and 25W, the formed concentrations were ND and 1.8 µg/m3. With benzoic acid and benzaldehyde at ~10 mg/mL, for tank device 1, values at 13W were as high as 5000 µg/m3. For tank device 2 at 25W, all values were ≤~100 µg/m3. These values may be compared with what can be expected in a conventional (tobacco) cigarette, namely 200,000 µg/m3.

89] **Recent updates on biomarkers of exposure and systemic toxicity in e-cigarette users and EVALI**
https://pubmed.ncbi.nlm.nih.gov/33501893/
- Due to the novelty of ENDS as well as their rapidly increasing use, research into biomarkers of e-cig exposure and toxicity have lagged behind their popularity, leaving important questions about their potential toxicity unanswered.

90] **E-Cigarette Flavoring Chemicals Induce Cytotoxicity in HepG2 Cells**
https://pubmed.ncbi.nlm.nih.gov/33748584/
- HepG2 cells were exposed to flavoring chemicals (isoamyl acetate, vanillin, ethyl vanillin, ethyl maltol, l-menthol, and trans-cinnamaldehyde), propylene glycol, and vegetable glycerin mixtures, and cell viability was measured. Data revealed that vanillin, ethyl vanillin, and ethyl maltol decreased HepG2 cell viability; repeated exposure caused increased cytotoxicity relative to single exposure, consistent with the hypothesis that frequent vaping can cause hepatotoxicity.

91] **Tobacco and menthol flavored nicotine-free electronic cigarettes induced inflammation and dysregulated repair in lung fibroblast and epithelium**
https://pubmed.ncbi.nlm.nih.gov/38200492/
- After exposure, HFL-1 showed decreased cell number with increased IL-8 levels in the tobacco flavor group compared to air. BEAS-2B also showed increased IL-8 secretion after PG/VG and tobacco flavor exposure, while menthol flavor exposure showed no change. Both menthol and tobacco-flavored e-cig exposure showed decreased protein abundance of type 1 collagen α 1 (COL1A1), α-smooth-muscle actin (αSMA), and fibronectin as well as decreased gene expression level of αSMA (Acta2) in HFL-1. After tobacco flavor e-cig exposure, HFL-1 mediated wound healing and tissue contractility were inhibited. Furthermore, BEAS-2B exposed to menthol flavor showed significantly decreased tight junction gene expressions, such as CDH1, OCLN, and TJP1.
- Overall, tobacco-flavored e-cig exposure induces inflammation in both epithelium and fibroblasts, and tobacco-flavored e-cig inhibits wound healing ability in fibroblasts.

92] **Vaping: Anesthesia Considerations for Patients Using Electronic Cigarettes**
https://pubmed.ncbi.nlm.nih.gov/32008615/
- The current literature suggests that components of these devices (the liquid and heating element) produce chemicals that can cause acute and chronic multiorgan toxicities. On a cellular level, the pulmonary, cardiovascular, immunologic, and pharmacologic effects of electronic cigarettes are most noteworthy.

93] **Chemical analysis of fresh and aged Australian e-cigarette liquids**
https://pubmed.ncbi.nlm.nih.gov/34528266/

- The measured levels of propylene glycol and glycerol often diverged from those recorded on the e-liquid label. All e-liquids contained one or more potentially harmful chemicals, including benzaldehyde, menthol, trans-cinnamaldehyde, and polycyclic aromatic hydrocarbons. Nicotine or nicotyrine were detected in a small proportion of e-liquids at extremely low concentrations.

94] **Vaped Humectants in E-Cigarettes Are a Source of Phenols**
https://pubmed.ncbi.nlm.nih.gov/32786548/
- Phenol emissions from ECIGs were tested at different powers, puff durations, PG/VG ratios, nicotine benzoate concentrations, and flow rates to assess the influence of these operating parameters on phenol formation.
- The phenol profile in the ECIG aerosol was dominated by the unsubstituted phenol that reached comparable levels to those of IQOS, combustible cigarettes, and waterpipe. In contrast, low levels of the more toxic phenolic compounds, like catechol and hydroxyquinone, were quantified in ECIG aerosols.
- Using this method, the study shows that phenols, which are not present in the simple solution of nicotine benzoate dissolved in mixtures of PG/VG, are formed upon vaping.

95] **Carbonyl Composition and Electrophilicity in Vaping Emissions of Flavored and Unflavored E-Liquids**
https://pubmed.ncbi.nlm.nih.gov/34941780/
- PG-VG emitted highest levels of formaldehyde, acetaldehyde, and acrolein. However, flavored e-liquids contributed to the production of a wider variety of carbonyls, with some carbonyls directly corresponding to the oxidation of alcohol moieties in flavoring compounds (e.g., trans-2-hexenol and benzyl alcohol transformed into trans-2-hexenal and benzaldehyde, respectively). Detections of formaldehyde-GSH and trans-2-hexenal-GSH adducts signify interactions of carbonyls with biological nucleophiles.

96] **Low-temperature (< 200 °C) degradation of electronic nicotine delivery system liquids generates toxic aldehydes**
https://pubmed.ncbi.nlm.nih.gov/33833273/
- The results demonstrate that the degradation of electronic nicotine delivery system (ENDS) liquids is strongly reliant upon the oxygen availability, both in the presence and absence of a material surface. When oxygen is available, propylene glycol and glycerol readily decompose at temperatures between 133 and 175 °C over an extended time period. Among the generated chemical species, formic and acrylic acids are observed which can negatively affect the kidneys and lungs of those who inhale the toxin during ENDS vapor inhalation. Further, the formation of hemi- and formal acetals is noted from both glycerol and propylene glycol, signifying the generation of both formaldehyde and acetaldehyde, highly toxic compounds, which, as a biocide, can lead to numerous health ailments.

97] **Flavored e-liquids increase cytoplasmic Ca2+ levels in airway epithelia**
https://pubmed.ncbi.nlm.nih.gov/31693394/
- However, longer exposures to BP e-liquid depleted ER Ca2+ stores and inhibited SOCE, suggesting that this e-liquid may alter Ca2+ homeostasis by short- and long-term mechanisms. Since dysregulation of Ca2+ signaling can cause chronic inflammation, ER stress, and abnormal cell growth, flavored e-cigarette products that can elicit cell Ca2+ responses should be further screened for potential toxicity.

98] **Formaldehyde and the transient receptor potential ankyrin-1 contribute to electronic cigarette aerosol-induced endothelial dysfunction in mice**
https://pubmed.ncbi.nlm.nih.gov/39067042/

- Collectively, these data suggest that ENDS use may increase CVD risk dependent on FA, TRPA1, and catecholamines, yet independently of either nicotine or flavorants. This study supports that levels of FA in ENDS-derived aerosols should be lowered to mitigate CVD risk in people who use ENDS.

99] **Utilizing primary human airway mucociliary tissue cultures to model ramifications of chronic E-cigarette usage**
https://pubmed.ncbi.nlm.nih.gov/37884163/
- We note several differences between how PG:VG and VEA vapors interact with and alter airway tissue cultures and suggest potential mechanisms for how VEA-vapors can exacerbate EVALI symptoms.

100] **Organizing pneumonia related to electronic cigarette use: A case report and review of literature**
https://pubmed.ncbi.nlm.nih.gov/29392888/
- Patient developed acute hypoxemic respiratory failure requiring intubation and mechanical ventilation. She was diagnosed with organizing pneumonia on open lung biopsy and was successfully treated with steroids along with abstinence from e cigarette use.

101] **Effects of Aftermarket Electronic Cigarette Pods on Device Power Output and Nicotine, Carbonyl, and ROS Emissions**
https://pubmed.ncbi.nlm.nih.gov/38032319/
- The greater power output with the aftermarket pods resulted in up to three times greater aerosol and nicotine output than the original product. ROS and CC emissions varied widely across brands. These results highlight that the use of aftermarket pods can greatly modify the performance and emissions of ENDS.

102] **Exposure to Aldehyde Cherry e-Liquid Flavoring and Its Vaping Byproduct Disrupt Pulmonary Surfactant Biophysical Function**
https://pubmed.ncbi.nlm.nih.gov/38186267/
- The study reveals that exposure to these vaping chemicals significantly interferes with the synthetic and clinical surfactant biophysical function. Further atomistic simulations reveal preferential interactions with SP-B and SP-C surfactant proteins. Additionally, data show surfactant lipid-vaping chemical interactions and suggest significant transfer of vaping chemicals to the experimental subphase, indicating a toxicological mechanism for the alveolar epithelium.

103] **Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping**
https://pubmed.ncbi.nlm.nih.gov/27934275/
- We show that, within the tested e-cigarette brands, thermal decomposition of flavoring compounds dominates formation of aldehydes during vaping, producing levels that exceed occupational safety standards.

104] **E-Cigarette Exposure Alters Neuroinflammation Gene and Protein Expression in a Murine Model: Insights from Perinatally Exposed Offspring and Post-Birth Mothers**
https://pubmed.ncbi.nlm.nih.gov/38540381/
- Gene expression analysis in the hypothalamus of 1 mo. old offspring exposed perinatally to E-cig aerosols, with and without nicotine, revealed significantly increased gene expression changes in multiple genes associated with neuroinflammation.

105] **Identification of newly formed toxic chemicals in E-cigarette aerosols with Orbitrap mass spectrometry and implications on E-cigarette control**
https://pubmed.ncbi.nlm.nih.gov/34448631/
- ENDS produce not only small toxic compounds such as aldehydes, but also large complex toxic compounds such as NIC-PG. Predicted development toxicity for NIC-PG is concerning for fetal development in pregnant women who use ENDS, children exposed to secondhand or thirdhand ENDS aerosols, and teenage ENDS users whose brains are still developing.

106] **Effects of Common e-Liquid Flavorants and Added Nicotine on Toxicant Formation during Vaping Analyzed by 1H NMR Spectroscopy**
https://pubmed.ncbi.nlm.nih.gov/35735356/
- We used 1H NMR spectroscopy to evaluate HPHCs and herein report that benzaldehyde, vanillin, benzyl alcohol, trans-cinnamaldehyde, and mixtures of these flavorants significantly increased toxicant formation produced during e-liquid aerosolization compared to unflavored e-liquids.
- Benzaldehyde, vanillin, benzyl alcohol, and a "flavorant mixture" with nicotine showed lower HPHC levels, having nicotine degradation factors <1 for acetaldehyde, acrolein, and total formaldehyde. HPHC formation was most inhibited in e-liquids containing vanillin + nicotine, with a degradation factor of ~0.5, while trans-cinnamaldehyde gave more HPHC formation when nicotine was present, with a degradation factor of ~2.5 under the conditions studied.

107] **Carbon Monoxide and Small Hydrocarbon Emissions from Sub-ohm Electronic Cigarettes**
https://pubmed.ncbi.nlm.nih.gov/30656934/
The effects of power, ECIG heating coil material, and coil geometry on the generation of small gases were assessed. Results showed that small gases, including CO, carbon dioxide, methane, ethylene, and acetylene, were detected in SOD-emitted gases. Electrical power and material of construction significantly affected the concentrations of the emitted gases. Nickel metal wire was more reactive than kanthal, nichrome, and stainless steel. Depending on use patterns and device operation, users of SOD devices may be exposed daily to similar levels of CO as are cigarette smokers.

108] **Assessment of the potential vaping-related exposure to carbonyls and epoxides using stable isotope-labeled precursors in the e-liquid**
https://pubmed.ncbi.nlm.nih.gov/34159432/
- Corresponding biomarkers of exposure were determined in the user's urine samples. 13C-labeled formaldehyde, acetaldehyde and acrolein were found in EC aerosol, while all seven labeled carbonyls were detected in smoke. The labeled biomarkers of exposure to formaldehyde (13C-thiazolidine carboxylic acid and 13C-N-(1,3-thiazolidine-4-carbonyl)glycine), acrolein (13C3-3-hydroxypropylmercapturic acid) and glycidol (13C3-dihydroxypropylmercapturic acid) were present in the urine of vapers indicating an EC use-specific exposure to these toxicants.

109] **In vitro toxicity and chemical analysis of e-cigarette aerosol produced amid dry hitting**
https://pubmed.ncbi.nlm.nih.gov/38876198/
- The results revealed a highly significant increase in cytotoxicity from dry hit treatments. Imaging showed thermal decomposition of the cotton wick after dry hitting, which was confirmed by energy dispersive x-ray spectroscopy with less oxygen in the dry hit cotton. Chemical byproducts were found via unique peaks in the dry hit condensate in the aromatic and alkene regions. Saturated condensate showed higher concentrations of detected metal species than dry-hit condensate.

110] **In vitro toxicological evaluation of aerosols generated by a 4th generation vaping device using nicotine salts in an air-liquid interface system**
https://pubmed.ncbi.nlm.nih.gov/38317149/

- PG/VG aerosols elicited a strong cytotoxic response characterised by a 50% decrease in cell viability and a 200% increase in lactate dehydrogenase (LDH) production, but had no effects on inflammation and oxidative stress. These effects occurred only at a ratio of 70/30 PG/VG, suggesting that PG is the major contributor to aerosol cytotoxicity. Both freebase nicotine and organic acids had no greater effect on cell viability and LDH release than at a 70/30 PG/VG ratio, but significantly increased inflammation and oxidative stress. Interestingly, the protonated form of nicotine in salt showed a stronger proinflammatory effect than the freebase nicotine form, while benzoic acid-based nicotine salts also induced significant oxidative stress. Flavoured commercial e-liquids was found to be cytotoxic at a threshold dose of ≈ 330 μg/cm².
- Our results showed that aerosols of e-liquids consisting only of PG/VG solvents can cause severe cytotoxicity depending on the concentration of PG, while nicotine salts elicit a stronger pro-inflammatory response than freebase nicotine. Overall, aerosols from fourth-generation devices can cause different toxicological effects, the nature of which depends on the chemical composition of the e-liquid.

111] **New Analytical Method for Quantifying Flavoring Chemicals of Potential Respiratory Health Risk Concerns in e-Cigarette Liquids**
https://pubmed.ncbi.nlm.nih.gov/34778213/

- We have developed an analytical method that accurately and precisely measures the concentrations of 20 flavoring chemicals of potential inhalation risk concerns: 2,3,5-trimethylpyrazine, acetoin, benzaldehyde, benzyl alcohol, butanoic acid, dl-limonene, ethyl maltol, ethyl salicylate, ethyl vanillin, eucalyptol, eugenol, furaneol, isovanillin, l-menthol, maltol, methyl salicylate, pulegone, trans-cinnamaldehyde, triacetin, and vanillin.
- Concentrations of pulegone, a suspected carcinogen, varied from below limit of quantitation (BLOQ) to 0.32 mg/ml, while acetoin and vanillin, known precursors to more cytotoxic byproducts, ranged from BLOQ to 1.52 mg/ml and from BLOQ to 16.22 mg/ml, respectively.

112] **A comparison of the electrical characteristics, liquid composition, and toxicant emissions of JUUL USA and JUUL UK e-cigarettes**
https://pubmed.ncbi.nlm.nih.gov/32355323/

- Compared to the US version, JUUL UK had approximately one-third the liquid nicotine concentration in the liquid (5.4 vs. 1.6 wt.%) and aerosol (4.7 and 1.3 wt.%). Other than nicotine concentration and yield, we found no differences in any other study outcome, including electrical power.

113] **Electronic-Cigarette Vehicles and Flavoring Affect Lung Function and Immune Responses in a Murine Model**
https://pubmed.ncbi.nlm.nih.gov/32825651/

- This suggests that e-cig aerosol vehicles may affect immunoregulatory molecules. We also found that the two e-cig aerosols dysregulated the expression of lung genes. Ingenuity Pathway Analysis revealed that the gene networks that are dysregulated by the VG/PG e-cig aerosol are associated with metabolism of cellular proteins and lipids.

114] **Electronic cigarette menthol flavoring is associated with increased inhaled micro and sub-micron particles and worse lung function in combustion cigarette smokers**
https://pubmed.ncbi.nlm.nih.gov/37038183/

- We discovered that addition of menthol flavoring to freshly prepared e-liquid base propylene glycol-vegetable glycerin leads to enhanced particle counts in all tested size fractions, similar to the effect of adding vitamin E acetate to e-liquid we previously reported. Similarly,

we found that menthol vs. non-menthol (tobacco) flavored pods from commercially available ECs leads to generation of significantly higher quantities of 1-10 μm particles upon inhalation.

115] **Enhancement of Benzene Emissions in Special Combinations of Electronic Nicotine Delivery System Liquid Mixtures**
https://pubmed.ncbi.nlm.nih.gov/38241642/
- The tested mixtures included PG, PG + nic + BA, VG, VG + nic + BA, 30/70 PG/VG, and 30/70 PG/VG + nic + BA. A carboxen polydimethylsiloxane fiber for a solid-phase microextraction was placed in a gas cell to trap benzene emitted from a Sub-Ohm Minibox C device. Benzene was adsorbed on the fiber during the puffing process and for an extra 15 min until it reached equilibrium, and then it was determined using gas chromatography-mass spectrometry. Benzene was quantified in VG but not in PG or the 30/70 PG/VG mixtures. However, benzene concentration increased in all tested mixtures upon the addition of nicotine benzoate salt. Interestingly, benzene was emitted at the highest concentration when BA was added to PG.

116] **Reducing toxic reactive carbonyl species in e-cigarette emissions: testing a harm-reduction strategy based on dicarbonyl trapping**
https://pubmed.ncbi.nlm.nih.gov/35518766/
- Liquid chromatography mass spectrometry analysis highlighted the formation of covalent adducts between aromatic rings and dicarbonyls in both e-liquids and vaped samples, suggesting that dicarbonyls were formed in the e-liquids as degradation products of propylene glycol and glycerol before vaping.

117] **PBPK modeling characterization of potential acute impairment effects from inhalation of ethanol during e-cigarette use**
https://pubmed.ncbi.nlm.nih.gov/32013640/

118] **In Vitro Toxicity and Chemical Characterization of Aerosol Derived from Electronic Cigarette Humectants Using a Newly Developed Exposure System**
https://pubmed.ncbi.nlm.nih.gov/32223225/
- Additionally, we find that the exposure of vaped PG causes elevated IL-6 expression, while the exposure of vaped GLY increases HMOX1 expression in human bronchial epithelial cells when the device is operated at high wattages. These findings suggest that vaporizing PG and GLY results in the formation of novel compounds and the exposure of vaped PG and GLY are detrimental to airway cells.

119] **E-cigarette vaping liquids and the flavoring chemical cinnamaldehyde perturb bone, cartilage and vascular development in zebrafish embryos**
https://pubmed.ncbi.nlm.nih.gov/34673467/
- Exposure to the liquids further caused non-overlapping and partially or completely missing intersegmental vessels. Hatching success was also reduced. Exposure to pure cinnamaldehyde replicated the effects of the vaping liquids with a 50% effect concentration (EC50) of 34-41 μM.
- Quantification of the amount of cinnamaldehyde in the vaping liquids by mass spectrometry revealed EC50s around 10-40 times lower than for pure cinnamaldehyde, suggesting that additional compounds or metabolites present in the vaping liquids mediate toxicity.

120] **Real-Time Assessment of E-Cigarettes and Conventional Cigarettes Emissions: Aerosol Size Distributions, Mass and Number Concentrations**
https://pubmed.ncbi.nlm.nih.gov/31480224/

- Our results showed that aerosols emitted from e-cig liquids had a different profile compared to those from conventional cigarettes. Although e-cigs initially produced higher particle mass and number concentrations, their emissions had much shorter lifetime of approximately 10-20 s, in comparison with the conventional and hand-rolling cigarette particulate emissions which had a dissipation time of approximately 1.4 h in a 35 m3 room.

121] **Chemical Evaluation of Electronic Cigarettes: Multicomponent Analysis of Liquid Refills and their Corresponding Aerosols**
https://pubmed.ncbi.nlm.nih.gov/28985322/
- We combined several techniques including gas-chromatography, high and ultra-performance liquid chromatography and inductively coupled plasma with mass spectrometry or ultraviolet and flame ionization detection in order to identify the main e-liquid constituents (propylene glycol, glycerol and nicotine), as well as multiple potentially harmful components (trace elements, polycyclic aromatic hydrocarbons (PAHs), pesticides and carbonyl compounds). Regarding propylene glycol, glycerol and nicotine concentrations, the six tested e-liquids comply with the advertised composition and contain only traces of pollutants.

122] **Nicotine and Carbonyl Emissions From Popular Electronic Cigarette Products: Correlation to Liquid Composition and Design Characteristics**
https://pubmed.ncbi.nlm.nih.gov/27798087/
- Nicotine yields varied from 0.27 to 2.91 mg/15 puffs, a range corresponding to the nicotine yield of less than 1 to more than 3 combustible cigarettes. Nicotine yield was highly correlated with ECIG type and brand, liquid nicotine concentration, and PG/VG ratio, and to a lower significance with electrical power, but not with pH and water content. Carbonyls, including the carcinogen formaldehyde, were detected in all ECIG aerosols, with total carbonyl concentrations ranging from 3.72 to 48.85 µg/15 puffs. Unlike nicotine, carbonyl concentrations were mainly correlated with power.
- In 15 puffs, some ECIG devices emit nicotine quantities that exceed those of tobacco cigarettes. Nicotine emissions vary widely across products but carbonyl emissions showed little variations. In spite of that ECIG users are exposed to toxicologically significant levels of carbonyl compounds, especially formaldehyde.

123] **E-cigarette-Induced Pulmonary Inflammation and Dysregulated Repair are Mediated by nAChR α7 Receptor: Role of nAChR α7 in ACE2 Covid-19 receptor regulation**
https://pubmed.ncbi.nlm.nih.gov/32702718/
- Sub-chronic e-cig exposure with nicotine increased the inflammatory cellular influx of macrophages and T-lymphocytes including increased pro-inflammatory cytokines in BALF and increased ACE2 Covid-19 receptor, whereas nAChR α7 KO mice show reduced inflammatory responses associated with decreased ACE2 receptor. Interestingly, matrix metalloproteinases (MMPs), such as MMP2, MMP8, and MMP9 were altered both at the protein and mRNA transcript levels in female and male, but WT mice exposed to PG alone showed a sex-dependent phenotype. Moreover, MMP12 was increased significantly in male mice exposed to PG with or without nicotine in a nAChR α7-dependent manner. Additionally, sub-chronic e-cig exposure with or without nicotine altered the abundance of ECM proteins, such as collagen and fibronectin significantly in a sex-dependent manner, but without the direct role of nAChR α7 gene. Overall, sub-chronic e-cig exposure with or without nicotine affected lung inflammation and repair responses/ECM remodeling, which were mediated by nAChR α7 in a sex-dependent manner.

124] **When Vaping Isn't Actually Safer: A Death From Toxic Alcohol Contaminated Vape Juice**

https://pubmed.ncbi.nlm.nih.gov/38833354/

- Clinical serum toxicology results returned after death revealed 235 mg/dL of methanol, and no ethylene glycol. Autopsy findings included ischemic changes of the gastrointestinal tract and cerebral edema with herniation. Postmortem toxicology performed on hospital admission blood revealed methanol (220 mg/dL), propylene glycol (59 mg/dL), Δ-9 THC and metabolites, and medications administered during hospitalization. The medical examiner determined the cause of death to be methanol and propylene glycol toxicity.

125] **E-cigarette aerosol exposure can cause craniofacial defects in Xenopus laevis embryos and mammalian neural crest cells**
https://pubmed.ncbi.nlm.nih.gov/28957438/

- Further assessment of embryos exposed to these particular e-cigAMs revealed cranial cartilage and muscle defects and a reduction in the blood supply to the face. Finally, the expression of markers for vascular and cartilage differentiation was reduced in a mammalian neural crest cell line corroborating the in vivo effects.

126] **The Impact of Device Settings, Use Patterns, and Flavorings on Carbonyl Emissions from Electronic Cigarettes**
https://pubmed.ncbi.nlm.nih.gov/32764435/

- The propylene glycol (PG)-based e-liquids generated higher formaldehyde and acetaldehyde than vegetable glycerin (VG)-based e-liquids. In addition, fruit flavored e-liquids (i.e., strawberry and dragon fruit) generated higher formaldehyde emissions than mint/menthol and creamy/sweet flavored e-liquids. While single-top coils formed 3.5-fold more formaldehyde per puff than conventional cigarette smoking, bottom coils generated 10-10,000 times less formaldehyde per puff.

127] **WHO Tobacco Control Papers**
https://escholarship.org/content/qt9s53b10n/qt9s53b10n.pdf

128] **The Culture of Vaping and Meaning of E-cigarettes**
https://www.duo.uio.no/bitstream/handle/10852/86438/1/PhD-Tokle-DUO.pdf

129] **The Vape Debate - A Case Study of Vaping Advocacy Group Counter-Marketing Strategies in the Media**
https://www.proquest.com/openview/ec3325a7db2b21c2a7d2d98903ea9ec3/1?pq-origsite=gscholar&cbl=18750&diss=y

130] **Hexavalent Chromium: Byproduct of 'dry-burning' E-Cig Coils (Vaping until it runs dry)**
https://www.osha.gov/hexavalent-chromium