

VAPING CHEMISTRY AND CANNABIS PRODUCT ADDITIVES

Professor Robert M. Strongin

Department of Chemistry, Portland State University, Portland, OR 97201

email: strongin@pdx.edu

Homepage: <https://www.pdx.edu/chemistry/profile/dr-robert-strongin>
<http://web.pdx.edu/%7Ejescobed/>

Published work:

Publons: <https://publons.com/researcher/1319679/robert-m-strongin/publications/>

Google Scholar: https://scholar.google.com/scholar?hl=en&as_sdt=0%2C38&q=robert+strongin&btnG=

Orcid ID: <https://orcid.org/0000-0003-3777-849>

National Library of Medicine:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/robert.strongin.1/bibliography/41163194/public/?sort=date&direction=ascending>

OUR LAB HAS STUDIED VAPING CHEMISTRY SINCE 2013

Selected recent cannabis-related manuscripts:

- Strongin, R. M. **Toxic ketene gas forms on vaping vitamin E acetate prompting interest in its possible role in the EVALI outbreak** *Proc. Nat. Acad. Sci. USA* **2020**, *117*, 7553-7554. (invited commentary).
- Meehan-Atrash, J.; Strongin, R.M. **Pine rosin identified as a toxic cannabis extract adulterant.** *Forensic Science International* **2020**, 110301.
- Meehan-Atrash, J.; Luo, W.; McWhirter, K. J.; Strongin, R. M. **Aerosol Gas-Phase Components from Cannabis E-Cigarettes and Dabbing: Mechanistic Insight and Quantitative Risk Analysis.** *ACS Omega* **2019**, *4*, 16111-16120.
- Meehan-Atrash, J.; Luo, W.; Strongin, R.M. **Toxicant formation in dabbing: the terpene story.** *ACS Omega* **2017**, *2*, 6112-6117.

OUR GOALS



Understand emerging products (concentrates) and ROAs (vaping, dabbing)



Elucidate vaping chemistry and aerosol product profiles



Help promote evidence-based harm reduction strategies

WHY CARE ABOUT CANNABIS PRODUCT ADDITIVES?

- **Can't GRAS (generally regarded as safe) food products be inhaled safely?**

The digestive tract is equipped to process and break down food and medicines, the lungs are not

- **The inhalation toxicity of many flavorings etc. additives is not currently known**

Why not? Largely because until now no one thought these products would be inhaled

Wasn't the EVALI outbreak last year just an outlier? An exceptional case?

(EVALI = e-cigarette or vaping product use-associated lung injury)

- Possibly, however, a significant lesson learned from tobacco control is that it typically takes decades for the adverse health effects of smoking to manifest

The rapidity of EVALI onset is one of its most unusual and concerning aspects

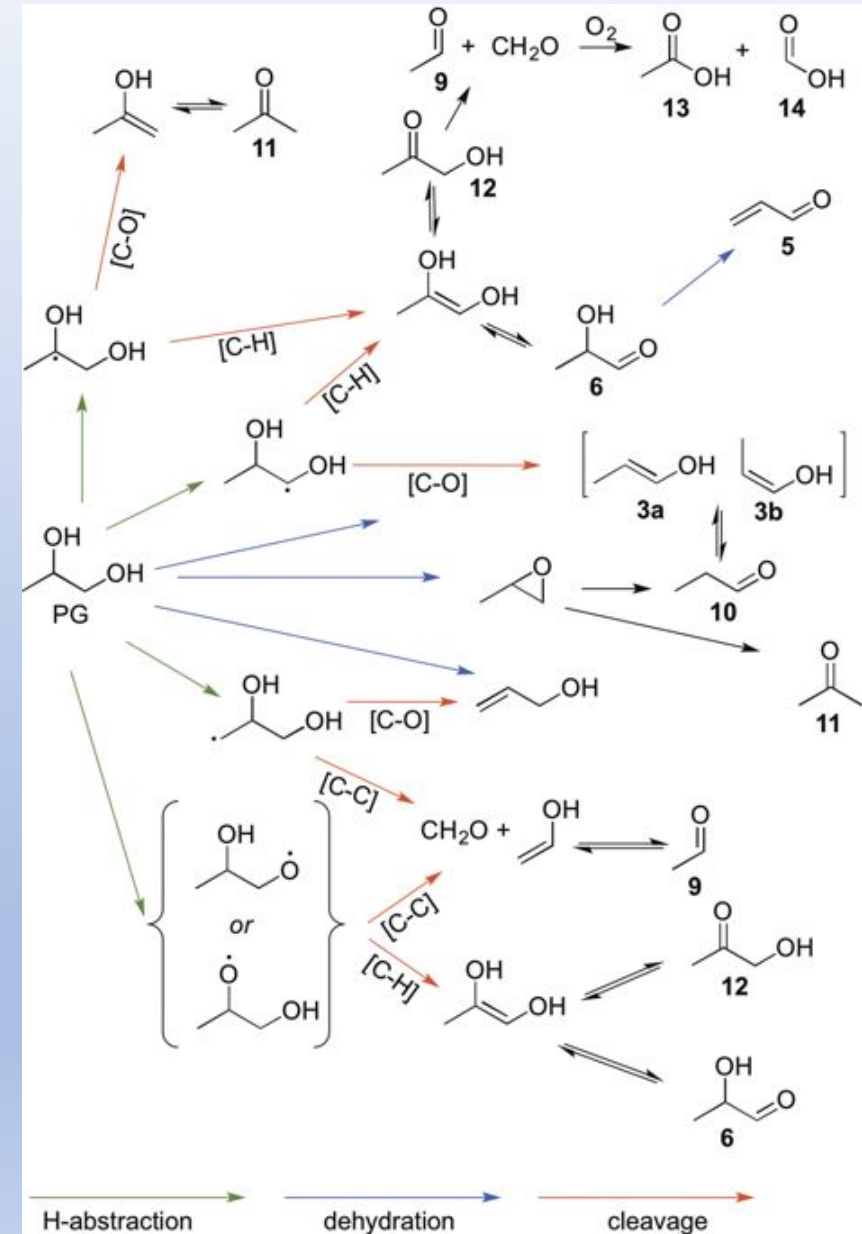
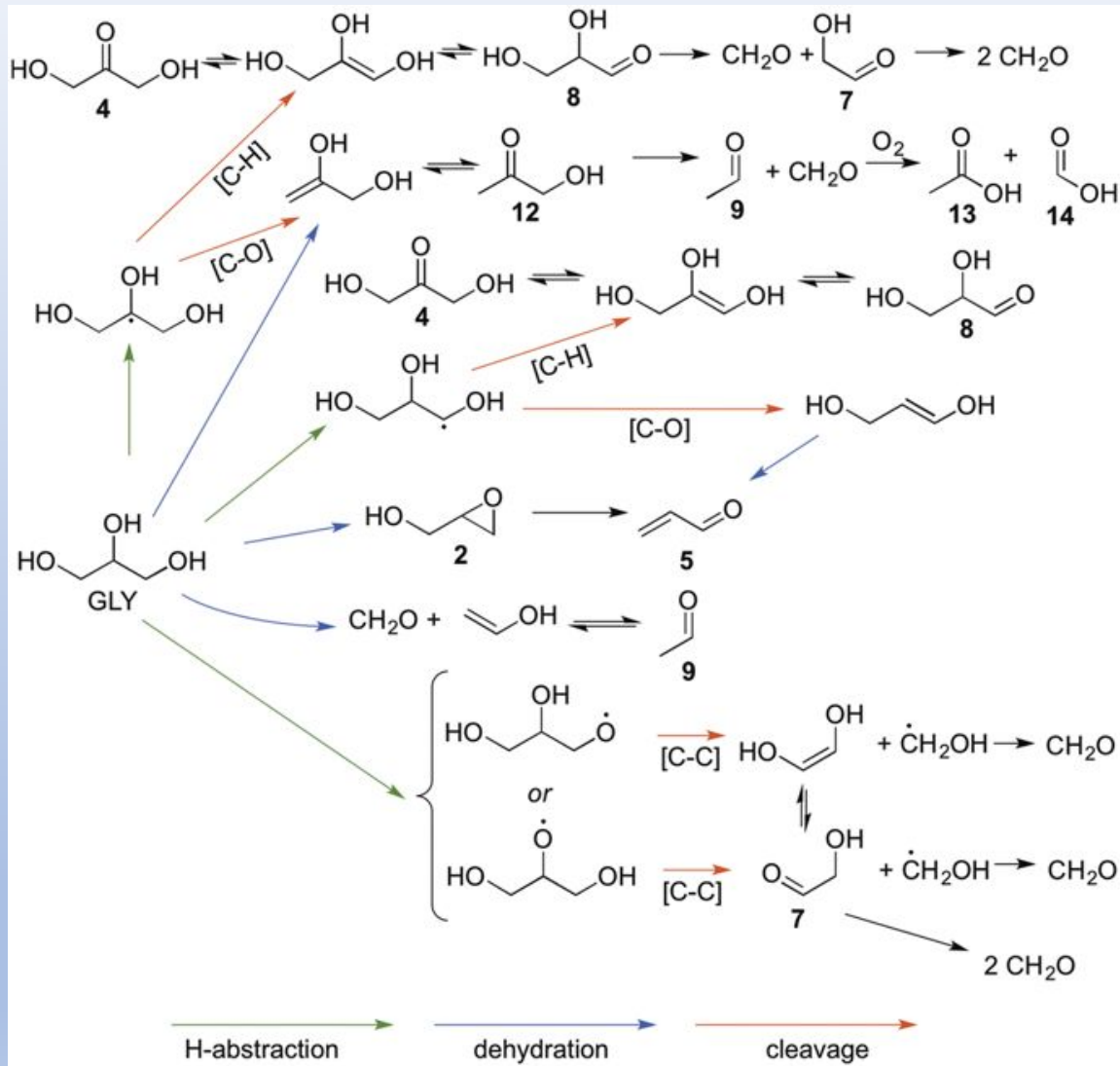
- Bottom line: not showing acute symptoms is not necessarily an indicator of safety

Aren't additives such as medium chain triglycerides, triethyl citrate and propylene glycol safe to inhale?

- There is no conclusive data
- Current users are thus unwittingly part of an ongoing human subjects study
- Toxicity depends on exposure; however, Bhatnager has shown that, unlike cancer, exposure to relatively lower levels of toxicants over time does not necessarily translate to a lower cardiovascular health risk

Bhatnagar, A., E-Cigarettes and Cardiovascular Disease Risk: Evaluation of Evidence, Policy Implications, and Recommendations. *Curr Cardiovasc Risk* 2016, 10, 24.

PROPYLENE GLYCOL AND GLYCEROL VAPING CHEMISTRY

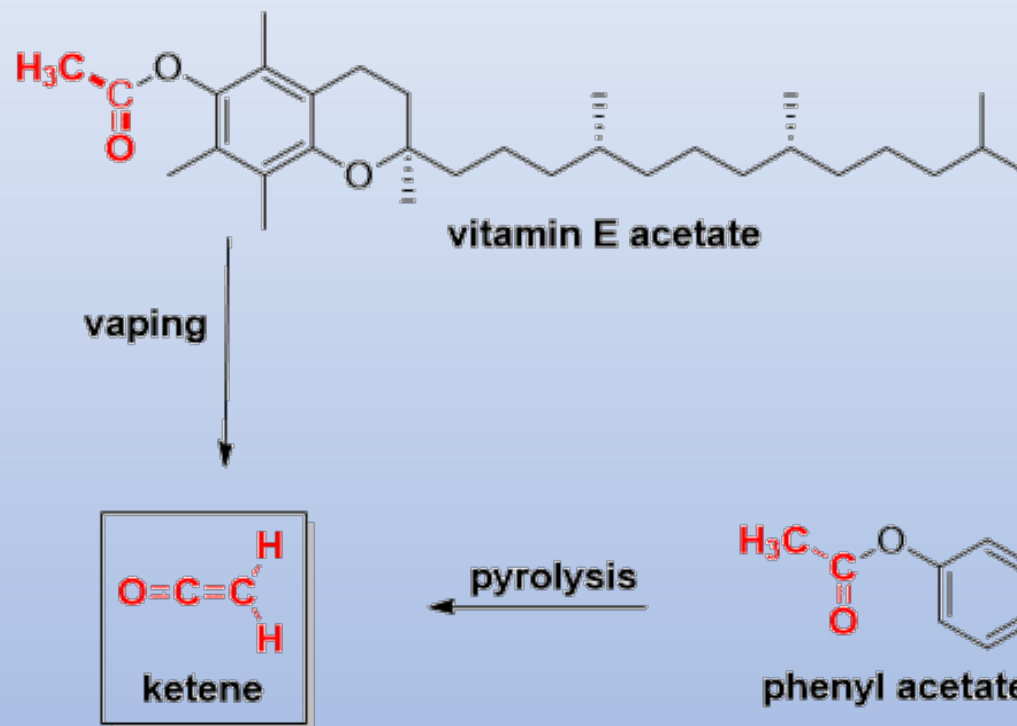


Strongin, R. M. E-Cigarette Chemistry and Analytical Detection Ann Rev Anal Chem 2019, 12, 23-39.

Aren't additives such as medium chain triglycerides, triethyl citrate and propylene glycol safe to inhale?

- **Possibly, but the GRAS designation (safe for ingestion) was apparently used for justifying vitamin E acetate as a cannabis product additive**
 - 2,3,5-trimethylhydroquinone is a starting material for synthetic vitamin E acetate that has been noted online as a commercial impurity in formulations. It is a known corrosive, with concerning inhalation toxicological effects (<https://toxnet.nlm.nih.gov>).
 - Vitamin E acetate degradation can afford ketene via thermolysis during vaping due to the known reaction of phenol acetate moiety. Ketene is hazardous, on par with phosgene.

The transformation of vitamin E acetate to ketene upon heating and aerosolization in a commercial vaping device



Ketene lung concentrations may attain severe (30-ppm) levels when vaping

<https://doi.org/10.26434/chemrxiv.11889828.v1>

D. Wu, D. F. O'Shea, Potential for release of pulmonary toxic ketene from vaping pyrolysis of vitamin E acetate. *Proc. Natl. Acad. Sci. U.S.A.* 117, 6349–6355 (2020).

R.M Strongin, Toxic ketene gas forms on vaping vitamin E acetate prompting interest in its possible role in the EVALI outbreak. *Proc. Natl. Acad. Sci. U.S.A.* 117, 6349–6355 (2020).

How did it become “OK” to add food and vitamin etc. additives to vaping products?

- The tobacco vaping industry normalized the use of flavors and additives that are banned for use in traditional cigarettes
- There are approximately > 8,000 different e-liquid formulations

Triacetin enhances levels of acrolein, formaldehyde hemiacetals and acetaldehyde in electronic cigarette aerosols

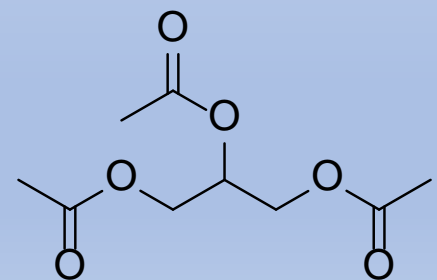
Vreeke, S; Peyton, D. H.; Strongin R. M. *ACS Omega*, 2018, 7, 7165-7170.

Question: Do flavorings enhance levels of aldehydes in e-cigarette aerosols?

Yes: Khlystov, A.; Samburova, V. Flavoring Compounds Dominate Toxic Aldehyde Production during 34 E-Cigarette Vaping. *Environ. Sci. Technol.* 2016, 50 (23), 13080-13085

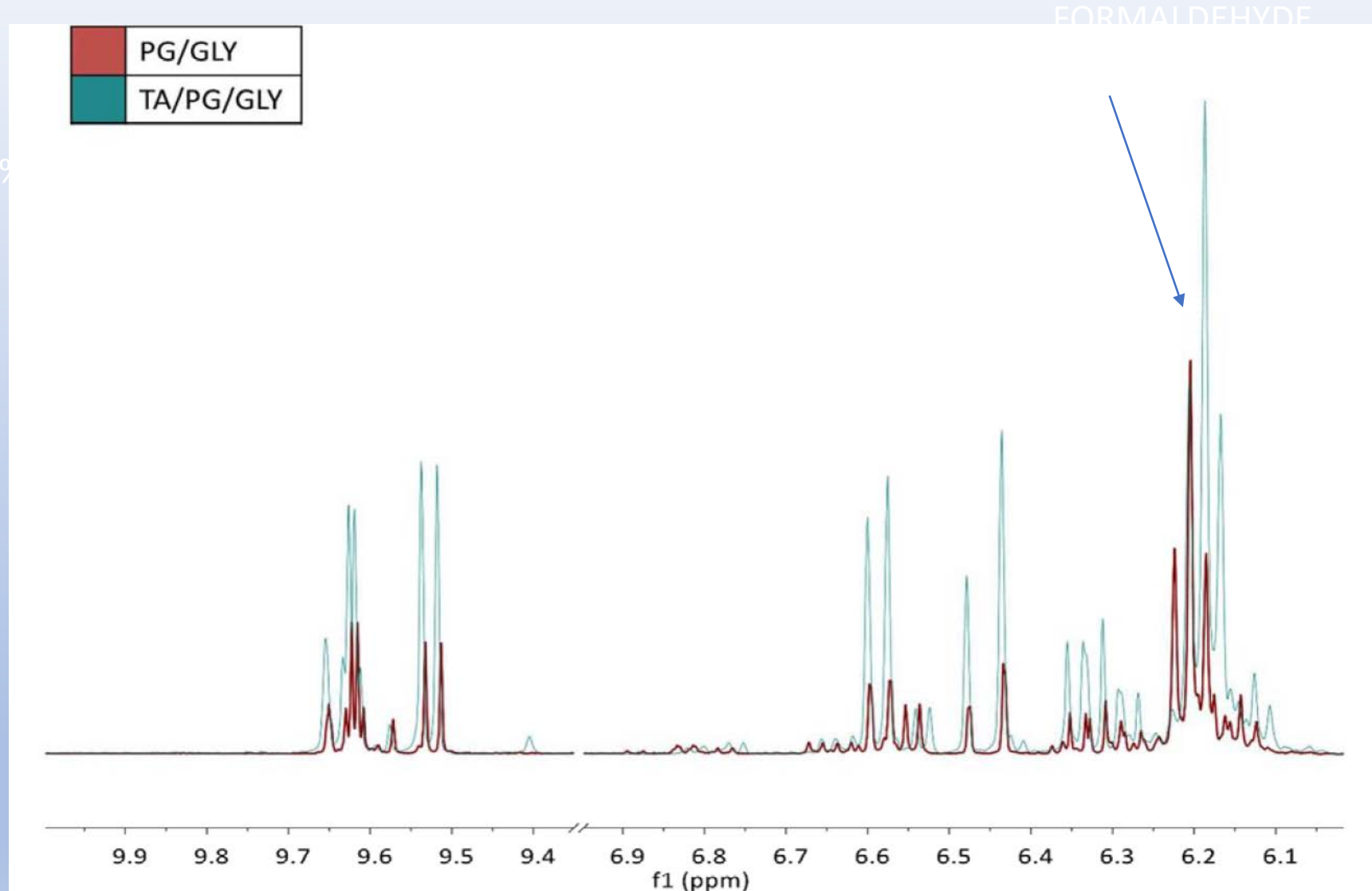
No: Farsalinos, K. E.; Voudris, V. Do flavouring compounds contribute to aldehyde emissions in e-cigarettes? *Food Chem. Toxicol.* 2018, 115, 212-217

Approach: Show chemical feasibility under real-world conditions



triacetin

Seeing is believing: 10%
TA clearly enhances
aerosol levels of
acrolein, acetaldehyde
and formaldehyde
hemiacetal



CURRENT CHALLENGES TOWARDS UNDERSTANDING HEALTH IMPACTS: MISINFORMATION/MISREPRESENTATION OF SCIENCE

- It is well-known that e-liquids are primarily composed of organic solvents and that conclusive epidemiological data will not be available for at least decade(s).

HOWEVER:

Prof. Robert West

“E-cigarettes are probably about as safe as drinking coffee. All they contain is water vapour, nicotine and propylene glycol”

Prof. Peter Hajek

“The case for regulating e-cigarettes as a pharmaceutical product is on a par with regulating coffee”

Clive Bates **“In fact the lowest size particles are water vapor”**

**There is no such thing
as a “water
nanoparticle”!!!!**


Attacks on legitimate, peer-reviewed scientific research: prominent, vocal advocates state that **users can self-regulate toxin intake-because toxins taste really bad!**

E-CIG INDUSTRY ATTACK ON SCIENTIFIC EVIDENCE

- **That vapers can self-regulate toxin intake was actually disproved in the researcher's own study**
- **No mention of formaldehyde hemiacetal in “replication” study**
- **Used a different method (derivatization and cartridges) in “replication” study**
- **Findings actually showed the inability of a large % of the subjects to detect toxin levels above the threshold, despite the biased conditions (power level increases evident to users)**


Food and Chemical Toxicology 109 (2017) 90–94

Contents lists available at [ScienceDirect](#)



Food and Chemical Toxicology


journal homepage: www.elsevier.com/locate/foodchemtox



E-cigarettes emit very high formaldehyde levels only in conditions that are aversive to users: A replication study under verified realistic use conditions

Konstantinos E. Farsalinos ^{a, b, c, *}, Vassilis Voudris ^a, Alketa Spyrou ^a, Konstantinos Poulas ^b

^a Department of Cardiology, Onassis Cardiac Surgery Center, Sygrou 356, Kallithea 17674, Greece
^b Department of Pharmacy, University of Patras, Rio-Patras 26500, Greece
^c National School of Public Health, Greece



How **NOT** to do a human subjects and/or a replication study →

Substance of the findings not important to the “audience”? Just declare victory despite the details.....

We revisited our prior study at an intermediate e-cigarette power level reported by industry supporters to be “non averse” to users

High levels of hemiacetal (and carbonyl formaldehyde) were found via our collection and analytical techniques-well above OSHA workplace limits for formaldehyde exposure

SCIENTIFIC REPORTS



OPEN

E-cigarettes can emit formaldehyde at high levels under conditions that have been reported to be non-averse to users

Received: 15 February 2018

Accepted: 1 May 2018

Published online: 15 May 2018

James C. Salamanca, Jiries Meehan-Atrash, Shawna Vreeke, Jorge O. Escobedo, David H. Peyton  & Robert M. Strongin 

USERS CAN SELF-REGULATE TOXIN INTAKE?

Vapers can self-regulate toxin intake?



Mitchell's lungs had stopped working and he was in intensive care on two different life support systems for about a week. (Mitchell family/Family Photo)

Vapers can self-regulate toxin intake?

Email I received August 26, 2019, from a vaper in the UK:

“Friends that vape have often tried my e-cigarette and coughed after the first puff yet I am able to pull long drags on the same device with no effect.

It came to mind that I may have developed a tolerance for the burned taste that would prevent a user from continuing to inhale the harmful chemicals.

I wondered how many people out there are unknowingly exposing themselves and more importantly children and vulnerable people to this danger.”

How did it become “OK” to add food and vitamin etc. additives to vaping products?

- The tobacco vaping industry normalized the use of flavors and additives banned for use in cigarettes via aggressive lobbying
- There are approximately > 8,000 different e-liquid formulations
 - What additives are found in cannabis vaping formulations?

HOW FAR CAN THE USE OF ADDITIVES IN CANNABIS PRODUCTS GO IN THE “POST” EVALI ERA?



r/CannabisExtracts · Posted by

Fake Dab Brands Mega Thread

All,

As you've all seen, pine resin is on the market, dab carts are testing positive for a litany of carcinogens, and adulteration of product is at an all time high from your average dealer to “name brands” or those even in dispensaries.

PINE ROSIN OR PINE RESIN?

Pine resin (liquid) is distilled to produce pine rosin, aka colophony, a brittle solid at rt



- USED IN SOLDER, MUSICAL INSTRUMENTS, ETC.
- IS A KNOWN INDUSTRIAL INHALATION HAZARD
- CAUSES OCCUPATIONAL ASTHMA/ACUTE AND CHRONIC LUNG INJURY
- AT A LEVEL OF JUST 1 % IN THC OIL, PUF HIT HAS ~ 3500 TIMES THE 15 MIN TIME WEIGHTED EXPOSURE THRESHOLD



pine rosin

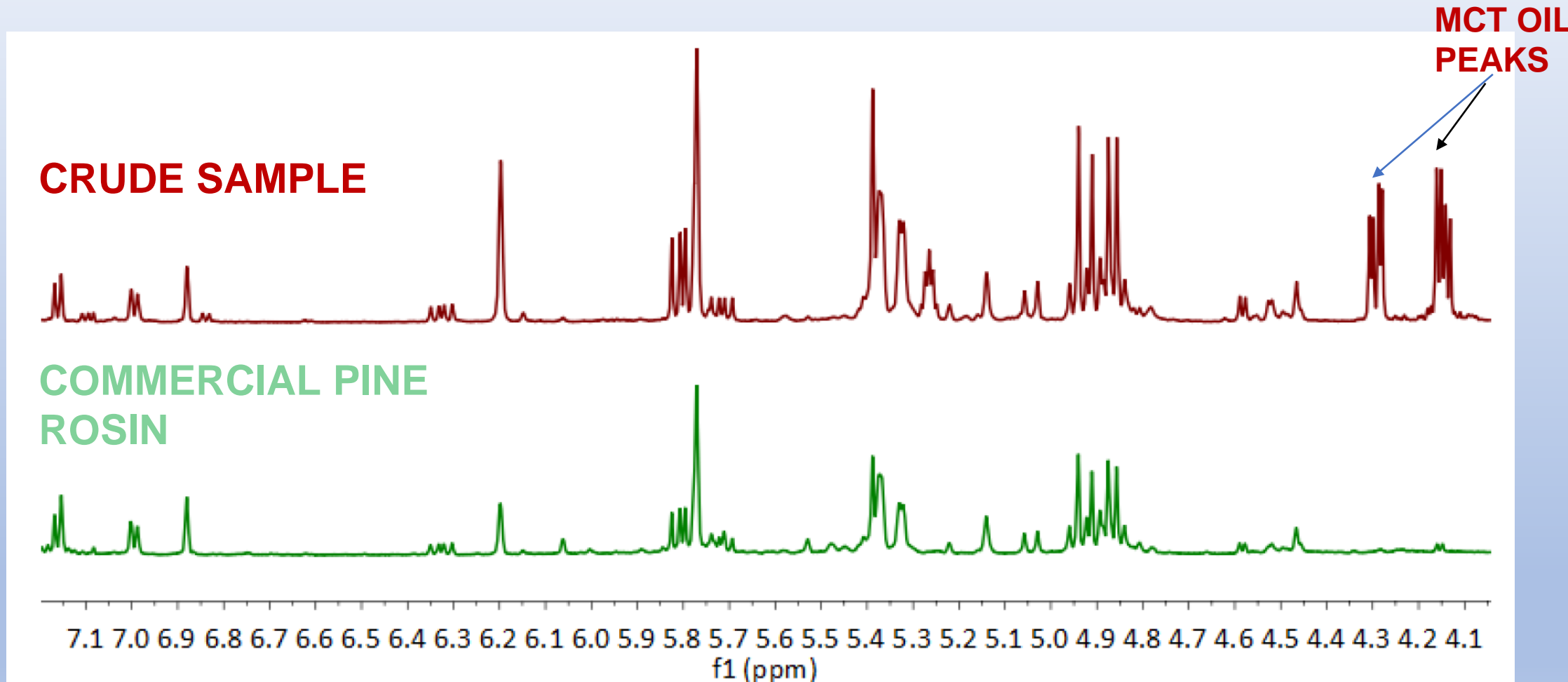


Pine rosin sample in the syringe was analyzed:
It contains MCT oil to make it fluid

PINE ROSIN CONSTITUENTS IDENTIFIED

Common Name	CAS Number	RT in LC/MS (min.)	NMR Shift (ppm)	Mass Accuracy (ppm)	% in Sample
Dehydroabietic acid	1740-19-8	16.5	6.88	0.03	3
Communic acid	2761-77-5	21.8	6.32	0.03	4
Pimarol	1686-59-5	23.9	NA	0.52	NA
Pimaric acid	127-27-5	23.9	5.71	1.25	3.2
Sandaracopimaric acid	471-74-9	23.9	5.22	1.25	1.5
Palustric acid	1945-53-5	23.9	5.39	1.25	14
Abietic acid	514-10-3	25.1	5.77	1.25	17
Oleamide	301-02-0	25.1	6.65-7.19	0.64	NA
Neoabietic acid	471-77-2	25.1	6.2	1.25	12
Isopimaric acid	5835-26-7	25.1	5.81	1.25	13
Sandaracopimarinal	3855-14-9	30.3	5.22	0	NA
MCT oil	438544-49-1	NA	4.3	NA	15

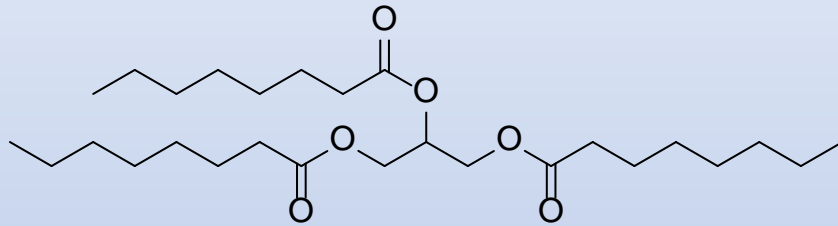
^1H NMR SPECTRA: OVERLAY OF CRUDE SAMPLE (TOP) WITH A COMMERCIAL SAMPLE (BOTTOM) OF PINE ROSIN



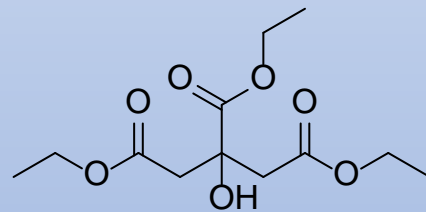
How did it become “OK” to add food and vitamin etc. additives to vaping products?

- The tobacco vaping industry has normalized the use of flavors and additives banned for use in cigarettes through aggressive lobbying
- There are approximately > 8,000 different e-liquid formulations
 - What additives are found in cannabis vaping formulations?

Examples of More “Mainstream” Product Additives



1,2,3-propanetriol trioctanoate
a common medium chain triglyceride



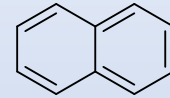
triethyl citrate

inhalation toxicity is not known

chemical reactions and products occurring when vaping these molecules are also not yet clear-*do these compounds decompose/react with other ingredients when heated and vaped?*

RESULTS OF INITIAL SCREENING OF 15 RANDOM COMMERCIAL TERPENE FORMULATIONS

Three of the products contain naphthalene

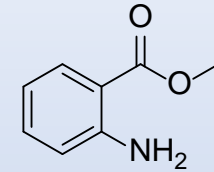


naphthalene

- Naphthalene is used in mothballs.
- Acute (short term) exposure of humans to naphthalene by inhalation, ingestion, and dermal contact is associated with hemolytic anemia, damage to the liver, and neurological damage.
- Cataracts have also been reported in workers acutely exposed to naphthalene by inhalation and ingestion.
- Chronic (long-term) exposure of workers and rodents to naphthalene has been reported to cause cataracts and damage to the retina.
- Hemolytic anemia has been reported in infants born to mothers who "sniffed" and ingested naphthalene (as mothballs) during pregnancy.
- Available data are inadequate to establish a causal relationship between
- exposure to naphthalene and cancer in humans. EPA has classified naphthalene as a Group C, possible human carcinogen.

U.S. Environmental Protection Agency. Toxicological Review of Naphthalene (CAS No. 91-20-3) in Support of Summary Information on the Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Cincinnati, OH. 1998.

RESULTS OF INITIAL SCREENING OF 15 RANDOM COMMERCIAL TERPENE FORMULATIONS



methyl anthranilate

Three of the products contain methyl anthranilate

- This grape flavoring molecule is used in many tobacco e-liquid formulations
 - Is one type of candy flavoring whose use in tobacco products has been condemned as an attempt to attract teen users
- Used as bird repellent
- Inhalation toxicity: NOT DETERMINED

Hazard statement(s):

H315 - Causes skin irritation

H319 - Causes serious eye irritation

H335 - May cause respiratory irritation

H401 - Toxic to aquatic life

H411 - Toxic to aquatic life with long lasting effects

Precautionary statement:

P261 - Avoid breathing dust/fume/gas/mist/vapours/spray

<http://www.thegoodscentcompany.com/data/rw1008211.html>

RESULTS OF INITIAL SCREENING OF 15 RANDOM COMMERCIAL TERPENE FORMULATIONS

One of the products contains polyethylene glycol (PEG)

PEG is a prevalent industrial chemical and a powerful laxative

- Formaldehyde inhalation has been linked to increased incidence of myeloid leukemia and nasopharyngeal cancer.
- The amount of formaldehyde produced by heating PEG is comparable to the amount of formaldehyde in a tobacco cigarette, and is 33 times higher than from heating medium chain triglycerides.

Troutt, William D. and DiDonato, Matthew D. **Carbonyl Compounds Produced by Vaporizing Cannabis Oil Thinning Agents.** *J Altern Complement Med.* 2017, 11, 879-884.

RESULTS OF INITIAL SCREENING OF 15 RANDOM COMMERCIAL TERPENE FORMULATIONS

Work is ongoing

- Do chemical reactions occur during storage resulting in unexpected/unwanted byproducts?
Terpenes are prone to oxidation, cracking, isomerization/interconversion reactions upon vaping.
- How do formulation components react upon heating/vaping?
For example, flavoring molecule additives increase toxic aldehyde production
Vreeke, S; Peyton, D. H.; Strongin R. M. *ACS Omega*, 2018, 7, 7165-7170

SOME CONCLUDING THOUGHTS

- **There is a need for conclusive, evidence-based inhalation toxicity data about additives used in cannabis extract formulations. This includes MCT oil and triethyl citrate.**
- **We have found that some commercial terpene formulations contain tobacco product flavorings (e.g., methyl anthranilate), as well as solvents such as propylene glycol and polyethylene glycol that produce toxic volatiles upon vaping**
- **Cannabis has been smoked for thousands of years – but there were no known instances of EVALI until relatively very recently, Why?**

ACKNOWLEDGEMENTS

Jiries Meehan-Atrash
Nicole Javalay
Alicia Ortiz

The National Institutes of Health
The US Food and Drug Administration

The presenter is solely responsible for the content in this presentation