The Development of Testing-Based Approaches to Screen for Hazardous Ingredients and Formulations Used in Heated Inhalation Devices with Particular Emphasis on Cannabis Products

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http://SupraRnD.ca

CROM SYMPOSIUM 2023 - February 13, 2023

Conflict of Interest Declaration

- Supra provides Analytical services and consulting services to companies producing vaping products
- Applicant and consultant on a variety of Health Canada Cannabis license applications, testing, research and processing
- Actively engaged in ASTM – D37 Committee on Cannabis. Engaged in AOAC – CASP program, ISO workshops

Scope of discussion – Product types

.... this is what

Heated Inhalation Consumer Products

- **e-cigarette products:** Deliver nicotine and flavors (terpenes & related)
  - evolved from a smoking cessation objective to stand alone consumer product
  - Cigarette smoking detrimental to health. Correlations to disease and death.
  - Flavor & Caffeine bans to reduce risk of youth attraction to addictive Nicotine
  - Electronic Nicotine Delivery Systems (ENDS) – specific subclass

- **Cannabis Vaporization & Concentrates:** Deliver Cannabinoids & Terpenes
  - Vaporization also perceived as a harm reduction approach
  - Products have been prescribed by physicians as medicinal treatment
  - Possible flavor bans and limits to Cannabis terpenes and flavors (Canada)

- **“Off label” Botanicals:** Mint, hops, other botanicals, added to herbal Vaporizers
  - Access to herbal vaporizers creates opportunities for unexpected use
  - Expect product types beyond ENDS and Cannabis

Contamination Monitoring

When **used as intended**, **high temperature vaporization** delivers a mixture of chemical agents to the intended user that can be **different than is present at room temperature** due to thermal rearrangement, oxidation and pyrolysis.

Chemical agents that the **consumer can be exposed to** are dependent on vaporized formulation, vaporizer temperature, as well as other factors.

Pharmaceutical potential

In the absence of dangerous chemical agents, there is potential for delivery of active ingredients with medicinal benefits.

Inhalation pharmacology bypasses 1st pass metabolism. Understanding dose of delivered compounds will help unravel proposed entourage effect.

Cannabis is prescribed as a medicinal product / treatment

Contamination Monitoring

Ingredients and formulations **must be evaluated at vaporization temperature** to evaluate nature of chemical agents that users could be exposed to and dose of delivered “medicine”.

Without regulations and standards to screen for potential risk from ingriedients, the **de facto screening standard is uncontrolled human trials with hospitalization and mortality as risk indicators**.

Vaporization health concerns

.... that's not good

- **As of February 4, 2020**, a total of 2,758 hospitalized e-cigarette, or vaping, product use-associated lung injury (EVALI) cases or deaths have been reported to CDC from 50 states, the District of Columbia, and two U.S. territories (Puerto Rico and U.S. Virgin Islands).
- Sixty-four deaths have been confirmed in 28 states and the District of Columbia **(as of February 4, 2020)**:
  - Alabama, California, Connecticut, Delaware, District of Columbia, Florida, Georgia, Illinois, Indiana, Kansas, Kentucky, Louisiana, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, New Jersey, New York, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, and Virginia
  - The median age of deceased patients was 51 years and ranged from 15-75 years **(as of January 14, 2020)**.
  - More deaths are currently under investigation.

https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html

Vaporization health concerns

Vitamin E Acetate in Bronchoalveolar-Lavage Fluid Associated with EVALI

Benjamin C. Blount, Ph.D., Mateusz P. Karwowski, M.D., M.P.H., Peter G. Shields, M.D., Maria Morel-Espinosa, Ph.D., Liza Valentin-Blasini, Ph.D., Michael Gardner, M.S., Martha Braselton, B.S., Christina R. Brosius, M.P.H., Kevin T. Caron, B.S., David Chambers, Ph.D., Joseph Corstvet, B.S., Elizabeth Cowan, Ph.D., et al., for the Lung Injury Response Laboratory Working Group*

Table 3. Frequency of Detection of Priority Toxicants in EVALI Case Patients and in Healthy Comparators.*

Toxicant	EVALI Case Patients (N=51)	Healthy Comparators			
		Nonusers (N=52)	E-Cigarette Users (N=18)	Cigarette Smokers (N=29)	All Comparators (N=99)
		number/total number (percent)			
Vitamin E acetate	48/51 (94)	0/52	0/18	0/29	0/99
Medium-chain triglyceride oil	0/49	0/34	0/11	0/18	0/63
Coconut oil	1/48 (2)	0/34	0/11	0/18	0/63
Plant oil	0/49	0/34	0/11	0/17	0/62

The NEW ENGLAND JOURNAL of MEDICINE

https://www.nejm.org/doi/full/10.1056/NEJMoa1916433

Vaporization health concerns

.... that's not good

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Butt YM, Smith ML, Tazelaar HD, et al. Pathology of vaping-associated lung injury. N Engl J Med 2019;381:1780-1. DOI: 10.1056/NEJMc1913069

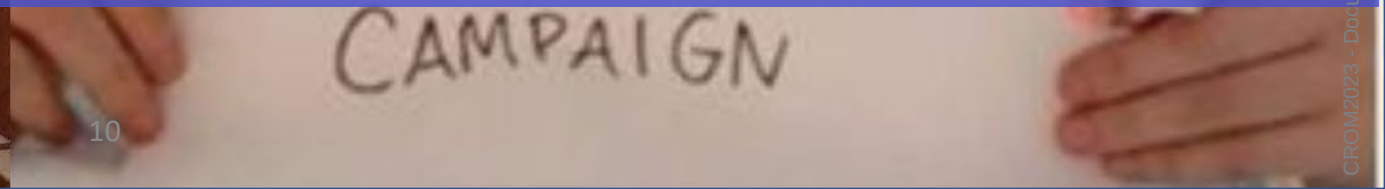
".. foamy macrophage accumulation and pneumocyte vacuolization were universal findings …. This pattern closely resembles the type of changes that are characteristic of toxic reactions to medications (especially amiodarone) or noxious chemical fumes, suggesting a similar mechanism of injury. "

Vaporization health concerns

…. how would a producer know

Vitamin E Acetate

- Is not considered a toxic agent or contaminant
- Is not a “Flavoring Compound”
- Generally Recognized as Safe (GRAS) if ingested
- No testing or safety standard indicated a problem
- Producers “innocently” made products that caused illness and deaths
- Oregon EVALI illness not linked to Vitamin E Acetate



Many reasons why solutions are hard

- **Many different types of Vaping devices**
  - Nearly impossible to standardize devices that could be used

- **Developing consensus on acceptable exposure levels difficult**
  - Determining actual exposure very challenging
  - Dependent on device, temperature, flow dynamics, etc.
  - What “dose” or “exposure” is safe. What about over consumption?

- **Many “GRAS” ingredients can be hazardous when heated**
  - EVALI also linked to Squalene/Squalane in Oregon

Potential Solutions

Approaches

- **Use highly controlled analytical instrumentation to examine possible degradation products**
  - High-Temperature GCMS provides ideal testing approach
    - "Vaporization Potential" VP^{240}
  - Many thermal degradation products are residual solvents

- **Develop reproducible "stress" test to screen ingredients**
  - Heat to temperature (240C), hold, cool and test for residual solvents
  - Use USP<467> residual solvent analysis for pass/fail criteria

- **Develop device testing approach**
  - ISO 20768:2018 Vapour products — Routine analytical vaping machine

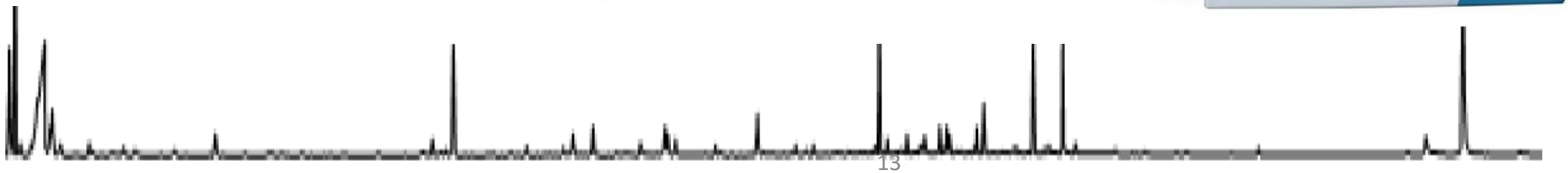
Head Space – GCMS Screening

.... our toolbox

Mass Spectrometer

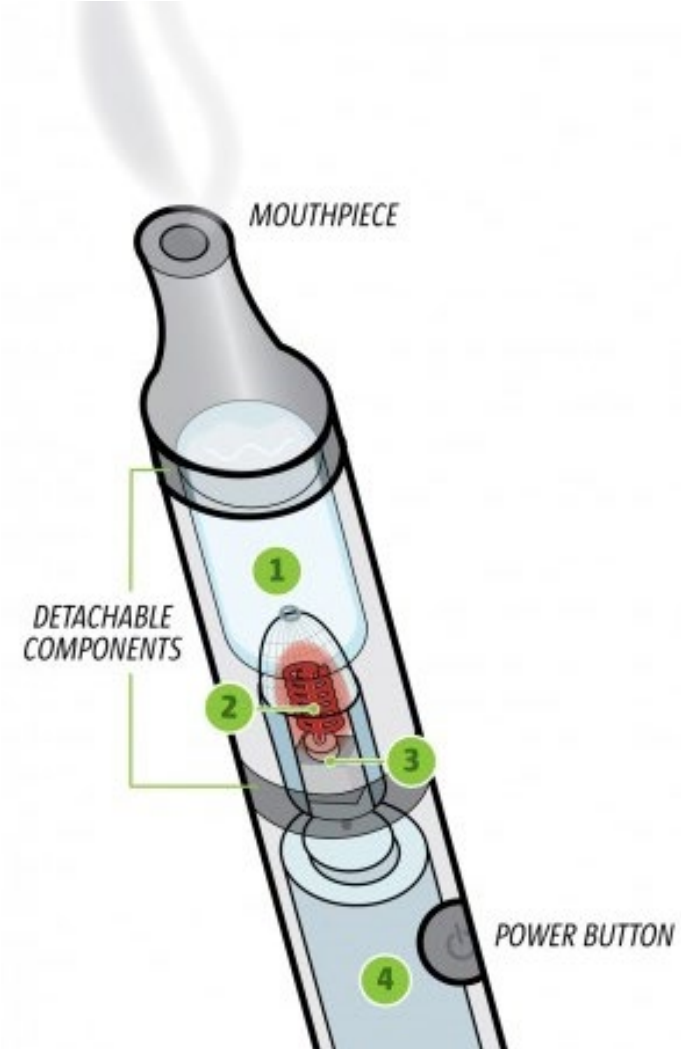
Gas Chromatograph

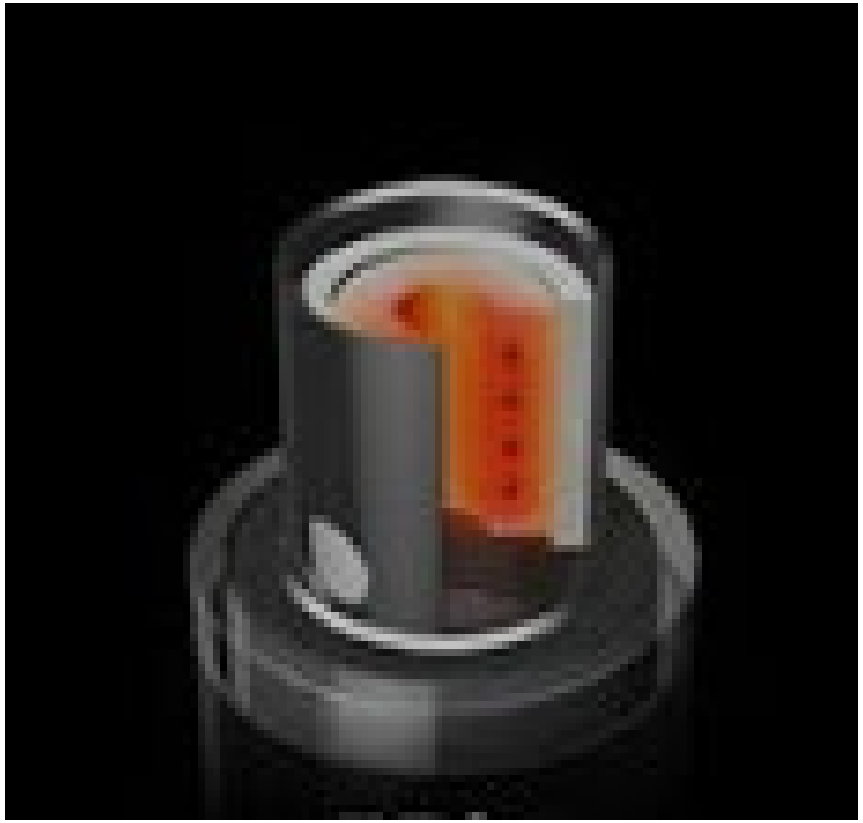
Head Space Autosampler



Controlled Vaporization Experiment

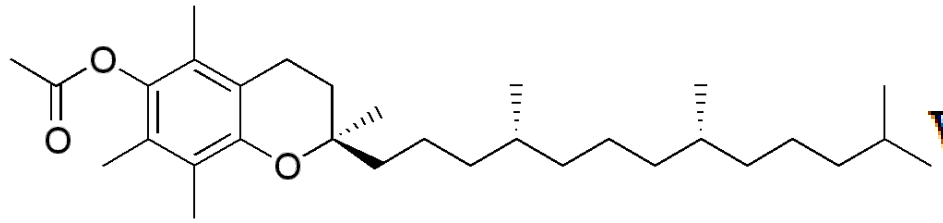
.... controlled surrogate



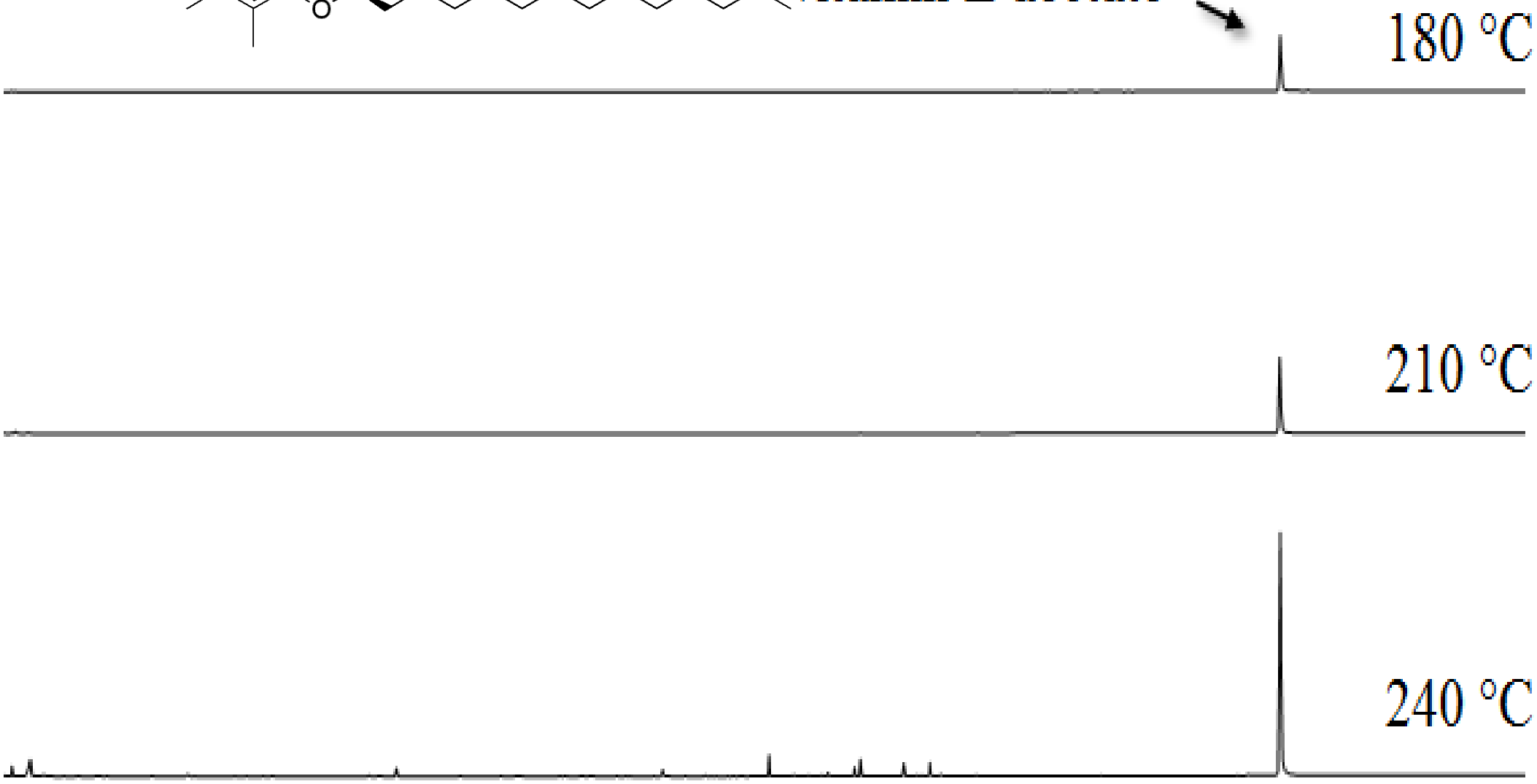


Vitamin E Acetate - VP

…. what's delivered

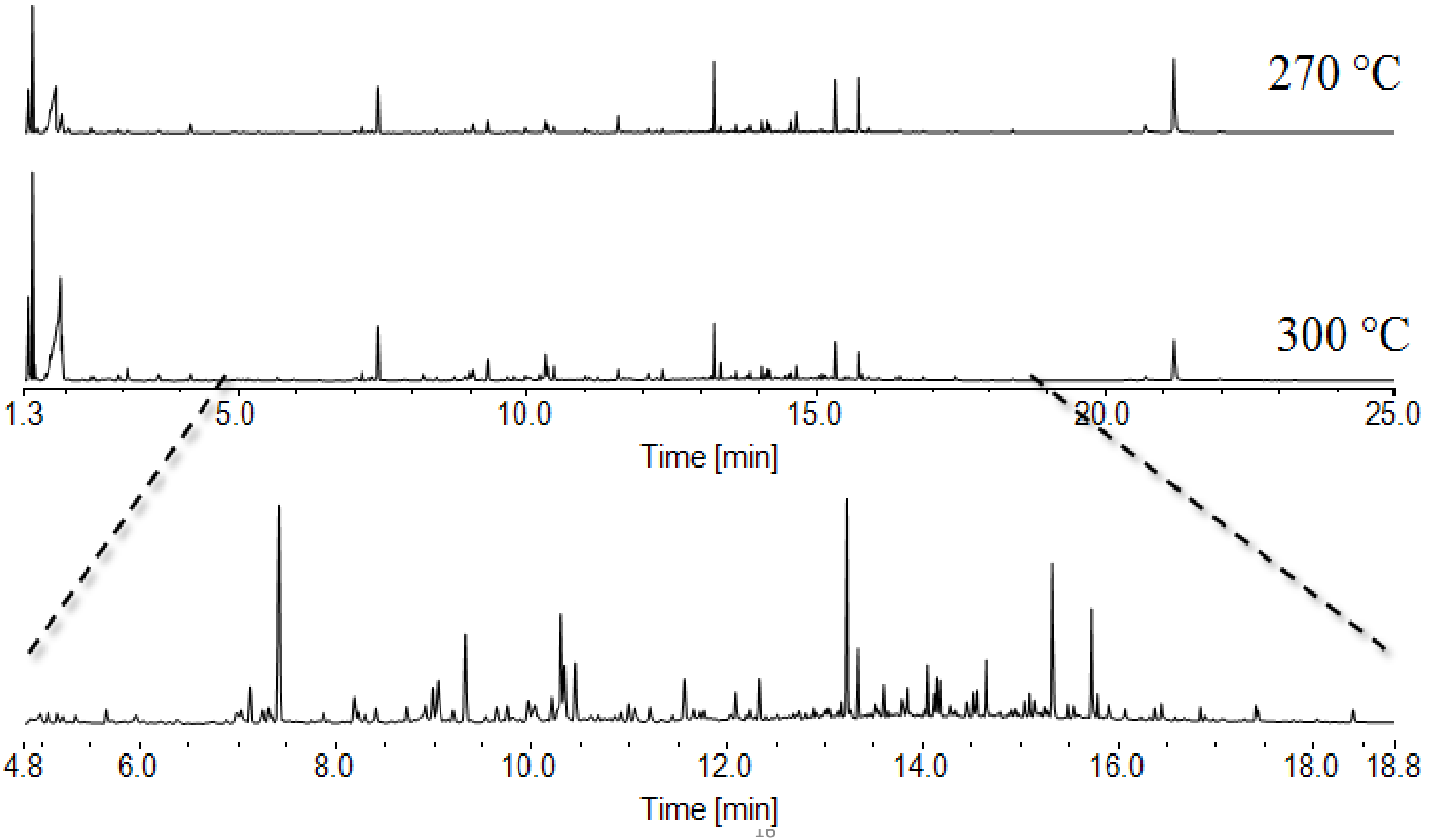


vitamin E acetate



Vitamin E Acetate - VP

…. nasty by degrees



Vitamin E Acetate - VP

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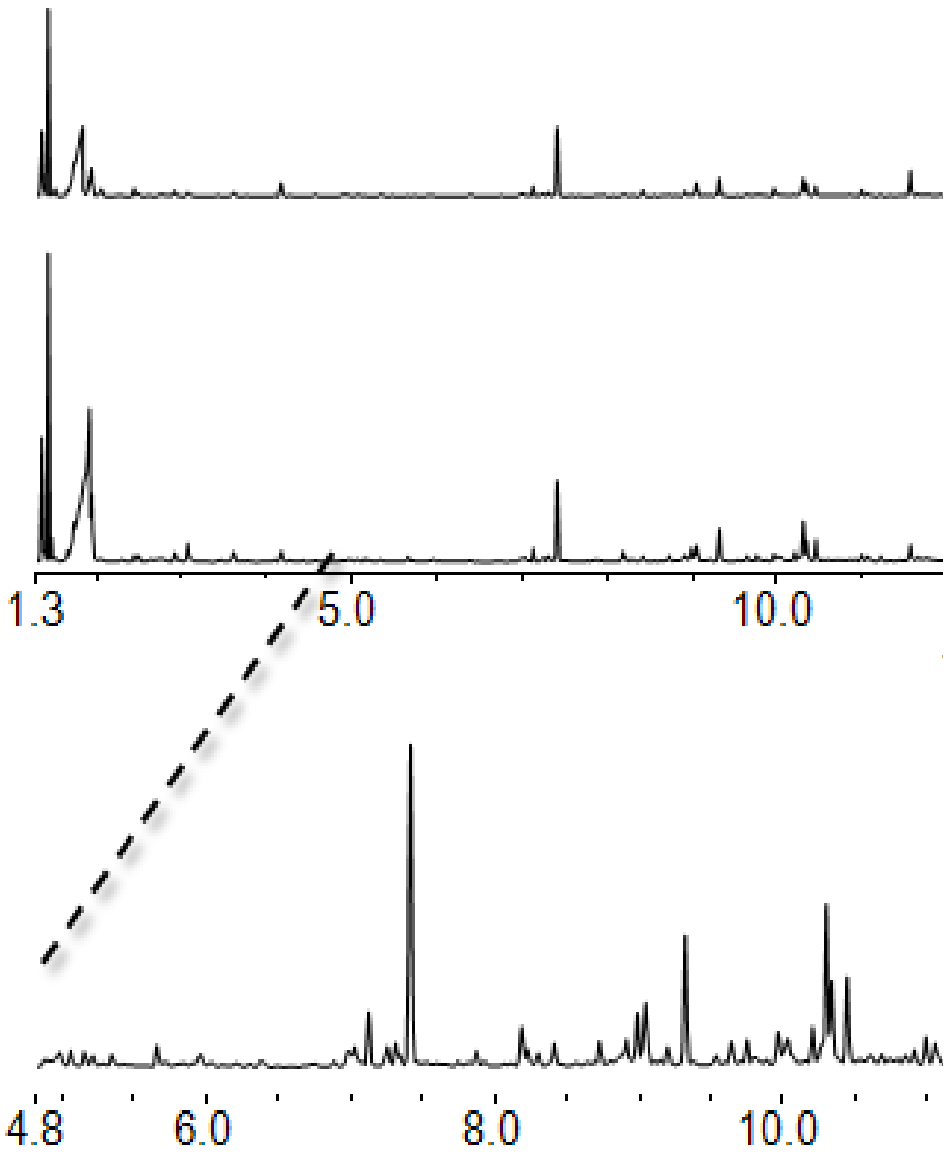

NIST ID	RT (min)	NIST Prob (%)
formic acid*	1.35	52
acetone*	1.42	68
isobutyraldehyde	1.64	91
acetic acid*	1.65	77
methacrolein	1.72	70
2-butanone*	1.93	78
isovaleraldehyde	2.43	81
3-methyl-2-butanone	2.48	50
propanoic acid	2.65	73
acrylic acid	2.71	82
2,2-dimethylTHF	2.76	75
2-pentanone	2.90	83
2,3-pentanedione	3.11	86
isobutyric acid	3.43	56
3-penten-2-one	4.06	68
2-hexanone*	4.56	26
isovaleric acid	4.93	91
2,2-dimethyl-3(2H)-furanone	6.01	91
2-heptanone	6.35	59
4-methyl valeric acid	6.93	79
2-methyl-6-heptanone	7.40	85

Potential Solutions

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    - "Vaporization Potential" VP^{240}
  - Many thermal degradation products are residual solvents

- **Develop reproducible "stress" test to screen ingredients**
  - Heat to temperature (240C), hold, cool and test for residual solvents
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- **Develop device testing approach**
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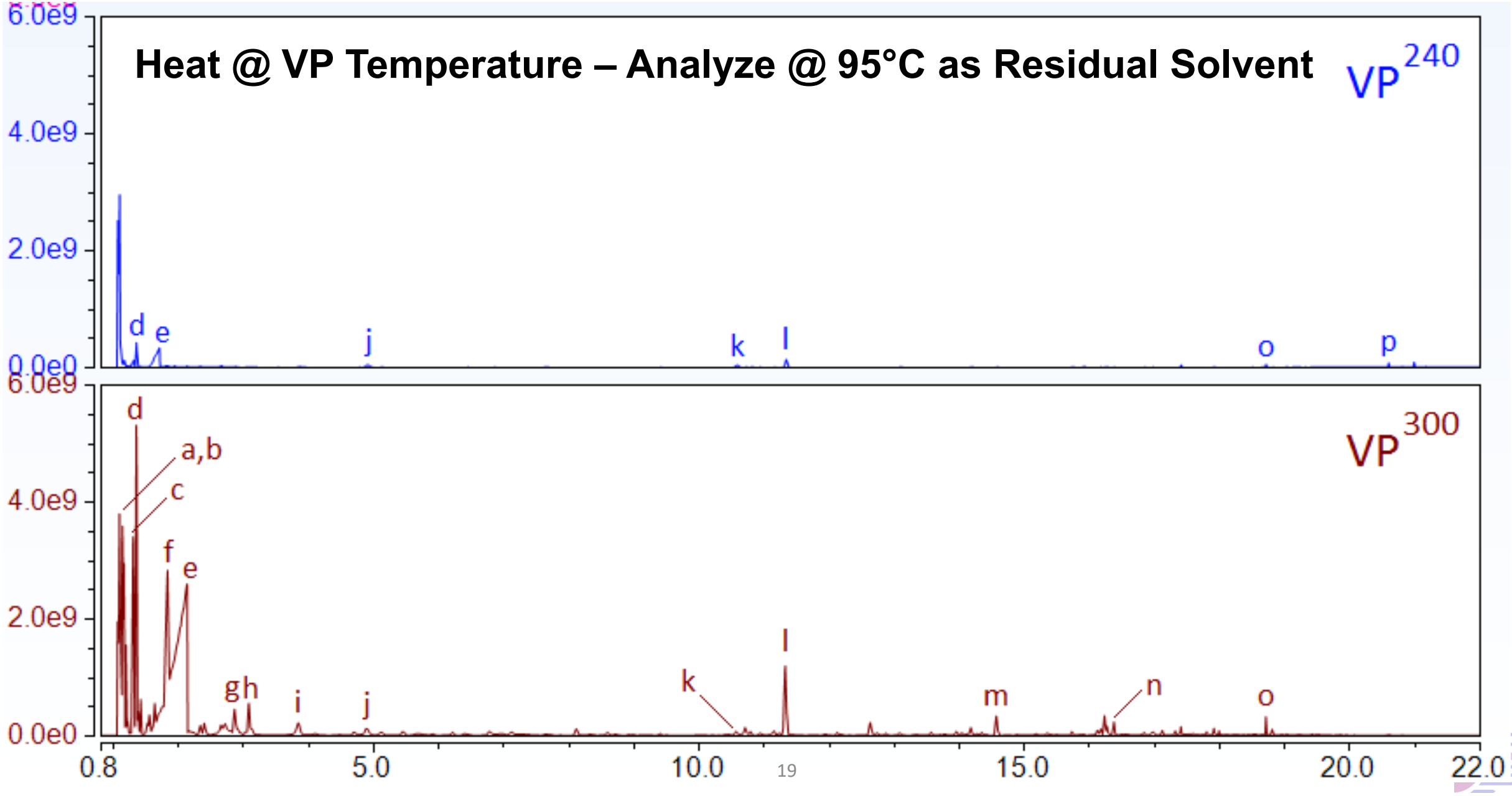
Vitamin E Acetate

.... problem is clear

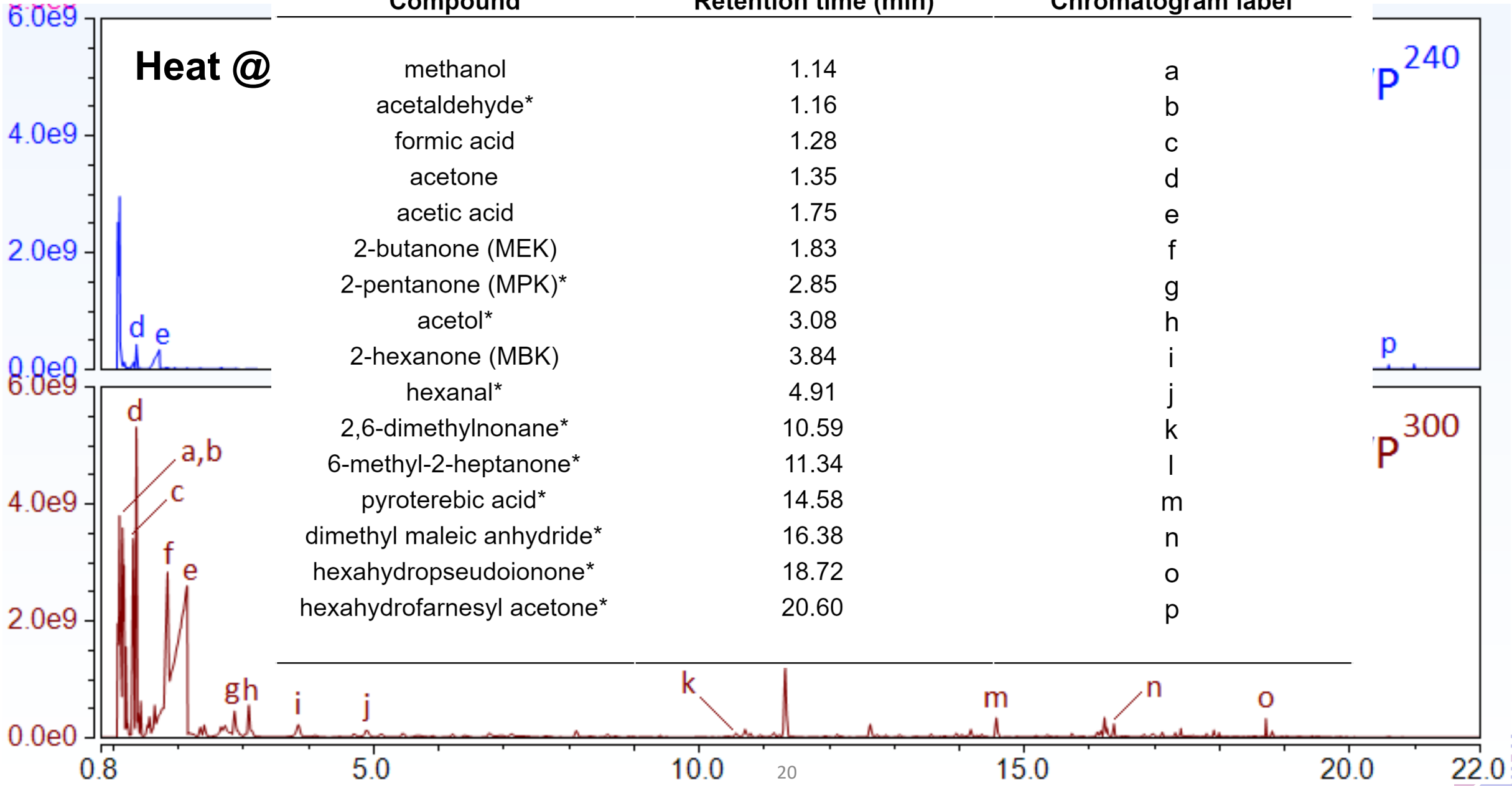


Vitamin E Acetate

.... problem is clean

Heat @

Compound	Retention time (min)	Chromatogram label
methanol	1.14	a
acetaldehyde*	1.16	b
formic acid	1.28	c
acetone	1.35	d
acetic acid	1.75	e
2-butanone (MEK)	1.83	f
2-pentanone (MPK)*	2.85	g
acetol*	3.08	h
2-hexanone (MBK)	3.84	i
hexanal*	4.91	j
2,6-dimethylnonane*	10.59	k
6-methyl-2-heptanone*	11.34	l
pyroterebic acid*	14.58	m
dimethyl maleic anhydride*	16.38	n
hexahydropseudoionone*	18.72	o
hexahydrofarnesyl acetone*	20.60	p



Vitamin E Acetate - Equivalent Residual Solvent

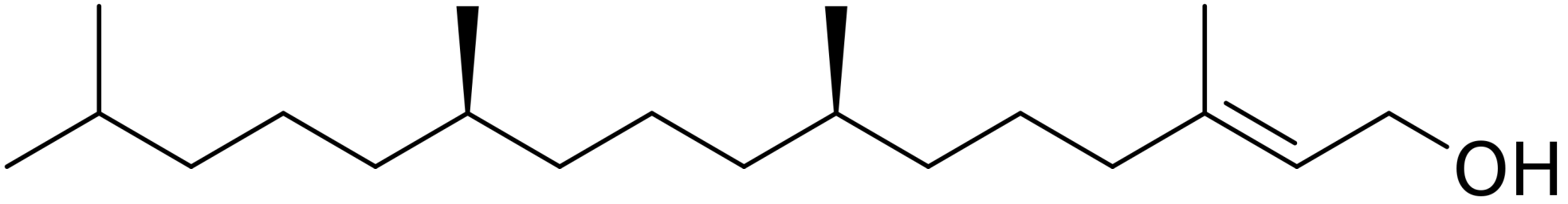
.... problem is clear

		Incubation Temperature (°C)				
	USP limit	VP^{180}	VP^{210}	VP^{240}	VP^{270}	VP^{300}
methanol	15	nd	nd	< 3	> 30	> 30
ethanol	5000	nd	nd	< 1000	< 1000	< 1000
formic acid*	5000	nd	nd	1448	> 10000	> 10000
acetone	5000	nd	< 1000	< 1000	> 10000	> 10000
acetic acid*	5000	nd	< 1000	5778	> 10000	> 10000
2-butanone (MEK)	5000	nd	nd	< 1000	1853	5249
benzene	2	nd	nd	nd	nd	< 0.4
4-methyl-2-pentanone (MIK)	5000	nd	nd	< 1000	< 1000	< 1000
toluene	890	nd	nd	nd	< 178	< 178
2-hexanone (MBK)	50	nd	nd	nd	89.5	> 100
m/p-xylene	1606†	nd	nd	nd	< 321	< 321

New Ingredient Screening

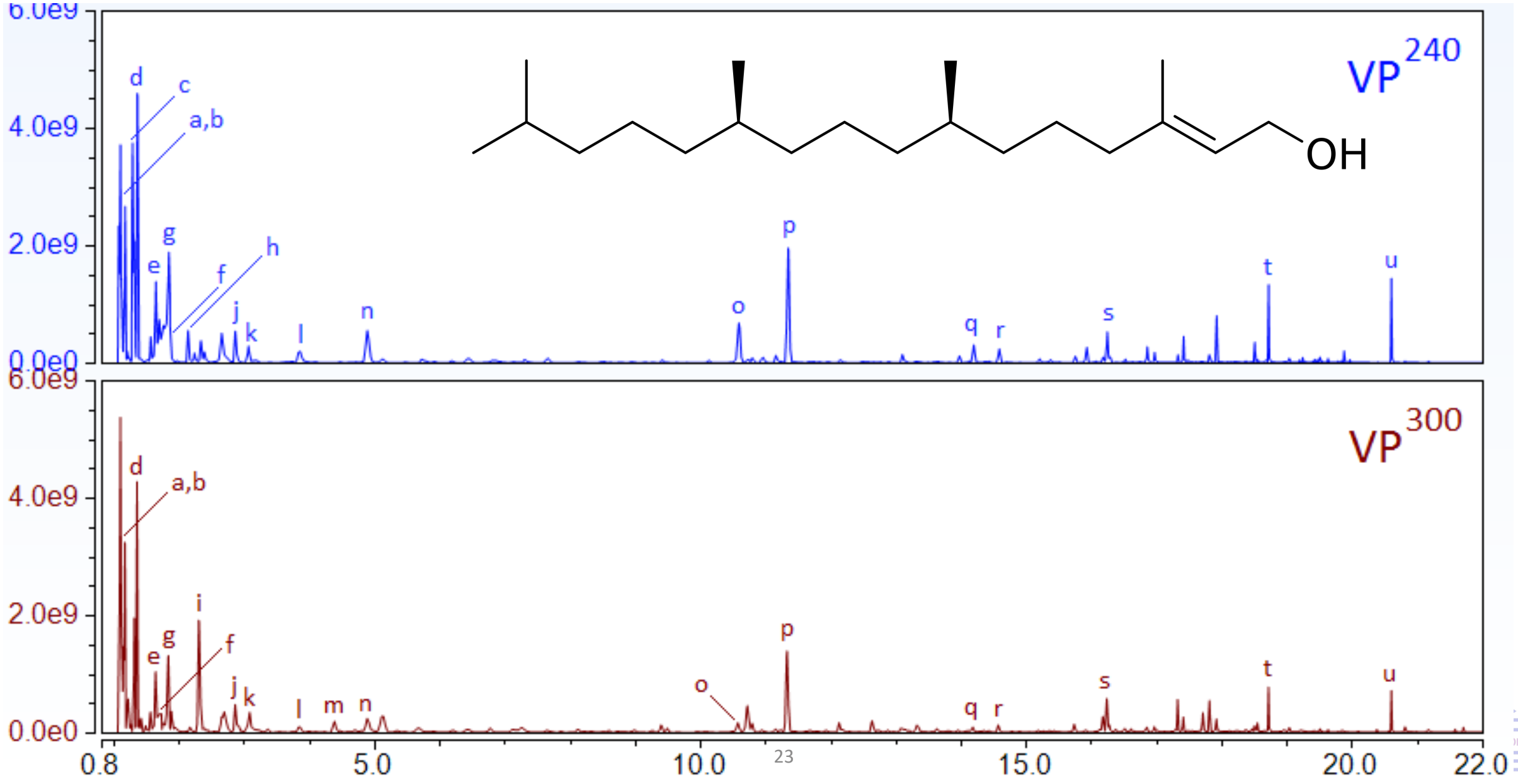
.... Good catch

In February 2020 we were asked to evaluate a new potential ingredient that was to be used in a commercial vape product. It was found in some Cannabis products so it was expected to be safe.



Phytol

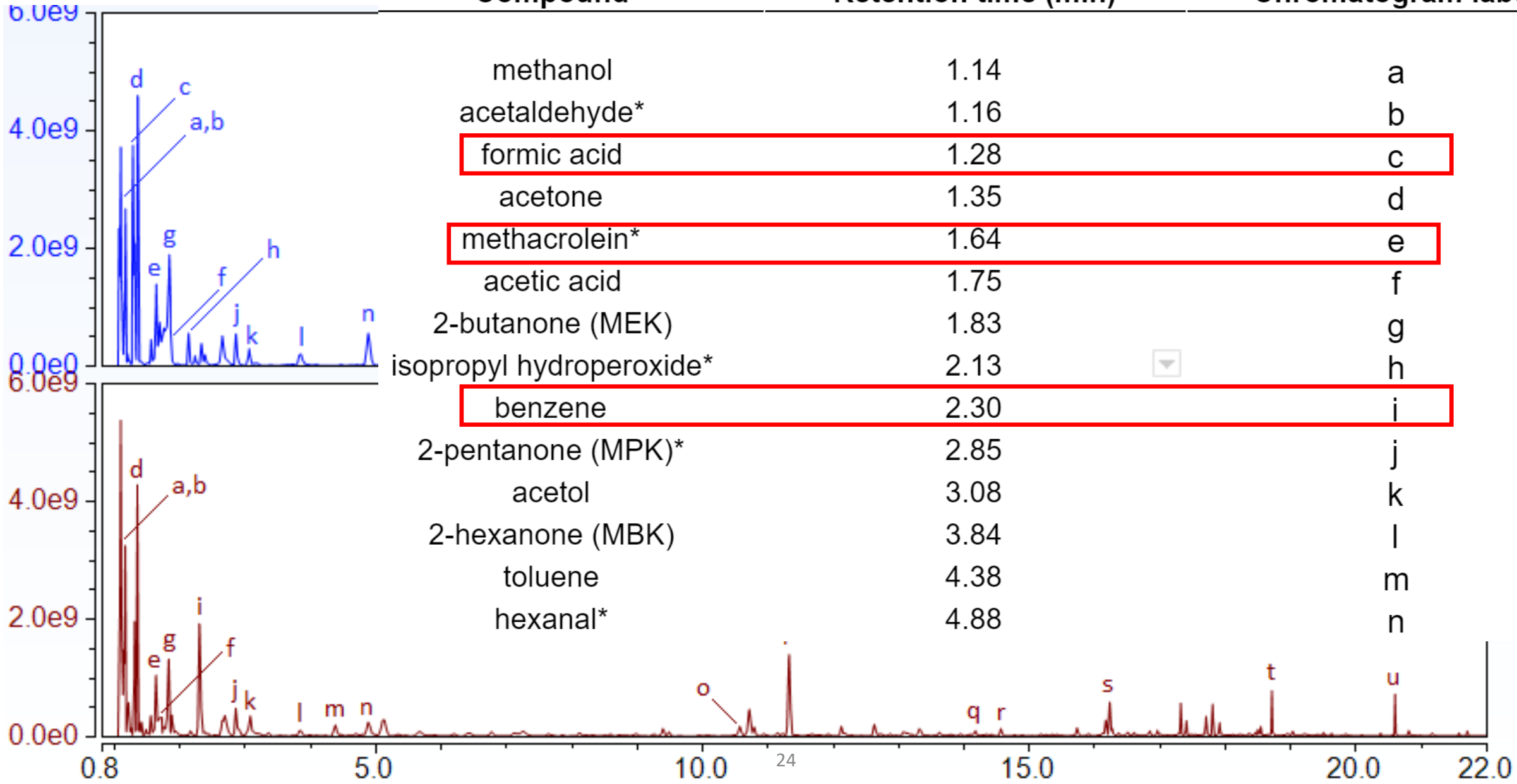
.... approach can be preventative



Phytol

…. approach can be preventative

Compound	Retention time (min)	Chromatogram label
methanol	1.14	a
acetaldehyde*	1.16	b
formic acid	1.28	c
acetone	1.35	d
methacrolein*	1.64	e
acetic acid	1.75	f
2-butanone (MEK)	1.83	g
isopropyl hydroperoxide*	2.13	h
benzene	2.30	i
2-pentanone (MPK)*	2.85	j
acetol	3.08	k
2-hexanone (MBK)	3.84	l
toluene	4.38	m
hexanal*	4.88	n



Phytol - Equivalent Residual Solvent

.... approach can be preventative

		Incubation Temperature (°C)				
	USP limit	VP^{180}	VP^{210}	VP^{240}	VP^{270}	VP^{300}
methanol	15	< 3	< 3	9.5	> 30	> 30
ethanol	5000	nd	nd	< 1000	< 1000	< 1000
formic acid*	5000	4000	> 10000	> 10000	> 10000	> 10000
acetone	5000	< 1000	< 1000	> 10000	> 10000	> 10000
acetonitrile	410	nd	nd	< 82	< 82	< 82
acetic acid*	5000	< 1000	< 1000	> 10000	4700	> 10000
2-butanone (MEK)	5000	< 1000	< 1000	1800	< 1000	1600
benzene	2	nd	nd	nd	> 4	> 4
4-methyl-2-pentanone (MIK)	5000	< 1000	< 1000	< 1000	< 1000	< 1000
toluene	890	nd	nd	< 180	1500	470
2-hexanone (MBK)	50	nd	nd	> 100	> 100	> 100
ethylbenzene	368†	nd	nd	nd	< 74	< 74
m/p-xylene	1606†	nd	nd	nd	< 320	< 320
o-xylene	196†	nd	nd	nd	< 39	< 39
cumene	70	nd	nd	nd	< 14	< 14

Phytol – Animal Studies

…. approach can be preventative

Health Canada Santé Canada

Address Locator: 0300A
Ottawa ON, K1A 0K9

August 7, 2020

Dear Licence Holder,

You have submitted a Notice of New Cannabis Product (NNCP) for one (or more) inhalable cannabis extracts.

Health Canada would like to inform your company that it was recently provided a copy of an experimental animal study sponsored by a cannabis company, Canopy Growth Corporation, which exposed rats to high levels of vaporized phytol, a substance that occurs naturally in cannabis, and that is added to some inhalable cannabis extracts. The study observed that high exposure to phytol resulted in serious harm to rats. This study has not yet been peer-reviewed and published.

Equivalent Residual Solvent Analysis (ERSA)

.... solution to solutions

Sample: Client A1 Flavored MCT	ppm	Incubation Temperature (°C)				
	USP limit	VP^{180}	VP^{210}	VP^{240}	VP^{270}	VP^{300}
methanol	15	< 3	< 3	< 3	< 3	> 30
ethanol	5000	nd	nd	< 1000	< 1000	130
formic acid*	5000	nd	nd	nd	nd	> 240000
2-propanol	5000	nd	nd	nd	< 1000	nd
acetone	5000	< 1000	< 1000	< 1000	2500	> 10000
acetic acid*	5000	nd	nd	< 2900	< 2900	> 232000
2-butanone (MEK)	5000	nd	nd	< 1000	< 1000	> 10000
benzene	2	nd	nd	nd	nd	> 4
4-methyl-2-pentanone (MIK)	5000	nd	nd	nd	nd	< 1000
toluene	890	< 178	< 178	<178	<178	360
2-hexanone (MBK)	50	nd	nd	nd	nd	64
cumene	70	nd	nd	nd	nd	18

Equivalent Residual Solvent Analysis (ERSA)

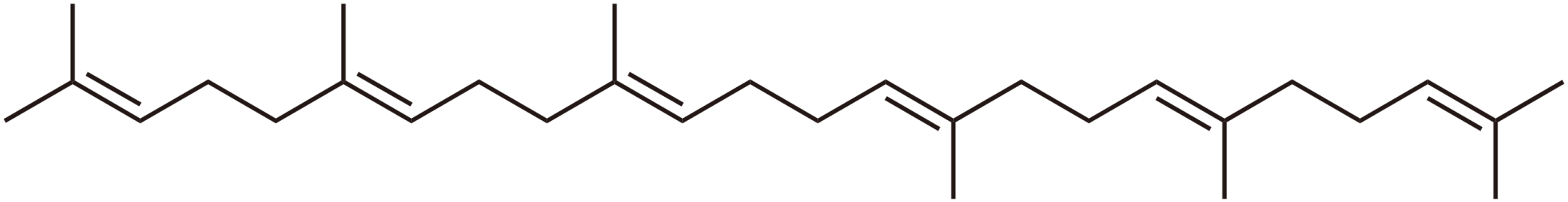
.... not all solutions are good

Sample: Client A2 Flavored MCT	ppm	Incubation Temperature (°C)				
	USP limit	VP^{180}	VP^{210}	VP^{240}	VP^{270}	VP^{300}
methanol	15	nd	< 3	3.4	> 30	> 30
ethanol	5000	< 1000	< 1000	< 1000	2100	1400
formic acid*	5000	nd	nd	220000	> 240000	> 240000
2-propanol	5000	nd	< 1000	< 1000	< 1000	1200
acetone	5000	< 1000	< 1000	> 10000	> 10000	> 10000
ethyl formate	5000	nd	nd	< 1000	< 1000	< 1000
acetic acid*	5000	nd	< 3000	16000	> 232000	> 232000
2-butanone (MEK)	5000	< 1000	< 1000	3300	6600	8000
benzene	2	nd	nd	nd	> 4	> 4
toluene	890	< 178	< 178	250	> 1780	> 1780
2-hexanone (MBK)	50	nd	> 100	> 100	> 100	> 100
cumene	70	nd	nd	< 14	70	> 140

New Ingredient Screening

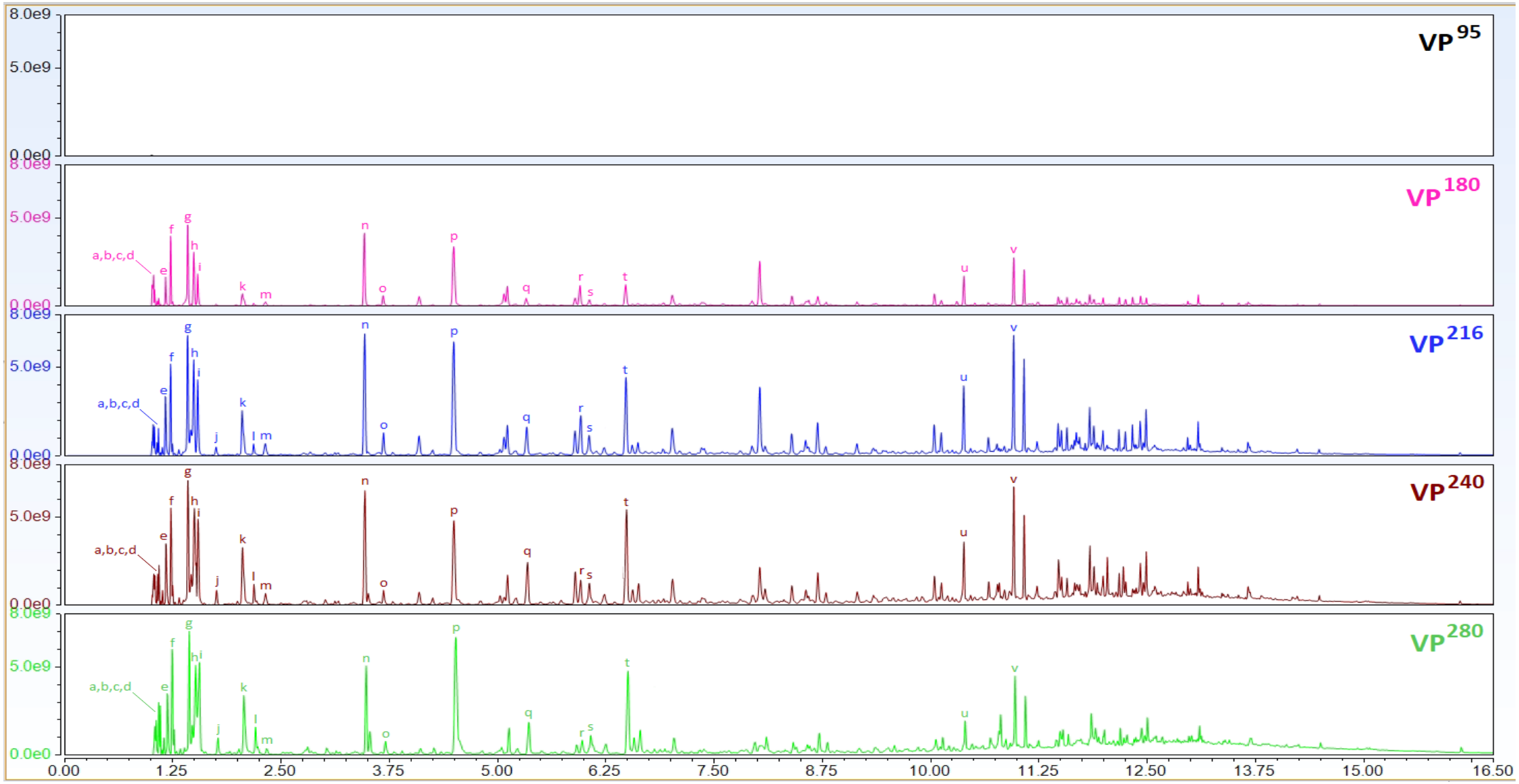
.... Good catch

Not all of the EVALI incidents could be traced to Vitamin E Acetate. In Oregon, Squalene was observed. We were commissioned by Oregon Liquor Control Commission to examine **Squalene (below),** Squalane and Vitamin E Acetate.



Squalene

.... Even worse



Thoughts about Vaporization Temperature

.... Right Direction

Quantitation of Select Terpenes/Terpenoids and Nicotine Using Gas Chromatography–Mass Spectrometry with High-Temperature Headspace Sampling

Trinh-Don Nguyen, Seamus Riordan-Short, Thu-Thuy T. Dang, Rob O'Brien and Matthew Noestheden*

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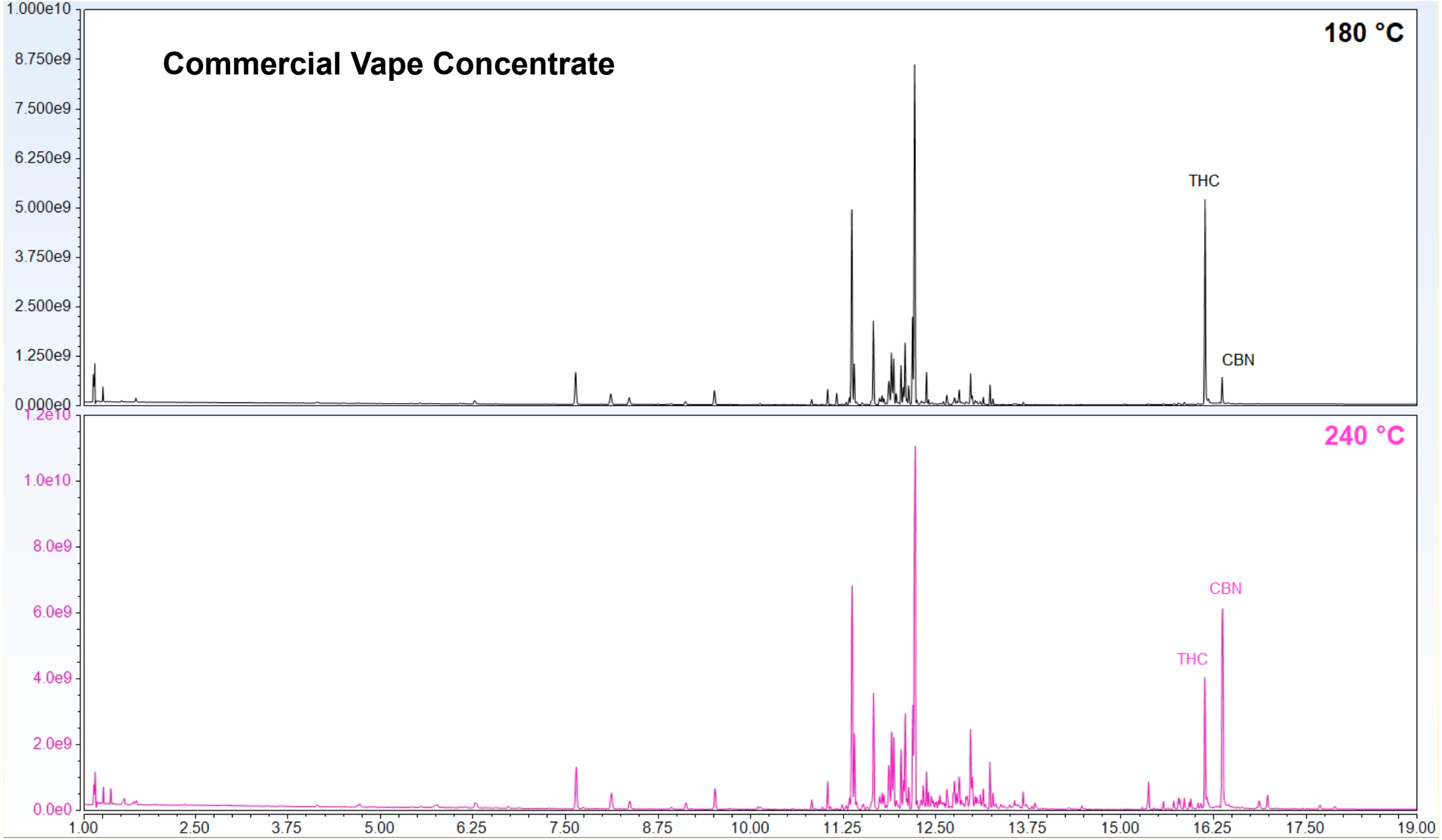
Vaporization Potential

.... more heat less THC



Thank you

…. questions

Questions or Comments??

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