

A Chemist's Perspectives : E-Cigarette liquids Containing Controlled Substances

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TABLE OF CONTENT

01.

INTRODUCTION

- REGULATIONS WORLDWIDE
- MALAYSIA REGULATIONS
- MALAYSIA'S COMMITMENT & CONCERN

02.

CONTROLLED SUBSTANCES IN E-CIG

- NICOTINE
- COMMON DRUGS
- PSYCHOACTIVE COMPOUNDS
- ETOMIDATE
- PSCILOCYBIN?

03.

CONCLUSION

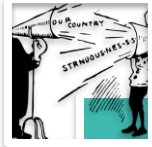
- INSIGHTS
- CHALLENGES IN FORENSIC INVESTIGATION
- RECOMMENDATION & WAY FOWARD

VARIETY IF E-CIGARETTE REGULATIONS WORLDWIDE



Scientific Uncertainty & Data Gaps

- Lacking of long-term safety data. (~20 years)
- Conflicting Research Outcomes. (harm reduction vs health risk)
- Diversity in E-Cig Products (hard to create universal safety guidelines)



Politics & Policy Influence

- Tobacco Control Frameworks (countries support)
- Lobbying and Industry Pressure
- Government Type & Policy Style.



Economic & Trade Considerations

- Taxation & Revenue
- Black Market Risks
- Manufacturing Influence



Public Health Priorities & Approaches

- Harm reduction (E.g. NZ & UK) Vs Prohibition (E.g. S'pore, Thailand)
- Youth Prevention vs Adult Cessation

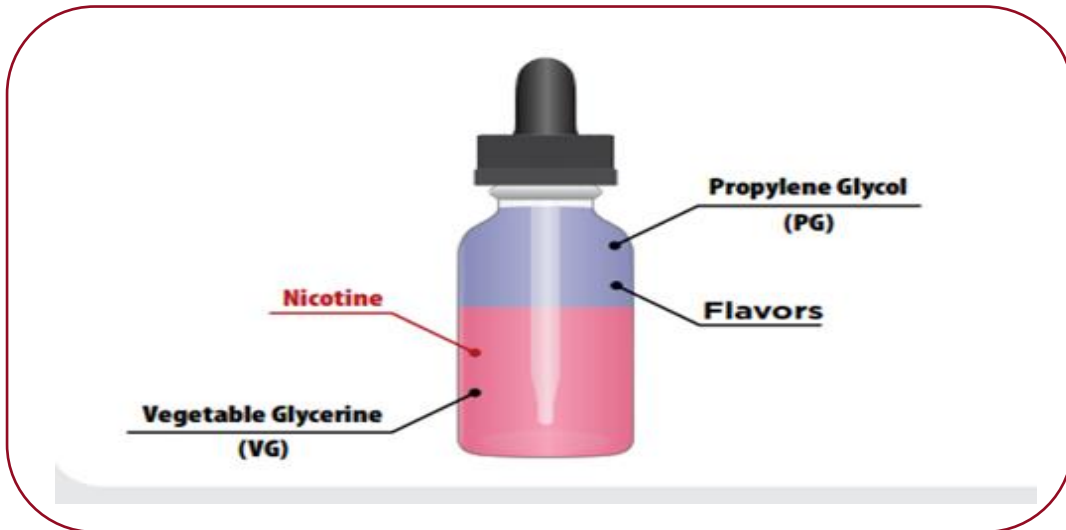
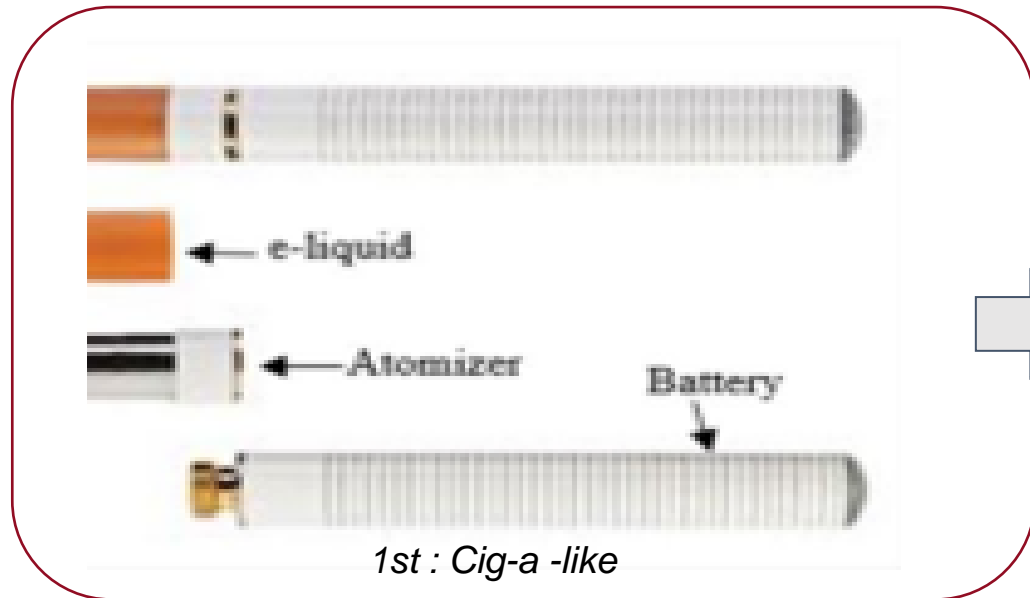


Social & Cultural Factors

- Smoking History & Perceptions (E.g. Countries with strong anti-smoking culture e.g. Aus & Thailand).
- Misinformation & Public Opinion (misunderstand vaping risks, media portrayal)

(I) Dangerous Drug Act 1952
(II) Poison Act 1952

What is E-Cigarettes & E-liquids



• Given increasing economic demand, as at 2024, the e-cigarette market has experienced significant growth and diversification since 2017. The number of unique e-cigarette products increased by over 20% in a year.

TIMELINE

Dangerous Drugs



2015

2016

2017

2018

Oct

Released of **National Strategic Plan for Tobacco Control** (2015-2020).

Nov

Official press statement on EC by **Ministry of Health**.

Nov

The **Ministry of Health** has conducted a first raid on vape stores nationwide.

Dec

National Fatwa Council has decided the rule of EC among Muslim is Forbidden.

Irsyad Al-Fatwa Series 63: The Ruling of E-Cigarette/Vape

(Al-Maidah : 5, 32)(Al-Baqarah,195)

Jan

Jan 2016: Johor is the first state banned EC.

Followed by Kelantan state.

Dec

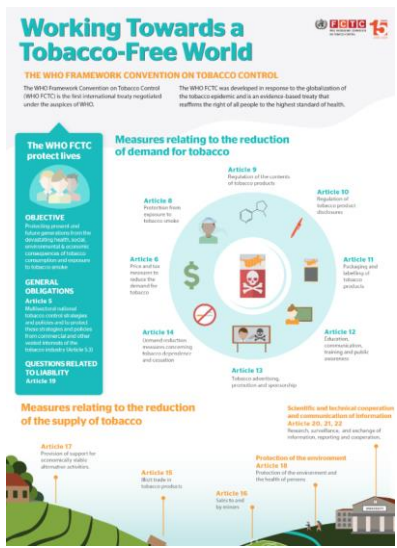
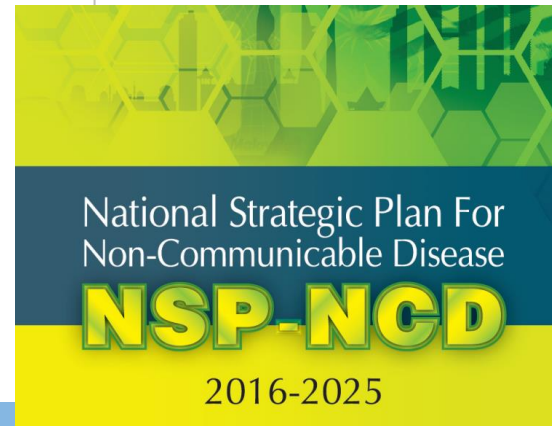
Three ministries have given a task to regulate EC use in Malaysia

- i. Ministry of Domestic Trade and Consumer Affairs.
- ii. Ministry of Health (MOH)
- iii. Ministry of Science, Technology & Innovation (MOSTI)

Feb

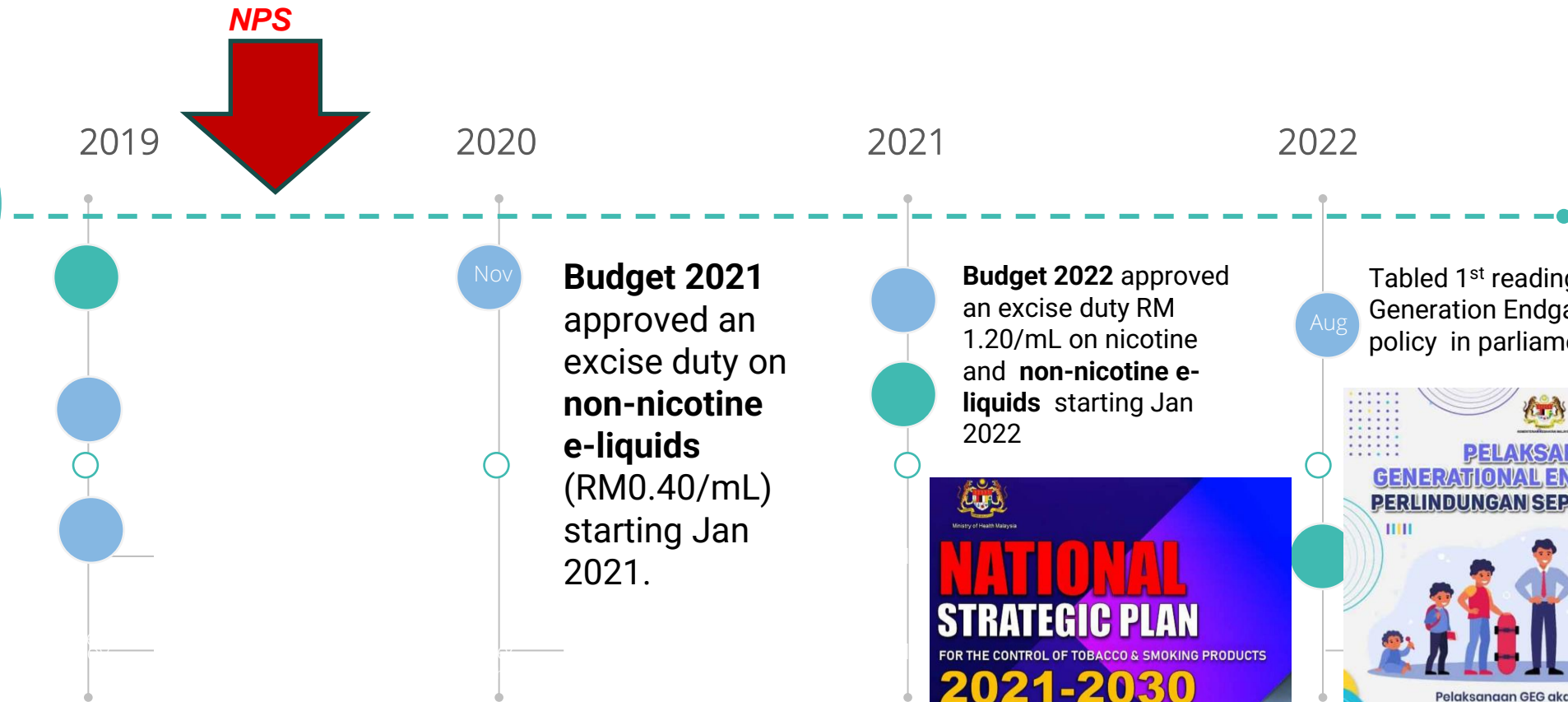
Ministry of Health conducted a massive raid across the country

Department of Chemistry Malaysia ,MOSTI receive the raid exhibit for analysis.



WHO Framework Convention on Tobacco Control (WHO FCTC)

TIMELINE



Budget 2021 approved an excise duty on **non-nicotine e-liquids** (RM0.40/mL) starting Jan 2021.

Budget 2022 approved an excise duty RM 1.20/mL on nicotine and **non-nicotine e-liquids** starting Jan 2022



Tabled 1st reading of Generation Endgame (GEG) policy in parliaments.



WHO Framework Convention on Tobacco Control (WHO FCTC)

END GAME TOBACCO USE BY 2045

TIMELINE



WHO Framework Convention on Tobacco Control (WHO FCTC)

END GAME TOBACCO USE BY 2045

GROWING PUBLIC CONCERNS

Fellow pharmacist friends, in the last few months I've noticed a few young males coming in macam zombie-suddenly aggressive, disinhibited, fitting, insomnia and psychosis. Semua dirawat sebagai otak berkuman. Urine drug test negative for cannabinoids/meth/BZDs.

There were at least 4 cases in my primary hospital and another 2 in my other hospital in the last 2 months.

Semua jantan, in teens/early 20s and all of them vape. Last week 2 of them were just in my ward together. So I had the chance to ask them to Google and show me the brand.

Also minta the accompanying Mums to bring me the vapes. Sama weh.

What's the correct way to check the substance in it or report it?

TIK TOK



Khayal hisap vape, murid tingkatan dua cedera jatuh bumbung



by Admin - November 14, 2024



KANGAR: Seorang murid tingkatan dua dari sebuah sekolah menengah di daerah Kangar, cedera di kaki selepas terjatuh dari bumbung tingkat satu sebuah bangunan di sekolah itu.



Ibu bapa dan guru ini pattern terbaharu Vape yg dijumpai oleh guru dalam Beg sekolah anak murid.. Mohon pantau anak tuan puan Penyalahan Penggunaan Vape di kalangan Kanak2 bawah umur.. Elakan Bahaya Vape Perisa Mushroom.. Lindungi anak Generasi Kita dr Bahaya Penyalahan Penggunaan Dadah.. Info drpd

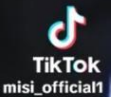


Vape perlu diharamkan secara total, titah Sultan Pahang

Bernama
18/11/2024 20:16 MYT



Bagi mengekang penyalahgunaan dadah, baginda bertitah semua pihak perlu berganding bahu memerangi masalah



CONCERNS FROM EC-LIQUIDS

- Studies on cigarette composition date back to the 1960S, e-cigarette liquid analysis began around 2010s, intensifying after 2015.

NICOTINE

addiction

ULTRA FINE PARTICLES/ HEAVY METALS

Ex: Nickel, tin and lead-
harmful to lungs



FLAVORANTS

Ex: Diacetyl , a chemical linked to
serious lung disease



VOLATILE ORGANIC COMPOUNDS (VOCs)

Ex: Benzene, Acrylamide,
Propylene Oxide –
Compounds that linked to
EVALI Disease. (WHO,2021)

ILLICIT DRUGS

Ex- Cannabis Related , New Psychoactive
substances(NPS), Other Substances

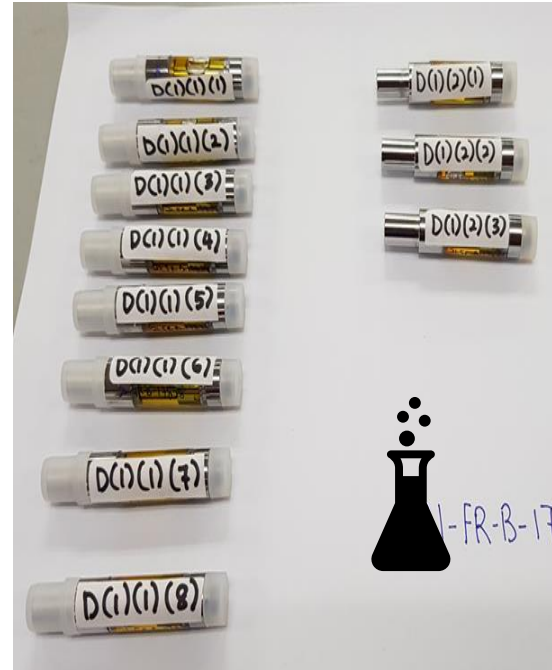
TYPES OF E-LIQUIDS ENCOUNTERED

NICOTINE ONLY



NICOTINE WITH OTHER SUBSTANCES

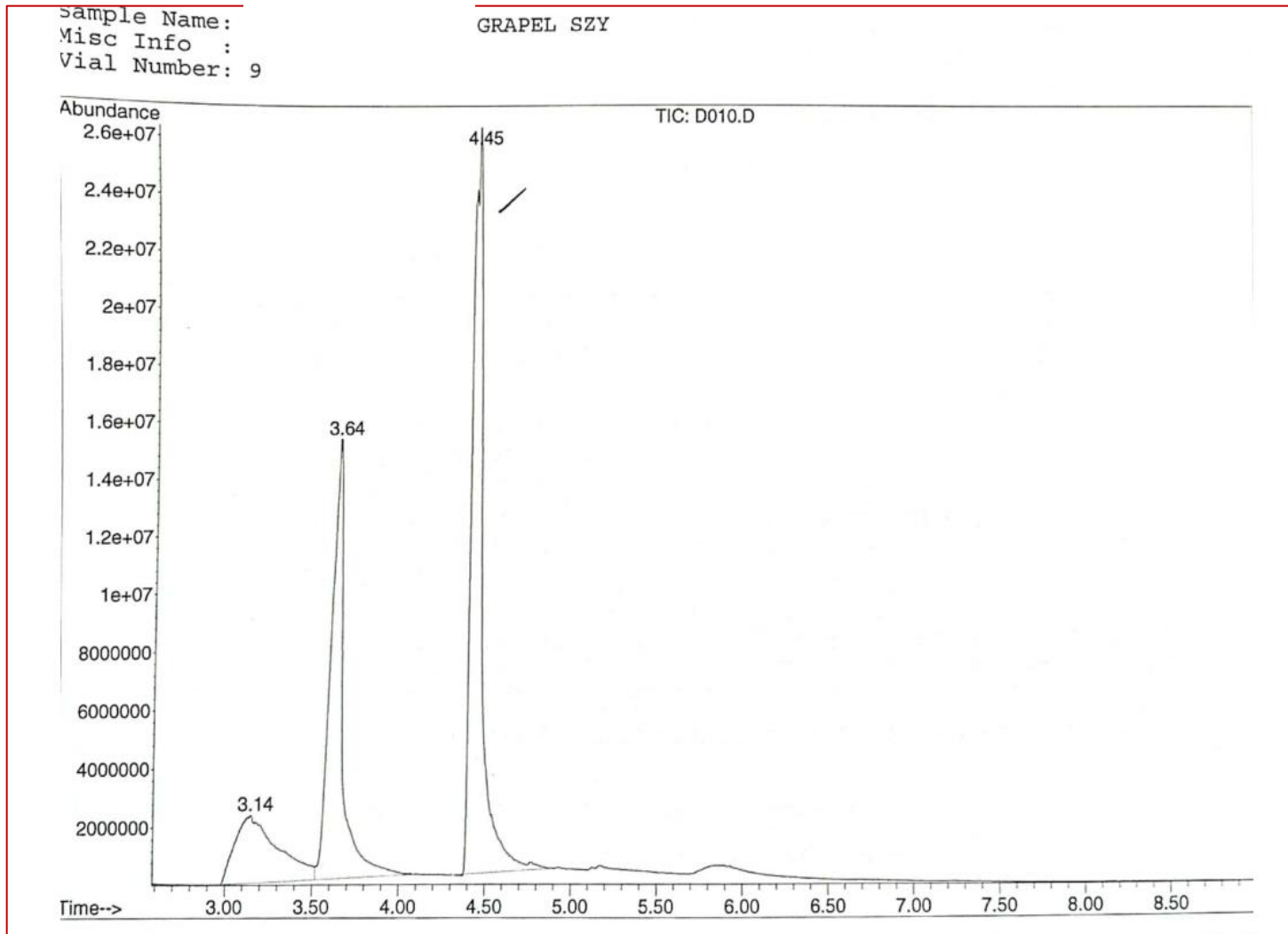
CANNABIS - RELATED



OTHER SUBSTANCES



(1) E-LIQUIDS (NICOTINE ONLY)



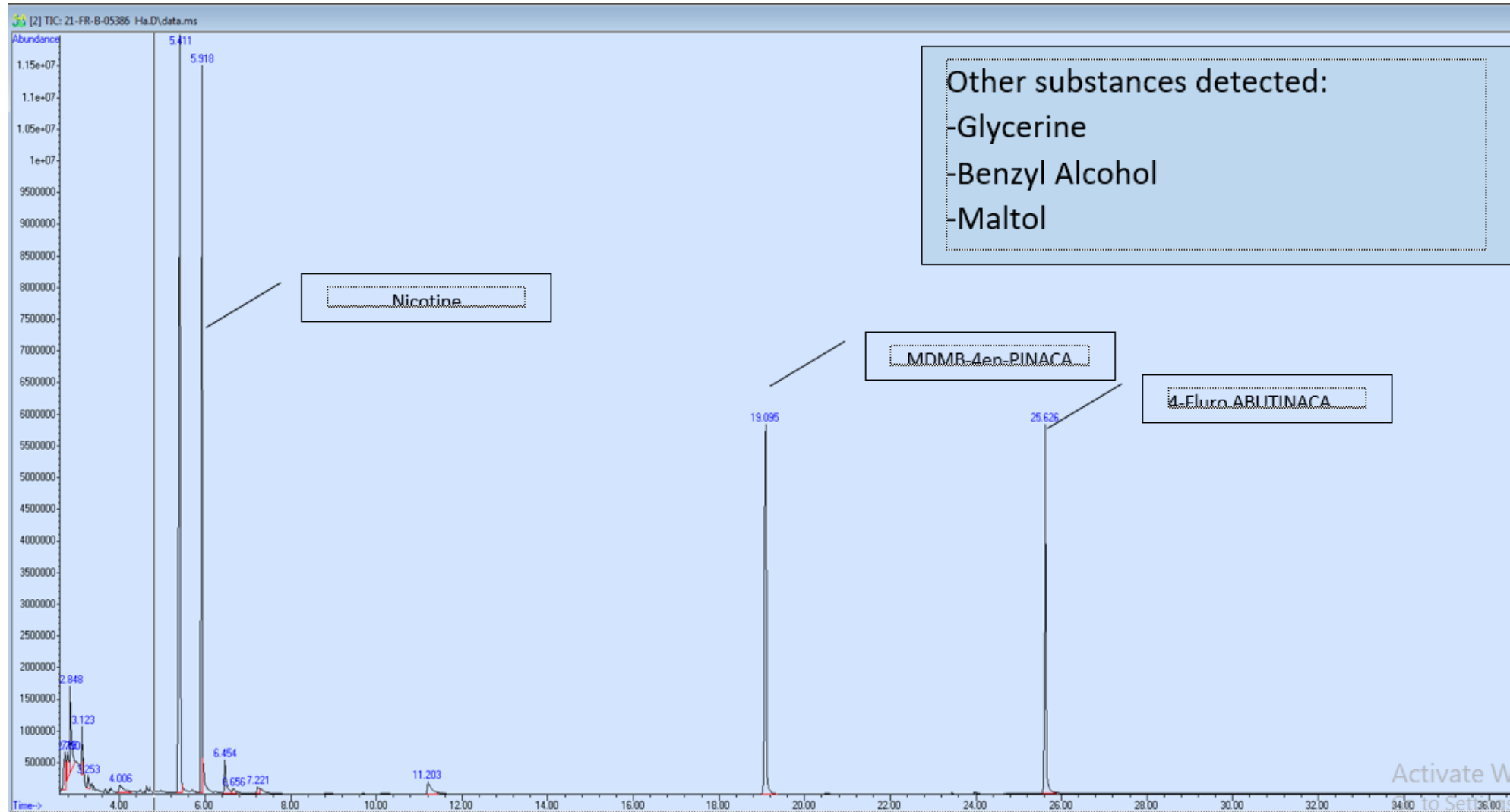
- Extraction using 1-Chlorobutane
- GCMS temperature programme :
80 °C (0.5min) → 280 °C (6 min) at 35./min,
injection temperature 260°C,
run time 10 min.



(2) E-LIQUIDS (NICOTINE + NPS)



(2) E-LIQUIDS (NICOTINE + NPS)



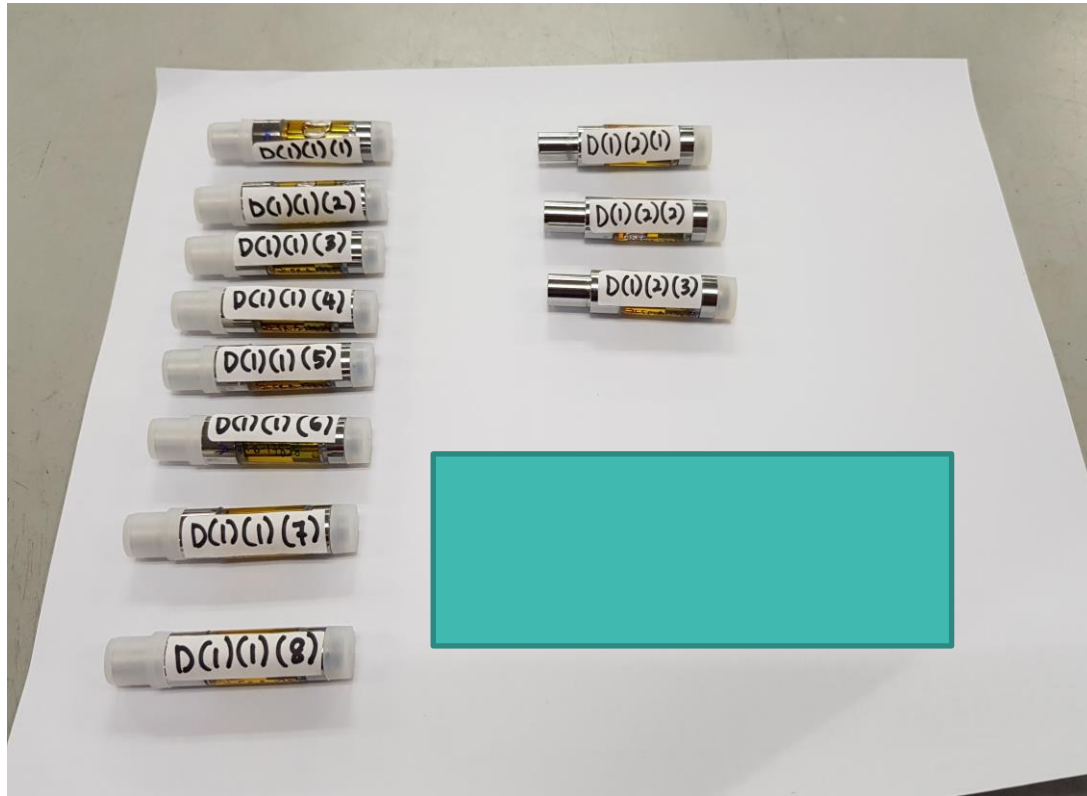
Extraction using absolute ethanol

GCMS

temperature programme :
80 °C (1.3min)--→
280 °C (6 min) ,
Inlet temperature
250°C, run time
40 min

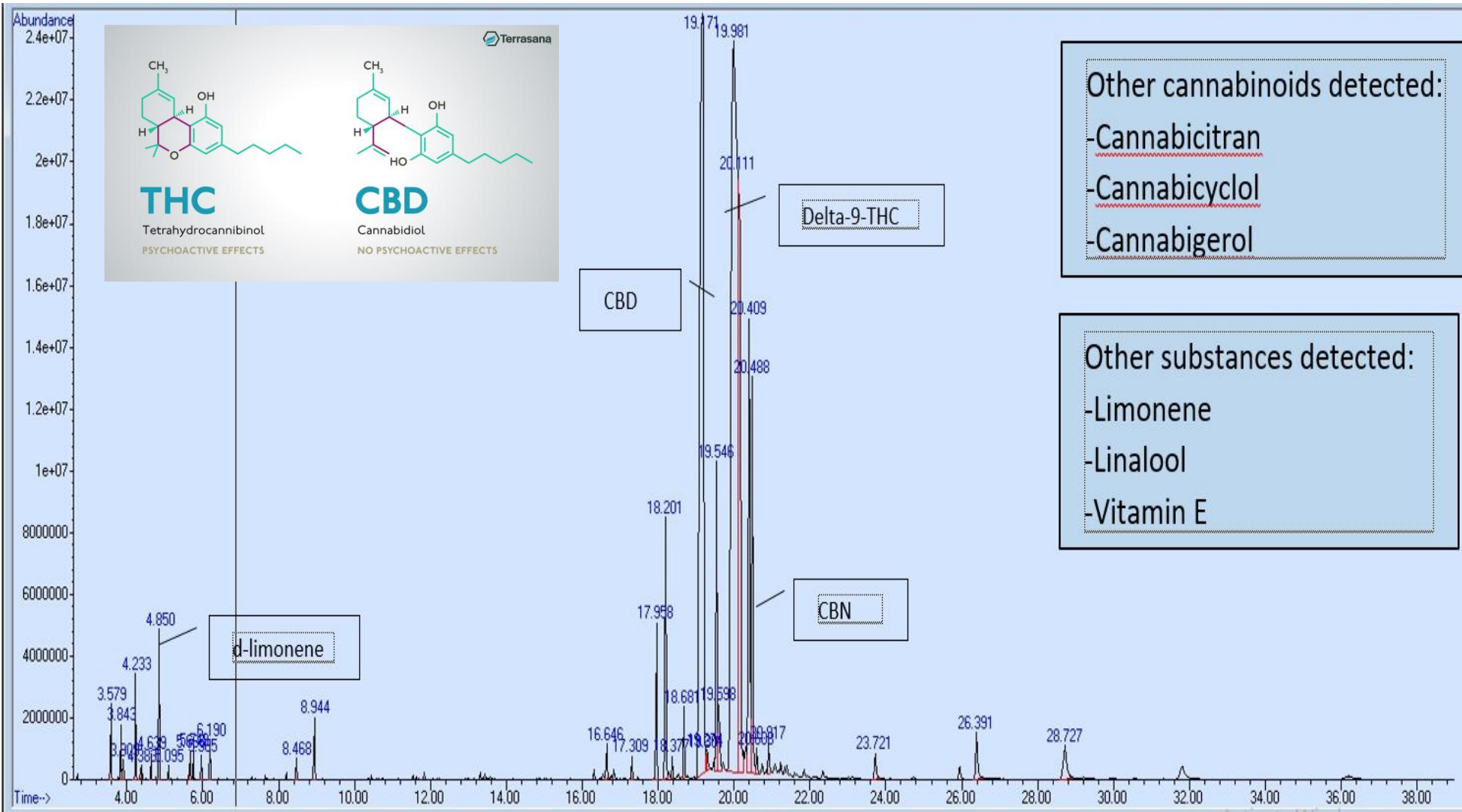


(3) E-LIQUIDS (CANNABIS RELATED)



- The Centers for Disease Control and Prevention (CDC) reported that approximately 80% of EVALI (E-Cigarette or vaping Product use-Associated Lung Injury) patients had used THC-containing vaping Products, many from informal sources. (CDC,2020)

(3) E-LIQUIDS (CANNABIS RELATED)



Other cannabinoids detected:
-Cannabicitran
-Cannabicyclol
-Cannabigerol

Other substances detected:
-Limonene
-Linalool
-Vitamin E

EXTRACTION USING ABSOLUTE ETHANOL

GCMS temperature programme :
80 °C (1.3min)--→ 280 °C (6 min) , Inlet temperature 250°C, run time 40 min



(3) E-LIQUIDS (CANNABIS RELATED)

▶ [Addict Behav.](#) Author manuscript; available in PMC: 2022 Oct 1.

Published in final edited form as: [Addict Behav. 2021 May 14;121:106990. doi: 10.1016/j.addbeh.2021.106990](#) [↗](#)

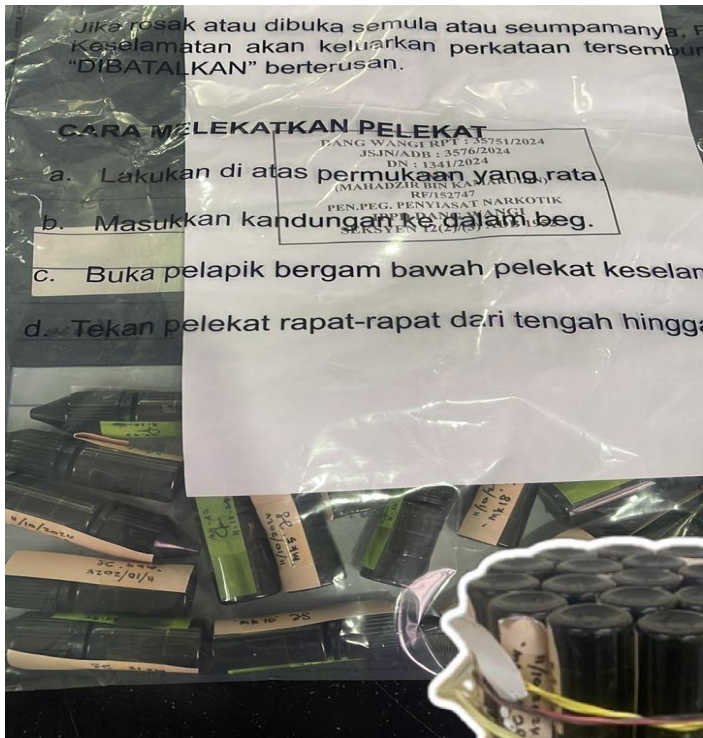
Tetrahydrocannabinol (THC)-containing e-cigarette, or vaping, product use behaviors among adults after the onset of the 2019 outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injury (EVALI)

[Katrina F Trivers](#)^a, [Christina V Watson](#)^a, [Linda J Neff](#)^a, [Christopher M Jones](#)^b, [Karen Hacker](#)^c

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PMCID: PMC8764700 NIHMSID: NIHMS1760286 PMID: [34087764](#)

(4) E-LIQUIDS (SYNTHETIC CANNABINOIDS)



(a) 5-Fluoro-ADB



(b) Nicotine + ADB-BUTINACA



(c) Nicotine + ADB-BUTINACA



(d) Negative



(e) Nicotine + 5F-ADB

(f) Nicotine + ADB-BUTINACA + MDMB - BUTINACA



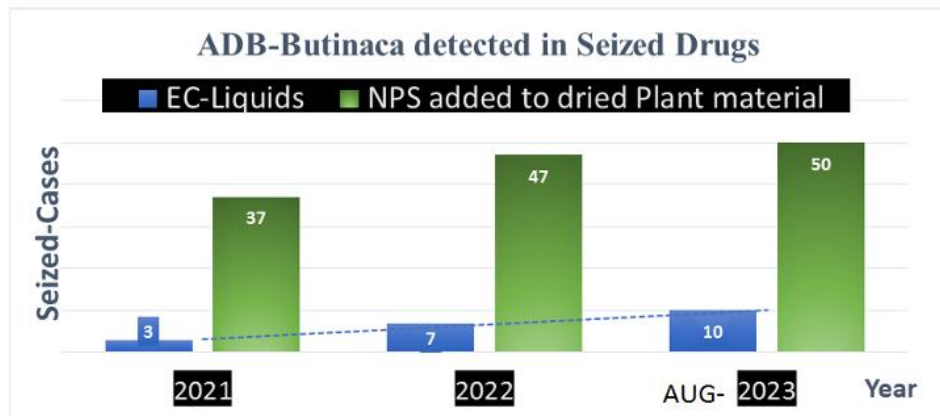
(g)

Liquid form used in e-cigarettes, vape pens, hookah pens



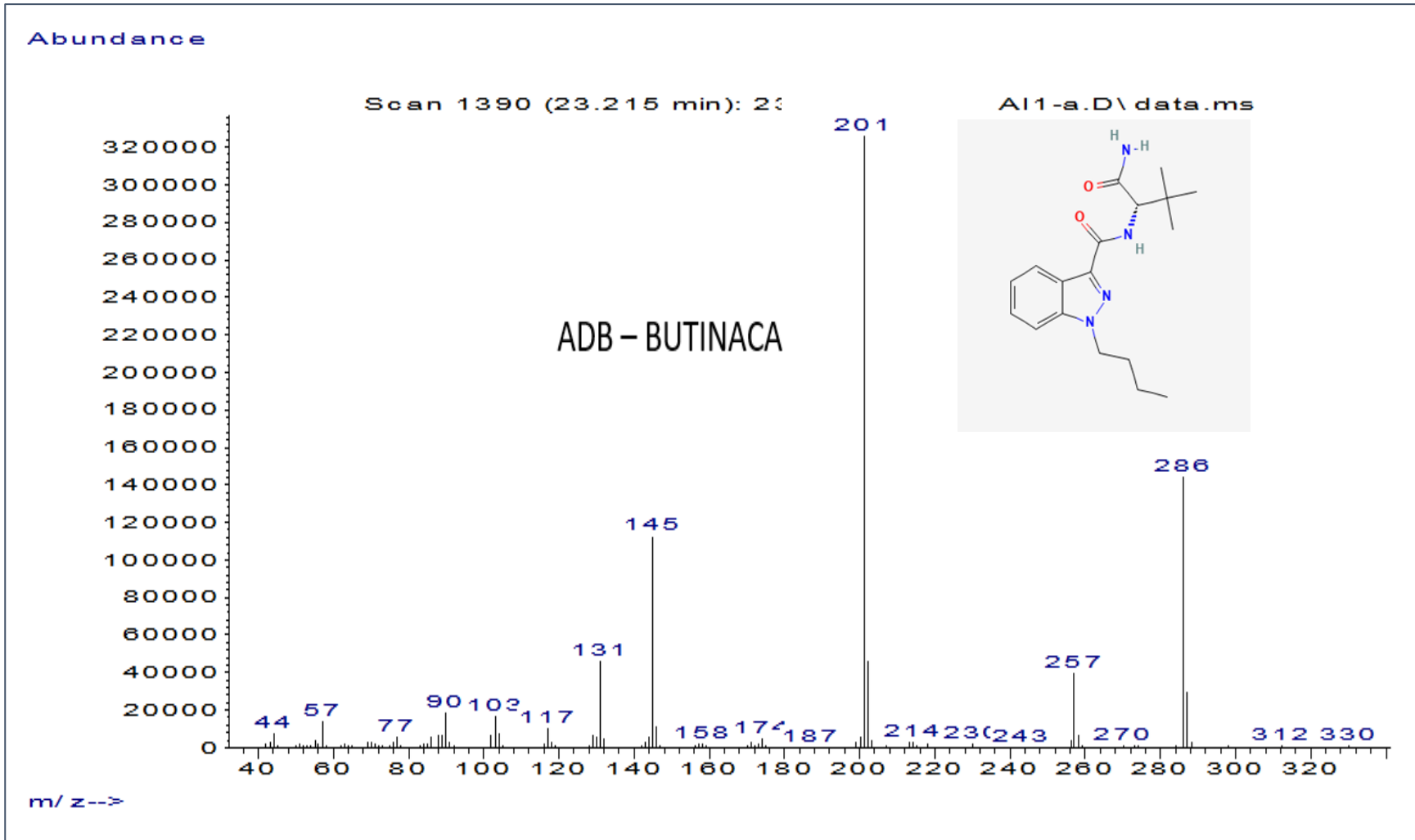
SYNTHETIC CANNABINOIDS

- Synthetic cannabinoids are sold under hundred of names.
- They are dissolved in solvent (e-cig liquids) or sprayed onto inert plant material, which is saturated and dried, leaving highly variable amounts of the substance.
- They are marketed as safe and legal alternatives to marijuana but are in fact more potent.



PIC Source: University of Melbourne

(4) E-LIQUIDS (SYNTHETIC CANNABINOIDS)



EXTRACTION USING ABSOLUTE ETHANOL

GCMS temperature programme :
80 °C (1.3min)--→
280 °C (6 min) , Inlet temperature 250°C, run time 40 min



(4) E-LIQUIDS (SYNTHETIC CANNABINOIDS)

No	NPS --> Dangerous Drugs Act 1952	Poison List?
1	N-[(2S)-1-Amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1H-indazole-3- carboxamide (ADB-CHMINACA, MAB-CHMINACA)	Yes
2	N-[(2S)-1-Amino-3,3-dimethyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl) methyl]-1Hindazole-3-carboxamide (ADB-FUBINACA)	Yes
3	N-[(2S)-1-Amino-3-methyl-1-oxobutan-2yl]-1(cyclohexylmethyl)-1H-indazole-3- carboxamide (AB-CHMINACA)	Yes
4	N-[(2S)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-pentyl-1Hindazole-3-carboxamide (AB-PINACA)	Yes
5	Methyl 3, 3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido) butanoate (MDMB-4en-PINACA)	Yes
6	Methyl (2S)-2-[[1-(5-fluoropentyl)-1H-indazole-3-carbonyl] amino]-3,3- dimethylbutanoate (5F-ADB/5F-MDMB-PINACA)	Yes
7	Methyl(2S)-2-([1-[(4-fluorophenyl)methyl]-1H-indazole-3-carbonyl] amino)-3- methylbutanoate (FUB-AMB)	Yes
8	1-(4-Cyanobutyl)-N- (2-phenylpropanoate)-1H-indazole-3- carboxamide (CUMYL-4CN-BINACA) (DD)	Yes
Akta Racun 1952		
1	N-(Adamantan-1-yl)-1-(5-fluoropentyl)- 1H-indazole-3-carboxamide (5F-APINACA)	
2	N-(Adamantan-1-yl)-1-pentyl-1H-indazole-3-carboxamide (APINACA)	
3	-[(2S)-1-Amino-3-methyl-1- oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide (AB-FUBINACA)	
4	N-[[1-(Cyclohexylmethyl)-1H-indol-3-yl]carbonyl]-3-methyl-L-valinate (MDMB-CHMICA)	
5	2-[[1-(4-Fluorobutyl)- 1H-indazole-3- carbonyl]amino]-3,3- dimethylbutanoate (4-F-MDMB-BINACA, 4F-ADB, 4F-MDMB-BUTINACA)	
6	Methyl 2-([1-(5-fluoropentyl)-1H-indazole-3-yl] carbonyl)amino)-3- methylbutanoate (5F-AMB)	
7	ethyl (2S)-2-[[1-(5- fluoropentyl)-1H-indole-3-carbonyl]amino]-3,3- dimethylbutanoate (5F-MDMB-PICA)	

SYNTHETIC CANNABINOIDS (SCS) AND REGULATORY CHALLENGE

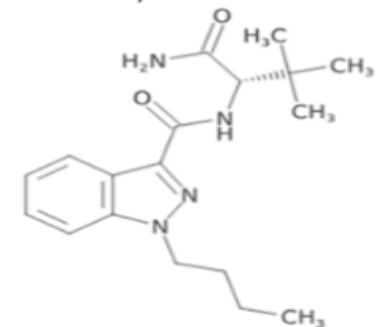
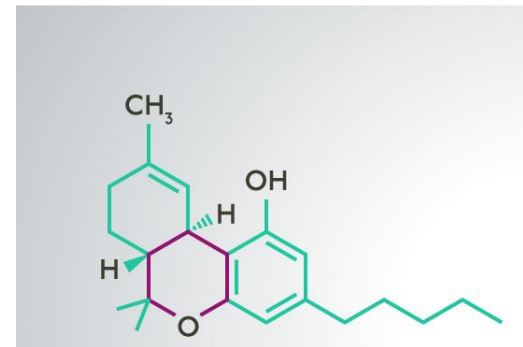
- **Synthetic cannabinoids (SCs) evolve rapidly** due to **chemical structure modifications**. Manufacturers alter components like the core, tail, linker, and linked groups to **circumvent legal controls**, leading to a diverse array of SCs.
- In Malaysia, SCs are regulated under the **Dangerous Drugs Act 1952 (DDA 1952) and Poison Act 1952**, with substances being **listed by specific names**. This approach can be challenging as new SCs with slight structural changes may not be covered until officially added to the list.
- In contrast, countries like **Australia** and **Hong Kong** implement **structure-based regulations**, banning entire classes of compounds based on their chemical frameworks.
- This method aims to proactively control new SC variants by targeting their core structures rather than individual names.

Key Differences Between THC and Synthetic Cannabinoids

Feature	THC (Natural)	Synthetic Cannabinoids
Source	Cannabis plant	Lab-synthesized
Receptor Affinity	Moderate (CB1/CB2)	High, often selective for CB1
Potency	Mild	Can be 100x stronger than THC
Metabolism	Liver enzymes	Slower metabolism, longer-lasting
Toxicity	Low	High (psychosis, seizures, cardiac arrest)

Key Differences in Chemical Structure

Feature	THC (Δ^9 -Tetrahydrocannabinol)	ADB-BUTINACA (Synthetic Cannabinoid)
Core Structure	Dibenzopyran ring	Indazole core
Functional Groups	Hydroxyl (-OH) at C1	Amide (-NHCO) and indazole rings
Binding Affinity	Moderate CB1 activation	High CB1/CB2 activation, more potent
Lipophilicity	Moderate	Higher due to additional alkyl chains
Potency	Lower (natural metabolism)	Stronger and longer-lasting



Source: PubChem

(5) E-LIQUIDS (ETOMIDATE) – A NEW CONCERN IN E-CIGARETTES



ETOMIDATE - A NEW CONCERN IN E-CIGARETTES

- **What is Etomidate?**

- A short-acting intravenous anesthetic used in medical settings.
- **CNS depressant with sedative properties.**
- Potential misuse in illicit drugs for sedative effects.

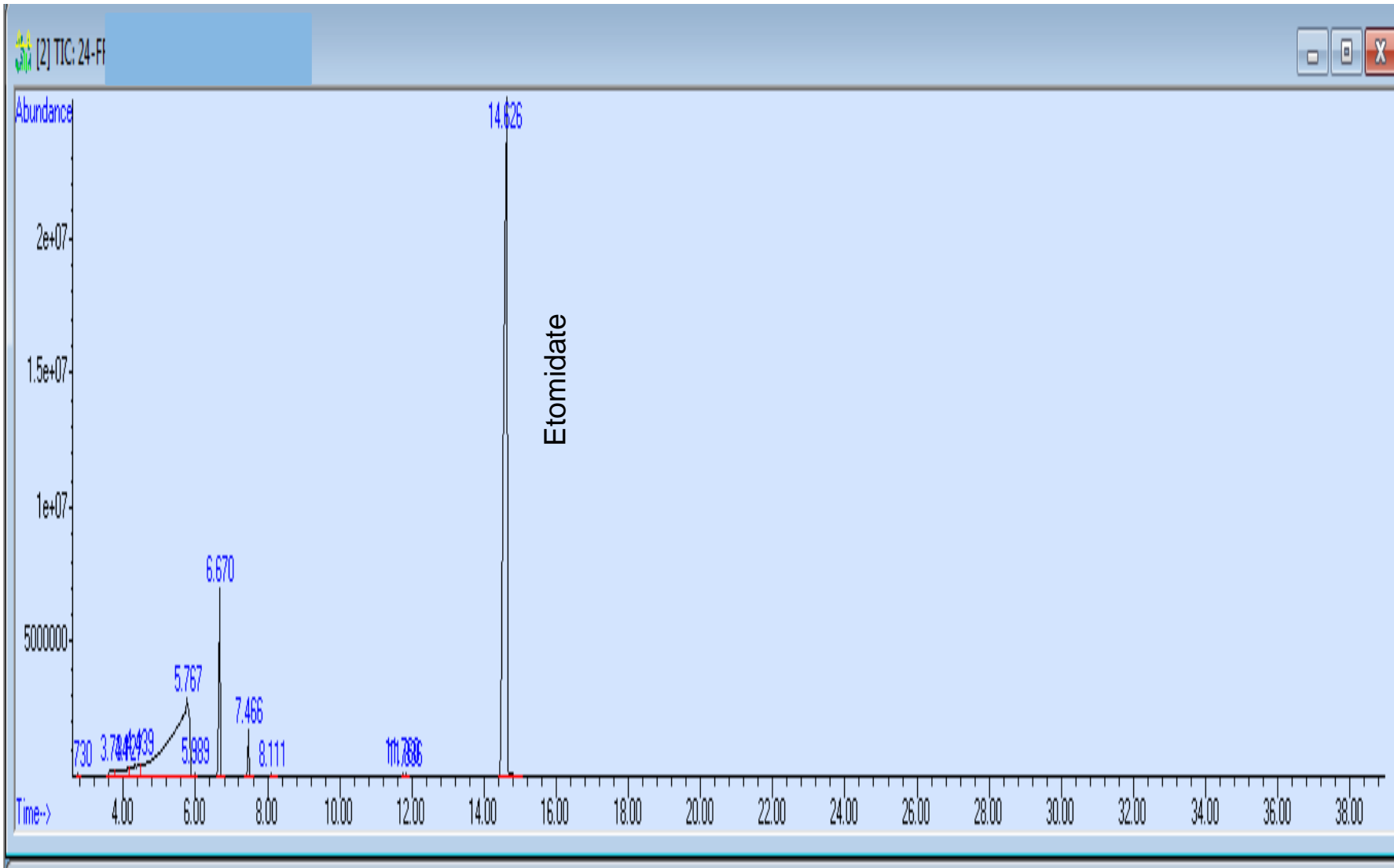
- 2. Why is Etomidate a Concern in E-Cigarettes?

- **Illicit Use in Vaping Liquids:** There have been reports of etomidate being detected in e-liquids.

- **Potential for Abuse:** Since etomidate induces sedation and altered consciousness, it may be misused and another innovative ways for recreational purposes when mixed into e-liquids.

- **Legal Status:** While etomidate is a regulated pharmaceutical, its presence in e-liquids violate drug control laws - the Poisons Act 1952 in Malaysia.

(5) E-LIQUIDS (ETOMIDATE)



EXTRACTION USING ABSOLUTE ETHANOL

GCMS temperature programme :
80 °C (2.0 min) --→
280 °C (5 min) , Inlet temperature 250°C, run time 40.5 min



THE PRESENCE OF CONTROLLED SUBSTANCES IN E-LIQUIDS

- **Nicotine** : Poison Act 1952.
- **Cannabis-related Compounds**: Delta-9-THC (Dangerous Drugs Act 1952).
- **Synthetic Cannabinoids**: Eg:MDMB-4en-PINACA, 4-Fluoro-ABUTINACA etc (Dangerous Drugs Act 1952 & Poison Act 1952)
- **New Trends: The emergence of Etomidate in Vape Liquids. (Poison Act 152)**
- **New Trends : The emergence of Magic Mushroom (Psilocybin/Psilocin) in EC-liquids?? (Dangerous Drug Act 1952)**

Psilocine, Psilocin, 3-(2-dimethylaminoethyl)-4-hydroxyindole

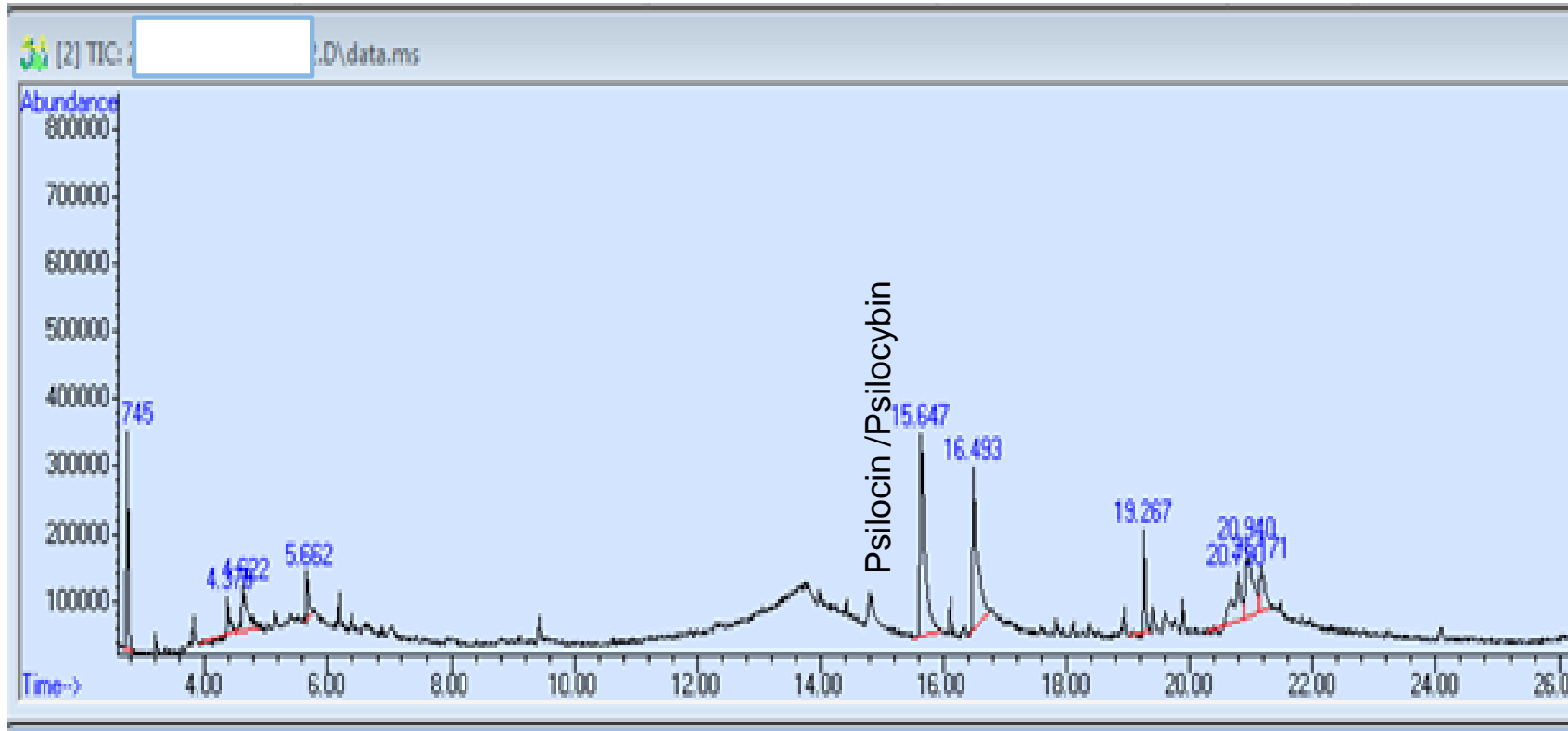
Psilocybine, 3-(2-dimethylaminoethyl)-indol-4-yl dihydrogen phosphate

MAGIC MUSHROOMS

- **Active Ingredients**
- Psilocybin, the primary psychoactive compound in magic mushrooms, is converted into psilocin once ingested. This conversion happens naturally in the body but can also occur in the vaporizing process. The magic mushroom vape cartridges typically contain either psilocybin or psilocin extracts, depending on the formulation.



GCMS RESULTS FROM THE “MAGIC MUSHROOM”

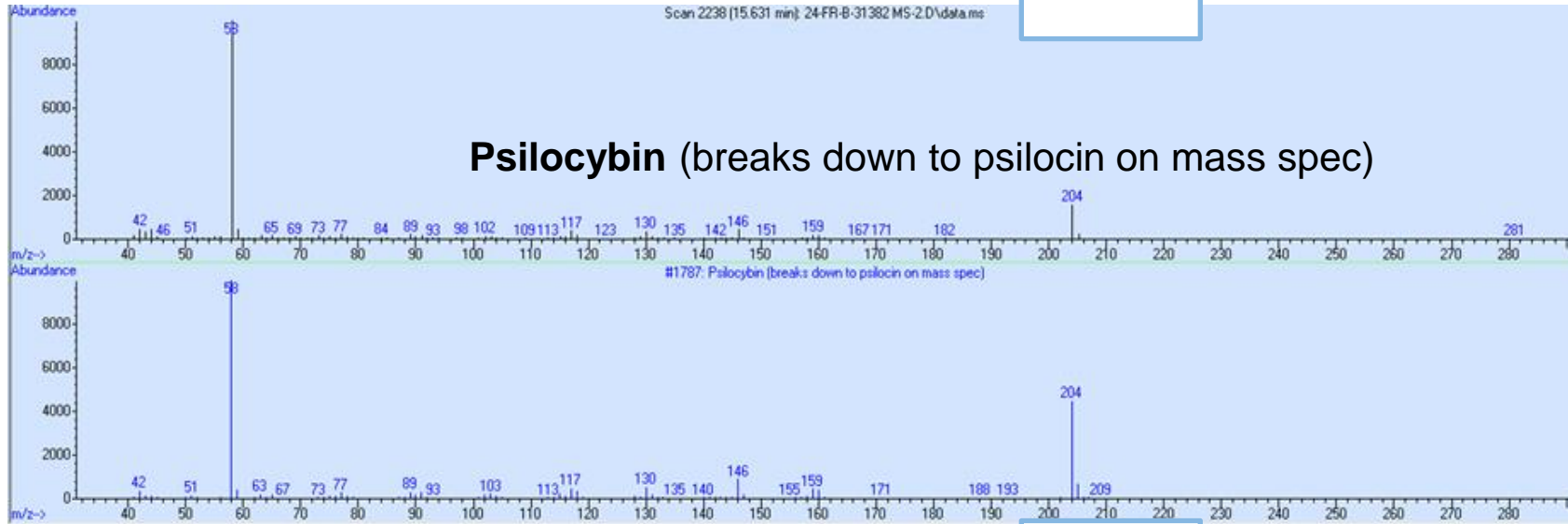


LIQUID - LIQUID EXTRACTION

- GCMS temperature programme :
- 80 °C (2.0 min) --→ 280 °C (5 min), Inlet temperature 250°C, run time 40.5 min



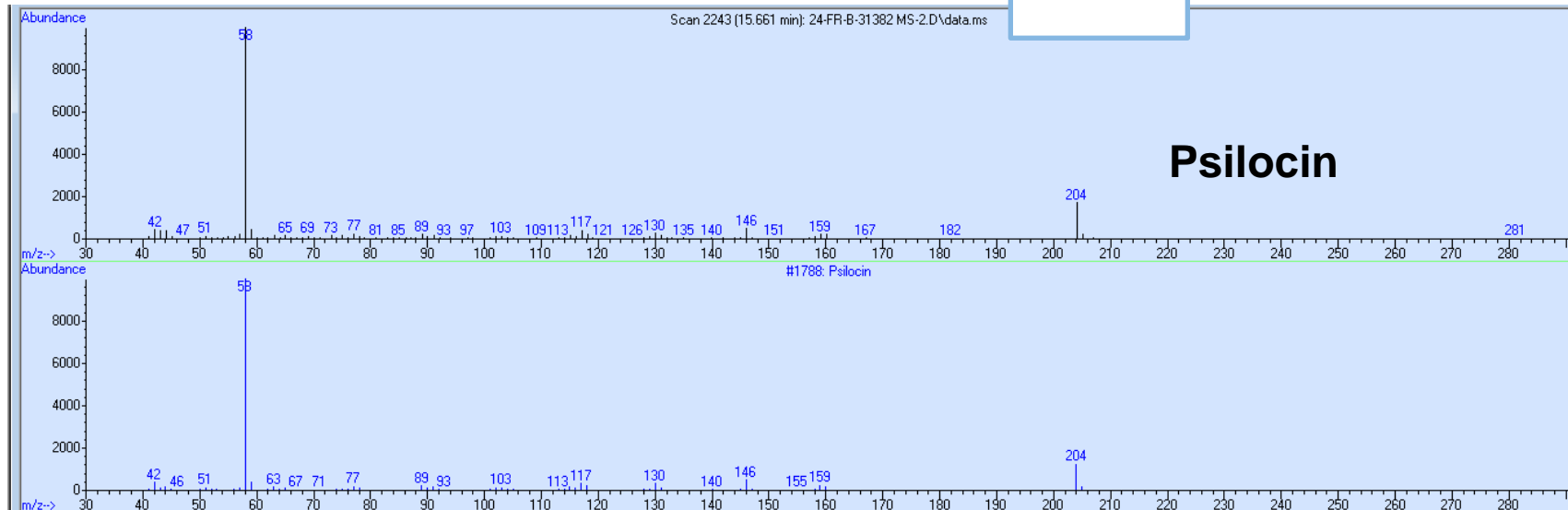
GCMS RESULTS FROM THE "MAGIC MUSHROOM"



Psilocybin = Prodrug

Psilocybin itself has no direct psychoactive effects.

Once ingested, the body metabolizes it into psilocin, which binds to serotonin receptors, producing hallucinogenic effects.



PSILOCYBIN AND PSILOCIN ANALYSIS IN EC LIQUIDS BY USING GCMS

- Detecting **psilocybin** or other psychoactive substances in vape liquids involves additional challenges due to the complex matrix, which often includes propylene glycol (PG), vegetable glycerin (VG), flavoring agents, and sometimes nicotine or illicit substances.

• Optimized Extraction Method for Vape Liquids

1. Sample Preparation:

- Dilute the vape liquid with **water or methanol** (1:10 or 1:20 dilution) to reduce viscosity and improve solubility of the active compounds.

2. Liquid-Liquid Extraction (LLE):

- Add an organic solvent (e.g., **chloroform** or **ethyl acetate**) to extract psilocybin. The polarity of psilocybin may require adjusting the pH:
 - Acidify the solution to pH ~2-3 with **HCl** to convert psilocybin into a protonated form.
 - Extract with an organic solvent.

3. Derivatization:

- Add **BSTFA with 1% TMCS** to the cleaned extract.
- Heat at **70–80°C for 30 minutes** to form the trimethylsilyl (TMS) derivative of psilocybin.



- We detect **negative** psilocybin and psilocin as to date.

•Source: *Forensic Science International* and *Journal of Analytical Toxicology & Trends in Analytical Chemistry (TRAC)*.

MISLEADING STATEMENT -AS AT TO DATE (19 FEB 2025)

- Recent news/reports/ social media posts have highlighted concerns about vape liquids branded as “Magic Mushroom.” According to the **National Poison Centre of Universiti Sains Malaysia**, individuals who used these products have experienced symptoms such as **mental delirium and severe abnormal behavior**.
- As the leading scientific provider in Malaysia ,the **Narcotic Division, Forensic Science Analysis Centre, Department of Chemistry Malaysia**, has clarified that while these vape liquids are marketed as containing “Magic Mushroom,” this is misleading.



MISLEADING STATEMENT -AS AT TODATE 19 FEB 2025

- Upon analyzing samples suspected to contain **psilocybin or psilocin**, the investigation found that they actually contained **synthetic drugs** rather than the naturally occurring psychedelic compound found in fungi.
- Despite the branding, these products have **no connection to psilocybin**.
- Instead, the detected **synthetic substances pose a greater health risk**, with the potential to cause **severe and possibly fatal poisoning symptoms**



INSIGHTS

- The lack of legal regulation over vape products is starting to affect the public.
- With each passing moment, more individuals fall into drug dependency through the rising trend of vape smoking.
- The public should stay vigilant for potential cases of synthetic drug poisoning, particularly in individuals experiencing unexplained mental confusion, seizures, or cardiovascular issues after vaping.
- Report to the authorities, and submit vape devices or e-liquids for laboratory analysis, as conventional field urine tests cannot detect synthetic drugs.

RECOMMENDATIONS & THE WAY FORWARD

- As e-cigarettes continue to rise in popularity, completely banning them could drive the market underground, increasing the illicit trade of unregulated and potentially harmful products. Instead, a more effective approach would be to focus on strict control measures, including:
 - **(1) Stronger Enforcement & Regulations**
 - Implementation of the Control of Smoking Products for Public Health Act 2024, effective 1 Oct 2024.
 - Ensuring better oversight of e-liquid composition and preventing the sale of illicit products.
 - **(2) Expansion of Laboratory Capabilities**
 - Strengthening drug screening using advanced analytical techniques such as LC-MS/MS to detect emerging adulterants in e-liquids.
 - **(3) Public Awareness Campaigns**
 - Educating consumers on the health risks of illicit and adulterated e-liquids.
 - Encouraging informed choices rather than relying on misleading industry claims.

RECOMMENDATIONS & THE WAY FORWARD

(4) Continuous Monitoring & Research :

- Establishing long-term surveillance on adulterated vape products, particularly those containing synthetic cannabinoids, illicit drugs, and toxic additives.

(5) SCs Structure-Based Regulation : Instead of listing synthetic cannabinoids (SCs) individually, adopting a structure-based regulation that bans entire chemical families, making it harder for new SCs to escape legal control.

(6) A Dedicated E-Cigarette Quality Control Centre :

Since e-cigarettes are difficult to ban, a dedicated regulatory center should be established to:

- ✓ Monitor and test e-liquids for harmful substances.
- ✓ Ensure product quality control before distribution.
- ✓ Implement standardized nicotine concentration limits.
- ✓ Identify and regulate new psychoactive substances in vaping products.

By taking proactive measures , we can protect public health, reduce illicit trade, and ensure safer consumer choices.

THANK YOU

FOR YOUR TIME



•Ts. ChM. SITI ZUBAIDAH BINTI MOHD YUSOFF
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