Toxicological assessment of aerosols emitted by cannabis inhalation methods: Does cannabis vaping using Electronic Non-Nicotine Delivery Systems (ENNDS) and vaporizers reduce exposure to toxicants compared to cannabis smoking?

Final report

(Contract ID: 142004544 / 321.4-4/46)

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Funded by:

Federal Office of Public Health (FOPH)
Scientific foundations section

Lausanne, on June 23rd, 2023

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Summary

Cannabis is mainly consumed by smoking joints, exposing users to high concentrations of various toxicants. Users are increasingly interested in potential safer alternatives to inhale cannabis, and thus reduce their exposure to toxicants. These alternatives, referred as method of inhalation in this report, include cannabis vaporizers and cannabis extract vaping using an electronic non-nicotine delivery system (ENNDS). However, a review of the literature confirmed that very few studies investigated the toxicological profiles of these alternatives in laboratory conditions and compared them to joints. Therefore, this study aimed to generate original data on the toxicity of cannabis aerosols emitted by vaporizers and ENNDS in comparison to cannabis smoke (without tobacco) using a smoking machine to generate emissions and by quantifying the concentrations of 91 compounds in emissions.

We identified 9 studies on the characterization of emissions from cannabis joints, 10 on vaporizers and 14 studies on toxicants and carcinogens released in ENNDS emissions. All studies on joints confirmed that combustible cannabis products (e.g., joints) expose users to harmful concentrations of several toxicants, including irritants and carcinogens. The studies concurred with a lower exposure to inhaled intoxicants from vaporizers and ENNDS compared to joints. However, very few studies investigated the composition of ENNDS emissions. In addition to toxicant concentrations, the efficiency in delivery of tetrahydrocannabinol (Δ^9-THC) is also a relevant parameter to measure for estimating the user satisfaction and, thus, the potential toxicant concentrations based on the way of using the device. The literature reported a low efficiency in delivery of Δ^9-THC in joints, ranging from 12% to 32%. For vaporizers, the efficiency ranged from 3% to 84%, depending on the heating temperature and methods. For ENNDS, the efficiency ranged from 5% to 80%. However, most of the studies on vaporizers tested only one medical device, and none compared the two different heating systems (i.e., conduction- and convention-based devices).

In our laboratory analyses, we used an in-house built smoking machine to generate emissions from three cannabis vaporizers (including a medical-grade device), five ENNDS, and joints with and without filters (without tobacco). Vaporizers strictly heated cannabis flowers (i.e., not waxy or solid concentrates), whereas ENNDS only used e-liquids containing cannabinoids extracted from cannabis flowers. Six different e-liquids were tested for ENNDS. In these emissions, we quantified the concentrations of six different chemical families of toxicants: aldehydes, volatile organic compounds (VOCs), phenolic compounds, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and heavy metals and trace elements. In addition, we quantified cannabinoids in the emissions to compare the efficiency of Δ^9-THC delivery for each device.

We observed a large reduction of the toxicant concentrations in cannabis vaporizers and ENNDS compared to joints. However, some irritants and carcinogens were still released in their emissions, and high aldehyde concentrations were observed for two of the six tested e-liquids, due to a high viscosity of the e-liquids leading to an overheating of the ENNDS coil. The addition of a filter to joints reduced substantially the toxicant concentrations in emissions compared to smoking joints without filters. However, PAH and other harmful and potentially harmful compounds, not present in ENNDS, were still emitted when using filters. The tested type of heating system (i.e., convection-based device or hybrid system) did not meaningfully influence the concentrations of the different compounds analyzed in the vaporizer emissions. The level of toxicants emitted was similar between the medical and non-medical devices.

The efficiency of Δ^9-THC delivery was higher with ENNDS (>99%) compared to joints with or without filters (36%) and to cannabis vaporizers (18%). While results from efficiency of Δ^9-THC delivery was consistent with the literature for joints, we found lower extraction efficiency for vaporizers and higher for ENNDS.

Cannabis users may benefit from cannabis vaporizers or ENNDS as alternatives method of inhalation to joints, due to reduced exposure to toxicants. However, a special attention to the choice of e-liquids containing THC and to devices must be made to avoid overheating of the ENNDS. As for vaporizers, their low efficiency of Δ^9-THC delivery may dissatisfy users. Further studies on use of these electronic devices are needed to determine real puffing regimes and to confirm the results obtained under laboratory conditions. The use of a filter in cellulose and active carbon to smoke joints may reduce the concentrations of several toxicants, but users are still exposed to several harmful and potential harmful compounds not present when using ENNDS.

Résumé

Le cannabis est principalement consommé sous la forme de joints fumés, ce qui expose les utilisateurs à des concentrations élevées de divers composés toxiques pour la santé. Cependant, les utilisateurs s'intéressent de plus en plus à des méthodes alternatives pour inhaler du cannabis et réduire ainsi leur exposition à ces substances toxiques. Ces options alternatives, mentionnées comme méthodes d'inhalation dans ce rapport, incluent notamment les vaporisateurs de cannabis et la vaporisation d'extraits de cannabis à l'aide d'un système électronique de délivrance sans nicotine (ENNDS). Une revue de la littérature a confirmé que très peu d'études ont examiné les profils toxicologiques de ces méthodes alternatives d'inhalation dans des conditions de laboratoire, et les ont comparées aux joints. Par conséquent, cette étude visait à générer des données objectives sur la toxicité des aérosols de cannabis émis par les vaporisateurs et les ENNDS en comparaison avec la fumée de cannabis (sans tabac) en utilisant une machine à fumer pour générer des émissions et en quantifiant les concentrations de 91 composés dans les émissions.

Nous avons identifié 9 études sur la caractérisation des émissions des joints de cannabis, 10 sur les vaporisateurs et 14 sur les substances toxiques et cancérigènes présentes dans les émissions des ENNDS. Toutes les études sur les joints fumés ont confirmé que les produits à base de cannabis combustibles (p. ex. les joints) exposaient les utilisateurs à des concentrations nocives de plusieurs substances dangereuses, y compris des produits irritants et des substances cancérigènes. Les études sur les vaporisateurs et les ENNDS ont confirmé les expositions réduites aux substances dangereuses inhalées par rapport aux joints. Toutefois, la composition des émissions des ENNDS n'a fait l'objet que de très peu d'études. En plus des concentrations de substances toxiques, l'efficacité de la libération du tétrahydrocannabinol (Δ^9-THC) dans les émissions est également un paramètre pertinent à mesurer pour évaluer la satisfaction de l'utilisateur et, par conséquent, les concentrations potentielles de substances toxiques en fonction de la manière d'utiliser l'appareil. La revue de littérature a indiqué que l'efficacité des joints pour libérer le Δ^9-THC est faible, allant de 12 % à 32 %. Pour les vaporisateurs, celle-ci variait de 3 % à 84 %, selon la température et les méthodes de chauffage. Cependant, la plupart des études sur les vaporisateurs n'ont testé qu'un seul dispositif médical, et aucune n'a comparé les deux dispositifs de chauffage (c'est-à-dire par conduction et par convection). Pour les ENNDS, elle variait de 5 % à 80 %.

Dans nos analyses en laboratoire, nous avons utilisé une machine à fumer construite par nos soins pour générer les émissions de trois vaporisateurs de cannabis (incluant un appareil de qualité médicale), de cinq ENNDS, et de joints avec et sans filtres (sans tabac). Les vaporisateurs ont strictement été utilisés avec du cannabis séché (c'est-à-dire sans résine ou

concentrés solides) et les ENNDS avec des e-liquides contenant des cannabinoïdes extraits de plantes de cannabis. Six e-liquides différents ont été testés avec les ENNDS. Dans ces émissions, nous avons quantifié les concentrations de six familles chimiques différentes de substances toxiques : des aldéhydes, des composés organiques volatils (COV), des composés phénoliques, des hydrocarbures aromatiques polycycliques (HAP), des amines aromatiques, ainsi que des métaux lourds et des éléments traces. Nous avons également quantifié les cannabinoïdes afin de comparer l'efficacité de la délivrance de Δ^9-THC pour chaque dispositif.

Nous avons observé une importante réduction des concentrations de substances toxiques dans les vaporisateurs de cannabis et les ENNDS par rapport aux joints. Cependant, certaines substances irritantes et cancérigènes étaient encore présentes dans leurs émissions, et des concentrations élevées d'aldéhydes avaient été observées pour deux des six e-liquides testés, en raison de l'importante viscosité des e-liquides, entraînant une surchauffe de la résistance de l'ENNDS. L'ajout d'un filtre aux joints a considérablement réduit les concentrations de substances toxiques dans les émissions par rapport aux joints fumés sans filtre. Toutefois, malgré l'utilisation d'un filtre, des HAP et d'autres composants nocifs ou potentiellement nocifs absents des ENNDS sont encore présents. Le type de système de chauffage testé (c'est-à-dire dispositif à convection ou système hybride) n'a pas vraiment influencé les concentrations des différents composés analysés dans les émissions des vaporisateurs. En outre, le dispositif médical était comparable aux autres vaporisateurs non-médicaux testés quant aux substances dangereuses émises.

L'efficacité de la délivrance de Δ^9-THC était plus élevée avec les ENNDS (> 99 %) par rapport aux joints avec ou sans filtres (36 %) et aux vaporisateurs de cannabis (18 %). Ces résultats sont cohérents avec la littérature portant sur les joints, mais l'efficacité d'extraction était plus faible pour les vaporisateurs et plus élevée pour les ENNDS.

Les personnes consommant du cannabis peuvent bénéficier des méthodes alternatives de consommation par inhalation comme les ENNDS, voire des vaporisateurs, notamment en raison d'une exposition réduite aux substances dangereuses pour la santé. Cependant, une attention particulière doit être portée au choix des e-liquides contenant du THC et aux dispositifs pour éviter la surchauffe de la résistance des ENNDS. Quant aux vaporisateurs, leur faible efficacité de délivrance du Δ^9-THC pourrait déplaire aux utilisateurs. D'autres études sur l'utilisation de ces appareils électroniques sont nécessaires pour déterminer les régimes réels de bouffées et pour confirmer les résultats obtenus dans des conditions de laboratoire. L'ajout d'un filtre en cellulose et en charbon actif pour fumer les joints permet de réduire les concentrations de plusieurs substances, mais l'utilisateur reste exposé à des substances nocives ou potentiellement nocives présentes dans les joints fumés qui sont absentes des ENNDS.

Zusammenfassung

Cannabis wird hauptsächlich in Form von gerauchten Joints konsumiert, wodurch die Nutzerinnen und Nutzer hohen Konzentrationen verschiedener gesundheitsschädlicher (toxischer) Stoffe ausgesetzt sind. Allerdings wächst das Interesse an potenziell sichereren Alternativen der Cannabis-Inhalation, um die Belastung durch gesundheitsschädliche Stoffe zu verringern. Zu diesen Alternativen, in diesem Bericht als Inhalationsmethoden bezeichnet, gehören Cannabis-Vaporisatoren und Geräte zum Verdampfen von THC-haltigen Flüssigkeiten (Electronic non-nicotine delivery systems, ENNDS oder auch E-Joints, Cannabis-E-Dampfer, elektronische Cannabis-Zigaretten). Eine Literaturübersicht hat bestätigt, dass nur sehr wenige Studien die toxikologischen Profile dieser alternativen Inhalationsmethoden unter Laborbedingungen untersucht und mit Joints verglichen haben. Mit der vorliegenden Studie sollten daher objektive Daten über die Toxizität von Cannabisaerosolen erhoben werden, die von Vaporisatoren und ENNDS im Vergleich zu Cannabisrauch (ohne Tabak) abgegeben werden, indem eine Rauchmaschine zur Erzeugung von Emissionen verwendet und die Konzentrationen von 91 Verbindungen in den Emissionen gemessen wurden.

Wir haben neun Studien zur Beschreibung der Emissionen von Cannabis-Joints gefunden, zehn zu Vaporisatoren und vierzehn zu toxischen und krebserregenden Substanzen in den Emissionen von ENNDS. Alle Studien zu Joints haben bestätigt, dass sich die Nutzerinnen und Nutzer von Cannabisprodukten zum Rauchen (z. B. Joints) schädlichen Konzentrationen mehrerer gesundheitsschädlicher Stoffe aussetzen, darunter Reizstoffe und Karzinogene. Studien zu Vaporisatoren und ENNDS haben die geringeren Belastungen durch eingeatmete gesundheitsschädigende Stoffe im Vergleich zu Joints bestätigt. Allerdings haben nur sehr wenige Studien die Zusammensetzung der Emissionen von ENNDS untersucht. Neben den Konzentrationen von gesundheitsschädigenden Stoffen ist auch die Umwandlungseffizienz von Tetrahydrocannabinol (Δ^9-THC) ein relevanter Parameter, der gemessen werden sollte, um die Zufriedenheit der Nutzerinnen und Nutzer und damit die potenziellen Konzentrationen der gesundheitsschädigenden Stoffe je nach Art der Nutzung des Geräts zu ermitteln. In der Literatur wird über eine geringe Umwandlungseffizienz von Δ^9-THC in den Joints berichtet. Diese lag zwischen 12 und 32 Prozent. Bei Vaporisatoren schwankte die Effizienz zwischen 3 und 84 Prozent, je nach Temperatur und Erhitzungsmethode. Bei ENNDS schwankte die sie zwischen 5 und 80 Prozent. Die meisten Studien zu Vaporisatoren haben jedoch nur ein einziges medizinisches Gerät getestet, und in keiner Studie wurden zwei verschiedene Erhitzungssysteme (z. B. konduktions- und konvektionsbasierte Erhitzer) miteinander verglichen.

In unseren Laboranalysen wurde eine selbstgebaute Rauchmaschine eingesetzt, um Emissionen von drei Cannabis-Vaporisatoren (darunter ein Gerät mit internationaler, medizinischer Zulassung), fünf ENNDS und (tabakfreien) Joints mit und ohne Filter zu erzeugen. In den Vaporisatoren wurden ausschliesslich Cannabisblüten (d. h. keine wachsartigen oder festen Konzentrate) erhitzt, während in den ENNDS nur E-Liquids verwendet wurden, die aus Cannabisblüten extrahierte Cannabinoide enthielten. Sechs verschiedene E-Liquids wurden für ENNDS getestet. In den Emissionen wurden die Konzentrationen von sechs verschiedenen chemischen Gruppen von Giftstoffen gemessen: Aldehyde, flüchtige organische Verbindungen (VOC), phenolische Verbindungen, polyzyklische aromatische Kohlenwasserstoffe (PAK), aromatische Amine sowie Schwermetalle und Spurenelemente. Ebenfalls gemessen wurden die Cannabinoide, um die Freisetzungswirkung von Δ^9-THC für jedes Inhalationsgerät zu vergleichen.

Wie erwartet konnten in Cannabis-Vaporisatoren und in ENNDS stark verringerte Konzentrationen gesundheitsschädigender Stoffe im Vergleich zu Joints nachgewiesen werden. Einige Reizstoffe und Karzinogene waren jedoch nach wie vor in den Emissionen enthalten. Bei zwei der sechs getesteten E-Liquids wurden hohe Aldehydkonzentrationen nachgewiesen, was auf eine hohe Viskosität der E-Liquids zurückzuführen war, die zu einer Überhitzung der ENNDS-Spule führte. Durch die Zugabe eines Filters in den Joints wurden die Konzentrationen der gesundheitsschädigenden Stoffe in den Emissionen im Vergleich zu Joints ohne Filter erheblich reduziert. PAK und andere schädliche und potenziell schädliche Verbindungen, die bei ENNDS nicht vorhanden sind, wurden jedoch auch bei Verwendung von Filtern freigesetzt. Die Art des getesteten Erhitzungssystems (d. h. Konvektionsgerät oder Hybridsystem) hatte keinen bedeutenden Einfluss auf die Konzentrationen der verschiedenen analysierten Verbindungen in den Emissionen der Vaporisatoren. Die Menge der abgegebenen gesundheitsschädigenden Stoffe war bei den medizinischen und den nichtmedizinischen Geräten ähnlich.

Die Umwandlungseffizienz von Δ^9-THC war bei ENNDS (>99 %) höher als bei Joints mit oder ohne Filter (36 %) und Cannabis-Vaporisatoren (18 %). Diese Ergebnisse stimmen mit der Literatur zu Joints überein, die Extraktionswirkung war bei Vaporisatoren jedoch geringer und bei ENNDS höher.

Vaporisatoren oder ENNDS scheinen für Konsumierende von Cannabis interessante alternative Inhalationsmethoden zu Joints zu sein, weil sie die Belastung durch gesundheitsschädliche Stoffe reduzieren. Allerdings sollte bei der Auswahl der THC-haltigen E-Liquids und der Geräte besonders darauf geachtet werden, dass die ENNDS nicht überhitzen. Bei den Vaporisatoren kann die geringe Umwandlungseffizienz von Δ^9-THC zu

Unzufriedenheit bei den Nutzerinnen und Nutzern führen. Weitere Studien zur Nutzung dieser elektronischen Inhalationsgeräte wären notwendig, um das Emissionsverhalten unter realen Bedingungen zu bestimmen und die unter Laborbedingungen erzielten Ergebnisse zu bestätigen. Die Verwendung eines Filters aus Zellulose und Aktivkohle zum Rauchen von Joints kann die Konzentrationen verschiedener gesundheitsschädlicher Stoffe verringern, aber die Konsumierenden sind immer noch mehreren schädlichen und potenziell schädlichen Verbindungen ausgesetzt, die beim Gebrauch von ENNDS nicht vorhanden sind.

Glossary

Term	**Definition**
Cannabinoid delivery	The amount of cannabinoids transferred from the heated cannabis product to the emissions, and available for inhalation by the user.
Cannabis vaporizer (or vaporizer)	An electronic device used to heat cannabis flowers or resin to vaporize cannabinoids below its combustion point. The vaporized cannabinoids can then be inhaled by the user. The device consists of a battery-powered heating system, a chamber or cartridge to hold the flowers or the resin, respectively, and a mouthpiece for inhalation. The device may heat the cannabis product by convection, by conduction, or by a combination of the two heating systems.
Clearomizer and atomizer	The clearomizer includes the coil (or heating system), the cartridge filled with the e-liquid, and the mouthpiece for inhalation in an ENNDS device. The atomizer includes the resistance, and it is the chamber where the e-liquid is vaporized.
Coil	The heating system of an ENNDS. It consists of a resistive wire, an internal metallic layer, and a grid. It varies depending on the ENNDS device model and brand.
Conduction-based device	The device heats directly the cannabis product in the chamber through a direct contact with a heating system.
Convection-based device	The device heats indirectly the cannabis product. A heating system, external to the chamber, heats air when the user activates the vaporizer. The warm air goes through the chamber to extract the cannabinoids before being inhaled by the user. The heating system depends on the device model and the brand. Some may use a combination of convection and conduction heating system.
Decarboxylation step	Transformation of the acid form of Δ9 THC and CBD present in plant, Δ9-THCA-A and CBD-A, into psychoactive Δ9-THC and active form of CBD
Efficiency of THC delivery	The achievement of delivering sufficient cannabinoids to satisfy users.
Electronic non-nicotine delivery system (ENNDS)	An electronic device used to heat an e-liquid containing cannabinoid to vaporize cannabinoids. The vaporized cannabinoids can then be inhaled by the user. The device consists of a coil (or battery-powered heating

	element), a cartridge filled with the e-liquid, and a mouthpiece for inhalation. In this report, the use of ENNDS is referred to "cannavaping".
Method of inhalation	The method or way to consume cannabis products by inhalation: joints with or without tobacco, ENNDS, and cannabis vaporizers.
Puffing regime (or topography)	The pattern of user behavior when inhaling nicotine or cannabinoid products.

1. Introduction

In Switzerland, an amendment to the Federal Narcotics Act (NarcA) has come into force allowing pilot trials with cannabis for recreational use to increase scientific knowledge about the effects of controlled access on areas such as health behavior, socioeconomic factors or aspects of public safety and security.[1] The most popular consumption mode in Switzerland is smoking a mix of cannabis and tobacco in joints.[2] Cannabis users expose themselves to high concentrations of toxicants that are formed during pyrolysis and incomplete combustion processes in addition to the contaminants originating from production (e.g., pesticides, metals, fertilizers, etc,).They are increasingly interested in choosing potentially safer alternatives to inhale cannabis, such as cannabis vaporizers or electronic non-nicotine delivery system (ENNDS), also called e-joint).[3–5] Users of cannabis vaporizers inhale emissions from a battery powered device that heats dried cannabis flowers to aerosolize cannabinoids.[6] Some new vaporizer devices may have an insert to use also cannabis concentrates or waxes. However, in this study, only devices using cannabis flowers were tested. Similarly, ENNDS users inhale aerosols from a battery powered device that heats e-liquids enriched with cannabinoids or cannabis concentrates ("cannavaping").[7] ENNDS are also called THC vape pens and are similar to devices used to vape nicotine (electronic nicotine delivery system; ENDS). Both cannabis vaporizers and ENNDS are categorized as "electronic devices", though they are used with different types of cannabis material (i.e., cannabis flowers in vaporizers and e-liquids in ENNDS), and vaporizers can offer more precise temperature control.[3] They may deliver cannabinoids at different concentrations and with different toxicants, thus posing different or overlapping potential risks to users. Laboratory tests of the toxicological emissions of alternative delivery systems can help to assess user exposure during cannabis vaporization and cannavaping.

We need to conduct independent scientific studies to confirm that alternative inhalation methods are safer than smoking cannabis and to inform researchers, stakeholders, and especially consumers, about the known toxicants emitted when using these electronic devices. A small number of studies has dealt with these alternative inhalation methods. They all suggest that cannabis vaporization and cannavaping expose the users to fewer inhaled toxicants than smoking cannabis because cannabis or its extract is heated at lower temperatures. We also need to test the comparative reduction in exposure when smoking joints with or without filters as there is a lack of data on filter use. Additionally, another important parameter to consider is the user satisfaction. It is estimated under laboratory conditions by measuring the efficiency in delivery of tetrahydrocannabinol (Δ^9-THC). This will determine whether the alternative inhalation method will be appropriate in term of cannabis administration, and the potential exposure to toxicants based on the way of using the device to adapt the cannabis administration regardless the strength of the cannabis product. However, these results need to be confirmed by rigorous independent laboratory analyses. Generating data in a controlled environment, based on standardized procedures, is a crucial step in preparing the ground for experiments on humans in controlled settings, then for clinical studies that measure exposure to inhaled toxicants in urine, and, finally, to clinical trials that determine the effects of these alternative delivery systems on clinical outcomes.

2. Objectives and research questions

In this study, we aimed to compare the toxicity of cannabis vaporization and cannavaping to cannabis smoke (without tobacco) with and without filters. To that end, we first summarized the existing data from previous studies, then quantified concentrations of cannabinoids and different toxicants in emissions using a smoking machine and standardized procedures to generate aerosols from joints with and without filters, three cannabis vaporizers and five ENNDS. We selected a list of toxicants based on a literature review to include different chemical families such as aldehydes, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), heavy metals, phenolic compounds, and aromatic amines.

More specifically, we addressed the following research questions:

a. What are the Δ^9-tetrahydrocannabinol (Δ^9-THC) delivery efficiencies of cannabis vaporizers and ENNDS, and how do they compare to joints with or without filters?

b. To what extent do the toxicological profiles of cannabis vaporizers and ENNDS emissions differ from those of joints (without tobacco) with and without filters?

c. Is the toxicological profile of emissions from the selected cannabis vaporizers and ENNDS comparable to that of alternative devices recommended as medical devices in some countries (e.g., Mighty vaporizer by Storz and Bickel®) regarding combustion compounds?

d. Does the type of heater system (i.e., convection-based device or hybrid system) influence the concentrations of the different compounds analyzed in the emissions?

e. To what extent does the toxicological profile of emissions depend on the type of electronic device, on the cannabis product used (e.g., type of e-liquids, cannabis flower, etc.), and on factors associated with user behavior (e.g., puffing regime)?

3. Literature review

First, we carried out a review of the existing literature to document and to identify gaps in the research on emission analysis of joints and electronic devices using cannabis products, such as vaporizers and ENNDS. The results are divided into chapters on the three main inhalation methods: joints, cannabis vaporizers, and ENNDS. Each category includes a summary of the selected studies, and an identification of gaps in the literature.

This literature review focuses on studies dealing with the analysis of toxicants in emissions generated by joints, cannabis vaporizers, and ENNDS, as well as the parameters that may influence their concentrations. We also gathered information related to the achievement of delivering sufficient cannabinoids to satisfy (or correspond to their usual Δ^9-THC consumption) users (or correspond to their usual Δ^9-THC consumption), and especially on the efficiency of Δ^9-THC delivery, as well as on the decarboxylation step (i.e., the transformation of the acid form of Δ^9-THC present in plant, Δ^9-THCA-A, into psychoactive Δ^9-THC). This latter is important to guarantee an efficient production of the major active components in cannabis.[8] This is an important parameter to consider, especially for electronic devices. If the cannabis products contain mainly the acidic forms and the device used to inhale these products has a temperature too low to efficiently transform and deliver the active forms, users might be unsatisfied. It is known that users, who are joint smokers, adapt their use, and thus, their cannabis consumption with other devices to reach a THC concentration in blood similar to the concentration obtained when they smoke joints.[9]

This will lead to a misuse of the device by consumers to increase the delivery of active forms, e,g, through increase of temperature, which would then result in increased toxicological exposure and health dangers as well. Another option might be for them to leave the device altogether, and, in the worst case, going back to smoking joints.

Only peer-reviewed studies were considered in this literature review. Searches were performed using PubMed and Web of Science databases[1]. Overall, 29 studies were selected.

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[1] Keywords used : Cannabis; vaporizer; vaping device; joint; marijuana; THC; aerosol; toxicant; delivery; vaporizing; toxicology

3.1. Joints

3.1.1. Literature summary

Nine studies quantified toxicant concentrations in joint emissions or their metabolites in users' biological matrices. In all the studies, joints consisted of cannabis flowers only, no tobacco was added. They showed that joints and tobacco cigarettes emit similar chemical compounds; however, their concentrations vary greatly between the two types of cigarettes. For both, plant materials are burnt to generate smoke containing the addictive compounds: nicotine for tobacco cigarettes and Δ^9-tetrahydrocannabinol (Δ^9-THC) for joints. Pyrolysis and incomplete combustion processes generate hundreds of compounds, many of which are toxicants or carcinogens (see Table 1). We found no study which tested the difference in emissions when smoking a joint with or without filters.

Table 1: Compounds emitted by joints and their potential health effects

Compound	Irritation (respiratory)	Respiratory symptoms	Cardiovascular symptoms	Reproductive system impairment	CNS toxicity	Cancer	Reference
Aldehydes:							
Acetaldehyde	X					X	U.S. EPA
Butyraldehyde	X	X					New Jersey Department of Health and Senior Services
Formaldehyde	X	X			X	X	ATSDR
Volatile organic compounds (VOCs):							
Acrylamide	X			X	X	X	ATSDR
Acrylonitrile	X	X			X	X	U.S. EPA
Ammonia	X	X					ATSDR
Benzene	X	X			X	X	CDC
Hydrogen cyanide		X	X		X		NIOSH
Propylene oxide	X	X			X	X	U.S. EPA
Pyridines	X	X			X		NIH
Styrene	X				X	X	ATSDR

Compound	**Irritation (respiratory)**	**Respiratory symptoms**	**Cardiovascular symptoms**	**Reproductive system impairment**	**CNS toxicity**	**Cancer**	**Reference**
Toluene	X				X		ATSDR
Vinyl chloride						X	U.S. EPA
Nitric oxides	X	X					ATSDR
Phenolic compounds	X	X	X		X		U.S. EPA
PAHs						X	ATSDR
Aromatic amines	X					X	OSHA
Metals:							
Arsenic	X	X	X	X	X	X	WHO
Cadmium		X	X			X	OSHA
Lead			X	X	X	X	WHO
Mercury		X		X	X		WHO

CNS: Central nervous system; ATSDR: Agency for Toxic Substances and Disease Registry; CDC: Centers for Disease Control and Prevention; NIH: National Institutes of Health; OSHA: Occupational Safety and Health Administration; U.S. EPA: United States Environmental Protection Agency; WHO: World Health Organization.

Graves et al. (2020) found that the number of compounds detected in cannabis smoke is about half that of tobacco smoke (2575 vs 4350 compounds, respectively).[10] Cannabis smoke contained more terpenes and concentrations of pyridine about seven times higher than tobacco smoke. Similarly, Moir et al. (2008) reported differences in concentrations of several chemical families between cannabis and tobacco smoke.[11] Higher concentrations of ammonia (20-fold), hydrogen cyanide (5-fold), four aromatic amines (4-fold), acrylonitrile (3-fold), and resorcinol (2-fold) were observed in cannabis smoke compared to tobacco smoke. On the other hand, lower concentrations of arsenic (5-fold), lead (5-fold), low-molecular weight carbonyls (including formaldehyde (2-fold) and acetaldehyde (1.3-fold)), phenolic compounds, and polycyclic aromatic hydrocarbons (PAHs) were observed in cannabis smoke compared to tobacco smoke. No tobacco-specific nitrosamines (TSNAs) and no compounds derived from nicotine were quantified in cannabis smoke. Mura et al. (2020) reported higher concentrations of ammonia, hydrogen cyanide, and nitric oxide in cannabis smoke compared to cigarette smoke.[12] According to Ward and Ebbert (2021), joints emitted lower concentrations of carbonyl compounds, except for butyraldehyde.[13] This was consistent with the results of Moir et al. (2008).[11]

Four studies confirmed that acrylonitrile is released as a result of pyrolysis and incomplete combustion processes at high temperatures. Ashley et al. (2020) and Smith et al. (2020) demonstrated that acrylonitrile was present when cannabis was smoked, but not when cannabis was vaped using a cannabis vaporizer or an ENNDS, respectively.[14,15] In addition, Smith et al. (2020) and Lorenz et al. (2021) quantified higher concentrations of urinary biomarkers of acrylonitrile and acrylamide in cannabis users compared to tobacco smokers.[15,16] Meier et al (2020) did not observe any differences in acrylonitrile metabolite concentrations between cannabis and tobacco smokers.[17] This could be due to the fact that cannabis smokers were co-users of cannabis and tobacco.

Most studies have analyzed the same known toxicants emitted by tobacco cigarette to assess the toxicity of cannabis smoke. Very few aimed to identify specific compounds related to cannabis smoke, which may be potentially harmful to users. To characterize cannabis blunt smoke, Klupinski et al. (2020) used non-targeted chemical analysis.[18] The authors identified five compounds never previously studied: mellein, 2-phenyl-2-oxazoline, and three phenols (2-, 3-, and 4-ethylphenol). Mellein and 2-phenyl-2-oxazoline are recognized to have a low toxicity, but the three phenols may be potential irritant to respiratory tracts.

The pattern of user behavior when inhaling nicotine or cannabinoid products, also called the puffing topography,[19] may explain the differences between tobacco and cannabis smoke. Several studies confirmed that the puffing topography in cannabis smokers was different from tobacco smokers.[10–12] Cannabis smokers take longer puffs with a higher puff volume. This may increase their exposure to toxicants compared to tobacco smokers. Overall, all these studies confirmed that the administration of Δ9-THC via combustible products expose users to harmful concentrations of several toxicants, including irritants and carcinogens.

Efficiency of Δ9-THC delivery in joints is low because Δ9-THC is a heat-sensitive compound and is degraded at high temperatures. Van der Kooy et al. (2009)[20] and Pomahacova et al. (2009)[21] reported 32.7 ± 2.3% and 28.7 ± 6.2% of total Δ9-THC in smoke, respectively, Fischedick et al. (2010)[22] observed a Δ9-THC delivery from 15.9 ± 5.3% to 29.8 ± 3.7% according to cannabis plant material, and Sheehan et al. (2019)[23] reported 12.6 ± 5.2% from 12 cannabis samples obtained from police seizure. This last study estimated that up to 50% of Δ9-THC was lost in sidestream smoke, up to 30% was degraded by pyrolysis, and 10% was trapped in joint butt when joint was smoked intermittently.[23] However, important variation of Δ9-THC delivery percentages was observed according to the smoking regime, and high percentages were specifically reported in experiments using a continuous-puff smoking regime (i.e., one long puff during all the experiment). For instance, Gieringer et al. (2004)[24] observed a Δ9-THC delivery of 78 ± 4% when cannabis was combusted in a glass pipe bowl and the smoke continuously pumped through an impinger containing methanol. The rest of Δ9-THC amount (22%) was probably degraded by pyrolysis.

Concerning the decarboxylation step, the high temperature of a burning joint leads to the complete transformation of Δ9-THCA-A into Δ9-THC. Pomahacova et al. (2009) and Fischedick et al. (2010) reported 1% of Δ9-THCA-A in smoke and no Δ9-THCA-A, respectively.[21,22] The more the acidic forms are decarboxylated to active components, the more the active forms are efficiently produced and available to the users.[8]

3.1.2. *Rationale for methods to test joints*

Self-administration of cannabinoids is currently mainly achieved by smoking joints. As reported in the literature review, emissions from joints closely resemble those from cigarettes. They contain carcinogens, respiratory toxicants, and cardiovascular toxicants. Many of these toxicants are related to pyrolysis and incomplete combustion processes, including aldehydes, volatile organic compounds (VOCs), aromatic amines, phenolic compounds, and polycyclic aromatic hydrocarbons (PAHs). Other chemical families of toxicants identified in both cannabis and tobacco cigarettes are metals, which are contaminants found in the plants. However, concentrations of both toxicants formed during pyrolysis and incomplete combustion processes and impurities present in plants may be different in cannabis smoke compared to tobacco smoke. This justifies why the joints we analyzed in the present study did not contain tobacco, although the consumption of mixed cannabis with tobacco is common in Europe.

Other differences between cannabis and tobacco cigarettes were previously reported. Cannabis smoke does not contain nicotine or impurities found in tobacco leaves (e.g., anabasine, anatabine, or tobacco-specific nitrosamines (TSNAs)). It contains cannabinoids (e.g., Δ^9-THC and CBD) and terpene (e.g., camphene, eucalyptol, and limonene); their compositions and concentrations depend on the plant species. This justifies why we did not measure nicotine and TSNA concentrations. Likewise, terpenes do not have acute toxicity; they were thus not analyzed in our study. Quantification of cannabinoids in cannabis smoke allowed us to compare the efficiency of Δ^9-THC delivery of different inhalation methods and cannabis products.

Cannabis vaporizers and ENNDS have the potential to administer cannabinoids without exposing the users to high concentrations of toxicants formed during pyrolysis and incomplete combustion processes in burning joints. Characterization of cannabis smoke, especially the quantification of aldehydes, VOCs, aromatic amines, PAHs, phenolic compounds, and metals, allows the comparison with emissions of cannabis vaporizers and ENNDS, and therefore to investigate potential harm reduction. The achievement of devices to deliver sufficient cannabinoids was also considered by measuring the efficiency of Δ^9-THC delivery and the decarboxylation step. These two parameters are relevant to estimate a potential misuse of the device or cannabis products to increase the active form delivery or the nonuse of the device due to an unsatisfaction of users. Results from laboratory analyses were also compared with values reported in the literature.

3.2. Cannabis vaporizers

3.2.1. Literature summary

There are very few studies on characterization of cannabis vaporizer emissions: only eight studies were identified. The first study was published in 2001 and the most recent in 2016, which implies that the available results are for older generation devices. However, all studies reported a reduction of pyrolytic products and an absence of incomplete combustion products in cannabis vaporizer emissions compared to joint emissions. Gieringer et al. (2001) and Abrams et al. (2007) did not find carbon monoxide (CO), a product of the incomplete combustion of organic materials in emissions and in exhaled breath of volunteers, respectively.[25,26] In addition, Fischedick et al. (2010) measured and compared the emission composition of a cannabis vaporizer and joints using three different medicinal cannabis extracts.[22] They observed that compounds identified in cannabis extracts and in emissions of the cannabis vaporizers were similar (i.e., no thermal degradation; decomposition caused by heat), while these compounds were thermally degraded in joints. Quality of cannabis plant was also an important parameter, as illicit samples showed higher levels of ammonia and other low molecular weight compounds compared to standard cannabis samples from the National Institute on Drug Abuse (NIDA).[27]

Efficiency of Δ^9-THC delivery varies across the studies, but cannabis vaporizers deliver Δ^9-THC with a comparable or even higher efficiency compared to joints. Only six studies reported a Δ^9-THC delivery efficiency using cannabis vaporizers (Table 2). Five tested the Volcano device (Storz & Bickel, Germany), which is approved as medical device in several countries, and two tested other devices in addition.

Pomahacova et al. (2009) reported Δ^9-THC delivery of 2.9 ± 0.2% at 170°C, 13.1 ± 1.0% at 200°C, and 44.3 ± 6.0% at 230°C.[21] The experiment was repeated two months later, and the Δ^9-THC delivery was around 31% at 230°C, while it was similar to the previous results for the other temperatures (estimated from a figure). They also investigated the effect of different amounts of cannabis loaded into the heating chamber and vaporized at 230°C on the Δ^9-THC delivery. They observed a Δ^9-THC delivery between 33 and 66% for amounts of cannabis varying from 50 to 500 mg (estimated from a figure). Delivery decreased to 15.4 ± 4.2% for 1000 mg. Lanz et al. (2016) reported THC delivery from 54.6 ± 6.0% to 82.7 ± 6.0%, but they did not use a standardized puffing regime and no information was reported on the flow or volume of each puff. The aspiration of the vapors was continuous at 420 mbar for three minutes, followed by one minute at 100 mbar. Therefore, results cannot directly be compared to other studies due to this experimental design. Studies under laboratory conditions are necessary to assess exposure to toxicants, but Abrams et al. (2007) showed that users adapted their behavior use and the inhaled cannabinoid dose to reach plasmatic Δ^9-THC concentrations similar to cannabis smokers.[25] The plasmatic Δ^9-THC concentrations were higher at 30 and 60 minutes after using a vaporizer than smoking a cannabis joint, but concentrations were not significantly different 6 hours after use. This suggests that Δ^9-THC absorption was faster using the vaporizer compared to when smoking a cannabis joint. Three different THC strengths were tested, and both vaporizer users and joint smokers inhaled more efficiently or more puffs at lower THC strengths compared to higher THC strengths. At lower THC strengths, the participants adapted their behavior to have a THC intake similar to the higher THC strengths. This might result in higher exposure to potentially harmful compounds, since with every additional puff from a joint or other device, additional byproducts with toxicological potential are being inhaled.

In the plant material, Δ^9-THC and CBD are present in their acidic form (Δ^9-THCA-A and CBD-A) . They must be decarboxylated before inhalation in order to induce psychotropic effects. This decarboxylation step is favored by heating cannabis (>130°C for a conversion in less than 10 minutes).[8] Hazekamp et al. (2006) observed a residual Δ^9-THCA-A concentration of about 3.8% in vapor extracts of the Volcano device at 230°C.[28] Pomahacova et al. (2009) observed Δ^9-THCA-A / Δ^9-THC ratios between 1 and 7% that were inversely proportional to the Volcano temperature (from 170 to 230°C).[21] Fischedick et al. (2010) reported Δ^9-THCA-A / Δ^9-THC ratios around 5–6% with the Volcano device at 200°C.[22] Lanz et al. (2016) reported a decarboxylation efficiency above 95% for all electrically-driven vaporizers.[29] Carrara et al. (2020) observed a complete decarboxylation after 2 min (corresponding to 2 L of air) for Mighty.[30] Delivery efficiency may depend on the temperature, the density, the weight, the consistency of the material used, the variety, and the potency of Δ^9-THC in the plants.[21,27]

Table 2: Efficiency of Δ^9-THC delivery of cannabis vaporizers reported by previous studies

	Gieringer et al. (2004)[24]	Hazekamp et al. (2006)[28]	Pomahacova et al. (2009)[21]	Fischedick et al. (2010)[22]	Lanz et al. (2016)[29]	Carrara et al. (2020)[30]
Device[1]	Volcano	Volcano	Volcano	Volcano	Volcano Medic Plenty Arizer Solo DaVinci Vape-or-Smoke	Mighty Medic DaVinci
Collection strategy[2]	Three collection balloons (3 x 8 L)	One collection balloon (8 L)	One collection balloon (8 L)	One collection balloon (8 L)	Aspiration of vapor (420 mbar, 3 min + 100 mbar, 1 min)	500 mL, 5 s, 30 s; 10 puffs
Temperature	226°C	226°C	170 – 230°C	200°C	210°C	210°C
Cannabis supplier[3]	NIDA (4.15% total Δ^9-THC)	NIDA (12% Δ^9-THCA-A)	Bedrocan BV (14.2% Δ^9-THCA-A and 2.7% Δ^9-THC)	Bedrocan BV (Bedrocan 18% Δ^9-THC, Bedrobinol 11% Δ^9-THC, and Bediol 6% Δ^9-THC)	Bedrocan BV (4.61% total Δ^9-THC)	Bedrocan BV (5% total Δ^9-THC)
Mass	200 mg	200 mg	500 mg	250 mg	50 mg	150 mg
Efficiency of Δ^9-THC delivery	36 – 61%	29%	2.9 – 44.3%	22 – 39.5%	54.6 – 82.7%	42 – 84 %

[1] Volcano, Plenty, and Mighty from Storz & Bickel (Germany), Arizer Solo from Arizer Tech (Canada), DaVinci from Organicix (USA), Vape or Some from Elemental Technologies (U.S.).

[2] For Volcano, a removable valve balloon is filled with hot air that passed through cannabis; for portable devices, either emissions are continuously drawn by a pump (e.g., in study of Lanz et al. (2016)) or a puffing regime is used (puff volume, puff duration, inter-puff duration; number of puffs) as in the study of Carrara et al. (2020).

[3] NIDA = National Institute on Drug Abuse (U.S.), Bedrocan BV (the Netherlands)

3.2.2. Literature gaps

Most of the reviewed studies have focused on only one device: the Volcano, which is a medical device for cannabis use in several countries. The most recent study compared different electrically-driven vaporizers with gas-powered devices. It showed that the Δ^9-THC delivery and the decarboxylation efficiencies were lower for gas-powered devices. The authors did not recommend using this type of device for therapeutic purposes. Therefore, we selected only electrically-driven vaporizers in this study. Our device selection included conduction and convection technologies to vaporize cannabis. No studies compared these two technologies from a toxicological point of view in the literature. Furthermore, there are no data on emission of the new generations of vaporizers.

All the studies used only dried cannabis flowers in vaporizers, and no data was available on cannabis extracts (e.g., resins).

3.3. ENNDS

3.3.1. Literature summary

ENNDS are becoming very popular due to their ease of use and discretion. They are used to vaporize cannabis extracts. Various cannabis extracts can be prepared from cannabis flowers with different extraction methods, such as pressurized liquid extraction, subcritical CO_2 extraction, supercritical fluid CO_2 extraction, pulsed electric field (PEF) extraction, microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), and enzyme-assisted extraction.[31] Based on the review of Lazarjani et al. (2021), solvent extraction is the most common method.[32] Cannabis extracts include two main categories: resins (hashish or hash among others) and concentrates (butane hash oil (BHO), wax, dabs, shatter, etc.).[33,34] These extracts can be smoked in joints or vaporized using water pipes (bong, hookah), dab rigs, weed pipes, or dedicated ENNDS (e.g., dab pens). Cannabis extracts can also be eaten if the product preparation included a decarboxylation step or if the products are baked before being ingested. Extracts may also be diluted in solvents (mainly propylene glycol and glycerol) to form e-liquids that can also be vaporized in ENNDS (e.g., vape pens).[35]

There are very few studies (n=12) that characterized toxicants and carcinogens in ENNDS emissions. Vaping cannabis products (with Δ^9-THC containing e-liquid) was often compared to nicotine vaping, despite the differences in composition of the e-liquid.[36] Data obtained on electronic nicotine delivery systems (ENDS) emissions can be useful to assess the safety risk of ENNDS, but cannabis extracts dissolved in e-liquid contain other substances that can potentially form other toxicants during the vaporization process. Among these substances, there are the terpenes as reported by several studies.[37–39] Terpenes are naturally present in the cannabis plants.

Cannabis extracts are often too viscous to allow a good flow from the cartridge to the heating element, so thinning agents are added to improve the flow.[40] This is particularly important because an insufficient e-liquid supply to the coil will result in high heating temperatures (i.e., dry puff due to an overheating of the coil). Thinning agents as well as terpenes may form aldehydes when vaporized. Most of the studies quantified aldehydes in ENNDS, and the concentrations varied across the studies.[37–43] Both Δ^9-THC and terpenes can also form carcinogens such as isoprene and other related compounds.[38,39,43] An emerging problem is also the appearance of synthetic cannabinoids that can be added to e-liquids or cannabis extracts. The health effects of these products are unknown.[42]

Research on ENNDS has greatly increased following the outbreak of E-cigarette or Vaping use-Associated Lung Injury (EVALI) in the USA. These studies represent the majority of the identified articles (n=7).[38,41,43–47] Their objective was to identify the compound(s) inducing the lung disease. Cannabis cartridges obtained during EVALI, and their aerosols, were analyzed by several research groups. Vitamin E acetate and his possible toxic thermal degradation product (ketene) were identified as potential compounds responsible for the disease. It was shown that the thermal degradation of vitamin E acetate was possible, but only at very high temperatures (>500°C), which may occur during dry puffs. Used cartridges obtained during EVALI presented burnt marks, indicating exposure to high temperatures. It was also suggested that a combination of hydrocarbons and oil, as well as toxicants and metals, may cause EVALI. In any case, little is known about the toxicology of less volatile oils and oil-based cannabinoid vaping products. These results did not apply to our current study, as vitamin E acetate was not added in the e-liquid we selected. However, these studies highlighted the need to care about the origin of e-liquids and the choice of ENNDS. Toxicant and carcinogen concentrations are mostly lower than those found in tobacco or cannabis smoke. Thus, these products should reduce health risks as suggested by Meehan-Atrash et al. (2019).[37]

Very few research groups reported Δ^9-THC deliveries in ENNDS. Varlet et al. (2016) spiked commercial free-nicotine e-liquids (60:30 PG/VG) with pure THC diluted in ethanolic solution or with pure THC and a standard of THCA-A in powder and fortified the spiked e-liquids with three concentrations of butane hashish oil (BHO). BHO was prepared from a home-made protocol to extract cannabinoids from cannabis flowers using butane gas. THC concentrations in spiked e-liquids were 4.3 mg/g of e-liquid, and THCA-A concentrations were 81 mg/g of e-liquid. Pure BHO contained 3% of THC and 73% of THCA-A before decarboxylation, and 59% of THC after decarboxylation. A second generation ENNDS with four wicks and a coil resistance of 3.8 Ω was used for generating emissions.[2] Varlet et al. (2016) also evaluated the decarboxylation efficiencies under different conditions (temperature and time) and mentioned that the decarboxylation of Δ^9-THCA-A in ENNDS was possible but at low efficiency.[7] They assumed that the duration of a puff was the main limiting factor for the optimal decarboxylation of Δ^9-THC.More recently, Meehan-Atrash et al. (2021) determined a Δ^9-THC delivery of 50-90% depending on liquid composition (pure Δ^9-THC with varying concentrations of β-myrcene) and device power.[49] Highly potent cannabis concentrates (e.g., BHO) can also be consumed in electronic devices without being diluted (Δ^9-THCA-A > 60%): the "dabbing" technique. Hädener et al. (2019) reported a Δ^9-THC delivery of 66.7–80.8%.[50] However, this cannabis use may produce higher concentrations of toxic byproducts, especially without a temperature control.

3.3.2. Literature gaps

Very few studies investigated the composition of ENNDS emissions. Several methods of extraction may be performed to extract Δ^9-THC and cannabinoids, as explained in the review of Meehan-Atrash et Rahman (2021)[43].

Higher terpene concentrations may be found in ENNDS emissions. They can be thermally degraded as reported by Meehan-Atrash et Rahman (2021) and Tang et al. (2021).[39,43] We quantified the degradation products of terpenes in our studies, such as benzene, isoprene, 1,3-butadiene, formaldehyde, acetaldehyde, acrolein, and valeraldehyde.

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[2] The smoking machine was set up with the following puffing regime: a volume of 70 mL, a puff interval of 30 s, and a puff duration of 3 s. For each puff of 3 s, the e-liquid temperature reached 165°C close to the coil. Δ^9-THC concentrations were measured in e-liquid mixtures and in emissions, and an estimation of Δ^9-THC deliveries between 5 and 24% were observed.[48] However, BHO was a viscous waxy cannabis concentrate, and the ENNDS device selected could be not appropriate to deliver efficiently Δ^9-THC through the wicks.

4. Methods

4.1. Cannabis products and selected devices

4.1.1. Cannabis products

Cannabis product quality varies depending on the origin of cannabis plants, cultivars, and methods of cultivation.[51] We purchased homogenized cannabis flowers (>1% THC) and six e-liquids containing cannabinoids from Swiss producers.

The joints were prepared using a cigarette rolling machine (regular for 70 mm; OCB, Republic Technologies International, Perpignan, France) with cigarette papers (69 x 36 mm; OCB Premium, Republic Technologies International, Perpignan, France), cardboard filters (deluxe tips medium size filters 60 x 20 mm; Miquel y Costas, Barcelona, Spain), and homogeneous dried cannabis flowers (Pure Holding AG, Zeiningen, Switzerland). We followed the WHO TobLabNet SOP 01 (Standard Operating Procedure for Intense Smoking of Cigarette) procedure for conventional cigarettes, and we marked the butt length (28 mm) and applied cellophane tape (20 mm) around the filter. Then, we weighted around 200 to 300 mg of cannabis per joint (247 ± 27 mg in average). The amount of cannabis flower was limited by joint size, but it was similar to the usual amount of consumption (per joint) of occasional users.[52]

We also decided to perform additional assays with filtered joints to determine the impact of adding a filter to cannabis cigarettes on exposure to hazardous compounds in smokers and on the cannabinoid delivery efficiency. No scientific evidence is available on the efficiency of joints in reducing harmful compounds. Hence, we selected a cellulose and active carbon combined filter (Hybrid Supreme Filters (30 mm long, 6.4 mm diameter)) to perform the assays. We selected an active carbon filter to retain a large number of toxicants in the filter and limit their concentrations in emissions as much as possible, since the active carbon filter is being considered the best type of filter available. We followed the same method than unfiltered joints.

Six e-liquids were tested in this study. Their composition and characteristics are described in Table 3. The first e-liquid (e-liquid #1) was prepared by Pure Holding AG (Zeiningen, Switzerland) using a solvent extraction of the same cannabis flowers tested in joints containing 10.3% total Δ^9-THC. This is a conventional extraction method used in the medical production of cannabis tinctures. However, the e-liquid was highly viscous due to a dilution of the cannabis extract in a mixture of polyethylene glycol / vegetable glycerin (PEG/VG). The Δ^9-THC content (4.21%) was also limited by the cannabis extract solubility. The second e-liquid (e-liquid #2) was prepared by CDC LAB SA (Plan-les-Ouates, Switzerland) using a CO_2 supercritical extraction method, which does not require solvents. The solvents used for diluting cannabis extract were propylene glycol / vegetable glycerin, which resulted in a much less viscous e-liquid. This e-liquid contained a low percentage of Δ^9-THC (<1%) and a high CBD concentration. We considered that the efficiency of Δ^9-THC delivery could be approximated by that of CBD, as these compounds are part of the same chemical family. E-liquid #3, #4, #5 and the CBD extract were also prepared by Pure Holding AG (Zeiningen, Switzerland) using a solvent extraction, but without using PEG and only PG, or PG/VG (80% / 20%). The cannabis flowers used to produce these four e-liquids were different from the e-liquid #1 and the joints as they were gathered in Fall 2022. The Δ^9-THC content was about 10% for e-liquids #3 and #4. E-liquid #5 only contained CBD at 10% as well as the CBD extract (Pure Distillate CBD (62%). CBD extract was available in a 0.55-ml cartridge that can only be used with the device Cable Pen by Yeitaeso. E-liquid #4 was poorly soluble, and it was sonicated for 5 minutes before filling the ENNDS device at each vaping experiment.

Table 3: Composition and THC and CBD content of the six e-liquids tested

	e-liquid #1	**e-liquid #2**	**e-liquid #3**	**e-liquid #4**	**e-liquid #5**	**CBD extract**
Type of cannabis extraction	Solvents	Supercritical CO_2	Solvents	Solvents	Solvents	Solvents
Percentage of cannabis extracts[1]	5.4%	-[2]	5.4%	5.4%	-	100%
Percentage of glycerol (VG)	18.9%	30%[3]	0%	20%	20%	0%
Percentage of propylene glycol (PG)	0%	70%[4]	100%	80%	80%	0%
Percentage of polyethylene glycol (PEG)	37.8% PEG400 18.9% PEG300 18.9% PEG200	0%	0%	0%	0%	0%
Δ^9-THC content	4.21%[4]	<1%[4]	8.8%[5]	11.5%[5]	0%	<0.2%[5]
CBD content	1.4%[4]	3.15%[4]	0.13%[5]	0.14%[5]	10%[5]	62%[5]
Viscosity	High	Low	Low	Low[6]	Low	High

[1] Cannabis extract consists of a mixture of cannabinoids and terpenes.
[2] Confidential information.
[3] Percentage of cannabis extracts was not taken into account.
[4] Δ^9-THC content was calculated as total Δ^9-THC = (Δ^9-THCA-A x 0.877) + Δ^9-THC; CBD content was calculated as total CBD = (CBD-A x 0.877) + CBD.
[5] Content quantified by the company.
[6] Poor solubility of cannabis extracts.

4.1.2. Choice of devices

We based our choice of cannabis vaporizers and ENNDS on recommendations by producers, clinical experts, specialized shop owners, consumers, review of numerous magazine articles and online reviews, and through direct testing of the devices selected.

Different types of heater systems are available in cannabis vaporizers: the convection mode, the conduction mode, and the hybrid system using both conduction and convection modes. The convection mode heats the air that passes through the cannabis to extract the cannabinoids. The conduction mode heats the plant material by direct contact with the heating element in the bowl. The hybrid system heats the air passing through cannabis flowers by direct contact with the bowl.

We selected three cannabis vaporizers: Wolkenkraft FX$^+$, a convection vaporizer, Arizer Air II, a hybrid vaporizer using both conduction and convection mode, and Mighty$^+$ by Storz & Bickel, a medical-grade device, which is also a hybrid heater system combining conduction and convection mode but heating cannabis mostly by convection. Table 4 summarizes the main characteristics of the three selected devices.

Table 4: Characteristics of the three selected cannabis vaporizers

	FX$^+$ by Wolkenkraft	**Air II by Arizer**	**Mighty$^+$ by Storz & Bickel**
			
Type of heating	Convection	Combination of convection conduction (hybrid system)	Combination of convection conduction (hybrid system)
Time to heat up	20 – 30 s	60 – 90 s	60 s
Temperature ranges	170 – 220°C	50 – 220°C	170 – 210°C
Herb capacity (chamber volume)	Up to 400 mg	100 – 200 mg	Up to 300 mg

For the choice of ENNDS, we selected four devices: the pod “OBY” by Aspire, the Endura T20-S by Innokin, the Nautilus X by Aspire, and Vape Pen by Noïd.Lab. In addition, we also tested the Cable Pen by Yeitaeso for the CBD extract only. For this device, only one replicate was performed due to the limited volume of the cartridge (0.55 mL) and the inability to refill the cartridge. Table 5 summarizes the main characteristics of the five selected devices.

Table 5: Characteristics of the five selected ENNDS

	OBY by Aspire	Endura T20-S by Innokin[1]	Nautilus X by Innokin[1]	Vape Pen by Noïd.Lab	Cable Pen by Yeitaeso
					
Coil	OBY Pod	Prism S	Aspire PockeX	Noïd.Lab	No information
Resistance	1.2 Ω	0.8 Ω	1.2 Ω	1.5 Ω	No information
Activation	Draw activated	Button activated	Button activated	Draw activated	Button activated
Reservoir capacity	2 mL	2 mL	2 mL	0.55 mL	0.55 mL

[1] Only the clearomizers were connected to the smoking machine.

4.2. Generation of emissions using the smoking machine

4.2.1. *Smoking machine and puffing regimes*

A smoking machine developed in our laboratory was used to generate smoke and aerosols to characterize and quantify potential toxicants in emissions. A schematic of the smoking machine is shown in Figure 1. It consists of a piston syringe, to simulate the volume inhaled by the user. It is directly linked through silicon tubing to vaporizers, joints or to a titling support for clearomizers to test ENNDS. Silicon tubing cross a four pinch valve system that allows testing three devices in a same run test, the fourth valve is for the outlet hose. The entire system is controlled through a control panel with a digital display to change parameters. The smoking machine can be adapted to test cigarettes and different electronic devices It has been used in several tobacco studies.[48,53,54] It was used to generate emissions from heated tobacco products (e.g., IQOS[53,55], Glo, and PloomTech; study funded by Canton of Vaud, manuscripts in preparation[54]) and ENDS (i.e., Innokin Endura T20-S used previously in the clinical trial entitled "ESTxENDS" (NCT03589989) funded by the Swiss National Foundation and led by Prof. Reto Auer).

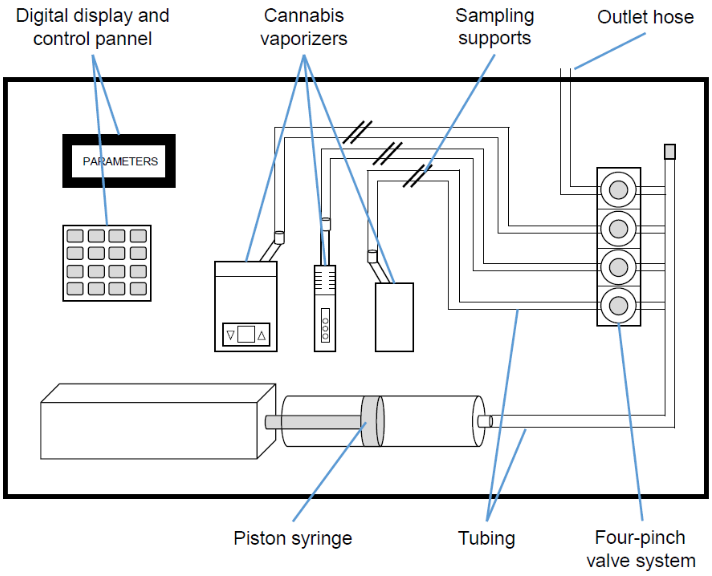

Figure 1: Schema of the smoking machine

Smoking conditions influence the chemical composition of aerosols. Therefore, it is important to choose a puffing regime that simulates the style and habits of users to closely evaluate exposure to potential toxicants and associated health risks.[51,56] The puffing regime (i.e., puff volume, puff duration, and puff interval) is programmed into the smoking machine. We used the ISO[57] and Health Canada Intense (HCI)[58] standard smoking regimes for conventional cigarettes, and the CORESTA[59] puffing regime for ENDS. Our smoking regime in this study followed the HCI standard to test joints because it accounts for the higher puff volume of joint smokers. We modified the CORESTA standard (55 mL, 3 s, 30 s) to test Δ^9-THC delivery using cannabis vaporizers and ENNDS. For vaporizers, there is no information on cannabis puffing regimes in the literature, but users may inhale large puffs. For ENNDS, we had to increase the puff volume (i.e., in comparison to the CORESTA standard) to be able to activate the OBY, because otherwise the flow was too low. Table 6 summarizes the puffing regimes used for each cannabis inhalation method to generate emissions.

The duration of an experiment is defined by the puff numbers, and it depends on the cannabis inhalation method tested. Thus, the puff numbers per collection were different between joints, cannabis vaporizers and ENNDS. For joints, the puff number was not fixed; joints were smoked until reduced to the butt length (28 mm). For vaporizers, puff number was fixed to 15 puffs, which corresponds to a session of 7.5 min of vaping. Users usually make three sessions of 5 min per day, but puff volume is unknown. For ENNDS, 50 puffs were collected, unless otherwise indicated.[57] Puffing number of ENNDS users is also not known, but toxicant concentrations are then adjusted by the mass of e-liquid consumed. The mass of vaporized e-liquid is the mass of e-liquid lost by the atomizer during the use of ENNDS. The e-liquid composition and the mass of vaporized e-liquid will influence the aerosol composition.[60] This is the reason why concentrations are adjusted by the mass of e-liquid consumed to be able to compare the results obtained for the selected e-liquids and the selected devices using the same puffing regime.

Table 6: Smoking regimes used for each tested cannabis products to generate emissions

Cannabis products	Smoking regime	Puff volume	Puff duration	Puff interval
Joints	HCI standard	55 mL	2 s	30 s
Cannabis vaporizers	Adapted CORESTA	80 mL	3 s	30 s
ENNDS	Adapted CORESTA	80 mL	3 s	30 s

mL: milliliter; s: second; ENNDS: electronic non-nicotine delivery system.

4.2.2. Chemical compounds selected

We focused on measuring toxicants related to pyrolysis and incomplete combustion processes, especially carcinogens and irritants. We also included specific markers of cannabis use. Lorenz et al. (2021) reported less acrylamide (classified carcinogen 2A by the International Agency for Research on Cancer (IARC)), acrolein (irritant) and acrylonitrile (classified carcinogen 2B by IARC) in cannabis smoke than in tobacco smoke.[61]

We quantified the following chemical families in emissions:

- Cannabinoids (7 compounds)
- Aldehydes (13 compounds)
- VOCs (20 compounds)
- Phenolic compounds (7 compounds)
- PAHs (16 compounds)
- Aromatic amines (8 compounds)
- Metals (20 compounds)

Each chemical family requires a different sampling method to be collected in smoke or aerosols. We performed three replicates for each chemical test and for each cannabis inhalation method. In addition, we tested three different temperatures for the vaporizers: 170, 190, and 220°C (210°C for the Mighty$^+$). We followed the standardized sampling methods validated by WHO Tobacco Laboratory Network (TobLabNet) to collect compounds from the different chemical groups when available, as our laboratory is member of this WHO network. The sampling method for each chemical group is detailed in Annexes A to F and summarized in Table 7.

Table 7: Summary of the sampling and analytical methods for each chemical family

Chemical family	Sampling method based on	Analytical instrument for quantification	Method description
Cannabinoids	Sheehan et al. (2019)[23]	HPLC-MS/MS	Annex A
Delta-9-tetrahydrocannabinol (Δ^9-THC)			
Delta-9-tetrahydrocannabinolic acid A (Δ^9-THCA-A)			
Delta-8-tetrahydrocannabinol (Δ^8-THC)			
Cannabidiol (CBD)			
Cannabidiolic acid (CBD-A)			
Cannabigerol (CBG)			
Cannabinol (CBN)			
Aldehydes	Gillman et al. (2016)[62]	HPLC-UV	Annex B
Formaldehyde			
Acetaldehyde			
Acrolein			
Acetone			
Propanal			
Crotonaldehyde			
Butyraldehyde			
Benzaldehyde			
Isovaleraldehyde			
Valeraldehyde			
Tolualdehyde			
Hexanal			
2,5-dimethylbenzaldehyde			
VOCs and Phenols	Health Canada standardized methods[63]	GC-MS	Annex C
VOCs:			
1,3-Butadiene			
Ethanol			
Isoprene			
Propylene oxide			
Benzene			
2-propenenitrile			
Toluene			
Ethylbenzene			
o-xylene			
m-xylene			
p-xylene			
Pyridine			
Styrene			
Glycidol			
Propylene glycol			
1,2-ethanediol			
1,3-propanediol			
Quinoline			

Chemical family	Sampling method based on	Analytical instrument for quantification	Method description
Diethylene glycol *Triacetin*			
Phenols: *o-Cresol,* *m-Cresol* *p-Cresol* *Phenol* *Catechol* *Hydroquinone* *Resorcinol*			
PAHs *Naphthalene* *Acenaphthylene* *Acenaphthene* *Fluorene* *Anthracene* *Phenanthrene* *Fluoranthene* *Pyrene* *Benzo[a]anthracene* *Chrysene* *Benzo[b]fluoranthene* *Benzo[k]fluoranthene* *Benzo[a]pyrene* *Indeno[1,2,3-cd]pyrene* *Dibenz[a,h]anthracene* *Benzo[g,h,i]perylene*	TobLabNet method (for benzo[a]pyrene)[64]	GC-MS	Annex D
Aromatic amines *Aniline* *o-toluidine* *m-toluidine* *p-toluidine* *1-aminonaphthalene* *2-aminonaphthalene* *3-aminobiphenyl* *4-aminobiphenyl*	Health Canada standardized methods[63]	GC-MS/MS	Annex E
Heavy metals *Beryllium (Be)* *Aluminum (Al)* *Vanadium (V))* *Chromium (Cr)* *Manganese (Mn)* *Iron (Fe)* *Cobalt (Co)* *Nickel (Ni)* *Copper (Cu)* *Zinc (Zn)* *Arsenic (As)* *Selenium (Se)*	OSHA (2019)[65]	ICP-MS	Annex F

Chemical family	Sampling method based on	Analytical instrument for quantification	Method description
Molybdenum (Mo) *Palladium (Pd)* *Silver (Ag)*			
Cadmium (Cd) *Tin (Sn)* *Antimony (Sb)* *Platinum (Pt)* *Lead (Pb)*			

4.3. Calculations

In cannabis plant, several cannabinoids (e.g., Δ^9-THC, CBD, CBG) are present in an acid form (e.g., Δ^9-THCA-A, CBD-A, CBGA) and have to be decarboxylated to induce psychoactive or physiological effects by inhalation. Total Δ^9-THC concentrations, which is determined by summing the concentrations of Δ^9-THC and of Δ^9-THCA-A measured in the cannabis products, were calculated using the following equation (EQ(1)):

$$\text{total } \Delta^9\text{-THC} = (\Delta^9\text{-THCA-A} \times 0.877) + \Delta^9\text{-THC} \qquad \text{EQ(1)}$$

To calculate the efficiency of Δ^9-THC delivery, the measured Δ^9-THC concentrations (adjusted by the weight of cannabis used in joints or the weight of e-liquid consumed by ENNDS) was divided by the total Δ^9-THC amount reported by the producer.

Concentrations of the different compounds quantified in emissions were highly variable depending on the cannabis products (i.e., joint, e-liquid#1, and e-liquid#2) or devices tested (i.e., cannabis vaporizers and ENNDS). These concentrations were adjusted by the Δ^9-THC concentrations measured in emission of the corresponding cannabis products or devices to allow a direct comparison between the devices. The adjusted concentrations were calculated using the following equation (EQ(2)):

$$[\text{compound}]_{adj}\ (\mu\text{g/mg THC}) = [\text{compound}]\ (\mu\text{g/g cannabis}) / [\Delta^9\text{-THC}]\ (\text{mg/g cannabis}) \qquad \text{EQ(2)}$$

With $[\text{compound}]_{adj}$ the adjusted concentration of the compound, [compound] the concentration of the compound, and [Δ^9-THC] the concentration of Δ^9-THC.

5. Results and discussion

5.1. Cannabis product tested

5.1.1. Joints

Twenty-four joints without filter and 18 joints with filter, both without tobacco, were consumed under the HCI smoking regime to estimate total particulate matter (TPM). The average weight of cannabis used in joint preparation and of joint butt after smoking, as well as average TPM and puff count, are presented in Table 8. For the joints with filter, only the parameters needed to adjust the results were measured.

The cannabis mass that was used was close to the average consumed amount of flowers in a joint in Switzerland.[52] Cannabis flowers represented around 50% of joint mass. Approximatively 70% of the cannabis was burnt, which results in a TPM of 55 ± 7 mg after smoking 5.6 puffs on average for joints without using a filter, and in a TPM of 25 ± 17 mg after smoking 6.8 puffs on average for joints using the selected filter. This estimation was calculated based on the mass difference between the initial joint and butt, or Δ joint mass (mg).

Table 8: Averages of cannabis weights in joint preparation and in joint butts expressed as mean ± standard deviation.

	Joints without filter (n=24)	**Joints with filter (n=18)**
Cannabis flower amount (mg) [mean ± SD]	262 ± 25	-
Joint weight (mg)[1] [mean ± SD]	506 ± 25	575 ± 37
Joint butt (mg)[2] [mean ± SD]	328 ± 24	413 ± 36
Δ joint weight (mg)[3] [mean ± SD]	178 ± 35	162 ± 39
TPM (mg)[4] [mean ± SD]	55 ± 7	25 ± 13
Puff count / joint [mean ± SD]	5.6 ± 1.1	6.8 ± 1.0

[1] Weight of joint included the mass of paper and of filter.
[2] The mass included the mass of ash.
[3] Δ joint mass is the mass difference between the initial joint and butt.
[4] Total particulate matter (TPM) collected on Cambridge filter pads.

5.1.2. Cannabis vaporizers

TPM for cannabis vaporizers were estimated from 15 generations for each temperature tested per device, or 45 generations in total per device. Each generation consisted of 15 puffs per device. The average weight of cannabis flowers loaded in vaporizer and recovered after aerosolizing as well as average TPM are presented in Table 9. For a same vaporizer, the loaded cannabis flower between the replicates were comparable; however, a higher mass was loaded in FX^+ compared to $Mighty^+$ and Air II. The final masses (already vaporized buds; AVB) were also similar between the replicates of a same device, but TPM increased with the heating temperature. Compared to joints (55.7 ± 7 mg), a TPM reduction of more than 85% was observed for vaporizers (0.7 ± 0.7 to 8.1 ± 0.7 mg). The lower temperature heating in vaporizers (190 to 220°C) compared to joints (> 600°C) results in an important decrease in gaseous emissions and in compounds.[66] The fact to heat the biomass (i.e., organic material) at relative low temperatures in vaporizers will avoid combustion, and consequently, the formation and emission of ash and of organic and inorganic particles.[67,68] TPM will decrease. The convection-based device (FX+) had a relatively higher differences between the initial and final masses of cannabis flowers (Δ mass) and a higher TPM compared to the two hybrid systems (Table 9). However, these values remain much lower than the cannabis cigarettes, and the initial mass loaded in the bowl is also higher than the two other devices. Furthermore, the differences are too slight between the three vaporizers that it is unlikely to conclude on the better efficiency of one heating mode.

Table 9: Averages of cannabis flower masses loaded initially and recovered at the end of aerosol generation in the three vaporizers at three temperatures expressed in milligrams (mg) as mean ± standard deviation.

	Mighty$^+$				**FX$^+$**				**Air II**			
	170°C (n=15)	**190°C (n=15)**	**210°C (n=15)**	**Total (n=45)**	**170°C (n=15)**	**190°C (n=15)**	**220°C (n=15)**	**Total (n=45)**	**170°C (n=15)**	**190°C (n=15)**	**220°C (n=15)**	**Total (n=45)**
Initial mass (mg)[1] [mean ± SD]	127 ± 14	122 ± 13	134 ± 10	**127 ± 13**	165 ± 23	166 ± 17	175 ± 20	**169 ± 20**	128 ± 33	130 ± 27	137 ± 31	**132 ± 30**
Final mass (mg)[2] [mean ± SD]	109 ± 13	101 ± 11	104 ± 8	**105 ± 11**	141 ± 17	140 ± 16	136 ± 17	**139 ± 17**	112 ± 29	110 ± 22	111 ± 23	**111 ± 24**
Δ mass (mg)[3] [mean ± SD]	18 ± 2	21 ± 3	29 ± 4	**23 ± 6**	24 ± 9	27 ± 3	38 ± 10	**30 ± 10**	16 ± 5	20 ± 6	26 ± 9	**21 ± 8**
TPM (mg)[4] [mean ± SD]	1.2 ± 0.6	3.0 ± 0.8	4.7 ± 1.3	**2.9 ± 1.7**	1.2 ± 0.8	2.7 ± 1.2	8.1 ± 0.7	**4.0 ± 1.5**	0.7 ± 0.7	1.1 ± 0.5	2.8 ± 1.3	**1.5 ± 1.5**

[1] Initial mass is the mass of cannabis flowers loaded initially in the vaporizer before aerosol generation.
[2] Final mass is the mass of cannabis flowers weighted at the end of aerosol generation (already vaped buds; AVB).
[3] Δ mass is the differences between the initial and final masses of cannabis flowers.
[4] Mass of the total particulate matter (TPM) collected on Cambridge filter pads during aerosol generation.

5.1.3. ENNDS

Table 10 shows the average masses of e-liquid consumed per ENNDS device tested and for each e-liquid for 9 generations or 25 generations for OBY using e-liquid #1, along with the sampling efficiency of ENNDS aerosol by filters. The sampling efficiency of aerosol is estimated in ENNDS emissions instead of TPM as emissions are mainly composed of a gas-phase material formed by condensation of the e-liquid.[69] E-liquid mass consumption was calculated per puff for each device and each e-liquid. The mass consumed for e-liquid #1 was twice lower than for the other e-liquids tested, regardless of the device. However, the mass of e-liquid consumed by devices is highly variable between each device, regardless the e-liquid tested. Results shown also that more aerosol per puff was generated by OBY compared to Nautilus X and Endura T20-S. Noïd.Lab pod and Cable Pen were the two ENNDS that generated the less aerosol per puff, about 6 mg/puff for all the e-liquid tested.

To estimate the sampling efficiency to trap aerosol by Cambridge filter pads (CFP), the mass weighted on the filter at the end of aerosol sampling was divided by the mass difference of the e-liquid tank from the start to the end of the aerosol generation. Sampling efficiency was close to 100% for all tested devices and all e-liquids.

Table 10: E-liquid consumption and aerosol sampling efficiency of the five selected ENNDS expressed as mean ± standard deviation.

ENNDS device	E-liquid	Mass per puff (mg)[1] [mean ± SD]	Sampling efficiency (%)[2] [mean ± SD]
OBY	E-liquid #1 (n=25)	8.9 ± 2.9	92 ± 2
	E-liquid #2 (n=9)	15.1 ± 3.0	89 ± 3
	E-liquid #3 (n=6)	15.9 ± 1.1	83 ± 1
	E-liquid #4 (n=6)	13.7 ± 3.1	86 ± 5
	E-liquid #5 (n=7)	15.2 ± 1.0	85 ± 2
Endura T20-S	E-liquid #1 (n=9)	3.7 ± 0.8	102 ± 4
	E-liquid #2 (n=9)	8.6 ± 0.3	102 ± 4
	E-liquid #3 (n=6)	10.5 ± 1.8	90 ± 4
	E-liquid #4 (n=6)	9.9 ± 1.3	90 ± 2
	E-liquid #5 (n=7)	10.5 ± 0.9	93 ± 2
Nautilus X	E-liquid #2 (n=9)	9.5 ± 1.3	97 ± 2
Noïd.Lab pod	E-liquid #3 (n=6)	6.3 ± 0.8	88 ± 2
	E-liquid #4 (n=6)	5.4 ± 0.9	93 ± 4
	E-liquid #5 (n=12)	5.8 ± 0.6	92 ± 3
Cable Pen	CBD extract (n=3)	6.4 ± 0.4	90 ± 1

[1] Mass per puff is the e-liquid consumption adjusted per puff.
[2] Sampling efficiency to trap ENNDS aerosol by Cambridge filter pads.

5.2. Cannabinoids and efficiency of Δ^9-THC delivery

In cannabis plant, Δ^9-THC and CBD are present in their acid forms (i.e., Δ^9-THCA-A and CBD-A) and must be decarboxylated before inhalation in order to induce psychotropic effects. This decarboxylation step is favored by heating cannabis (>130°C for a conversion in less than 10 minutes).[8] The delivery of the two major cannabinoids, Δ^9-THC and CBD, was highly variable across devices and temperatures of use.

- *Joints*

In joint smoke, only 3% of total Δ^9-THC was still in acid form due to the high temperature of combustion, while this percentage rose to 44% in the cannabis flowers recovered from joint butts. Efficiency of Δ^9-THC delivery with joints without filter was around 35 ± 4%, which was consistent with the results of previous studies (see Chapter 3.1.1), and with filter around 44 ± 7% (Table 11). Approximatively 31% of total Δ^9-THC was left in joint butts, which indicated that more than 30% of total Δ^9-THC was degraded or lost in joint sidestream (i.e., smoke emitted from the lighted end of the joint between puffs). This can be partially explained by the heat-sensitivity of Δ^9-THC. The addition of a filter does not influence the efficiency of Δ^9-THC delivery, the cannabinoid concentrations are similar in the emissions of joints with and without filter (Table 11).

- *Cannabis vaporizers*

Like joint smoke, emissions of cannabis vaporizers contained low percentage of total Δ^9-THC in acid form (1-3%) (see Table 11). In already vaped buds (AVB; cannabis flowers after a vaporizing session), the ratio Δ^9-THCA-A / Δ^9-THC was lower than 1% for Mighty$^+$ and FX$^+$, but varied from 1% (at 220°C) to 15% (170°C) for Air II, confirming that the heating process was not optimal for this device (see Table 12).

Very few studies assessed the efficiency of Δ^9-THC delivery through cannabis vaporizers, and their results varied from 2.9% to 84% according to the experimental protocols (see Chapter 3.2.1). Table 13 shows that efficiency of Δ^9-THC delivery in aerosols was two times lower than in joint smoke (18 ± 6% vs 35 ± 4%) for the selected devices, and at the maximum heating temperature. Mighty$^+$ at 210°C (18 ± 6%) and FX$^+$ at 220°C (18 ± 5%) had similar efficiency, while Air II at 220°C had a lower Δ^9-THC delivery (8 ± 2%). At lower heating temperature, Δ^9-THC concentrations in emissions were decreasing, and less than 6% of Δ^9-THC was effectively delivered at 170°C for all vaporizers. Lastly, the type of heater system did not influence the efficiency of Δ9-THC delivery in aerosols, it is probably more dependent on the design of the device.

Table 11: Comparison of cannabinoid concentrations measured in emissions from three cannabis vaporizers at three temperatures and joints (with or without filter).

Cannabinoids	Mighty$^+$ [mg/g cannabis][1]			FX$^+$ [mg/g cannabis][1]			Air II [mg/g cannabis][1]			Joints [mg/g cannabis][1]	
	170°C	190°C	210°C	170°C	190°C	220°C	170°C	190°C	220°C	Without filter	With filter
Δ^9-THC	5.45 ± 0.48	12.8 ± 2.50	18.6 ± 5.89	2.29 ± 0.54	6.25 ± 1.40	18.3 ± 5.40	1.06 ± 0.54	2.64 ± 0.71	8.12 ± 2.26	54.6 ± 5.68	44,3 ± 7,2
Δ^9-THCA-A	0.07 ± 0.01	0.13 ± 0.04	0.13 ± 0.03	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.002	0.04 ± 0.02	0.05 ± 0.01	0.12 ± 0.02	1.74 ± 0.61	1,4 ± 0,2
Δ^8-THC	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	<LOQ
CBD	0.03 ± 0.01	0.07 ± 0.01	0.11 ± 0.004	0.01 ± 0.003	0.03 ± 0.005	0.12 ± 0.03	0.007 ± 001	0.002 ± 0.004	0.05 ± 0.01	0.22 ± 0.003	0,2 ± 0,1
CBD-A	<LOQ	<LOQ	<LOQ	nd	nd	nd	nd	nd	<LOQ	0.02 ± 0.004	<LOQ
CBG	0.30 ± 0.06	0.77 ± 0.12	1.39 ± 0.16	0.12 ± 0.03	0.37 ± 0.08	1.59 ± 0.39	0.04 ± 0.02	0.13 ± 0.05	0.44 ± 0.12	4.58 ± 0.65	3,8 ± 0,6
CBN	0.14 ± 0.04	0.66 ± 0.12	1.35 ± 0.64	0.04 ± 0.01	0.22 ± 0.04	2.07 ± 0.69	0.01 ± 0.007	0.05 ± 0.02	0.29 ± 0.15	1.60 ± 0.05	3,3 ± 0,7

Δ^9-THC: Delta-9-tetrahydrocannabinol; Δ^9-THCA-A: Delta-9-tetrahydrocannabinolic acid A; Δ^8-THC: Delta-8-tetrahydrocannabinol; CBD: Cannabidiol; CBD-A: Cannabidiolic acid; CBG: Cannabigerol; CBN: Cannabinol; nd: non-detected; <LOQ: below the limit of quantification.

[1] Results are expressed in milligrams per gram of cannabis (mg/g cannabis) for cannabis vaporizers and joints as mean ± standard deviation.

Table 12: Cannabinoid concentrations in dried cannabis flowers, "already vaped buds" (AVB) from three cannabis vaporizers at three different temperatures, and joint butts.

	Concentrations [mg/g cannabis][1]										
Cannabinoids	**Cannabis flowers**	**Mighty[+]**			**FX[+]**			**Air II**			**Joint butts[2]**
		170°C	**190°C**	**210°C**	**170°C**	**190°C**	**220°C**	**170°C**	**190°C**	**220°C**	
Δ^9-THC	6.76 ± 0.69	90.9	68.2	54.6	91.8	74.5	40.0	95.1	89.9	88.9	19.1
Δ^9-THCA-A	94.8 ± 26.3	0.45	0.59	0.19	0.35	0.12	0.14	14.0	3.37	1.14	14.9
Δ^8-THC	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
CBD	0.06 ± 0.009	0.33	0.25	0.20	0.29	0.28	0.21	0.23	0.48	0.35	0.09
CBD-A	0.44 ± 0.04	0.01	0.005	<LOQ	0.01	0.002	<LOQ	0.09	0.09	0.02	0.10
CBG	0.88 ± 0.06	6.84	5.98	5.98	6.69	6.89	4.79	5.42	6.65	7.59	1.50
CBN	0.47 ± 0.19	3.31	4.42	8.80	3.33	5.65	10.6	2.56	3.14	6.08	0.62

Δ^9-THC: Delta-9-tetrahydrocannabinol; Δ^9-THCA-A: Delta-9-tetrahydrocannabinolic acid A; Δ^8-THC: Delta-8-tetrahydrocannabinol; CBD: Cannabidiol; CBD-A: Cannabidiolic acid; CBG: Cannabigerol; CBN: Cannabinol; nd: non-detected; <LOQ: below the limit of quantification.

[1] Results are expressed in milligrams per gram of cannabis (mg/g cannabis), and as mean ± standard deviation for cannabis flowers. Only one replicate was analyzed, except for cannabis flowers (n=3).

[2] Mass included the joint residues and ash.

Table 13: Total Δ^9-THC percentages in cannabis flowers, in emissions of three vaporizers at three different temperatures, and in joints.

Cannabis product	Heating temperature	Δ^9-THC percentage in plant material [%] (Mean ± SD)[1]	Δ^9-THC percentage in emissions [%] (Mean ± SD)	Total percentage [%] (Mean ± SD)
Cannabis flowers	-	87 ± 23	-	87 ± 23
Mighty$^+$ ABV	**170°C**	89	5 ± 0.5	94 ± 0.5
	190°C	67	13 ± 2	79 ± 2
	210°C	53	18 ± 6	71 ± 6
FX$^+$ ABV	**170°C**	89	2 ± 1	92 ± 1
	190°C	72	6 ± 1	79 ± 1
	210°C	39	18 ± 1	57 ± 1
Air II ABV	**170°C**	104	1 ± 1	105 ± 1
	190°C	90	3 ± 1	93 ± 1
	210°C	87	8 ± 2	95 ± 2
Joint residues[2]	**> 600°C[70]**	31[3]	55 ± 6	86 ± 6

[1] Total Δ^9-THC concentrations in ABV were analyzed in only one, except for cannabis flowers.
[2] Joint residues consisted of the unburnt cannabis from the butt and the ash (only measured for joints without filter).
[3] Residues of three joints were mixed for the extraction and analysis.

Several parameters may affect Δ^9-THC delivery in cannabis vaporizers. The predicted boiling point of Δ^9-THC being around 417°C, Δ^9-THC will be transferred in emission via evaporation.[71] Evaporation is reliant on the vapor pressure (exponential relationship with the temperature), contact surface, and gas flow on the surface. Therefore, increasing temperature favors evaporation, which explains why we observed higher Δ^9-THC delivery at 210-220°C. Gas flow on the surface was defined by the puffing regime and was identical for all generation experiments with cannabis vaporizers. However, higher Δ^9-THC delivery efficiency might be obtained by increasing puff volume and/or puff duration; this will break the equilibrium between the gas phase and the liquid phase to promote evaporation. Consequently, users may potentially inhale higher Δ^9-THC concentrations than concentrations measured in laboratory, especially if they inhale puffs with a greater volume than 80 mL (laboratory conditions).

Evidence on real use conditions in users is needed to determine accurate puffing regime and confirm the the Δ^{9}-THC delivery efficiency in real conditions.

The duration of the generation of emissions seemed adequate as the cannabis flowers turned dark brown (at maximum temperature), except for Air II for which a color gradient was observed due to a lack of homogeneity in the heating of the sample. In the brochure on introduction and administration methods of medical cannabis by Vapormed (by Storz & Bickel; producer of Mighty^{+}), they reported a Δ^{9}-THC delivery between 49% (150 mg of hemp flower) and 53% (50 mg of hemp flowers) at 210°C with Mighty^{+} Medic.[72] However, the puffing regime used for these tests was not specified, and it is mentioned that "in order to reach these values, the patient must inhale until no more aerosol can be seen during exhalation".[72] In a non-independent scientific study commissioned by Storz & Bickel in 2018, Δ^{9}-THC deliveries of Mighty Medic (1st generation of Mighty) with 150 mg hemp flowers at 180°C was comprised between 50 and 60%.[73] However, incomplete information was also reported on puffing regime and puff volume was missing. They collected 20 puffs using a puff duration of 6 s every 30 s with a vacuum pump set at 4 mbar. They also extracted the already vaped buds (AVB) and reported 1-2% total Δ^{9}-THC, implying that ~40-50% of total Δ^{9}-THC was degraded or deposited in the device or collection system parts. In our study, we loaded 127 ± 13 mg of cannabis flowers in the Mighty^{+}, but the Δ^{9}-THC delivery was almost three times lower than what we could expect according to the manufacturer's information.

The lower Δ^{9}-THC delivery efficiency (around 18%) that we obtained for cannabis vaporizers may be explained by different factors. First, our lower efficiency compared to the previous studies may be explained by volume differences of heated air passing though the cannabis sample. The air volume was very high in the previous studies (≥ 5 L) compared to our study (1.2 L; 15 puffs of 80 mL). Secondly, we also observed an influence of the heating temperature on Δ^{9}-THC delivery efficiencies, like Pomahacova et al. (2009)[21]. The authors explained the lower Δ^{9}-THC delivery efficiency by a lower decarboxylation of Δ^{9}-THCA-A at lower temperatures, but this was not what we observed. Our hypothesis is that higher temperatures will favor the evaporation of cannabinoids, and this may be associated with a higher release of cannabinoid contained in the trichromes at increasing temperatures[71]. This hypothesis may be confirmed by higher concentrations of CBD and CBG in emissions at higher temperatures, with ratios similar to those observed for Δ^{9}-THC (~3x higher at 190°C and ~10x higher at 220°C). Lastly, Δ^{9}-THC also underwent thermal degradation. In our study, the total Δ^{9}-THC percentage (see Table 13) was only 57% in FX^{+} and 71% in Mighty^{+} at maximum temperature. This meant that 30-40% of Δ^{9}-THC was degraded. It is known that part of Δ^{9}-THC may be oxidized to form CBN, this transformation being temperature dependent.[74] This Δ^{9}-THC oxidation was also observed in our study. We estimated the percentage of total CBN by calculating the ratio of total CBN (i.e., concentration in emissions plus concentration in AVB) to theoretical Δ^9-THC concentration (i.e., 10.3%), and we obtained 3% and 12% at a heating temperature of 170°C and 210/220°C, respectively. However, our study protocol was not designed to study these three hypotheses, and further studies are needed to understand the influence of puffing regime and session duration on Δ^9-THC degradation.

- *ENNDS*

We tested five cannabis vaping devices or ENNDS – one pod system (OBY), two systems using clearomizers (Endura T20S and Nautilus X), and two vape pens (Noïd.Lab pod and Cable Pen). The devices were tested with six e-liquids. E-liquid #1 was prepared from the same plant material used in joints and cannabis vaporizers. Table 14 presents the cannabinoid concentrations in emissions of the five ENNDS using different e-liquids and a CBD extract. Except e-liquid #2, all the other e-liquids did not contain neither Δ^9-THCA-A nor CBD-A, this was due to a decarboxylation step added during the e-liquid manufacturing. This step was not added in e-liquid #2 manufacturing, and results show that the vaporization process did not completely decarboxylate Δ^9-THCA-A and CBD-A. The proportion of CBD-A and CBD in aerosols was almost 50:50. This low CBD-A decarboxylation might be explained by a too short period of time during which the coil reached high temperatures (150-250°C; during puffs) in ENNDS compared to vaporizers that heated continuously, as proposed by Varlet et al. (2016).[7] Consequently, a decarboxylation of Δ^9-THCA-A and CBD-A during e-liquid manufacturing should be carried out to ensure that all Δ^9-THC and CBD is administered in active form.

Table 15 shows that Δ^9-THC deliveries were close to 100% for all ENNDS tested, and for both e-liquids tested, making ENNDS, and especially the vape pen Noïd.Lab pod, the most effective cannabis device to administer Δ^9-THC by inhalation. With a Δ^9-THC concentration in e-liquid of 4.21%, vaping 30 puffs would be equivalent to smoking one joint. However, the high viscosity of the tested e-liquid #1 due to the use of PEG in the formulation (PEG/VG; 70:30) induced overheating of the coils, and real users would probably experience a bad taste. An overheating of the resistance was not observed with the second e-liquid (PG/VG; 70:30), as it was less viscous. This was confirmed by a concentration of CBN that was approximatively 30 times lower in aerosols of e-liquid #2 compared to aerosols of e-liquid #1, regardless of the device.

Total CBD deliveries were also close to 100% for all the ENNDS tested; however, there was an inconsistency between e-liquids, with a delivery efficiency about 50% for e-liquid #5, 80% for e-liquids #3 and 4, and 100% for e-liquids #1 and 2. Total CBD deliveries were very low for the CBD extract, only 20%. However, the CBG and CBN concentrations were much higher compared to the other e-liquids. Table 15 reports percentages of Δ^9-THC and CBD deliveries higher than 100%.

This is due to the use of different analytical instruments to quantify THC and CBD in e-liquids tested and in emissions. This might lead to an analytical error with a tolerance margin of around 20% in analytical results.[75] In addition to the precision (represented by the standard deviation), the accuracy is also important and should be within the tolerance margin of 20%. We used the THC and CBD concentrations reported in the certificates of analysis provided by the manufacturers to estimate the delivery rates we should obtain for THC and CBD in emissions, but we did not analyze e-liquids for THC and CBD in our laboratory. Based on these concentrations, THC delivery was more efficient for e-liquid #3, containing 100% PG, compared to e-liquids #2 and 4, containing PG/VG. For CBD, this was more inconsistent. Therefore, the solvent use in the e-liquid influenced the delivery efficiency of the cannabinoids.

Table 14: Cannabinoid concentrations in emission from five ENNDS using five different e-liquids and a CBD extract

		Cannabinoids [mg/g e-liq][1]						
Devices	**E-liquid**	**Δ^9-THC**	**Δ^9-THCA-A**	**Δ^8-THC**	**CBD**	**CBD-A**	**CBG**	**CBN**
OBY	**E-liquid #1**	42.2 ± 2.37	nd	nd	13.7 ± 1.30	nd	1.55 ± 0.11	1.13 ± 0.06
	E-liquid #2	0.71 ± 0.09	0.42 ± 0.03	nd	13.7 ± 6.72	22.9 ± 2.07	0.63 ± 0.07	0.05 ± 0.002
	E-liquid #3	105 ± 19.3	<LOQ	<LOQ	1.0 ± 0.2	<LOQ	5.6 ± 1	1.1 ± 0.2
	E-liquid #4	105 ± 11.5	<LOQ	<LOQ	1.1 ± 0.1	<LOQ	6.1 ± 1	1.2 ± 0.3
	E-liquid #5	0.2 ± 0.0	<LOQ	<LOQ	40.4 ± 1.9	<LOQ	2 ± 0.2	<LOQ
Endura T20-S	**E-liquid #1**	47.1 ± 3.51	0.05 ± 0.03	nd	15.4 ± 0.9	nd	2.42 ± 0.37	1.71 ± 0.29
	E-liquid #2	1.12 ± 0.14	0.25 ± 0.02	nd	22.9 ± 4.19	14.8 ± 1.21	0.96 ± 0.11	0.06 ± 0.01
	E-liquid #3	91.4 ± 13.9	<LOQ	<LOQ	0.9 ± 0.2	<LOQ	4.9 ± 1	1.3 ± 0.2
	E-liquid #4	104.3 ± 15.3	<LOQ	<LOQ	1.2 ± 0.1	<LOQ	6.6 ± 0.8	1.5 ± 0.1
	E-liquid #5	0.2 ± 0.1	<LOQ	<LOQ	47.1 ± 5.6	<LOQ	2.2 ± 0.3	<LOQ
Nautilus X	**E-liquid #2**	0.73 ± 0.44	0.19 ± 0.13	nd	10.1 ± 6.07	15.6 ± 14.4	0.50 ± 0.40	0.04 ± 0.03
Noïd.Lab pod	**E-liquid #3**	131 ± 21.9	<LOQ	<LOQ	1.3 ± 0.1	<LOQ	7.3 ± 0.9	2.1 ± 0
	E-liquid #4	127.6 ± 10.5	<LOQ	<LOQ	1.2 ± 0.1	<LOQ	7.2 ± 0.6	2.1 ± 0.2
	E-liquid #5	1.9 ± 0	<LOQ	<LOQ	66 ± 5.1	<LOQ	3.2 ± 0	<LOQ

		Cannabinoids [mg/g e-liq][1]						
Devices	**E-liquid**	**Δ^9-THC**	**Δ^9-THCA-A**	**Δ^8-THC**	**CBD**	**CBD-A**	**CBG**	**CBN**
Cable Pen	**CBD extract**	11.5 ± 0	<LOQ	59.7 ± 0	106.8 ± 0	<LOQ	20.1 ± 0	22.3 ± 0

Δ^9-THC: Delta-9-tetrahydrocannabinol; Δ^9-THCA-A: Delta-9-tetrahydrocannabinolic acid A; Δ^8-THC: Delta-8-tetrahydrocannabinol; CBD: Cannabidiol; CBD-A: Cannabidiolic acid; CBG: Cannabigerol; CBN: Cannabinol; nd: non-detected; <LOQ: below the limit of quantification.

[1] Results are expressed in milligrams per gram of vaporized e-liquid (mg/g e-liq) as mean ± standard deviation.

Table 15: Total Δ^9-THC and CBD percentages in emissions of five ENNDS using five different e-liquids and a CBD extract

ENNDS device		**Δ^9-THC percentage in emissions [%] (Mean ± SD)**	**CBD percentage in emissions [%] (Mean ± SD)**
OBY	e-liquid #1[1]	100 ± 6%	98 ± 9%
	e-liquid #2[2]	90 ± 12%	107 ± 20%
	e-liquid #3	118 ± 22%	76.9 ± 15%
	e-liquid #4	91.5 ± 10%	78.6 ± 7%
	e-liquid #5	-	40.4 ± 2%
Endura T20-S	e-liquid #1[1]	112 ± 8%	110 ± 6%
	e-liquid #2[2]	112 ± 15%	114 ± 11%
	e-liquid #3	102 ± 16%	69.2 ± 15%
	e-liquid #4	90.9 ± 13%	85.7 ± 7%
	e-liquid #5	-	47.1 ± 6%
Nautilus X	e-liquid #2[2]	99 ± 20%	105 ± 32%
Noïd.Lab pod	e-liquid #3	147% ± 25%	100 ± 7.7%
	e-liquid #4	111% ± 9%	85.7 ± 7%
	e-liquid #5	-	66 ± 5%
Cable Pen	CBD extract	-	17.2%

[1] Δ^9-THC and CBD contents in e-liquid #1 were 4.21% and 1.4%, respectively (according to the manufacturer's certificate of analysis)

[2] Total Δ^9-THC and CBD contents in e-liquid #2 were 0.12 ± 0.01% and 3.15 ± 0.13%, respectively (according to the manufacturer's report of analysis)

5.3. Aldehydes

Aldehyde formation is closely linked to combustion or pyrolysis processes due to the thermal degradation of several substances. Several aldehydes are of particular concern, such as formaldehyde (carcinogenic to humans; IARC Group 1), acrolein (probably carcinogenic to human; IARC Group 2A), acetaldehyde (possibly carcinogenic to humans; IARC Group 2B), and crotonaldehyde (possibly carcinogenic to humans; IARC Group 2B). Table 18 presents the aldehyde concentrations in the emissions of cannabis vaporizers, ENNDS using e-liquids containing THC, and joints. Aldehyde concentration was higher in joint smoke compared to vaporizer emissions. This was due to the high temperatures of combustion (700-950°C), which are more than three times higher compared to the heating temperature of vaporizers.[76]

- *Joints*

Table 16 compares aldehyde concentration measured in joint smoke in our lab with concentrations from previous studies of Moir et al. (2008)[10] and Ward and Ebbert (2021)[13]. Our results, expressed as µg/g cannabis, were about twice as high as the concentrations reported in the previous studies. Differences may arise from various parameters, such as the plant material (e.g., provenance, preparation, quantity), the joint constituents (e.g., cigarette paper, filter), and the puffing regime. However, we observe an important reduction of several aldehyde compounds, including formaldehyde, acetaldehyde and crotonaldehyde, when a filter was added to the joints. The filter could thus potentially reduce the aldehyde exposure of joint smokers. Nevertheless, the aldehyde concentrations remain higher in joint emission with filter compared to vaporizer emission at the highest temperature (Table 17).

Table 16: Comparison of aldehyde concentrations in joint smoke with previous studies

Aldehydes	Moir et al. (2008)[10] [µg/g cannabis][1]		Ward and Ebbert (2021)[13] [µg/g cannabis][2,3]		Our results [µg/g cannabis][3] (joints without filter)
	ISO regime[4]	Extreme regime[5]	Brand A[6]	Brand B[7]	
Formaldehyde	32.6 ± 3.51	86 ± 15.3	60 ± 10	70 ± 10	252 ± 112
Acetaldehyde	583 ± 57.2	1321 ± 128	1050 ± 100	1680 ± 40	3077 ± 392
Acrolein	70.6 ± 5.85	191 ± 16.8	150 ± 60	170 ± 10	317 ± 50.7
Proprionaldehyde	42 ± 4.16	95.7 ± 8.28	80 ± 10	120 ± 3	164 ± 17.2
Crotonaldehyde	30 ± 1.95	73.4 ± 9.96	60 ± 10	50 ± 4	170 ± 26.4
Butyraldehyde	60.5 ± 4.94	142 ± 10.4	120 ± 10	150 ± 2	377 ± 45.4

[1] Mean aldehyde concentrations in mainstream expressed as µg/joint were transformed to µg/g cannabis assuming a cannabis mass of 769 mg/joint for ISO regime and 773 mg/joint for Extreme regime.
[2] Mean aldehyde concentrations expressed in mg/joint were transformed to µg/g cannabis assuming a cannabis mass of 1 g/joint.
[3] Health Canada Intense (HCI) puffing regime: puff volume of 55 mL, puff duration of 2 s and interval of a 30 s.
[4] ISO puffing regime: puff volume of 35mL, puff duration of 2 s and puff interval of 60 s.
[5] Extreme puffing regime: puff volume of 70 mL, puff duration of 2 s and interval of a 30 s.
[6] Joints contained ~1 g plant material with 90 mg of cannabis.
[7] Joints contained ~50 mg of CBD (total mass not specified).

- *Cannabis vaporizers*

As shown in Table 17, acetaldehyde and butyraldehyde were quantified in vaporizer emissions. Their concentrations increased with the temperature of use. The other selected aldehydes were under the limit of quantification, except for propanal and benzaldehyde that were quantified at 220°C with the FX^+ device. Temperature and carbon dioxide concentrations are two known factors that influence aldehyde emission.[77] Higher temperature and higher carbon dioxide concentration will favor aldehyde emission. This is proven by the results of this study.

The convection-based device (FX^+) emitted higher concentrations of acetaldehyde compared to the two hybrid systems. However, similar aldehyde concentration was observed for the three devices when it was adjusted by Δ^9-THC concentration. Propanal and benzaldehyde were only measured in the FX^+ emission, but at very low concentrations compared to joints. It may thus be possible that convection-based devices emit a higher concentration of aldehydes compared to hybrid heating systems.

Table 17: Comparison of aldehyde concentrations measured in emissions from vaporizers (three temperatures) and joints (with and without filter)

Aldehydes	Mighty$^+$ [µg/g of cannabis][1]			FX$^+$ [µg/g cannabis][1]			Air II [µg/g cannabis][1]			Joints [µg/g cannabis][1]	
	170°C	190°C	210°C	170°C	190°C	220°C	170°C	190°C	220°C	Without filter	With filter
Formaldehyde	nd	nd	<LOQ	nd	nd	<LOQ	nd	nd	<LOQ	252 ± 112	127 ± 28.2
Acetaldehyde	67.6 ± 5.8	102 ± 3	200 ± 11	59.4 ± 8.8	112 ± 5	312 ± 38	63.5 ± 10.3	73.2 ± 21.7	159 ± 0.1	3077 ± 392	1'056 ± 212
Acrolein	nd	nd	<LOQ	nd	nd	<LOQ	nd	nd	<LOQ	317 ± 50.7	<LOQ
Propionaldehyde	nd	<LOQ	<LOQ	nd	<LOQ	16.9 ± 1.6	nd	<LOQ	<LOQ	164 ± 17.2	<LOQ
Crotonaldehyde	nd	nd	<LOQ	nd	nd	<LOQ	nd	nd	<LOQ	170 ± 26.4	<LOQ
Butyraldehyde	29.2 ± 3.9	32.7 ± 2.8	41.4 ± 3.3	25.8 ± 1.3	37.6 ± 1.4	44.8 ± 4.8	21.5 ± 2.8	23 ± 3.9	32.2 ± 0.1	377 ± 45.4	84.5 ± 14.2
Benzaldehyde	nd	nd	nd	nd	nd	21.2 ± 2.2	nd	nd	<LOQ	277 ± 41.6	<LOQ
Isovaleraldehyde	nd	<LOQ	<LOQ	<LOQ	13.9 ± 0.7	<LOQ	<LOQ	<LOQ	<LOQ	173 ± 17.7	<LOQ
Hexanal	nd	nd	nd	nd	nd	nd	nd	nd	nd	<LOQ	133 ± 30.8

nd: non-detected; <LOQ: below the limit of quantification.

[1] Results are expressed in micrograms per gram of cannabis (µg/g cannabis) for cannabis vaporizer and joint as mean ± standard deviation.

Table 18: Aldehyde concentrations adjusted by Δ^9-THC concentrations in emission from three cannabis vaporizers at three temperatures, from two ENNDS using e-liquids #1, #3 and #4, and from joints.

		Aldehydes [µg/mg Δ9-THC][1]								
Devices		**Formaldehyde**	**Acetaldehyde**	**Acrolein**	**Propanal**	**Crotonaldehyde**	**Butyraldehyde**	**Benzaldehyde**	**Isovaleraldehyde**	**Hexanal**
Mighty+	170°C	-	12.4 ± 1.5	-	-	-	5.35 ± 0.86	-	-	-
	190°C	-	8.00 ± 1.58	-	-	-	2.56 ± 0.55	-	-	-
	210°C	-	10.7 ± 3.5	-	-	-	2.22 ± 0.73	-	-	-
FX+	170°C	-	26.0 ± 7.3	-	-	-	11.3 ± 2.7	-	-	-
	190°C	-	17.8 ± 4.1	-	-	-	6.0 ± 1.4	-	2.2 ± 0.5	-
	220°C	-	17.0 ± 5.4	-	0.9 ± 0.3	-	2.5 ± 0.77	1.2 ± 0.4	-	-
Air II	170°C	-	60.1 ± 31.9	-	-	-	20.4 ± 10.7	-	-	-
	190°C	-	27.7 ± 11.1	-	-	-	8.73 ± 2.79	-	-	-
	220°C	-	19.6 ± 10.2	-	-	-	3.96 ± 1.28	-	-	-
OBY	1-15 puffs[2]	1.32 ± 0.71	0.84 ± 0.29	-	-	81.5 ± 16.5	-	-	-	-
	16-30 puffs[2]	164 ± 61	77.4 ± 25.0	4.88 ± 1.66	3.50 ± 0.45	32.1 ± 27.9	8.84 ± 1.96	-	-	-
	1-25 puffs[3]	-	0.07 ± 0.01	-	-	-	-	-	-	-
	1-25 puffs[4]	0.32 ± 0.15	0.13 ± 0.03	-	-	-	-	-	-	-
Endura T20-S	1-30 puffs[2]	2.58 ± 0.57	1.93 ± 0.56	-	-	-	-	-	-	-
	1-25 puffs[3]	-	0.10 ± 0.02	-	-	-	-	-	-	-

		Aldehydes [µg/mg Δ9-THC][1]								
Devices		**Formaldehyde**	**Acetaldehyde**	**Acrolein**	**Propanal**	**Crotonaldehyde**	**Butyraldehyde**	**Benzaldehyde**	**Isovaleraldehyde**	**Hexanal**
	1-25 puffs[4]	0.1 ± 0.02	0.09 ± 0.02	-	-	-	-	-	-	-
Noïd.Lab pod	1-25 puffs[3]	-	-	-	-	-	-	-	-	-
	1-25 puffs[4]	-	-	-	-	-	-	-	-	-
Joints	Without filter	7.06 ± 3.25	86.4 ± 15.1	8.90 ± 1.78	4.61 ± 0.73	4.77 ± 0.94	8.74 ± 2.33	7.78 ± 1.50	4.85 ± 0.77	-
	With filter	2.86 ± 0.77	23.8 ± 6.00	-	-	-	1.91 ± 0.43	-	-	3.00 ± 0.83

- : non detected.

1 Results are expressed in micrograms per milligram of Δ^9-THC (µg/mg Δ^9-THC) as mean ± standard deviation.

2 Aerosol collection was performed separately for puffs 1 to 15 and for puffs 16 to 30 with the same pod using E-liquid #1.

3 Aldehyde concentrations adjusted by Δ9-THC concentrations in emission from e-liquid #3.

4 Aldehyde concentrations adjusted by Δ9-THC concentrations in emission from e-liquid #4.

Cannabis vaporizers expose users to harmful aldehydes, however, less than joints. Bloor et al. (2008) observed acetaldehyde (24.5 ppm) in the emission of a vaporizer (lower than in joint smoke; 40–45 ppm).[27] Table 18 presents the aldehyde concentrations adjusted by Δ^9-THC concentration (EQ(2)) to compare emissions of vaporizers with joints. Joints emitted higher aldehyde concentrations than vaporizers, and several aldehydes are not present in vaporizer emission, including formaldehyde and acrolein - even higher temperatures. Based on these results, cannabis vaporizers tested appeared to be a preferable alternative to joints. Aldehyde concentrations were inversely proportional to the used temperature of cannabis vaporizers. Mighty$^+$ was the device with the lowest concentration, followed by FX$^+$ and Air II.

- *ENNDS*

Table 19 presents the aldehyde analysis in ENNDS emissions generated using five e-liquids and a CBD extract. For ENNDS with e-liquid #1, high concentrations of formaldehyde, acetaldehyde, acrolein, crotonaldehyde, and butyraldehyde (i.e., in the range of mg/g e-liquid) were measured with OBY. The high aldehyde concentration confirmed that e-liquid #1 was too viscous and not suitable for this device. Concentration increased with the number of puffs and was correlated with a decrease in mass loss (i.e., amount of e-liquid used), indicating a poor supply of e-liquid to the coil resulting in overheating. Users would probably not use this device with such viscous e-liquids, as they may experience a burnt taste. We replicated the experiment with e-liquid #1 using another vaping device (Endura T20-S; 30 puffs), and only formaldehyde and acetaldehyde were above the limit of quantification, at lower concentrations than OBY (122 µg/g e-liq and 91 µg/g e-liq, respectively). However, these concentrations were ten times higher than concentrations measured in our previous study using nicotine-containing e-liquids (PG/VG). This was consistent with the study of Troutt et al. (2017) that reported higher aldehyde concentrations emitted when PEG is heated compared to PG.[40] All aldehyde concentrations in e-liquid #2 aerosols (PG/VG) were below the limits of quantification for both OBY and Endura T20-S, indicating that this e-liquid formulation was more suitable for both devices. However, we measured high concentration of aldehydes (e.g., 490 µg/g e-liq and 430 µg/g e-liq of formaldehyde and acetaldehyde, respectively) in the Nautilus X aerosol using e-liquid #2. The coil used (PockeX) for this device was more suitable for the e-liquid with a high percentage of VG.

Formaldehyde is only quantified above the LOQ in the emission of all the ENNDS tested when VG is added in the composition of the e-liquids #4 and #5 compared to e-liquid #3 without VG, except for the Noïd.Lab pod (Table 18 and Table 19). The emission of e-liquids #3, #4, and #5 did not contain any other aldehydes than formaldehyde and acetaldehyde, regardless the device. No aldehyde concentration was measured in the emission of Noïd.Lab pod. Regarding the CBD extract, benzaldehyde and hexanal was measured in addition to formaldehyde and acetaldehyde in the emission of the Cable Pen vape pen. The CBD extract did not contain any PG or VG to dilute the CBD extract, but waxes and fats that may explain these results.

Expressed as ratio of aldehyde to Δ^9-THC concentrations (Table 18), Noïd.Lab pod had the best ratios compared to all the devices tested, followed by Endura T20-S, except for formaldehyde (3 µg/mg Δ^9-THC) that was absent in vaporizer emissions.

Table 19: Aldehyde concentrations in emission from five ENNDS using five e-liquids and a CBD extract

			Aldehydes [µg/g e-liq][1]								
Devices	**E-liquids**	**Puff number**	**Formaldehyde**	**Acetaldehyde**	**Acrolein**	**Propanal**	**Crotonaldehyde**	**Butyraldehyde**	**Benzaldehyde**	**Isovaleral-dehyde**	**Hexanal**
OBY	E-liquid #1	1-15 puffs	55.6 ± 30.0	35.7 ± 12.0	nd	nd	3440 ± 668	<LOQ	nd	nd	-
		16-30 puffs	6’901 ± 2’536	3’268 ± 1’038	206 ± 69	148 ± 17	1’358 ± 1’176	373 ± 80	nd	nd	-
	E-liquid #2	1-30 puffs	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	nd	nd	<LOQ	-
	E-liquid #3	1-25 puffs	<LOQ	6.9 ± 0.6	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	E-liquid #4	1-25 puffs	34 ± 15.4	13.9 ± 2.6	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	E-liquid #5	1-25 puffs	10.3 ± 3.5	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Endura T20-S	E-liquid #1	1-30 puffs	122 ± 25	91.0 ± 25.4	<LOQ	nd	<LOQ	nd	nd	nd	-
	E-liquid #2	1-30 puffs	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	nd	nd	<LOQ	-
	E-liquid #3	1-25 puffs	<LOQ	9.2 ± 0.7	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	E-liquid #4	1-25 puffs	10.3 ± 0.3	9.5 ± 1.5	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	E-liquid #5	1-25 puffs	37.5 ± 25.7	12.1 ± 2.4	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Nautilus X	E-liquid #2	1-30 puffs	488.3 ± 246	428.8 ± 246.8	32.8 ± 9.2	76 ± 28.1	<LOQ	nd	nd	62.9 ± 26.3	-
Noïd.Lab pod	E-liquid #3	1-25 puffs	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	E-liquid #4	1-25 puffs	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	E-liquid #5	1-25 puffs	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ

			Aldehydes [µg/g e-liq][1]								
Devices	E-liquids	Puff number	Formaldehyde	Acetaldehyde	Acrolein	Propanal	Crotonaldehyde	Butyraldehyde	Benzaldehyde	Isovaleral-dehyde	Hexanal
Cable Pen[2]	CBD extract	1-25 puffs	17.6	14.9	<LOQ	<LOQ	<LOQ	<LOQ	15.1	<LOQ	47.4

-: not analyzed; nd: non detected; <LOQ: below the limit of quantification.

[1] Results are expressed in micrograms per gram of vaporized e-liquid (µg/g e-liq) as mean ± standard deviation.

[2] Only one replicate was performed due to the small volume of the cartridge (0.55 mL).

5.4. Volatile organic compounds (VOCs) and phenols

Table 21 and Table 23 present the VOC and phenol concentrations in the emissions of cannabis vaporizers, ENNDS, and joints. Like aldehydes, VOCs can be formed during combustion and pyrolysis processes. This explained why we detected more VOCs in joint smoke, in cannabis vaporizers at maximum heating temperature, and in OBY that overheated using e-liquid #1. Phenol compounds were only measured in joint smoke (Table 21).

- *Joints*

Moir et al. (2008) reported VOC concentrations (including phenols) ten times higher than our results (Table 20).[11] These differences emphasized the influence of the joint composition, the amount of cannabis added in the joint, and the puffing regime on the presence of toxicants in emissions. The addition of the selected filter reduces the concentration of VOCs and phenols in joint emission by a factor of two or more for most of the compounds, except for p-cresol and glycidol (Table 21 and Table 22). These two compounds were quantified in higher concentrations in emission of joints with filters than without filters. It might be due to analytical variations of the instrument as the experiments with and without filters were not performed nor analyzed at the same time. However, after adjusting glycidol concentrations by the Δ^9-THC concentration (Table 22), the glycidol concentrations in emissions of joints with filters are comparable to those in vaporizer emission at the highest temperatures.

We did not analyze 1,3-propanediol in emission of joints without filters. We can expect to measure it as 1,3-propanediol may be produced from glycerol (from biomass) by hydrogenolysis.[78] Our results confirmed this hypothesis as similar concentrations of 1,3-propanediol were measured in the emissions of joints and of vaporizers whereas no concentration was quantified in ENNDS emission, except when CBD extracts were used (Table 21 and Table 23, respectively). Any harmful effects were observed in rats exposed by inhalation to vapor or to a mixture of vapor and aerosol of 1,3-propanediol.[79] It is therefore not expected to be harmful for humans exposed through inhalation.

Table 20: Volatile organic compound (VOC) concentrations quantified in joint smoke; comparison with previous study

	Moir et al. 2008 [µg/g de cannabis][1]		Our results [µg/g de cannabis] (joints without filter)
	ISO regime[2]	Extreme regime[3]	
VOCs:			
1,3-butadiene	103 ± 9.62	179 ± 22	49.9 ± 5.3
Isoprene	96.2 ± 8.45	171 ± 24.6	21.1 ± 0.7
Benzene	75.8 ± 7.67	109 ± 11.5	18.0 ± 0.7
Pyridine	45 ± 5.59	120 ± 11.5	17.6 ± 2.2
Toluene	161 ± 19.5	257 ± 32.3	18.0 ± 1.0
Styrene	22.4 ± 2.99	57.8 ± 5.43	5.79 ± 0.76
Quinoline	1.38 ± 0.34	3.47 ± 0.44	<LOQ
Phenols:			
o-Cresol	23.0 ± 1.95	60.5 ± 5.05	6.60 ± 0.27
m- + p-Cresol	75.2 ± 8.71	203 ± 15.5	28.5 ± 1.0
Phenol	119 ± 13.7	343 ± 25.9	41.7 ± 1.27
Hydroquinone	39.1 ± 3.77	92.2 ± 3.75	11.4 ± 0.8
Catechol	83.1 ± 9.49	208 ± 24.6	44.5 ± 1.14

[1] Mean aldehyde concentrations in mainstream expressed in µg/joint were transformed to µg/g cannabis assuming a cannabis mass of 769 mg/joint for ISO regime and 773 mg/joint for Extreme regime.
[2] ISO puffing regime: puff volume of 35mL, puff duration of 2 s and puff interval of 60 s.
[3] Extreme puffing regime: puff volume of 70 mL, puff duration of 2 s and interval of a 30 s.

- *Cannabis vaporizers*

Overall, VOC emission was non-detectable or below the limit of quantification in cannabis vaporizers, except for glycidol, and 1,3-propanediol. These compounds were detected at the maximum heating temperatures, and their concentrations increased with the temperature of use. However, higher concentration was observed in cannabis vaporizers and ENNDS compared to joints. VOC concentrations adjusted to THC concentration was higher in joint smoke compared to aerosols from a cannabis vaporizer, except for glycidol and 1,3-propanediol, as shown in Table 22. No differences were observed between the types of heating systems.

- *ENNDS*

Glycidol concentrations were higher in OBY than in Endura T20-S for all the e-liquids tested. Glycidol is a thermal degradation product of vegetal glycerin (VG), this may explain its presence in ENNDS emissions using e-liquid #1 and e-liquid #2, and its low concentrations in e-liquids #3, 4 and 5 that contained low VG concentrations in their composition.[80] Glycidol is classified as probably carcinogenic to humans (IARC; Group 2A).[79,81] Users are thus still exposed to some toxicants when using vaporizing devices, even if they considerably reduced their exposure to most of them. Unlike e-liquid #1, all VOC and phenol concentrations measured were below the LOQ for e-liquid #2, except for ethanol, styrene, propylene glycol, and diethylene glycol as VOC compounds, and p-cresol as phenol compound (Table 23). Likewise, all concentrations of VOC compounds and phenols were close or below the LOQ for e-liquids #3, 4, and 5, and for all ENNDS tested.

Table 21: Comparison of VOC and phenol concentrations measured in emissions from three cannabis vaporizers at three temperatures and joints (with and without filter).

Compound	**Mighty+ [µg/g cannabis][1]**			**FX+ [µg/g cannabis][1]**			**Air II [µg/g cannabis][1]**			**Joints [µg/ g cannabis][1]**	
	170°C	**190°C**	**210°C**	**170°C**	**190°C**	**220°C**	**170°C**	**190°C**	**220°C**	**Without filter**	**With filter**
VOCs:											
1,3-Butadiene	nd	nd	nd	nd	<LOQ	<LOQ	nd	nd	nd	49.9 ± 5.3	7.3 ± 5.3
Isoprene	nd	nd	nd	nd	<LOQ	<LOQ	nd	nd	nd	21.1 ± 0.7	-[2]
Propylene oxide	nd	nd	nd	nd	nd	<LOQ	nd	nd	<LOQ	1.33 ± 0.06	-
Benzene	nd	nd	nd	nd	nd	nd	nd	nd	nd	17.9 ± 0.7	6.8 ± 1.9
Glycidol	<LOQ	<LOQ	6.09 ± 1.32	<LOQ	3.52 ± 0.53	8.52 ± 0.62	<LOQ	<LOQ	5.76 ± 1.22	3.13 ± 0.46	34.2 ± 15.1
Pyridine	nd	nd	nd	nd	<LOQ	<LOQ	nd	nd	nd	17.6 ± 2.2	4.3 ± 2.1
Toluene	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	18.0 ± 1.0	-[2]
1,3-Propanediol	<LOQ	6.15 ± 0.34	6.71 ± 0.51	3.48 ± 1.68	5.12 ± 0.33	5.98 ± 0.30	<LOQ	4.36 ± 0.15	5.80 ± 0.90	-	3.1 ± 0.3
Ethylbenzene	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	5.56 ± 0.62	1.6 ± 0.8
o-Xylene	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	4.80 ± 0.61	2.2 ± 1.4

Compound	**Mighty+ [µg/g cannabis][1]**			**FX+ [µg/g cannabis][1]**			**Air II [µg/g cannabis][1]**			**Joints [µg/ g cannabis][1]**	
	170°C	**190°C**	**210°C**	**170°C**	**190°C**	**220°C**	**170°C**	**190°C**	**220°C**	**Without filter**	**With filter**
m-/p-Xylene	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.7 ± 0.7
Styrene	nd	nd	nd	nd	nd	<LOQ	nd	nd	nd	5.79 ± 0.76	1.3 ± 0.6
Quinoline	nd	nd	nd	nd	nd	nd	nd	nd	nd	<LOQ	-
Phenols:											
o-Cresol	nd	nd	nd	nd	nd	nd	nd	nd	nd	6.60 ± 0.27	2.0 ± 0.4
m-Cresol	nd	nd	nd	nd	nd	nd	nd	nd	nd	24.8 ± 0.71	1.0 ± 0.2
p-Cresol	nd	nd	<LOQ	nd	<LOQ	<LOQ	nd	nd	<LOQ	3.70 ± 0.25	8.1 ± 1.5
Phenol	nd	nd	nd	nd	nd	nd	nd	nd	nd	41.7 ± 1.27	11.1 ± 0.8
Hydroquinone	nd	nd	nd	nd	nd	nd	nd	nd	nd	11.4 ± 0.8	8.8 ± 1.8
Catechol	nd	nd	nd	nd	nd	nd	nd	nd	nd	44.5 ± 1.1	17.1 ± 2.1

-: not analyzed; nd: non-detected; <LOQ: below the limit of quantification.

[1] Results are expressed in micrograms per gram of cannabis (µg/g cannabis) for cannabis vaporizer and joint as mean ± standard deviation.

[2] Some contaminations were detected, and it is not possible to report the results in this table.

Table 22: VOC and phenol concentrations adjusted by Δ^9-THC concentrations in emission from three cannabis vaporizers at three temperatures, from two ENNDS using e-liquid #1, and from joints (with and without filter)

	Concentration [µg/mg Δ^9-THC][1]												
	Mighty$^+$			FX$^+$			Air II			Endura T20-S	OBY	Joints[1]	
Compound	**170°C**	**190°C**	**210°C**	**170°C**	**190°C**	**220°C**	**170°C**	**190°C**	**220°C**	**E-liquid #1**	**E-liquid #1**	**Without filter**	**With filter**
VOCs:													
1,3-butadiene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.01 ± 0.01	0.91 ± 0.14	0.17 ± 0.12
Isoprene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.39 ± 0.04	-
Propylene oxide	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.02 ± 0.003	-
Benzene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.33 ± 0.04	0.15 ± 0.05
Glycidol	nd	nd	0.33 ± 0.13	nd	0.56 ± 0.15	0.47 ± 0.14	nd	nd	0.71 ± 0.25	0.47 ± 0.61	0.77 ± 0.09	0.06 ± 0.01	0.77 ± 0.36
Pyridine	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.03 ± 0	0.32 ± 0.05	0.10 ± 0.05
Toluene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.33 ± 0.04	-
1,3-Propanediol	nd	0.48 ± 0.1	0.36 ± 0.12	1.52 ± 0.82	0.82 ± 0.19	0.33 ± 0.1	nd	1.65 ± 0.45	0.71 ± 0.23	nd	0.04 ± 0.01	-	0.07 ± 0.01
Ethylbenzene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.10 ± 0.02	0.04 ± 0.02
o-Xylene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.09 ± 0.01	0.05 ± 0.03

	Concentration [µg/mg Δ^9-THC][1]											
	Mighty$^+$			FX$^+$			Air II			Endura T20-S	OBY	Joints[1]	
Compound	**170°C**	**190°C**	**210°C**	**170°C**	**190°C**	**220°C**	**170°C**	**190°C**	**220°C**	**E-liquid #1**	**E-liquid #1**	**Without filter**	**With filter**
m-/p-Xylene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.02 ± 0.02
Styrene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.11 ± 0.02	0.03 ± 0.01
Quinoline	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	-
Phenols:													
o-Cresol	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.12 ± 0.01	0.05 ± 0.01
m-Cresol	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.45 ± 0.05	0.02 ± 0.01
p-Cresol	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.07 ± 0.01	0.18 ± 0.05
Phenol	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.76 ± 0.08	0.25 ± 0.05
Hydroquinone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.21 ± 0.03	0.20 ± 0.05
Catechol	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.81 ± 0.09	0.39 ± 0.08

-: not analyzed; nd: non-detected.

[1] Results are expressed in micrograms per milligram of Δ^9-THC (µg/mg Δ^9-THC) as mean ± standard deviation.

Table 23: VOC and phenol concentrations in emission from five ENNDS using five e-liquids and a CBD extract

	Concentration [µg/g e-liq][1]											
	OBY					Endura T20-S					Nautilus X	Cable Pen
Compound	**E-liquid #1**	**E-liquid #2**	**E-liquid #3**	**E-liquid #4**	**E-liquid #5**	**E-liquid #1**	**E-liquid #2**	**E-liquid #3**	**E-liquid #4**	**E-liquid #5**	**E-liquid #2**	**CBD extract**
VOCS:												
1,3-Butadiene	0.60 ± 0.29	-	nd	nd	nd	nd	-	nd	nd	nd	-	nd
Isoprene	<LOQ	-	-	-	-	nd	-	-	-	-	-	-
Acrylonitrile	-	nd	0.1 ± 0	0.1 ± 0	<LOQ	-	nd	<LOQ	<LOQ	<LOQ	nd	0.4
Ethanol	-	11.5 ± 1.5	-	-	-	-	13.7 ± 1.5	-	-	-	21.7 ± 1.1	-
Benzene	nd	nd	<LOQ	<LOQ	<LOQ	nd	nd	<LOQ	<LOQ	<LOQ	nd	<LOQ
Glycidol	32.5 ± 3.4	nd	1.5 ± 0.1	4.1 ± 0.3	3.5 ± 0.1	22.0 ± 28.9	nd	2.1 ± 0.1	2.8 ± 0.6	3 ± 0.1	nd	5.9
Propylene oxide	<LOQ	nd	-	-	-	nd	nd	-	-	-	nd	-
Pyridine	1.12 ± 0.19	nd	<LOQ	<LOQ	0.3 ± 0	<LOQ	nd	<LOQ	<LOQ	0.4 ± 0	nd	<LOQ
Toluene	<LOQ	<LOQ	-	-	-	<LOQ	<LOQ	-	-	-	<LOQ	-
1,3-Propanediol	1.76 ± 0.41	nd	nd	nd	nd	<LOQ	nd	nd	nd	nd	nd	66.9
Ethylbenzene	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ

	Concentration [µg/g e-liq][1]											
	OBY					Endura T20-S					Nautilus X	Cable Pen
Compound	**E-liquid #1**	**E-liquid #2**	**E-liquid #3**	**E-liquid #4**	**E-liquid #5**	**E-liquid #1**	**E-liquid #2**	**E-liquid #3**	**E-liquid #4**	**E-liquid #5**	**E-liquid #2**	**CBD extract**
VOCS:												
o-Xylene	<LOQ	<LOQ	0.5 ± 0.3	1.3 ± 0.8	<LOQ	<LOQ	<LOQ	0.4 ± 0.3	0.3 ± 0.4	<LOQ	<LOQ	0
m-/p-Xylene	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.5
Styrene	<LOQ	<LOQ	0.1 ± 0.01	0.2 ± 0.02	0.2 ± 0.01	nd	<LOQ	0.2 ± 0.1	0.2 ± 0.01	0.1 ± 0.1	<LOQ	0.5
Quinoline	nd	-	-	-	-	nd	-	-	-	-	-	-
Phenols:												
o-Cresol	nd	<LOQ	<LOQ	<LOQ	nd	nd	<LOQ	<LOQ	<LOQ	nd	<LOQ	nd
m-Cresol	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
p-Cresol	<LOQ	<LOQ	<LOQ	<LOQ	nd	<LOQ	<LOQ	<LOQ	<LOQ	nd	<LOQ	0.6
Phenol	nd	<LOQ	0.3 ± 0	0.3 ± 0	<LOQ	nd	<LOQ	0.4 ± 0	0.3 ± 0	<LOQ	<LOQ	0.7
Hydroquinone	nd	nd	<LOQ	<LOQ	<LOQ	nd	nd	<LOQ	<LOQ	<LOQ	nd	<LOQ
Catechol	nd	nd	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	nd	nd	0.3 ± 0.2	0.3 ± 0.04	0.5 ± 0.2	nd	1.8

-: Not analyzed; nd: not detected; <LOQ: below the limit of quantification.

[1] Results are expressed in micrograms per gram of vaporized e-liquid (µg/g e-liq) as mean ± standard deviation, except for CBD extract as only one replicate was performed.

Table 23 (Suite)

Compound	Concentration [µg/g e-liq][1]		
	Noïd.Lab pod		
	E-liquid #3	E-liquid #4	E-liquid #5
VOCS:			
1,3-Butadiene	<LOQ	<LOQ	<LOQ
Isoprene	-	-	-
Acrylonitrile	<LOQ	<LOQ	<LOQ
Ethanol	-	-	-
Benzene	<LOQ	<LOQ	<LOQ
Glycidol	2.3 ± 0.3	5.3 ± 0.7	5.8 ± 0.5
Propylene oxide	-	-	-
Pyridine	<LOQ	<LOQ	0.5 ± 0.4
Toluene	-	-	-
1,3-Propanediol	nd	nd	nd
Ethylbenzene	<LOQ	<LOQ	<LOQ

Compound	**Concentration [µg/g e-liq][1]**		
	Noïd.Lab pod		
	E-liquid #3	**E-liquid #4**	**E-liquid #5**
VOCS:			
o-Xylene	4.3 ± 2.7	2 ± 0.4	<LOQ
m-/p-Xylene	0.2 ± 0.2	<LOQ	<LOQ
Styrene	0.5 ± 0.1	0.3 ± 0.3	0.2 ± 0.2
Quinoline	-	-	-
Phenols:			
o-Cresol	<LOQ	<LOQ	nd
m-Cresol	nd	nd	nd
p-Cresol	<LOQ	nd	nd
Phenol	0.6 ± 0.1	0.4 ± 0.3	nd
Hydroquinone	<LOQ	<LOQ	<LOQ
Catechol	0.3 ± 0	0.4 ± 0.1	0.5 ± 0.4

-: Not analyzed; nd: not detected; <LOQ: below the limit of quantification.

[1] Results are expressed in micrograms per gram of vaporized e-liquid (µg/g e-liq) as mean ± standard deviation.

5.5. PAHs

Table 25 presents the PAH concentration in cannabis vaporizer emission, ENNDS using e-liquid #1, and joints. Overall, PAHs were only above the limit of quantification in the emission from joints and ENNDS using e-liquid #1, except for naphthalene, which was also measured in FX+ emission at 220°C.

PAHs are formed during partial combustion processes when the temperature is very high (above 350°C).[82] The temperature of a burning joint (800–900°C during a puff) explained the presence of PAHs in joint smoke.[76] For low-molecular weight PAHs, our results are comparable to the ones of previous studies (Table 24).

Although high-molecular weight PAHs were detected through GC-MS, they could not be quantified due to a very low extraction recovery rate of these PAHs from CFP filters. Extraction recovery was poor and it decreased with the molecule size (from 75% for naphatalene-D8 to 20% for benzo[g,h,i]perylene-D12). We tested different extraction solvents (hexane, dichloromethane, and dichloromethane-acetone mixture) and extraction techniques (rotary shaking machine, ultrasonic bath, and Soxhlet extractor), but that did not improve the recovery. We also tested two glass microfiber filters (grade GF and Cambridge Filter Pad, Whatman; Merck KGaA, Darmstadt, Germany) and a purification step with deactivated silica. We therefore reported PAH concentration under LOQs for fluoranthene, pyrene, benzo[a]anthracene, chrysene, benzo[b]fluoranthene, and benzo[a]pyrene. These high-molecular weight PAHs were only detected in joint smoke, and not in ENNDS and cannabis vaporizer aerosols. Conversely, the low-molecular weight PAHs were not detected in the emission of joints with a filter and of ENNDS using e-liquids #3, 4, 5 and the CBD extract. These analyses were performed later, and samples were frozen for 2 months before analyses, resulting in a potential evaporation of the more volatile PAHs.

We also identified and quantified three PAHs in emission of the ENNDS OBY using e-liquid #1. This was another indication that an overheating resistance can generate various toxicants.

The addition a filter to joints reduced the concentration of all measured PAHs in emissions (Table 25). Nonetheless, smokers are still exposed to high concentrations of PAHs. Likewise, high PAH concentrations were measured in emission of CBD extract, especially benzo[a]anthracene and phenanthrene. Fluoranthene, pyrene, anthracene, chrysene, and dibenzo[a,c]anthracene were also measured. This might be due to the high viscosity of the CBD extract, inducing an overheating of the resistance of the vape pen Cable pen like for OBY using e-liquid #1. The device thus exposed users to high concentrations of PAHs.

Table 24: Polycyclic aromatic hydrocarbon (PAH) concentrations quantified in joint smoke; comparison with a previous study

PAHs	Moir et al. 2008 [ng/g de cannabis][1]		Our results [ng/g de cannabis] (joints without filter)
	ISO regime[2]	Extreme regime[3]	
Naphthalene	21779 ± 3116	18626 ± 3381	6226 ± 636
Acenaphthylene	5274 ± 588	3721 ± 739	4421 ± 1429
Acenaphthene	1749 ± 131	1129 ± 211	492 ± 103
Fluorene	1395 ± 94	1129 ± 87	2724 ± 612
Anthracene	1476 ± 98	897 ± 144	1235 ± 296
Phenanthrene	6414 ± 398	4027 ± 617	5467 ± 785
Fluoranthene	1238 ± 79	801 ± 101	676 ± 172
Pyrene	792 ± 78	515 ± 49	738 ± 201
Benzo[a]anthracene	319 ± 21	220 ± 27	253 ± 61
Chrysene	635 ± 36	428 ± 35	334 ± 18
Benzo[b]fluoranthene	148 ± 9.1	104 ± 10	169 ± 20
Benzo[k]fluoranthene	35.5 ± 3.6	25.5 ± 2.8	<LOQ
Benzo[a]pyrene	131 ± 12	90.2 ± 8.1	253 ± 61
Indeno[1,2,3-c,d]pyrene	59.7 ± 8.8	35.5 ± 4.3	2.4 ± 1.1
Benzo[g,h,i]perylene	54.4 ± 12.5	38.8 ± 6.5	2.1 ± 0.4

[1] Mainstream mean aldehyde concentrations expressed in µg/joint were transformed to µg/g cannabis assuming a cannabis mass of 769 mg/joint for ISO regime and 773 mg/joint for Extreme regime.
[2] ISO puffing regime: puff volume of 35mL, puff duration of 2 s and puff interval of 60 s.
[3] Extreme puffing regime: puff volume of 70 mL, puff duration of 2 s and interval of a 30 s.
[4] The compound was detected but could not be quantified due to bad extraction recovery.

Table 25: Comparison of PAH concentrations in emission from three cannabis vaporizers at three temperatures, from one ENNDS using e-liquid #1, one vape pen using CBD extract, and from joints (with and without filter)

PAHs	Mighty+ [ng/g of cannabis][1]			FX+ [ng/g cannabis][1]			Air II [ng/g cannabis][1]			OBY [ng/g e-liq][1]	Joints [ng/g cannabis][1]		Cable pen CBD extract [ng/g e-liq][1]
	170°C	190°C	210°C	170°C	190°C	220°C	170°C	190°C	220°C		Without filter	With filter	
Naphthalene	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	103 ± 18	<LOQ	<LOQ	<LOQ	119 ± 13	6226 ± 636	-	-
Acenaphthylene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	4421 ± 1429	-	-
Acenaphthene	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	492 ± 103	-	-
Fluorene	nd	nd	nd	nd	nd	nd	nd	nd	nd	94 ± 18	2724 ± 612	-	-
Anthracene	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	51 ± 6.6	1235 ± 296	1009 ± 131	222
Phenanthrene	nd	nd	nd	nd	nd	nd	nd	nd	nd	<LOQ	358 ± 72	3653 ± 399	1324
Fluoranthene	nd	nd	nd	nd	nd	nd	nd	nd	nd	<LOQ	676 ± 172	1225 ± 154	606
Pyrene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	738 ± 201	1561 ± 201	532
Benzo[a]anthracene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	394 ± 42.6	286 ± 84.4	4558
Chrysene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	334 ± 18.4	332 ± 116	152
Benzo[b]fluoranthene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	169 ± 20.4	168 ± 36.1	nd

PAHs	Mighty+ [ng/g of cannabis][1]			FX+ [ng/g cannabis][1]			Air II [ng/g cannabis][1]			OBY [ng/g e-liq][1]	Joints [ng/g cannabis][1]		Cable pen CBD extract [ng/g e-liq][1]
	170°C	190°C	210°C	170°C	190°C	220°C	170°C	190°C	220°C		Without filter	With filter	
Benzo[k]fluoranthene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	<LOQ	114 ± 21.3	nd
Benzo[a]pyrene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	253 ± 61.3	257 ± 35.9	nd
Indeno[1,2,3-cd]pyrene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	2.41 ± 1.11	141 ± 19.5	nd
Dibenzo[a,c]anthracene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	4.23 ± 4.06	23.6 ± 8.2	121
Benzo[g,h,i]perylene	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	2.09 ± 0.42	226 ± 43.9	nd

-: not analyzed; nd: not detected; <LOQ: below the limit of quantification.

[1] Results are expressed in micrograms per gram of cannabis (µg/g cannabis) for cannabis vaporizer and joint, and in micrograms per gram vaporized e-liquid (µg/g e-liq) for ENNDS as mean ± standard deviation, except for the CBD extract as one replicate was performed only.

5.6 Aromatic amines

Three aromatic amines (aniline, p-toluidine, and 1-aminonaphthalene) were quantified in cannabis vaporizers at the maximum heating temperature as shown in Table 27. The higher concentration was mainly measured in the emission of the convection-based device (FX$^+$). Concentration in aerosols was below the one in joint smoke, except for 1-aminonaphthalene. All compound concentrations were under the limit of quantification in all ENNDS tested, except for the vape pen Cable pen filled with the CBD extract product. Four aromatic amines were quantified for this combination, but at lower concentrations than in joints.

In comparison to the study of Moir et al. (2008), we only measured concentration of 1-aminonaphthalene and 2-aminonaphthalene and at lower concentrations (Table 26).[11] This difference may be explained by the cannabis composition, the cannabis conditioning, the amount of cannabis added in the joint, and the puff regime (see 5.4 VOCs and phenols in emissions).

The addition of a filter to joints did not reduce the aromatic amine concentration in emission. However, these analyses were performed at a different period than the joints without filter and samples were frozen for two months before analyses. Analytical variations of the instrument and the variability between experiments might explain this difference in the results.

Table 26: Aromatic amine concentration quantified in joint smoke; comparison with a previous study

Aromatic amines	Moir et al. 2008 [ng/g de cannabis] [1]		Our results [ng/g de cannabis] (joints without filter)
	ISO regime[2]	Extreme regime[3]	
1-aminonaphthalene	110 ± 17.2	230 ± 22.0	39.9 ± 4.1
2-aminonaphthalene	43.7 ± 4.55	85.8 ± 8.80	10.1 ± 1.8
3-aminobiphenyl	11.9 ± 0.82	24.3 ± 2.33	<LOQ
4-aminobiphenyl	8.02 ± 0.57	17.5 ± 1.94	<LOQ

[1] Mainstream mean aldehyde concentrations expressed in µg/joint were transformed to µg/g cannabis assuming a cannabis mass of 769 mg/joint for ISO regime and 773 mg/joint for Extreme regime.
[2] ISO puffing regime: puff volume of 35mL, puff duration of 2 s and puff interval of 60 s.
[3] Extreme puffing regime: puff volume of 70 mL, puff duration of 2 s and interval of a 30 s.

Table 27: Comparison of amine aromatic concentrations in emission from three cannabis vaporizers, two ENNDS using e-liquid #1, one vape pen using CBD extract, and joints (with or without filter)

Aromatic amines	Mighty+ [ng/g of cannabis][1]			FX+ [ng/g cannabis][1]			Air II [ng/g cannabis][1]			Endura T20-S [ng/g e-liq][1]	OBY [ng/g e-liq][1]	Joints [ng/g cannabis][1]		Cable pen CBD extract [ng/g e-liq][1]
	170°C	190°C	210°C	170°C	190°C	220°C	170°C	190°C	220°C			Without filter	With filter	
Aniline	<LOQ	<LOQ	75.6 ± 13.0	<LOQ	<LOQ	152 ± 57	<LOQ	<LOQ	68.5 ± 14.6	<LOQ	<LOQ	677 ± 95.0	-[2]	-[2]
o-Toluidine	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	557 ± 50.2	-[2]	-[2]
m-Toluidine	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	221 ± 27.0	-[2]	-[2]
p-Toluidine	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	46.8 ± 16.4	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	191 ± 21.0	-[2]	-[2]
1-aminonaphthalene	<LOQ	<LOQ	28.3 ± 14.8	<LOQ	<LOQ	36.2 ± 20.0	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	39.9 ± 4.13	102 ± 9.62	37.0
2-aminonaphthalene	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	10.1 ± 1.83	28.7 ± 4.16	19.9
3-aminobiphenyl	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	10.3 ± 1.54	6.26
4-aminobiphenyl	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	10.8 ± 2.06	20.9

<LOQ: below the limit of quantification.

[1] Results are expressed in micrograms per gram of cannabis (µg/g cannabis) for cannabis vaporizer and joint and in micrograms per gram vaporized e-liquid (µg/g e-liq) for ENNDS as mean ± standard deviation, except CBD extract as one replicate was performed only.

[2] The internal standard added in the samples was not appropriate to accurately quantified the compound with the analytical method used.

5.6. Heavy metal and trace elements

Heavy metal and trace element concentrations were first analyzed in burnt cannabis flower (see Table 28) in order to calculate a transfer rate from flower to aerosols if some metal concentration was measured in aerosols. Several metals were quantified in the plant material in trace levels, such as iron, manganese, copper, aluminum, nickel, molybdenum, tin, palladium, cadmium, and platinum. Only five were above 10 µg/g cannabis: iron (194 ± 18 µg/g cannabis), manganese (144 ± 6 µg/g cannabis), zinc (75 ± 0.4 µg/g cannabis), copper (22 ± 0.6 µg/g cannabis), and aluminum (15 ± 1 µg/g cannabis). The same four metals, except aluminum, were reported by Amendola et al. (2021) in concentrations above 10 µg/g cannabis in cannabis plants grown in Italy (459, 154, 104, and 22.5 µg/g cannabis for iron, manganese, zinc, and copper, respectively).[83] These metals are essential trace elements.[84]

Table 28: Metal concentrations in cannabis flower

Metals	Acronyms	Concentration in cannabis flower (µg/g)
Aluminum	Al	15.4 ± 1.4
Vanadium	V	<LOQ
Chromium	Cr	<LOQ
Manganese	Mn	144 ± 6
Iron	Fe	194 ± 18
Cobalt	Co	<LOQ
Nickel	Ni	1.33 ± 0.03
Cupper	Cu	21.9 ± 0.6
Zinc	Zn	75.3 ± 0.4
Arsenic	As	<LOQ
Selenium	Se	<LOQ
Molybdenum	Mo	0.75 ± 0.13
Palladium	Pd	0.07 ± 0.03
Silver	Ag	<LOQ
Cadmium	Cd	0.07 ± 0.03
Tin	Sn	0.28 ± 0.15
Antimony	Sb	<LOQ
Platinum	Pt	0.08 ± 0.04
Thallium	Tl	<LOQ

Metals	Acronyms	Concentration in cannabis flower (µg/g)
Lead	Pb	<LOQ

Table 29 presents the heavy metal and trace element concentrations in the emissions of cannabis vaporizers, ENNDS using e-liquid #1, and joints. Metals were not quantified in the other e-liquids neither in the emissions of Nautilus X, Noïd.Lab pod, and Cable Pen. No metals were detected in the emissions of cannabis vaporizers and joints, or at trace amounts for few metals. Although several metals were identified and quantified in the plant material, they were not measured in vaporizer and joint emissions. They might not be vaporized during the aerosolization or combustion processes and remained in the “already vaped bud” or in the ashes. This emphasizes the limited concentration of metals inhaled during the use of cannabis, smoked or vaporized. Moir et al. (2008) also reported metal concentrations under limits of quantification for chromium, nickel, arsenic, selenium, and lead.[11] However, they quantified mercury (3.51 ± 0.31 µg/joint) and cadmium (14.6 ± 1.2 µg/joint) in joint smoke. This emphasizes the importance of the cannabis growing area, as the plant easily absorbs heavy metal from the soil.[85] In our study, we could not analyze mercury due to analytical issues.

In ENNDS, aluminum, nickel, and copper were above the limits of quantification in aerosols. The same metals were previously identified in a study on nicotine-containing e-liquids with the Endura T20-S. It was shown that the three metals originated form the metallic part of the electronic device. The type of metal and its concentration in emission will depend on the metal used in the device.

Table 29: Comparison of metal concentrations in emission from three cannabis vaporizers, one ENNDS using e-liquid #1, and joints.

Metals	**Mighty+ [µg/g of cannabis][1]**			**FX+ [µg/g cannabis][1]**			**Air II [µg/g cannabis][1]**			**OBY [µg/g e-liq][1]**	**Joints (without filter) [µg/g cannabis][1]**
	170°C	**190°C**	**210°C**	**170°C**	**190°C**	**220°C**	**170°C**	**190°C**	**220°C**		
Aluminum	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.60 ± 0.07	<LOQ
Vanadium	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Chromium	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Manganese	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Iron	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Cobalt	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Nickel	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.69 ± 0.19	<LOQ
Cupper	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	4.61 ± 0.75	<LOQ
Zinc	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Arsenic	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Selenium	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Molybdenum	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ

Metals	Mighty+ [µg/g of cannabis][1]			FX+ [µg/g cannabis][1]			Air II [µg/g cannabis][1]			OBY [µg/g e-liq][1]	Joints (without filter) [µg/g cannabis][1]
	170°C	190°C	210°C	170°C	190°C	220°C	170°C	190°C	220°C		
Palladium	0.14 ± 0.07	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Silver	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Cadmium	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Tin	0.12 ± 0.04	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Antimony	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Platinum	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Thallium	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Lead	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ

[1] Results are expressed in micrograms per gram of cannabis (µg/g cannabis) for cannabis vaporizer and joint and in micrograms per gram vaporized e-liquid (µg/g e-liq) for ENNDS as mean ± standard deviation.

6. Limitations

This study focused on cannabis dried flowers produced by a Pure Holding AG (Zeiningen, Switzerland) and on an e-liquid formed by the extraction of the same flowers. Extrapolation of these results to illegal cannabis samples is questionable due to the various quality and composition of cannabis flowers.[86–89] We did not test cannabis extracts, such as resin. These products were not produced by the Swiss company.

Cannabis flower primarily contains cannabinoids and aromas such as terpenes, both at concentrations that depend on the cannabis plant species. In this study, we did not analyze terpenes. However, terpenes can be degraded in pyrolysis and incomplete combustion processes to form volatile organic compounds (VOCs), such as benzene, isoprene, 1,3-butadiene, formaldehyde, acetaldehyde, acrolein, and valeraldehyde.[39,49] Some of these compounds were quantified in the present study.

Likewise, we did not analyze several compounds that are specific to cannabis smoke and quantified in higher concentrations than in tobacco smoke. This was due to the lack of an analytical method to quantify these compounds in our laboratory. Hence, we did not quantify ammonia and hydrogen cyanide in emission. We could not measure neither acrylonitrile due to a calibration issue, although Ashley et al. (2020) and Smith et al. (2020) measured higher metabolite concentration in urine of cannabis users compared to tobacco users.[14,15]

We adapted the puffing regime from methods standardized to cigarettes and ENDS as there is no scientific data on puffing regimes of cannabis smokers. Real users of cannabis vaporizers and ENNDS might have various puffing behaviors, or topographies, and, consequently, might be exposed to different toxicant concentrations using these devices. Moreover, the Δ^9-THC delivery efficiency measured under laboratory conditions (i.e., 80 mL, 3 s, 30 s; 15 puffs) for the cannabis vaporizers and ENNDS might change according to how the consumers use their devices.

We did not measure the cannabinoid concentrations in e-liquids #1 and #2, but used the concentrations reported by the manufacturers. Consequently, the high calculated percentages for the Δ^9-THC delivery efficiency (>100%) are probably due to inter-laboratory variability. ENNDS remained the most effective devices to deliver THC compared to vaporizers and joints under the laboratory conditions we used to test these devices.

7. Synthesis and policy recommendations

The concentrations of aldehydes, VOCs, phenols, aromatic amines, and PAHs were notably reduced in emissions of the three cannabis vaporizers (Mighty$^+$, FX$^+$, and Air II) and the four ENNDS (OBY, Endura T20-S, Nautilus X, and Noïd.Lab pod) compared to joint smoke. The concentration of several toxicants was also reduced in emission of the ENNDS Cable pen using the CBD extract; however, high concentration of PAHs and of aromatic amines were quantified. Consequently, users are still exposed to several toxicants, including carcinogens, and the benefit to use this device with the CBD extract is very limited compared to smoke joints. Table S13 of Annex G summarizes the differences in concentrations of the analyzed chemical family groups between the different cannabis inhalation methods tested.

Based on these results and on the current scientific knowledge, the following recommendations may be emphasized to support policy makers to regulate cannabis products and the cannabis inhalation methods:

i. E-liquids containing THC:
    - Establish and define standards in the e-liquid production (e.g., only use PG/VG, specific extraction method, information on decarboxylation process, addition of flavors, etc.).
    - Inform clearly on the labels about cannabinoid concentrations (including the concentration of the acid forms to know the decarboxylation rate), all the ingredients in the composition of the e-liquids (including their percentage in the formulation), the extraction method used, the list of compounds for flavours, etc.
    - Legally request companies to perform analyses in laboratory to ensure the product safety and to provide the results for each batch processing. A list of specific analyses may be defined to reduce risk for consumers. This list should be defined by federal offices (e.g., Federal food safety and veterinary office, Federal office of public health) and regularly updated.
    - Create a commission or a department to verify the quality control of the products put on the market.
    - Determine a list of ingredients to ban in e-liquids (e.g., PEG, vitamin E acetate, etc.)

ii. Filters for joints:
    - Inform users that while using filters in joints reduces exposure to inhaled intoxicants, the characteristics of the smoke are similar to joints without smoke. Very harmful toxins (PAH, aromatic compounds) are only partially filtered out

and these are either not present or at negligible concentrations when using ENNDS or vaporizers.
    - Determine the potential risk reduction when filters are added to joints in humans.
    - Study the different types of filters available for joints (e.g., cellulose, active carbon, etc.) to define the most efficient one to retain the potentially toxic compounds without reducing cannabinoid uptake.

iii. Passive smoking:
    - Fund a volunteer study in an exposure chamber to confirm the reduction of passive smoke and emissions when ENNDS and vaporizers are used compared to joints.
    - Define regulation in closed public areas according to the volunteer study.

There remain several gaps in knowledge to support policy makers to accurately regulate the cannabis products and their inhalation methods. There is a need to carry out further research studies, and specifically on clarification of risks and benefits from extraction methods to produce safe and stable e-liquids, passive smoking risks, on the cannabinoid pharmacokinetics for the cannabis alternative inhalation methods, on the potency to increase THC addiction by using e-liquids containing THC, and on phase III and IV clinical studies.

8. Conclusion

In Switzerland, cannabis is mainly consumed in the form of joints, often mixed with tobacco. Cannabis smokers are thus exposed to high concentrations of toxicants resulting from pyrolysis and combustion processes. Cannabis vaporizers and ENNDS were suggested as potential safer alternatives to joints, as these electronic devices operate at lower temperatures. This was confirmed by the present study under laboratory conditions. No PAHs and no phenols were observed in emissions of the three cannabis vaporizers (Mighty$^+$, FX$^+$, and Air II) using dried cannabis flowers, and the four ENNDS (OBY, Endura T20-S, Nautilus X, and Noïd.Lab pod) using Δ^9-THC containing e-liquids. The lowest concentrations of VOCs and aldehydes were detected in the ENNDS emissions. However, the ENNDS device and the e-liquid are highly important to consider and to accurately select. The ENNDS using the CBD extract still generated high concentrations of PAHs and of aromatic amines, exposing users to several toxicants, including carcinogens.

The type of heater systems tested for vaporizers did not influence the emission composition based on the compounds analyzed. The convection mode (FX$^+$) could potentially emit higher concentrations of aldehydes and of aromatic amines compared to the two hybrid systems tested. However, the difference were very slight and additional data are needed to confirm these results. The medical device Mighty$^+$ was comparable to the two other tested vaporizers in term of safety. In comparison to ENNDS, Mighty+ is less efficient to deliver THC, but has similar concentrations of the different compounds in its emissions, except maybe higher aromatic amine concentrations.

Regarding efficiency of Δ^9-THC delivery in emissions, ENNDS were the most efficient devices to use, with a Δ^9-THC delivery efficiency around 100%. In comparison, cannabis vaporizers were the less efficient devices, with a Δ^9-THC delivery efficiency around 18% (at maximum temperature). This was twice as low as in joints. Approximatively 40% of Δ^9-THC remained in the cannabis flowers, while the rest was thermally degraded and/or deposited on the device surfaces. However, several parameters influence the efficiency of cannabis vaporizers, such as the temperature of use, the puffing regime, the quantity and type of cannabis product, and the design of the device. Our study may have underestimated the Δ^9-THC delivery efficiency by using a too low puffing volume. Consequently, further studies are needed to understand the effects of these parameters on Δ^9-THC degradation. There is a crucial lack of data on the use and puffing regime by users of vaporizers and of ENNDS to simulate closer realistic scenarios of use in laboratory and to confirm our results.

On the perspective of a harm reduction approach, vaporizers and ENNDS emitted much less potential toxic compounds compared to joints. Users could still be exposed to several irritants and carcinogens, such as acetaldehyde, butyraldehyde, and glycidol, however, with the notable exception of one ENNDS, these devices do not appear to be a source of exposure to very harmful toxins such as PAH or aromatic compounds. For ENNDS, the choice of the device as well as the composition of the e-liquid is essential. An e-liquid not adapted to the device may induce overheating and at higher exposure to toxicants than joints, as we observed for e-liquid #1 and CBD extract. The results emphasize the potential toxicity for users to use PEG as solvent to dilute cannabinoids (e.g., e-liquid #1). However, the extraction procedure used in e-liquid #2 was not optimal neither. The e-liquid #2 was unstable in the long term (separation of the e-liquid in two phases). This was due to the lack of the decarboxylation step and the non-use of solvents. Consequently, the preparation of the Δ^9-THC containing e-liquid and compatibility of e-liquid with ENNDS were the most crucial parameters influencing toxicant and cannabinoids emissions.

Overall, our results show that among all the devices tested, the ENNDS using a THC-containing e-liquid previously tested for its toxicity profile may be an alternative to suggest in a clinical trial due to the high Δ^9-THC delivery efficiency and the high potential reduction to several toxicants and carcinogens compared to joints. The low THC delivery of vaporizers in addition to the absence of tobacco and nicotine might be less attractive, especially to regular cannabis consumers. Our results further emphasize the need for transparency and independent analysis in order to guarantee a true safety to users while there is a variety of cannabis products and devices available on the market. The improvement of scientific knowledge in combination with an appropriate regulation should promote less harmful products. Several clarifications are specifically requested on risks and benefits from extraction methods to produce safe and stable e-liquids, passive smoking risks, and the efficiency of the cannabis alternative inhalation methods to deliver cannabinoids.

Testing the cannabis inhalation methods under laboratory conditions was the first step to prepare a volunteer study in controlled conditions to verify the cannabinoid pharmacokinetics in users and the passive smoking risk, and a pilot trial to assess the effects of these safer alternatives on clinical outcomes.

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10. Annexes

A. Cannabinoids - HPLC-MS/MS parameters

Cannabinoid sampling was based on Sheehan et al. (2019)[23], and the analysis was performed by high performance liquid chromatography (HPLC; Dionex Ultimate 3000 system, Thermo Scientific, Reinach, Switzerland) equipped with a MS/MS Detector (TSQ Quantiva, Thermo Scientific, Reinach, Switzerland).

Specifically, emissions from cannabis vaporizers, ENNDS, and joints were collected on a 47 mm cut CFP filter (Cambridge Filter Pad, Whatman F319-04, 92 mm; Merck KGaA, Darmstadt, Germany) based on Sheehan et al. (2019).[23] For sampling cannabinoids in ENNDS aerosols, only 15 puffs were collected due to the high cannabinoid concentrations.

Filters were then extracted with methanol (15 mL; LC-MS grade) in an ultrasonic bath for 1 h, and centrifuged at 4000 rpm for 5 min. Filter extracts were then diluted 10 times (for Δ^9-THCA-A, Δ^8-THC, CBD, CDBA, CGG, and CBN) and 1000 times (for Δ^9-THC) in methanol in two separated vials. The diluted extracts were further diluted two times in water (LC-MS grade).

Cannabinoid analysis was performed by high performance liquid chromatography (HPLC; Dionex Ultimate 3000 system, Thermo Scientific, Reinach, Switzerland) equipped with a MS/MS Detector (TSQ Quantiva, Thermo Scientific, Reinach, Switzerland) using a routine method. The compounds were separated using a ZORBAX Eclipse Plus C18 column (1.8 µm, 100 x 2.1 mm, Agilent). Injection volume was 5 µL and column temperature was maintained at 50°C. The mobile phase consisted of: eluent A composed of 5 mM ammonium formate buffer (pH 7.7) and eluent B acetonitrile. Each analysis had a run time of 12 minutes. The solvent gradient used is described in the Table S1.

Limits of quantification (LOQs) were 1 ng/mL for all compounds. Cannabidiol-D_3 and delta-9-tetrahydrocannabinol-D_3 (Merck KGaA, Darmstadt, Germany) were used as internal standards.

Table S1 – Solvent gradient for the analysis of cannabinoids with HPLC-MS/MS

Time [min]	Flow [mL/min]	Eluent A [%]	Eluent B [%]
0	0.4	70	30
5	0.4	5	95
7.5	0.4	5	95
7.6	0.4	70	30
12	0.4	70	30

Eluent A: 5 mM ammonium formate buffer (pH 7.7); eluent B: acetonitrile

Due to close retention times between Δ^8-THC and Δ^9-THC, both were quantified by peak height instead of peak area.

For mass spectrometry, electrospray ionization (ESI) in positive mode was used, except for Δ^9-THCA-A and CBD-A (negative mode). The vaporizer temperature was 270°C and the ion transfer tube 300°C. MS/MS detector parameters and retention time can be found in Table S2.

Table S2 – Retention times and tandem mass (MS/MS) detection parameters used for the quantification of cannabinoids

Compounds	Retention time (min)	Ion Polarity	Quantification transition (m/z)	Collision Energy (V)	RF Lens (V)	Confirmation transition 1 (m/z)	Collision Energy (V)	RF Lens (V)	Confirmation transition 2 (m/z)	Collision Energy (V)	RF Lens (V)	Normalised with (IS)
Cannabidiol-D$_3$ (CBD-D$_3$) (IS)	6.84	Positive	318.20 / 196.10	29	46							
Delta-9-tetrahydrocannabinol-D$_3$ (Δ^9-THC-D$_3$) (IS)	7.51	Positive	318.20 / 196.10	29	46							
Cannabidiolic acid (CBD-A)	4.66	Negative	357.30 / 229.10	41	81	357.30 / 245.10	28	81	357.30 / 339.10	19	81	CBD-D$_3$
Delta-9-tetrahydrocannabinolic acid A (Δ^9-THCA-A)	5.34	Negative	357.20 / 191.10	32	84	357.20 / 229.10	23	84	357.20 / 245.10	30	84	Δ^9-THC-D$_3$
Cannabigerol (CBG)	6.82	Positive	317.30 / 123.10	32	51	317.30 / 207.10	12	51	317.30 / 193.10	17	51	CBD-D$_3$
Cannabidiol (CBD)	6.84	Positive	315.20 / 193.10	33	46	315.20 / 259.10	25	46	315.20 / 123.10	41	46	CBD-D$_3$
Cannabinol (CBN)	7.26	Positive	311.30 / 223.10	30	64	311.30 / 179.10	48	64	311.30 / 43.10	55	64	CBD-D$_3$
Delta-9-tetrahydrocannabinol (Δ^9-THC)	7.51	Positive	315.20 / 193.10	33	46	315.20 / 259.10	25	46	315.20 / 123.10	41	46	Δ^9-THC-D$_3$
Delta-8-tetrahydrocannabinol (Δ^8-THC)	7.54	Positive	315.20 / 193.10	33	46	315.20 / 259.10	25	46	315.20 / 123.10	41	46	Δ^9-THC-D$_3$

IS for internal standard

B. Aldehydes – HPLC-UV parameters

Aldehyde sampling was based on the method of Gillman et al. (2016), and the quantification was performed by a routine high-performance liquid chromatography-ultraviolet (HPLC-UV) method accredited ISO 17025.[62]

Emissions of cannabis vaporizers, ENNDS and joints were sampled in two successive glass impingers with fritted nozzle containing a solution of a 2,4-dinitrophenylhydrazine (DNPH) derivatization solution (30 mL each; 1.3 mM DNPH; Merck KGaA, Darmstadt, Germany), with 10 mM phosphoric acid (85%; Merck KGaA, Darmstadt, Germany) in H_2O/ACN (v/v, 50:50). For sampling aldehydes in ENNDS aerosols, only 30 puffs were collected to avoid overheating the device, which leads to higher concentrations of aldehydes.

One sample (1 mL) of each impinger was collected and directly analyzed by HPLC (Dionex Ultimate 3000 system, Thermo Scientific, Reinach, Switzerland) equipped with a UV Detector (DAD-3000 RS rapid separation diode array detector, Thermo Scientific, Reinach, Switzerland). Compounds were separated using a Hypersil Gold column (1.9 µm, 100 x 0.1 mm; Thermo Scientific, Reinach, Switzerland). Injection volume was 5 µL and column temperature was maintained at 40°C. The mobile phase consisted of: eluent A composed of water/tetrahydrofuran (95:5, v/v) and eluent B acetonitrile. Each analysis had a run time of 17 minutes. Solvent gradient is described in the Table S3 and retention times are shown in Table S4. Limit of quantification (LOQ) was 0.05 µg/mL (calibration ranges from 0.05 µg/mL to 5 µg/mL for each compound).

Table S3 – Solvent gradient for the analysis of aldehydes by HPLC-UV

Time [min]	Flow [mL/min]	Eluent A [%]	Eluent B [%]
0	0.6	68	32
5	0.6	60	40
13	0.6	42	55
13.2	0.6	20	80
14.5	0.6	20	80
14.7	0.6	68	32
17	0.6	68	32

Table S4 – Retention times of aldehydes

Compounds	Retention time (min)
Formaldehyde	2.07
Acetaldehyde	2.95
Acetone	4.11
Acroleine	4.29
Propanal	4.85
Crotonaldehyde	6.01
Butyraldehyde	7.02
Benzaldehyde	8.14
Isovaleraldehyde	9.05
Valeraldehyde	9.41
Tolualdehyde	10.18
Hexanal	11.74
2,5-dimethylbenzaldehyde	11.95

C. Volatile organic compounds (VOCs) – GC-MS parameters

The collection of VOCs and phenols was based on Health Canada standardized methods.[63] Emissions from cannabis vaporizers, ENNDS, and joints were collected on 47 mm cut CFP filters (Cambridge Filter Pad, Whatman F319-04, 92 mm; Merck KGaA, Darmstadt, Germany), and a glass impinger with fritted nozzle containing dichloromethane (15 mL; distilled) and placed in a cooling bath (0°C). Filters were then extracted with dichloromethane (15 mL) in a laboratory shaker for 20 min.

Aliquots of filter extracts and impinger solutions were analyzed by gas chromatography – mass spectrometry (GC-MS; Thermo Trace 1310 GC with Triplus RSH autosampler + Thermo ISQ LT, Thermo Scientific, Reinach, Switzerland). VOCs analyses were carried out on two instruments equipped with two different columns: VF-WAXms column (30 m, 0.25 mm, 0.25 µm; Agilent, Basel, Switzerland) and VF-624ms column (60 m, 0.25 mm, 1.40 µm; Agilent, Basel, Switzerland). Toluene-D8 (Merck KGaA, Darmstadt, Germany) was used as internal standard. LOQ was 40 ng/mL for each compound (calibration ranges from 10 ng/mL to 1 µg/mL for each compound) for both VOCs and phenols. Volume injection was 1 µm, split ratio was 20, split flow was 30 mL/min, and injection temperature was 250°C. Helium flow rate was 1.5 mL/min. Each analysis had a run time of 27 minutes. The temperature gradient used is described in the Table S5.

Table S5 – Temperature gradient for the analysis of volatile organic compounds (VOCs) by GC-MS

No	Retention time [min]	Rate [°C/min]	Target value [°C]	Hold time [min]
1	5	0	40	5
2	11	5	70	0
3	16	10	120	0
4	20	20	200	0
5	27	40	280	5

We could not analyze six VOC compounds: ethanol, acrylonitrile, ethylene glycol, diethylene glycol, propylene glycol, and triacetin, as well as one phenol compound: resorcinol, in e-liquid #1. This was due to contamination issues (ethanol), calibration issues (acrylonitrile and triacetin), and discrepancies between the two columns used (ethylene glycol, diethylene glycol, propylene glycol, and resorcinol). In addition, three VOC compounds were not quantified in e-liquid #2 (1,3-butadiene, isoprene, and quinoline), because of a lack of standards.

For mass spectrometry, electron impact (EI) was used. The ion source temperature was 230°C and the MS transfer line 250°C. MS parameters, retention time and LOQs can be found in the Table S6.

Table S6 – Retention times, limits of quantifications (LOQs), and tandem mass (MS/MS) detection parameters used for the quantification of volatile organic compounds (VOCs)

Compounds	**Retention time (min)**		**LOQs [ng/mL]**	**Quantification ion (m/z)**	**Confirmation ion 1 (m/z)**	**Confirmation ion 2 (m/z)**
	VF-WAXms	**VF-624ms**				
Toluene-D8 (IS)	4.23	16.53		98.1	100.1	70.1
1,3-butadiene		4.32	10	54.07	39.06	53.07
Ethanol		6.16	10	45.07	46.08	43.05
Isoprene		6.56	10	67.07	68.09	53.05
Propylene oxide	1.47	6.86	10	58	43	57
Benzene	2.647	12.99	10	78.07	77.07	51.08
2-Propenenitrile	3.402	8.71	10	53.05	52.06	51.05
Toluene	4.337	16.63	10	91.03	92.07	65.06
Ethylbenzene	6.908	18.82	10	91.04	106.06	65.05
o-Xylene		18.97	10	91.06	106.1	105.1
m-/p-xylene		19.46	10	91.06	106.09	105.09
omp-Xylene	7.357		10	91.04	106.06	105.06
Pyridine	8.691	16.38	10	79.04	52.06	51.06
Styrene	11.082	19.48	10	104.05	78.06	103.05
Glycidol	15.469	16.40	10	44.07	43.06	45.08
Propylene Glycol	17.187	17.52	10	45.07	43.06	44.08

Compounds	**Retention time (min)**		**LOQs [ng/mL]**	**Quantification ion (m/z)**	**Confirmation ion 1 (m/z)**	**Confirmation ion 2 (m/z)**
	VF-WAXms	**VF-624ms**				
1,2-Ethanediol	17.527	16.52	10	43.07	62.06	44.07
1,3-Propanediol	18.799	19.37	10	57.05	58.07	45.08
Quinoline	19.855	23.57	10	129	102	128
Diethylene glycol	20.023	21.23	10	45.07	75.05	76.06
o-cresol	20.18	22.07	10	108	107	79
Phenol	20.203	21.49	10	94	66.08	65.06
Triacetin	20.549	23.84	-	43.01	103.01	145.01
m-cresol	20.581		10	108	107	79
p-cresol	20.618		10	108	107	79
m-/p-cresol		22.29	10	107.07	108.08	77.02
Catechol	22.642	23.60	50	45.07	109.98	89.06
Hydroquinone	23.672	24.10	10	110.02	45.07	89.06
Resorcinol	23.989	24.23	10	110.02	45.07	89.06

IS for Internal standard.

[1] Only limits of quantification (LOQs) corresponding to the selected column are reported.

D. Polycyclic aromatic hydrocarbons – GC-MS/MS parameters

PAH collection was based on WHO Toblabnet method (for benzo[a]pyrene).[64] Emissions of cannabis vaporizers, ENNDS, and joints were collected on 47 mm cut CFP filters (Cambridge Filter Pad, Whatman F319-04, 92 mm; Merck KGaA, Darmstadt, Germany) and a glass impinger fritted nozzle containing hexane (15 mL) and placed in a cooling bath (0°C). Filters were then extracted with hexane (15 mL) in a laboratory shaker for 20 min.

Aliquots of both filter extracts and impinger solutions were analyzed by gas chromatography – mass spectrometry (GC-MS; Thermo Trace 1310 GC with Triplus RSH autosampler + Thermo ISQ LT, Thermo Scientific, Reinach, Switzerland) equipped with a DB – EUPAH column (30 m, 0.25 mm, 0.25 µm; Agilent, Basel, Switzerland). The LOQ was 20 ng/mL for each compound. Polycyclic aromatic hydrocarbons (PAH's) were analyzed by a Gas Chromatography/Tandem Mass Spectrometry (GC-MS/MS) instrument equipped with a DB – EUPAH column (30 m, 0.25 mm, 0.25 µm; Agilent, Basel, Switzerland). Volume injection was 1.5 µm, splitless mode with a splitless time of 0.2 min, the split flow was 50 mL/min, and the injection temperature was 320°C. Helium flow rate was 1.2 mL/min. Each analysis had a run time of 37 minutes. The temperature gradient used is described in the Table S7.

Table S7 – Temperature gradient for the analysis of polycyclic aromatic hydrocarbons (PAHs) by GC-MS/MS

No	Retention time [min]	Rate [°C/min]	Target value [°C]	Hold time [min]
1	0	Run		
2	1	0	80	1
3	5	30	200	0
4	10	10	250	0
5	25	3	295	0
6	37	15	325	10

For mass spectrometry, Electron impact (EI) was used. The ion source temperature was 270°C and the MS transfer line 320°C. MS/MS detector parameters, retention time and LOQs can be found in the Table S8.

Table S8 – Retention times, limits of quantifications (LOQs), and tandem mass (MS/MS) detection parameters used for the quantification of polycyclic aromatic hydrocarbons (PAHs)

Compounds	LOQ (µg/ml)	Retention time (min)	Ion Polarity	Quantification transition (m/z)	Collision Energy (V)	Confirmation transition 1 (m/z)	Collision Energy (V)	Normalized with (IS)
Naphtalene-D8 (IS)		4.656	Positive	136.1 / 136.0	15			
Acenaphtene-D10 (IS)		6.432	Positive	164.1 / 162.0	20	164.1 / 160.0	30	
Pyrene-D10 (IS)		12.313	Positive	212.0 / 210.0	30			
Benzo[a]pyrene-D12 (IS)		25.167	Positive	264.1 / 264.0	35	264.1 / 260.0	30	
Benzo[ghi]perylene-D12 (IS)		30.918	Positive	288.1 / 284.0	60	288.1 / 286.0	40	
Naphthalene	0.018	4.6	Positive	128.1 / 77.0	30	128.1 / 102.0	20	Naphthalene D8
Acenaphthylene	0.019	6.271	Positive	152.1 / 126.0	30	152.1 / 102.0	20	Acenaphthene D10
Acenaphthene	0.016	6.491	Positive	153.1 / 151.0	45	153.1 / 126.0	40	Acenaphthene D10
Fluorene	0.014	7.118	Positive	165.1 / 139.0	30	165.1 / 163.0	30	Acenaphthene D10
Anthracene	0.016	8.809	Positive	178.1 / 152.1	25	178.1 / 176.1	20	Acenaphthene D10
Phenanthrene	0.015	8.918	Positive	178.1 / 152.0	25	178.1 / 176.1	20	Acenaphthene D10

Compounds	**LOQ (µg/ml)**	**Retention time (min)**	**Ion Polarity**	**Quantification transition (m/z)**	**Collision Energy (V)**	**Confirmation transition 1 (m/z)**	**Collision Energy (V)**	**Normalized with (IS)**
Fluoranthene	0.015	11.471	Positive	202.1 / 200.1	30	202.1 / 176.1	35	Pyrene D10
Pyrene	0.017	12.292	Positive	202.1 / 200.1	35	202.1 / 176.1	30	Pyrene D10
Benzo[a]anthracene	0.021	16.97	Positive	228.1 / 226.0	35	228.1 / 202.0	30	Benzo a pyrene D12
Chrysene	0.019	17.328	Positive	228.1 / 226.0	35	228.1 / 202.0	30	Benzo a pyrene D12
Benzo[b]fluoranthene	0.020	22.831	Positive	252.1 / 250.0	35	252.1 / 226.0	30	Benzo a pyrene D12
Benzo[k]fluoranthene	0.007	23.103	Positive	252.1 / 250.0	35	252.1 / 226.0	30	Acenaphthene D10
Benzo[a]pyrene	0.023	25.29	Positive	252.1 / 250.1	35	252.1 / 226.1	30	Benzo[a]pyrene D12
Indeno[1,2,3-c,d]pyrene	0.014	29.606	Positive	276.1 / 272.0	60	276.1 / 274.0	40	Benzo[g,h,i]perylene D12
Dibenzo[a,c]-anthracene	0.011	29.627	Positive	278.1 / 276.0	60	278.1 / 274.0	30	Benzo[g,h,i]perylene D12
Benzo[g,h,i]perylene	0.018	31.112	Positive	276.1 / 272.0	60	276.1 / 274.0	40	Benzo[g,h,i]perylene D12

IS for Internal standard.

E. Aromatic amines– GC-MS/MS parameters

Aromatic amine sampling was based on the method of Health Canada standardized methods[63], and the quantification was performed by gas chromatography – tandem mass spectrometry (GC-MS/MS).

Emissions of cannabis vaporizers, ENNDS, and joints were collected on 47 mm cut CFP filters (Cambridge Filter Pad, Whatman F319-04, 92 mm; Merck KGaA, Darmstadt, Germany). Filters were then extracted with dichloromethane (15 mL) in a laboratory shaker for 20 min. Filter extracts were concentrated to 1 mL under a nitrogen flow with a Pierce Reacti-Therm III evaporator (Thermo Scientific, Reinach, Switzerland) and derivatized with heptafluorobutyric anhydride (HBFA, 10 µL; Merck KGaA, Darmstadt, Germany) at 60°C for 2h.

Aromatic amines were analyzed by GC-MS/MS (Thermo Trace 1310 GC with Triplus RSH autosampler + Thermo TSQ 8000 Evo, Thermo Scientific, Reinach, Switzerland). 3-aminobiphenyl-D9 (Merck KGaA, Darmstadt, Germany) was used as internal standard. LOQs were between 15 to 50 ng/mL depending on the compounds.Aromatic amines were analyzed by a gas chromatography - tandem mass spectrometry (GC-MS/MS) instrument equipped with a CP-Sil 8 CB column (30 m, 0.25 mm, 0.25 µm; Agilent, Basel, Switzerland). Volume injection was 1 µm in splitless mode with a splitless time of 0.1 min, a split flow of 18 mL/min, and an injection temperature of 280°C. Helium flow rate was 1.2 mL/min.

Each analysis had a run time of 20 minutes. The temperature gradient used is described in Table S9.

Table S9 – Temperature gradient for the analysis of aromatic amines by GC-MS/MS

No	Retention time [min]	Rate [°C/min]	Target value [°C]	Hold time [min]
1	0	Run		
2	0.6	0	40	0.6
3	19.933	12	260	1

For mass spectrometry, electron impact (EI) was used. The ion source temperature was 270°C and the MS transfer line 270°C. MS/MS detector parameters, retention time and LOQs can be found in Table S10.

Table S10 – Retention times, limits of quantifications (LOQs), and tandem mass (MS/MS) detection parameters used for the quantification of aromatic amines

Compounds	LOQ (µg/ml)	Retention time (min)	Ion Polarity	Quantification transition (m/z)	Collision Energy (V)	Confirmation transition 1 (m/z)	Collision Energy (V)	Confirmation transition 2 (m/z)	Collision Energy (V)
3-aminobiphenyle D9* (IS)		16.0	Positive	374 / 162	10	374 / 162	25	205 / 162	10
Aniline*	0.046	8.8	Positive	120 / 77	10	120 / 77	10	92 / 65	10
o toluidine*	0.031	9.4	Positive	134 / 91	10	134 / 91	10	106 / 79	10
m toluidine*	0.028	9.9	Positive	134 / 91	10	134 / 91	10	106 / 79	10
p toluidine*	0.027	10.1	Positive	134 / 91	10	134 / 91	10	106 / 79	10
1-aminonaphthalene*	0.013	13.9	Positive	142 / 115	20	142 / 115	10	115 / 89	15
2-aminonaphthalene*	0.012	14.5	Positive	142 / 115	20	142 / 115	10	115 / 89	15
3-aminobiphenyl*	0.027	15.9	Positive	168 / 141	25	168 / 141	10	153 / 152	10
4-aminobiphenyl*	0.033	16.3	Positive	365 / 168	20	168 / 141	10	141 / 112	10

* Derivatized form of the amines (amides); IS for Internal standard.

F. Heavy metals – ICP-MS parameters

Emissions of cannabis vaporizers and joints were collected on 37 mm MCE filters (5 µm; SKC mixed cellulose ester membrane filters, Blandford Forum, United Kingdom), which were then digested in acidic conditions (nitric acid and hydrochloric acid). ENNDS emissions were collected in two empty 50 mL plastic centrifuged tubes DECCS 14 2TDS, Medivac, Parma, Italy) placed in a cooling bath (isopropanol/dry ice at -78°C). Condensed aerosol in both tubes was diluted and mixed in 0.5% HNO_3 (5 mL).

Metal concentrations in cannabis plant were quantified by dissolving cannabis herb (200 mg) in nitric acid (4 mL), and heating for 15 minutes at 95°C. Hydrochloric acid (4 mL) was then added, and the solution was left at 95°C for 15 additional minutes. Finally, 50 ml of water was added before the analysis by ICP-MS.

The metal quantification was performed using inductively coupled plasma mass spectrometry (ICP-MS; iCAP TQ, Thermo Scientific, Reinach, Switzerland).[90] ICP-MS instrument was operated at 1550 W, with an argon cool flow of 14 L/min. The nebulizer flow was 1.1 L/min, and the auxiliary flow was 0.8 L/min. The spray chamber temperature was 2.7°C. Collision cell was operated with kinetic energy discrimination (KED). Sampling depth was 5 mm.

The standard solutions of metals for calibration curves were bought from Labkings (Hilversum, Netherlands), except Iron (Fe) from SCP Science (Marktoberdorf, Germany) and their certified concentrations are shown in Table S11. Yttrium (Y) was used as internal standard.

Table S11 – Certified concentrations of metal stock solutions used to prepare calibration standard solutions expressed in micrograms per milliliter (µg/mL).

Metals	Certified Concentration (µg/mL)	Metals	Certified Concentration (µg/mL)
Be	5.010	**As**	20.01
Al	20.01	**Se**	50.02
V	20.01	**Mo**	19.99
Cr	5.002	**Pd**	4.986
Mn	10.00	**Ag**	2.002
Fe	1000	**Cd**	5.002
Co	10.01	**Sn**	2.009
Ni	10.01	**Sb**	9.984
Cu	500.5	**Pt**	1.993
Zn	998.2	**Pb**	100.1

Limits of quantification (LOQs) for each metal are presented in Table S12. Calibration ranges went from 1’000’000-fold to 200-fold dilution of the standard solutions (for several metals, LOQs were higher than the lowest points of the calibration curves).

Table S12 – Limits of quantification (LOQs) of metals for emissions (smoke vapor and aerosol) and cannabis herb, expressed in nanograms per milliliter (ng/mL).

Metals	LOQs in emissions (ng/mL)	LOQs in cannabis herb (ng/mL)
Al	0.1	0.1
V	0.05	0.05
Cr	0.025	0.025
Mn	0.025	0.025
Fe	0.25	0.25
Co	0.025	0.025
Ni	0.025	0.025
Cu	1.25	1.25
Zn	2.5	2.5
As	0.05	0.05
Se	2.5	2.5
Mo	0.05	0.05
Pd	0.01	0.01
Ag	0.01	0.01
Cd	0.01	0.01
Sn	0.01	0.01
Sb	0.025	0.025
Pt	0.005	0.005
Tl	0.01	0.01
Pb	0.25	0.25

G. Synthesis

Table S13 summarizes the main results and the differences in concentrations of the analyzed chemical family groups between the different cannabis inhalation methods tested.

Table S13:Emission comparison between vaporizers, ENNDS and joints with a filter per chemical family groups.

Chemical groups	**Vaporizers**	**ENNDs**	**Joints with a filter** *(cellulose with activated carbon)*
Cannabinoids	Low delivery efficiency compared to joints and ENNDS.	Highest delivery efficiency compared to joints. A decarboxylation of Δ^9-THCA-A and CBD-A is requested during the e-liquid manufacturing. Solvents use in e-liquids may influence the cannabinoid delivery.	Delivery efficiency similar to joints smoke without filters. No reduction of efficiency. Lower delivery than ENNDS.
Aldehydes	Only **acetaldehyde** and **butyraldehyde** were quantified in emissions of the three devices. Increase of the concentrations with the heating temperature (for both compounds).	Only **acetaldehyde** and **formaldehyde** were quantified in emissions of the five devices (except Nautilus X that emitted also acrolein and propanal). Noïd.Lab pod was the device generating the less aldehyde concentrations while	Medium decrease of aldehyde concentrations compared to joints without filter.

Chemical groups	**Vaporizers**	**ENNDs**	**Joints with a filter** *(cellulose with activated carbon)*
	High decrease of acetaldehyde concentrations compared to joints, but butyraldehyde concentrations similar to joints. Higher concentrations of acetaldehyde compared to ENNDS.	Nautilus X was the device generating the most. Lower concentrations in emissions compared to vaporizers and joints	
VOCs and phenols	No phenols quantified. Only **glycidol** and **1,3-propanediol** were quantified in emissions of the three devices. At the highest heating temperature, **glycidol** concentrations were similar to joints.	No phenols quantified. All VOC concentrations were close or below the LOQ, except **glycidol**, for all the 5 ENNDS. **Ethanol** quantified when used in e-liquids. High concentration of **1,3-propanediol** for CBD extract (higher than joints)	Medium decrease of VOC and phenol concentrations compared to joints without filter.
HAPs	No PAH quantified.	No PAH quantified for the 4 ENNDS. PAHs quantified at high concentrations in emissions of CBD extract and at low concentrations in emission of viscous e-liquids.	Medium decrease of PAH concentrations compared to joints without filter.

Chemical groups	**Vaporizers**	**ENNDs**	**Joints with a filter** *(cellulose with activated carbon)*
Aromatic amines	At high heating temperatures, **aniline** and **1-aminonaphtalene** were quantified in emissions of the three devices. **P-toluidine** was also quantified in emissions of FX+. Very low concentrations compared to joints.	No aromatic amines quantified in the emissions of the 4 ENNDS devices. Four aromatic amines quantified in the emissions of Cable pen using CBD extract. Lower concentrations compared to joints.	No decrease in concentrations. Need further experiments as there were some limitations in the analytical methods.
Metals	No metals quantified in emissions of the three devices.	Higher concentrations of Al, Ni, and Cu compared to joints. Metals come from the coil and the devices.	Not analyzed as all concentrations were below the limit of quantifications in emissions of joints without filter.