WHO Expert Committee on Drug Dependence

Critical Review

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Extracts and tinctures of cannabis

World Health Organization

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

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Extracts and tinctures of cannabis

Section 1: Chemistry

Contents

1. Cannabis extracts[1]

1.1 Substance identification

1.1.1 International Nonproprietary Name (INN)

N/A

1.1.2 Chemical Abstract Service (CAS) Registry Number

89958-21-4[2]

1.1.3 Other Chemical Names

N/A

1.1.4 Trade names

N/A

1.1.5 Street Names [1]

- *CO_2 Oil*: cannabis extract obtained by supercritical carbon dioxide extraction.
- *Butane hash oil (BHO), Propane hash oil (PHO) and Solvent extracts*: Resinous extract of the cannabis inflorescence made using butane, propane or other organic solvents, respectively.
- *Wax*: Solvent extract heated at low temperatures and whipped vigorously to remove all residual solvent. Consistency similar to wax with ranges from a variety of amber shades complete with a milder aroma and flavor profile.
- *Budder*: Similar to wax but the consistency of budder is oily and malleable, while wax is crumbly and more solid. Budder contains a higher moisture content because it is whipped less than wax.
- *Live resin*: Live resin is made the same way as wax, but the starting product is fresh frozen cannabis inflorescence. It is known for its flavor, which resembles the aroma and taste of the cannabis plant. It ranges in color from light amber to yellow-gold and has a moist, shiny

[1] Cannabis extracts: this term refers to a plant extract mixture from the leaves and flowers of *Cannabis sativa*.
[2] Definition: Extractives and their physically modified derivatives such as tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene-free fractions, distillates, residues, etc., obtained from Cannabis sativa, Moraceae.

looking exterior with a strong, rich smell. Recently several products with the "live" in their name appeared like "*sugar live*" and "*budder live*" that are all obtained by frozen starting materials.

- *Shatter*: Shatter refers to a solvent extract collected onto parchment paper and placed in a vacuum oven for 45 min to a full day to achieve optimal consistency. Shatter ranges in color from light to dark amber and has a high terpene content, with a characteristic aroma and flavor. It presents a THC content ranging from 20 to 50% [2].
- *Taffy*: Similar to "*shatter"* but the solvent of the extract is evaporated differently resulting in a "taffy". While shatter is typically stable and easy to handle, taffy is closer to "*budder*" in its consistency and stability.
- *Distillate:* Extract obtained by short-path distillation technique. Different fractions are obtained each containing terpenes, cannabinoids and other compounds. It appears like a clear oil. If terpene fractions are added to cannabinoid fractions then distillate possesses the characteristic aroma.
- *Pie Crust/Honeycomb:* Extract obtained by solvent extraction, collected onto parchment paper and placed into a vacuum oven for solvent evaporation. During solvent evaporation, the extracts is pressed to promote faster nucleation, turning the material from a shiny shatter looking substance to more of a cookie crumble, honeycomb look. The final product delivers an amber color with a strong aroma and overall flavor.
- *Caviar:* Caviar is made by soaking cannabis inflorescence in hash oil. Afterwards, the soaked flower is coated in kif [1]and dried.
- *Jelly Hash:* Jelly hash is a mixture of kif and hash oil.
- *Rosin:* Rosin is obtained by the use of heat and high pressure to isolate the resinous oils from the trichome heads to create a solid form of translucent resin. As there is no solvent used, it is not an extract or tincture according to the usual definitions. However, it will be considered here as it has many similarities to cannabis extracts .

1.1.6 Physical Appearance

Color, taste, smell and physical state strongly depend on the manufacturing procedure (see also "Street name" paragraph).

- Supercritical Carbon Dioxide (CO_2) Extract: Amber resinous oil with terpenes smell.

[1] Kif: the term refers to the thricomes that are sifted from dried cannabis; after collection, this material can be heated and pressurized to obtain hashish.

- Butane hash oil (BHO), Propane hash oil (PHO) and other organic solvent extracts: Their appearance depends strongly on subsequent treatment. The color varies from light to dark amber. The smell depends on terpenes composition of starting material and subsequent heating (see "street name" paragraph).
- Edibles: appearance identical to common baked food, such as cookies, fudge, brownies, bread. Taste is very similar to common food because the cannabis taste is masked by other ingredients. Smell does not resemble cannabis odor because terpenes are lost with baking. [2].
- Rosin: Amber resin. The smell depends on the terpene composition of the starting material and the temperature reached during compression.
- Distillates: Clean oil. The smell depends on the eventual addition of terpene fraction.
- E-liquids: clean homogenous viscous oil. Color depends on the type of extract employed. Smell depends on the terpene content, but sometimes other flavors are added to the e-liquid that mask the cannabis smell [3].

1.1.7 WHO Review History

Cannabis extracts and tinctures are scheduled in Schedule I of the Single Convention on Narcotic Drugs as amended by the 1972 Protocol (the "Single Convention").

1.2 Chemistry

1.2.1 Chemical Name

1.2.1.1 IUPAC Name:

N/A

1.2.1.2 CA Index Name:

N/A

1.2.2 Chemical Structure

1.2.2.1 Free base:

N/A

1.2.2.2 Molecular Formula:

N/A

1.2.2.3 Molecular Weight:

N/A

1.2.3 Stereoisomers

N/A

1.2.4 Methods and Ease of Illicit Manufacturing

The following are documented methods for the preparation of different cannabis extracts.

1.2.4.1 Supercritical Carbon Dioxide (CO_2) Extraction

Cannabis inflorescence is treated with supercritical carbon dioxide, which is highly pressurized liquid CO_2. The extract is separated from the CO_2 that is recovered and passed back through the cannabis inflorescence several times until the extraction process is complete. The pressure and temperature of the gas can be fine-tuned to change the solvent extracting ability. The biggest advantage of CO_2 extraction is that it leaves no harmful residues in the resulting product [4, 5].

1.2.4.2 Butane hash oil (BHO)

Butane hash oil (BHO) is a resinous, nonpolar extract of cannabis inflorescence made using butane as a solvent, which is eventually purged under vacuum at room temperature. The final extract can contain from 50 to 90% of the active ingredient, either (–)-*trans*-delta-9-tetrahydrocannabinol (Δ^9-THC) or cannabidiol (CBD), and a terpene content from 0.1 to 34%, but it can be increased by dipping BHO in a vial of terpenes prior to use ("terpene dipping") [6]. BHO has recently become controversial due to explosions resulting from its illicit, unregulated manufacture, some of which have caused injury to workers. Along with cannabinoids and terpenes, butane also extracts plant fats, which can rapidly oxidize and turns the extraction rancid [4]. Because the process does not involve heating the extract, the plant native not-intoxicating delta-9-tetrahydrocannabinolic acid (THCA) does not decarboxylate into the active Δ^9-THC.

Modern techniques also include steps to "de-wax" the product by dissolving the crude BHO in isopropyl alcohol and chilling in a freezer, and, finally, filtering off the precipitated waxes in a process known as "winterization" [6].

1.2.4.3 Edibles

Cannabis is also employed for the preparation of food products. "Bhang" is a traditional Indian drink still used nowadays made with chopped and macerated cannabis leaves to which milk is often added [2]. Rather than cannabis flowering tops as such, their extracts are generally employed for the preparation of food products. As cannabinoids are practically insoluble in water, they are usually extracted with alcohol or fats. These extracts can be incorporated in a wide range of food products, including brownies, cookies, cakes, bread and fudge [2]. Otherwise, macerated cannabis can be combined with butter obtaining the "cannabutter" or "butteruana", which is often green because of the presence of chlorophyll [2]. The levels of Δ^9-THC in edibles are highly variable.

1.2.4.4 Propane Hash Oil (PHO)

Similar to BHO, but it uses propane as the solvent. Although this method usually demands higher pressure, it also requires a lower boiling point, which means better terpene preservation and faster/more effective purging. Propane has risen in popularity for solvent-based extraction in recent years and is generally considered a cleaner final product than BHO. Propane is slightly more expensive than butane, but it provides for extracts with higher flavor and consistency [1].

1.2.4.5 Rosin

This cannabis product exploits heat and pressure to instantaneously squeeze a resinous mixture from the initial starting material. The process can be used either with the inflorescence or to clean up hashish and kif into a high purified hashish oil [7]. The result is a translucent, sappy, and sometimes shatter-like product. Rosin can even present the same flavor, potency, and yield of solvent-based extraction products. Its popularity comes from the ease of a solventless technique. The final product is indistinguishable from BHO. Industrial-sized presses capable of processing large amounts of hashish oil within seconds are already available on the market. These machines scale up to multiple tons of pressure to extract at extremely low temperatures, thus preserving terpenes [7].

1.2.4.6 Distillates

Distillates are concentrated extracts of cannabis inflorescence through which a specific solvent passes and collects cannabinoids and terpenes. The process occurs at high temperatures and the vapors are eventually condensed in a cooling system and collected into a beaker. This process is repeated many times until the inflorescence is exhausted [1]. Due to the high temperature, these products are poor in terpenes, but the latter can be added after manufacturing. After solvent extraction, the product appear as a slurry, which needs to undergo solvent purging prior to its use.

A new process called "short-path distillation" consists of separating and collecting cannabinoids from contaminants to produce a clean and clear final extract [1].

1.2.4.7 Other organic solvent extracts

Other hydrocarbon solvents that can be employed for cannabis extractions include chloroform and hexane. However, hexane is a neurotoxic solvent, although it has a high extracting ability [4]. This is the reason why it is used only in laboratories for research purposes. Pentane is occasionally used in its place because of its low cost.

1.2.4.8 E-liquids

E-liquids are usually prepared as solutions of concentrated cannabis extracts (e.g. resin or oils like BHO) and propylene glycol (PG). PG can be also mixed with other types of cannabis extracts, such as those obtained with either supercritical CO_2, ethanol or 2-propanol. All the crude extracts need to be de-waxed prior to use in order to avoid excessive viscosity of the liquid [3]. The solution is introduced into the small tank of a vaping system, such as an electronic cigarette. Considering that BHO can contain even 80% Δ^9-THC and each puff consumes 5 mg of e-liquid (BHO:PG, 1:3 w/w), a single puff can deliver a Δ^9-THC content up to 1.3 mg [3].

1.2.5 Chemical Properties

1.2.5.1 Melting point

N/A

1.2.5.2 Boiling point

N/A

1.2.5.3 Solubility

N/A

1.2.6 Identification and Analysis

The identification is based on chemical analysis, demonstrating the presence of cannabinoids, such as Δ^9-THC, its degradation product cannabinol (CBN) and/or CBD. The sample is prepared by dilution with an organic solvent like ethanol, methanol, hexane or chloroform.

1.2.6.1 Color test

These are only presumptive tests and a positive result should be confirmed by more accurate analytical techniques such as chromatography.

The literature reports principally three color tests:

- Fast Corinth V salt test
- Fast Blue B salt test
- Rapid Duquenois test (Duquenois-Levine test)

A detailed description of the color tests is reported in "Recommended Methods for the Identification and Analysis of Cannabis and Cannabis Products" of the United Nations Office on Drugs and Crime [8].

1.2.6.2 Thin layer chromatography (TLC)

The TLC methods employed for cannabis plant could be applied to cannabis extracts such as that reported in the monography of the Cannabis Flos in the German Pharmacopoeia for the qualitative determination of the main cannabinoids in the plant inflorescence [9]. Hazekamp *et al.* developed and validated a simple and rapid high performance TLC (HPTLC) method for the quantification of Δ^9-THC, which was proved to be accurate and reproducible [10]. Moreover, it allowed for the qualitative analysis of other main cannabinoids present in cannabis extracts. The identification of cannabinoids is generally based on the comparison of the retention factor (RF) value with that of authentic standards, whereas the visual evaluation is obtained by dipping the TLC plate into aqueous Fast Blue B solution (FBB), which is a selective stain for cannabinoids [10]. In addition, this method can be applied to both polar and non-polar C18 silica gel plates, which provide opposite elution order of cannabinoids.

Nonetheless, TLC encompasses some limitations in terms of specificity and sensitivity, which are fairly low compared to other analytical platforms and thus the results must be taken with caution.

1.2.6.3 Gas Chromatography (GC)

Gas chromatography (GC) is one of the most widely employed approaches for the analysis of cannabinoids in plant materials and they could be adapted to cannabis extracts [11-13]. It is necessary to consider that this system operates at very high temperatures, which unavoidably leads to the decarboxylation of the carboxylated cannabinoids, such as THCA, cannabidiolic acid (CBDA), cannabigerolic acid (CBGA), cannabichromenic acid (CBCA), etc. The result is that the corresponding decarboxylated cannabinoids are generated (Δ^9-THC, CBD, cannabigerol (CBG), cannabichromene (CBC), etc.), unless a derivatization step is encountered prior to the chromatographic analysis. Therefore, the GC analysis implies two critical points: derivatization and decarboxylation of carboxylated cannabinoids. The former is a chemical reaction with a chemical reagent, which is often incomplete [14]; the latter is complicated in a similar way as it is largely affected by the temperature and geometry of the injector [15], thus leading to unreproducible results. Nonetheless, this is one of the official methods employed by the authorities for the determination of cannabinoids in cannabis derived products.

GC is generally interfaced to a flame ionization detector (FID) or to a mass spectrometry (MS) detector. The advantage of FID consists of a more accurate quantitative response with respect to MS due to the use of authentic standards, whilst MS allows for higher specificity and sensitivity compared to FID. However, MS requires the use of deuterated standard, which are expensive and not commercially available for all minor cannabinoids.

A detailed description of a GC-FID method for the determination of Δ^9-THC in cannabis inflorescence and resin is described by the European Union for outdoor cannabis plantations for industrial hemp and could be adapted to cannabis extracts [16].

GC methods could also be employed to analyze the volatile component of cannabis extracts represented by terpenes [17].

1.2.6.4 Liquid chromatography (LC)

Liquid chromatography (LC) coupled to mass spectrometry (LC-MS) can be probably be considered as the method of choice for the qualitative and quantitative determination of cannabinoids in cannabis products [18-28]. In contrast to GC, LC based techniques do not lead to decomposition of the sample as they operate

at room temperature allowing the direct analysis of carboxylated cannabinoids in the extracted sample [29].

Columns for LC analysis are generally based on reverse phase (RP) C18 stationary phases, although hydrophilic interaction liquid chromatography (HILIC) stationary phases have also been employed [30]. It is important to employ stationary phases with a high resolution power [5, 17, 31-33], especially in the case of co-eluting cannabinoids. In particular, it is difficult to obtain a baseline resolution for Δ^9-THC and Δ^8-THC, for CBDA and CBGA, and for CBD and CBG [17, 34]. Ultra-high performance liquid chromatography (UHPLC with sub-2 µm diameter of the particles of the stationary phase) can be a valuable solution to overcome this issue [17, 35-46] due to fast analyses and high separation efficiency.

A considerable improvement in the separation power can be achieved using 2D chromatography, which consists of the combination of two dimensions of different separation mechanisms in series [47]. The whole eluate (comprehensive 2D chromatography) or selected fractions ("heart-cut" 2D-chromatography) from the first dimension are collected and injected into the second dimension, where they are further separated by an orthogonal separation mechanism [48]. This analytical trick is particularly useful when chromatographic resolution of numerous compounds is desired, especially for cannabinoids, many of which are isomers difficult to separate by only one separation mechanism [49].

As for GC, different types of detectors can be employed with LC, such as ultraviolet (UV), fluorescence (FLD) and mass spectrometry (MS). UV detection is the most used for the analysis of cannabinoids in those cannabis products (cannabis plant, resin, extracts, tincture etc.) where the amount of the main cannabinoids is relatively high [13, 17, 34, 47, 49-51]. The monograph of Cannabis Flos of the German Pharmacopoeia describes a LC-UV method for the purity test of the main cannabinoids, CBDA and THCA detected at 306 nm, and CBD, Δ^9-THC, Δ^8-THC and CBN detected at 225 nm [9].

In the case of poor resolution of co-eluting cannabinoids like CBG and CBD, MS can provide a higher level of specificity based on the *m/z* of the molecular ions. In the case of isomers like Δ^9-THC and Δ^8-THC, a high-resolution fragmentation spectrum could help in the identification based on the fragments generated [52]. However, quantification of cannabinoids by MS requires the use of deuterated standards with the same considerations made for GC-MS.

Very few studies have reported the use of LC coupled to FLD since fluorescence spectra of cannabinoids are strongly affected by the pH of the mobile phase [13].

1.2.6.5 Nuclear magnetic resonance (NMR)

Nuclear magnetic resonance (NMR) spectroscopy can be a valid alternative to chromatographic techniques [49, 53-55]. In fact, quantitative NMR can be a highly accurate and reproducible technique with relatively short analysis time. The major advantage of NMR is the lack of sensitivity toward impurities present in the plant extract such as chlorophyll and lipids [53, 54, 56]. On the other hand, the major drawbacks are the high instrumental costs and the necessity of highly specialized personnel that put a limit to the use of this technique [57].

1.2.6.6 Immunoassay (IA)

Immunoassay (IA) is based on the recognition of a class of compounds with similar chemical structure by an antibody, but it generally provides scarce selectivity due to the difficulty in finding antibodies that are specific for each cannabinoid. Therefore, an IA is suitable for a preliminary assessment of the presence of cannabinoids, but a positive IA should always be confirmed with other more sensitive and specific techniques such as either GC-MS or LC-MS [57, 58].

1.2.6.7 Other analysis

Any concentrate should be tested to ensure that it contains no solvent residues. Since these types of extraction can also extract and concentrate heavy metals, pesticides and mold toxins, a complete laboratory safety screening is highly recommended.

1.3 Ease of Convertibility Into Controlled Substances

N/A

2. Cannabis tinctures[1]

2.1 Substance identification

2.1.1 International Nonproprietary Name (INN)

N/A

2.1.2 Chemical Abstract Service (CAS) Registry Number

89958-21-4[2]

2.1.3 Other Chemical Names

N/A

2.1.4 Trade names

N/A

2.1.5 Street Names

- *Tincture*
- *Tincture of cannabis*
- *Liquid marijuana*
- *Liquid THC*
- *Green dragon*
- *Mayzack*
- *Tink.*

2.1.6 Physical Appearance

Dark green or brown liquid.

2.1.7 WHO Review History

See data reported for cannabis extracts.

[1] Cannabis tinctures: this term refers to specific alcohol extractions of the flowering tops or other parts of *Cannabis sativa*.

[2] Definition: Extractives and their physically modified derivatives such as tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene-free fractions, distillates, residues, etc., obtained from Cannabis sativa, Moraceae.

2.2 Chemistry

2.2.1 Chemical Name

2.2.1.1 IUPAC Name:

N/A

2.2.1.2 CA Index Name:

N/A

2.2.2 Chemical Structure

2.2.2.1 Free base:

N/A

2.2.2.2 Molecular Formula:

N/A

2.2.2.3 Molecular Weight:

N/A

2.2.3 Stereoisomers

N/A

2.2.4 Methods and Ease of Illicit Manufacturing

The following are documented methods for the preparation of cannabis tinctures.

Ethanol is a very effective solvent for the extraction of most of the substances contained in cannabis inflorescence. It has a high extraction efficiency and is more effective than water and hydrocarbon solvents (e.g. hexane) [59].

Ethanolic tinctures have a long history of use through oral or sublingual administration and ingestion. Extracts and tinctures appeared early in the United States Pharmacopoeia (USP) and other pharmaceutical references and were manufactured and marketed by pharmaceutical companies such as Merck in

Germany, Burroughs-Wellcome in Britain, and Eli Lilly in the United States [60]. The process for making tinctures involves the heating of the inflorescence with the aim to facilitate the decarboxylation of the carboxylated forms into their decarboxylated derivatives. Hot ethanol extraction has been used in the National Institute of Drug Abuse (NIDA) Drug Supply Program (DSP) to remove essentially all of the THCA, Δ^9-THC, and other cannabinoids from cannabis and produce both an extracted plant material that can be used as a placebo for research and a crude phytocannabinoid tincture that can be used as a drug product or in dosage formulations [60]. To ensure complete extraction, the temperature of the ethanol is typically increased to approximately 60 °C. The ethanol is recirculated for 24 hours. Then, the solvent is replaced with fresh ethanol, and the process is repeated daily for at least 3 days. This approach can dramatically increase the total cannabinoid extraction and yield [60]. Otherwise, it can be taken as such after a simple extraction in ethanol at its boiling temperature (78 °C) for about 30 minutes; in order to avoid solvent loss by evaporation, a condenser can be put on top of the extraction flask [5].

However, it is noteworthy that ethanol is not a very selective extraction solvent, and many other chemical constituents are also removed (chlorophylls, flavonoids, etc.). The ethanol can be evaporated to produce a crude cannabis extract with a high concentration of cannabinoids.

2.2.5 Chemical Properties

2.2.5.1 Melting point

N/A

2.2.5.2 Boiling point

N/A

2.2.5.3 Solubility

N/A

2.2.6 Identification and Analysis

The identification is based on chemical analysis, demonstrating the presence of cannabinoids, such as Δ^9-THC, its degradation product CBN and/or CBD. Cannabis tinctures can be used directly for analysis or diluted in an appropriate solvent. The analytical methods are the same employed for cannabis extracts (see

"Identification and analysis" paragraph of Cannabis extracts) such as color test, thin layer chromatography, gas chromatography, liquid chromatography, nuclear magnetic resonance and immunoassay.

2.3 Ease of Convertibility Into Controlled Substances

N/A

3. Cannabis oils

3.1 Substance identification

3.1.1 International Nonproprietary Name (INN)

N/A

3.1.2 Chemical Abstract Service (CAS) Registry Number

89958-21-4[1]

8016-24-8[2]

3.1.3 Other Chemical Names

N/A

3.1.4 Trade names

N/A

3.1.5 Street Names

- Rick Simpson Oil or Phoenix Tears: RSO
- Hemp seed oil
- Essential oil
- Medicinal cannabis oil

3.1.6 Physical Appearance

3.1.6.1 Rick Simpson Oil or Phoenix Tears

Dark-brown dense resinous oil.

[1] Definition: Extractives and their physically modified derivatives such as tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene-free fractions, distillates, residues, etc., obtained from Cannabis sativa, Moraceae.
[2] Definition: Extractives and their physically modified derivatives. It consists primarily of the glycerides of the fatty acids linoleic, oleic, linolenic and palmitic. (Cannabis sativa, Leguminosae.) Unspecified: Hemp oil. Other Names: Fats and Glyceridic oils, hemp seed Oils, hemp seed Hempseed oil, Oleum cannabis

3.1.6.2 Hemp seed oil

Dark green oil with a pleasantly nutty taste.

3.1.6.3 Essential oil

A pale yellow liquid with a typical cannabis scent that depends on the terpene qualitative and quantitative composition.

3.1.6.4 Medicinal cannabis oil

Dark green-yellow oil. The smell depends on the preparation mode and the cannabis variety employed.

3.1.7 WHO Review History

See data reported for cannabis extracts with the exception of hemp seed oil, which is not a "cannabis extract" according to art. 28 of the 1961 Convention that excluded seeds and fibers from the scheduled substances.

3.2 Chemistry

3.2.1 Chemical Name

3.2.1.1 IUPAC Name:

N/A

3.2.1.2 CA Index Name:

N/A

3.2.2 Chemical Structure

3.2.2.1 Free base:

N/A

3.2.2.2 Molecular Formula:

N/A

3.2.2.3 Molecular Weight:

N/A

3.2.3 Stereoisomers

N/A

3.2.4 Methods and Ease of Illicit Manufacturing

The following are documented methods for the preparation of different cannabis oils.

3.2.4.1 Rick Simpson Oil or Phoenix Tears

Rick Simpson is a Canadian medical cannabis patient known because of his campaign for the promotion of a solvent extraction method that produces an oil he calls “Phoenix Tears”. Simpson reports that his Phoenix Tears cannabis extraction has cured the cancers of many people. However, his claims are anecdotal evidence and generalizing them to all forms of cancer is quite unwise [4]. Moreover, what is more worrying is that the process requires light naphtha as a solvent, which is often used as paint thinner. Light naphtha is excellent for extracting cannabinoids, but difficult to purge from the final extract. Simpson claims that the healing power of his oil can overcome the risk of solvent residue exposure [4].

3.2.4.2 Hemp seed oil

Pure hemp seed oil is not a “cannabis oil” according to art. 28 of the 1961 Convention that excluded seeds and fibers from the scheduled substances. It is included here for clarification and completeness; see also the discussion of cannabinoids as impurities below.

Cannabis sativa L. produces small fruits, botanically defined as “achenes”, although they are usually named “seeds”, which are variable in size depending on the cultivar. The actual “seed” is enclosed in the pericarp, which represents the protective “shell”. Most of the seed consists of an embryo, mainly the two cotyledons (embryonic leaves), rich in oils, proteins and carbohydrates, that represents the nourishment of the plant during germination [2]. Hemp seeds possess an extremely high nutritional value due to a high content of unsaturated fatty acids (about 80% of fatty acids) and proteins (about 25%) [61]. It is not to be ruled out that other minor components, such as terpenes and cannabinoids, could contribute to the surprising beneficial effects of hemp seeds [62].

After removal of the bracts, the seeds are squeezed or macerated, and finally pressed at high pressure to give the hemp seed oil and a mushy residue, the "husk", which is used as fertilizer or compressed into tablets and used for cattle feed [63]. The hemp seed oil obtained by cold pressing finds its main use as food. Polyunsaturated fatty acids (PUFA) constitute about the 80% of the total fatty acids, including linoleic, α- and γ-linolenic acid, which offer an omega-6 to omega-3 PUFA ratio considered optimal for nutrition [64]. Cold-pressed hemp seed oil may also serve as dietary source of natural antioxidants (γ-tocopherol, vitamin E, etc.) for disease prevention and health promotion [64, 65]. Although hemp seeds do not contain any cannabinoid, their contact with the resin secreted by the epidermal glands located on flowers and leaves and/or a bad selection of the bracts of the perigonium, which have the highest cannabinoid content, can cause the presence of the latter in the hemp oil. Hence, cannabinoids actually represent "impurities" of the hemp seed oil [63]. Their concentration depends on both the cultivar and the cleaning process of the seed. Cultivars of *Cannabis sativa* that can be used in the European Union (EU) for seed production are those authorized with a level of Δ^9-THC lower than 0.2%. As a result, Δ^9-THC contamination in hemp seed oil is generally extremely low and only exceptionally it exceeds the limit of 5 mg/kg (5 ppm, maximum Δ^9-THC limit in food suggested by the German legislation in 2000) [66-68].

If consumed as such without heating, it should preserve the plant native cannabinoid acids, the most abundant of which is CBDA [63].

3.2.4.3 Essential oil

Essential oil is obtained by steam distillation of the flowers and leaves of cannabis plant. As reported by Mediavilla and Steinemann, even for Δ^9-THC-rich cannabis varieties, Δ^9-THC content in the essential oil did not exceed 0.08% [69].

Essential oil include volatile oils and ethereal oils and are designated as "non fixed" (that they can evaporate quickly) [2]. It has to be distinguished from the vegetable oil of cannabis, which is actually hemp seed oil (a "fixed" oil). Similarly, essential oil should not be confused with other oils, such as hash oil, which is rich in cannabinoids; the essential oil is instead composed of that extremely wide range of volatile compounds, which are responsible for the characteristic scent of the cannabis plant [2]. Like other essential oils, *Cannabis sativa* essential oil consists of a complex mixture of organic (hydrocarbon) chemicals and particularly includes terpenes and oxygenated compounds such as alcohols, esters, ethers, aldehydes, ketones, lactones, phenols, and phenol ethers [2]. Terpenes typically dominate essential oils. These chemical species are made up of units of isoprene: $CH_2=C(-CH_3)-CH=CH_2$. Monoterpenes consist of two isoprene units, while sesquiterpenes consist of three units. "Terpenoids" are related compounds, although

the term is often used as a synonym of terpenes. Many terpenes are extremely odoriferous, detectable by smell at very low concentrations. Their most important feature is that they are strongly inherited and little influenced by environmental factors [60].

About 140 terpenoids are known in *Cannabis sativa*, although none is unique to just this species [2]. The two most abundant terpenes in *Cannabis sativa* are α-pinene and limonene, followed by myrcene. Other common terpenes of *Cannabis sativa* include linalool, β-caryophyllene, caryophyllene oxide, nerolidol, and phytol. Mediavilla and Steinemann found that *Cannabis sativa* essential oils with high sesquiterpene concentrations have a bad smell, while oils with high monoterpene percentages (but a low α-humulene or caryophyllene oxide concentration) had pleasant smells [69]. Depending on the biotype, monoterpenes represent 48%-92% of the volatile terpenes and sesquiterpenes represent 5%-49% [69]. Monoterpenoids usually make up most of the essential oil of cannabis [2]. The aroma of *Cannabis sativa* is particularly due to the monoterpenes pinene and limonene, which frequently comprise over 75% of the volatiles and often dominate the "headspace" odor near the plant. However, the monoterpenes evaporate relatively faster than other components, so the composition of essential oil actually in the harvested plant may differ from the volatiles released around the fresh plant. Consequently, the odor of the living plant is not necessarily indicative of the relative composition of the plant essential oil or of the odor of the dried plant [2].

The composition of essential oils has been found to vary considerably among strains and cultivars of *Cannabis sativa* [69].

The terpenes of *Cannabis sativa* are manufactured in the same epidermal glands (secretory glandular trichomes) in which the cannabinoids of cannabis are produced and, together with the latter, make up the resinous secretion of the glands [2]. Indeed, the cannabinoids and terpenoids have a parental biosynthetic precursor in common (pyrophosphate).

3.2.4.4 Medicinal cannabis oil

Extraction of *Cannabis sativa* with olive oil or sesame oil is a common practice used in pharmacy for the preparation of medicinal extracts (or galenical preparations). A widely employed methodology is to heat the inflorescence suspended in olive oil (1 g in 10 mL) in a water bath at 98 °C for 2 hours [70]. Olive oil is a lipophilic solvent with a good extraction efficiency towards cannabinoids and all the other components of cannabis inflorescence (terpenes and flavonoids). Indeed, a nearly complete extraction of the main cannabinoids can be achieved in olive oil, along with a 70:30 THCA to Δ^9-THC ratio [5]. However, due to the relatively high temperature, most monoterpenes are lost from the preparation. In order to overcome this

issue, it is possible to put a condenser on top of the extraction flask so as to reflux any volatile component [5].

3.2.5 Chemical Properties

3.2.5.1 Melting point

N/A

3.2.5.2 Boiling point

N/A

3.2.5.3 Solubility

N/A

3.2.6 Identification and Analysis

3.2.6.1 Hemp seeds oil

Hemp seed oils are widely sold for human food and, depending on national regulatory, an appropriate label with chemical composition should be reported [71].

Several methods based on liquid chromatography coupled to ultraviolet detection (LC-UV) or gas chromatography coupled to flame ionization detection (GC-FID) and mass spectrometry detector (GC-MS) for cannabinoids analysis in hemp seed oil have been reported [11, 57].

3.2.6.2 Essential oil

The principal methods to evaluate the composition of cannabis essential oil are based on gas chromatography coupled to flame ionization detector (GC-FID) and mass spectrometry detector (GC-MS) and one method based on Raman spectroscopy [72-76].

3.2.6.3 Rick Simpson Oil or Phoenix Tears and Medicinal cannabis oil

Several analytical methods are reported regarding cannabinoids qualitative andquantitative determination in cannabis oils. Chromatographic methods coupled to several detection techniques such as UV and mass spectrometry are the most widely employed [56]. Based on the specific matrix available, specific sample

pre-treatment and chromatographic method should be followed. In general, the chromatographic techniques can be divided into:

3.2.6.4 Thin-layer chromatography (TLC)

It is quite difficult to separate (–)-*trans*-Δ^8-THC from (–)-*trans*-Δ^9-THC employing a normal and polar stationary phase [14]. A two-dimensional TLC method has been developed with the advantage to obtain a better resolution of the two isomers [77].

1. Gas chromatographic method with mass spectrometry or flame ionization detection (GC-MS or GC-FID)

These methods are widely employed in several laboratories and permit to determine Δ^9-THC with or without preliminary derivatization [14, 78].

2. Liquid chromatography (LC)

LC methods are generally coupled to ultraviolet (LC-UV) and/or mass spectrometry (LC-MS) detection. They offer the advantage of a very high sensitivity without a derivatization step [43, 79-82].

3.3 Ease of Convertibility Into Controlled Substances

N/A

4. Aqueous extracts[1]

4.1 Substance identification

4.1.1 International Nonproprietary Name (INN)

N/A

4.1.2 Chemical Abstract Service (CAS) Registry Number

89958-21-4[2]

4.1.3 Other Chemical Names

N/A

4.1.4 Trade names

N/A

4.1.5 Street Names

Marijuana tea

4.1.6 Physical Appearance

Green-brown aqueous solution.

4.1.7 WHO Review History

See data reported for cannabis extracts.

4.2 Chemistry

4.2.1 Chemical Name

4.2.1.1 IUPAC Name:

N/A

4.2.1.2 CA Index Name:

N/A

[1] Aqueous extracts e.g. marijuana tea.

[2] Definition: Extractives and their physically modified derivatives such as tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene-free fractions, distillates, residues, etc., obtained from Cannabis sativa, Moraceae.

4.2.2 Chemical Structure

4.2.2.1 Free base:

N/A

4.2.2.2 Molecular Formula:

N/A

4.2.2.3 Molecular Weight:

N/A

4.2.3 Stereoisomers

N/A

4.2.4 Methods and Ease of Illicit Manufacturing

The following are documented methods for the preparation of cannabis aqueous extracts.

A simple, and probably one of the oldest, method is the use of boiling water to make a tea (infusion) for oral administration. In a systematic laboratory study, Hazekamp *et al.* took a cannabis chemotype legally grown in the Netherlands with a THCA content of 191 mg/g (19.1%) and a Δ^9-THC content of 6 mg/g (0.6%) of dry weight plant material and prepared a standard tea using the procedures recommended by the Netherlands Office of Medicinal Cannabis [83]. One gram of cannabis was added to one liter of boiling water and simmered for 15 min. The remaining solids were removed with a common tea-sieve. Samples of the tea were lyophilized to complete dryness, reconstituted in ethanol, and analyzed using a validated LC method. Although the amount of Δ^9-THC in 1 g of inflorescence amounted to nearly 200 mg (the sum of Δ^9-THC and its precursor THCA), the whole one liter volume of standard tea contained only a fraction of this amount (about 43 mg of THCA and 10 mg of Δ^9-THC) in the water phase [83]. This is due to the poor solubility of these highly lipophilic compounds, given that the extraction of the solid residue with organic solvents accounted for almost all the amount of these cannabinoids [83]. Since incomplete conversion of THCA into Δ^9-THC was also observed in the tea, the water was boiled for longer periods, thus doubling the concentration of Δ^9-THC in the liquid, but did not result in complete conversion, or significantly increase the concentration of THCA extracted, again suggesting that thermal conversion rates and limited solubility under these conditions are the predominant factors affecting the final concentrations of phytocannabinoids in tea [83].

Another study conducted by Pacifici *et al.* demonstrated the scarce efficiency of water in extracting cannabinoids from cannabis inflorescence [84]. The authors employed 500 mg of medicinal cannabis in 500 mL of water and left to boil for 15 minutes. After filtration, the tea was analysed by ultra-high performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS), which revealed a recovery of total cannabinoids more than three times lower than that obtained with oil extraction [84].

Therefore, in order to compensate for the low solubility of Δ^9-THC in water, users of tea often add a small amount of vegetable oil or butter and increase boiling time [60].

4.2.5 Chemical Properties

4.2.5.1 Melting point

N/A

4.2.5.2 Boiling point

N/A

4.2.5.3 Solubility

N/A

4.2.6 Identification and Analysis

LC based methods employing UV and MS detection have been developed for the qualitative and quantitative determination of cannabinoids in aqueous cannabis extracts by Hazekamp *et al.* and Pacifici *et al.* [21,22].

4.3 Ease of Convertibility Into Controlled Substances

N/A

5. Nabiximols / CBD in preparation with other cannabis-related ingredients [1]

5.1 Substance identification

5.1.1 International Nonproprietary Name (INN)

N/A

5.1.2 Chemical Abstract Service (CAS) Registry Number

56575-23-6

5.1.3 Other Chemical Names

- *GW 1000*
- *GW 1000-02*
- *Nabidiolex*
- *SAB 378*
- *Sativex*
- *Tetranabinex*

5.1.4 Trade names

Sativex®

5.1.5 Street Names

N/A

5.1.6 Physical Appearance

A yellow-brown solution in a spray container.

5.1.7 WHO Review History

See data reported for cannabis extracts.

5.2 Chemistry

5.2.1 Chemical Name

IUPAC Name:

N/A

CA Index Name:

N/A

5.2.2 Chemical Structure

Free base:

N/A

Molecular Formula:

N/A

Molecular Weight:

N/A

5.2.3 Stereoisomers

N/A

5.2.4 Methods and Ease of Illicit Manufacturing

Nabiximols, trade name Sativex®, is a pharmaceutical formulation manufactured in the United Kingdom by incorporating purified botanically derived drug substances containing Δ^9-THC and CBD (initially isolated from cannabis inflorescence with supercritical liquid CO_2) in an accurately measured ratio into a final drug product containing ethanol, propylene glycol, and peppermint oil as excipients [60].

Sativex® is in form of a dose spray produced by GW Pharmaceuticals and approved for the spasticity of multiple sclerosis. According to the patient information leaflet, each 0.1 mL spray contains 3.8 to 4.4 mg and 3.5 to 4.2 mg of two extracts (delta-9-tetrahydrocannabinol Botanical Drug Substance (THC BDS) [Tetranabinex] and Cannabidiol Botanical Drug Substance (CBD BDS) [Nabidiolex]) from *Cannabis sativa* L. leaf and flower, corresponding to 2.7 mg of Δ^9-THC and 2.5 mg of CBD [60].

The process of manufacturing Sativex® at GW Pharmaceuticals was reviewed by Potter and by Guy *et al.* [85, 86].

GW Pharmaceuticals has selected two cannabis plants strains each producing principally Δ^9-THC or CBD. The plants are propagated and grown in a highly regulated glasshouse environment. GW pharmaceuticals have standardized grown conditions in order to minimize the variabiliality in the final concentrations of phytocannabinoids in cannabis inflorescence. The dried plant material, including the foliage and flora, is uniformly heated to decarboxylate the precursors, THCA and CBDA, to Δ^9-THC and CBD, respectively. The plant material is then extracted by supercritical liquid CO_2 extraction to obtain the two soft extracts:

Tetranabinex and Nabidiolex. One milliliter of the final oromucosal solution contains 38-44 mg and 35-42 mg of the two extracts corresponding to 27 mg Δ^9-THC and 25 mg CBD [87].

5.2.5 Chemical Properties

5.2.5.1 Melting point

N/A

5.2.5.2 Boiling point

N/A

5.2.5.3 Solubility

N/A

5.2.6 Identification and Analysis

For regulatory approval, validated analytical methods to evaluate the chemical composition of inflorescences (botanical raw material (BRM)), soft extracts Tetranabinex and Nabidiolex (botanical drug substance (BDS)) and finished product (botanical drug product BDP) were developed by GW Pharmaceutical. Guy *et al.* reported that cannabis inflorescences employed to prepare the two BDS are subject to several tests such as extraneous matter and identification assay for cannabinoids and carboxilated cannabinoids, confirmatory thin-layer chromatography (TLC), loss on drying (moisture), aflatoxins and microbial bioburden [86].

Since the pharmaceutical product is a botanical product, rather than a new chemical entity, characterization of more than 90% of the composition of the whole extract is required. Guy *et al*. reported that the chemical profile of each soft extract has been chararcterized and qualitative compositions comprise: principal cannabinoids (Δ^9-THC (>90% of the cannabinoid fraction in Tetranabinex); CBD (>85% of the cannabinoid fraction in Nabidiolex); minor cannabinoids (CBC, CBG, CBN, tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), THCA, CBDA, cannabicyclol (CBL), cannabitriol (CBT), cannabielsoin (CBE), cannabichromivarin (CBCV)); terpenes (monoterpenes: myrcene, limonene, linalool, α-pinene; sequiterpenoids: *trans*-caryophyllene, α-caryophyllene, caryophyllene oxide, *cis*-nerolidol, *trans*-nerolidol; diterpenoids: phytol; triterpenoids: squalene); fatty acids (linolenic acid, palmitoleic acid, linoleic acid, palmitic acid, oleic acid, stearic acid, myristic acid, arachidic acid and behenic acid); sterols (β-sitosterol, campesterol and stigmasterol); carotenoids (β-carotene, lutein); chlorophylls and related compounds

(phaeophytin); vitamins (vitamin E); phenolic compounds (flavonoids, coumarins, cinnamic acids and psoralens) [86].

Validated analytical methods were developed by GW Pharmaceutical to ensure quality control of the finished product (BDP) in compliance with the guidelines of regulatory authorities [86].

5.3 Ease of Convertibility Into Controlled Substances

N/A

6. References

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Extracts and tinctures of cannabis

Section 2: Pharmacology

Contents

1. General Pharmacology

Studies to be included in the report are those involving:

- Cannabis extracts
    - Cannabis tinctures
    - Cannabis oils
    - Aqueous extracts
- Nabiximols

All products mentioned above are extracts derived from the cannabis plant, usually from dried and cured inflorescence (flowering heads plus resin-containing trichomes). Trichomes are especially rich in cannabinoids and terpenes (i.e., aromatic oils that are released upon heating and give cannabis inflorescences and extracts their characteristic odors and tastes). The purpose of the extraction process is to separate and concentrate the desired constituents of the plant (i.e., cannabinoids, terpenes) and to discard undesirable constituents (e.g., chlorophyll, tar and other extraneous plant matter). The process through which extraction is accomplished determines the classification of the resultant product (i.e., tincture, oil, aqueous extract). The potency of the final product is determined by the concentration of active cannabinoids (namely Δ^9-tetrahydrocannabinol; Δ^9-THC) contained in the inflorescence as well as by the efficiency of the extraction process. Nabiximols is a standardized proprietary blend of Δ^9-THC and cannabidiol (CBD) extracted from the cannabis plant and formulated into an oromucosal spray.

1.1 Routes of administration and dosage

"Dosage" of cannabis extracts most often refers to amount of Δ^9-THC contained in the preparation (and its ratio to CBD, if the extract contains both compounds). In humans, cannabis extracts may be delivered through various routes of administration, including sublingual, oral, inhalation (smoking or vaping), rectal, and transdermal. With exception of nabiximols, which has recommended doses, dosage of cannabis extracts is self-determined by the user and may change over time due to the development of tolerance. Route of administration affects the ease with which dosage may be self-titrated. When a cannabis extract is vaped, its psychoactive effects occur rapidly, allowing users a quick way to assess their intake relative to past uses. Although this rapid feedback would allow titration of dose to desired effect with extracts containing different concentrations of Δ^9-THC, research has shown that titration is usually partial: users who smoke or vape products with higher Δ^9-THC contents than their regular product tend to up-titrate, resulting in greater overall

exposure.[1] In addition, cannabis extraction techniques may result in variable Δ^9-THC yield in the final product and precise measurement of Δ^9-THC and CBD levels in available products often is lacking.[2-5] Self-determination of dosage of orally administered cannabis extracts has the extra complication of a delayed onset of action. Below, typical routes of administration for each of the extracts covered in this report are discussed separately.

1.1.1 Cannabis tinctures

Cannabis tinctures are cannabis extracts for which extraction is accomplished through use of ethanol as a solvent for the cannabinoids contained in crushed cannabis inflorescence or other parts of the plant. Efficiency of the process is enhanced through use of higher concentrations of ethanol; for example, 80-90% ethanol yields tinctures with ten times higher Δ^9-THC concentrations than those made with 40% ethanol.[2] These alcohol-based preparations usually are delivered sublingually or used to infuse edibles or beverages (i.e., oral administration).

1.1.2 Cannabis oils

Cannabis oils are typically derived through using a hydrocarbon solvent (e.g., butane, propane) to extract Δ^9-THC (or other desired cannabinoids) from cannabis, although other solvents or processes (e.g., carbon dioxide, ice water extraction) are also possible. Use of a flammable hydrocarbon to extract cannabis oil (e.g., butane hash oil) may result in a higher yield of Δ9-THC (vs. water or ethanol extraction procedures), but it is also associated with increased risk (e.g., explosion, residual butane). The resulting product from any of these extraction methods may differ in consistency from runny oil to butter, wax, and shatter (in increasing order of viscosity).

Because Δ9-THC is highly soluble in lipids, oil extracts tend to be stable over longer periods of time and often contain high Δ9-THC concentrations.6 Oils may be incorporated into food (i.e., “edibles”) beverage for oral administration or may be vaped or “dabbed.”7, 8

1.1.3 Aqueous cannabis extracts

Aqueous cannabis extracts are extracts that are derived through use of water to extract cannabinoids from the cannabis plant. These extracts are most often used as a tea-like beverage.

Δ^9-THC's poor solubility in water limits its concentration in aqueous solutions; hence, aqueous cannabis extracts are notably weak and stability of the formulation over time is poor.[4, 6]

1.1.4 Nabiximols (Sativex®)

Nabiximols (Sativex®) is a cannabis extract formulated into an oromucosal spray. It has been approved for medical use in some European countries and in Canada, while still under review by the Food and Drug Administration in the United States. Each "puff" of nabiximols contains 2.7 mg Δ^9-THC and 2.5 mg CBD as well as small concentrations of minor cannabinoids and terpenes contained in the specially bred cannabis from which nabiximols is extracted.[9] The typical dose is two puffs, administered up to 4 times daily. Absorption occurs through the buccal membrane or sublingually, dependent upon where the spray is directed in the oral cavity. It is marketed as an adjunctive treatment for spasticity and neuropathic pain associated with multiple sclerosis and has also been employed as a treatment for pain caused by advanced cancer.[10-12]

1.2 Pharmacokinetics

Δ^9-THC and/or CBD are the primary targets for cannabis extractions, with terpenes sometimes included as a secondary target. The ratio of Δ^9-THC:CBD contained in an extract is determined by the ratio of these cannabinoids in the plant strain and by the choice of part(s) of the plant used to make the extract. For example, hemp seed oil contains negligible concentrations of Δ^9-THC and CBD because the hemp seeds from which it is derived have low concentrations of these cannabinoids. In contrast, cannabis plants bred for recreational use typically have high Δ^9-THC concentrations with negligible CBD content whereas those bred for medicinal use may have comparable levels of both compounds (e.g., nabiximols) or high concentrations of CBD and negligible Δ^9-THC (e.g., pure CBD oil; excluded from this report).

In the plant, Δ^9-THC is present primarily in its acid form, Δ^9-THCA, which is rapidly decarboxylated to Δ^9-THC upon heating or burning, as occurs during smoking or in many, but not all, extraction processes. Consequently, the bulk of the extant research on cannabis pharmacokinetics has focused on Δ^9-THC. This section will begin with a discussion of the pharmacokinetics of Δ^9-THC delivered via routes of administration common for extracts (i.e., inhalation via vaping; oral via consumption in edibles or beverages; sublingual via tinctures) and will end with a discussion of the pharmacokinetics of nabiximols.

Section 2: Pharmacology

Two excellent comprehensive reviews served as the basis for much of this section on Δ^9-THC.[13, 14] Route of administration strongly affects the absorption of Δ^9-THC contained in the extracts and its time course. As mentioned above (section 4A), extracts are administered through several routes of administration: inhalation (vaping), oral (food or beverage), or sublingual (tinctures).

Combustion byproducts (e.g., tar, ammonia, carcinogens) are a concern with smoking cannabis, as they are with smoked tobacco.[15] Consequently, inhalation of cannabis extracts (primarily oils) using stationary or portable vaporizers (including vape pens) has increased.[16-18] Research on possible impact on the pharmacokinetics, pharmacodynamics and toxicological effects of vaping cannabis extracts (as compared with smoking cannabis) has not yet caught up with this recent trend. In the few studies that have been done, pharmacokinetic profiles of vaped versus smoked cannabis / cannabis extracts appear to be similar.[19, 20] For example, Hazekamp et al.[20] found that inhalational administration of pure Δ^9-THC or Δ^9-THC contained in bulk cannabis using a Volcano® vaporizer resulted in comparable exhaled concentrations of Δ^9-THC. Based upon studies of smoked cannabis, absorption of Δ^9-THC from inhalation is rapid and measurable levels are observed in plasma seconds after the first puff.[13, 21] While peak plasma levels typically occur in 3-10 minutes after smoking, peak "highs" do not occur until 20-30 minutes after smoking,[13] although others have reported an earlier peak.[21] Because Δ^9-THC concentrations in the plasma may have already started to fall before maximal effect, plasma levels are not the best predictor of intoxication.[22] Bioavailability of Δ^9-THC after cannabis smoking or vaping ranges from 10 to 56%, with several factors contributing to the variability, including dose, smoking efficiency/ topography, history of cannabis use, and individual differences in physiology.[13, 14] In addition, approximately 30-40% of the Δ^9-THC concentration inhaled through smoking or vaping is directly exhaled, suggesting incomplete pulmonary absorption.[20]

Compared to absorption of Δ^9-THC in inhaled cannabis, absorption of Δ^9-THC following oral ingestion is slow and maximal plasma levels are lower, typically resulting in flatter concentration-time curves.[14] Peak plasma levels typically occur in 60-120 minutes after ingestion; however, delays of up to 4-6 hours have also been reported.[13] Rate of absorption may be affected by dose, vehicle, degradation of the drug in the gut, individual differences in physiology, and the presence/absence of food.[14, 23] Estimated bioavailability averages 6%, with considerable variability among individuals.[24] Ingestion is accompanied by significant first-pass metabolism in the liver, further decreasing the amount of Δ^9-THC that reaches sites of action.

Absorption of Δ^9-THC after sublingual administration has not been investigated extensively, except in the context of extracts containing mixtures of cannabinoids (e.g., nabiximols, as discussed below). Two of the sparse studies that specifically examined absorption of Δ^9-THC after sublingual administration found that its bioavailability was improved when administered to rabbits in a vehicle containing beta-cyclodextrin (as compared to oral administration).[25, 26] The authors suggested that cyclodextrin-induced increase in Δ^9-THC aqueous solubility may have contributed to this enhanced bioavailability. In humans, only minor differences in oral and sublingual absorption of a Δ^9-THC formulation (> 98% pure; Namisol®) were observed, with plasma Δ^9-THC levels showing slightly lower peaks and slower elimination following sublingual administration.[27] Whether the amount of alcohol delivered with Δ^9-THC in sublingual tincture preparations would affect its pharmacokinetics has not been determined.

Due to its high lipophilicity, Δ^9-THC is highly bound to plasma proteins and is readily distributed to highly vascularized tissues (e.g., liver, heart, lung) after absorption.[13] First-pass metabolism (with oral administration only), plasma-protein binding and rapid distribution to tissues contribute to rapidly falling plasma levels of Δ^9-THC following absorption, even as pharmacological effects (including centrally mediated subjective effects) continue.[13, 14, 24] These prolonged cannabinoid behavioral effects, which occur despite reduced Δ^9-THC plasma levels, may result from slow elimination of Δ^9-THC from the brain, coupled with the cannabimimetic effects of its highly penetrant and equipotent active metabolite, 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-Δ^9-THC).[13, 28] Body fat also serves as a storage reservoir for Δ^9-THC and its metabolites, as Δ^9-THC is eliminated from fat tissues even more slowly than from brain.[13]

Metabolism of Δ^9-THC contained in cannabis extracts occurs primarily in the liver and is extensive, with almost 100 metabolites having been identified.[13] Hydroxylation of the C-11 site to form 11-OH-Δ^9-THC is the initial step of the biotransformation in most species, including humans.[29, 30] This major metabolite is psychoactive, as indicated by its cannabimimetic effects in mice,[31] its substitution for Δ^9-THC in rat drug discrimination,[32] and its similar psychological effects in men.[28, 33] Data from early studies suggested that 11-OH-Δ^9-THC may have greater brain penetrance than Δ^9-THC.[13] However, unlike with orally administered Δ^9-THC, cannabis smoking (and presumably vaping) results in low brain levels of 11-OH-Δ^9-THC (vs Δ^9-THC).[14] Although hydroxylation of Δ^9-THC at C-11 to form 11-OH-Δ^9-THC is most common, hydroxylation may also occur at C-8, resulting in formation of 8alpha-OH-THC and beta-OH-THC in rodents[29] and 8beta-OH-THC in human hepatic microsomes.[34] I.v. administration of the epimers to a small sample of men revealed that both

epimers were active.[35] The primary CYP isoenzymes that catalyze the hydroxylation reactions are CYP2C9 and CYP3A4.[34, 36] A secondary metabolite, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (11-COOH-Δ^9-THC or THC-COOH), is formed through oxidation of 11-OH-Δ^9-THC.[37] THC-COOH lacks cannabimimetic effects and is further metabolized to its glucuronide conjugate, which is water soluble and excreted in urine.[14, 36] Due to its extensive metabolism, relatively little Δ^9-THC is eliminated from the body unchanged. Δ^9-THC is excreted primarily in the feces (65-80%) and in the urine (20-35%).[13]

1.2.1 Nabiximols

Δ^9-THC and CBD are the two primary constituents in nabiximols. The pharmacokinetics of Δ^9-THC are described above. The pharmacokinetics of CBD resemble those of Δ^9-THC.[13] Absorption of smoked CBD is rapid, with bioavailability averaging about 6% after oral administration.[38] As seen with Δ^9-THC, primary metabolism occurs via oxidation,[14] with 7-hydroxy-CBD and CBD-7-oic acid as major metabolites.[39, 40] However, unlike with Δ^9-THC, a high percentage of CBD is eliminated unchanged in the feces.[13, 14]

Pharmacokinetic investigation with nabiximols reveals considerable individual variability, as is characteristic of cannabinoids.[9, 14] Absorption of Δ^9-THC and CBD are rapid following sublingual administration of nabiximols, with slightly higher bioavailability for Δ^9-THC than CBD.[9] Enhanced levels of plasma 11-OH-Δ^9-THC suggest that a portion of the drug may be delivered orally (i.e., swallowed) rather than sublingually.[41] Multiple doses do not result in significant accumulation in plasma.[9]

Animal work has suggested that CBD may hinder or delay Δ^9-THC metabolism through competition for or inactivation of CYP P450 enzymes,[42, 43] resulting in enhancement of Δ^9-THC's in vivo effects.[44] However, this research generally used higher concentrations of CBD (in relation to Δ^9-THC concentration) than are typically present in most cannabis strains or in nabiximols. In contrast, lower CBD concentrations failed to accentuate Δ^9-THC's effects in rodents.[44] The degree to which a similar metabolic interaction occurs in humans is uncertain, with extant evidence suggesting that it does not at the ratios of Δ^9-THC:CBD normally seen in cannabis or in nabiximols.[13, 41, 45, 46] Further, the results of a study on the pharmacokinetics of nabiximols in a small sample of cannabis users is supportive of this hypothesis.[41]

1.3 Pharmacodynamics

To date, over 500 naturally occurring compounds have been identified in cannabis, including cannabinoids (> 100 chemicals unique to the plant), terpenoids, and alkaloids.[47-50] However, except for Δ^9-THC and CBD (in some plants), most of these other compounds are present in the plant in relatively small quantities. In addition, the extraction process is designed to concentrate the desired constituents (usually Δ^9-THC and/or CBD). Hence, the degree to which other compounds may contribute to the array of pharmacological and behavioral effects produced by cannabis extracts is largely unknown. The discussion below focuses primarily on the pharmacodynamics of Δ^9-THC followed by a summary of the pharmacodynamics of hemp seed oil and nabiximols. The predominance of Δ^9-THC-like effects are dependent upon how much of Δ^9-THC is contained in the extract, how much of the extract is consumed, and its route of administration.

1.3.1 Cannabis Extracts: Focus on Δ^9-THC

When administered to animals, Δ^9-THC produces a characteristic profile of pharmacological effects which includes a tetrad of effects in mice and rats (locomotor suppression, antinociception, hypothermia and ring/bar immobility), discriminative stimulus effects (rats, mice, pigeons, rhesus monkeys), reinforcing effects (squirrel monkeys), and static ataxia (dogs).[51-53] These cannabimimetic effects are produced through interaction with an endogenous cannabinoid system that serves to maintain physiological homeostasis as one of its primary functions.[54] Within this endocannabinoid system, two cannabinoid receptors, CB_1 and CB_2, have been identified.[55, 56] While CB_1 receptors are widespread and abundant in the brain and periphery, CB_2 receptors are confined primarily to the periphery,[57] although recent evidence suggests that CB_2 receptors may be present in the brain under certain conditions.[58] Δ^9-THC is a partial agonist at both types of cannabinoid receptors, at approximately equal affinities (K_i = 41 and 36 nM for CB_1 and CB_2 receptors, respectively).[59] Further, the affinities of cannabis vapor (created in Volcano® vaporizer) and pure Δ^9-THC for the CB_1 receptor are similar for cannabis extract containing an equivalent amount of Δ^9-THC,[60] emphasizing the degree to which Δ^9-THC is predominant in the pharmacology of the vaped cannabis extract. Δ^9-THC's psychoactivity is mediated via activation of CB_1 receptors in the brain in a manner resembling activation by their endogenous ligands (e.g., anandamide and 2-arachidonoylglycerol). For example, research has shown that the discriminative stimulus effects of Δ^9-THC in animals were reversed by pre-injection with rimonabant, a selective CB_1 receptor antagonist, but not by injection with SR144528, selective CB_2 receptor antagonist.[61] Similarly, the

reinforcing effects of THC in squirrel monkeys were reversed by rimonabant,[62] as were its antinociceptive, hypothermic and cataleptic effects in rodents[63] and its induction of static ataxia in dogs.[53] Antagonists of other major neurotransmitter systems (e.g., dopamine, acetylcholine, norepinephrine, mu opioid) did not alter the discriminative stimulus effects of Δ^9-THC in rats.[32] Consistent with these in vivo results, Δ^9-THC does not have significant affinity for non-cannabinoid receptors of these major systems.[64] In humans, rimonabant attenuated the acute psychological and physiological effects of a smoked marijuana cigarette containing 2.64-2.78% Δ^9-THC,[65, 66] suggesting that the antagonism results from preclinical Δ^9-THC antagonism experiments are translational.

While Δ^9-THC produces its characteristic pharmacological effects via activation of CB_1 and CB_2 receptors, the brain's endocannabinoid system has extensive interconnections with a variety of other neurotransmitter systems, including dopamine, GABA, glutamate, opioid, and norepinephrine.[67-70] Hence, activation of this system through exogenous administration of Δ^9-THC may have widespread indirect effects on modulatory endocannabinoid-induced regulation of these other neurotransmitters.[71] Of note, similar to the action of many other drugs of abuse, acute administration of Δ^9-THC induces dopamine efflux in reward-related brain areas.[68] In contrast, withdrawal from Δ^9-THC after chronic administration is associated with decreased activation of dopamine neurons.[72, 73]

1.3.2 Hemp Seed Oil

Hemp seed oil may be extracted via a cold-pressing process from the seeds of cannabis plants that contain negligible amounts of Δ^9-THC (typically < 0.3% in the U.S. and < 0.2% in the EU).[74, 75] Alternatively, it is extracted from cannabis plants that contain Δ^9-THC and CBD, but only the seeds (which do not contain Δ^9-THC) are used. In the latter case, Δ^9-THC, CBD, or their acidic analogs (THCA and CBDA, respectively) may be present as contaminants resulting from harvesting, extraction, or storage processes.[76] Unlike cannabis extracts that contain high Δ^9-THC concentrations, hemp seed oil is used primarily for its putative nutritional benefits, as the oil is rich in unsaturated fatty acids (e.g., 3-, 6- and 9-omega) and proteins.[75] In small-sample studies, hemp seed oil did not produce Δ^9-THC-like psychoactive effects when consumed orally or inhaled.[76, 77]

1.3.3 Nabiximols: Δ^9-THC and CBD extract

Nabiximols is a botanical extract of the cannabis plant. Ninety percent of the medication is comprised of a combined ~ 1:1 ratio of Δ^9-THC and CBD, with other minor cannabinoids and

terpenes comprising the remaining plant-derived ingredients. Given their high concentrations, Δ^9-THC and CBD undoubtedly play a role as primary contributors to nabiximols' pharmacological effects. As discussed above, many of the major psychoactive and therapeutic effects of Δ^9-THC are mediated through its interaction with CB_1 and/or CB_2 receptors. However, unlike Δ^9-THC, CBD has minimal affinity for CB_1 receptors and it does not produce cannabimimetic pharmacological or subjective effects in animals or humans.[78, 79] Animal research has posited various potential therapeutic indications for CBD, including as a treatment for epilepsy, pain and inflammation, anxiety, and psychosis.[38, 80, 81] While the effectiveness of CBD for many of these indications has not been explored, extant evidence suggests that it may have efficacy for the treatment of severe refractory epilepsy (e.g., Dravet syndrome).[82, 83] Hence, CBD may have pharmacological effects independent of any interaction with Δ^9-THC. Putative mechanisms through which CBD may produce its pharmacological effects include activation of transient receptor potential vanilloid 1 (TRP-V1) channels or 5-HT_{1A} receptors, antagonism of alpha-1 adrenergic or mu opioid receptors, or antagonism of GPR55, an orphan G-protein coupled receptors.[38, 84, 85]

While the degree to which CBD's independent effects contribute to nabiximols' therapeutic profile is unclear, previous research with Δ^9-THC and CBD combinations has suggested that CBD is not likely to contribute to the cannabimimetic subjective effects that have been observed at acute supratherapeutic nabiximols doses.[86, 87] Further, interactions among Δ^9-THC, CBD, and the other minor cannabinoids and terpenes present in nabiximols have also been posited to contribute to the overall therapeutic benefit of nabiximols through an "entourage" effect.[88-90] The mechanism(s) through which an "entourage" effect might work to effect nabiximols' therapeutic and adverse effect profile has not been completely delineated. The hypothesis that CBD-induced inhibition of Δ^9-THC pharmacokinetics may contribute to nabiximols' effects has not been supported by research in humans.[41, 45]

2. Dependence Potential

2.1 Animal Studies

Although the dependence potential of cannabis extracts has not been studied explicitly in animals, Δ^9-THC, the primary psychoactive constituent in many extracts, has been investigated in numerous studies, as reviewed by Maldonado.[91] In rodents, only weak physical signs of withdrawal are observed with spontaneous termination of repeated Δ^9-THC administration. In contrast, antagonist-precipitated withdrawal is associated with more pronounced signs. Rimonabant administration induces somatic signs such as wet dog shakes, paw tremors, facial rubbing and ataxia as well as behavioral signs such as suppression of operant responding for food.[92-98] Rimonabant-precipitated withdrawal from Δ^9-THC has also been reported in rhesus monkeys and in dogs.[53, 99]

2.1.1 Nabiximols

The dependence potential of nabiximols has not been evaluated in animals.

2.2 Human Studies

Cannabis dependence is characterized by the development of withdrawal symptoms upon abstinence from regular use. Multiple lines of evidence have converged to confirm and characterize a cannabis withdrawal syndrome.[100, 101] In humans, onset of withdrawal typically occurs within 24 to 48 hours of abstinence following a period of regular use. The sequalae of physical and psychological symptoms comprising the withdrawal syndrome may include mood changes, irritability, increased anger, anxiety, craving, restlessness, sleep impairment, stomach pain, and decreased appetite, with most individuals reporting four or more symptoms.[102-106] Psychological symptoms predominate, with peak intensity usually 2 to 6 days after last use. Similar to withdrawal from other drugs of abuse (e.g., nicotine), maximal discomfort lasts 2 to 3 weeks with gradual return to baseline,[107] although disruption of sleep may linger.[108]

The dependence potential of cannabis extracts has not been specifically evaluated; however, previous studies show that regular exposure to cannabis containing high concentrations of Δ^9-THC increases the probability and severity of dependence.[105, 109, 110] These results suggest that regular use of some types of extracts would be more likely to be associated with dependence than others. For example, due to the limited solubility of Δ^9-THC in water, its concentration is relatively low in

aqueous extracts (e.g., estimated at 10 mg Δ^9-THC per liter of aqueous solution).[4, 6] In tinctures, Δ^9-THC concentration is highly affected by the percentage of ethanol in the vehicle, with 80-90% ethanol resulting in tinctures with higher Δ^9-THC concentrations than those made with 40% ethanol.[2] Given the notable lipid solubility of cannabinoids, including Δ^9-THC, cannabis oil extracts contain the highest Δ^9-THC concentrations and would be expected to have the highest potential for dependence.[6, 8] In addition to cannabis oil extracts that are used primarily for making cannabis edibles and for vaping, cannabis oil extracts include products such as wax and shatter in which Δ^9-THC is highly concentrated. In surveys of college students and regular cannabis users, frequent use of butane hash oil, a high-potency product, was associated with greater dependence and perceived lack of control over cannabis use.[7, 8]

2.2.1 Nabiximols

Although the dependence potential of nabiximols has not been evaluated in humans, an earlier review of its abuse and dependence potential[111] mentioned an unpublished study, in which 44% of patients who experienced a 2-week interruption of nabiximols treatment exhibited an increase in some signs of cannabis withdrawal (e.g., disrupted sleep). Other studies have examined the efficacy of nabiximols for the treatment of cannabis withdrawal syndrome and reported that it was effective in ameliorating withdrawal symptoms in treatment and non-treatment seeking cannabis users.[112, 113]

3. Abuse Potential

3.1 Animal Studies

Cannabis extracts vary in the concentration(s) of Δ^9-THC and/or CBD they contain and their typical route of administration (e.g., inhalation via vaping, oral, sublingual). Of these two cannabis constituents, only Δ^9-THC produces classic Δ^9-THC-like pharmacological effects in animals; available evidence suggests that CBD does not have abuse potential.[32, 114, 115] Hence, most research which has examined the abuse potential of cannabis in animal models has used systemic injection of Δ^9-THC as a proxy. In a few instances, combusted or aerosolized Δ^9-THC has been tested. Specific evaluation of cannabis extract (vs. pure Δ^9-THC) has been rare. Consequently, a major distinguishing factor among these studies is route of administration, a factor that also varies across cannabis extracts. The extant preclinical animal research on the abuse potential of Δ^9-THC has been discussed in the review of Δ^9-THC and is summarized here. In addition, results of several recent studies that have explored the use of vaporizers or electronic cigarette technology to expose animals to aerosolized cannabinoids (i.e., animal model of vaping) are described.[116-119]

Briefly, while robust i.v. self-administration of Δ^9-THC has been shown in squirrel monkeys,[62, 120-124] investigators have noted difficulties in training a robust i.v. Δ^9-THC self-administration in rats,[125, 126] although self-administration of the synthetic aminoalkylindole cannabinoid, WIN55,212-2, has been reported in at least two labs.[126-128] In contrast, Δ^9-THC produces robust and pharmacologically selective discriminative stimulus effects in several species, including rats (i.p.),[32] rhesus monkeys (i.m.),[129, 130] mice (i.p.),[131, 132] and pigeons (i.m.).[133] In rodents and/or rhesus monkeys, full substitution for Δ^9-THC has been demonstrated for other psychoactive phytocannabinoids, CP55,940, WIN55,212-2, and an array of abused synthetic cannabinoids.[32, 114, 129, 130, 134-138]

Inhalational studies of cannabinoids have used combusted cannabis with defined amounts of Δ^9-THC and other cannabinoids (e.g., CBD) or they have employed newer methods of vapor exposure using a vaporizer or e-cigarette apparatus to aerosolize Δ^9-THC, cannabis extract, or synthetic cannabinoids.[116-119] These studies have shown that exposure to cannabis smoke containing Δ^9-THC produced a concentration-dependent profile of effects in rodents that is shared with systemically injected Δ^9-THC: suppression of locomotor activity, antinociception, hypothermia and catalepsy.[44, 139-142] Similarly, this tetrad of cannabinoid effects was also observed in rats exposed to Δ^9-THC or crude cannabis extract (containing comparable Δ^9-THC concentrations), which were aerosolized

using an e-cigarette apparatus.[116] However, when Δ^9-THC was delivered via a Volcano® vaporizer, rats exhibited different effects than when it was administered i.p. Whereas i.p. Δ^9-THC produced conditioned place aversion, aerosolized Δ^9-THC failed to produce this effect or produced conditioned place preference.[117] Locomotor stimulation and increased feeding behavior were also noted with aerosolized Δ^9-THC, but not with i.p. Δ^9-THC.[118] Because determination of exact dose is complicated in inhalational studies using modified vaporizers, the degree to which dose ranges were equivalent for the two routes of administration (i.p. vs. inhalation) was not examined.

3.1.1 Nabiximols

Although the abuse potential of nabiximols has not been explicitly evaluated in animals, its two constituents (Δ^9-THC and CBD) have been tested in tandem in drug discrimination and a place conditioning paradigm.[78] In male Long-Evans rats trained to discriminate 3 mg/kg Δ^9-THC from vehicle, CBD failed to substitute for Δ^9-THC when tested alone at doses up to 10 times the Δ^9-THC training dose. It also did not alter Δ^9-THC's discriminative stimulus or response rates when tested at CBD:Δ^9-THC ratios of 1:1 to 10:1. In contrast, CBD at 1:1 and 10:1 CBD:Δ^9-THC ratios attenuated the conditioned aversive effects produced by 10 mg/kg Δ^9-THC in ICR mice. In a select group of rats trained to self-administer i.v. Δ^9-THC, CBD also did not affect Δ^9-THC's reinforcing effects.[125] These results suggest that CBD contained in nabiximols may attenuate the aversive effects of Δ^9-THC, but is unlikely to affect its subjective or reinforcing effects.

3.2 Human Studies

Prior research has suggested that the cannabis constituent responsible for the plant's reinforcing and subjective effects is Δ^9-THC.[87, 143-146] Cannabis extracts vary in their average Δ^9-THC concentrations, with butane hash oil containing maximal amounts and aqueous extracts containing the least.[3, 4, 6, 8] Given these differences in Δ^9-THC content, it would not be surprising if the different types of extracts were associated with variations in abuse potential; however, empirical data to support this hypothesis are lacking. The abuse potential of cannabis extracts has not been specifically evaluated in humans. One study with oral administration of cannabis extract containing a 2:1 ratio of Δ^9-THC (20 mg, up to 4 in an acute administration) and CBD found that the most prominent effects were tiredness, dizziness, and drowsiness.[147] These results are consistent with earlier an earlier finding that oral administration of Δ^9-THC or cannabis produced greater sedation than smoking.[144] The abuse potential of high potency cannabis extracts, especially via vaporizer, has not yet been evaluated. However, as use of portable vaporizers (e.g., vape pens and other

devices) increases in popularity among youth and young adults, use of cannabis extracts in these devices is likely to follow, albeit users may continue to employ more than one method to use cannabis (e.g., vaping and smoking).[18]

3.2.1 Nabiximols

A randomized double-blind clinical trial was conducted to evaluate the abuse potential of nabiximols in recreational cannabis users.[86] Participants were administered acute bolus doses of nabiximols containing Δ^9-THC concentrations of 10.8, 21.6, or 43.2 mg and comparable concentrations of CBD. Whereas 10.8 mg did not induce subjective effects associated with cannabis use, cannabis-like effects (e.g., drug-liked, stoned, and increased marijuana ratings on the Addiction Research Center Inventory) were reported at higher doses. Notably, however, the usual dose of nabiximols contains a daily total of 21.6 mg Δ^9-THC delivered over the course of 3-4 divided dosings. Karschner et al.[148] reported similar findings with lower doses of nabiximols. Abuse also has not been reported in post-market surveillance of nabiximols.[86, 149]

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Extracts and tinctures of cannabis

Section 3: Toxicology

Contents

1. Toxicology

1.1 Sativex® (Nabiximols)

Sativex is a registered medicine that is essentially a tincture formulation containing Δ^9-THC, CBD and a cannabis-extracted botanical drug substance (BDS), that is solubilised in ethanol and propylene glycol. A 100 µl spray of Sativex contains 2.7 mg Δ^9-THC and 2.5 mg CBD which is applied to oromucosal membranes. It is recommended that a maximum of 12 sprays are administered per day (giving a total daily dose of 32.4 mg of Δ^9-THC and 30 mg of CBD).

Like Δ^9-THC and cannabis (see Reports 1 and 3), Sativex may transiently increase heart rate and blood pressure early in therapy. Following Sativex dosing in healthy volunteers up to 18 sprays twice daily, there were no clinically relevant changes in heart rate, blood pressure or QT, PR or QRS interval duration *(1)*.

Sativex does not appear to be mutagenic or carcinogenic. Sativex was not mutagenic in several Salmonella typhimurium and Escherichia coli strains in the Ames test *(1)*. Nor did it lead to chromosome disruptions of breakages *in vivo* in mice and rats in the micronucleus tests, or in rat hepatocytes in the unscheduled DNA synthesis assay *(1)*. Sativex did not promote genotoxicity in a forward mutation assay in mouse L5178Y cells *(1)*. The US National Toxicology Program has shown that Δ^9-THC does not have mutagenic or carcinogenic effects (also see Report 3) *(2)*. As these data were available with Δ^9-THC, GW Pharmaceuticals conducted a long-term carcinogenicity study in rats with a CBD-rich cannabis extract otherwise known as CBD BDS *(1)*. Rats received oral doses of 5-50 mg/kg/day of CBD BDS which revealed no carcinogenic effects.

Treatment of rats with a 1:1 Δ^9-THC BDS and the CBD-rich extract (CBD BDS) mixture did not affect fertility at doses up to 12.5 mg/kg/day of Δ^9-THC and CBD, a dose greatly exceeding the maximal dose recommended in humans *(1)*. Publicly available data do not exist on the impact of Sativex on male fertility (please also see Report 1 and 3). There is no relevant publicly available data on the effects of Sativex on human reproduction. There was no evidence for teratogenicity in rats and rabbits treated with oral doses of a 1:1 Δ^9-THC BDS and CBD BDS mixture up to 12.5 mg/kg/day of each active component *(1)*. The highest dose was reported to have maternal toxicity in rabbits but the specific nature of this toxicity was not described *(1)*. Foetal weights and impaired skeletal ossification was observed in rabbits following the highest doses of the 1:1 Δ^9-THC BDS and CBD BDS mixture that was tested.

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Rats orally administered 4 mg/kg/day of a 1:1 Δ^9-THC BDS and CBD BDS mixture from the time of fertilisation to weaning resulted in a lower body weight gain and slightly impaired righting reflex in the offspring *(1)*, however this dose would exceed the equivalent maximum daily dose in humans that is recommended by the manufacturer. Following oral administration of a 1:1 mixture of Δ^9-THC BDS and CBD BDS, high concentrations of Δ^9-THC and CBD were measured in the breast milk of lactating rats *(1)*. Oral administration of 1:1 Δ^9-THC:CBD BDS from the time of fertilisation to weaning impaired nursing behaviour and pup survival at doses of greater than 5 mg/kg/day *(1)*.

The effects of Sativex on driving performance in a driving simulator or in an on-road test have not been assessed. It was shown to have no effect on driving-related ability in 33 multiple sclerosis patients using the Vienna test system, which is a series of cognitive tests that evaluate visual pursuit, reaction time, stress reactivity and traffic perception *(3)*. This study was not placebo-controlled and compared driving ability to baseline performance after 4-6 weeks of daily Sativex treatment (5 sprays per day).

1.2 Cannabis extracts, tinctures, oils and aqueous preparations

Very little information exists on the toxicology of cannabis extracts, tinctures, oils and aqueous preparations. Some toxicity data suggests that the toxicity of pure Δ^9-THC does not differ to that of a full-spectrum cannabis extract rich in Δ^9-THC that also contains relatively low concentrations of other plant components such as cannabinoids, terpenoids, and flavonoids. For example, one study compared the effects of Δ^9-THC and a cannabis extract matched for Δ^9-THC content on rate of resorptions in pregnant mice *(4)*. It showed that both Δ^9-THC and the cannabis extract equivalently increased the rate of resorptions, and so the additional compounds in the cannabis extract did not modify the actions of Δ^9-THC. There are other data suggesting that CBD may modulate the effects of Δ^9-THC, and that increasing CBD content in Δ^9-THC-rich cannabis may reduce the adverse dose-related psychopharmacological effects of Δ^9-THC such as psychosis and memory impairment *(5)*. Clearly more research is needed to examine whether other plant components found in cannabis extracts modulate the toxicological effects of Δ^9-THC, or whether the extracts themselves have unique toxicity.

Cannabis extracts, oils and aqueous preparations come in different varieties based on the cannabis strains they have been extracted from, or via cannabinoid fortification. Apart from subtle differences in minor cannabinoid and terpene content, various preparations abound with a spectrum of relative Δ^9-THC and CBD content; from Δ^9-THC-rich strains where the abundance of Δ^9-THC is higher than CBD, through strains

matched in CBD and Δ^9-THC content (so called 1:1 strains), through to CBD-rich strains, where CBD content is higher than that of Δ^9-THC. Cannabis is not just street cannabis, which contains high THC content and virtually no CBD content *(6)*. CBD-rich cannabis extracts and oils are increasingly being used in the community, most notably in the treatment of severe childhood epilepsies such as Dravet syndrome and Lennox-Gastaut syndrome, where current therapies are ineffective or have significant side-effects *(7-9)*. These severe epilepsies have a large seizure burden and are associated with sudden death (sudden unexpected death in epilepsy (SUDEP)). These patients also display severe developmental delays in cognitive, language, and social and motor function. Recent open label or retrospective studies report that CBD-rich extracts, and possibly Δ^9-THC-rich extracts at relatively lower doses (<0.5 mg/kg/day), administered sublingually or orally were perceived to reduce seizure burden and improve cognition, psychomotor function and sleep in intractable epilepsy patients *(7-9)*. It may also be that other cannabinoids in the plant contribute to the anticonvulsant action of the extracts, as various other cannabinoids beyond Δ^9-THC and CBD have been shown to be anticonvulsant in animal models *(10, 11)*. The toxicity of CBD-rich extracts is likely closer in nature to purified CBD formulations than Δ^9-THC-rich extracts, however more research is needed. GW pharmaceuticals has likely examined the toxicity of CBD-rich extracts as mentioned in section 1.1. above but this information is not readily available, although would have assisted in the recent FDA registration of Epidiolex, a CBD-rich cannabis oil containing 98% CBD and 2% BDS (botanical drug substance). These cannabis extracts appear to be well-tolerated and safe as highlighted in recent studies (see section 2: Adverse reactions in humans) *(7-9)*.

The production of cannabis concentrates has proliferated in recent times with the rise of legal recreational and medicinal cannabis. There are several methods for producing concentrates: 1) dry processes to produce kief or finger hash; 2) water-based methods to make hashish, bubble and ice wax; 3) CO_2 extraction to produce CO_2 oils; and 4) solvent-based methods to produce isopropanol oil, butane hash oil, Rick Simpson oil, honey oil, honeycomb, wax, and shatter *(12)*. The latter solvent-based methods have arisen in the unregulated recreational and medicinal cannabis milieu of the US, and contain up to 80% Δ^9-THC, unlike cannabis flower which often contains 15% Δ^9-THC content *(6)*. The solvents used can be accessed easily at low cost and include naptha, isopropanol, acetone, hexane, ethyl alcohol and butane. One of the potential health issues associated with the use of these preparations is that they may contain residual solvent which is then ingested by the user. CO_2 extraction methods offer a safer alternative to solvent-based methods and are increasingly being used, however these methods require technical knowledge and more expensive infrastructure.

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Another issue with the use of cannabis concentrates is that their production methods also concentrate other contaminants in the final product such as pesticides, which are prevalent in unregulated cannabis markets *(13)*. Indeed, 70% of pesticide contaminants are transferred to the user in cannabis smoke *(13, 14)*. Concentrates are being increasingly consumed using e-cigarettes and vape pens. Cannabis oils are viscous, and for them to flow easily from the cartridge to the heating element, thinning agents such as propylene glycol and polyethylene glycol 400 are often used (note: cannabis oils produced from CO_2 extraction are less viscous and do not require thinning agents to be used in vape pens). Unfortunately, thinning agents can produce high concentrations of toxic acetaldehyde and formaldehyde when heated in these devices *(15)*. In addition, terpenes found in cannabis concentrates such as myrcene can be converted to the toxic degradants methacrolein (an irritant) and benzene (a carcinogen) as a result of dabbing, a widespread method of smoking concentrated cannabis oils which involves combustion *(16)*.

Very little information exists on the toxicology of aqueous preparations such as cannabis tea, but it is likely to have insignificant toxicity when consumed appropriately. The preparation process endorsed by the Office of Medicinal Cannabis in the Netherlands involves the use of 1 g of cannabis flower and placing it in 1 L of boiling water for 15 min *(17)*. This yields approximately 3.5 mg of Δ^9-THC per cup which is a threshold dose for subjective effects in a naïve user *(13)*.

Cannabis was first introduced into western medicine largely in the form of cannabis ethanolic tinctures in the 19th century *(18)*. Such formulations are still in use today, either as artisanal preparations or as a registered medicine in the form of Sativex. The issue with artisanal tinctures is that the exact ethanolic formulation or starting cannabis material may vary leading to inconsistent cannabinoid content *(18)*. Other than that, there is no evidence to suggest that cannabis tinctures have any unique toxicity above and beyond that observed with Δ^9-THC-rich cannabis and Δ^9-THC alone.

Hemp seed oils are unlikely to have any significant toxicity and are accepted as foods and animal feed in many countries around the world with strict caps on low concentrations of Δ^9-THC (e.g. 10µg of Δ^9-THC/gram of hemp seeds (10ppm)) *(19)*. The oil is rich in various nutrients such as polyunsaturated fatty acids (PUFAs) such as omega-3 and 6 fatty acids, and a broad range of vitamins and minerals. Hemp seed oils theoretically should not contain significant cannabinoid content, as the seed has low concentrations of cannabinoids - the seed of hemp-type and drug-type cannabis contains no greater than 0.5 and 2 µg of Δ^9-THC per g of seeds respectively *(19, 20)*. However, suboptimal manufacturing processes invariably lead to contamination with Δ^9-THC, mainly due to the hull being incompletely removed from the seed and the seed

being inadequately washed *(21-23)*. There is one suspected case of a cannabinoid poisoning in a child who consumed hemp seed oil, however the amount of Δ^9-THC in the product was very low *(21)*.

2. Adverse reactions in humans

2.1 Sativex® (Nabiximols)

In the Australian Therapeutic Goods Administration's product information sheet the percentage of patients experiencing specific adverse events was outlined in 805 Sativex-treated participants and 741 placebo participants *(24)*. Overall there was a higher number of participants reporting adverse effects in the Sativex group (66%) than the placebo group (45%). The most commonly reported adverse reactions observed were dizziness (24.8 % in the Sativex group versus 7% in the placebo group) and fatigue (11.1 % in Sativex group versus 6.6% in the placebo group). These reactions were usually mild to moderate and resolved within days of treatment *(25)*. As Sativex is an oromucosal spray, rare instances have been reported of pain and discomfort, as well as distorted taste, mouth ulceration and glossodynia (burning sensation in the mouth and tongue) *(25)*. Like with Δ^9-THC and cannabis, psychiatric adverse events may occur in some patients. Psychiatric adverse events observed in clinical trials included: disorientation (Sativex 4.0% versus placebo 0.5%); depression (Sativex 1.9% versus placebo 0.8%); euphoria (Sativex 2.2% versus placebo 0.9%); and dissociation (Sativex 1.7% versus placebo 0.1%). In one study in healthy participants given 18 sprays of Sativex twice daily, 4 out of 41 experienced a transient psychotic reaction *(1)*.

2.2 Cannabis extracts, tinctures, oils and aqueous preparations

The adverse reactions produced by Δ^9-THC-rich cannabis extracts, tinctures, oils and aqueous preparations in humans are likely to be similar to those observed with Δ^9-THC-rich cannabis and Δ^9-THC (see Report 1 and 3). The abuse of cannabis oils for recreational purposes is an increasing concern given our knowledge that cannabinoid toxicity, like for all drugs, is dose-dependent. Acute exposure to higher Δ^9-THC doses may increase the likelihood of tachycardia, orthostatic hypotension, fainting and drug-induced psychotic reactions *(13, 26-28)*. A cross-sectional survey of 83,867 cannabis users showed that use of butane hash oil engendered greater restlessness, anxiety, memory impairment, and was less pleasurable than use of cannabis flower *(29)*.

A recent study examined the tolerability of a CBD-rich cannabis extract for 20 weeks in 20 intractable epilepsy patients where the average daily dose was 13.3 mg/kg/day for CBD and 0.27 mg/kg/day for Δ^9-THC *(7)*. The CBD-rich extract was safe and well-tolerated and had the following main side-effects: somnolence/fatigue (89.5%), anorexia, (52.6%), and diarrhea (31.6%). Somnolence and fatigue likely arises

due to CBD increasing the blood concentrations of concomitantly administered sedative anticonvulsant drugs, most commonly being the benzodiazepine clobazam *(10)*. The cannabis extracts were associated with reduced seizure frequency, EEG spike activity, and improved overall quality of life. Another study examined a CBD-rich extract (CBD which ranged from 1-20 mg/kg/day and Δ^9-THC capped at 0.5 mg/kg/day) in 74 pediatric epilepsy patients *(9)* and found 46% of patients reported side-effects, with the most prevalent being somnolence (22%), seizure aggravation (18%) and gastrointestinal complaints (7%). 5 patients (7%) discontinued cannabis use due to adverse reactions.

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Extracts and tinctures of cannabis

Section 4: Therapeutic use

Contents

1. Marketing Authorizations (as a Medicinal Product)

Nabiximols (trade name Sativex®, GW Pharma) is a cannabis extract with equal proportions of plant-derived tetrahydrocannabinol (THC) and cannabidiol (CBD) available as an oromucosal spray. It was developed in the United Kingdom in response to anecdotal reports of THC as useful in treating multiple sclerosis-related symptoms; CBD was included to modulate the adverse effects of THC.[1]

2. Listing on the WHO Model List of Essential Medicines

Not listed.

3. Therapeutic Applications

3.1 Extent of Therapeutic Use

Nabiximols has received marketing authorization for the treatment of spasticity due to multiple sclerosis (MS) in Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Lichtenstein, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland and the United Kingdom. It has regulatory approval for MS spasticity in Canada, Australia, New Zealand, Brazil, Colombia, Chile, United Arab Emirates, Kuwait and Israel. Canada and Israel have additionally approved nabiximols for neuropathic pain in MS and for chronic cancer pain. There is an ongoing review of nabiximols data at the United States Food and Drug Administration.

An analysis of data from retrospective registries in the UK, Germany, and Switzerland (N=941) and a prospective safety study in Spain (N=204) found positive benefit to risk ratio in the use of nabiximols. In both studies, after approximately one year of treatment, physicians approved continued use of the agent because of the benefit derived by their patients. There were few adverse events and no evidence of abuse, misuse, or addiction, but it is not clear that these observational data represent a rigorous assessment of these concerns.[2]

Other extracts and tinctures of cannabis are available in countries such as Germany, Netherlands, Australia, Malta, and Canada as products in compounding pharmacies.

3.2 Epidemiology of Medical Use

There are large numbers of patients afflicted with MS or cancer who may be eligible to use nabiximols. As of 2013, MS affects at least 2.3 million individuals globally.[3] Prevalence rates vary by continent and latitude. Prevalence is high (>30 per 100,000) in northern Europe and North America; medium (5-30 per 100,000 in southern Europe and southern US; and prevalence is low (<5 per 100,000) in Asia.[4]

Muscle spasticity is a debilitating symptom that affects many patients with MS. In a registry of more than 20,000 North American patients with MS, the degree and frequency of spasticity were: minimal, 31%; mild, 19%; moderate, 17%; severe, 13%; total, 4%.[5] In a systematic review of pain in more than 7000 adults with MS, the prevalence of neuropathic pain was 26%.[6] The prevalence of cancer worldwide and the frequency of pain in those suffering from cancer make treatment of cancer-related pain an important clinical consideration. The 2017 World Cancer Report reported that in 2012 there were 14 million new cancer cases. There were 8.7 million people (older than 15 years) alive who had had a cancer diagnosed in the previous year, 22.0 million with a diagnosis in the previous 3 years, and 32.6 million with a diagnosis in the previous 5 years. Globally, nearly 1 in 6 deaths is due to cancer.[7] Up to 75% of patients with cancer may experience chronic pain due directly to their disease[8], about 40% experience neuropathic pain syndromes.[9] As cancer mortality has declined, the number of patients living with cancer-related pain may increase.

3.3 Effectiveness of Therapeutic Uses

(See Table 2&3)

3.3.1 Hemp Seed, Evening Primrose Oils

3.3.1.1 Multiple Sclerosis

In a double-blind, randomized trial, patients with multiple sclerosis who received co-supplemented hemp seed and evening primrose oils had decreased extended disability status scores and lower liver transaminase levels compared to patients treated with a dietary intervention alone.[10]

3.3.2 Cannabis Sativa Extract

3.3.2.1 Dementia

Cannabis oil containing THC as an add-on pharmacotherapy for dementia produced a significant reduction in Clinical Global Impression (CGI) and Neuropsychiatric Inventory (NPI) scores in an open-label trial involving eleven patients, ten of whom completed the study.[11]

3.3.2.2 Motor Neuron Disease

A preliminary report of results from a randomized, double-blind, placebo-controlled multicenter trial of cannabis sativa extract in patients with motor neuron disease, treatment with cannabis sativa extract produced in the modified Ashworth Scale and pain scores. However, while there was a trend for improvement of all outcome measures, most outcomes were not significantly affected.[12]

3.3.2.3 Neurogenic Symptoms

Extracts containing THC, CBD, and THC and CBD in a 1:1 ratio produced a significant reduction in neurogenic symptoms including bladder control, muscle spasms, and spasticity in a series of randomized, double-blind, placebo-controlled crossover studies in 24 patients with chronic medical illnesses (18 were participants with multiple sclerosis) associated with neurogenic symptoms.[13]

3.3.3 Oral cannabinoid extract

3.3.3.1 Glaucoma

In one small randomized, double-blind, placebo-controlled crossover trial of oral THC extract, cannabidiol, and placebo in six participants with ocular hypertension or early stage glaucoma, oral THC extract and cannabidiol did not separate from placebo on measures of intraocular pressure.[14]

3.3.3.2 Multiple Sclerosis, Spasticity

There have been four randomized, double-blind, placebo-controlled trials of oral cannabinoid extracts for symptoms related to multiple sclerosis. Improvements were modest: one study with 630

participants with MS demonstrated significant improvements in spasticity and pain by self-report, as well as urge incontinence and another study with 249 participants showed that oral cannabinoid extract pharmacotherapy led to reduction in muscle stiffness and improved sleep.[15,16] Two other studies (n=50 and n=14, respectively) failed to demonstrate a difference in spasticity by self-report or Ashworth Scale and no reduction in tremor.[17,18]

3.3.3.3 Nausea and Vomiting Due to Chemotherapy

A considerable evidence base shows that cannabis and specific cannabinoids are effective pharmacotherapy for nausea and vomiting due to chemotherapy. The two United States FDA-approved cannabinoids, dronabinol and nabilone, received indications for nausea and vomiting due to chemotherapy as a result of three randomized controlled trials of dronabinol (and four studies of levonantradol, a synthetic analog of dronabinol) and 14 randomized controlled trials of nabilone for this indication. There have been six studies of oral THC capsules as pharmacotherapy for this indication, five of which used the anti-emetic prochlorperazine as a comparator and one that used the anti-histamine hydroxyzine as a comparator.[19-25] All studies suggested a greater benefit of cannabinoids versus both placebo and active comparators, but these benefits did not reach statistical significance in all studies. Additional studies looking at cannabis with differing ratios of THC to CBD for nausea and vomiting due to chemotherapy are underway and use more contemporary anti-emetic therapy as a control.[26]

3.3.3.4 Parkinson's disease

In 17 patients with Parkinson's Disease, treatment with oral cannabinoid extract did not produce improvements in dyskinesia compared to placebo.[27]

3.3.3.5 Sleep Disorder

Three trials involving oral cannabinoid extracts have evaluated sleep as a secondary outcome measure. All three provided some evidence that oral cannabinoids extracts outperform placebo in measures of sleep.[15-17]

3.3.3.6 Chronic Pain

In a prospective, non-randomized, single-arm clinical trial of 338 patients with different chronic pain conditions, 12 months of treatment with cannabis extract led to a significant reduction in pain

intensity and pain disability. Pain intensity as measured on visual analog scale significantly decreased from baseline to 12 months (X^2=61.375; P<0.001) and pain disability scores as measured on the Pain Disability Index also were significantly decreased from baseline to 12 months(X^2=39.423; P<0.001).[Poli et al. 2018)]

3.3.3.7 Anxiety

In a prospective, non-randomized, single-arm clinical trial of 338 patients with different chronic pain conditions, 12 months of treatment with cannabis extract led to a significant reduction in anxiety. Self-assessment using the Hospital Anxiety and Depression Scale demonstrated a statistically significant reduction in anxiety (X^2=30.362; P<0.001).[18]

3.3.3.8 Depression

In a prospective, non-randomized, single-arm clinical trial of 338 patients with different chronic pain conditions, 12 months of treatment with cannabis extract led to a significant reduction in pain intensity and pain disability. Self-assessment using the Hospital Anxiety and Depression Scale demonstrated a statistically significant reduction in depression (X^2=27.786; P<0.001).[18]

3.3.4 Nabiximols

3.3.4.1 Anxiety Disorder

No studies of cannabis or cannabinoids with anxiety measures as primary outcomes have been conducted. Rog et al. found evidence in a secondary outcome measure that nabiximols reduced anxiety compared to placebo in 66 participants with multiple sclerosis.[28]

3.3.4.2 Attention-deficit/hyperactivity Disorder (ADHD)

Nabiximols oromucosal spray did not produce a difference in the primary endpoint compared to placebo in a randomized, placebo-controlled trial in 30 adults with ADHD. The nabiximols group demonstrated nominally significant improvement in hyperactivity/impulsivity and cognitive measure of inhibition and no difference in adverse events compared to the placebo group.[29]

3.3.4.3 Cannabis Withdrawal, Craving

In an eight-week randomized, double-blind, placebo-controlled trial, treatment with nabiximols significantly reduced cannabis withdrawal symptoms but not craving in nine community-recruited participants with cannabis use disorder. No difference in adverse events was noted.[30]

3.3.4.4 Chronic Pain

In a randomized, double-blind, placebo-controlled trial, nabiximols treatment led to significant improvements in pain on movement, pain at rest, and quality of sleep among 58 patients over five weeks of treatment. It had no effect on morning stiffness, however.[31] Four other randomized controlled trials of nabiximols in patients with advanced cancer pain refractory to opioids failed to produce differences from placebo on the primary study endpoints. Improvement was observed in some secondary endpoints such as overall quality of life.[32-34]

3.3.4.5 Depression

There have been no studies of cannabis or cannabinoids with measures of depression as the primary outcome. Three studies of nabiximols (n= 360, 66, and 666) found no difference between nabiximols and placebo in depression outcomes.[13,28,34]

3.3.4.6 Huntington's Disease

The only randomized, double-blind, placebo-controlled trial of nabiximols for Huntington's Disease failed to demonstrate any difference between nabiximols and placebo on motor, cognitive, behavioral, or functional scores in 26 patients (24 completed the study) treated over twelve weeks.[35] Other cannabinoids, namely nabilone and cannabidiol, not included in this pre-review, have been studied as pharmacotherapy for Huntington's Disease, yielding improvements in chorea and no difference from placebo, respectively.

3.3.4.7 Multiple Sclerosis, overactive bladder

In a pilot prospective study of 21 patients with overactive bladder due to multiple sclerosis, 4 weeks of treatment with nabiximols led to significant reduction in overactive bladder symptoms. Post-void residual

volume was also significantly reduced, but bladder volume at the first desire and maximal cystometric capacity were not significantly increased.[37]

3.3.4.8 Multiple Sclerosis, spasticity

Two meta-analyses addressed the literature of cannabis and cannabinoids for spasticity in multiple sclerosis. Whiting et al. reported that the pooled odds of patient-reported improvement on a global impression-of-change score was greater with nabiximols than with placebo (OR, 1.44, 95% C.I.= 1.07-1.94).[36] Meanwhile, Koppel et al. concluded that nabiximols is "probably effective" for reducing patient-reported spasticity scores.[37] Both meta-analyses stated that treatment with nabiximols does not produce differences in objective spasticity compared to placebo, although it was noted that the Ashworth Scale is not ideal to detect such differences.

Five randomized, double-blind, placebo-controlled trials of nabiximols for spasticity in multiple sclerosis have been conducted (one utilized a crossover design). Of these trials, three demonstrated that nabiximols treatment led to a significant difference in spasticity[38-40], while nabiximols treatment failed to separate from placebo in the other two trials.[39,41] Further investigation of either secondary endpoints or of those previously in spasticity clinical trials showed decreases in subjective measures of spasticity and a recent observational study of patients with multiple sclerosis on nabiximols showed this as well.[41-43]

3.3.4.9 Neuropathic Pain

Of seven randomized, double-blind, placebo-controlled trials of nabiximols for neuropathic pain, three produced positive results on primary endpoints, and four did not. The three positive trials all showed significant reductions in neuropathic pain while two of the three also showed significant improvements in sleep quality.[28,44] The other studies did show a significant difference between nabiximols and placebo on measures of neuropathic pain.[45-48] All studies demonstrated an increased incidence of adverse events in the nabiximols group compared to placebo. A multi-center, open-label study of nabiximols in 380 patients with peripheral neuropathic pain showed that treatment with nabiximols was beneficial for the majority of patients, the medication was well-tolerated, and patients did not develop tolerance.[51]

3.3.4.10 Sleep Disorder

Two studies have evaluated nabilone (not included in this pre-review) as a pharmacotherapy for sleep disorder. Nineteen other placebo-controlled studies for chronic pain and multiple sclerosis have evaluated sleep as an outcome. Thirteen of these studies involved nabiximols, which was associated with greater average improvement in sleep quality and sleep disturbance.[13,28,31,34,38,44,46,47,49-52]

Table 2: Randomized Controlled Trials of Extracts and Tinctures of Cannabis

Intervention	Administration Method	Dose Evaluated	Comparator	Number of Studies Described in this Report	Indication
Hemp Seeds, Evening Primrose Oils	Oil	18-21 g/day	Olive Oil	1	Multiple Sclerosis
Cannabis Sativa Extract	Oil	Maximum 15 g/day	None, Open-Label	1	Dementia
	Spray	Unspecified Dose	Placebo	1	Motor Neuron Disease
	Spray	2.5-120 mg/day	Placebo	1	Neurogenic Symptoms
Oral cannabinoid extract	Capsules	5 mg/day	Placebo	1	Glaucoma
	Capsules	10-30 mg/day	Placebo	4	Multiple Sclerosis
	Capsules	5-30 mg/day	Prochlorperazine, Hydroxyzine, or Placebo	7	Chemotherapy-induced nausea and vomiting
	Capsules	10 mg/day	Placebo	1	Parkinson Disease
	Capsules	25-30 mg/day	Placebo	3	Sleep Disorder

Key: THC= delta-9-tetrahydrocannabinol, CBD= cannabidiol

Intervention	Administration Method	Dose Evaluated	Comparator	Number of Studies Described in this Report	Indication
Nabiximols	Oromucosal Spray	Titrated to a maximum of 48 sprays/Day 2.7 mg THC/2.5 mg CBD per spray	Placebo	1	Anxiety
		Maximum 14 sprays/day			ADHD
		Maximum 40 sprays/day	Placebo	1	Cannabis Withdrawal, Craving
		Maximum 6-16 sprays/day	Placebo	1	Chronic Pain
		Maximum 16-48 sprays/day	Placebo	5	Depression
		Maximum 12 sprays/day	Placebo	3	Huntington's Disease
		Maximum 48 sprays/day	Placebo	1	Multiple Sclerosis, Spasticity

3.4 Table 3: Randomized Controlled Trials of Extracts and Tinctures of Cannabis cont.

		Maximum 4-40 sprays/day Maximum 48 sprays/day	Placebo Placebo Placebo	7 7 13	Neuropathic Pain Sleep Disorder

Key: THC= delta-9-tetrahydrocannabinol, CBD= cannabidiol

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Extracts and tinctures of cannabis

Section 5: Epidemiology

Contents

1. Industrial use

In our rapid systematic review of the peer-reviewed literature, there were no studies that focused on the industrial use of cannabis tinctures and extracts. At this point, industrial use seems to be limited to therapeutic use.

Tinctures, often sublingual, and sprays are routes of administration for medical cannabis. Typically, tinctures are mixed with ethanol, but vinegars and glycerin may also be used. The sublingual extracts are dropped under the tongue and held for a period of time sufficient to permit absorption by the branches of the lingual artery, including the sublingual and deep lingual arteries. If used properly, onset of action and bioavailability may be faster and higher for this route compared with oral administration, as is often observed with other drugs. Tinctures may be a favorable option in the future, as they mitigate the dosing and bioavailability issues associated with orally ingested cannabis and eliminate issues of tolerability with inhaled cannabis (1).

Overall, the use of tinctures is not widespread today, and evidence supporting the therapeutic use of tinctures is limited.

Nabiximols is used therapeutically as an oromuscosal spray, contains 27 mg THC and 25 mg cannabidiol per ml. The medication is licensed for use in the United Kingdom, Spain, Czech Republic, Germany, Demark, Sweden, Italy, Austria, Canada, Poland, France (for spasticity due to multiple sclerosis), but currently not in the United States (initial target indication for US FDA approval is cancer pain). The pharmaceutical is used for spasticity, pain, nausea and vomiting, and, to date, more than 19 trials have been conducted (2).
There are a number of other tinctures and oils containing cannabidiol, which are currently being used under medical cannabis legislation or illegally, but unsanctioned (3). Some of these have been included in randomized controlled trials (2).

2. Non-medical use, abuse and dependence

2.1 Background

Tinctures and extracts of cannabis for medical reasons date to Chinese applications documented 4000-5000 years ago (1, 4). In Europe and North America, use was introduced in the 19th century. However, in part due to the current status, cannabis medications are relatively rare, and this includes extracts and tinctures. There is a clear link between the medical availability of psychoactive drugs and it non-medical use. Thus, if cannabis extracts and tinctures are only rarely used medically, non-medical use is also expected to be rare.

For non-medical use, the cannabis extracts and tinctures are usually consumed in the form of oil or as wax, which is also called butane cannabis oil (derived from the process required to make it; BCO). Smoking BCO is also called dabbing, but cannabis extracts can be vaporized, eaten and drunk as well.

2.2 Epidemiology of use of cannabis extracts and tinctures

There were three prevalence studies found in the literature specifically related to tincture and extract use (5-7) and two studies using web search queries and sales data to illustrate the temporal trends of cannabis concentrates (8, 9). However, the vast majority of data has been obtained from few high-income countries, most prominently from the United States of America, which makes inferences on the global picture impossible.

One of the studies reported global data from an ad-hoc internet sample of drug users, whereas the others were based on high-school and university students from the United States. Obviously, these studies can only give a very selective view on the prevalence of tinctures and abstracts.

The global study (6) was based on the Global Drug Survey, an online-survey answered by 181,870 drug users from over 50 countries in 2015 and 2016. In this study, 46% of respondents were past-year cannabis users, out of which 7% reported using BCO. The proportion of users of cannabis oil amongst cannabis users might be an overestimate and should be treated with caution (6), as we have no indication what population this arbitrary sample represents.

Section 5: Epidemiology

In this Global Drug Survey, motives for cannabis use (i.e., recreational vs. medicinal) of 5,922 BCO users were assessed (6). Among the surveyed BCO users, 1.2% considered their cannabis use to be exclusively medical, while the majority specified both recreational and medical use motives (57.1%), and exclusively recreational use was reported by four out of ten respondents (41.7%). Compared to non-BCO users, BCO users appeared to be more prone to medicinal cannabis use and also to source their cannabis through prescriptions or their own cultivation. As indicated above, it is not clear to which population these results can be generalized (6).

In an anonymous survey conducted in Connecticut (US) in 2014 (5), application of wax and cannabis oil in e-cigarettes was studied in a sample of high-school students. Among lifetime cannabis users (N=1,123), experience with vaporization of cannabis oil and wax was found at 15.5% and 10.2%, respectively. These rates were higher for those with lifetime experience of e-cigarettes (cannabis oil: 22.9%, wax: 14.8%) (5).
In another cross-sectional study of 821 university students in a U.S. state where medical cannabis use is legal but recreational use is not, respondents completed an online survey about their health and health behavior as part of course credit or extra credit. Participants who had used cannabis in the past year (33%, n=273) completed questions about their use of BCO and cannabis-related problems. Among past-year cannabis users, 44% (n=121) had used BCO in the past year. More frequent BCO use was associated with higher levels of physical dependence, even after accounting for potential confounders (7).

To illustrate temporal trends of use of cannabis extract, a study used cannabis sales data in the state of Washington in the United States of America. The authors showed that the market share of cannabis extracts increased by 146% between October 2014 and September 2016 (8), while the expenditure share of edibles, tinctures, and suppositories amounted to 12.1% at the end of the observation period. A growing interest in dabbing was further confirmed in a case study tracking over 1.5 million web search queries between 2004 and 2015. In this period, search terms related to dabbing increased substantially over time, with the steepest slope in more recent years. In 2015, interest in dabbing has surpassed the more traditional cannabis consumption forms like smoking and oral ingestion by 28% and 58%, respectively (9).

2.3 Links to mental and physical health problems

The already reported study in US university students (7) found that frequency of BCO use was associated with higher levels of physical dependence. This study corroborates the evidence in Report 1 on the association between levels of THC potency and risk of dependence (10). In an online survey, frequent

users of cannabis concentrates were compared to users who never use concentrates and to users who frequently use concentrates but rarely concentrates. While cannabis concentrate users on average reported more cannabis use disorder symptoms and elevated anxiety levels, no differences were found with regard to overall mental and physical wellbeing (sleep, PTSD, pain, depression, quality of life, diet)(11).

3. Nature and magnitude of public health problems related to misuse, abuse and dependence

In our rapid systematic review, there were three studies that focused on the nature and magnitude of the public health problem related to the use of cannabis tinctures and extracts (12). In a study by Romanowski that looked at legalization of cannabis in four states, charts of patients who presented to the burn center with suspicion of BCO-related injuries between January 2007 and December 2014 were examined. Results showed that there was an increase in burn injuries related to the production of BCO. Three patients died as a result of their injuries. Patients required a mean of 12+/-48.4 ventilator days, and 27.1+/-59.4 days in the hospital. Results showed that there was a steep rise in the number of patients who presented with burn-associated BCO production in the region over that time period. These burn injuries are a public health concern in the United States (12-14).

In another cross-sectional study from Colorado, United States, researchers utilized the National Burn Repository to capture all hydrocarbon burns reported to the local burn center from January 1st, 2008, through August 31st, 2014. Results showed that twenty-nine cases of BCO burns were admitted to the local burn center during the study period. Zero cases presented prior to medical liberalization, 19 (61.3%) during liberalization of medical use (October 2009-December 2013), and 12 (38.7%) in 2014 since legalization. Nineteen patients required skin grafting, eight received wound care only, one required surgical fracture repair, and one required surgical debridement. Since the legalization of cannabis in Colorado, hydrocarbon burns associated with cannabis oil production have increased (13).

In a study by Loflin et al., researchers gathered preliminary information on BCO users and tested whether BCO use was associated with more medical problems than using herbal cannabis. In a sample of 357 participants, the study did not find higher rates of accidents or burns among BCO users (14).

4. Licit production, consumption, international trade

The results of our systematic review did not yield any articles related to licit production, consumptions, and international trade of cannabis extracts and tinctures.

5. Illicit manufacture and traffic

As indicated above, the UN monitoring system, mainly UNODC, annually updates on illicit production and trade. According to the last World Drug Report, seizures of tinctures played a comparatively negligible role in 2015 (15).

Appendix 1: Search Strategy for Extracts and Tinctures of Cannabis

The same general procedure was used for searching (albeit with different keywords – see below), processing and quality control for extracts and tincture of cannabis as employed in Report 1.(10) Table A1 shows the results.

Table A1: Search Strategy for extracts and tinctures of cannabis

No.	Searches	Results
1	Human/ or humans/	36244807
2	limit 1 to yr ="2000 -Current"	21066974
3	(bibliography or case reports or clinical conference or conference abstract or conference paper or conference proceeding or "conference review" or comment or editorial or in vitro or letter).pt.	8530671
4	2 not 3	16300231
5	epidemiology or exp epidemiology/	3693795
6	prevalence or exp prevalence/	1580556
7	incidence or exp incidence/	1888341
8	population or exp population/	3537733
9	5 or 6 or 7 or 8	8094152
10	cannabis or exp cannabis/	71067
11	marijuana or exp marijuana/	68545
12	10 or 11	89320
13	12 and extract	1540
14	12 and tincture	30
15	12 and oil	712
16	12 and aqueous	148
17	Nabiximols	742
18	13 or 14 or 15 or 16 or 17	2923
19	4 and 9 and 18	233
20	Dependence	588264
21	Abuse	549267
22	Disorder	2664499

23	self-medication	19180
24	Therapeutic	2333110
25	20 or 21 or 22 or 23 or 24	5766886
26	4 and 18 and 25	567
27	19 or 26	681
28	remove duplicates from 27	587

We followed the final epidemiology terms of reference for the formal inclusion and exclusion criteria and added additional relevant inclusion/ exclusion criteria that were pertinent to the focus of our report on the epidemiology of cannabis extracts and tinctures. The formal inclusion and exclusion criteria are found in Appendix 2.

Of 587 studies retrieved from the search, N=35 were included for full-text eligibility after title and abstract screen, of which 32 were excluded for the following reasons: full-text not available (N=2), review articles (N=14), did not contain data on epidemiology of cannabis (N=1), did not mention tinctures or extracts (N=15). After full-text screening and adding N=3 articles from the original search for Reports 3 & 4, 6 full-text articles were included in this report. Review articles were excluded at the full-text screening stage from analysis but were kept for the background of the report. In Figure A1, a flow diagram shows each of the identification, screening, eligibility, and inclusion phases of the systematic review.

Note on terminology

With regard to chapter headings, we used the headings as specified in the WHO Request for Proposals. In the text, we did not use terms like misuse or abuse, which are not, or not consistently, defined within the current medical classification systems (16, 17), and thus we only use the terms cannabis use, cannabis use disorders and cannabis dependence. All terms are defined in the text, based on the above cited current medical classification systems.

The literature searches were not restricted to the above-mentioned medical terminology.

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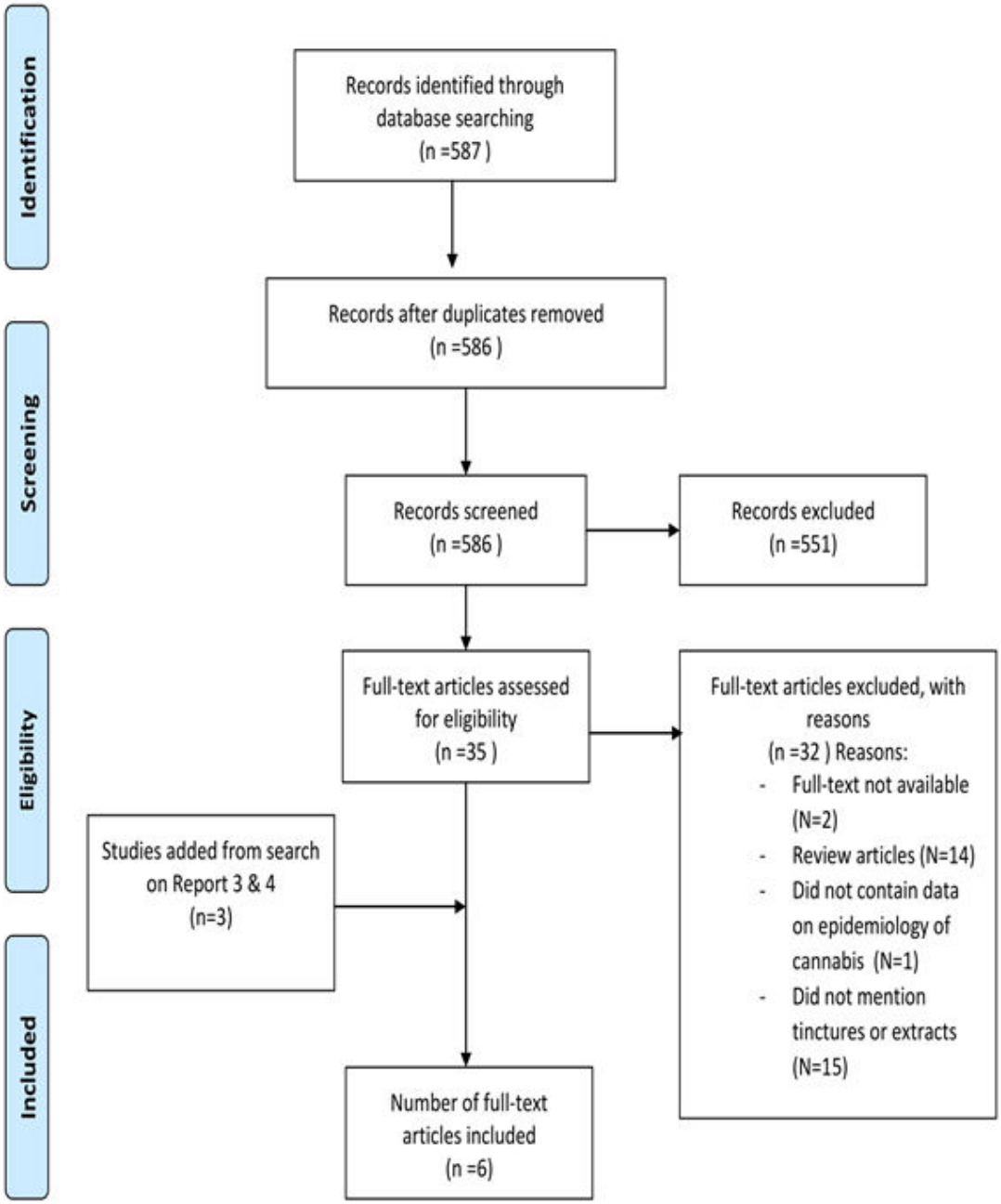
Figure 1: PRISMA diagram for Report 2



Template for the flow chart: (18)

Appendix 2: Report 2 Inclusion and Exclusion Criteria

For Report 2, the formal inclusion and exclusion criteria were:

Inclusion Criteria

Studies to be included in the report are those involving:

- Cannabis extracts: this term refers to a plant extract mixture from the leaves and flowers of Cannabis sativa
- Cannabis tinctures: this term refers to specific alcohol extractions of the flowering tops or other parts of Cannabis sativa.
- Cannabis oils (e.g., Butane Hash Oil, Hemp Seed Oil)
- Aqueous extracts (e.g., cannabis tea)
- Nabiximols (e.g., Sativex®)
- Reviews on cannabis that include the epidemiology
- Any clinical conditions for which cannabis was used medically or for therapeutic use (also being admitted to a psychiatric facility for cannabis use)
- Driving under the influence of cannabis
- Self-medication and the epi of self-medication is reported

Exclusion criteria

Studies to be excluded from the report involve:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
    - Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants except when delta-9-THC is extracted from the cannabis plant. (-)-trans-delta-9-tetrahydrocannabinol
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD) when not in a preparation with other cannabis-related ingredients
- Isomers of tetrahydrocannabinol (THC)
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)- 6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol
- Articles focusing solely on therapeutic use without epidemiology of cannabis extracts or tinctures
- Methodological development papers or conference abstracts

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- Abstract and full-text was not available
- In vivo or animal studies
- Randomized Control Trials
- Small populations such as club patrons, ship sailors, etc.
- Sexual assault and violent offenders
- <100 sample size

Appendix 3: Abbreviations

BCO:	Butane Cannabis Oil
CI:	95% Confidence interval
DSM-IV:	Diagnostic and Statistical Manual of Mental Disorders – 4th Edition
DSM-5:	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition
DUI:	Driving Under the Influence
EMCDDA:	European Monitoring Centre for Drugs and Drug Addiction
ESPAD:	European School Survey Project on Alcohol and Other Drugs
EU:	European Union
GBD:	Global Burden of Disease
ICD-10:	International Classification of Diseases – 10th Revision
INCB:	International Narcotics Control Board
IUPAC:	International Union of Pure and Applied Chemistry
MC:	Medical cannabis (abbreviated only in the respective chapter)
UNODC:	United Nations Office on Drugs and Crime
THC:	Tetrahydrocannabinol (Δ9-tetrahydrocannabinol)
WDR:	World Drug Report
WHO:	World Health Organization

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Extracts and tinctures of Cannabis

Annex 1: Member State Questionnaire

1. Introduction

Definition for the questionnaires used as the basis of this report: The term "extracts and tinctures" refers to substances that have been extracted from the Cannabis sativa plant. This term does not include synthetic preparations.

Examples:

- Liquid concentrate (e.g., hash oil, hemp oil, butane honey oil, etc)
- CBD oil
- Solid concentrate (e.g., shatter, budder)
- Edibles (e.g., prepared food products)
- Liquids (e.g., marijuana tea)
- Tinctures (e.g., concentrated amounts ingested orally or taken under the tongue)
- Topical ointments (lotions, salves, balms applied, etc.)
- Nabiximols (e.g., Sativex®)
- Epidiolex
- Arvisol

85 representatives of 84 countries answered the questionnaire:

Algeria, Argentina, Armenia, Australia, Austria, Bahrain, Barbados, Belarus, Belgium, Benin, Bhutan, Brazil, Brunei Darussalam, Bulgaria, Burundi, Canada, Colombia, Cook Islands, Cote D'Ivoire, Cyprus, Czech Republic, Democratic Republic of the Congo, Denmark, Ecuador, Egypt, El Salvador, Eritrea, Estonia, Ethiopia, Fiji, Finland, France, Gabon, Georgia, Germany, Greece, Guatemala, Honduras, Hungary, India, Indonesia, Ireland, Israel, Italy, Jamaica, Japan, Kenya, Kuwait, Latvia, Lebanon, Lithuania, Luxembourg, Malaysia, Malta, Mauritius, Mexico, Monaco, Montenegro, Mozambique, Nauru, Netherlands, New Zealand, Nicaragua, Niue, Palau, Poland, Portugal, Republic of Korea, Republic of Moldova, Romania, Russian Federation, Saint Lucia, Serbia, Singapore, Spain, Sri Lanka, Sweden, Switzerland, Thailand, Trinidad and Tobago, United Kingdom of Great Britain and Northern Ireland (the), United Republic of Tanzania, United States of America, Zimbabwe.

i. **Q4**

Q4: Do you have any information about the use of **extracts and tinctures of cannabis** for any purpose (including medical or non-medical use) in your country?

54 (64%) countries answered yes, 31 (36%) answered no.

2. Results: Approved medical use

a. Medical use

Q5: At **national level**, are extracts or tinctures of cannabis legally approved for medical use in your country?

Countries with approved medical uses: Argentina, Austria, Belgium, Brazil, Canada, Colombia, Czech Republic, Denmark, Estonia, Finland, Georgia, Germany, Greece, Ireland, Israel, Italy, Jamaica, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, United Kingdom of Great Britain and Northern Ireland (the).

There are a number of other approved medical uses such as the use of extracts of cannabis by some traditional medical practitioners (Ayurveda) for their patients in Sri Lanka, and individual-based use in Australia, or use with Ministerial approval in New Zealand. A number of countries referred to more general laws, which would apply for extracts and tinctures of cannabis as well.

Q6: Please indicate any approved therapeutic indications for the medical use of **extracts and tinctures of cannabis** in your country:

Disease condition	**Number of countries**	**%**
Epilepsy	4	16
Multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury	14	56
Arthritis	1	4
Parkinson's disease	1	4
Tourette's syndrome	2	8
Glaucoma	2	8
Anxiety	1	4
Depression	1	4
PTSD	2	8
Alzheimer's disease	1	4
Irritable bowel syndrome	1	4
Cancer	1	4
HIV/AIDS	3	12
Chronic pain	2	8
Crohn's disease	1	4
None specified	3	12
Other: often defined specific by product (e.g., spasticity due to Multiple Sclerosis for Sativex only in three countries; or regulated via guidelines to MDs; only other disease category	11	44

mentions was refractory epilepsy)		

None of the 25 countries indicated use for the following: dystonia, Huntington's disease, schizophrenia/psychosis, skin disease, Inflammatory bowel disease, liver disease, obesity/diabetes, attention deficit disorder.

Q7: Please Indicate any symptoms that **extracts and tinctures of cannabis** are approved to treat.

Symptom	**Number of countries**	**%**
Acute pain	3	13
Chronic non-cancer pain	4	17
Cancer pain	3	13
Nausea/ vomiting	3	13
Appetite stimulant	3	13
Headaches/ migraines	0	0
Muscle spasms	15	65
Seizures	3	13
Sleep problems	1	4
Alcohol withdrawal symptoms	0	0
Opioid withdrawal symptoms	0	0
Palliative care	3	13
Other	10	43

Countries answering were mainly from Europe (16) and the Americas (6); with one answer from Africa.

Q8. Please indicate whether there are any permitted marketed products of **extracts and tinctures of cannabis**:

Sativex (27 mg/mL THC; 25 mg/mL) has been approved in 16 countries: Austria, Belgium, Canada, Colombia, Czech Republic, Denmark, Finland, France, Germany, Greece (under investigation), Ireland, Poland, Portugal, Spain, Sweden, UK.

Metavil has been approved in Brazil (no specs)

A number of medications has been approved in the Netherlands with various strengths of CBD (Bedrolite at 2% and 10% CDB) or THC (Bedica, Bedrocan) or mixtures (Bediol CBD 2,0% / THC 1,3%); in Germany several medications based on THC and CBD are permitted but not approved.

In Jamaica, 61 products with cannabis extracts (tinctures, capsules, topicals, suppository) have been registered for sale in pharmacies, but none are available at this time on pharmacy shelves.

In Italy, there are medicinals (galenic) prepared in pharmacy, on medical prescription. Concentration is determined by the medical doctor.

In Israel, different medications are approved.

Q9: Are there any ongoing **approved clinical trials** in your country that are developing **extracts and tinctures of cannabis** for medical use?

In eight of the 24 countries (33%) answering there are ongoing trials: Canada, France, Israel, Jamaica, Germany, Mexico, Spain, Sweden.

Q10: Please indicate product name/ trial number/ study phase of any ongoing trials that are developing products of **extracts and tinctures of cannabis** for medical use.

Canada: a number of trials, on several products and in several Phases
France: GW42003-P (CBD)-EUDRA CT 2014-001834-27-Phase 4 - an open label extension study to investigate the safety of cannabidiol (GBP42003-P; CBD) in children and adults with inadequately controlled Dravet or Lennox Gastaut Syndromes
Germany: Sativex; Eudra-CT: 2016-000564-42/Phase: 3
Germany: Sativex; Eudra-CT: 2004-002531-32/Phase: 3
Germany: Sativex; Eudra-CT: 2013-001247-31/Phase: 4
Germany: Sativex; Eudra-CT: 2013-001247-31/Phase: 4
Germany: Sativex; Eudra-CT: 2012-004800-37/Phase: phase on bio-equivalence
Israel: Medical Grade Cannabis Products - Detailed at IMC-GMP
Jamaica: Prana P1 THC Activated Capsules
Mexico: SATIVEX/ GWCA1103 /Phase 3
Spain: Epidiolex (Cannabidiol)/2015-002939-18/Phase 2
Spain: Epidiolex (Cannabidiol)/2015-002154-12/Phase 3
Spain: Epidiolex (Cannabidiol)/2014-001834-27/Phase 3
Spain: Epidiolex (Cannabidiol)/2014-002939-34/Phase 3
Spain: Epidiolex (Cannabidiol)/2014-002940-42/Phase 3
Sweden: CBD/EudraCT No 2015-002939-18
Sweden: Sativex/EudraCT No 2014-00553-39

Q11: Do individuals require a prescription to obtain **medical extracts and tinctures of cannabis**?

All countries answering, where medical extracts are dispensed, answered yes (22 countries): Argentina, Austria, Belgium, Brazil, Canada, Colombia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Israel, Italy, Jamaica, Mexico, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland.

Q12. What types of professionals are allowed to **prescribe extracts and tinctures of cannabis**?

All 21 countries with valid responses answered medical doctors/psychiatrists.
In addition, Canada specified that only a medical doctor can prescribe products that have received market authorization and a DIN under the Food and Drugs Regulations (i.e., Sativex). Under the Access to Cannabis for Medical Purposes Regulations, medical doctors and nurses can authorize cannabis oil for medical purposes.
In Israel, only specialist medical doctors who have been taught and trained to prescribe Medical Grade Cannabis Products are allowed to prescribe (according to the IMC-GCP).
In Mexico, narcotic drugs can also be prescribed by dentists and veterinarians.

Q13. What kinds of settings are approved to legally **dispense extracts and tinctures of cannabis** in your country?

Professional	**Number of countries**	**%**
At a doctor's office	1	5
Pharmacies	19	86
Online	1	5
Retail shops	0	0
Licensed/specialized cannabis dispensaries	0	0
Hospitals	8	36
Outpatient clinics	0	0
Palliative care facilities	1	5
Nursing homes	1	5
Other (Under the access to Cannabis for Medical Purposes Regulations cannabis oil for medical purposes can be purchased by registered clients from federally licensed producers (by phone or online with secure delivery by mail or courier) in Canada)	1	5

Q14: If patients use medical **extracts and tinctures of cannabis** on prescription or recommendation of a health professional, will they be **reimbursed** for the costs of their medication?

No reimbursement in nine (41%) of all 23 countries answering (in two countries, reimbursement is currently discussed), reimbursement depending on circumstances (e.g., depending on insurance company, on the diagnoses, on the pharmaceutical or on the individual case) in 8 (36%) of the countries, and usual reimbursement in 5 (23%) of the countries (Argentina, Denmark, France, Italy, Spain).

Q15: Are any clinical guidelines used in your country for the prescribing of medical **extracts and tinctures of cannabis**?

Guidelines are available in seven of 22 (32%) countries answering (Canada, Denmark, Germany, Israel, Italy, Jamaica, Sweden).

Q16. Is there a regulatory agency in your country that monitors **extracts and tinctures of cannabis** for medical use? There are regulatory agencies monitoring in 20 of the 22 countries answering (91%).

b. National legislation

Q17: How would you describe the trend in the number of users of **extracts and tinctures of cannabis** for medical use over the last 3 years?

Six of 20 countries answering (30%) did not know, 11 countries (55%) indicated an increasing trend (for 7 of these the numbers were substantially increased), two (10%) indicated no change, and one (5%) a slightly decreasing trend. Most of the countries with substantially increasing numbers of users of extracts and tinctures of cannabis for medical use over the last 3 years were in Europe (7 out of 11).

Q18: In the past 3 years, has your country changed its national legislation around access to cannabis-related substances for **medical use**?

17 out of 56 (30%) have changed their legislation around access to cannabis related substances for medical use: Argentina, Australia, Belgium, Brazil, Colombia, Denmark, Estonia, Fiji, Germany, Greece, Israel, Italy, Jamaica, Malta, Mexico, New Zealand, Poland.

Q19: If yes, what types of legislative changes has your country made for **medical use** of **extracts and tinctures of cannabis**?

Legislative change	**Number of countries**	**%**
Change to the legal status of medical cannabis	13	62
Changes to the supply of medical cannabis (e.g., changes in licensing, import – or export of products)	11	52
Changes to access to medical cannabis (e.g. variety in products, therapeutic indications, etc.)	9	43
Other	7	33

With the exception of one country in Africa, legislation was mainly changed in high-income countries in Europe and the Americas.

Q20: Is your country currently considering changes to its national legislation around access to **extracts and tinctures of cannabis** for medical use?

Legislative changes prepared for medical use of extracts and tinctures of cannabis	**Number of countries**	**%**
No	33	69
Yes	15	31
Total	48	100

Legislative changes are currently mainly prepared in European countries (eight countries), but also in four American, one Asian, one African and one Australasian country.

Q21: In your opinion, how do you feel **the changed legislation around access** to **extracts and tinctures of cannabis** for medical use would impact / has impacted public health in your country?

The majority of the countries who answered indicated not to know the impact of changed availability on public health (17 of 26 for decreased availability: 65%; 18 of 37 for increased availability: 49%).

As for potentially decreased availability of extracts and tinctures of cannabis for medical use, 4 out of 26 countries (15%) saw a substantial or slightly negative impact, and 5 (19%) expected no impact.

As for increased availability, 10 out of 39 countries (27%) saw either a slightly or substantially positive impact, 3 (8%) expected no impact, and 6 (16%) a slightly or substantially negative effect.

There were no distinct regional patterns.

3. Results: Prevalence of non-medical use

a. Non-Medical use (Countries with approved non-medical use can be named)

Q22: On a **national level**, are **extracts and tinctures of cannabis** *legally* available for non-medical use in your country?

Five out of 59 (8%) countries answering (Georgia, Hungary, Ireland, Romania, United Kingdom of Great Britain and Northern Ireland), all in Europe, indicated legal availability of extracts and tinctures of cannabis for non-medical use.

Q23: Are **extracts and tinctures of cannabis** used for cultural, ceremonial, or religious purposes in your country?

Five of the 53 countries (9%) which answered indicated cultural, ceremonial or religious use (related to Rastafarian and Maya religion mainly; Jamaica; Guatemala; Barbados; Fiji; Saint Lucia).

b. Public health impact of use

i. Prevalence data

1. Adults:

Q24: Does your country collect prevalence data around the use of **extracts and tinctures of cannabis**?

Seven out of 54 countries answering (13%) indicated to collect such data: Armenia, Estonia, Guatemala, Ireland, Italy, Jamaica, New Zealand.

Q25. Prevalence of use of **extracts and tinctures of cannabis** amongst adults (over 18 years of age)?

While two countries provided such data, the prevalence and the description point to data on cannabis use in general rather than to the prevalence of use of extracts and tinctures of cannabis specifically.

2. Youth:

Q26: Prevalence of use of extracts and tinctures of cannabis for non-medical use amongst **young people** (below 18 years of age).

See answer to **Q25** for adults.

3. General trends

Q27: How would you describe the number of users of **extracts and tinctures of cannabis** for non-medical use over the last 3 years in your country?

For adults, seven out of nine countries that answered (78%) indicated an increase, for youth, six out of seven countries (86%) indicated an increase. The remaining answers indicated no change.

ii. Primary care presentations
Q28-29

Q28: Does your country collect data about presentations to **primary care settings** due to the use of **extracts and tinctures of cannabis**?

Of the 53 countries that responded, 4 (8%) indicated such a collection of data: Armenia, Ireland, Italy, Republic of Moldova.

Q29: Number of primary care presentations relating to **extracts and tinctures of cannabis**.

No country presented data.

iii. Emergency presentations

Q30: Does your country collect data about presentations to **emergency care settings** due to the use of **extracts and tinctures of cannabis**?

Of the 50 countries reporting, five (10%) indicated such a collection of data: Armenia, Guatemala, Italy, Malta, New Zealand.

Q31: Number of individuals in the past year presenting to emergency settings relating to the use of **extracts and tinctures of cannabis**.

No country presented data, and comments indicated that the data collections were about cannabis-attributable presentations to emergency care settings in general.

Q32: Please list the adverse effects presented for **extracts and tinctures of cannabis** at the emergency room/department.

Three countries commented on reasons for presentations: injuries, cannabis use disorders/withdrawal, and psychiatric comorbidity were each mentioned three times.

iv. Drug treatment presentations

Q33: Does your country collect data about presentations to substance misuse treatment settings due to the use of **extracts and tinctures of cannabis**?

Drug treatment for use of extracts and tinctures of cannabis	**Number of countries**	**%**
No	35	70
Unsure	10	20
Yes	5	10
Total	50	100

*It is possible that these data pertain to cannabis in some of the countries that responded (see general comments to the questionnaire **in** **Q43**).*

Q34: Number of individuals in the past year presenting to **substance misuse treatment** due to **extracts and tinctures of cannabis**

No data on treatments reported.

v. Poison Centres

Q35: Does your country collect data about calls to poison centres due to the use of **extracts and tinctures of cannabis**?

Poison centre visits due to use of extracts and tinctures of cannabis	**Number of countries**	**%**
No	33	65
Unsure	13	25
Yes	5	10
Total	51	100

While THC is measured, the origin of the THC is not clear. Mostly this would be due to consumption of cannabis in other forms than extracts and tinctures of cannabis (see general comments to the questionnaire in **Q43***)*

Q36: Number of calls to **poison control centres** due to the use of **extracts and tinctures of cannabis.**

No data reported that could be clearly attributed to extracts and tinctures.

vi. Cases of impaired driving

Q37: Does your country collect data about cases of impaired driving due to the use of **extracts and tinctures of cannabis**?

Impaired driving due to use of extracts and tinctures of cannabis	**Number of countries**	**%**
No	34	69
Unsure	13	27
Yes	2	4
Total	49	100

While THC is mostly measured in biological tests for impaired driving, the origin of the THC is not clear. Mostly this would be due to consumption of cannabis in other forms than extracts and tinctures of cannabis (comments on Q37 *and general comments to the questionnaire in* Q43*).*

Q38: Number of cases of **impaired driving** due to **extracts and tinctures of cannabis:**

Not applicable.

c. National legislation

Q39: In the past 3 years, has your country changed its national legislation around access to **extracts and tinctures of cannabis** for non-medical use?

While four of 53 countries claimed to have changed the law (8%), detailed answers to Q39 and Q40 would indicate that these changes may not concern the non-medical use of extracts and tinctures of cannabis.

Q40: If yes, what types of legislative changes has your country made for **non-medical use** of **extracts and tinctures of cannabis?**

N.A., see answer to question 39.

Q41: Is your country currently considering changes to its national legislation around access **extracts and tinctures of cannabis** for non-medical use?

Four out of 46 countries (9%) indicated such potential changes; however, it is unclear if they pertain to **extracts and tinctures of cannabis.**

Q42: In your opinion, how do you feel the changed legislation around access to **extracts and tinctures of cannabis** for non-medical use would impact / has already impacted public health in your country?

Potential impact on public health for these few countries with implemented and planned legislative changes cannot be ascertained. For decreased medical use, 19 out of 26 countries (73%) indicated not to know, for increased medical use, the proportion was 60% (21 out of 35 countries).

4. Comments from countries

Most of the comments were about general legislation and discussion of cannabis policy in general with few specific comments regarding extracts and tinctures of cannabis. The comments on extracts and tinctures were strictly about medical use, and some countries indicated no indication of non-medical use.

Countries also indicated that they filled in general information about cannabis products instead of the intended specific information on extracts and tinctures. Two countries indicated some pressure from industries for more medical use of cannabis.

5. Conclusions

Extracts and tinctures of cannabis are currently in use in a minority of countries, most frequently Sativex, a combination of THC and CBD (oronasal spray).

There seems to be some activity regarding new indications for extracts and tinctures of cannabis, as evidenced by changes in legislation and the number of randomized clinical trials. To date there does not seem to be misuse of cannabis-based extracts and tinctures..

As corroborated by the answers of the countries to the questionnaire on prevalence and potential complications of non-medical use of extracts and tinctures, the answers to these questions are not conclusive and have to be taken very cautiously. Some countries explicitly specified in the general comments that they were not answering specifically for extracts and tinctures, while others indicated general references to laws, which also did not seem to be specific.

Overall, extracts and tinctures of cannabis seem to play a limited medical role for specific indications, and little role for non-medical use.