WHO Expert Committee on Drug Dependence

Critical Review

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Cannabis and cannabis resin

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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Chemistry
Giuseppe Cannazza (University of Modena and Reggio Emilia), Italy
Cinzia Citti (University of Modena and Reggio Emilia), Italy

Pharmacology
Jenny Wiley (RTI International), USA

Epidemiology
Vidhi Thakkar (Centre for Addiction and Mental Health), Canada
Haya Fernandez (Centre for Addiction and Mental Health), Canada
Omer S.M. Hasan (Centre for Addiction and Mental Health), Canada
Jakob Manthey (Institute for Clinical Psychology and Psychotherapy), Germany
Jurgen Rehm (Centre for Addiction and Mental Health), Canada
Astrid Otto (Centre for Addiction and Mental Health), Canada
Charlotte Probst (Centre for Addiction and Mental Health), Canada
Julian Sauer (Centre for Addiction and Mental Health), Canada

Toxicology
Jonathon Arnold (University of Sydney), Australia

Therapeutic Use
Kevin P. Hill (Harvard Medical School), USA
Judith Spahr, (Thomas Jefferson University) USA
Charles V. Pollack. (Thomas Jefferson University) USA
Brock Bakewell (Thomas Jefferson University), USA

The Member State questionnaire report was prepared by Jurgen Rehm, Astrid Otto, and Jakob Manthey.
Technical editing was provided by Ann Morgan and Susan Kaplan.
Administrative support was provided by Afrah Vogel and Christine Berling.

Cannabis and cannabis resin

Section 1: Chemistry

Contents

1. Substance identification

Cannabis sativa L. (Linnaeus)

Cannabis plant

The flowering or fruiting tops of the cannabis plant (excluding the seeds and leaves when not accompanied by the tops) from which the resin has not been extracted, by whatever name they may be designated (1961 Convention, Article 1, para.1).

Cannabis resin

The separated resin, whether crude or purified, obtained from the cannabis plant (1961 Convention, Article 1, para.1).

1.1 International Nonproprietary Name (INN)

Not applicable

1.2 Chemical Abstract Service (CAS) registry number

8063-14-7[1]

1.3 Other chemical names

Not applicable

1.4 Trade names

1.4.1 *Cannabis plant*

The dried cannabis inflorescence (the complete flower head) is one of the most commonly encountered formulations for administration of cannabinoids. Cannabis can be grown and marketed for either medicinal or recreational purposes. Medical cannabis is produced in several countries. For example, Aurora Cannabis Inc. is one of 26 authorized producers in Canada that also exports its products abroad. In the Netherlands, medicinal cannabis is grown and marketed by Bedrocan B.V. under contract to the Dutch Ministry of Health and made available as the herbal inflorescence in Dutch pharmacies on prescription. Bedrocan B.V. grows six varieties according to a controlled regimen and with a standardized level of three cannabinoids: (–)-*trans*-delta-9-tetrahydrocannabinol (Δ^9-THC), cannabidiol (CBD) and cannabinol (CBN). The Ministry also exports cannabis for medicinal use to Canada, the Czech Republic, Finland, Germany and Italy, and to authorized researchers around the world. The Italian *Stabilimento Chimico Farmaceutico Militare* developed the variety FM2, dispensed for medicinal purposes in the national territory.

The flowering tops or buds of a wide range of varieties are also available through dispensaries and medicinal programmes in the United States of America and elsewhere and are sold under popular names such as “skunk”, “kush”, “diesel”, and “haze”. In contrast to medicinal cannabis, the chemical content, the pharmacological and organoleptic effects of these products are not often readily discernible from the label and, in some instances, even through rigorous quantitative analysis of cannabinoids, can be unpredictable. Recently, a series of recreational varieties of cannabis with low Δ^9-THC content (<0.2% in Europe and <1% in Switzerland), called “cannabis light”, have come on to the popular market and are sold as a smoking product (e.g. Artur, CannLab, Hempy, etc.).

[1] Unspecified “Cannabis”. The CAS registry number should be combined with text terms for complete reference search results.

1.4.2 *Cannabis resin*

Not applicable

1.5 Street names

1.5.1 *Cannabis plant*

The mixture of plant parts prepared differs from country to country, and the following names are not always exact synonyms of cannabis as defined above, or of one another *(1).*

Note: a = beverage, b = confectionery, c = preparation containing cannabis.

ait makhlif; aliamba; anassa; anhascha; assis;[a] assyuni; banbalacha; bambia; bang, -a, -o; banghi, -a; bangi-aku; bangue; benghia;[b] bhang, -a; bhangaku; cáñamo indiano; canapa; canape indiana; canepa indiana; cangonha; canhama; canhamo; cannabis indica; cannabis indicae herba; cannabis sativa; cannacoro; can yac; capsh;[b] caroçuda; chanvre; chanvre indien; chur ganja; chur gunjah; chutras; chutsao; da-boa; dacha; dagga; darakte bang; dawamesk;[b] diamba; dirijo; djamba; djoma; dokka; donajuanita; dormilona; durijo; el kif; elva; erva maligna; erva do norte; esrar; fêmea; fininha; fininho; finote; flat ganja; flat gunjah; fokkra; fumo brabo; fumo de caboclo; gandia; ganja, -h; ganja yala; ganjika; ganjila; ghanja; gnaoui; gongo; gozah; grahni shardool; greefe; griefo; grifa; griffa; guabza; guaza; gunjah; gunjha; gunza; hamp, -a; hanf; hanfkraut; haouzi; hemp; hen nab; herba cannabis; herba cannabis indicae; herbe de chanvre indien; hursini; hushish; igbo; ikinji;[b] Indian hemp; indische; hennepkruid; indischer hanf; indisk hampa; intianhamppu; intsangu; isangu; janjah; jatiphaladya churna; jea; juana; juanita; jvalana rasa;[c] kamashwar modak;[c] kamesvara modaka;[c] kanab; kanabis; karpura rasa; khanh chhah; khanje; kif; kif ktami; kinnab; kiste kibarfi;[b] kulfi;[b] kulphi;[b] kumari asava;[c] liamba; lianda; lutki;[a] maconha; maconia; madan modak;[c] madi; magiyam; makhlif; malva; maraguango; marajuana; mariajuana; marigonga; marigongo; mariguana; marihuana; marijuana; mariquita; maruamba; matekwane; mbanje; meconha; misari; mnoana; momea; mota; mulatinha; mundyadi vatika; namba; ntsangu; nwonkaka; nwunkaka; opio do pobre; pang a, -o; peinka; penek; penka; pito; pot; pretinha; purnadhi legiyam; rafe; rafi; rafo; riamba; rongony; rora; rora ganja; rosa maria; round ganja; roundgunjah; sabsi; sadda; siddhi; soñadora; soussi; subji; summitates cannabis; suruma; tahgalim; takrouri; takruri; tedrika; teloeut; teriaki; tronadora: umya; urumogi; wee; wewe; yamba; yesca; yoruba; zacate chino; Zahra;[a] zerouali; ziele konopi indyjskich.

1.5.2 *Cannabis resin*

Note: a = beverage, b = confectionery, c = preparation containing cannabis resin.

Berch;[a] bers;[a] bheng; charas; charras; charris; chastig;[a] chastry;[a] chats raki;[a] chira, -s; churrus; chus; garaouich; garawiche; garawish; garoarsch; gauja; gosale;[c] hachich, -e; hachichet el keif;[c] hachisch; hafion;[c] haloua; hasach;[b] haschich; haschisch; hascisc; hascise; hash; hasheesh; hashish; hasis; hasjisj; haszysz; haxix, -e; heloua; kamonga; ma'agoun;[b] maagun;[b] maajoun; madjun;[b] magoon;[b] majoom;[b] majun;[b] malak; manzoul;[b] manzul; mapouchari;[a] masmach;[b] momeka; mosjuk;[b] n'rama; resin cannabis indicae; sighirma; teridka[b]

1.6 Physical appearance

1.6.1 *Cannabis plant*

1.6.1.1 Smell

The characteristic scent of the cannabis plant is mainly attributable to a mixture of volatile compounds, including monoterpenes, sesquiterpenes and other terpenoid-like compounds. About 140 terpenoids are known in cannabis, the most abundant of which are pinene, limonene, myrcene, linalool, β-caryophyllene, caryophyllene oxide, nerolidol and phytol. Some of the terpenes in cannabis have a pleasant odour: limonene is fruity, linalool has a rather sweet smell. Depending on the biotype, monoterpenes represent 48–92% of the volatile terpenes and sesquiterpenes represent 5–49% *(2, 3).* The aroma of cannabis comes mainly from the monoterpenes, pinene and limonene, which frequently comprise over 75% of the volatile constituents *(3, 4)* and often dominate the "headspace" odour near the plant. However, the monoterpenes evaporate relatively faster than other components, so the smell of the harvested plant may differ from that of the fresh plant. High Δ^9-THC cannabis varieties tend to have pleasanter odours than hemp (low Δ^9-THC) cultivars.

1.6.1.2 Appearance

Female inflorescences are available either undivided or disintegrated more or less into their individual components. The cannabis inflorescence appears as densely arranged bracts and flowers, which form a highly compressed panicle of 1–5 cm in length and width, with slightly projecting dark green bracts. It also comprises light brown to brown pistils and stigma branches with an overall length of up to 1 cm. The sepals are green to bright green and, like the bracts, densely covered with yellowish-white hairs and agglutinated by resin. The inflorescence can also be in the form fragments of peduncles, bracts and panicle sections, as well as individual flowers and flower organs. An individual flower has a length of 5–10 mm, sometimes with a short peduncle and consists of a hood-like, green to bright green sepal, a whitish ovary with a diameter of 1–2 mm, which may contain a small brown ovule, and a brown pistil with two long, lean stigma branches. Fragments of bracts are dark green to green coloured, those of peduncles are bright green. Bracts and all flower organs, except the pistils, are more or less densely covered with excreted resin-adhesive glandular hairs *(5)*.

1.6.2 *Cannabis resin*

1.6.2.1 Smell

The smell is similar to that of cannabis plant.

1.6.2.2 Appearance

The resin can resemble a resinous secretion of the plant, which is produced in the glandular trichomes, but also occurs as finer plant material, which appears as loose or pressed sticky powder, depending on the method of production *(6).* Sale-ready cannabis resin differs in colour from sandy to reddish to black. It differs in consistency from putty-like to brittle and dusty. These differences may be attributed to:

- the variety of cannabis plant used and the way it was cultivated and cured;
- the presence of non-resinous plant matter;
- the extent to which the resin has been pressed, heated or otherwise handled;
- age;
- adulterants introduced by manufacturers.

Darkening may result from oxidation caused by rough handling and/or bad storage conditions. A green colour may be indicative of the presence of unwanted plant material rather than pure resin.

1.7 WHO review history

Cannabis and cannabis resin are scheduled in Schedules I and IV of the Single Convention on Narcotic Drugs 1961 as amended by the 1972 Protocol (the "Single Convention") *(7)*. Cannabis plant and cannabis resin have not been scientifically reviewed by the World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD) since the review by the Health Committee of the League of Nations in 1935 *(7)*.

2. Chemistry

2.1 Name

Cannabis sativa L. (Linneus)

2.2 Chemical name

2.2.1 *IUPAC name:*

Not applicable

2.2.2 *CA index name:*

Not applicable

2.3 Chemical structure

2.3.1 *Free base:*

Not applicable

2.3.2 *Molecular formula:*

Not applicable

2.3.3 *Molecular weight:*

Not applicable

2.4 Stereoisomers

Not applicable

2.5 Taxonomy

The genus *Cannabis* belongs to the family of Cannabaceae. Notwithstanding the ongoing debate on whether the genus *Cannabis* is represented by one or more species, it is currently considered as monospecific (*Cannabis sativa* L.) with two subspecies (*Cannabis sativa* L. subsp. *sativa*, and *cannabis sativa* L. subsp. *indica*) and four varieties (*Cannabis sativa* L. subsp. *sativa* var. *sativa*; *Cannabis sativa* L. subsp. *sativa* var. *spontanea* Vavilov; *Cannabis sativa* L. subsp. *indica* var. *indica* (Lam) Wehmer; *Cannabis sativa* L. subsp. *indica* var. *kafiristanica* (Vavilov) *(3, 6, 9, 10).* Such a taxonomy was proposed by Small and Cronquist combining morphological and chemical characteristics (fruit morphology and Δ^9-THC content) *(9).*
The scheme with the features of all subspecies and varieties as proposed by Small is outlined below (3).

2.5.1 *Cannabis sativa subsp. sativa*

Plants of limited intoxicant ability, Δ^9-THC usually comprising less than 0.3% (dry weight) of upper third of flowering plants (sometimes up to 1%) and usually less than half of cannabinoids of resin. Plants cultivated for fibre or oil or growing wild in regions where such cultivation has occurred.

2.5.1.1 Cannabis sativa subsp. sativa var. sativa

Mature achenes relatively large, although less than 3.8 mm long, tending to be persistent, without a basal constricted zone, not mottled or marbled, the perianth poorly adherent to the pericarp and frequently more or less sloughed off.

2.5.1.2 Cannabis sativa subsp. sativa var. spontanea Vavilov

Mature achenes relatively small, commonly less than 3.8 mm long, readily disarticulating from the pedicel, with a more or less definite, short, constricted zone towards the base, tending to be mottled or marbled in appearance because of irregular pigmented areas of the largely persistent and adnate perianth.

2.5.2 *Cannabis sativa subsp. indica (Lam.)*

Plants of considerable intoxicant ability, Δ^9-THC usually comprising more than 1% (dry weight) of upper third of flowering plants and frequently more than half of cannabinoids of resin. Plants cultivated for intoxicant properties or growing wild in regions where such cultivation has occurred.

2.5.2.1 Cannabis sativa subsp. indica var. indica (Lam.) Wehmer

Mature achenes relatively large, rarely less than 3.8 mm long, tending to be persistent, without a basal constricted zone, not mottled or marbled, the perianth poorly adherent to the pericarp and frequently more or less sloughed off.

2.5.2.2 Cannabis sativa subsp. indica var. kafiristanica (Vavilov)

Mature achenes relatively small, usually less than 3.8 mm long, readily disarticulating from the pedicel, with a more or less definite, short, constricted zone towards the base, tending to be mottled or marbled because of irregular pigmented areas of the largely persistent and adnate perianth.
The *sativa* subspecies are common in Asia, Europe and North America, whereas the varieties of the subspecies *indica* grow mainly in the Asian continent.

Nonetheless, the chemical and morphological distinctions that characterize cannabis taxonomy are not often easily distinguishable. The plant seems to be easily modified by environmental factors. Indeed, most commercially available cannabis plants are actually hybrids of *sativa* and *indica*.

2.6 Cultivation

Cannabis sativa (C. sativa) is one of the world's oldest cultivated plants and one of the oldest plant sources of food and textile fibre (11). Cultivation of C. sativa for textile fibre originated in western Asia and was subsequently introduced to Europe between 1000 and 2000 BC (12). The first account of medicinal use of C. sativa came from the Chinese book of herbal remedies by the Emperor Shen Nung who is thought to have lived around 2700 BC. Its introduction into western medicine for the treatment of pain, glaucoma, nausea, depression and neuralgia occurred much later, during the early nineteenth century (12).
Cannabis is an annual flowering plant, generally dioecious, i.e. the male and female flowers are on separate plants, although monoecious plants, with the male and female flowers on the same plant, also occur (Fig. 1) *(13).* Fertilization occurs by means of wind-borne pollen. Stem male plants are usually taller but less robust than the pistillate female plants. Stems are erects and can vary in height from 0.2–6 metres, although most plants reach 1–3 metres. Both height and ramification of the plant largely depend upon environmental and genetic factors, as well as the cultivation method *(6).*

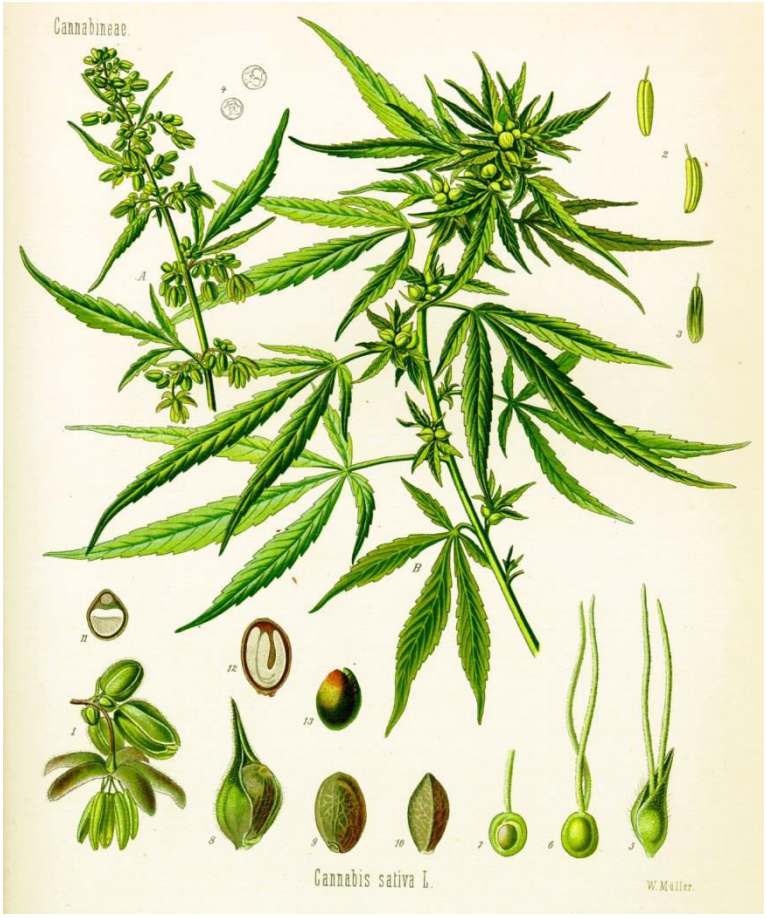

Fig. 1. Cannabis sativa *L. A) Flowering male staminate. B) Fruiting female pistillate plant: 1 male staminate flower; 2 stamen (anther and short filament); 3 stamen; 4 pollen grains; 5 female pistillate flower with bract; 6 female flower without bract; 7 female flower showing ovary, longitudinal section; 8 fruit (the fruit is the seed, technically achene) with bract; 9 fruit without bract; 10 fruit (side view); 11 fruit (cross-section); 12 fruit (longitudinal section); 13 fruit without pericarp (hulled).*

Source: (13).

The cannabis plant flowers over time or when it detects the coming of autumn, as evidenced in the shortening of days (14). This allows the plants that germinated late to quickly complete their life cycle. The exact photoperiod needed to induce flowering varies according to the variety: temperate climate plants tend to flower later in the season, whereas rigid climate plants have to reproduce in a shorter time (14). A 12-hour dark cycle is sufficient to induce flowering in most, if not all, varieties (14).

Two types of trichomes, non-glandular and glandular, are present on C. sativa (6). Non-glandular trichomes are numerous, unicellular, rigid and curved hairs, with a slender pointed apex. They occur in two forms.

- Cystolithic trichomes are found on the upper surface of cannabis leaves. They have a characteristic bear-claw shape and may have calcium carbonate crystals (cystoliths) visible at their bases. Frequently, the trichome is broken and the cystolith freed.
- Non-cystolithic trichomes occur mainly on the lower side of the leaves, bracts and bracteoles and lack the enlarged base.

The simultaneous presence of these bear-claw shaped trichomes on the upper surface and the fine, slender non-cystolithic trichomes on the lower surface of the leaves account for the unique characteristics of cannabis.

The other form of trichomes is glandular trichomes. They occur as:

- sessile glands, i.e. trichomes without a stalk, which are generally found on the lower epidermis;
- small bulbous glandular trichomes with one-celled stalks;
- long multicellular stalks on the bracteoles surrounding the female flowers (multicellular stalked glandular trichomes).

In all glandular trichomes, the essential part of the gland is a more or less hemispherical head, with specialized secretory "disk cells" at its base above which is a non-cellular cavity where secreted resin is accumulated, enlarging the covering sheath, a waxy cuticle, of the head into a spherical blister.

2.7 Phytocannabinoids

Cannabis contains a characteristic class of terpenophenolic secondary metabolites, called phytocannabinoids to distinguish them from synthetic and endogenous cannabinoids *(15).*

Notwithstanding numerous publications that state that they are unique to cannabis, there are reports in the literature that phytocannabinoids also occur in other plants such as *Helichrysum (16).* However, phytocannabinoids are more characteristic of cannabis than any other plant, and the major cannabinoids of *C. sativa* occur only in this species. One hundred and twenty phytocannabinoids have been recorded for *C. sativa* to date and can be classified into 11 general types: (–)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC), (–)-*trans*-Δ^8-tetrahydrocannabinol (Δ^8-THC), cannabigerol (CBG), cannabichromene (CBC), cannabidiol (CBD), cannabinodiol (CBND), cannabielsoin (CBE), cannabicyclol (CBL), cannabinol (CBN), cannabitriol (CBT), and miscellaneous types *(12, 17, 18).* Δ^9-THC and CBD are the most important plant cannabinoids. Δ^9-THC is the principal intoxicant constituent of *C. sativa* and CBD, which is not intoxicating, is the principal cannabinoid of non-intoxicating forms of *C. sativa*.

The cannabis varieties selected for fibre and oilseed production are *C. sativa* subsp. *sativa* and the resin produced in the secretory glands usually has limited amounts of Δ^9-THC, but large amounts of CBD. In contrast, plants that have been selected for their intoxicating drug properties are generally high in Δ^9-THC and are placed in *C. sativa* subsp. *indica*. As reported by Small, "*sativa* type" cannabis varieties have little or no CBD, while "*indica* type" cannabis varieties frequently have substantial amounts of both Δ^9-THC and CBD *(3).*

Although CBD and Δ^9-THC have such relevance when talking about cannabis, these molecules are not enzymatically synthesized in the plant, which instead produces cannabidiolic acid (CBDA) and tetrahydrocannabinolic acid (THCA) (Fig. 2). CBDA and THCA are the major components of the cannabis inflorescence. THCA is devoid of intoxicating properties and is not a scheduled substance. A chemical reaction triggered by heat leads to the decarboxylation of these compounds producing the corresponding decarboxylated species CBD and Δ^9-THC as occurs when marijuana is smoked or otherwise heated. Other minor cannabinoids are cannabichromenic acid (CBCA) and cannabigerolic acid (CBGA) (Fig. 2), which is the "stem cell" of the other carboxylated cannabinoid. These compounds, upon decarboxylation, lead to the derivatives cannabichromene (CBC) and cannabigerol (CBG), respectively (Fig. 2). There are also different isomers of Δ^9-THC resulting from variations or isomerization in the position of the double bond in the alicyclic carbon ring, like Δ^8-THC. It has been suggested that Δ^8-THC might be an isolation artefact since it is thermodynamically more stable than Δ^9-THC *(19).*

Other minor phytocannabinoids are the propyl homologues of the C-3 *n*-pentyl side-chain of the different phytocannabinoids including Δ^9-THC, CBC, CBD and CBG; these are termed as Δ^9-tetrahydrocannabivarin (Δ^9-THCV), cannabichromevarin (CBCV), cannabidivarin (CBDV) and cannabigerovarin (CBGV), respectively. Moreover, cannabinol (CBN) can be recorded, which derives from the oxidation of Δ^9-THC. A schematic representation of the biosynthetic route of CBGA, THCA, CBDA and CBCA, their conversion into CBG, Δ^9-THC, CBD and CBC, respectively, and the oxidation of Δ^9-THC to CBN is reported in Fig. 2.

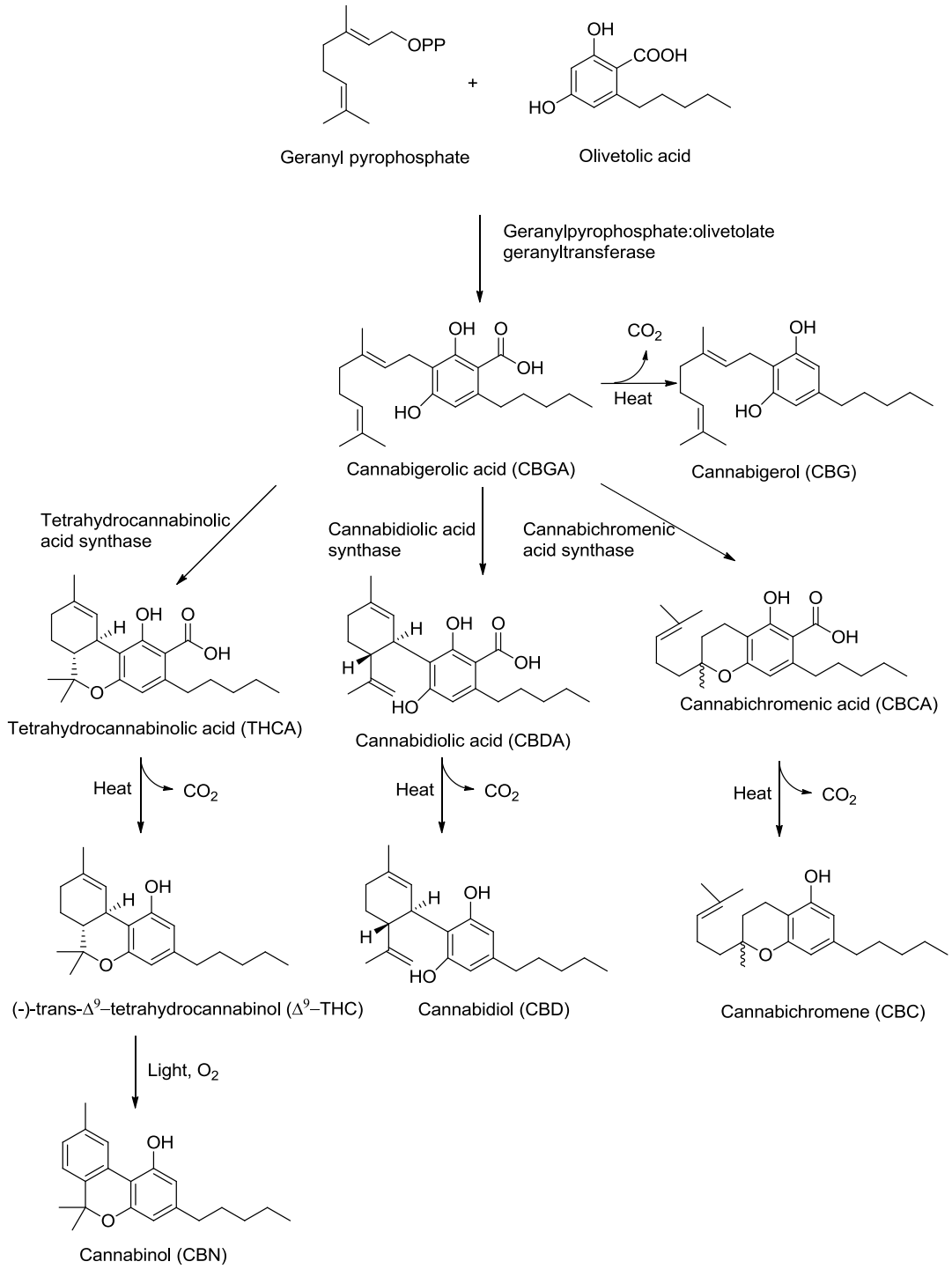

Fig. 2. Biosynthetic route of CBGA, THCA, CBDA and CBCA, their conversion respectively into CBG, Δ^9-THC, CBD and CBC and the oxidation of Δ^9-THC to CBN.

Δ^9-THC degrades over time mainly to CBN. The ratio of CBN to Δ^9-THC is an indicator of the age of herbal cannabis since harvest of stored marijuana. It has been proposed that samples with a ratio of CBN to Δ^9-THC concentrations of less than 0.013 are less than six months old, and those with a ratio between 0.04 and 0.08 are between one and two years old *(6)*. However, high temperature, moisture, light and oxygen, all accelerate the conversion kinetics of Δ^9-THC to CBN.

Intact gland heads appear to provide some protection against Δ^9-THC degradation. It has been reported that Δ^9-THC in cannabis preparations degrades by about 30% in the first year, while in herbal cannabis it decomposes at a rate of 6.9% loss/year at room temperature *(3, 20, 21)*

A very simple way to distinguish between drug-type and fibre-type cannabis is to determine the concentration ratio of the main cannabinoids Δ^9-THC, CBN and CBD *(6, 22).* If the concentration ratio (or the peak area ratio in gas chromatograms obtained employing a gas chromatographer with a flame ionization detector (GC-FID)) of the sum of Δ^9-THC and CBN divided by the concentration (or GC-FID peak area) of CBD is <1, then the cannabis plant is considered to be fibre-type; if the ratio is >1 it is considered drug type.

Small et al. established a limit of 0.3% of Δ^9-THC in dry weight content in the inflorescence and this criterion was subsequently adopted in the European Union (Δ^9-THC levels were lowered to 0.2% from 0.3% in 2001), Australia and Canada. A level of about 1% Δ^9-THC is considered the threshold for cannabis to have intoxicating potential, so jurisdictions such as Switzerland have permitted the cultivation of cultivars with this level. Even though, in the illicit market, the part of the plant with the highest Δ^9-THC content is selected, a 0.3% Δ^9-THC level in the flowering parts of the plant is too low in intoxicant potential to actually be used for illicit production of marijuana or other types of cannabis drugs *(3).*

2.8 Δ^9-THC distribution in cannabis plant

Absolute cannabinoid content varies in different parts of the plant, increasing in the following order: perigonal bracts covering the female flower or achenes, younger and smaller leaves, older and larger leaves, smaller stems and larger stems[1] *(3).*

Δ^9-THC content variation between the plant parts has been reported in "Recommended methods for the identification and analysis of cannabis and cannabis products" by the United Nations Office on Drugs and Crime (UNODC) (6) as follows:

- 10–12% in pistillate flowers;
- 1–2% in leaves;
- 0.1–0.3% in stalks;
- < 0.03% in the roots.

Δ^9-THC concentration increases from the seedling to the flowering stage, then cannabinoids start to degrade. Determining the optimum harvesting stage is a critical step in cannabis cultivation since it significantly affects the yield of cannabinoids *(24).*

Resin production and Δ^9-THC content are affected by cultivation conditions such as plant density, supplies of essential factors including light, warmth, water, nutritional elements and carbon dioxide (CO_2) *(3).*

According to Small, the qualitative variation in cannabinoid production seems to be much more influenced by genetics than by the environment *(3).*

2.9 Breeding

Δ^9-THC and, more recently, CBD are the subject of breeding to increase or decrease their content in plants. For several decades, clandestine marijuana breeders have produced "improved" types of drug plants, and hundreds of selections have been named and offered in the illicit trade. Many named selections are described by Backes *(25)*. A wide range of cannabis varieties with different characteristics in terms of

[1] Small and Naraine suggested that female flowers are devoid of resin glands so they do not contain cannabinoids. The resin glands highly concentrated on the perigonal bracts covering the flower, and resin falls off from trichomes and contaminate stigmas 3. Small E. Cannabis: a complete guide. Kindle ed. ed. Boca Raton, Florida: CRC Press; 2017, 23. Small E, Naraine SGU. Size matters: evolution of large drug-secreting resin glands in elite pharmaceutical strains of Cannabis sativa (marijuana). Genetic Resources and Crop Evolution. 2016;63(2):349-59.

morphology and chemical composition are grown. Also, a vernacular classification has developed, which uses the scientific terms but does not keep their actual meaning. Therefore, many varieties with fantasy names can be found: Afghan, AK–47, blueberry, blue dream, bubba kush, chem, '91/chemdawg, cherry cough, g13, granddaddy purple, harlequin, haze, Hindu Kush, Jack Herer, la confidential, Malawi gold, Neville's haze, Northern Lights #5 × haze, og kush, pincher creek, purple urkle, S.A.G.E., sensi star, skunk #1, sour diesel, strawberry cough, trainwreck and white widow.

Each of these varieties has a different chemical composition of the resin in terms of terpenes and phytocannabinoids. In the vernacular language, these varieties can be distinguished as *sativa* and *indica*, but they do not have the same scientific taxonomic value.

2.10 Methods and ease of illicit manufacturing

There is a persisting traditional belief that only the fruiting and flowering tops and leaves next to the flowering tops contain significant quantities of the psychoactive constituent (Δ^9-THC); therefore, only these parts of the plant are sold on the illicit market. However, illicitly consumed herbal cannabis also includes bigger leaves located at a greater distance from the flowering tops *(6)*. Also, the leaves next to the male flowering tops of potent cannabis plants contain remarkable amounts of Δ^9-THC. However, the content is much lower than that of female plants and male plants are therefore not materials of first choice. The central stem and main side stems contain little Δ^9-THC but they may still be used in the production of cannabis oil *(6).*

The dried leaves and flowers of the cannabis plant are found unchanged in the illegal market, i.e. raw from the plant (also called "dried flower"), processed as compressed slabs or coins, or as ground-up material. The presentation of the herbal material in illicit markets varies widely, from region to region as well as within the countries of each region.

High-quality product can be made by sieving crushed herbal cannabis to remove those parts of the plant that contain relatively low levels of, or no, cannabinoids. All material that passes through the sieving process has been derived from the flowering and fruiting tops of the herbal material; therefore, a relative enrichment of Δ^9-THC occurs. In the illicit market, the product is known as "kif", a characteristic product of north Africa *(6).* Such material has a high cannabis resin content and can be compressed into slabs, which appear very similar to cannabis resin slabs (hashish). However, under the microscope, such slabs are found to have retained essential herbal characteristics, and are considered a sort of "purified marihuana".

A third way of producing high-quality herbal cannabis is indoor production and in some western European countries, this is the dominant production method. Very potent hybrids, such as "skunk" and "white widow", are generally produced by optimized cultivation methods *(6).*

The main propagation method is cloning of the mother plants. Places used for indoor cultivation are often equipped with automated nutrition and water supplies, air-conditioning, systems to filter and deodorize outlet air and automated illumination to mimic day and night phases. The combination of ideal growing conditions and particular genetic pool generates herbal cannabis with a total Δ^9-THC content of more than 10%, cannabis resin with 25% Δ^9-THC and cannabis oil with 60% Δ^9-THC *(6).* The drug-containing parts can be cut off or the entire plant is suspended upside down and air-dried. Drying is complete when the leaves next to the flowering tops are brittle. Depending on the humidity and ambient temperature, this takes approximately 24–72 hours. The residual water-content in this material is about 8–13%. This material is directly suitable for smoking in a joint and can be stored for many months, although Δ^9-THC degrades with time when exposed to air, light and moisture.

The following paragraphs describe some cultivation practices mainly employed for illicit manufacturing with the aim to increase the Δ^9-THC concentration in the final product.

2.10.1 *Sinsemilla*

For the production of phytocannabinoids, female plants are preferred since they produce higher amounts of cannabinoids (it has been reported 20 times higher than male ones). Whereas pollinated female plants produce seeds when they reach maturity, unpollinated plants are seed-free (sinsemilla) with a higher yield of phytocannabinoids in the female flower heads ("buds"). To avoid pollination, it is necessary to remove the male plants as they appear, ensuring that the female plants are not exposed to pollen.
In vernacular language, "sinsemilla" is a term referring to high Δ^9-THC cannabis prepared mostly from unfertilized female inflorescences. In the United Kingdom of Great Britain and Northern Ireland, *sinsemilla* is often called "skunk" and "kush" in North America *(3, 24).*

2.10.2 *Cloning*

Selection of a female clone based on the desired chemical composition and morphological characteristics of the resin is a way to ensure the consistency in the chemical profile. Vegetative propagation in soil or hydroponics of a selected mother plant is the preferred way to obtain cannabis for pharmaceutical purposes *(3, 24).*

2.10.3 *Feminized seeds*

The sex of a cannabis plant is determined mainly by genetic factors, but chemical substances and environmental factors may induce the plant to express a preferential sex rather than the other one. As an example, by treating the plants with Ethephon (2-chloroethylphosphonic acid) it is possible to induce feminization of the plants. Alternatively, "feminized" seeds can be obtained using female plants selfed with pollen that they are forced to produce by chemical or environmental sex-reversal techniques *(3, 24).*

2.10.4 *Indoor cultivation*

Indoor cultivation under controlled environmental conditions can generate three or four crops per year, depending upon the required per-plant biomass yield; as a comparison, outdoor cultivation produces only one crop per year. Indoor cultivation enables the entire plant life cycle to be controlled. Hence, parameters such as light (intensity and photoperiod), temperature, CO_2 level, air circulation, irrigation, relative humidity and plant nutrition are factors that may be fine-tuned to obtain a desirable cannabinoid profile. Indoor cultivation is the preferred mode of cultivation, starting from cloned plants to assure complete control of genetic and environmental factors that can influence the chemical and morphological profile of cannabis plants *(3, 24).*

2.10.5 *Processing*

Once the plant is harvested, which usually happens at the time of maximum phytocannabinoid concentration, it is dried. The drying process can occur at 25–30 °C in a dry, well-ventilated dark environment or, especially in industrial production, at 40 °C for 15 hours. After the drying process, the foliage should be crisp. Fresh plants can generally reach a moisture content of about 80%, which may be reduced to 5–10% (usually about 8%) before packaging.
Once dried, the foliage and floral material is stripped from the stalk and twigs, which are almost devoid of cannabinoids. For production of ground-up (manicured) marijuana, the floral and other tissues in the flowering stem (mostly the perigonal bracts and smallest leaves) are screened. Loose gland heads, rich in cannabinoids, tend to fall off and accumulate in the collection container.

The demand for buds is increasing and they are often processed by hand (either trimmed or crumbled), a rather labour-intensive process. For sales presentation, the smallest leaves (with lower levels of cannabinoids) are often trimmed away from the buds with scissors or machines. This is best done before the buds are too well-dried, as the cannabinoid-rich trichomes tend to drop away with handling because well-dried buds are brittle.

To prevent Δ^9-THC degradation caused by exposure to oxygen and light, cannabis should be protected from air (in tightly sealed containers) and kept in the dark. The recommended storage temperatures are as follows:

- short-term, 18–20°C
- long-term, −20°C.

2.10.6 *Manicured cannabis*

"Manicured cannabis" is composed of flowering parts of the plant coupled with associated small leaves, prepared using intoxicant varieties. It is comparable in texture to smoking tobacco. Cannabis is conventionally prepared by (1) breaking up the dried flowering tops and removing all but the smallest twigs, (2) forcing the resulting material through a coarse screen, and (optionally) (3) crumbling. The result is a mixture of plant particles, including the tiny secretory trichome glands that contain most of the resin (some resin is smeared on plant particles during preparation) *(3).*

Until two decades ago, in the western world, cannabis often included a substantial content of seeds (which do not contain Δ^9-THC) and foliage (which contains limited Δ^9-THC). As a result, cannabis in the past usually contained no more than 5% Δ^9-THC, often less. Currently, cannabis rarely has seeds or larger leaves, and the Δ^9-THC content is at least 5% and may be as much as 25%. Meanwhile, CBD content fell from approximately 0.28% in 2001 to <0.15% in 2014 *(3).*

2.10.7 *Cannabis resin*

The resinous secretions produced in the glandular trichomes can be collected to obtain a product with a Δ^9-THC amount higher than that present in the whole plant inflorescence as most of the plant material is removed. Cannabis resin consists of finer plant material, which appears as loose or pressed sticky powder, depending on the method of production *(6).*

The production of cannabis resin is mainly carried out in two regions: the countries around the southern and the eastern part of the Mediterranean, and the countries in South and South-West Asia. The most relevant difference lies in the production technique and sieving is an important part of the process in both regions *(6).*

2.10.8 *Cannabis resin from Mediterranean countries*

In this region, the dried herbal material is typically threshed out against a wall so that the resin-producing parts can detach from the more fibrous parts of the plant. The material is then sieved to remove seeds and major fibrous parts. Although macroscopic botanical characteristics are absent at this stage, microscopically the material still exhibits many botanical traits. The material appears as a fine sticky powder and can be compressed into slabs. In some countries (eastern Mediterranean) the material is placed in cloth bags before compression, while in other countries (North Africa) cellulose wrapping is added before compression. In other countries (north-eastern Mediterranean and Central Europe) cannabis resin is illicitly sold without having been compressed into slabs *(6).*

2.10.9 *Cannabis resin from south and south-west Asia*

A common practice to obtain cannabis resin in these regions consists of rubbing the fruiting and flowering tops of a fresh plant against rubber sheeting so as to transfer the resin from the plant to the sheet. Otherwise, it can be done by a person walking through a field of cannabis plants wearing rubber sheeting or leather. In this way, resin accumulates on the surface, then the sheeting or leather may be scraped clean, and the material can be compressed into slabs *(6).*

Alternatively, the flowering and fruiting tops may be collected in a similar way to that used in herbal cannabis production, allowed to dry, and then be reduced into a coarse powder by hands. This powder is then sieved in order to obtain a fineness similar to that of the Mediterranean region. The fine powder is stored in leather bags for four to five months, then exposed to the sun for a short time sufficient for the resin to melt. After being put back into the leather bags for a few days, the resin is removed and kneaded well with wooden rods so that a certain amount of oily material appears on its surface. Kneading continues until a material suitable for pressing into slabs has been produced *(6).*

A different method consists of dipping the plant material in boiling water in order to remove the resin from the fruiting and flowering tops. After cooling the extracted liquid, a layer of solidified resin forms on its surface. The resin is removed and pressed into slabs. However, in this way water is introduced into the resin, thus causing production of moulds over time. Little cannabis resin is made in this more elaborate way *(6).*

2.10.10 *Cannabis resin from "pollinators" and "ice-o-lators"*

An efficient method for the separation of resin consists of a device similar to a tumble-dryer lined with a finely woven net placed in a box, lined with plastic. This so-called "pollinator" is partly filled with dried and deep-frozen flowering and fruiting tops of the cannabis plant in order to reduce the stickiness of the resin. During rotation of the pollinator, the THC-rich parts of the leaves and flowering tops break and pass through the net. They stick to the plastic walls and can be collected as a fine powder. This method allows a THC enrichment of up to 8-fold compared to the starting material. A similar method is used to produce the so-called "ice hash", in which the dried plant material is put in a coarse sieve with ice cubes and then shaken with a mechanical paint stirrer. The frozen resin balls drop off the plant. Progressively finer sieves are used until a powdered product similar to the above is achieved *(6).*

2.11 Chemical properties

2.11.1 *Melting point*

Not applicable

2.11.2 *Boiling point*

Not applicable

2.11.3 *Solubility*

Not applicable

2.12 Identification and analysis

2.12.1 *Cannabis plant*

Cannabis inflorescence can be identified based on its morphological characteristics alone, provided that the required ones are present.

2.12.1.1 Macroscopy assay

The seed variety and environmental factors (light, water, nutrients and space) affect the morphological characteristics of the cannabis plant *(6)*. Each male flower consists of five whitish-green minutely hairy sepals about 2.5–4 mm long and five pendulous stamens, with slender filaments and stamen. The female flowers are more or less sessile and are borne in pairs. Each flower has a small green bract enclosing the ovary with two long, slender stigmas projecting well above the bract *(6).* A detailed description of the macroscopic characteristics is provided in the monograph on Cannabis Flos in the German pharmacopoeia *(5).*

2.12.1.2 Microscopic assay

Cannabis inflorescences can be identified by their trichomes, the microscopic structures on the surface of the plant. Two types of trichomes occur: non-glandular and glandular ones. A detailed description of the microscopic characteristics is provided in the monograph on Cannabis Flos of the German pharmacopoeia *(5)* and in *Recommended methods for the identification and analysis of cannabis and cannabis products* published by the United Nations Office on Drugs and Crime *(6).*

2.12.1.3 Chemical test

a. Sample extraction

Sample extraction is of the utmost importance since it strongly influences the results of chemical analysis. This is a crucial point, especially when chromatographic techniques are employed for the analysis of either cannabis plant or cannabis resin. Extraction usually consists of treatment with a suitable solvent, generally ethyl alcohol, which possesses a high extracting efficiency towards cannabinoids. EtOH 96% (v/v) is the solvent proposed in the monograph on Cannabis flos in the German Pharmacopoeia *(5)*. The use of ethyl acetate, hexane, methanol, chloroform and mixtures of organic solvents has been reported in the literature *(26–30).* Water is not generally a suitable solvent for extracting cannabinoids from plant material *(31)*. Another methodology worth noting is supercritical fluid extraction, usually with supercritical carbon dioxide. Besides the preservation of thermolabile and light-sensitive compounds, this solvent is able to extract terpenes, while cannabinoids are extracted with EtOH as co-solvent (10–20% in carbon dioxide) *(32, 33).*

b. Colour test

The colour tests are only presumptive, and a positive result should be confirmed by a more accurate analytical technique such as chromatography.
Three colour tests are described in the literature:

- fast Corinth V salt test;
- fast blue B (FBB) salt test;
- rapid Duquenois test (Duquenois-Levine test).

A detailed description of the colour tests is provided in Recommended methods for the identification and analysis of cannabis and cannabis products of the United Nations Office on Drugs and Crime (6).

c. Thin-layer chromatography

There are a few thin-layer chromatography (TLC) methods for the qualitative and semiquantitative analysis of cannabis inflorescence and resin, employing a variety of different stationary and mobile phases, and slightly different sample preparation and visualization techniques *(6).* The monograph on Cannabis Flos in the German Pharmacopoeia reports a TLC-based method for the qualitative determination of the main cannabinoids in the plant inflorescence *(5)*. 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 *(34).* Moreover, it allowed for the qualitative analysis of the other main cannabinoids present in cannabis. 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 FBB solution, which is a selective stain for cannabinoids *(34).* 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 has some limitations in its specificity and sensitivity, which are fairly low compared to other analytical platforms and thus the results must be interpreted with caution.

d. Gas chromatography

Gas chromatography (GC) is one of the most widely employed approaches for the analysis of cannabinoids in plant materials *(35–37)*. It is necessary to take into account that this system operates at very high temperatures, which unavoidably lead to the decarboxylation of the cannabinoids (THCA, CBDA, CBGA, CBCA, etc.). The result is that the corresponding decarboxylated cannabinoids are generated (Δ^9-THC, CBD, CBG, CBC, etc.), unless a derivatization step occurs 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 not often complete *(38)*; the latter is complicated in a similar way, as it is largely affected by the temperature and geometry of the injector *(39),* thus leading to unreproducible results. Nonetheless, this is one of the official methods employed by the authorities for the determination of cannabinoids in cannabis plant material.
GC is generally interfaced to a flame ionization detector (FID) or to a mass spectrometry (MS) detector. The advantage of FID is that it provides a more accurate quantitative response with respect to MS due to the use of authentic standards, while MS allows for higher specificity and sensitivity than FID. However, MS requires the use of deuterated standards, which are expensive and not commercially available for all minor cannabinoids.
A GC-FID method for the determination of Δ^9-THC in cannabis inflorescence and resin has been described in detail by the European Union for outdoor cannabis plantations for industrial hemp. This method has been adapted to take into account the practical aspects and variety of cannabis inflorescence and resin *(40).*
GC methods are also employed to analyse the volatile component of cannabis plant represented by terpenes (41).

e. Liquid chromatography

Liquid chromatography (LC) coupled to mass spectrometry (LC-MS) is probably the method of choice for the qualitative and quantitative determination of cannabinoids in cannabis products *(42–52)*. In contrast to GC, LC-based techniques do not lead to decomposition of the sample as they take place at room temperature, allowing the direct analysis of carboxylated cannabinoids in the extracted sample *(27).*
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 *(53).* It is important to employ stationary phases with a high-resolution power *(41, 54–57),* 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 *(41, 58).* Ultra-high performance liquid chromatography (UHPLC

with sub-2 µm diameter of the particles of the stationary phase) can overcome this issue *(41, 59-70)* due to fast analyses and high separation efficiency.
A considerable improvement in the separation power can be achieved using two-dimensional (2D) chromatography, which consists of the combination of two dimensions of different separation mechanisms in series *(26)*. 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 *(71).* 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 using a single separation mechanism *(26).*
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 plant materials, where the amount of the main cannabinoids is relatively large *(26, 37, 41, 58, 72–74).* The monograph on Cannabis flos in the German Pharmacopoeia describes an 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 *(5).*
In the case of poor resolution of co-eluting cannabinoids like CBG and CBD, MS can provide greater specificity based on the *m/z* of the molecular ions. For isomers like Δ^9-THC and Δ^8-THC, a high-resolution fragmentation spectrum could help in the identification based on the fragments generated *(32)*. However, quantification of cannabinoids by MS requires the use of deuterated standards and the same considerations apply as 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 *(38).*

f. Nuclear magnetic resonance

Nuclear magnetic resonance (NMR) spectroscopy can be a valid alternative to chromatographic techniques *(72, 75–77).* In fact, quantitative NMR can be a highly accurate and reproducible technique and has a relatively short analysis time. The main advantage of NMR is the lack of sensitivity to impurities present in the plant material such as chlorophyll and lipids *(75, 76, 78)*. However, the use of this technique is limited by the high instrument costs and the necessity for highly specialized personnel *(79).*

g. Immunoassay

Immunoassay (IA) is based on the recognition of a class of compounds with similar chemical structure by an antibody, but it generally provides poor 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 GC-MS or LC-MS *(79, 80).*

2.12.2 *Cannabis resin*

Cannabis resin does not keep the morphological characteristics of the plant; therefore, a macroscopic or microscopic assay may not be the best way to identify it. Hence, a chemical analysis, using TLC, GC or LC, is required to detect the presence of the main cannabinoids (Δ^9-THC, CBD and CBN) *(6).*

Risk of contamination and adulteration of cannabis plant and resin

The quality of cannabis products purchased in the illicit market is often uncertain, thus prompting many people to grow and prepare their own supplies *(3)*.
Cannabis may be contaminated in different ways, generally due to negligent cultivation, preparation or storage techniques. This can introduce dangerous fungi, aflatoxins (toxic fungal metabolites), other

microbes (particularly bacteria), pesticide residues and heavy metals. Law enforcement in some countries has employed Paraquat (*N,N′*-dimethyl-4,4′-bipyridinium dichloride) herbicide to control illicit cannabis, notably in Mexico, and there has been concern that imported cannabis could be contaminated *(81).* However, according to Barceloux, "the high combustion temperatures in marijuana cigarettes destroys Paraquat; therefore, there is no significant risk of Paraquat-induced pulmonary fibrosis from cannabis smoking" *(82).* Very often, illicit growers produce chemically contaminated cannabis. They may use banned plant growth regulators to force early flowering and production of bigger and more compact buds, such as paclobutrazol (1-(4-chlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)pentan-3-ol), or daminozide (4-(2,2-dimethylhydrazinyl)-4-oxobutanoic acid), which degrades into the dangerous chemical hydrazine *(3)*. A number of "growth enhancers" of uncertain chemical nature are used very popularly. Sullivan et al. examined how the presence in cannabis of three commonly employed pesticides, bifenthrin (2-methyl-3-phenylphenyl)methyl (1S,3S)-3-[(Z)-2-chloro-3,3,3-trifluoroprop-1-enyl]- 2,2-dimethylcyclopropane-1-carboxylate), diazinon (O,O-diethyl O-[4-methyl-6-(propan-2-yl)pyrimidin-2-yl] phosphorothioate), and permethrin ((±)-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate), as well as the plant growth regulator paclobutrazol, produced contaminants in the resulting inhaled smoke *(83).* Recovered residues were about 70%, "suggesting that the potential of pesticide and chemical residue exposures to cannabis users is substantial and may pose a significant toxicological threat" *(83)*.

Hair (from humans or domestic animals), although not particularly hazardous, is commonly found in street cannabis.

Addition of sand, chalk particles, or tiny glass shards give cannabis a more desirable appearance as well as increasing the density. In the United Kingdom of Great Britain and Northern Ireland, during the Victorian era, lead was a common adulterant, used for example to colour cheese. Because street cannabis is sold by weight, many dealers have added lead particles to their products, poisoning the consumers *(84).* It is also not uncommon to add dangerous drugs or plants to cannabis *(3).*

Cannabis resin is not devoid of risks of adulteration. Actually, the resin is even more susceptible to contamination compared to the cannabis plant; sometimes up to 80% of the final product can be made of impurities (soil, henna, paraffin wax, bee wax, rosin, glue, flour, liquorice, milk powder, coffee, used motor oil, animal excrement, or even medical drugs) *(85)*.

3. Ease of convertibility into controlled substances

Not applicable

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Cannabis and cannabis resin

Section 2: Pharmacology

Contents

1. General Pharmacology

Studies included in this pharmacology pre-review are those involving:

- Cannabis as defined by the International Drug Control Conventions as "the flowering tops of the cannabis plant from which the resin has not been extracted." The term "cannabis" generally refers to a dried preparation of the flowering tops or other parts of the cannabis plant.

- Cannabis resin which is defined as "the separated resin, whether crude or purified, obtained from the cannabis plant". It is normally in solid form and is sometimes known as hashish.

Most of the studies covered herein involve cannabis delivered via smoking. While the flowering tops of the cannabis plant may be vaped, this practice is relatively new and scientific literature on its distinct pharmacological effects (vs. smoking) are not available. Vaping cannabis-derived oils will be described in the extracts pre-review. Similarly, the initial step in creation of cannabis edibles typically involves extracting and concentrating cannabinoids contained in the cannabis plant. Hence, the literature on these products will also be covered in the cannabis extracts pre-review.

1.1 Routes of administration and dosage

To date, over 500 naturally occurring compounds have been identified in the cannabis plant, including cannabinoids (> 100 chemicals unique to the plant), terpenoids, and alkaloids.[1-3] Early research identified Δ^9-tetrahydrocannabinol (Δ^9-THC) as the primary constituent in cannabis that produces its characteristic psychological effects.[4] While other constituents are certainly psychoactive (e.g., Δ^8-THC and cannabinol), they are several-fold (1-10 times) less potent, and their concentrations in the plant and in its resin are at least 100 times lower than that of Δ^9-THC.[5, 6] In part, the higher concentration of Δ^9-THC has resulted from selective breeding of cannabis plants for this constituent over many generations. For these reasons, special emphasis has been placed on delineation of the pharmacology of this constituent in much of the subsequent research, especially research related to the abuse liability of the cannabis plant.

In the plant, Δ^9-THC is present primarily in its acid form, Δ^9-THCA; however, it is rapidly decarboxylated to Δ^9-THC upon heating or burning, as occurs during smoking or in the extraction process. Concentrations of Δ^9-THC contained in cannabis vary across strains and across the plant itself, with resin (i.e., hashish) and unfertilized female flowers (i.e., sinsemilla) having high concentrations compared to other parts such as the leaf. In addition, significant increases in Δ^9-THC concentrations in seized or purchased cannabis have been documented over recent years in several countries, including the U.S. and U.K.[5, 6] For example, average Δ^9-THC concentration in cannabis samples in the U.S. in 1995 was ~4%; by 2014, average Δ^9-THC concentration had increased to ~12%,[7] with some samples containing over 20% Δ^9-THC.[7-9] Concentrated extracts contained even higher concentrations of Δ^9-THC (average ~ 68%).[9] Concomitant decreases in cannabidiol (CBD) concentration have also been noted, with negligible CBD in sinsemilla and an average of 2.3% CBD in cannabis resin.[7, 8] Selective breeding and greater use of plant parts with higher Δ^9-THC concentrations (e.g., sinsemilla), both driven by consumer demand for stronger cannabis, may have contributed to this increased availability of high-Δ^9-THC/low-CBD cannabis.[7-9] Hence, "dosage" for cannabis and its resin usually refers to Δ^9-THC dose/concentration rather than to amounts of the other cannabinoid and non-cannabinoid constituents contained in the cannabis plant.

Cannabis and cannabis resin (i.e., hashish) are typically administered via inhalation after combustion (i.e., smoking). Because each inhalation of smoke from a cannabis cigarette or other delivery device (e.g., pipe, vaporizer) delivers a proportion of the chemicals contained in the cannabis, Δ^9-THC concentration is an important consideration in determination of how much Δ^9-THC enters the body through the lungs. Other factors that affect amount of Δ^9-THC that ultimately is absorbed include topography of smoking behavior (e.g., puff volume and duration, number of puffs), individual differences in lung physiology, and amount lost to side stream smoke or pyrolysis.[10-14] Desired Δ^9-THC dosage is self-determined by the user and may change over time due to the development of tolerance.

1.2 Pharmacokinetics

In humans, the predominant route of administration of cannabis or cannabis resin is inhalation after combustion (i.e., smoking). For this reason, discussion of the pharmacokinetics of cannabis and its resin will concentrate on inhalation as a route of administration. 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 the extraction process. Hence, 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 smoking cannabis followed by a brief review of the pharmacokinetics of CBD and possible

metabolic interactions of Δ^9-THC and CBD. Two excellent comprehensive reviews served as the basis for much of this section.[11, 13]

1.2.1 *Δ^9-Tetrahydrocannabinol*

Absorption of Δ^9-THC in smoked cannabis is rapid and measurable levels are observed in plasma seconds after the first puff.[11, 14] While peak plasma levels typically occur in 3-10 minutes after smoking, peak "highs" do not occur until 20-30 minutes after smoking,[11] although others have reported an earlier peak.[14] 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.[15] Bioavailability of Δ^9-THC after cannabis smoking 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.[11, 13] In addition, approximately 30% of the Δ^9-THC concentration in the plant material may be destroyed by pyrolysis and an additional variable amount may be lost in side stream smoke.[11]

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) after absorption from the lung.[11] Although smoking cannabis avoids the significant first-pass metabolism associated with orally administered Δ^9-THC, plasma-protein binding and rapid distribution to tissues contribute to rapidly falling plasma levels of Δ^9-THC following cannabis smoking, even as pharmacological effects (including centrally mediated subjective effects) continue.[11, 13, 16] In experienced cannabis smokers, cannabis-induced subjective effects (e.g., "good drug effect," "high," "stoned") have been found to be stronger during the distribution and elimination phases than during absorption.[17] 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).[11, 18] 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.[11]

Metabolism of Δ^9-THC contained in cannabis smoke occurs primarily in the liver and is extensive, with almost 100 metabolites having been identified.[11] 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.[19, 20] This major metabolite is psychoactive, as indicated by its cannabimimetic effects in mice,[21] its substitution for Δ^9-THC in rat drug discrimination,[22] and its similar psychological effects in men.[18, 23] Data from early studies suggested that 11-OH-Δ^9-THC may have greater brain penetrance than Δ^9-THC.[11] However, unlike with orally administered Δ^9-THC, cannabis smoking results in low brain levels of 11-OH-Δ^9-THC (vs Δ^9-THC).[13] 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 8α-OH-THC and 8β-OH-THC in rodents[19] and 8α-OH-THC in human hepatic microsomes.[24] I.v. administration of the epimers to a small sample of men revealed that both epimers were active, but potency of the 8α-epimer exceeded that of the 8β-epimer.[25] The primary CYP isoenzymes that catalyze the hydroxylation reactions are CYP2C9 and CYP3A4.[24, 26] 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.[27] THC-COOH lacks cannabimimetic effects and is further metabolized to its glucuronide conjugate, which is water soluble and excreted in urine.[13, 26] 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%).[11]

1.2.2 *Cannabidiol*

The pharmacokinetics of cannabidiol (CBD) and other minor phytocannabinoids contained in the cannabis plant, including cannabinol (CBN), cannabigerol (CBG), and tetrahydrocannabivarin (THCV), following smoked cannabis resemble that observed with Δ^9-THC.[11] Absorption of smoked CBD is rapid, with bioavailability averaging about 31%. As seen with Δ^9-THC, primary metabolism occurs via oxidation at C9 and at the side chain.[13] However, unlike with Δ^9-THC, a high percentage of CBD is eliminated unchanged in the feces.[11, 13]

Animal work has suggested that CBD may hinder or delay Δ^9-THC metabolism through competition for or inactivation of CYP P450 enzymes,[28, 29] resulting in enhancement of Δ^9-THC's in vivo effects.[30] However, this research generally used higher concentrations of CBD (in relation to Δ^9-THC concentration) than are typically present in most cannabis strains. In contrast, lower CBD concentrations failed to accentuate Δ^9-THC's effects in rodents.[30] 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.[11, 31-33]

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.[1-3, 34] However, except for Δ^9-THC, most of these other compounds are present in the plant in relatively small quantities. The degree to which they may contribute to the array of pharmacological and behavioral effects produced by cannabis is largely

unknown. Hence, the discussion below focuses primarily on the pharmacodynamics of Δ^9-THC followed by a summary of the possible contribution of other constituents to cannabis' effects.

1.3.1 Δ^9-Tetrahydrocannabinol

When administered to animals, Δ^9-THC produces 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).[35-37] These cannabimimetic effects are produced through interaction with an endogenous cannabinoid system that serves to maintain physiological homeostasis as one of its primary functions.[38] Within this endocannabinoid system, two cannabinoid receptors, CB_1 and CB_2, have been identified.[39, 40] While CB_1 receptors are widespread and abundant in the brain and periphery, CB_2 receptors are confined primarily to the periphery,[41] although recent evidence suggests that CB_2 receptors may be present in the brain under certain conditions.[42] 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).[43] Further, the affinities of cannabis smoke and pure Δ^9-THC for the CB_1 receptor are similar for cannabis containing an equivalent amount of Δ^9-THC,[44] emphasizing the degree to which Δ^9-THC is predominant in the pharmacology of smoked cannabis. 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.[45] Similarly, the reinforcing effects of THC in squirrel monkeys were reversed by rimonabant,[46] as were its antinociceptive, hypothermic and cataleptic effects in rodents[47] and its induction of static ataxia in dogs.[37] 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.[22] Consistent with these in vivo results, Δ^9-THC does not have significant affinity for non-cannabinoid receptors of these major systems.[48] In humans, rimonabant attenuated the acute psychological and physiological effects of a smoked marijuana cigarette containing 2.64-2.78% Δ^9-THC,[49, 50] 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.[51-54] 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.[55] 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.[52] In contrast, withdrawal from Δ^9-THC after chronic administration is associated with decreased activation of dopamine neurons.[56, 57]

1.3.2 Cannabidiol and Other Minor Cannabinoids

In addition to cannabidiol (CBD), minor phytocannabinoids in cannabis include cannabinol (CBN), cannabigerol (CBG), tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), and cannabichromene (CBC).[34] Some of these phytocannabinoids bind to the CB_1 receptor with high affinity: CBN (K_i=13 nM) and THCA (K_i=23.5 nM); others had low or negligible affinity: CBG (K_i=897 nM) and CBDV (K_i=14,711 nM).[58] These minor phytocannabinoids may affect the pharmacology of cannabis via two basic mechanisms: (1) the pure constituent may have pharmacological effects and/or (2) the constituent may interact with Δ^9-THC and alter its effects (e.g., "entourage" effect).[2, 59] While research has examined the pharmacological effects of some of these phytocannabinoids (especially CBD), much of this research has focused on potential therapeutic effects and has utilized doses of a single constituent that would far exceed its concentration in a cannabis cigarette.[2, 60-64] Hence, with exception of CBD (discussed in the extracts pre-review),[65] this research with single constituents does not provide clear information about the pharmacodynamics of cannabis as it is used in humans. Similarly, research that has used smoked cannabis (which presumably contains all naturally occurring chemicals in the plant) has not offered clear support for the "entourage" hypothesis, with a possible exception of pharmacokinetic interaction between CBD and Δ^9-THC.

2. Dependence Potential

2.1.1 Animal Studies

Three labs have investigated the dependence potential of smoked cannabis in animals. In mice, daily ~5-min exposure to cannabis smoke (3.46% Δ^9-THC; 0.05-0.18% CBD, CBN, CBG, and THCV) for 5 days resulted in rimonabant-precipitated withdrawal characterized by an increase in paw tremors.[66] Estimated ED_{50} for Δ^9-THC in the smoked cannabis was 3.6 mg/kg whereas the ED_{50} for i.v. Δ^9-THC was 4.1 mg/kg. Administration of i.v. Δ^9-THC reversed withdrawal-induced paw tremors; however, smoked cannabis did not. Serum Δ^9-THC levels after exposure to the smoke of cannabis containing 100 or 200 mg of Δ^9-THC was comparable to those obtained with 3 mg/kg Δ^9-THC i.v., but concentrations of Δ^9-THC in the brain with smoked cannabis bore greater similarity to those obtained with 1 mg/kg Δ^9-THC i.v. Whereas serum Δ^9-THC concentrations dropped more rapidly after i.v. administration than after smoking, brain concentrations decreased in parallel.

In rats, daily 1-hour exposure to cannabis smoke (5.7% Δ^9-THC) five times a week for eight weeks also induced dependence.[67] As with mice, rimonabant administration precipitated withdrawal, which was characterized by large increases in grooming and eye blinks as well as smaller increases in ptosis, wet dog shakes, and forepaw flutters. While these results showed that rimonabant-precipitated withdrawal occurred after daily exposure to Δ^9-THC-containing cannabis smoke in rodents, the potential for a similar regimen of smoke exposure to induce spontaneous withdrawal after abrupt cessation was not examined in these rodent studies.

In rhesus monkeys, examination of the dependence potential of smoked cannabis (2.6% Δ^9-THC) occurred prior to rimonabant availability; hence, only spontaneous withdrawal could be evaluated. Two exposure regimens were used, with some monkeys receiving exposure to the smoke of one cannabis cigarette per day seven days a week while others were exposed to the same Δ^9-THC amount for two days per week. In each case, exposure was continued for one year. Evaluation during the active exposure phase of the study revealed increases in progressive ratio responding for food reinforcement in control monkeys, which were not observed in cannabis-exposed monkeys.[68] This response suppression lasted for 2-3 months after termination of cannabis exposure before recovery to control levels. Abrupt cessation of smoke exposure was associated with disruption of responding in progressive ratio and conditioned position responding in both control and cannabis-exposed groups, suggesting that it was related to the interruption of daily routine rather than to withdrawal from cannabis *per se*.[68] Seven months after the last exposure to cannabis

smoke, a subset of monkeys was sacrificed and the caudate and hypothalamus of each monkey was removed for analysis. Results revealed no long-term changes in either monoamine concentrations[69] or CB_1 receptor densities.[70] Although this multi-dimensional study does not offer support for the hypothesis that smoked cannabis has the potential to produce dependence in monkeys, the percentage of Δ^9-THC contained in the cannabis used in the study (2.6%) was several-fold lower than the concentrations of Δ^9-THC in cannabis that is now available (e.g., ~12% Δ^9-THC in samples seized in 2014 in the United States).[5]

2.1.2 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. In recognition of this evidence, the fifth edition of the *Diagnostic and Statistical Manual*, used for diagnosis of mental illness and substance abuse disorders in the U.S., outlines criteria for the syndrome and includes a specific diagnostic code for "Cannabis Use Disorder."[71] The International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) also recognizes cannabis dependence, but does not list specific withdrawal criteria.[72] The body of evidence supporting these classifications encompasses laboratory studies in inpatients, ecological momentary assessment and self-report investigations in outpatients, and structured online surveys.[73-81]

Estimated percentage of regular cannabis users who have experienced at least one episode of cannabis withdrawal during abstinence (e.g., when trying to quit) range from 16 to 33%, dependent upon the sample used for study.[73, 82] Because worldwide use of cannabis is more extensive than any other illicit substance, with estimates ranging from 2.7 to 4.9%,[83] the absolute number of people across the globe who have experienced cannabis withdrawal is quite large. However, rates of dependence are not equal in all countries. Rather, they exhibit geographical diversity, which is related to economic and cultural factors as well as to variability in the availability of specific types of cannabis.[77, 84] For example, a vast array of cannabis products with various Δ^9-THC concentrations can be purchased in Colorado, the first U.S. state to legalize non-medicinal use of cannabis. In contrast, availability in Uruguay is restricted to five strains.[84] Rank order prevalence of cannabis dependence is highest in Australasia > North America > Western Europe > Central Asia and least in Southern Latin America.[77]

The availability of high potency cannabis is associated with increased prevalence of cannabis dependence,[77] with cannabis potency being assessed in terms of Δ^9-THC concentration. Chemotypes of cannabis include high potency plants that are usually cultivated indoors under carefully controlled conditions (> 15% Δ^9-THC); low potency plants that often are grown outdoors (~ 9% Δ^9-THC); and compressed blocks of plant

matter (~ 5% Δ^9-THC plus CBD).[84] While considerable variability in Δ^9-THC concentrations has been observed across chemotypes, this classification scheme is helpful because it emphasizes the role that Δ^9-THC plays in the development of dependence. Interestingly, chronic smoking of cannabis over a period of years has been associated with CB_1 receptor downregulation in humans,[85] an effect that also occurs in rodents who have been administered repeated doses of Δ^9-THC or other cannabinoid agonist.[86]

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.[73-75, 78, 82] 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,[76] although disruption of sleep may linger.[81] Partial recovery of CB_1 receptor functioning occurs over a similar period of time, suggesting that cannabis dependence is related to Δ^9-THC-induced changes in the endocannabinoid system.[87] Withdrawal symptoms are alleviated by re-administration of oral Δ^9-THC[88] and increased self-reported severity of symptoms is associated with return to cannabis smoking (i.e., self-medication).[89] While dependence may develop with regular use of cannabis of low potency,[78] regular use of high potency cannabis is associated with enhanced severity of withdrawal symptoms as well as with increased risk memory impairment and paranoia.[84] Nevertheless, users report that high potency cannabis provides the “best high” and is most preferred.[84]

3. Abuse Potential

3.1.1 Animal Studies

Because of the technical challenges which accompany exposure of animals to smoke from combustion of cannabis or its resin, only a few behavioral pharmacologists have pursued investigation of the abuse potential of cannabis in animals. Rather, most have used systemic injection of Δ^9-THC as a proxy for cannabis. However, this approach ignores at least two factors that may be relevant to the translational implications of this preclinical research for the abuse potential of cannabis: (1) in humans, cannabis or its resin is typically self-administered via smoking rather than by injection and differences across route of administration could conceivably affect abuse potential; and (2) in addition to Δ^9-THC, cannabis contains numerous other cannabinoid and non-cannabinoid chemicals that may alter or add to Δ^9-THC's behavioral effects.[1]

A handful of studies have attempted to overcome these challenges through using inhalation exposure to combusted cannabis with defined amounts of Δ^9-THC and other cannabinoids, such as CBD, CBN, CBG, and THCV. Whereas an older study demonstrated that exposure to smoke from combustion of cannabis containing 2.1% Δ^9-THC (and 0.2% CBN and CBD) produced immediate and short-acting (~ 3 minutes) hyperactivity followed by longer duration (> 1 hour) hypoactivity,[90] more recent studies have used cannabis with higher (5.19-5.7%) concentrations of Δ^9-THC, but with similarly low concentrations of other cannabinoid constituents. In rats, acute exposure to Δ^9-THC-containing cannabis smoke increased locomotor activity followed by decreases at later time points.[67] Decreased rearing also was observed, an effect that was reversible by the CB_1 receptor antagonist rimonabant. In mice, nose-only inhalation of smoke from cannabis with these higher Δ^9-THC concentrations produced characteristic cannabinoid effects of antinociception, catalepsy, and hypothermia that were similar in magnitude to those induced by i.v. Δ^9-THC.[30, 91, 92] Locomotor suppression effects were also observed; however, these effects were obscured by comparable effects seen in mice exposed to placebo smoke. All observed effects in the tetrad battery (regardless of route of Δ^9-THC administration) were attenuated by pre-injection with rimonabant, suggesting that they were CB_1 receptor-mediated. Further, potencies for i.v. Δ^9-THC were similar to those obtained with smoked cannabis containing comparable quantities of Δ^9-THC. Based on the accumulated data, the authors concluded that the characteristic behavioral effects of Δ^9-THC in the tetrad battery in mice were not altered by the low concentrations of CBD and other cannabinoids normally present in cannabis;[30, 92] i.e., Δ^9-THC alone was responsible for these effects. In contrast, when a higher concentration of CBD (30 mg/kg) was administered i.v., Δ^9-THC concentrations in the brain and serum were increased and

its antinociceptive effects were enhanced.[30] These results are consistent with previous data showing that higher concentrations of CBD inhibit Δ^9-THC metabolism via cytochrome P450 mechanisms.[28] Further, these increases in Δ^9-THC concentrations in brain and serum were not observed after exposure to Δ^9-THC-containing cannabis smoke,[30] a route of administration that would avoid first-pass metabolism.

3.1.2 Human Studies

Although development of robust i.v. Δ^9-THC self-administration in animal models has been relatively elusive until recently, cannabis is readily self-administered by humans despite possible negative legal consequences.[93] In the 2015 World Drug Report, estimates of global prevalence of cannabis use ranged from 2.7 to 4.9% and the trend was towards increases.[83] The reinforcing effects of smoked cannabis also have been demonstrated in a number of laboratory-based self-administration procedures. Smoked cannabis is readily self-administered by experienced users.[94] In these studies, participants chose to smoke cannabis cigarettes (Δ^9-THC content ranging from 1.8 to 5.8%) rather than placebo cigarettes in choice procedures [95-97] and preferred higher doses over lower doses within this range.[98, 99] When given the opportunity, most subjects were willing to work to smoke cannabis.[98, 100] However, when given a choice between smoking cannabis (1.8 or 3.9% Δ^9-THC) or performing a computer task for money, the degree to which subjects preferred cannabis or money depended upon the amount of work required to earn the money. When the performance criteria for money were high, subjects chose to smoke cannabis, but when the criteria were low, their choice switched to money.[98, 101] These results suggest that preference for cannabis is malleable dependent upon its availability and response cost of alternative reinforcers.

A drug discrimination model has also been employed to examine the subjective effects of smoked cannabis in humans. Chait and colleagues[102] found that study participants readily learned to discriminate cannabis smoke (2.7% Δ^9-THC) from placebo cigarette smoke, with high (~90%) accuracy. Cannabimimetic discriminative stimulus effects were characterized by rapid onset (often after as little as two puffs), were dependent upon Δ^9-THC concentration, and lasted up to120 minutes. Self-reported subjective effects associated with smoked cannabis in laboratory studies include dose-dependent increases in ratings of "drug effect," "high" or "stoned."[96, 100, 103, 104] Similar effects were produced by Δ^9-THC alone when administered orally or when smoked.[100, 103, 105] These results suggest that the cannabis constituent responsible for the plant's reinforcing effects is Δ^9-THC. This hypothesis receives further support from the finding that orally administered doses of CBD (200-800 mg) did not alter self-administration of smoked cannabis or associated increases in ratings of "high" or "stoned."[96] Similarly, the effects of smoked cannabis on subjective, physiological, and performance measures varied with the concentration of Δ^9-THC, but not with

concentration of the minor constituents CBD and cannabichromene (CBC).[106] Rimonabant reversal of intoxication induced by cannabis smoking has been reported in one study,[49] but not in another,[50] both conducted in the same laboratory.

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Cannabis and cannabis resin

Section 3: Toxicology

Contents

1. Toxicology

Most of the evidence for possible toxicity associated with cannabis use comes from observational, population-based studies, which are not as rigorous as the placebo-controlled, randomized–controlled trials (RCTs) used to evaluate therapeutic efficacy. The limitations of observational, population-based studies must be kept in mind when evaluating the possible toxicity of cannabis. Such studies are limited by multiple confounders and an inability to produce evidence from which to unequivocally infer causation. In addition, most of the available evidence of adverse effects involves cannabis use within an illegal, recreational context, where the cannabis that is self-administered is of unregulated quality and is administered by smoke inhalation. The increasing use of medicinal cannabis, particularly of regulated cannabis products that are consumed orally, will provide future opportunities to assess whether toxic effects of cannabis are minimized in the context of medicinal use.

1.1 Lethal dose

Cannabis is not associated with acute fatal overdoses. A recent consensus report by the National Academies of Science, Engineering and Medicine (NASEM) concluded that there is insufficient evidence to support or refute associations between cannabis use and increased risk of all-cause mortality and overdose lethality in humans *(1)*. Lethality studies in animals show the doses needed to induce mortality are well beyond what could possibly be consumed by a human *(2)* - see Report 3 for specific data on lethal doses in animals for the main psychoactive constituent of cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC).

1.2 Effects on the cardiovascular system

Cannabis ingestion acutely promotes transient tachycardia and increased supine blood pressure in humans *(1, 3)* (also see Report 3 for the specific effects of purified Δ^9-THC on cardiovascular function). With repeated exposure, tolerance develops to these effects, and, in some instances, repeated cannabis exposure lowers blood pressure and heart rate beneath the baseline *(4)*.

There is an uncertain association between cannabis use and heart attack but any association appears at best to be weak *(1).* A study of 3882 patients with acute myocardial infarction found that six of the patients had used cannabis 1 hour prior to the myocardial infarction event, resulting in a relative risk of 3.2 *(6).* However, a more recent larger scale study of 2 451 933 patients with acute myocardial infarction showed that recreational cannabis use caused only a small, yet significant increase in the risk of myocardial infarction (odds ratio (OR) = 1.03) *(7).* However, cannabis use was associated with a reduced risk of atrial fibrillation in a recent population study (OR = 0.87) *(8).* Smoked cannabis may decrease the

latency to exercise-induced angina in angina pectoris patients, most likely due to carbon monoxide in the smoke decreasing blood oxygenation and increasing cardiac ischaemia *(5).* There have been case reports of exercise-induced myocardial infarction occurring in healthy young cannabis users, however smoking and tobacco use preclude strong conclusions being drawn on the relationship between cannabis and myocardial infarction *(1, 2)*. A single cannabis-*associated* fatality which was attributed to a cannabis-induced coronary event was reported in a study that examined 2198 emergency hospital admissions across 14 European countries over a 6 month period *(3)*. While the terminal metabolite of Δ^9-THC was detected in the urine indicating prior cannabis use, the individual also had a history of regular alcohol and tobacco use and had been recently diagnosed with epilepsy and had refused anticonvulsant treatment. Rare case reports of fatalities likely due to coronary events have been reported that were associated with acute ingestion of cannabis, however in these instances the individuals were also found to have polymorphisms in genes associated with lethal channelopathies (e.g. *KCNH2* and *SCN5A*) *(4)*.

There is some limited population evidence to suggest that smoking cannabis increases the risk of ischaemic stroke, although it is hard to disentangle the contribution of tobacco smoking in this association *(1, 9).* When novel drug delivery modes other than smoking become more widely available (e.g. vaporization, sublingual or oral administration), associations between cannabis use and cardiovascular events may become less pronounced, or even absent. It is noteworthy that cannabis vapour contains less carbon monoxide than cannabis smoke. It has been reported that there was almost no carbon monoxide in cannabis vapour, whereas there was close to 5 ppm of carbon monoxide in cannabis smoke *(10).*

1.3 Effects on the respiratory system

Smoking has traditionally been the predominant route of cannabis administration as it enables efficient cannabinoid uptake by the lungs and rapid distribution to the CNS. Regular cannabis users may experience higher rates of chronic bronchitis (cough, increased sputum production, wheezy airways). This is due to the irritant effects of smoking on the airways, rather than cannabinoids per se damaging the airways *(1, 9).* Cannabis smoking acutely improves airway dynamics and forced expiratory capacity due to the bronchodilatory effects of Δ^9-THC (also see Report 3 for the specific effects of purified Δ^9-THC on respiratory function) *(11)*. The largest study to date on cannabis and respiratory function followed 5000 people over 20 years and reported a dose–response relationship: those using low levels of cannabis (3–5 joints per month) had improved respiratory function, whereas respiratory function in heavy users was impaired *(12).* Increasing use of vaporizers and other non-smoking modes of delivery is likely to reduce respiratory complications associated with cannabis as suggested by a recent study *(13).*

1.4 Effects on the immune system

There is a wealth of data from studies on cells and animals supporting the notion that cannabinoids have immunosuppressant and anti-inflammatory effects *(14).* However, there are only limited data from studies in humans, although these studies do support anti-inflammatory effects *(1).* For example, one study of 20 cannabis users showed that they had lower CD4+ T-cell concentrations of interleukin (IL)-17 (a pro-inflammatory cytokine) and an increase in IL-10 (an anti-inflammatory cytokine) relative to controls *(15).* Studies assessing the effects of cannabis in immunocompromised HIV patients have not demonstrated any clinically meaningful adverse effects on immune function and susceptibility to infection, although the data are limited *(1).*

Illicit and unregulated cannabis may sometimes be contaminated with various microbes including *Staphylococcus aureus*, *Escherichia coli* and Aspergillus. Aspergillus is a fungus that can cause pulmonary aspergillosis, which is potentially lethal to immunocompromised patients *(16).* Many cases of aspergillosis have been documented in cannabis users *(16, 17).* In countries such as the Netherlands, where there is a government-regulated cannabis supply, the cannabis flower products are treated (often with gamma irradiation) to remove microbial contamination to a pharmaceutically acceptable level, obviating this issue *(18).*

1.5 Mutagenicity and cancer

A wealth of preclinical literature demonstrates that cannabinoids reduce cancer cell proliferation, inducing apoptosis in these cells, as well as inhibiting cancer cell migration and angiogenesis in numerous cancer cell types *(19).* There is moderately strong epidemiological evidence that cannabis use does not increase the risk of cancers of the lung, head and neck (reviewed in *(1)*). A systematic review of six case–control studies on 2159 lung cancer patients and 2985 controls found a statistically nonsignificant trend towards cannabis smoking (> 1 joint per day) increasing lung cancer risk *(20).* A systematic review and meta-analysis of nine case–control studies comparing 5732 patients with head and neck cancer with 8199 controls found cannabis use did not increase the risk of head and neck cancers (including upper head and neck squamous cell carcinoma, and upper digestive tract, nasopharyngeal and oral cavity cancers) *(21).* Cannabis smoking has been reported to increase the risk of testicular cancer 2.5-fold *(22–24).* Any association between cannabis use and cancer reported in epidemiological studies is confounded by the act of smoking, as pyrolysed plant material typically contains carcinogens. Again, the development of safer cannabis drug delivery technologies may well mitigate cancer risks by avoiding smoke inhalation during delivery.

1.6 Fertility and teratogenesis

There is strong population-based evidence that illicit cannabis smoking during pregnancy reduces the birthweight of offspring *(1).* A recent systematic review and meta-analysis showed that maternal cannabis users gave birth to babies with birthweights on average 109 g lower than non-cannabis-using mothers *(25).* Whether the lower birthweights can be specifically attributed to cannabinoids is unclear. It might be explained by the ingestion of carbon monoxide in cannabis smoke *(1).* Animal studies confirm that maternal exposure to Δ^9-THC reduces birthweights, albeit only at very high doses (see Report 3 on Δ^9-THC). There is limited evidence that cannabis use increases pregnancy complications such as stillbirth, spontaneous abortion and fetal distress (reviewed in *(1)*). One study examining 13 859 cases and 6556 controls found an association between cannabis use (for 1 month prior to pregnancy through to the third trimester) and birth defects. There was a significantly increased risk of: anencephaly (OR = 2.2), oesophageal atresia (OR = 1.4), diaphragmatic hernia (OR = 1.4) and gastroschisis (OR = 1.2) *(26).* At present, there is insufficient evidence to determine whether exposure to cannabis in utero is associated with impaired cognitive development or propensity to substance abuse, although some preclinical research with Δ^9-THC suggests this *(1).*

1.7 Effects on cognitive function

Acute cannabis use impairs certain types of cognitive function and can interfere with attention, learning and memory (reviewed in *(1)*). A modest proportion of people who start using cannabis in adolescence and consume the drug for decades, show reductions in IQ (as much as an 8-point reduction in those who started as early as 13 years and had used it to the age of 38 years) *(29).* However, those who had commenced cannabis use in early adulthood and had been abstinent for a year did not display any reduction in IQ, suggesting a lack of residual effects.

A recent systematic review and meta-analysis of 69 cross-sectional studies with 2152 cannabis users and 6575 controls found only a small effect size for reduced cognitive functioning in frequent or heavy cannabis users *(30).* Given the small effect size, the study's authors questioned the clinical significance of such cognitive impairments for the majority of cannabis users. No relationship could be found between the age of onset of cannabis use and cognitive function. Furthermore, no association between cannabis use and reduced cognitive function could be found in studies with a greater than 72-hour abstinence period, suggesting that the effects of cannabis use on cognition were reversible. Reductions in the odds of completing high school have been associated with adolescent cannabis use, but the evidence is

contentious due to numerous confounders (gender, socioeconomic status, education, polydrug abuse) *(1, 31).*

Some studies, involving small numbers of participants, have reported structural abnormalities in brain regions important to cognitive function, mood and reward *(32–34).* However, such effects appear to be absent in larger studies that controlled for confounders such as alcohol use, tobacco use, gender, age and other variables *(35, 36).*

1.8 Mental health

A frequently cited adverse effect of cannabis use is increased risk of psychosis, where the user experiences disordered thinking, hallucinations and delusions. There are frequent reports of acute cannabis intoxication precipitating a short-lasting psychotic state that reverses once the effects of the drug have abated *(37).* Human population studies have linked cannabis use to schizophrenia, which is characterized by hallucinations, delusions and cognitive dysfunction, with cannabis increasing the risk of developing the disorder by around 2-fold *(1, 37).* The relationship between cannabis use and risk of schizophrenia appears to be dose-dependent: heavier cannabis use increases the risk of developing schizophrenia *(1).* There is also some evidence that cannabis use during adolescence may bring forward the age of schizophrenia onset *(38).* It has been argued that reducing the incidence of cannabis-induced schizophrenia would be difficult, because it has been estimated that 4700 young people would need to be dissuaded from cannabis use to prevent a single case of schizophrenia *(42).*

The argument that cannabis causes schizophrenia is contentious, however, as some have observed that sharp increases in global cannabis use in recent decades have not increased the incidence of schizophrenia *(39).* However, other studies have linked increased prevalence of cannabis use in specific localities with increased incidence of schizophrenia *(40, 41).*

Importantly, most of the evidence that cannabis causes schizophrenia comes from studies of people using during adolescence, and adolescence is the period of highest risk for developing schizophrenia. The rates of cannabis-induced psychosis may be lower in patients who commence cannabis use in adulthood. The vast majority of people who use cannabis will never develop a psychotic disorder, and those who do are likely to have some genetic vulnerability to cannabis-induced psychosis *(43).*

The NASEM report on cannabis noted moderate evidence that cannabis use increases manic symptoms in bipolar disorder patients; the risk of developing depression (albeit a small increased risk); suicidal

ideation, suicide attempts and completions in heavy users; and, the development of social anxiety disorders *(1).*

1.9 Driving under the influence of drugs

There is an array of evidence to support the idea that people driving under the influence of cannabis are more likely to be involved in a car accident (reviewed in *(1)*), although the level of risk is generally not as great as with alcohol *(31)*. A relatively recent culpability study conducted in France reported that drivers under the influence of alcohol or cannabis were respectively 17.8 and 1.65 times more likely to be responsible for a fatal accident *(5)*. A large systematic review that incorporated results for 239 739 participants from 21 case–control and culpability studies in 13 countries, showed that cannabis use caused a low-to-moderate (20–30%) increase of being in an accident *(1, 44).* The relatively low risk may be due to cannabis users overestimating their level of impairment and recruiting strategies to compensate for the effects of cannabis on their driving performance *(45).* By contrast, alcohol-intoxicated individuals underestimate their level of impairment. Laboratory studies show that cannabis acutely impairs certain types of cognitive function and psychomotor skills and can diminish driving performance under certain conditions *(46, 47).* These cognitive and performance deficits are less apparent in experienced cannabis users due to tolerance, and may even be absent *(48).* Some studies suggest that drivers under the influence of cannabis drive more slowly, make fewer attempts to overtake, and leave greater distances between themselves and the vehicle in front *(49).* However, other studies have shown that cannabis use impairs reaction time, lane control, speedometer monitoring, hand and body steadiness and braking time as well as promoting inappropriate responses in an emergency scenario *(50–53).*

Population studies suggest that the combined use of alcohol and cannabis additively or synergistically accentuates the risk of being involved in a motor vehicle accident *(6-8)*. This is supported by driving simulator studies administering cannabis and alcohol under controlled conditions, although there is some complexity to the interaction which is dependent on the driving skill being examined. For example, when examining lateral control of driving, the combination of cannabis and alcohol exposure additively increased standard deviation of lateral position (SDLP) *(9)*. However, when evaluating longitudinal control, cannabis appeared to mitigate the ability of alcohol to increase driving speeds *(10)*.

Passive inhalation of second-hand cannabis smoke has been shown under experimental conditions to lead to measurable concentrations of Δ^9-THC and its metabolites in the blood, raising the possibility of individuals testing positive at the road-side despite not actively ingesting cannabis *(11-13)*. Under extreme experimental conditions of exposure (e.g. being confined in a small unventilated chamber or van for 1

hour with numerous people smoking cannabis), passive inhalation of cannabis smoke had mild subjective effects, slightly increased heart rate and caused minor impairments in psychomotor function and working memory *(14)*. Although, these conditions were so extreme that participants who did not wear goggles experienced irritation to their eyes and mucous membranes. The blood Δ^9-THC concentrations following extreme passive exposure were much lower than that observed following active cannabis smoking. Under normal conditions of everyday life, second-hand smoke exposure doesn't lead to significant blood cannabinoid concentrations, and the terminal metabolite of Δ^9-THC, 11-nor-Δ^9-THC-carboxylic acid (THC-COOH), is usually below the detectable level in urine *(11)*.

2. Adverse reactions in humans

Cannabis consumption causes euphoria, laughter and talkativeness. It is an appetite stimulant, and may promote dry mouth and dizziness as well as increasing visual, olfactory and auditory perceptions *(1, 54, 55).* Conjunctival reddening occurs, due to vasodilation of blood vessels in the eyes. Time perception may be altered and some users may experience anxiety and panic reactions *(56)*. Cannabis intoxication can impair attention and short-term memory function *(57).* In inexperienced users, cannabis ingestion can promote a mild tachycardia and postural hypotension that can be associated with dizziness and syncope *(15)*. The pharmacological effects of cannabis are subject to tolerance following repeated exposure and therefore many of the marked reactions observed in naive users are diminished in frequent users.

Cannabis exposure can precipitate acute psychotic reactions in vulnerable individuals such as those with a history of psychosis or those with a family history of schizophrenia *(58).* These reactions are relatively rare, for example, only 7 cases of psychosis associated with cannabis use alone were found in a study that examined emergency hospital admissions across 14 European countries over a 6 month period *(3)*. There are case reports of cannabis-induced psychotic reactions in healthy individuals and the effects appear partly dependent on the dose of Δ^9-THC found in the cannabis *(16)*. One recent case report provided a very detailed description of an adult male, with no reported family history of mental disorder, who had a psychotic reaction following the administration of vaporised cannabis containing 25 mg of Δ^9-THC *(16)*. This case report is unique in that the researchers were present to directly document the case, as the individual was one of 31 people participating in a cannabis psychopharmacology study. The individual experienced hallucinations that were high in magnitude on hallucination ratings scales, but the experience was qualitatively distinct to the profile observed with other hallucinatory drugs such as psilocybin dextromethorphan, and salvinorin A. The participant was heavily sedated and was in a dissociative state characterized by an out-of-body experience. He exhibited cognitive impairment with altered auditory and visual perceptions. He was sometimes unresponsive to experimenter enquiries and reported feeling faint,

dizzy, nauseous, with paresthesias in his arms and legs. The state resolved completely within 5 hours. The author concluded that the effects observed with cannabis in the case study were of a less severe character than with synthetic cannabinoid poisonings.

There also exist case reports of cannabis promoting severe nausea and vomiting in some users, which is known as the cannabinoid hyperemesis syndrome *(17, 18)*. While rare, cannabinoid hyperemesis syndrome is characterised by episodes of severe nausea and vomiting in long-term cannabis users, and compulsive bathing behaviour. In most instances the syndrome resolves upon cessation of cannabis use. It is possible this syndrome might be misdiagnosed, as another syndrome exists called cyclic vomiting syndrome which is very similar and is also associated with bathing behaviour.

Young children may be particularly vulnerable to the effects of cannabis. There are several recent case reports of young children accidentally ingesting cannabis and experiencing respiratory depression, tachycardia and temporary coma *(1, 59–61).* This increasing risk of overdose and related adverse effects in paediatric populations may be greater in US states that have legalized cannabis use *(1).*

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Section 4: Therapeutic use

Contents

1. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

1.1 Extent of therapeutic use and epidemiology of medical use

It is estimated that between 3% and 5% of the world's population has tried cannabis for nonmedical reasons *(1)*. Among users of medicinal cannabis, an international survey of 953 participants from 31 countries found that most were current users under the care of a health professional and had been using cannabis-based medications for several years. Most had experience with herbal products (administered by smoking) before the onset of their medical conditions, or after onset but prior to a physician's recommendation for cannabis therapy. The survey found that the five medical conditions for which cannabinoids were most often used as treatment were back pain, sleep disorders, depression, post-injury pain and multiple sclerosis *(2).*

A literature review on cannabis use recommended by physicians reported a prevalence ranging from < 1.7% among Israeli cancer patients to 17.4% in the USA for a range of conditions, pain being the most common. Among those who reported self-medicating, a range from 15% in Canadian patients with chronic pain to 30% in British patients with multiple sclerosis was noted. Pain, sleep disturbances and anxiety were the most common reasons given for cannabis use *(3).* Two studies have noted that there are no significant demographic differences between adults who use medicinal cannabis and those who use cannabis recreationally, although in an adjusted analysis one study found that medicinal cannabis users had higher daily cannabis use, were more likely to be in poorer health, and had lower levels of both alcohol use disorders and non-cannabis drug use *(4).*

As of April 2018, 29 states in the USA as well as the District of Columbia (DC), and the territories of Guam and Puerto Rico had laws on medicinal cannabis in place, although cannabis for any use remains illegal at the federal level. These states and territories stipulate, in aggregate, more than 50 different conditions for which a physician may certify or approve a patient for medicinal cannabis use. There are an estimated 2 254 782 patients using medical cannabis in the USA. In a review of data based on 96 100 adults aged 18 years and older who participated in the 2013–2014 US National Survey on Drug Use and Health, 0.8% (95% confidence interval (CI), 0.7–

0.9%) of this population used cannabis for medical purposes only. Of medicinal cannabis users, 78.8% (95% CI, 75.7–81.9%) lived in states where medicinal cannabis was legal *(5).* In the USA, approximately one in eight users of cannabis consider their use to be treatment for a medical issue *(1).*

Canada has had medicinal cannabis laws in place since 2001 and from April to July 2017, there were 201 398 registered medical cannabis clients in Canada *(6).* The Netherlands legalized medicinal cannabis in 2003. From 2011 to 2016, 95 022 prescriptions were dispensed there *(7).*

Israel legalized medicinal cannabis in the early 1990s. Up to October 2017, more than 32 000 patients had been authorized to use the product *(8).* Australia has had medicinal cannabis laws in place since 2013, Argentina since 2017, Austria since 2008, Chile and Colombia since 2015, the Czech Republic since 2012, Denmark since 2011, Germany and Portugal since 2017, Italy and Uruguay since 2013and Jamaica, since 2015.

Barriers to medicinal use in the USA include the reticence of physicians to recommend it. Reasons for this include: the lack of high-quality scientific data, physicians' concerns about physical and mental health risks of cannabis, the Schedule I Drug Enforcement Agency status of cannabis, its lack of approval by the Food and Drug Administration, and physicians' fear of losing their medical licences. Other barriers to use are that health care institutions direct their physicians not to certify patients due to legal status or other reasons, and the lack of insurance coverage for the drug *(9).* Barriers to research in the USA include the difficulty of navigating through several federal agencies as well as research ethics boards and local and state oversight concerns. There are also issues related to quality, quantity, and kind of product available from the current single federal source of cannabis for research use and the lack of adequate funding sources.

The European Medicines Agency has stated that the use of cannabis as a medicine must follow the laws of each Member State. European countries control cannabis under the United Nations drug control conventions, which do permit, to a certain extent, the use of drugs for medical and scientific purposes. The laws of the European Union Member States are not harmonized regarding medicinal cannabis use.

There are also challenges in research design *(10).* Controlling for the placebo effect is difficult due to the characteristic odour and taste of cannabis; this issue can sometimes be managed by using routes of administration such as injections or coated capsules. The differing effects of cannabis due to varied absorption processes have to be considered *(11).* Study participants' expectations, however, cannot be overcome as easily. In addition, ensuring that study participants do not use cannabis obtained outside the study (whether licitly or illicitly, and regardless of cohort (test or control group) assignment) is not always possible.

1.2 Effectiveness of therapeutic use

(See Table 4.1)

1.2.1 Appetite stimulation in HIV/AIDS infection

In a randomized, double-blind, placebo-controlled trial of 67 participants with HIV infection, both dronabinol and smoked cannabis led to significantly greater weight gain than administration of a placebo. This safety study also showed that both dronabinol and smoked cannabis were safe in this population and did not adversely affect viral load in comparison to placebo *(12).*

1.2.2 Autism

There have been no randomized, double-blind, placebo-controlled trials of cannabis or cannabinoids as pharmacotherapy for autism.

1.2.3 Chronic pain

Results from investigations evaluating cannabis pharmacotherapy for pain demonstrate the complex effects of cannabis-related analgesia. Many randomized, controlled clinical trials have shown cannabis to be an effective analgesic *(13).* Most of these studies, however, focused on testing the effects of plant-derived cannabinoids. In the meta-analysis by Whiting et al. (2015), for example, only 5 of the 28 trials assessed the effects of vaporized or smoked cannabis plant flower *(14).*

No randomized, placebo-controlled trials of cannabis for treatment of chronic pain have been published. One recent study, not included in the meta-analysis by Whiting et al., was a placebo-controlled trial of inhaled aerosolized cannabis, which demonstrated a dose-dependent

reduction in diabetic peripheral neuropathy spontaneous pain ratings among patients with treatment-refractory pain *(see 1.2.6 below).* More recently, Wilsey et al. conducted a randomized, placebo-controlled crossover trial of vaporized cannabis among 42 participants with central neuropathic pain related to spinal cord injury and disease *(15).* The results indicated that vaporized cannabis reduced neuropathic pain according to the rating scale, but there was no evidence of a dose-dependent effect. The active doses did not significantly differ from each other in terms of analgesic potency, the lower dose appeared to offer the best risk-benefit ratio in patients with neuropathic pain associated with injury or disease of the spinal cord. These authors concluded that additional research is needed to examine how interactions among cannabinoids may influence analgesic responses.

A large prospective cohort study evaluated the safety of cannabis administered by smoking, oral consumption, or vaporization and found an increase in adverse events in the group who used cannabis compared to the control group of chronic pain patients who did not use cannabis. There was no difference in the occurrence of serious adverse events between the two groups *(16).* A recent retrospective chart review demonstrated that cannabis improved measures of pain and quality of life *(17).*

A retrospective cross-sectional survey of patients with chronic pain showed that cannabis pharmacotherapy was associated with a decrease in self-reported opioid use of 64%. In addition, the number of medication classes used decreased significantly in all respondents after cannabis use (2.38 vs. 1.81, respectively, $p<.001$) as did the side effects of medication on everyday functioning (6.51 vs. 2.79, $p<.001$)(18).

Studies on cannabis treatment of neuropathic pain are covered in 1.2.8, below.

1.2.4 Cocaine Use

There are no randomized, double-blind, placebo-controlled trials of cannabis pharmacotherapy for cocaine use disorder. In a longitudinal analysis of 122 people who use illicit drugs, periods of intentional cannabis use were associated with decreased frequency of crack cocaine use compared to the time period before the intentional cannabis use (Adjusted Odds Ratio=1.89, 95% Confidence Interval: 1.02-3.45) (19).

1.2.5 Crohn disease

In the only randomized, double-blind, placebo-controlled trial of the use of smoked cannabis for patients with Crohn disease, no difference in remission, the primary outcome, was observed between users of cannabis and those given a placebo, and the cannabis smoker group did not show a significant response on the Crohn Disease Activity Index *(20).*

1.2.6 Diabetic neuropathy

A randomized, double-blind, placebo-controlled cross-over study in 16 patients with diabetic peripheral neuropathy who had treatment-refractory pain, assessed the short-term efficacy and tolerability of inhaled cannabis. Inhaled cannabis was found to be associated with a dose-dependent reduction in pain associated with diabetic peripheral neuropathy *(21).*

1.2.7 Epilepsy

Only the cannabinoid, cannabidiol has been studied as a pharmacotherapy for epilepsy.

1.2.8 Neuropathic pain

Three randomized controlled trials have shown smoked cannabis to be an effective treatment for neuropathic pain. Ellis et al. demonstrated that cannabis reduced HIV-associated distal sensory predominant neuropathy when added to concomitant analgesic therapy *(22).* Similarly, two studies showed that smoked cannabis reduced central, peripheral and HIV-associated neuropathic pain when used as the primary pharmacotherapy *(12, 23).*

1.2.9 Migraine and cluster headaches

A preliminary investigation, which was presented at a scientific conference in 2017, found no difference between cannabis and amitriptyline for prophylaxis of cluster or migraine headaches, although the control arm might not represent optimal control therapy. In a subset of participants with a history of childhood migraine, acute administration of cannabis as abortive therapy decreased attack pain from both migraines and cluster headaches *(24).*

1.2.10 Opioid withdrawal

Despite intense interest in the effects of cannabis on opioid use disorder, especially in the USA, there have been no randomized controlled trials of cannabis for this disorder. In one

observational study of patients with opioid use disorder undergoing a methadone taper, smoked cannabis did not lead to a reduction in opioid withdrawal symptoms *(25).*

1.2.11 Parkinson disease

In an open-label, uncontrolled, observational study of smoked or vaporized cannabis for the treatment of pain in 20 patients with Parkinson disease, cannabis significantly decreased motor disability and pain scores *(26).* A second open-label, uncontrolled, observational study of smoked cannabis in 22 participants with Parkinson disease reported significant improvement in total motor disability scores in the cannabis smokers *(27).* A retrospective study of 47 patients with Parkinson disease, a mean duration of 19.1±17.0 months of a mean daily dose of 0.9±.05g of medical cannabis led to improvement (effect size r^2) in falls (0.89), pain relief (0.73), depression (0.64), tremor (0.64), muscle stiffness (0.62), and sleep (0.60) (28).

1.2.12 Post-traumatic stress disorder

Only nabilone has been studied in a trial on patients with post-traumatic stress disorder, and that agent is not included in this pre-review.

1.2.13 Psychosis

Two studies of cannabidiol's effects on psychosis (not included in this pre-review) have been reported, but no other studies of cannabis or other cannabinoids as pharmacotherapy for psychosis are available.

1.2.14 Tourette Syndrome

In a retrospective study of 19 adults with Tourette Syndrome, treatment with cannabis resulted in a 60% decrease in tic scores on the Yale Global Tic Severity Scale (from 30.5±7.2 to 12.2; $p<0.001$) and 18 of 19 participants were "much improved" on the Clinical Global Impressions Improvement scale (29).

Table 4.1: Randomized Controlled Trials of cannabis plant and cannabis

Intervention	Administration method	Dose evaluated	Comparator	Number of studies described in this report	Indication

Cannabis	Smoking, vaporizer	3.95% THC	Placebo	1	Appetite stimulation in people with HIV/AIDS Infection
		1–12.5% THC	Placebo or no cannabis	4	Chronic pain
		230 mg THC	Placebo	1	Crohn disease
		1–7% THC	Placebo	1	Diabetic neuropathy
		1–8% THC	Placebo	3	Neuropathic pain
		10–200 mg THC	Amitriptyline (M), verapamil (C)	1	Migraine and cluster headache
		Unspecified	None – observational	1	Opioid withdrawal
		1g	None – observational	2	Parkinson disease
		2.5–9.4% THC	Placebo	2	Sleep disorder

C: cluster headache; M: migraine headache; THC; delta-9-tetrahydrocannabinol.

2. Listing on the WHO Model List of Essential Medicines

Not listed.

3. Marketing authorizations (as a medicinal product)

Bedrocan cannabis (the Netherlands) produces five standardized plant varieties (whole dried flower) for patient use, which are available on prescription to patients under direct care of a physician. The different varieties are put on the market by the Office of Medicinal Cannabis and also available for patients in Australia, Canada, Czech Republic, Denmark, Germany, Italy, Sweden, Norway, Poland, Finland, Israel and the Netherlands. For research purposes, the Bedrocan varieties are available in Australia, Brazil, Canada, Czech Republic, Denmark, Finland, Germany, Israel, Italy, Macedonia, the Netherlands and Poland. In addition, five Canadian companies produce cannabis, and the following companies export cannabis: Tilray to Australia, Brazil, Chile, Croatia, Germany and New Zealand; Canopy Growth Corporation to Australia, Brazil and Germany; Aurora Cannabis to Germany; Cronos Group to Germany; and Aphria to Australia.

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Appendix 1.

4.1.1 Search methodology for therapeutic use

Published articles on the topic of medical cannabis were identified by searching electronic databases. A PubMed search was made for articles published from 1948 to April 2018, Cochrane Central Register of Controlled Trials up to 2018, and Cochrane Database of Systematic Reviews up to 2018. The search terms used included cannabis, cannabinoids and tetrahydrocannabinol. The limits used were “administration and dosage”, “therapeutic use”, “humans” and “clinical trial”. The PubMed search resulted in 647 references, the Cochrane Central Register of Controlled Trials in 663 and the Cochrane Database of Systematic Reviews search resulted in 13 references. A total of 128 articles were identified for an initial review. There were six systematic reviews selected for initial review. As a result, the main emphasis was on randomized clinical trials.

Cannabis and cannabis resin

Section 5: Epidemiology

Contents

1. Industrial use

In our rapid systematic review, there were no articles that focused on industrial use of cannabis plant and resin. There are two classes of industrial use: pharmaceutical industry and hemp-related industry. These classes which will be discussed in the section on **Licit Production, consumptions, and international trade** below.

2. Non-medical use, abuse, and dependence

In this section, the global and regional distribution of a) non-medical cannabis use and b) cannabis use disorders are presented and, if available, time trends are reported. Non-medical cannabis use (i.e., without a valid prescription) implies various cannabis use motives, the majority of which can be distinguished using the following two major categories:

- Self-medication
- Recreational/leisure use

For both categories, there is a risk of cannabis use disorders, which is a term that has been used differently in different classification systems. In DSM-IV (1), the term "cannabis use disorders" was generally used for the combined categories of "abuse" and "dependence", and in DSM-5 (2) for the unidimensional concept combining both former categories. However, in ICD-10 (3), the term is not defined, although it is sometimes used to combine dependence and harmful use. We will use the term as used in the Global Burden of Disease Study (GBD; http://www.healthdata.org/gbd), as most of our data on cannabis use disorders were taken from this study (See legend of Table 7 for more details).

Thus, non-medical cannabis use as reported in this section involves a heterogeneous group of users with different use motives and also includes those with a cannabis use disorder. On the other hand, cannabis use disorder only involves persons meeting the diagnostic criteria of ICD-10 or DSM-IV or DSM-5 classifications, regardless of their motives. In the latter section, the risk of cannabis use disorder for cannabis users is elaborated on the global as well as on the regional level.

Most of the data reported in this section has been obtained from the United Nations Office of Drugs and Crime system (UNODC http://www.unodc.org/ (4); published in the annual World Drug Report; last available report for the year 2017: https://www.unodc.org/wdr2017/index.html - (5)), by a variety of regional agencies (for example the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA); published in the annual European Drug Reports; report for the last available year: (6)), and by the GBD ((7); last annual report on illicit drug exposure and attributable burden (8)), all of which on routinely collect data on illicit drug use and use disorders. The prevalence figures refer to at least one use occasion/meeting diagnostic criteria within the past 12 months.

2.1 Non-medical cannabis use

2.1.1 Global and regional prevalence of cannabis use

We refer to the World Drug Report 2017 (5) for data on the prevalence of cannabis use. About 192 million adults are estimated to have used cannabis in 2016 (lower estimate: 165 million; upper estimate: 234 million), with about the same absolute number of users in Africa, the Americas and Asia (see Table 1 for details). In terms of prevalence for the 15-64 age group (see (9) for methodology), estimates are highest for West and Central Africa (13.2%) and North America (12.9%), followed by Oceania (11.0%) (for the definition of regions used by UNODC see (10)).

These prevalence data are based on government surveys and other available data, mainly from general population surveys. These data on country prevalence can be found on the website of UNODC (11), which also features data about cannabis use among young people (adolescents) (12). Data on cannabis use seems to be spotty between countries and years. For all of the years, there is data on adult cannabis use for 100 countries. However, for the year 2016, the last year where data was available, data stems from only 17 countries.

A more inclusive data search for a shorter period of time was conducted for the GBD 2010 study (13-16). Overall, the search identified national estimates of prevalence for cannabis use in the general population for 56 countries for the time frame between 1990 and 2008. The overwhelming majority of data was available for the time frame between 2005 and 2007.

In some instances, estimates may have been derived indirectly from treatment statistics using the multiplier method. This method estimates the prevalence by adjusting the number of people receiving cannabis treatment (from health registries) by the proportion of cannabis users who report receiving drug treatment (from surveys).

All methodologies to estimate the prevalence of illicit drugs have weaknesses. For general population surveys, major weaknesses relate to the sampling frame, which in most cases does not include high-risk populations such as institutionalized people, and to the fact that participants may be reluctant to disclose illicit drug use due to its illegality (16); for the multiplier method, the source for the multiplier is key (17). As a consequence, bias cannot be excluded, and the amount of bias will depend on a number of factors not the least on the stigmatization of cannabis in the respective culture (18).

Table 1: 12-month prevalence of cannabis use in the general population aged 15-64 by region (5)

Region or subregion	Cannabis					
	Number (thousands)			Prevalence (percentage)		
	Best estimate	Lower	Upper	Best estimate	Lower	Upper
Africa	**51,930**	**37,110**	**75,930**	**7.6**	**5.5**	**11.2**
East Africa	-	-	-	-	-	-
North Africa	-	-	-	-	-	-
Southern Africa	-	-	-	-	-	-
West and Central Africa	34,260	28,520	42,420	13.2	11.0	16.3
Americas	**52,900**	**51,600**	**55,080**	**8.0**	**7.8**	**8.3**
Caribbean	630	230	1,730	2.2	0.8	6.1
Central America	820	410	1,320	2.8	1.4	4.4
North America	41,510	41,330	41,680	12.9	12.9	13.0
South America	9,940	9,630	10,340	3.5	3.4	3.6
Asia	**56,610**	**47,750**	**71,180**	**1.9**	**1.6**	**2.4**
Central Asia	1,480	440	2,440	2.6	0.8	4.2
East and South-East Asia	9,650	4,460	21,490	0.6	0.3	1.3
Near and Middle East/South-West Asia	-	-	-	-	-	-
South Asia	-	-	-	-	-	-
Europe	**27,860**	**27,180**	**28,610**	**5.1**	**5.0**	**5.2**
Eastern and South-Eastern Europe	5,490	5,120	5,830	2.4	2.3	2.6
Western and Central Europe	22,370	22,060	22,780	7.0	6.9	7.1
Oceania	**2,850**	**2,130**	**3,250**	**11.0**	**8.3**	**12.6**
Australia and New Zealand	2,070	2,070	2,070	11.0	11.0	11.0
Melanesia	-	-	-	-	-	-
Micronesia	60	40	80	16.6	10.7	22.7
Polynesia	-	-	-	-	-	-
GLOBAL ESTIMATE	**192,150**	**165,760**	**234,060**	**3.9**	**3.4**	**4.8**

With respect to gender and cannabis use, women generally had a lower 12-month prevalence of cannabis use, but these gender differences in prevalence seem to get smaller in recent cohorts (19, 20). In a meta-analysis of studies by Chapman and colleagues (20), the gender-ratio decreased from 2:1 (i.e., cannabis use prevalence of men twice as high as of women) in the 1941-1945 cohorts to 1.3:1 in the 1991-1995 cohort. Even seemingly different results such a widening of the absolute gap in the United States do not necessarily

contradict this overall finding: for example, between 2007 and 2014, the gap between men and women became wider (in terms of absolute prevalence difference), but the gender ratio decreased (i.e. ratio of % male to % female; (21)).

Thus, while there are biological differences in cannabis use-related behaviours and the effects of cannabis on the brain and other organs (22), the main determinants of cannabis use seem to be more social. This may be different for cannabis use disorders, as other research has shown that the transition from use to use disorders is more genetically determined than the transition between non-use and use (23, 24).

In a recent INCB report on women and drug use (25), the following additional points were raised:

- While in general, women start using drugs later than men do, once women started, their rate of cannabis use progresses more rapidly compared to men, and they tend to develop a substance use disorder more quickly than men do.

- The genetic disposition for problematic cannabis use impacts women to a greater extent than men. Based on twin studies, for women, 59% of problematic cannabis use could be attributed to shared genes, while 51% was attributed to shared genes among men.

With regard to data availability of cannabis use prevalence, the vast majority of data has been collected in high-income countries (described in detail in the next section). For low- and middle-income countries, there are few recent general population studies assessing the prevalence of cannabis use. For India, the most populous lower-middle income country, household survey data suggest that about 3.0% of males aged 12 to 60 years were cannabis users in 2000-2001 (26). Other data on cannabis use prevalence in low-and middle-income countries in WHO regions have been obtained from the UNODC data base (27, 28). Among adults in the Southeast Asian region, cannabis use prevalence varies between 0.9% (Myanmar, 2005) and 4.2% (Bhutan, 2009). Prevalence data on youths in the same countries show a reverse pattern (Bhutan: 0.1%, 2010; Myanmar: 0.5%, 2004), with relatively high estimates for Bangladeshi (12-months: 3.0%, 2001) and Indian youths (Past-month: 3.0%, 2001). In the WHO Eastern Mediterranean region, data on cannabis use prevalence in the adult population is very scarce and only available for Tunisia (2.6% in 2013) and Egypt (6.2% in 2006) and there is even less data available on youths (Egypt, 12-months: 1.4%, 2013). In low- and middle-income countries in WHO African region, cannabis use prevalence appears to vary largely, with estimates ranging between 1.0% (Togo, 2009) and 14.3% (Nigeria, 2008). Data on cannabis use among youths in the African region mirrors the variations among adults, with comparatively low estimates in Togo (12-months: 1.2%,

2009) and very high estimates in Ghana (12-months: 17.1%, 2007) and Madagascar (12-months: 18.5%, 2004).

2.2 Global and regional trends in cannabis use prevalence

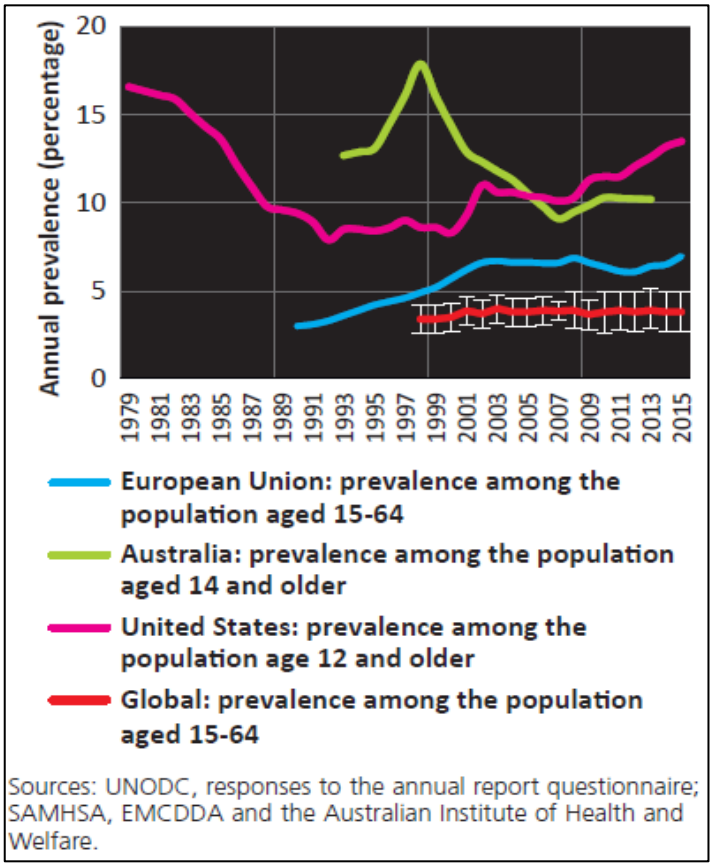


Figure 1: Annual cannabis prevalence: United States, European Union, Australia, Global level (5)

Figure 1 gives the global and selected regional 12-month prevalence of cannabis use for the past decades (not age-adjusted). The global numbers seem pretty stable for the last 15 years, but there is a lot of change in the regional trends. For the US, the 12-month prevalence since 1980 decreased for more than 10 years and began increasing in the late 1990s. In Europe, as defined by the European Union, there had been an upward trend since the late 1990s, with more stability in since 2000. In Australia, trends were downward from the late 1990s to about 2007 and have been stable since. This indicates that regional trends in cannabis use can be quite contrary to global patterns.

Regional time trends of cannabis use have been examined only in a handful of studies. The most comprehensive assessment stems from international school surveys, such as the 'European School Survey

Project on Alcohol and Other Drugs' (ESPAD, see http://www.espad.org/) (29) and the WHO funded 'Health Behaviour in School-aged Children' (HBSC, (30)), as there are no multi-national general population surveys on cannabis use conducted in comparable populations over time. The above-mentioned school surveys provide data for high-income countries in Europe and North America. As cannabis use is largely concentrated among 15 to 30-year-olds, school surveys can indicate relevant trends for the user population.

Figure 2 provides select trends among 15 to 16-year-olds based on the ESPAD surveys, which provides comparable data on student drug use every four years (31). Results show similar trends as for the EU general population: increases between 1995 and 2003 (see Figure 1 above), and an almost flat line since 2007.

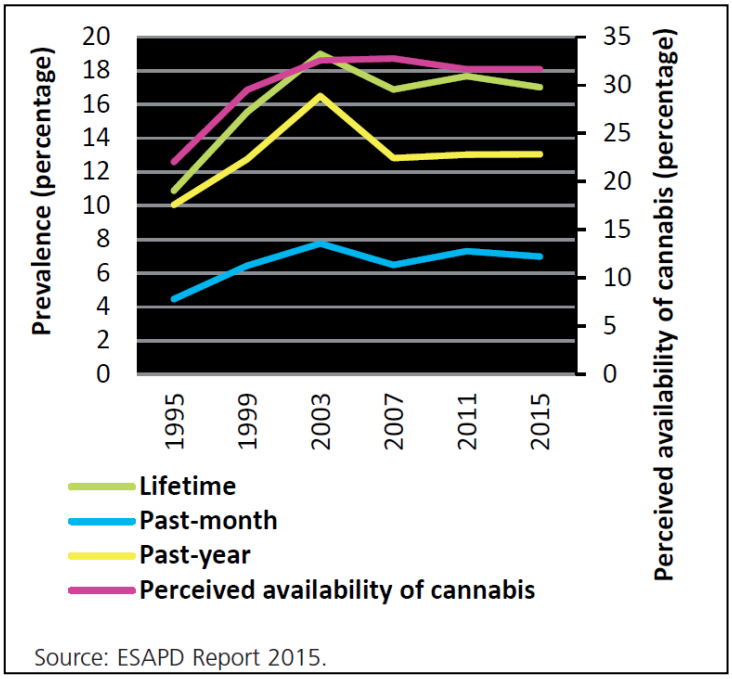


Figure 2: Cannabis prevalence among 15-16 year-olds, Europe (5)

The detailed results (not shown here but in (31)) show parallel temporal developments for boys and girls, with boys having higher prevalence on all indicators for the entire time period. ESPAD also included measures on the perceived availability of cannabis, which follows a similar trend curve as use (for both sexes combined and gender-specific with boys also showing higher perceived availability (31)).

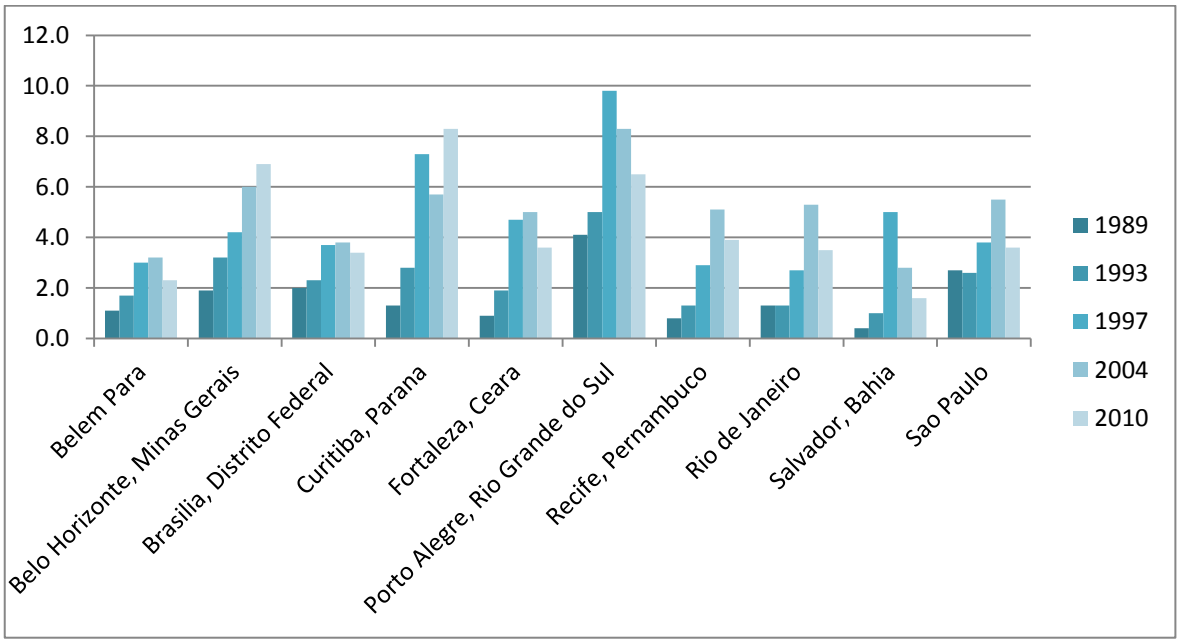
In terms of sub-regions of Europe, ESPAD data on 28 European countries from five waves between 1999 and 2015 were used to assess temporal trends in monthly cannabis use prevalence among adolescents by

sex. The results indicate that cannabis use increased in Southern European countries (boys: 1999 = 7.9%; 2015 = 8.7%; girls: 1999 = 5.0%; 2015 = 5.9%) and on The Balkans (boys: 1999 = 7.7%; 2015 = 10.1%; girls: 1999 = 5.8%; 2015 = 7.4%), whereas decreases were observed among Western European boys (1999 = 21.3%; 2015 = 13.4%;(32)).

According to the HBSC data, a decrease in 12-month adolescent cannabis use between 2002 and 2006 could be observed in most of the 31 European and North American countries (33). Using the same data and including the subsequent wave of 2010, another study examined trends of cannabis-only and co-use with tobacco. For cannabis-only, a smaller number of adolescent users was found in Anglo-Saxon countries (Ireland, UK) and North America (Canada, USA), whereas there was no significant change across all regions. The 12-month prevalence of cannabis co-use with tobacco decreased in all observed regions with different magnitude (strongest in Anglo-Saxon countries from 14.6 to 8.4%).

In Latin America, survey data in major cities from Brazilian students suggest that 12-month prevalence of cannabis use among elementary and high school students from grade 6 and older has been increasing from the late 1980s to 2004, with city specific trends between 2004 and 2010 (see Figure 3; (34)).

Figure 3: Trends in 12-month prevalence (in %) of cannabis use in major Brazilian cities 1989 -2010



For a few countries, repeated general population surveys provide trend data beyond adolescents. In North American high-income countries, the decreasing prevalence of cannabis use among youths could be

reiterated in general population surveys. In the USA, data on youths from the annual 'National Survey on Drug Use and Health' (NSDHU) suggest a decline of 12-month cannabis use prevalence between 15.8% (2002) and 13.1% (2014), which mainly occurred during 2002 to 2007 (35). However, data from the same survey suggest that cannabis use prevalence in the older population (50 years or older) increased between 2006/2007 (2.8%) and 2012/2013 (4.8%; (36)). Looking at NSDHU data for the entire adult population (aged 12 years or older) confirms these trends: Overall, cannabis use increased significantly between 2002 (past-month: 6.2%; 12-month: 11.0%) and 2014 (past-month: 8.4%; 12-month: 13.2%) but not among 12 to 17-year-olds (37). In another general population survey, the rising 12-month prevalence between 2001/2002 (4.1%) and 2012/2013 (9.5%) was corroborated (38).

Similar trends were also seen in Canada between 2004 and 2015, where 12-month cannabis use increased in the population aged 25 to 64, whereas use rates decreased among 15 to 24-year-olds (39).

For Europe, cannabis use over time constitutes a rather heterogeneous picture when considering national or regional data. According to the 2017 EMCDDA Drug Report (40), recent national surveys show upward (7 out of 15), stable (6 out of 15) or downward trends (2 out of 15) since 2014. Looking at data from the last decade on adults aged 15 to 34, 12-month cannabis use decreased in Spain and the UK but increased in France, Denmark, Finland, Ireland, Germany, and Sweden, with some degree of stability in more recent years. In France, the highest 12-month prevalence was recorded with 22% (41), which continues a rising trend of lifetime use prevalence between 1992 and 2000 (42). In Germany, data from eight waves of a general population survey were used to assess trends of cannabis use. For both men and women aged 18 to 59, 12-month cannabis use became more prevalent between 1995 (men: 6.5%, women: 2.3%) and 2015 (men: 8.7%, women: 5.3%; (43)). In Italy, one study compared data from population surveys and wastewater samples collected across the country. Between 2010 (3.0%) and 2012 (1.8%), both data sources point to a reduction of past-month cannabis use, followed by an increase in 2014 (3.7%; (44)).

In Australia, a general population survey conducted in nine waves between 1993 and 2016 indicates stable lifetime use prevalence at around 35%. 12-month use decreased slightly from 12.7% (1993) to 10.4% (2016). While pronounced declines were present in younger age groups (youths aged 14-19: 2001 = 27.7%; 2016 = 15.9%), cannabis use increased in the middle-aged population (persons aged 40-49: 2001 = 11.8%; 2016 = 16.2%; (45)).

2.3 General population studies from the systematic search

There are a number of prevalence studies in the peer-reviewed literature specifically related to cannabis plant and resin use (for search and inclusion/exclusion criteria see Appendices 1 and 2). Interestingly, none of these studies are classic household or telephone surveys of the general population. It is likely that most general population surveys, are either in the grey literature, or they deal with so many specific topics that cannabis is not one of their keywords. This means that from our peer-reviewed searches no additional data can be added to the international and national monitoring mentioned above.

These peer-reviewed prevalence studies occurred in the Central African Republic, Canada, United States, Germany, France, Spain, and Italy, among others, and varied widely in the study population (from toddlers to school children to adults to drivers), methodology and, not surprisingly, also in the prevalence. As seen in Table 2, the prevalence in these general population studies ranged from 0% to 38.6% (44, 46-68).

The highest prevalence of recent cannabis consumption (self-reports validated by urinalysis) of 38.6% was reported in a cross-sectional study from the Lobaye district in the Central African Republic in 2016 (65). The study was done in the Aka population, a population of foragers of the Congo Basin. Cannabis use was high mainly in men (70.9%) and seemed to be associated with unconsciously[1] self-medicating for helminthiasis (a parasitic worm infestation). Similar behaviours have been observed for other tribes and for other drugs, supporting an evolutionary perspective on the origin of drug use (69, 70).

The lowest prevalence of 0 was reported from a wastewater study in four mega-cities in China in the year 2012, where no cannabis derivative above the threshold was detected, thus indicating no, or very minimal, cannabis use (71). Another very small prevalence was reported in France relating to 29 cases of under three-year-old children with cannabis ingestion over a time period of 10 years in a hospital with 42,000 patients annually (72).

Part of the prevalence variations was attributable to measurement bias (self-reported measures, urine, blood, saliva, or wastewater testing; see Table 2). Most importantly, self-reported prevalence usually reflects 12-month use, whereas biological testing usually refers to shorter time-periods, based on the windows of detection. In Table 2, studies with self-reported prevalence have a superscript “a”; these prevalence numbers are based on 12-month prevalence unless otherwise notified. Studies that reported the prevalence based on biological testing have a superscript of “b”. Most tests are based on urine or saliva

[1] The authors of the paper explicitly mention “unconscious” self-medication. In this report, we only speak about self-medication, as in many studies it is not empirically determined whether the self-medication was made consciously or not.

samples. For urine, cannabis use can be detected anywhere from a few days to up to one month or more in the past, depending on the frequency of use (daily use can be detected the longest) (73). The window for detection is shorter for blood and, in fact, so short that for some of the planned *per se* laws for cannabis and traffic participation (74), detection via blood may become virtually impossible (75). Another method to assess cannabis use prevalence is wastewater analysis, which requires a fair number of assumptions on average cannabis consumption per occasion, and on average THC content per standard joint or per standard use. The resulting prevalence ranged from 0.35-3.73% (44, 62, 64). Most of the wastewater analysis studies focused on THC concentration and the prevalence and level of THC from these studies will be further discussed in Report 3 (76).

It is important to note that twenty studies (out of N=103) conducted biological tests for cannabis use, whereas the remaining studies relied on self-report measures, primarily through questionnaires (44, 46, 49, 51-55, 57-62, 64, 66-68, 77, 78). Most of the international monitoring efforts rely on studies using self-report measures. The few studies which compared self-report with biological measures found a fair degree of convergence, but by no means a perfect agreement (79, 80).

Obviously, the convergence of self-report and biological testing will depend on the context of assessment (for instance, in treatment situations, where treatment continuation in some situations may be contingent on use), on the perception of anonymity, and on the degree of stigma for cannabis use. Of note, one study used wastewater analysis to correct prevalence estimates based on self-report, concluding that self-reports underestimate true prevalence by 52% (62).

Table 2: Epidemiological results from general population studies (representing a country or region)

Name of Country/ Sub-region	**Study Type**	**Median Year**	**Sample Size (N)**	**Prevalence %**	**Keywords**
Germany (46)	Primary, cross-sectional	1999	964	9.8[a,b]	University students, athletes
France/11 cities (77)	Primary, case-control	2000.5	1,800	7.5[b]	Injured drivers, random roadside testing
Denmark (78)	Secondary, cross-sectional	2002	3,516	7.2[b]	Blood analysis, driving under the influence
Austria (49)	Secondary, cohort	2002	1,902	5.1[b]	Urine analysis, males, illicit drug use

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Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence %	Keywords
Thailand/ Southern region Songkhla, Pattani, Phuket and Surat Thani (50)	Primary cohort	2003	30,011	2.3-3.4[a]	Lifetime cannabis use, high school students
Norway/ Oslo (51)	Secondary, cross-sectional	2003.5	103	13.0[b]	Acute, fatal poisonings, autopsy
Netherlands (66)	Primary, cohort	2004	7,610	2.3[a&b]	Women who delivered babies, paternal and maternal cannabis use, self-report, urine testing
Switzerland (52)	Secondary, cross-sectional	2005	4,668	27.7[b]	Blood analysis, driving under impairment
United States/ New Orleans (68)	Secondary, cross-sectional	2005	416	17.2[b]	inner city population at delivery admission, urine toxicology screen
France (53)	Secondary	2006	3,493	16.1[a & b]	Self-reported cannabis use and urine analysis, military staff
United States/ Colorado (54)	Secondary, cohort	2010	588	2.4%[b]	Unintentional ingestion of cannabis by children up to age 12 visiting a hospital
Mexico/ Cuernavaca (55)	Primary, cross-sectional	2008[c]	174	1.2[b]	Drug use among college students
France/ Toulouse (72)	Retrospective, cross-sectional	2009	Not clear; 42,000 patients annually	Very small[b]	Accidental cannabis resin poisoning, children up to 3 years of age visiting hospital
Finland (57)	Secondary, cross-sectional	2007	13,315	22.2[b]	Driving under influence, blood analysis
Spain/Catalonia (58)	Cohort study	2007	1,026,690	4.0[b]	Wastewater analysis
Italy/ Northern region (59)	Secondary, cross-sectional study	2009.5	43,535	1.3[b] monthly prevalence	Transport-related occupations; quasi-random testing

Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence %	Keywords
Afghanistan/ 11 provinces (60)	Secondary, cross-sectional	2011	19,025	3.9[a&b]	Self-reported cannabis use, urine, hair and saliva testing
Norway (61)	Primary, cross-sectional	2011	2,437	0.7[b]	Saliva analysis, employees, cannabis use
Spain (67)	Cohort	2011	209	2.9[a]	Pregnant mothers, cannabis use during and before pregnancy
Italy/ 17 cities (44)	Wastewater analysis	2012	-	3.7[b]	Wastewater analysis
Switzerland/ Lausanne (62)	Wastewater analysis	2013.5	223,900	9.4[b]	Wastewater analysis in addition to self-report
United States/ Connecticut (63)	Primary, cross-sectional	2014	3,847	29.2[a]	High school students, cannabis use, e-cigarettes
Spain/Vitoria (64)	Wastewater analysis	2015	1,508,972	0.35-1.0 daily consumption[b]	Wastewater analysis
Central African Republic/ Lobaye district (65)	Primary, cross-sectional	2016[c]	379	38.6[a]	Self-report, cannabis use, indigenous

[a] = self-report, [b]= biological testing, [c]= publication year, data collection period unavailable

2.3.1 Self-medication

Up to this point, we have reported prevalence of cannabis use in various populations. In many countries, this use is not medical, if medical is defined by cannabis being prescribed by the medical system (for a description of the medical systems, see point on medical cannabis programs with **licit production, consumption, international trade** below). As indicated above, non-medical cannabis use may have a variety of motives, with self-medication and recreational use being the two major ones.

The following point is about self-medication. Cannabis has some therapeutic potential ((5, 81-84); for actual use see (85)). While there are no global estimates of the proportion of people which use cannabis for self-medication or for purely recreational purposes, the high proportion of people with certain diseases in Table 3 indicates that self-medication plays an important role as a motive for cannabis use.

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Several studies reported that cannabis plant and resin use were used for a range of medical conditions. It should be noted that some studies did not directly assess the reason for the use of cannabis (i.e., medical use, self-medication, recreational use; likely for most as self-medication). For those studies where this was assessed, many patients reported a perception of cannabis lowering the symptom load for their respective medical condition. While the studies showed variability in prevalence, the prevalence figures in clinical populations were all markedly above the rate of cannabis use in the general adult population. Table 3 provides a list of clinical conditions for which cannabis plant and resin was used and the prevalence of cannabis use among patient/people affected by these conditions.

Table 3: Prevalence of clinical conditions and prevalence of cannabis use among patients

Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence (%)[a, b]	ICD Chapter, Clinical Condition	Findings
Canada/ Ontario (86)	Mixed study (cross-sectional multicenter survey and retrospective chart review)	2000	104	43.0[a]	I, HIV	29% reported medical use for HIV. A significantly higher number of women compared to men used cannabis for pain management (45% vs. 5%, $p < 0.02$). The most commonly reported reason for medical cannabis use was appetite stimulation/weight gain (70%).
United Kingdom (87)	Primary, cross-sectional	2000	2,969	18.3[a]	XVIII, VI, V, XIII, VI, chronic pain, multiple sclerosis and depression, arthritis and neuropathy	Medical cannabis use was reported by patients with chronic pain (25%), multiple sclerosis and depression (22% each), arthritis (21%) and neuropathy (19%). Of 948 reported users, 648 (68%) reported that cannabis made their symptoms overall "much better", 256 (27%) reported a "little better", 36 (4%) reported "no difference" and eight subjects (0.8%) reported a "little worse" (four subjects) or "much worse" (four subjects).
Spain/ Vitoria in the Spanish Basque Country (88)	Primary, cohort	2002	92	57.0[a]	V, first psychotic episode	25 patients used cannabis before their first psychotic episode and continued use during follow-up (CU), 27 used cannabis before their first episode but stopped its use during follow-up (CUS), and 40 never used cannabis

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Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence (%)[a, b]	ICD Chapter, Clinical Condition	Findings
						(NU). The functional outcome of CUS patients improved more than that of NU patients. Moreover, the functional outcome of CUS patients improved progressively, while their negative symptoms diminished significantly. Continued use of cannabis (CU) had a deleterious effect on outcomes. CU patients only improved in their positive symptoms and showed a nonsignificant tendency to increase their negative symptoms.
Canada/ Alberta (89)	Primary, cross-sectional	2001	136	21.0[a]	VI, seizures	Of the 136 subjects with seizures, 65 (48%) had used cannabis in their lifetime; 28 (21%) were active users; 20 (15%) had used in the past month; 18 (13%) were frequent users, and 11 (8.1%) were heavy users.
France/ Paris, Marseille (90)	Primary, cross-sectional	2009	139	45.0[a]	VI, cluster headaches	Among the 27 patients (19.4% of the total cohort) who had tried cannabis to treat cluster headache (CH) attacks, 25.9% reported some efficacy, 51.8% variable or uncertain effects, and 22.3% negative effects.
Canada/ Halifax (91)	Primary, cross-sectional	2002	205	17.0[a]	VI, Multiple Sclerosis	Seventy-two subjects (36%) reported ever having used cannabis for any purpose; 29 respondents (14%) reported continuing use of cannabis for symptom treatment. Medical cannabis use was associated with recreational cannabis use. The symptoms reported by medical cannabis users to be most effectively relieved were stress, sleep, mood, stiffness/spasm, and pain.
United Kingdom (92)	Primary, case control	2002.5	445	64.0[a]	V, psychotic disorder	No assessment of symptom relief as primary aim was etiological (i.e., link between use and disease).
United States	Primary,	2005	500	11.0[b]	XVIII, chronic	No data on symptom relief.

Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence (%)[a, b]	ICD Chapter, Clinical Condition	Findings
(93)	cohort				pain	
Canada/ Toronto (94)	Primary, cross-sectional	2006	291	47.8[a] for inflammatory bowel disease 43.0 – prevalence for cannabis use in the last month	XI, VI, inflammatory bowel, multiple sclerosis disease	Comparable proportion of ulcerative colitis (UC) and Crohn's disease (CD) patients reported lifetime [48/95 (51%) UC vs. 91/189 (48%) CD] or current [11/95 (12%) UC vs. 30/189 (16%) CD] cannabis use. Of lifetime users, 14/43 (33%) UC and 40/80 (50%) CD patients used it to relieve IBD-related symptoms, including abdominal pain, diarrhea and reduced appetite. Patients were more likely to use cannabis for symptom relief if they had a history of abdominal surgery [29/48 (60%) vs. 24/74 (32%); P=0.002], chronic analgesic use [29/41 (71%) vs. 25/81 (31%); P<0.001], complementary alternative medicine use [36/66 (55%) vs. 18/56 (32%); P=0.01] and a lower short inflammatory bowel disease questionnaire score (45.1±2.1 vs. 50.3±1.5; P=0.03).
United Kingdom/ London, Kent (95)	Primary, case-control	2006[c]	254	18.0[a]	VI, multiple sclerosis	68% (75/110) had used cannabis to alleviate symptoms of MS (MS-related cannabis use). Forty-six (18%) had used cannabis in the last month (current users), of whom 12% (31/254) had used it for symptom relief. Compared to patients who could walk unaided, cannabis use was more likely in those who were chair-bound (adjusted Odds Ratio 2.47; 1.10-5.56) or only able to walk with an aid (adjusted Odds Ratio 1.56; 0.90-3.60). Pain and spasms were common reasons for cannabis use. Seventy-one per cent of individuals who had never used cannabis said they would try the drug if it were available on prescription.

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Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence (%)[a, b]	ICD Chapter, Clinical Condition	Findings
Nether lands (96)	Primary, cross-sectional	2007.5	17,698	67.0[a]	V, mental health	No reasons given for cannabis use, but associations between cannabis use and mental health outcomes.
United States/ Minnesota, Wisconsin (97)	Secondary, retrospective	2010.5	2,333	10.0[b]	V, psychiatric inpatients	
United States/ Washington (98)	Secondary, cross-sectional	2011.5	3,809	11.2[b]	XVIII, non-cancer chronic pain	The most common non-opioid substance detected was THC (11.2 % of urine drug tests (UDT). There was no significant association between opioid regimen characteristics and illicit drugs. Patients preferred cannabis as a primary method for managing pain. Physicians were reluctant to prescribe daily opioids for cannabis users.
Israel (99)	Primary, cross-sectional	2012	250	16.4[b]	V, mental health	No data on reasons of use or on associations with symptom relief/self-medication.
Africa/ Uganda (100)	Secondary, cross-sectional	2014	100	17.0[a&b]	V, psychiatric patient	No data on reasons of use or on associations with symptom relief/self N medication.
United States/ Arkansas (101)	Review, cohort	2014.5	140	76.0[a&b]	I Viral hepatitis	Drug screening identified 9/140 patients who used RDU/THC. Substance use was highly prevalent among HCV patients. No data on symptom relief/self-medication.
United States/ Miami (102)	Primary, cross-sectional	2015	229	27.0%[b]	XIX, ocular trauma	No data on reasons of use or on associations with symptom relief/self N medication.
United States/ Washington (103)	cohort	2015.5	926	24.0[a&b]	II, Neoplasms	Previous use was common (607 of 926 [66%]); 24% (222 of 926) used cannabis in the last year, and 21% (192 of 926) used cannabis in the last month. Random urine samples found similar percentages of users who reported weekly use (27 of 193 [14%] vs 164 of 926 [18%]). Active users

Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence (%)[a, b]	ICD Chapter, Clinical Condition	Findings
						inhaled (153 of 220 [70%]) or consumed edibles (154 of 220 [70%]); 89 (40%) used both modalities. Cannabis was used primarily for physical (165 of 219 [75%]) and neuropsychiatric symptoms (139 of 219 [63%]). Legalization significantly increased the likelihood of use in more than half of the respondents.

[a] = self-report, [b] = biological testing, [c]=publication year, data collection period unavailable

Legend: Definition of the ICD-10 chapters (104) used in the Table above:

I Certain infectious and parasitic diseases
II Neoplasms
III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
IV Endocrine, nutritional and metabolic diseases
V Mental and behavioral disorders
VI Diseases of the nervous system
VII Diseases of the eye and adnexa
VIII Diseases of the ear and mastoid process
IX Diseases of the circulatory system
X Diseases of the respiratory system
XI Diseases of the digestive system
XII Diseases of the skin and subcutaneous tissue
XIII Diseases of the musculoskeletal system and connective tissue
XIV Diseases of the genitourinary system
XV Pregnancy, childbirth and the puerperium
XVI Certain conditions originating in the perinatal period
XVII Congenital malformations, deformations and chromosomal abnormalities
XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
XIX Injury, poisoning and certain other consequences of external causes
XX External causes of morbidity and mortality
XXI Factors influencing health status and contact with health services
XXII Codes for special purposes

2.4 Epidemiological studies on THC content (cannabis potency)

Cannabis contains close to 500 active and other compounds (105). Delta-9-tetrahydrocannabinol (THC) is the principle ingredient linked to the psychoactive properties of cannabis, and thus important for use and public consequences. In the following, when we speak about potency we refer to the concentration of THC. Studies in cannabis potency are key for the descriptive epidemiology of cannabis use: cannabis

potency is one of the key determinants linking cannabis use and public health impact such as an increased risk for (106, 107) or an earlier onset of psychotic episodes ((108); for a review see (109)).

We will give a short overview on global epidemiological trends of THC use based on international monitoring efforts. Obviously, stable trends over time in use and use disorders may imply stable trends for THC as well. The more/less cannabis is used, ceteris paribus, the higher/lower the load of THC. The ceteris paribus condition refers to three factors. The above statement is only true, if:

- the level of THC (or potency of cannabis) is constant;
- the cannabis use behavior (110) (e.g., number of puffs, inhaled volume, the size of a standard joint; the THC content per standard joint; see (111) for future considerations on standardization) is constant; and
- the measurement procedures over time did not change.

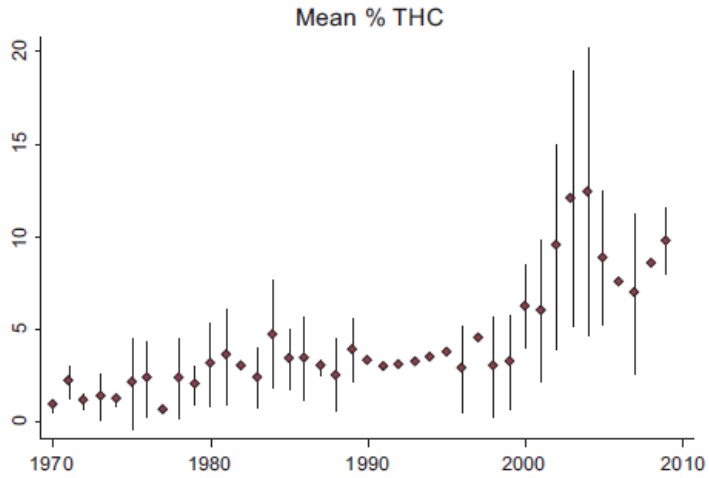
As we will see below, at least the first assumption does not hold true for the past decades, and there are reasons to believe that the other assumptions may also be problematic.

2.5 Trends in cannabis potency

Overall, potency, as measured by level of THC content, has increased over the past decades for both herbal cannabis and for resins. The annual reports of the INCB report increases for potency for Africa (25), historically high levels of THC content for Europe with prior increases in potency (25, 41, 112-114), and increases for North America (115, 116). Many of these trends have been based on regular (repeated) analyses of seized cannabis herbs and resin.

The international monitoring reports had been corroborated by a series of reviews, most importantly the systematic review and meta-analysis of Cascini and colleagues (117) on herbal cannabis. The authors performed a meta-analysis by year on 21 studies containing 75 total mean THC observations from 1970 to 2009 using a random effects model. While there was much variability between studies, there was a significant association between year and mean THC content in herbal cannabis, revealing a temporal trend of increasing potency over the years (see Figure 4).

Figure 4: Per-year meta-analysis graph showing the mean Delta-9-tetrahydrocannabinol concentration with 95% CI (117)



Another systematic review (118) corroborated this as well as trend studies in individual countries (see below).

2.5.1 Wastewater analyses of cannabis potency

Population surveys on the use of illicit substances such as cannabis are an invaluable tool for building an understanding of the epidemiology of the substance. However, there are limitations to self-report, especially about matters involving legality such as illicit substance use: stigma and fear of consequences may affect the validity and reliability of these estimates (for general considerations and a meta-analysis for a select population see (79, 119)), biasing prevalence and other epidemiological indicators downwards. Objective measures thus are indispensable as an additional source of information for obtaining a realistic picture of the use of illicit substances in the general population. While cannabis contains close to 500 active and other compounds (see above (105)), THC is the principal active ingredient linked to the psychoactive properties, which in turn are linked to use and public health consequences. Thus, THC is a good indicator for monitoring cannabis use as relevant for potential public health consequences.

Wastewater analyses of THC can also serve as an objective measure to supplement and/or correct self-reported data on prevalence. Several studies have found that prevalence estimates from wastewater analyses reflect prevalence estimates from surveys (e.g., (58, 120)). One study even found wastewater analyses over several years to mirror the time trends seen in population surveys (44). However, there can also be disagreement between the two methods (121). In order to make such comparisons about prevalence, a number of crucial assumptions have to be made, most importantly about use patterns of

cannabis users (110), and about standard size and potency of cannabis products (122, 123). However, wastewater analyses are more accurate in providing estimates of total consumption of THC rather than in drawing inferences about prevalence.

Consumption of THC varies across the globe (see Table 4). In China, THC consumption appears to be negligible; THC was undetectable in the wastewater of Beijing, Shanghai, Guangzhou and Shenzhen (120), which are four megacities in this country. This is in line with data from population surveys in mainland China (120). Consumption in Spain (64) and the Caribbean (124) were as much as five times higher than estimates for regions in Switzerland (62, 125).

Geographical differences in consumption also exist within the same country. In an analysis of 17 cities in Italy, consumption of THC was significantly higher in large cities with populations greater than 350,000 (Bologna, Florence, Milan, Naples, Palermo, Rome, Turin) compared to smaller cities (44). A study of 9 cities in Finland (Helsinki, Tampere, Turku, Savonlinna, Espoo, Jyväskylä, Oulu, Seinäjoki and Vaasa) found THC to be undetectable in the wastewaters of rural towns Savonlinna and Seinäjoki (126). Helsinki, the most populated capital city in Finland with 43% of the inhabitants in this analysis, had the highest THC consumption and accounted for 59% of the reported THC consumption (126). In the years 2006–2007, two analyses in Spain differed markedly by a factor of ten (58, 121); the THC consumption in Catalonia, Spain (58) was noted to be in line with national survey estimates of prevalence whereas the consumption in North-Eastern Spain based on analysis of the Ebro River basin was considerably lower (121). In general, at least in European high-income countries, THC consumption appears to be higher in more metropolitan areas.

Wastewater analyses also can give insights into the sociodemographic characteristics of users. Within the city of Milan, THC consumption was found to be significantly higher in the East which hosts poorer and more marginalized inhabitants (127). Wastewater analyses of school populations in Bologna, Florence, Milan, Naples, Palermo, Rome, Turin and Verona found THC consumption to be higher in schools focused on classic, scientific or artistic education as compared to vocational or professional schools (127).

Boleda and colleagues (58) estimated that the calculated consumption of 3,466 mg/day/1000 people was equivalent to a 4% prevalence of cannabis use in a population of around 1 million, which may conceptualize what these consumption values represent in terms of prevalence. Furthermore, a consumption of 3,466 mg/day/1000 people in Catalonia, Spain would mean a total of approximately 3.466 kg of THC consumed daily (58). It is worth noting that these consumption values are calculated based on the total population served by the wastewater plants sampled for analysis, which does not necessarily limit by a relevant age

range and so would include pediatric and geriatric populations with no or much lower consumption of cannabis.

Table 4: Wastewater analysis estimates of THC consumption

Country/Sub-region	Median Year	Population served (N)	Average THC consumption (mg/day/1000 people)
United Kingdom/London (125)	2005	5,500,000	7,500
Italy/Milan (125)	2005.5	1,250,000	3,000
Switzerland/Lugano (125)	2006	120,000	6,500
Spain/Catalonia (58)	2007	1,026,690	3,466
Spain/North-Eastern (121)	2007.5	2,800,000	680
Italy/Milan (127)	2010.5	–	8,300
Italy/8 schools in 8 cities (128)	2011.5	6,126	106–1,201
China/Beijing, Shanghai, Guangzhou and Shenzhen (120)	2012	11,400,000	No detectable THC
Finland/9 cities (126)	2012	2,021,000	4,320
Italy/17 cities (44)	2012	–	4,350
France/Martinique (124)	2013	47,200	37,500
Switzerland/Western (62)	2013.5	223,900	1,600
Spain/Valencia (64)	2015	1,500,000	23,300
Costa Rica/Liberia, Puntarenas (129)	2017*	49,973	7,160–10,700

*Date of publication

Trends in THC consumption are also apparent over the years. Consumption in the Italian cities of Bologna, Florence, Milan, Naples, Palermo, Rome, Turin, Bari, Cagliari, Perugia, Pescara, Verona, Gorizia, Merano, Nuoro, Potenza and Terni between 2010–2014 found THC consumption to be stable between 2010–2012 but found an overall increase in THC consumption by 2013–2014 that was not observed in any other illicit substance measured (44). This increase was most evident in small cities with a population of less than 120,000 inhabitants (Gorizia, Merano, Nuoro, Potenza, Terni) and medium cities with a population of 120,000–350,000 (Bari, Cagliari, Perugia, Pescara, Verona) (44). Wastewater analyses of Italian schools in Rome, Turin and Verona also showed an increase in THC consumption from 2010–2013 (127). The city of

Milan, Italy showed an over two-fold increase in THC consumption from 3,000 mg/day/1000 people to approximately 8,300 mg/day/1000 people between a wastewater analysis in 2005–2006 (125) and another in 2010–2011 (127). Increases in THC consumption were also observed in Spain between two studies conducted in 2007–2008 (58, 121) and another in 2015 (64). On the other hand, Switzerland appears to have seen a decrease in THC consumption from approximately 6,500 mg/day/1000 people (125) to 1,600 mg/day/1000 people (62) between a wastewater analysis done in 2006 and another done in 2013–2014, although the 2014 prevalence estimate by wastewater analysis was higher than the self-reported prevalence in population surveys (62). It is also possible that these differences may be due to differing geographical locations within the country.

It should be noted that an upward trend in THC may have different underlying reasons: a higher proportion of people may use cannabis, or the cannabis use prevalence remained the same but the cannabis consumed has higher potency, or both. Similarly, stable or downward trends in wastewater analyses could have different underlying reasons, and we would need more knowledge about trends in standard units such as joints (123).

2.5.2 Potency measured from cannabis samples (herbal, resin, extract, tinctures)

Potency of cannabis, as defined by THC content, varies across countries (see Table 5). The underlying samples come from a variety of sources: police seizures, studies, where samples were obtained from legal sources (coffee shops, medical cannabis), or studies where users were asked to bring along their illicit cannabis, which was then measured for THC potency.

Data from individual countries converge with data from INCB reports indicating that potencies in North America increased at a higher rate matching and even overcoming historically high potencies observed in Europe. Between 2008–2013, the THC content of cannabis in the United States (130, 131), the Netherlands (132), France (72) and Italy (133) were similar, ranging from to 7.5-13.0% in herbal cannabis and 10.3-17.4% in resin. The potency of random cannabis samples seized by Norwegian police from 2013–2014 was markedly lower at 1.9% and 3.8% for herbal and resin respectively (134), however online data from the KRIPOS section of the Norwegian police report potencies at higher levels which is more in line with other geographies (135). In The Netherlands, potency of domestically grown cannabis, whether herbal or resin, was noticeably higher than imported cannabis (136). Potency of herbal cannabis has been consistently lower than resin (72, 133, 134, 137) except for one study in which regular users provided their own supply (132).

Following global trends, the THC content of cannabis in individual countries appears to be increasing over time, as evidenced by studies mainly conducted in high-income countries. Italy saw increases in potency of 2-3% from 2010 to 2012 (133) and France saw increases of 1-3% in just one year, as reported by the French Observatory of Drugs and Drug Addictions (72). An extensive study of the THC content in 39,157 cannabis seizures across the 51 states in the U.S. each year from 1990–2010 observed a steady increase of approximately 7% over the ten-year period, which has been corroborated by other studies (130, 131, 138). Finally, trends in the UK were upwards as well (136, 139), whereas the THC content in the Netherlands (137) decreased in the time period between 2005 and 2015, but there was an increase from 2000 to 2015, due to the first years following 2000 (140). Thus, the data from this line of research seem to corroborate the data from chemical analyses of seizures and wastewater analyses (see above).

Changes in the legality of cannabis may be one of the causes of increases in THC content. Between 1990–2010, U.S. states that allowed medical cannabis had an average potency 3.5% higher than states without this law (131). With the legalization of recreational cannabis use, the potency of retail cannabis in 2015–2016 is 10–20% higher than the THC content found in seized illegal cannabis in 2010 (130, 131). This increase in potency associated with legalization has been suggested to be due mainly to an increase of highly potent cannabis strains, which are the result of a professionalized breeding process and intensive growing methodology (136).

Table 5: THC content and concentration in cannabis samples

Country	Median Year	Sample Size (N)	Sample description	Average THC content (%)
United States (131)	1990	741	Herbal cannabis	3.8
United States (131)	1995	3,742	Herbal cannabis	4.0
United States (138)	1995	3,763	Herbal cannabis/resin/oil	4.0
United States (131)	2000	1,894	Herbal cannabis	5.4
United States (138)	2000	1,929	Herbal cannabis/resin/oil	5.3
Netherlands (137)	2005	110	Domestic herbal cannabis	17.8
Netherlands (137)	2005	14	Imported herbal cannabis	18.9

Netherlands (137)	2005	16	Domestic resin cannabis	6.7
Netherlands (137)	2005	55	Imported resin cannabis	20.0
United Kingdom (136)	2005	–	Herbal cannabis	16.9
United Kingdom (136)	2005	445	Resin cannabis	5.9
United Kingdom (136)	2005	–	Herbal cannabis	16.2
United States (131)	2005	2,233	Herbal cannabis	8.1
United States (138)	2005	2,295	Herbal cannabis/resin/oil	8.0
Netherlands/Alkmaar, Amsterdam, Arnhem, Nijmegen, Utrecht (132)	2008.5	70	Herbal cannabis	12.4
Netherlands/Alkmaar, Amsterdam, Arnhem, Nijmegen, Utrecht (132)	2008.5	36	Resin cannabis	12.2
Italy/Venice (133)	2010	544	Herbal cannabis	5.66
Italy/Venice (133)	2010	704	Resin cannabis	6.20
Netherlands (137)	2010	114	Domestic herbal cannabis	17.8
Netherlands (137)	2010	15	Imported herbal cannabis	7.5
Netherlands (137)	2010	9	Domestic resin cannabis	32.6
Netherlands (137)	2010	56	Imported resin cannabis	19.1
United States (131)	2010	2,023	Herbal cannabis	10.7
United States (138)	2010	2,260	Herbal cannabis/resin/oil	10.4
Australia (141)	2010.5	206	Herbal/resin Cannabis	14.9
Italy/Venice (133)	2011	581	Herbal cannabis	5.14
Italy/Venice (133)	2011	704	Resin cannabis	7.22
Australia (141)	2012	13	Indoor eradicated cannabis crop	19.2
Australia (141)	2012	13	Outdoor eradicated cannabis crop	15.5

France (72)	2012	–	Herbal cannabis	10
France (72)	2012	–	Resin cannabis	16
Italy/Venice (133)	2012	846	Herbal cannabis	7.51
Italy/Venice (133)	2012	569	Resin cannabis	10.31
France (72)	2013	–	Herbal cannabis	13
France (72)	2013	–	Resin	17.4
Norway (134)	2013.5	21	Resin	1.9
Norway (134)	2013.5	20	Herbal cannabis	3.8
United States (138)	2014	427	Herbal cannabis/resin/ cannabis oil	11.8
Netherlands (137)	2015	110	Domestic herbal cannabis	16.2
Netherlands (137)	2015	17	Imported herbal cannabis	4.8
Netherlands (137)	2015	7	Domestic resin cannabis	31.6
Netherlands (137)	2015	66	Imported resin cannabis	17.8
United States/Seattle (130)	2015	–	Cannabis flower	21.2
United States/Colorado (130)	2016	–	Retail cannabis	28–32

Finally, in an analysis of web-based cannabis products for the medical cannabis program of Canada, the majority of products had THC > 15% (range 7%-30%; (142)).

2.5.3 THC in other populations

Four studies retrieved in this rapid review assessed THC concentrations in general populations: employees, students and foragers (see Table 6). As these samples were not hospitalized nor chosen to investigate specific illnesses, cannabis use is presumed to be used predominantly for non-medical purposes. The method of detection used by studies was either urine or saliva analysis. The length of detection of cannabis via THC or its metabolites varies across methodology: 23–43 hours in serum, 15–34 hours in saliva and up to one month in urine (143). THC concentrations in saliva have been found to be higher than blood concentrations by a factor of 15 (144). Concentrations of THC above 25 ng/mL in saliva (61) and above 400 ng/mL in urine are indicative of recent use (46). The cannabis cut-off concentration for workplace urine

drug testing in the United States, Canada, Europe and Australia is 50 ng/mL (59) while a cut-off of 2 ng/mL has been suggested for saliva (61). The World Anti-Doping Agency lists cannabis as a prohibited substance and has a lower cut-off concentration of 15 ng/mL urine (145).

High prevalence of cannabis use was found in the Aka people of the Central African Republic with an average urine concentration of THC of 663 ng/mL (65). Cannabis use was found mostly in men (65), which is in line with global trends (146). Findings of increased cannabis use and dependence in minority and indigenous populations have been found in Australia and the United States and may be related to socioeconomic factors as well (146-148). However, in the case of the Aka people, the high prevalence of cannabis use (over 70% in men in the general population), coupled with high THC level seemed to be associated with unconsciously self-medicating against helminthiasis (i.e., the infestation with parasitic worms). Indeed, THC (above 50 ng/mL in urine) seemed to be associated with less infestation (65). Similar behaviors have been observed for other indigenous tribes and for other drugs, supporting an evolutionary perspective on the origin of the use of drugs, which are now in part illegal (23, 70, 149).

Abuse of cannabis and other illicit substances in the workplace has led to mandatory workplace drug testing by some businesses (150). The majority of employees among 22 businesses in Norway between 2008 and 2013, who tested positive for THC presence, had saliva concentrations above 2 ng/mL and below 25 ng/mL (61). In this study, concentrations as high as 300 ng/mL were observed (61). Not specific to cannabis, but illicit drug use was found to be higher in those employed in the restaurant and bar industry (61). As this type of profession is associated with cannabis use, it may also impact risk of cannabis dependence (61).

A systematic review revealed that cannabis is the second most common drug used by athletes and that use begins early in life (151); prevalence of 13-19% has been found in high school athletes in Europe (46). Some athletes admitted to using cannabis specifically for performance purposes (8-12.5%) (151). The prevalence of cannabis use among elite students applying to the German Sport University Cologne was 9.8% with the majority having urine concentrations of THC between 15-100 ng/mL; of the students who tested positive, 8.5% had concentrations above 400 ng/mL, indicating very recent use (46). None of the students disclosed use of cannabis (46). Cannabis use for presumed performance enhancement due to its relaxing effect (145) is considered non-medical use impacting overall prevalence of use and use disorders in athletes.

Table 6: THC concentrations for non-medical use

Country/Region	Median Year	Sample Size (N)[a-c]	Prevalence (%)[d-f]	Average THC concentration [Range] (ng/mL)	Mode THC concentration range (ng/mL) [Prevalence %]
Germany/Cologne (46)	1999	964[a]	9.8[d]	[<1,000][d]	15–100[3.8][e]
Norway (61)	2011	2437[b]	0.7[e]	[0.63–300][e]	2.0–24[0.4][e]
United States/Connecticut (63)	2014	3847	29.2[f] 4.5[f] (cannabis oil); 3.0[f] (THC wax); 6.7[f] (dried leaves)	–	–
Central African Republic/Congo Basin (65)	2016*	379[c]	38.6[d]	663[1.3–4,100][e]	–

* = Date of publication, a = students, b = employees, c = foragers, d = urine analysis, e = saliva analysis, f = self-report; majority THC concentration prevalence refers to the percentage of positive cases found in this range out of the total sample (N)

The above studies can only be seen as examples of the non-medical use of cannabis, relatively arbitrary, as they mainly reflect peer-reviewed academic publications, which were not planned to provide systematic monitoring for THC content in non-medical use. However, they may serve to illustrate a major point. Cannabis use in general, and THC level in particular, in the general population, differ vastly by subgroup, and by cannabis use motives. If there are no medications against worm infestations, and cannabis use offers some relief, this form of self-medication leads to high prevalence numbers in populations where such infestations are frequent (65). Self-medication will lead to higher prevalence (152), and to more frequent use, leading to higher THC levels for any average day tested, with details depending on the actual test used (73, 75). As cannabis is being perceived as positively impacting on performance in sports (153), we can expect frequent use of cannabis among highly competitive athletes, and high THC levels (130, 151). Finally, prevalence of recreational cannabis use depends on the culture, its availability in comparison to other psychoactive substances, and on the knowledge and risk evaluation with respect to outcomes (154), but there are indications that the proportion of users becoming dependent is associated with THC potency (140, 155).

2.6 Cannabis use disorders

2.6.1 Global and regional prevalence of cannabis use disorders

We refer to the GBD 2016 study (8) for data on cannabis use disorders, defined as a maladaptive pattern of cannabis use leading to clinically significant impairment or distress (for definitions see (2)). In fact, cannabis use disorders are both a use pattern and a consequence of cannabis use (for a discussion (156, 157)), and they are used as the exposure variable, on which the GBD study models their burden of disease estimates (8). The 12-month prevalence data for cannabis use disorders for the year 2016 (last year available) are presented in Table 7.

Table 7: Estimates of cases and age-standardized rates of past 12-month cannabis use disorders by GBD region, 2016 (18)

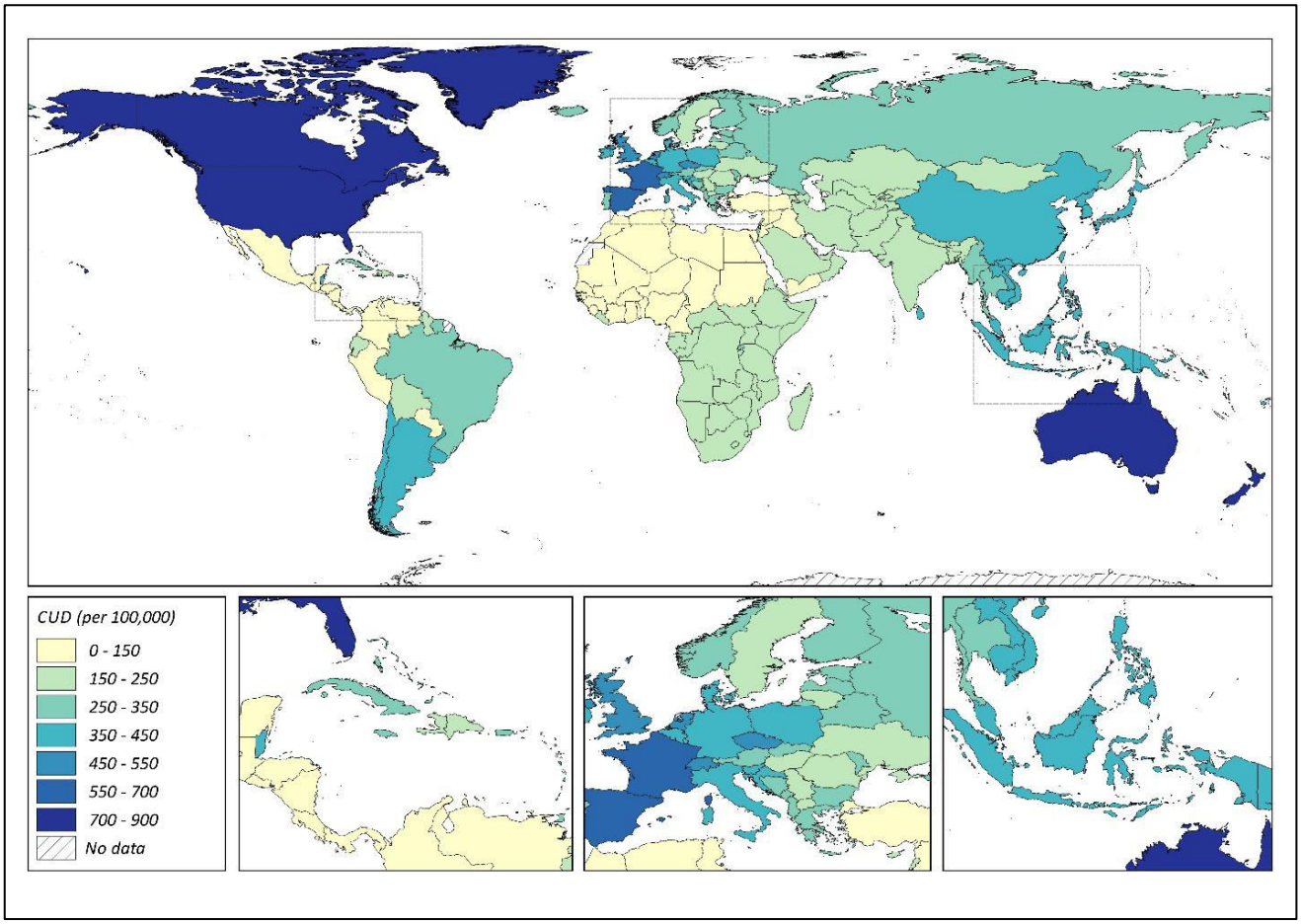
Region	**Number (95%UI)**	**Age-standardized rates (95%UI)**
Andean Latin America	96,039 (80,064, 113,733)	153.0 (128.5, 180.0)
Australasia	204,356 (173,840, 239,002)	747.9 (628.5, 882.3)
Caribbean	125,274 (104,993, 150,503)	267.6 (224.8, 321.1)
Central Asia	223,432 (183,517, 268,722)	236.4 (194.9, 286.1)
Central Europe	315,919 (272,341, 367,104)	307.7 (259.3, 363.7)
Central Latin America	292,011 (253,898, 337,547)	107.5 (93.9, 123.4)
Central Sub-Saharan Africa	201,430 (166,923, 244,647)	179.1 (151.1, 212.9)
East Asia	5,309,873 (4,469,006, 6,321,707)	375.9 (310.7, 453.2)
Eastern Europe	509,604 (433,670, 595,384)	270.1 (223.6, 323.8)
Eastern Sub-Saharan Africa	810,801 (651,792, 1,002,111)	206.8 (170.3, 249.6)
High-income Asia Pacific	545,997 (462,577, 639,490)	367.5 (303.0, 437.2)
High-income North America	2,958,300 (2,608,023, 3,360,240)	884.3 (772.7, 1013.2)
North Africa and Middle East	937,912 (778,990, 1,128,230)	151.4 (126.4, 180.5)
Oceania	49,970 (403,00, 61,303)	408.2 (334.8, 495.8)
South Asia	3,813,357 (3,162,055, 4,567,296)	204.1 (171.1, 242.8)
Southeast Asia	2,535,601 (2,090,990, 3,071,113)	362.5 (299.3, 438.8)

Southern Latin America	262,563 (216,085, 316,247)	402.0 (330.0, 485.7)
Southern Sub-Saharan Africa	180,866 (151,028, 217,342)	204.0 (172.4, 241.9)
Tropical Latin America	621,982 (523,521, 731,778)	268.8 (226.4, 316.9)
Western Europe	1,586,190 (1,405,343, 1,771,515)	450.8 (391.5, 509.2)
Western Sub-Saharan Africa	513,031 (428,970, 610,676)	133.4 (113.5, 155.9)
Global	**22,094,508 (18,964,678, 25,855,498)**	**289.7 (248.9, 339.1)**

Note. Data in the table above were extracted from the IHME website of GBD study 2016 (158, 159). Age-standardized rates are rates per 100,000 people, estimated using the GBD world population age standard. Past 12-month cannabis use disorders were operationalized by cannabis dependence as defined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (1) and the International Classification of Diseases (ICD-10,(3)). Data are derived from systematic review of peer-review and grey literature, including estimates from studies published since 1980, and data were modelled using DisMod-MR 2.1. 95% uncertainty intervals (UIs) were derived from 1000 draws from the posterior distribution in the estimation process. Data were available for 151 countries for cannabis dependence. The UIs capture uncertainty from multiple modelling steps and from sources such as model estimation and model specification. Grouping of countries reflect the standard GBD classification (160).

Map 1 illustrates age-standardized 12-month prevalence of cannabis use disorder by country.

Map 1: Age-standardized 12-month prevalence of cannabis use disorders in 2016 by country (158)



CUD: Cannabis use disorders

Compared to women, cannabis use disorder prevalence among men was about-two-fold (in 2016: men 0.41%; women: 0.19%). Across the lifespan, cannabis use disorder prevalence peaked among 20 to 24-year-olds (0.97%, women: 0.61%, men: 1.3%). Globally, 65% of people with cannabis use disorder were less than 30 years old (women: 63%, men: 66%; all data from (159)).

Data from the GBD 2016 study allow for a systematic comparison of countries with different sociodemographic indices (SDI, as defined by IHME) with regard to the age-standardized rate of cannabis use disorders in the population. By far highest rate (596 out of 100,000 people) of cannabis use disorders was found in countries with high SDI, as compared to largely similar rates in countries with middle (288 per 100,000) and high-middle SDI (298 per 100,000). The lowest rates of cannabis use disorders were reported in low (190 per 100,000) and low-middle (208 per 100,000) countries.

With regard to treatment of cannabis use disorders, we used data from a global survey initiative led by the World Health Organization aiming to assess the global provision of treatment for substance use disorder. In the first survey, drug treatments systems were described for more than 130 countries but results were not specified by drug type (161). For all drugs, the majority of countries have inpatient facilities for detoxification available (91%), whereas outpatient (72%) and residential facilities (59%) were less common. The lack of outpatient and residential facilities for drug treatment was greater in low- as compared to high-income countries. Data on treatment coverage for drug use disorders in general suggests that specialized treatment facilities are used by less than 50% of the population in need, with higher proportions in in high-income countries. In the second survey conducted in 2014, data were stratified by substance class. Results for cannabis dependence (N=84 countries) suggest that in one third of countries less than 10% of people in need are treated, while less than one fifth of countries reported high (i.e., more than 40%) treatment coverage (162) (for data by country, see WHO, (163)). Overall, global inferences on the treatment of cannabis use disorders can hardly be made due to lack of data for many countries.

2.6.2 Global trends in prevalence for cannabis use disorders

In terms of trends, as analyzed via linear regression, the age-adjusted time trends for 12-month prevalence of cannabis use disorders from 1990 (0.32%, 95% CI: 0.27-0.38%), 2000 (0.32%, 95% CI: 0.28-0.38%), 2010 (0.31%, 95% CI: 0.26-0.36%) to 2016 (0.30%, 95% CI: 0.26-0.35%) were decreasing for all three base years, with most rapid falls since 2000 (158). Downward trends of similar magnitude were observed for males (1990: 0.43%, 2000: 0.43%, 2010: 0.41%, 2016: 0.41%) and females (1990: 0.21%, 2000: 0.21%, 2010: 0.20%, 2016: 0.19%). It is hard to reconcile the trends on cannabis use and cannabis use disorders, especially given the developments in cannabis potency (76). If potency is increasing and prevalence of cannabis use is stable, then prevalence of cannabis use disorders should be stable or increasing, as there is some evidence that higher potency leads to higher risks for cannabis use disorders. In addition, it is not clear why the gender ratio of prevalence of cannabis use has been decreasing, whereas the ratio of cannabis use disorders has been stable. Again, such data would assume a differential mechanism over time about the transition to use disorders by gender, which has not been discussed to date.

Thus, we strongly urge using standardized assessment of all indicators in global monitoring and the use of modelling methodology to achieve consistent prevalence estimates of cannabis, cannabis use disorders and potency.

2.6.3 Risk of cannabis use disorder among cannabis users

The 12-month prevalence of cannabis use from Table 1 for the year 2015 and the 12-month prevalence of cannabis use disorders for the same year allow us a very crude estimate of the risk for use disorders given use. Among the general population aged 15 to 64 years old in 2015, there were 0.45% (own calculations based on data from (159)) with cannabis use disorders, and 3.8% with cannabis use, which results in about 8 users per one person with a use disorder. In other words, globally approximately every 8th user is dependent. However, this ratio is by no means constant between countries, or within countries. For example, with the increasing normalization of cannabis use in the United States, the ratio of number of users to a person with use disorders increased (38, 164). Thus, other ratios have been mentioned.

Hall in his overview paper estimated that around one in 10 regular cannabis users develops dependence (165) . Obviously, while dependence is part of cannabis use disorders, not all cannabis use disorders would qualify as dependence, and so a higher ratio for dependence would be suspected. Volkow (166) gives 9% or a ratio of 1:11 for dependence (for general population studies, see (167, 168)). The proportion among users developing dependence increases to 17% in adolescents and as high as 25–50% with daily consumption (166). The data available to generate these estimates are from high-income countries only, mostly from the US. Thus, the variation in proportion of users with a use disorder cannot be assessed to date and the impact of political and cultural factors is yet to be determined.

2.6.4 Data quality and consistency of epidemiological data

The aim of this report was to summarize available data. However, at this point, we need to highlight that

- …the global epidemiological data based for prevalence of cannabis use and cannabis use disorders is surprisingly small, and de facto too small to report reliable trends;

- …the data seem inconsistent: it seems highly unlikely that cannabis use prevalence is stable, cannabis use disorder prevalence is decreasing, yet potency is increasing. Ceteris paribus, if potency is increasing, the rate of people with cannabis use disorders per cannabis user should increase as well (see (110, 140, 169)). Trends in the opposite direction thus seem implausible. Another inconsistency seems to be divergent trends on gender ratio between cannabis use and cannabis use disorders.

Section 5: Epidemiology

While it is not the aim of this report to try to further discuss potential inconsistencies, we would like to highlight that valid epidemiological indicators are the basis for any monitoring and surveillance system (170).

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

There are a number of different public health problems related to cannabis use and cannabis use disorders. For this section, it is vital to clarify terminology: the term cannabis-related is used in a variety of contexts, but could also refer to statistical associations, which are not causal. The term cannabis-attributable refers to a causal impact of cannabis (i.e., as defined in, but not limited to, comparative risk assessments) (8). For comparative risk assessments, we not only need to establish causality, but also be able to quantify the causal impact, against a chosen counterfactual scenario, which is usually no cannabis use (171). Further, we use the term 'harm' instead of 'public health problems' for brevity and consistency with the burden of disease framework.

This section will start with A) an overview of cannabis-attributable and cannabis-related harm, followed by B) a summary of quantified harm, and C) harm to others. Lastly, we provide results from the rapid review related to cannabis exposure among populations, particularly vulnerable populations, to consequences of cannabis use.

3.1 Overview of cannabis-attributable and cannabis-related harm

There are a number of systematic reviews and overviews on harm concerning the use and use disorders of cannabis. Below, we will mainly list conditions, where a likely causal impact can be established. This overview is based on the major reviews of the literature on risk relations of cannabis (165, 166, 172-175) and the prevalence and public health importance of the outcomes (159):

- Obviously, causality is clear for all cannabis use disorders, as they are linked to cannabis use by definition (for further mechanisms: (166)). These disorders make up the largest part of the burden of disease as measured in DALYs. These figures have been estimated every year as part of the GBD studies ((159); see also (176, 177)).
- Acute effects of cannabis, which may be relevant to public health include:
    - Cognitive effects including impaired short-term memory, altered judgement and impaired motor coordination, which increase the risk of injuries (best studied with traffic injuries under the influence of cannabis, where causality has been established despite some negative epidemiological results).
    - The altered judgement may also lead to problematic decisions with respect to increasing risk of sexually transmitted diseases.
    - For high doses of cannabis, increased risk of psychotic events.

- The following chronic consequences other than cannabis use disorders can be seen for:
    - Impairment of the brain (especially of the adolescent brain).
    - Poor educational outcome and partially lasting cognitive impairments, with increased likelihood of dropping out of school.
    - Increased risk for chronic bronchitis or symptoms thereof.
    - Increased risk of chronic psychotic disorders (including schizophrenia) in persons with a predisposition to such disorders. The odds of developing schizophrenia and other psychosis-related outcomes were nearly four times higher among ever cannabis users as compared to never-users (178), with a dose response relationship (106).

In addition to these conditions, there are a number of associations where causality has not been fully established or where causality cannot be quantified. Lung cancer is the most important of these associations, where the impact of smoking cannabis can be considered likely, but which is hard to quantify, as smoked cannabis is often mixed with tobacco, which constitutes the major risk factor for lung cancer (8). Then there are associations with almost all mental disorders, where the causal direction or potential impacts of third variables like genetic vulnerabilities are not clear. As an example, while it may well be true that cannabis use can lead to certain mental disorders such as depression, depression may also lead to cannabis use (self-medication), and both depression and cannabis use, and cannabis use disorders are linked to genetic factors, thus introducing a spurious correlation. For depression, a meta-analysis has quantified an increased risk of depression among cannabis users (odds ratio = 1.17) and in particular among heavy users (odds ratio = 1.62)(179).

3.2 Quantifying cannabis-attributable harm

Cannabis-attributable harms have been systematically quantified in the GBD 2016 study (8), which calculated the burden of disease attributable to cannabis use disorder, expressed in disability-adjusted life years (DALYs). One DALY represents one year of life lost either due to premature mortality or due to living with disability (180). For 2016, cannabis use disorders caused 646,480 DALYs (CI: 400,640-944.870). This constituted an increase of 3.7% (CI: 1.2-6.0%) from 2006 (i.e., over the past 10 years). However, after age-adjustment, there was actually a decrease in cannabis-attributable disease burden (-4.2%; 95% CI -5.9-2.4%). In other words, this increase in cannabis-attributable burden of disease was due to changes in the age distribution of populations (i.e., a growing share of young people globally). In interpreting the GBD studies it should be mentioned that only a part of the cannabis-attributable disease and mortality outcomes were included, and thus important outcomes such as cannabis-attributable traffic injury were not included (for more complete list see above).

The most comprehensive analyses of public health harm attributable to cannabis were undertaken for Canada: most of the cannabis-attributable burden of disease as measured in DALYs was linked to cannabis use disorders, whereas most of cannabis-attributable deaths were linked to driving under the influence of cannabis (176, 177). Cannabis-attributable lung cancer, due to smoking cannabis with tobacco, may be more important for mortality but, to date, it has been very hard to separate the impact of cannabis from the impact of tobacco (173).

In terms of harm, most harm is caused by frequent or heavy use, especially heavy use over time ((166, 172, 175); for definitions of heavy use and its relationship to use disorder, see (156, 157)). Thus, prevalence of use *per se* is not a good indicator of public health harm. This is one reason why the GBD comparative risk assessment (171) is based on cannabis use disorders. Alternatively, concepts like daily cannabis use, usually operationalized by use of cannabis on at least 5 days of the week, could have been used (181). For example, in Europe, it has been estimated that 13% of all cannabis users would be daily users. The resulting ratio of daily users was about 8:1, which would be very similar to the ratio for cannabis use disorders (see above; for details of the calculation see (181)).

For a more accurate estimation of cannabis harm, the actual population exposure to THC, the principal psychoactive constituent of cannabis, would be required as there are indications for a dose response relationship between cannabis potency and cannabis use disorder (110, 140, 169). However, this estimation is not possible to date, as it would require better knowledge about the dose per standard unit, or per use occasion (123). Moreover, any THC monitoring would require biological measures either on the individual or aggregate level, which would be costly at the country level.

3.3 Harm to others

Cannabis use, like the use of other legal and illicit psychoactive substances, causes harm not only to the users themselves but also to others (182). For cannabis use, although harm to others has not been quantified to date, two pathways can be identified:

- Maternal cannabis causes problems in the newborn: it was clearly linked to lower birth weight and there are substantial theoretical justifications that cannabis interferes with neurodevelopment (172, 183).

- As cannabis use impairs driving (184), harm to others results when cannabis-impaired drivers cause injuries in other traffic participants.

As can be seen below, there have been studies presenting epidemiological evidence on maternal cannabis use and driving under the influence of cannabis. Moreover, there have been studies on the epidemiology of exposure to cannabis in children, both acute (poisoning) and chronic. Chronic exposure of cannabis legally constitutes child abuse in several countries and has been associated with respiratory problems, cognitive impairment and increased risk of cannabis use later in life (130).

3.4 Cannabis exposure among public-health relevant vulnerable and special populations

A number of studies from our rapid systematic review reported cannabis exposure among populations, which are particularly vulnerable to consequences of cannabis use. These reports focused on two topics (see Table 8 and Table 9): three studies on ongoing chronic cannabis exposure in the environment (185-187) and 31 studies on driving under the influence of cannabis (188-219).

Three studies focused on screening for cannabis among newborns (i.e., cannabis exposure during pregnancy) or in young children (chronic cannabis exposure in the household (185-187)), either via meconium or hair analyses. Such screenings are conducted as part of the assessment of child abuse, as illicit drugs in children's environment are considered as abuse by law in several countries. The prevalence of these studies ranged from about 5% in two studies to 13.6%; however, the higher figure was found in a selective sample of children admitted to an emergency department.

Table 8: Summary of screening studies for cannabis among infants and children

Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence (%) [a, b]	Keywords
Spain/ Barcelona (185)	Primary, cohort	2003	974	5.3[b]	Newborn meconium analysis, prenatal cannabis exposure, gestational drug use
United States/ Iowa (186)	Secondary, cross-sectional	2009	616	4.9[b]	Children, child abuse, urine and hair analysis
Spain (187)	Repeated cross-sectional	2013	228	13.6[b]	Hair analysis, children, emergency department

a=self-report, b=biological testing, c=publication year, data collection period unavailable

For THC contents of these populations see Appendix 5.

Section 5: Epidemiology

Several other studies focused on driving and roadside testing for cannabis resin and plant (188-219). As seen in Table 9, results of these studies showed that the prevalence of cannabis use among drivers tested on the roadside through various types of testing (blood, urine, saliva) varied widely, in part due to testing methodology, in part due to definition of samples (e.g., random testing of drivers; drivers involved in fatal crash; injured drivers; drivers with at least one positive result for substance use), and in part reflecting cultural differences in driving under the influence of cannabis.

Table 9: Prevalence of cannabis use among drivers in different countries

Name of Country/ Sub-region	Median Year (field work)	Sample Size (N)	Prevalence (%) [a, b]	Keywords
Australia/ Victoria (188)	1994.5	3,398	8.5[b] for THC and 13.4 for secondary THC metabolite	Blood analysis, driver fatality, cannabis use, used for culpability analyses
Australia/ Southern Australia (218)	1995.5	2,500	2.8[b]	Injured drivers, blood analysis, accidents
United States (189)	1999.5	150,010	5.2[b]	Blood analysis, driving records
Australia/ Victoria (190)	2001	436	7.6[b]	Blood analysis, injured drivers, hospital admission
Germany (191)	2001	177	5.5[b]	Driving under influence, blood analysis, suspected impaired drivers
Australia/ Victoria (192)	2004	13,176	0.7[b]	Blood or saliva testing, random screening, drivers
Brazil/ Sao Paulo (193)	2005	1,250	0.4[b]	Positive oral fluid testing, questionnaires, truck drivers
Norway (219)	2002.5	112,348	21.5[b] among suspected self-impaired drivers	Blood analysis
Sweden (195)	2002.5	22,777	21.1[b] among drivers suspected for driving under the influence of substances	Driving under the influence, blood analysis
Norway (196)	2005	676	7.2[b]	Blood findings, motor vehicle accident fatality
United Kingdom (197)	2005[c]	1,396	3.7[b]	Saliva analysis, drivers, random testing

Name of Country/ Sub-region	Median Year (field work)	Sample Size (N)	Prevalence (%) [a, b]	Keywords
Norway/ Southeastern region (198)	2005.5	10,816	0.6[b]	Saliva analysis, random roadside survey, drivers
Sweden (199)	2005.5	200	4.5[b]	Blood analysis, fatally injured drivers
Australia/ Victoria (200)	2006.5	2,638	14.5[b]	Drivers, blood analysis, motor vehicle fatalities; reanalysis of (83)
New Zealand (201)	2006.5	1,046	30.0[b]	Blood analysis, car accident fatality
Brazil, Norway (220)	2008.5	3,326	0.4[b]	Driving under influence, roadside surveys, oral fluid testing
Hungary (202)	2008.5	2,738	0.6[b]	Saliva analysis, driver random testing
Spain/Valladolid (203)	2008.5	2,632	10.8[a&b]	Oral samples, roadside survey, drivers
Australia/ Victoria (204)	2009	1,714	9.8[b]	Hospitalized drivers, motor vehicle accidents, blood testing
Belgium/Netherlands (205)	2009	535	5.6[b]	Seriously injured drivers, blood samples
Brazil/ Porto Alegre (206)	2009	609	6.9[b]	Saliva use, traffic accidents, hospital admission
Italy (207)	2009	5,592	0.2[b]	Hair testing, drivers
Australia/ Victoria (209)	2009.5	853	42.0[b] among all the positive samples	Saliva analysis, randomly stopped drivers
Brazil/ Sao Paolo (210)	2009.5	993	0.3[a &b]	Truck drivers, urine analysis, reported use
Canada/British Columbia (211)	2011	1,097	12.6[b]	Drivers, emergency department
United States/ Washington (212)	2011	25,719	19.0[b]	Drivers, blood testing, legalization
Italy/ Milan (213)	2014	1,258	3.6[b]	Drivers, accidents, blood tests
Brazil/ Sao Paolo (214)	2014.5	762	1.0[b]	Truck drivers, cannabis use, oral analysis
Norway/Finnmark (215)	2014.5	3027	1.1[b]	Driving population
Italy/ Northern region	2018[c]	3,359	3.9[b]	Urine drug testing, roadside testing

Name of Country/ Sub-region	Median Year (field work)	Sample Size (N)	Prevalence (%) [a, b]	Keywords
(216)				

a=self-report, b = biological testing, c=publication year, data collection period unavailable

While prevalence varied, it should be stressed that driving under the influence of cannabis is a public safety threat (184), not only to the drivers themselves, but also to other traffic participants (see point on Harm to others above).

As a limitation to the presented estimates, the vast majority of identified studies collected data in high-income countries from Europe, North America, and Oceania. A few estimates were obtained in Brazil (prevalence ranging between and 0.3% and 6.9%). In a recent contribution (221) aiming to provide an international overview on the prevalence of driving under the influence of cannabis, all presented estimates were obtained from high-income countries only. To our knowledge, prevalence data on driving under the influence of cannabis in low- and middle-income countries are not available.

3.5 THC concentration while driving under the influence of cannabis

The cognitive impairment associated with THC is the major underlying reason for harm due to driving under the influence of cannabis (222). As a consequence, knowledge about levels of THC among drivers is important to public health. Of 41 studies retrieved on driving under the influence (DUI), 20 studies with inclusion of THC levels are summarized in Table 10. Studies on the prevalence of use of cannabis in DUI drivers that did not include information on THC concentrations in drivers can be found above.

In regard to driving under the influence of cannabis, the concentration of THC present in the driver is of great interest as it is used as a measure of impairment and therefore used to define proposed legal limits. There is no global consensus on the concentration of THC at which driving ability is impaired at this point. Blood THC concentrations may not be the best indicator of impairment due to delayed psychotropic effects following redistribution from blood to brain tissue; by this logic, lower blood THC concentrations may then indicate higher impairment (47, 223). Studies on culpability of drivers involved in car crashes have had contradictory findings, suggesting either no relationship (218) or a weak positive association (201) with the presence of cannabis but also that drivers with lower blood THC concentrations (5 ng/mL or less) are more likely to be culpable than those with higher measured concentrations (201).

Observed clinical impairment has also been associated with increasing THC concentration, whether measured by saliva (203) or blood analysis (134). Maximum THC concentrations in blood have been found to be observed minutes after smoking cannabis and to taper off in hours (224). As a result of the rapid decline in THC concentration after smoking (143), measured concentrations from mandatory blood testing may be significantly lower than concentrations while driving, thereby bypassing set legal limits (52, 212, 225).

Laboratory delays in testing samples can also lead to decreases in THC concentrations (212). Studies have found differences of approximately 10% between prevalence of THC detection and prevalence of THC metabolite detection in drivers suspected of DUIs which may lead to differing legal consequences regardless of evident impairment (57, 212). One must also consider that chronic cannabis users can maintain blood concentration levels above 2 ng/mL even after seven days of abstinence, further complicating discussions about set legal limits (57).

The average blood concentration of THC found in positively tested drivers fall in the range of 1-8 ng/mL; Australia (204), Norway (224), Switzerland (Senna) and the United States (212) fall on the higher end of that range as compared to Sweden (199), Finland (57) and Denmark (226), while France (227) and New Zealand (201) seem to lie somewhere in this range.

There does not appear to be a correlation between legal limits of THC concentrations for DUIs and the average concentrations found in drivers. High mean concentrations were found in a study conducted in the United States in Washington which has a fairly high THC limit of 5.0 ng/mL in blood for adults over 21 years of age (212), however Australia had similar findings despite a zero-limit policy (204). Finland and France also share zero-limit policies while Denmark, Norway, Switzerland, Sweden and the United Kingdom have blood THC concentration limits of 2 ng/mL or less.

There may be a relationship between prevalence of THC detection and DUI thresholds; random roadside testing found prevalence of 0.7% (192) and 0.6% (202) in the zero-limit countries of Australia and Hungary, respectively, whereas prevalence in random roadside testing was 3.7% in the United Kingdom (197), with one of the higher blood concentration limits of 2 ng/mL, and 10.8% in Spain (203), where the DUI thresholds are 0 but the measurement is usually set at 5 ng/ml (74, 228).

In many high-income countries, legal DUI thresholds have been implemented and motor vehicle drivers can be arrested for violation. However, systematic data on DUI offences is not available as most countries do not differentiate between cannabis and other drug-related offences (e.g., New Zealand (229), Canada

(230), Germany (231)). In the United States of America, a recent report to Congress (232) has highlighted that data collection on DUI arrests is not standardized and incomplete across states, making it impossible to assess the nationwide scope of DUI-related problems.

Over time, THC concentrations found in drivers have remained relatively stable. The majority of impaired drivers in France had blood concentrations of THC less than 5.0 ng/mL both from 2003 to 2005 (47) and between 2005 and 2006 (227). In Australia, average blood THC concentrations in fatally injured and hospitalized drivers were 10.0 ng/mL across 1990–1999 (188) and 7.0 ng/mL in 2009 (204) with similar prevalence of detected use at 8.5% and 9.8% respectively, demonstrating a fairly stable trend over ten years. Two studies in Denmark found the average blood THC concentration in impaired drivers in Denmark to be higher at 5.9 ng/mL between 2002–2006 (78) than the 1.5 ng/mL average in hospitalized drivers from 2008–2009, though whether this disparity is related to time, population or other methodological factors is not known (226). Interestingly, one study in Norway found that between 2000 and2010, the average blood THC concentrations of drivers using cannabis alone gradually increased over time from 4.0 ng/mL in 2000 to 6.6 ng/mL in 2010 (224); another study between 2013–2014 (134) found average blood THC concentrations of 4.3 ng/mL. However, in cases where THC was the only substance present, the average blood concentration was 7.08 ng/mL from 2013-2014 (134). Blood concentrations in impaired drivers in Sweden appear to fluctuate around 2 ng/mL: a study spanning between 1995 and2004 observed a minor increase from 1.8 ng/mL to 2.3 ng/mL (225), while a second study from 2005 found an average concentration of 1.1 ng/mL (199); it is worth noting that between 1995–2004 the average blood THC concentration was 2.1 ng/mL overall but 3.6 ng/mL in the absence of any other substance (225). Average concentrations in impaired Swiss drivers were also higher when THC was the only substance detected: 8.1 ng/mL compared to 5.8 ng/mL (52). Higher blood THC concentrations in cases with only THC detected as compared to cases with multiple substances seems to be a consistent pattern (52, 134, 225). Two longitudinal studies, both conducted over 10 years in Nordic countries, reported increases in the average blood THC concentration found in drivers who use cannabis (224, 225), suggesting a possible time trend, at least in this geographical location.

Table 10: THC concentrations in drivers

Country/Region	**Median Year**	**Sample Size (N)[a–e]**	**Prevalence (%)[f-h]**	**Average THC concentration [Range] (ng/mL)**	**Majority THC concentration range (ng/mL)[Prevalence %]**
Australia (188)	1994.5	3398[a]	8.5[f]	10.0 [0.7–228][f]	–

Australia (218)	1995.5	2500[b]	2.8[f]	–	1.0–2.0[1.1][f]
Sweden (225)	1999.5	8794[e]	NA[f]	2.1[0.3–67][f]	<1.0[43][f]
France (47)	2003.5	2003[a]	28.9[f]	–	0.2–5.0[20.9][f]
Australia (192)	2004	13,176[c]	0.7[f,g]	[3–19][f] 81[5–6484][g]	–
Denmark (78)	2004	3516[d]	7.2[f]	5.9[0.2–79.4][f]	–
Norway (224)	2005	1748[e]	NA[f]	5.0[f]	–
Switzerland (52)	2005	4668[d]	49[f]	5.8[1.0–62][f]	>2.2[27.7][f]
United Kingdom (197)	2005*	1396[c]	3.7[g]	506[7–4538][g]	–
France (227)	2005.5	611[d]	41.6[f]	[0.1–49.9][f]	1.0–5.0[20.6][f]
Norway (196)	2005.5	676[a]	7.2[f]	–	1.3–6.5[5.9][f]
Sweden (199)	2005.5	200[a,b]	4.5[f]	1.1[0.3–5.0][f]	–
New Zealand (201)	2006.5	1046[a]	30.0[f]	–	2.0–5.0[10.7][f]
Finland (57)	2007	13315[d]	22.2[f]	3.8[1.0–60][f]	–
Denmark (226)	2008.5	840[b]	3.7[f]	1.47[0.2–6.65][f]	–
Hungary (202)	2008.5	2738[c]	0.6[g]	[1.46–433][g]	–
Spain (203)	2008.5	2632[c]	10.8[g]	–	>100[3.4][g]
Australia (204)	2009	1714[b]	9.8[f]	7.0[f]	–
United States (212)	2011	25719[d]	19.0[f]	7.4[2–90][f]	>5[10.8][f]
Norway (134)	2014	6134[e]	NA[f]	4.33[f]	–

***** = Data of publication, **a** = fatally injured, **b** = hospitalized, **c** = random roadside survey, **d** = suspected DUIs, **e** = THC-positive sample, **f** = blood analysis, **g** = saliva analysis, **h** = urine analysis; majority THC concentration prevalence refers to percentage of positive cases found in this range out of the total sample (N)

4. Licit production, consumption, international trade

In the last report of the INCB (233), the following overview was given: the licit use of cannabis has been increasing considerably since 2000. Before 2000, licit use was restricted to scientific research and was reported only by the United States. Since 2000, more and more countries have started to use cannabis and cannabis extracts for medical purposes (see subheading Medical Cannabis Use below), as well as for scientific research. In 2000, total licit production of cannabis was 1.4 tons; by 2016 it had increased to 211.3 tons. In 2016, the United Kingdom was the main producer, with 95 tons (44.9 per cent of the total), followed by Canada, with 80.7 tons, mostly intended for domestic consumption. They were followed by Portugal (21 tons), Israel (9.2 tons), the Netherlands and Chile (both 1.4 tons). In terms of exports, the United Kingdom continued to be the main exporter of cannabis (2.1 tons, or 67.7 percent of the total international trade).

There is another industrial sector of cannabis cultivation in some countries which involves growing low-potency cannabis (hemp) for industrial use under controlled circumstances (234). In European and North American countries, to be legally classified as hemp the crop may not contain more than 0.2% or 0.3% of THC, respectively. While national regulations vary, such cultivation is ongoing in several countries, to produce paper, paper, textiles, rope or twine, and construction materials based on fiber from stalks. Grain from industrial hemp is used in food products, cosmetics, plastics and fuel. Finally, medical uses of hemp are explored. The biggest producers of hemp products (fiber and seeds) appear to be North Korea and China (234).

4.1 Medical cannabis programs

In several high-income countries, especially within North America and Europe, medical cannabis (MC) programs have proliferated, and their impact on public health has become a focus (9, 10). In this section, MC programs are defined as full authorization of natural cannabis products (usually supplied in herbal form). In most countries with MC programs, magistral preparations of cannabis (medical product prepared in the pharmacy for an individual patient), and/or cannabinoid-based medicines such as dronabinol (main constituent: THC) or nabiximols (main constituents: THC and cannabidiol), are made available as well. For this section, we will concentrate on countries where natural cannabis products have been fully authorized.

Globally, MC programs have been implemented in the American and European region and Australia. As of November 2017, medical cannabis can be used legally in Australia, Canada, Chile, Colombia, Germany, Israel, Jamaica, The Netherlands, Peru, and in 29 US states (235).

In Europe, the European Medicine Agency did not authorize any natural cannabis material. Consequently, natural cannabis for medical use in Europe has only been made available in two countries (Germany, The Netherlands) through their own medical agencies. In these countries, herbal cannabis can be sourced via pharmacies after obtaining the relevant prescription. In the remaining European countries with MC programs, patients need to resort to cannabinoid-based medicines or magistral preparations of cannabis (for an overview of Europe, see Figure 5 below).

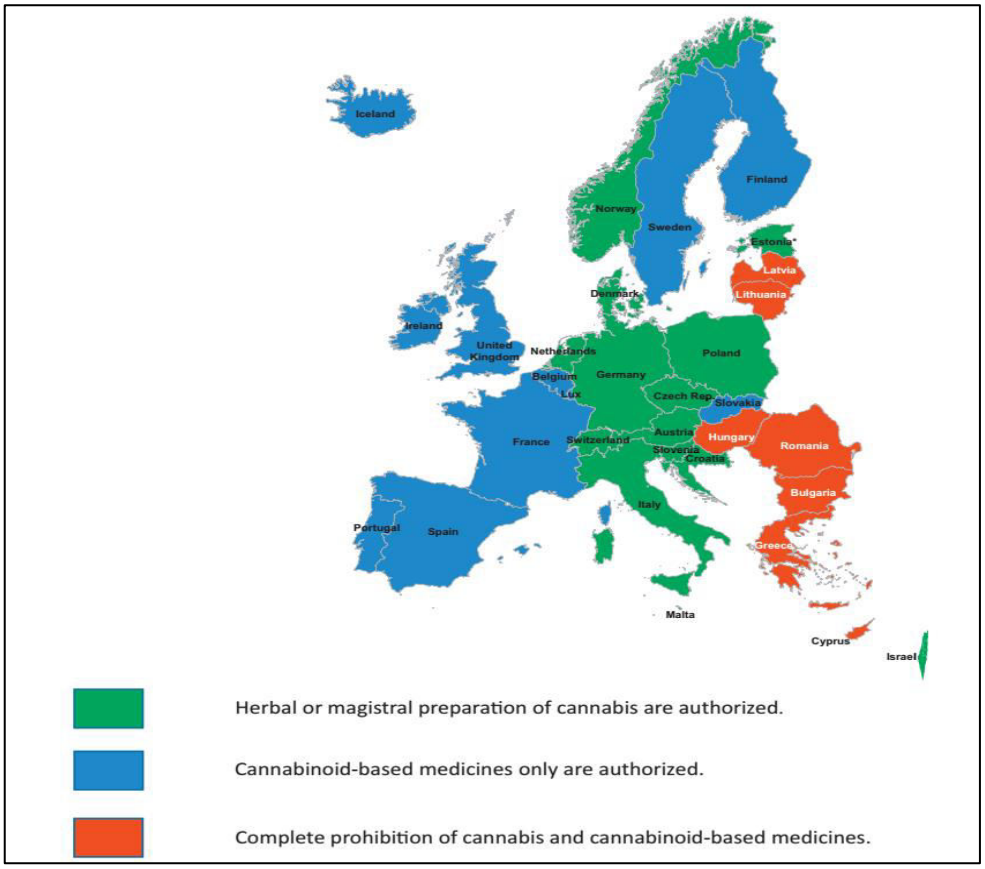
In Israel, patients can get prescriptions for natural cannabis (and cannabinoid-based medicines) from specially trained doctors and source the products from certified suppliers. In Canada, prescriptions can be made by any medical doctor or nurse practitioner with a valid license based on the Access to Cannabis for Medical Purposes Regulations (236). In the USA, natural cannabis products have not been approved as medicines on the federal level by the Food and Drug Administration, but several cannabinoid-based drugs have. However, on the state level, MC programs usually involve authorization of natural cannabis material, which can be sourced via specialized dispensaries or by own cultivation (237) (for an overview of the United States, see Figure 6). In 2017, it has been estimated that 2.25 million people used medical cannabis in the United States (see Figure 7 below for a statewide breakdown of users).

Several other American countries have effective MC programs in place, including Chile (238), Colombia (239), Jamaica (240), Peru(241), and Uruguay. In the latter, a bill legalizing recreational use of cannabis was passed in 2013. During a slow but gradual implementation of the new legislation, a medical cannabis decree has been introduced as well (5). Both recreational and non-recreational cannabis users can join local cannabis clubs, which are entitled to cultivate cannabis plants for their members (maximum number of members: 45; (242)). Alternatively, cannabis can be obtained through selected pharmacies after formal registration. As of April 2017, 90 cannabis clubs and 23,300 people have been registered with the National Institute for Regulation and Control of Cannabis (243), however, the ratio of recreational to medical users is not known.

In Australia, medical cannabis is not registered in the Australian Register of Therapeutic Goods. Thus, natural cannabis products need to be imported from Europe or Canada and can only be dispensed to individual patients from the treating practitioner upon approval from the state or federal agencies (244).

Outside of these regions, very few discussions around legalizing cannabis for medical purposes are observed, with the exception of South Africa (245).

Figure 5: Medical cannabis programs in Europe



Source: (235)

Figure 6: Types of access to cannabis by US state (5)

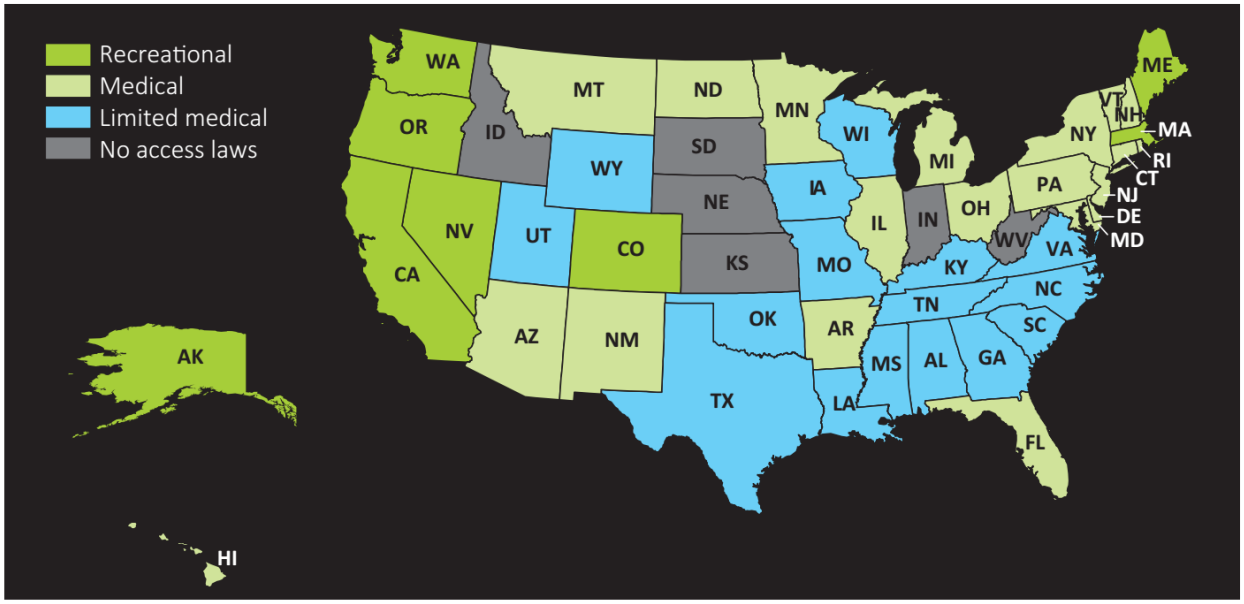
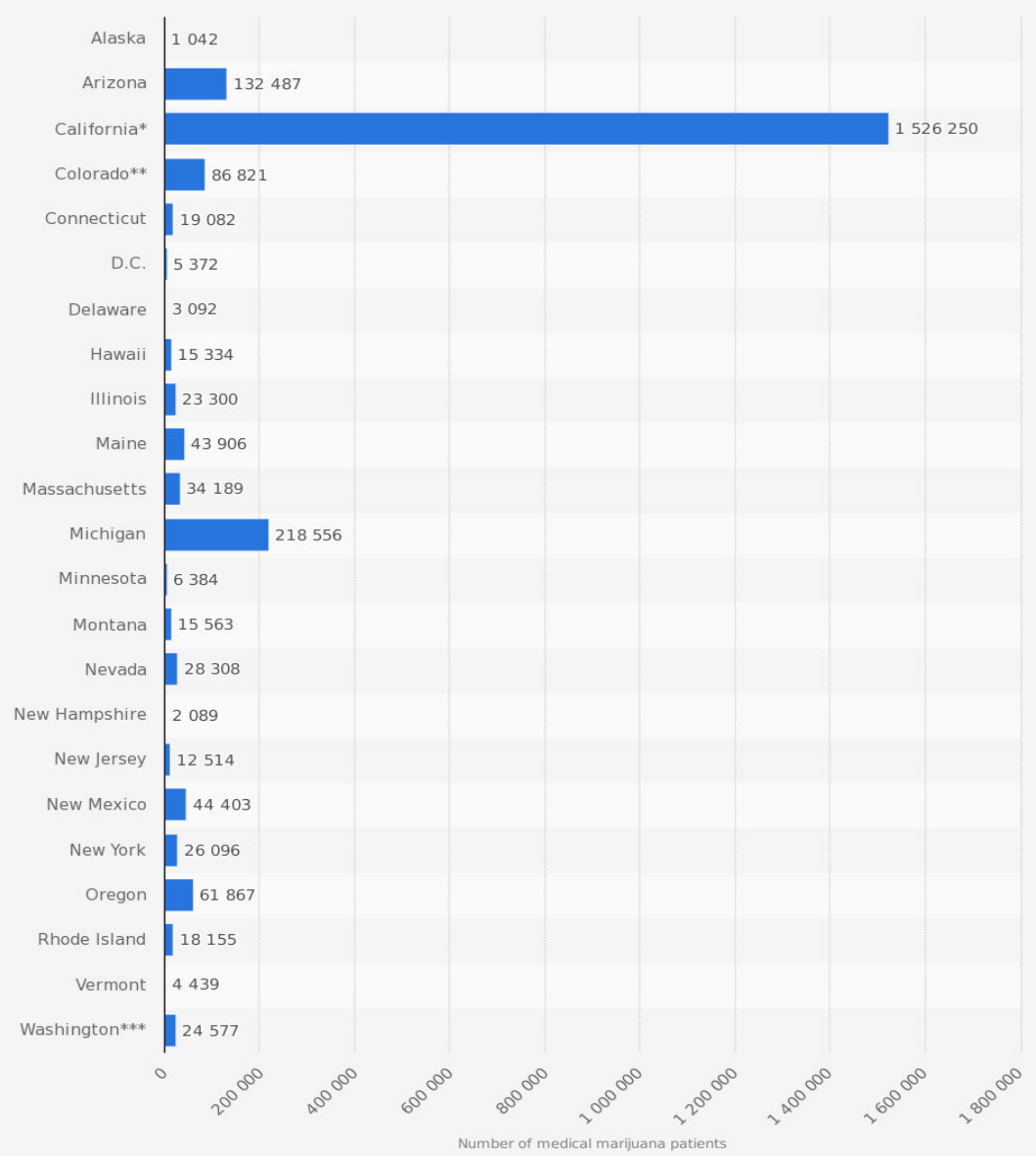


Figure 7: Number of legal medical cannabis patients in the U.S. as of August 2017, by state



Source: (246)

Due to the scheduling of cannabis as an illicit drug, there are policy implications of medical cannabis programs (247). In several instances in North America, the introduction of medical cannabis was seen as a way to give up prohibition without having to legalize or officially decriminalize cannabis use, and regulation was set up in a way to create the fewest barriers. Obviously, in analyzing the situation, there should be a distinction made between countries or states where cannabis has been legalized and others. For the latter, there is no reason why the medical use of cannabis should not be regulated by the same procedures as other medications, and this would require restricting cannabis to specific conditions, where its effectiveness has been demonstrated in randomized clinical trials (248, 249).

However, the current situation offers a chance to look into the public health consequences of a natural experiment, where medical cannabis is used by many as self-medication for various conditions, including conditions such as mood and anxiety disorders or psychosis, where there are clear contraindications (106, 250, 251). North America may serve as a test case for public health consequences of the recent proliferation of medical cannabis (252, 253). For instance, currently, there is a lot of research on the impacts of increased availability of medical cannabis on alcohol use or opioid prescriptions in the general population (alcohol: (254); opioid prescription: (255, 256)). It will be important to assess the overall public health balance of these programs in a rigorous way, looking at potential positive and negative consequences before drawing premature conclusions.

5. Illicit manufacture and traffic

In our systematic search of the peer-reviewed literature, we found no article focused on illicit production of cannabis plant and resin or traffic. However, as indicated above, the UN monitoring system, mainly UNODC, annually updates on illicit production and trade. We will in the following summarize the main points from the World Drug Report 2017, mostly referring to the year 2015 (5):

- Cannabis continues to be the most widely illicitly produced drug worldwide, cultivated in 135 countries covering 92% of global population. Most of this production is for herbal cannabis. The production countries for resin are more limited, with the vast majority of resin originating from Morocco, Afghanistan, Lebanon, India, and Pakistan.

- Eradication of production venues is one policy response, with the largest efforts reported in Northern America.

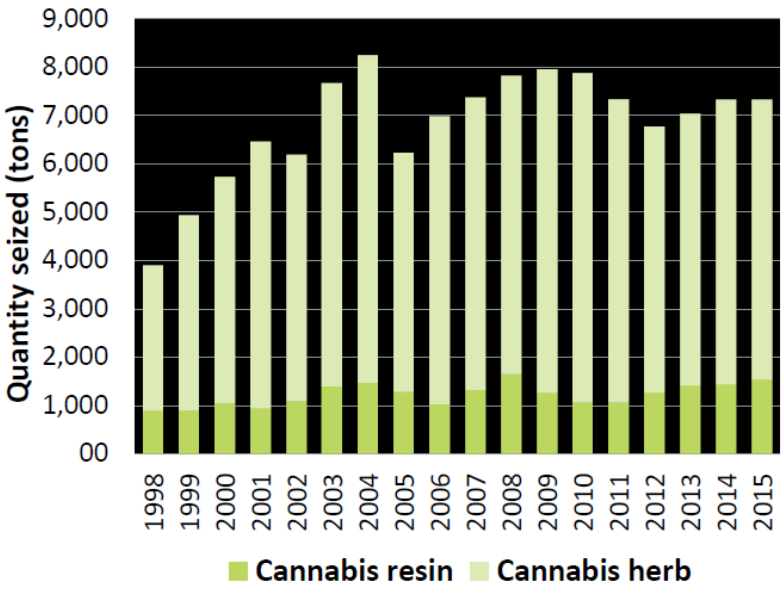
- Seizure of illicit cannabis is another policy aimed at reducing supply. Almost all countries responding to the UNODC survey reported any cannabis seizures in 2015, and cannabis seizures made up 53% of all drug seizures worldwide 2015. As noted in Figure 8 below, the amount of cannabis resin seized was about 1,500 tons and the amount of cannabis herb seized was slightly higher than 7,000 tons.

- Based on quantities intercepted, and with cautionary interpretation, as reporting standards differ, the trafficking of cannabis seems to have stabilized at a high level in the past decade (compared with the level in the late 1990s). Most of the seizures took place in North America.

- Seizures differed by type of cannabis: for herbs, the largest amounts were seized in the Americas (for details, see below); for resin, the largest amounts were seized in Spain, Pakistan and Morocco.

- In 2015, almost two-thirds (64 percent) of the total quantity of global cannabis herb seized was seized in the Americas, most notably in Mexico, followed by the United States, Paraguay and Brazil. Following a peak in 2010, however, seizures of cannabis herb in North America declined by 55 percent until 2015 (despite rising levels of cannabis consumption in these countries), reflecting a possible fall in cannabis production in Mexico, as well as an overall reduction in the priority given to cannabis interdiction as the cultivation, production, trade and consumption of cannabis has become legal in several jurisdictions in the United States in recent years. By contrast, cannabis herb seizures more than doubled over the period 2010-2015 in Africa and South America.

Figure 8: Global quantities of cannabis resin and herb seized (5)



Source: UNODC, based on responses to the annual report questionnaire.

Appendix 1: Systematic Search on the epidemiology of Cannabis Plant and Cannabis Resin

The background section gives general knowledge on the epidemiology of cannabis use as derived from global monitoring efforts. This knowledge was supplemented with systematic searches of peer-reviewed literature, based on the PRISMA guidelines (257, 258).

Search strategy

Various search strategies were independently explored for all four epidemiological reports (1: Cannabis plant and cannabis resin; 2: Extracts and tinctures of cannabis; 3: Delta-9-tetrahydrocannabinol (THC); 4: Isomers of THC) by the authors independently using different combinations of keywords and MeSH terms pertinent to epidemiology, cannabis-related compounds, substance use, abuse, dependence, self-medication and therapeutic use. This was done to determine the best search strategy for each report and the least overlap between reports, to identify most relevant studies, given the limited time to prepare this pre-review.

The following databases were searched using OVID on March 8, 2018:

1. Embase
2. Medline
3. PsycINFO

With no language restrictions, the search was limited to the literature published in 2000 and onwards. Table A1 shows the exact search strategy that was implemented.

Table A1: Search strategy for Report 1 Cannabis plant and resin

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 plant	4095
14	12 and resin	378
15	13 or 14	4352
16	4 and 9 and 15	247
17	Dependence	588264
18	Abuse	549267
19	Disorder	2664499
20	self-medication	19180
21	Therapeutic	2333110
22	17 or 18 or 19 or 20 or 21	5766886
23	4 and 15 and 22	693

24	16 or 23	809
25	remove duplicates from 24	613

Further processing and quality control

Results from the searches were screened in parallel by different authors, and any studies relevant to any of the other three reports were exchanged between the authors during the review.

Reviewing the studies for inclusion was a two-step screening process:

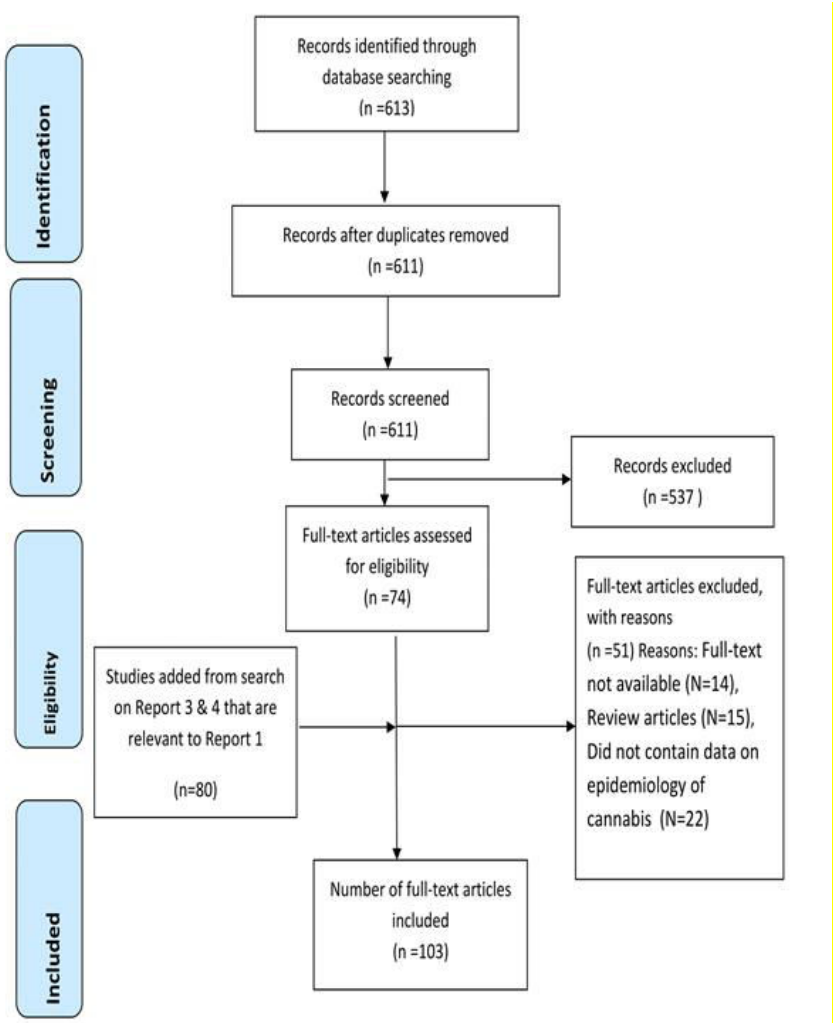
1. Based on title and abstract screening, studies with minimal uncertainty were excluded.
2. Based on full-text review of studies remaining after step 1, studies were selected for final inclusion and data was extracted.

We followed the final epidemiology terms of reference for the formal inclusion and exclusion criteria as provided by the WHO and added additional relevant inclusion/exclusion criteria that were pertinent to the focus of our report on the epidemiology of cannabis plant and resin (see Appendix 2 below).

Each step of the review was led by a pilot screening of 20 studies to maintain consistency between the authors taking part in the review. In addition, coding of studies was compared systematically for 20 studies between VT, HF, OSMH and JR. The authors also met on a weekly basis throughout the duration of the review to discuss the progress of the reports and to resolve any conflicts during study selection and coding.

Of 613 studies retrieved from the search, 74 were included for full-text eligibility after title and abstract screen, of which 51 were excluded for the following reasons: full-text not available (N=14), review articles (N=15), did not contain data on the epidemiology of cannabis (N=22). After full-text screening and adding 80 articles from the search for Report 3 and 4, 103 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.

Figure A1: PRISMA diagram for Report 1



Template for the flow chart: (258)

Appendix 2: Inclusion and exclusion criteria for Report 1 - part Cannabis Plant and Cannabis Resin

In general, we followed the final epidemiology terms of reference for the formal inclusion and exclusion criteria. For Report 1, the formal inclusion and exclusion criteria were:

Inclusion Criteria

Studies to be included in the report are those involving:

- Cannabis as defined by the International Drug Control Conventions as "the flowering tops of the cannabis plant from which the resin has not been extracted"2. The term "cannabis" generally refers to a dried preparation of the flowering tops or other parts of the cannabis plant.
- Cannabis resin which is defined as "the separated resin, whether crude or purified, obtained from the cannabis plant." It is normally in solid form and is sometimes known as "hashish"
- Any clinical conditions for which cannabis was used medically or for therapeutic use (also being admitted to a psychiatric facility for cannabis use)
- Reviews on cannabis that include the epidemiology
- Driving under the influence of cannabis
- Self-medication and the epidemiology of self-medication is reported

Exclusion Criteria

Studies to be excluded from the report involve:

- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols)
- Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants
    - (-)-trans-delta-9-tetrahydrocannabinol
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
    - Pure cannabidiol (CBD)
    - 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

Section 5: Epidemiology

- Methodological development papers or conference abstracts
- 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: Search Strategy for peer-reviewed articles on Delta-9-tetrahydrocannabinol

Following databases were searched using OVID on March 8, 2018:

1. Embase
2. Medline
3. PsycINFO

The search was restricted to literature published in 2000 and onwards. Various search strategies were explored by the authors independently using different combinations of keywords and MeSH terms pertinent to epidemiology, cannabis-related compounds, substance abuse, self-medication and therapeutic use. This was done to determine an optimal unanimous search strategy for each report, to identify the most relevant studies, respecting the short timeframe available to prepare this Pre-Review. The final search strategy is listed in Table A2.

Table A2: Search strategy for THC

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	delta-9-tetrahydrocannabinol	6047
11	tetrahydrocannabinol or thc	25380
12	dronabinol or exp dronabinol/	13589
13	10 or 11 or 12	29610

14	4 and 9 and 13	1331
15	remove duplicates from 14	1055

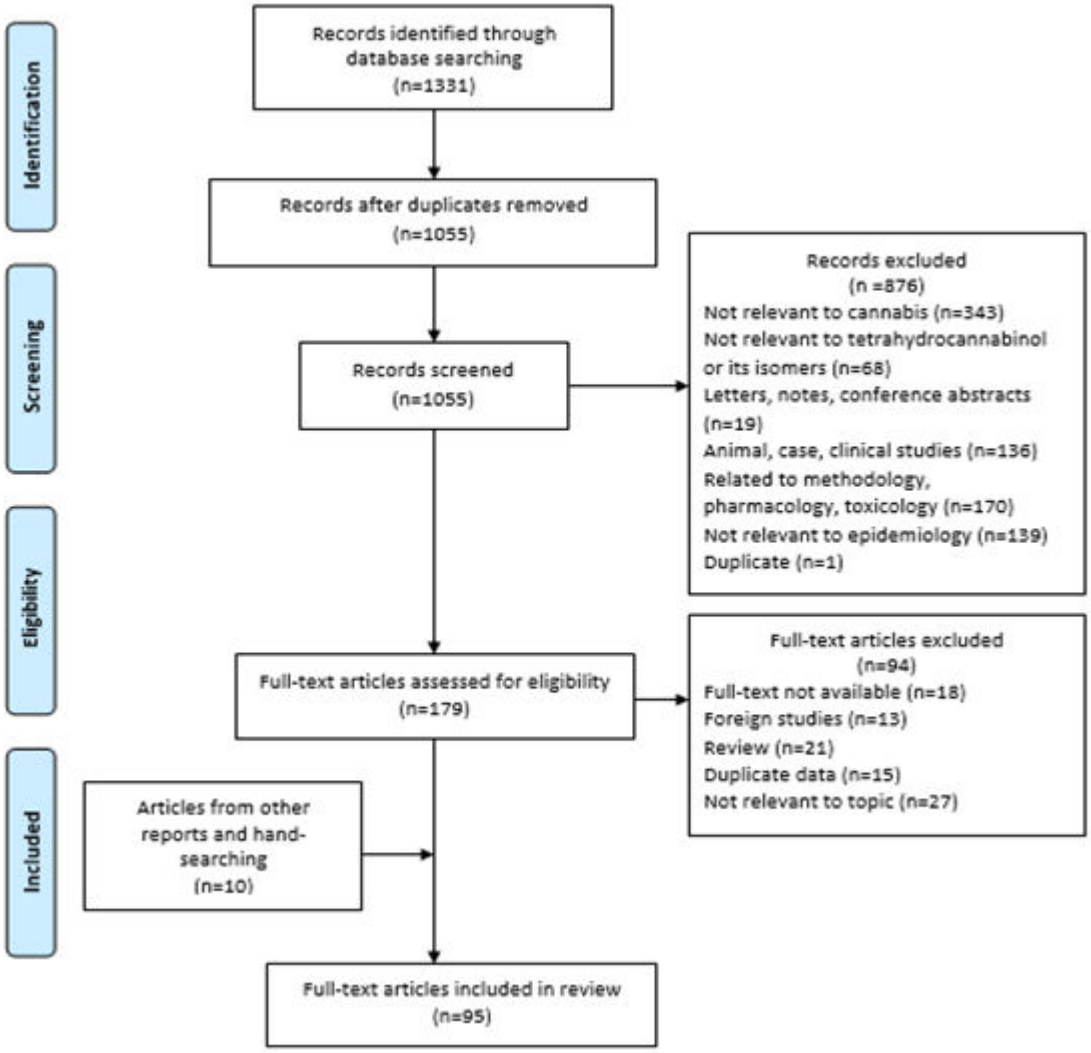
A full list of references can be found in a separate Reference Appendix document.

Reviewing the studies for inclusion was a two-step screening process:

1. Based on title and abstract screening, studies with minimal uncertainty were excluded.
2. Based on full-text review of studies remaining at step 1, studies were selected for final inclusion and data was abstracted at this point.

Each step of the review was led by a pilot screening of 20 studies to maintain consistency between the authors taking part in the review. In addition, coding of studies was compared systematically for 20 studies between VT, HF, OSMH and JR. The authors also met on a weekly basis throughout the duration of the review to discuss the progress of the reports and to resolve any conflicts during study selection and coding. The results of the searches and details of processing are summarized in Figure A2.

Figure A2: PRISMA Diagram for Reports 3 (258)



Of 1055 studies retrieved from the search, 179 were included after screening of title and abstract (see below). After full-text screening, 95 studies were included in this report. Review articles were excluded from analysis but were kept for the background of the report and inserted into the various chapters.

Appendix 4: Inclusion and exclusion criteria for Report 1 - part THC

Retrieved articles were screened with inclusion and exclusion criteria as follows:

Inclusion criteria for both reports report 1 - part THC

Studies to be included are those involving:

- Epidemiological data on THC and/or THC isomers
- Potency data on THC and/or THC isomers
- Any clinical conditions for which THC and/or THC isomers was used medically or for therapeutic use
- Driving under the influence of cannabis with concentration measurements of THC and/or THC isomers
- Reviews on cannabis with a focus on THC and/or THC isomers

Exclusion criteria

Studies to be excluded are those involving:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g., nabiximols), except those that are pure delta-9-THC Pure cannabidiol
- Conference abstracts, letters and notes
- Clinical trials, case studies, animal studies
- Primary focus on pharmacology, toxicology and methodology
- Specialized populations such as nightclub patrons, ship sailors, etc.
- Sexual assault and violent offenders
- <100 samples size
- Full-text unavailable
- Foreign articles

Included articles were then allocated to Reports 3 and 4 on the basis of the following:

Report 1 - part THC specific inclusion criteria

- Pure delta-9-tetrahydrocannabinol that is obtained either directly from the cannabis plant or synthesized
- The stereochemical variants of delta-9-tetrahydrocannabinol:
    - (-)-trans-delta-9-tetrahydrocannabinol (also known as dronabinol)
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol

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 (2, 3), 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.

Synthetic cannabinoids are a different class of drugs, formally not included in our reports, and usually subsumed as one category under newly psychoactive substances (259). A recent review, which includes epidemiology, has been conducted by Castaneto and colleagues ((260); see (261) for a summary on synthetic cannabinoids in Japan). Because of recent increases in use of synthetic cannabinoids in high-income countries, synthetic cannabinoids have come into focus both in terms of clinical use (262) and in terms of public health (263-265).

Appendix 5: THC concentrations in vulnerable populations

One other public health problem related to cannabis use is exposure to vulnerable populations, such as children or fetuses. There is evidence that cannabis exposure during pregnancy may impact fetal growth and neurodevelopment (266). Cannabis use may also be associated with preterm birth, particularly in chronic users (266). Respiratory problems and cognitive symptoms have been found in children through passive exposure (130). Exposure may also lead to intentional cannabis use later in life. Cannabis use by pregnant women has been reported as a wide range of 3-34% (266) and has been found to be increasing with time (130).

Three studies explored THC concentrations from hair analyses in Spain, a country with comparatively high if not the highest cannabis consumption in the European Union (267) (see Table A3). Analysis of illicit substances in hair is a useful tool when concerned with passive exposure and to investigate substance use during months prior to testing; however, concentrations of THC in hair tend to be very low regardless of chronic use (267). Thus, sensitivity of hair analysis is limited, especially for low exposure, and it cannot be reliably used to determine amount of consumption (268).

As can be expected from inadvertent exposure, average THC concentrations found in hair of children aged 2–11 years was considerably lower than concentrations found in the hair of parents (267). However, hair concentrations found in children (267) were comparable to those found in the hair of pregnant women, 2.9% of whom self-reported cannabis use during pregnancy (67). This may be indicative of long-term exposure.

Concentrations of THC in fetal plasma match that of the THC in maternal plasma due to its ability to pass through the placental barriers (269). In a study of 209 women, no relationship between cannabis use during pregnancy and neonatal outcomes was found (67).

In Barcelona, Spain, three studies conducted in the same hospital in 1998, 2008 and 2013 introduced the possibility of detecting a time trend of cannabis exposure to children; two hair analysis studies in 1998 and 2008 with a combined total of 277 children did not find any cannabinoids (187), whereas in 2013 there was a drastic increase to 11.4% (267). There did not appear to be an association between parental socioeconomic status and ethnicity with THC detection in their offspring.

Table A3: THC concentrations from hair analysis in children and fetuses

Country/Region	Median Year	Sample Size (N)[a,b]	Prevalence (%)	Average THC concentration [Range] (ng/mL)
Spain/Barcelona (187)	2003	277[a]	None detected	–
Spain/Vigo (67)	2011	209[c]	3.8	[0.0426–0.1972]
Spain/Barcelona (267)	2013	114[a] 114[b]	11.4 15.8	0.16 1.36

a = children admitted to emergency department, b = parents, c = pregnant women

Appendix 6: 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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Cannabis and cannabis resin

Annex 1: Member State Questionnaire

1. Introduction

Definition for the questionnaires used as the basis of this report: The dried flower/ leaf of the cannabis Sativa plant or resin prepared from the plant.

Examples:

- Marijuana
- Weed
- Pot
- Hashish
- Kief

a. Overview of Responses

i. Q2

Q2: Please indicate your country.

Representatives of 90 countries answered the questionnaire:

Algeria, Armenia, Australia, Austria, Bahrain, Barbados (2 representatives), Belarus, Belgium, Benin, Bhutan, Brazil, Brunei Darussalam, Bulgaria, Burundi, Canada, Colombia, Cook Islands, Cote D'Ivoire, Cyprus, Czech Republic, Denmark, Ecuador, Egypt, El Salvador, Eritrea, Estonia, Ethiopia, Finland, France (2 representatives), Gabon, Georgia, Germany, Ghana, Greece, Guatemala, Honduras, Hungary, India, Indonesia, Ireland, Israel, Italy, Jamaica, Japan, Kenya (2 representatives), Latvia, Lebanon, Lithuania, Luxembourg, Madagascar, Malaysia, Mali, Malta, Marshall Islands, Mauritius, Mexico, Micronesia, Monaco, Montenegro, Mozambique, Nauru, Netherlands, New Zealand, Nicaragua, Niue, Palau, Papua New Guinea, Philippines, Poland, Portugal, Republic of Korea, Republic of Moldova, Russian Federation, Saint Lucia, Serbia, Singapore, Slovenia, Solomon Islands (2 representatives), Spain, Sri Lanka, Sweden, Switzerland, Thailand, Togo, Tonga, Trinidad and Tobago, United Kingdom of Great Britain and Northern Ireland (the), United States of America, Zambia, Zimbabwe

ii. **Q4**

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

73 (80%) answered yes, 18 (20%) answered no.

2. Results: Approved medical use

a. Medical use

i. **Q5**

1. Description of countries that have approved medical uses

Q5: At **national level**, is cannabis plant or resin legally approved for medical use in your country?

Yes (16%): Canada, Colombia (cannabis extracts only), Czech Republic, Denmark, Estonia, Germany, Greece, Israel , Netherlands, Philippines, Slovenia, Sri Lanka

Other (13%): Australia, Barbados, Ecuador, Finland, Jamaica, Mexico, New Zealand, Poland, Switzerland, Zambia. Among the countries who replied other, some of the answers can be classified as a yes, some as a no.

ii. **Q6-Q16**

Q6: Please indicate any approved therapeutic indications for the medical use of **cannabis plant/cannabis resin of cannabis** in your country:

Disease condition	**Number of countries**	**%**
Epilepsy	2	13
Multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury	2	13
Arthritis	1	6
Dystonia	0	0
Huntington's disease	0	0
Parkinson's disease	2	13
Tourette syndrome	2	13
Glaucoma	1	6
Anxiety	0	0
Depression	1	6
PTSD	1	6
Schizophrenia / psychosis	0	0
Alzheimer's disease/ dementia	0	0
Skin disease	1	6
Irritable bowel syndrome	0	0
Inflammatory bowel disease	0	0
Liver disease	0	0
Obesity / diabetes	0	0

Cancer	1	6
HIV/AIDS	1	6
Chronic pain	2	13
Crohn's disease	1	6
Attention Deficit Disorder (ADD)	0	0
None specified	4	25
Other (one country indicated palliative care (Israel), and in some countries indications are currently in preparation (Slovenia, Greece); several countries indicate that there are no limitations and/or the decision remains with the prescribing doctor (Denmark, Canada, Poland, Germany, Estonia, Finland))	11	69

Q7: Please Indicate any symptoms that **cannabis plant/cannabis resin** is approved to treat:

Symptom	**Number of countries**	**%**
Acute pain	3	25
Chronic non-cancer pain	2	17
Cancer pain	2	17
Nausea/ vomiting	2	17
Appetite stimulant	2	17
Headaches/ migraines	0	0
Muscle spasms	2	17
Seizures	1	8
Sleep problems	0	0
Alcohol withdrawal symptoms	0	0
Opioid withdrawal symptoms	0	0
Palliative care	2	17
Other (as above, several countries indicate that there are no limitations with respect to approved symptoms to treat and the decision remains with the medical doctor)	9	75

Q8. Please indicate whether there are any permitted marketed products of **cannabis plant/cannabis resin**:
Approved products are:

- Bedrocan THC 22% / CBD <1.0% sativa flos (Netherlands)
- Bedrobinol THC 13.5% / CBD <1.0% sativa flos (Netherlands)
- Bediol THC 6.3% / CBD 8% sativa granulate (Netherlands)
- Bedica THC 14% / CBD <1.0% indica granulate (Netherlands)
- Bedrolite THC <1.0% / CBD 9% sativa granulate (Netherlands)
- "Medical-Grade Cannabis Products" - Detailed in IMC-GCP (Israel)
- A list of cannabis products approved by the German regulatory agency

Q9: Are there any ongoing **approved clinical trials** in your country that are developing **cannabis plant/cannabis resin** for medical use?

Out of 16 responses, 4 indicated ongoing trials (25%) and 1 answered “other” (6%), which related to allocated money for trials.

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

- In **Canada**, several trials are conducted, unspecified
- In **Israel**, "Medical-Grade Cannabis Products" are studies as detailed in IMC-GCP
- In **The Netherlands**, a clinical study on fibromyalgia and cannabis (second phase) is being conducted at Leiden University Medical Centre
- In the **United States of America**, Study of Four Different Potencies of Smoked Marijuana in 76 Veterans With PTSD, Sponsor: Multidisciplinary Association for Psychedelic Studies, Location: Scottsdale Research Institute, Phoenix, Arizona, United States, clinicaltrials.gov identifier: NCT02759185.

Q11: Do individuals require a prescription to obtain **cannabis plant/cannabis resin**?

In 11 out of 14 responses, medical cannabis plant or resin is only dispensed on the basis of a prescription (79%). In two further countries (14%), patients either require a medical document by their healthcare provider proving medical support for medicinal cannabis use or a narcotic prescription and license.

Q12. What types of professionals are allowed to **prescribe cannabis plant/cannabis resin**?

Professional	**Number of countries**	**%**
Medical doctor / psychiatrist	7	54
Osteopath	0	0
Nurse/nurse prescriber	0	0
Pharmacist	0	0
Psychologist	0	0
Physiotherapist	0	0
Healthcare worker	0	0
No prescription is required	0	0
Other (authorized products by medical doctor and nurses (Canada); as narcotics by dentists or veterinarians (Mexico); specialist doctors after receiving particular training from regulatory agency (Israel); profession not yet regulated (Estonia, Greece))	7	54

Q13. What kinds of settings are approved to legally **cannabis plant/cannabis resin** in your country?

Setting	**Number of countries**	**%**
At a doctor's office	0	0
Pharmacies	8	62
Online	1	8
Retail shops	0	0
Licensed/specialised cannabis dispensaries	0	0
Hospitals	4	31
Outpatient clinics	0	0
Palliative care facilities	1	8
Nursing homes	0	0
Other (medical cannabis can be bought by registered patients from licenced producers (phone, online) or in hospital pharmacies (Canada); setting not yet regulated (Mexico, Greece); setting with specially trained staff (Israel))	6	46

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

Out of 12 responses, 2 answered "yes, by NHS" (17%) and 5 answered "No, patients cannot be reimbursed" (42%). The 5 "other" responses (42%) related to partial insurance coverage or income tax deduction (Canada), for patients with terminal illnesses only (Germany) or after individual application only (Estonia).

Q15: Are any clinical guidelines used in your country for the prescribing of medical **cannabis plant/cannabis resin**?

There are clinical guidelines in 5 countries (38%):

- **Canada:** clinical guidelines for medical purposes by The College of Family Physicians of Canada; several guidelines for the use of cannabis for medical purposes by Health Canada (see website)
- **Denmark:** guide to doctors with indications and evidence by the Danish Medicines Agency
- **Germany:** compilation of frequently asked questions relating to the medical prescription by The German Medical Association (Bundesärztekammer)
- **Israel:** The IMC-GCP (Good Clinical Practice)

Q16. Is there a regulatory agency in your country that monitors **cannabis plant/cannabis resin** for medical use?

There are 12 countries (86%) with regulatory agencies:

- Canada: Health Canada
- Colombia: Fondo Nacional de Estupefacientes - Ministerio de Justicia y el Derecho
- Czech Republic: Ministry of Health
- Denmark: The Danish Medicines Agency
- Estonia: State Agency of Medicines
- Finland: Finnish Medicines Agency
- France: ANSM
- Germany: Federal Institute for Drugs and Medical Devices (BfArM); pharmacovigilance system
- Israel: Israeli Medical Cannabis Agency (IMCA)
- Mexico: COFEPRIS

- Netherlands: Office of Medicinal Cannabis
- Slovenia: Agency for Medicinal Products and Medicinal Devices

b. National legislation

i. Q17-21

Q17: How would you describe the trend in the number of users of **cannabis plant/cannabis resin** for medical use over the last 3 years?

As for cannabis plant, 5 out of 12 respondents (42%) couldn't judge how the number of medical cannabis users developed in their country. Further, in 5 countries (42%) the number has slightly or substantially increased whereas in 2 countries (17%) the number remained the same.

As for cannabis resin, 8 out of 10 respondents (80%) couldn't judge how the number of medical cannabis users developed in their country. For the remaining two countries, slight or substantial increases were reported (20%).

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

Out of 72 responses, 56 reported no legislation change in the past 3 years (78%). In 16 countries (22%) legislation has changed. Changes related to regulatory procedures (Canada), whereas other changes are still being discussed (Barbados, Mexico).

Q19: If yes, what types of legislative changes has your country made for **medical use** of **cannabis plant/cannabis resin**?

Legislative change	**Number of countries**	**%**
Change to the legal status of medical cannabis	10	50
Changes to the supply of medical cannabis (e.g. changes in licensing, import – or export of products)	8	40
Changes to access to medical cannabis (e.g., variety in products, therapeutic indications, etc.)	7	35
Other	11	55

Q20: Is your country currently considering changes to its national legislation around access to to cannabis and cannabis-related substances for medical use?

In the majority of countries, legislative changed are currently not considered (49 responses, 77%). There are 15 countries from Europe, the Americas, Asia, and Australasia currently considering changing the legislation. Changes will occur with respect to amendments to access via growing own supply (Canada), whereas in other countries, parliamentary discussions are ongoing but the specific results are still unclear (Ireland, Mexico, Portugal, Trinidad and Tobago, Zambia,). In two countries, there are no majorities for legislative changes yet (Belgium, USA).

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

- Many of the countries who answered indicated not to know the impact of changed availability on public health (19 of 33 for decreased availability: 58%; 23 of 47 for increased availability: 49%).
- As for decreased availability, 6 out of 33 countries (18%) saw/expected a substantial or slightly negative impact, 6 (18%) saw/expected no impact, while 2 (6%) saw/expect a slightly positive effect.
- As for increased availability, 10 out of 47 countries (21%) saw/expected a slightly or substantially positive impact, 2 (4%) saw/expected no impact, while 12 (26%) saw/expected a slightly or substantially negative effect.
- With respect to effects from increased availability, European countries rather tended to report a positive impact (6 out of 10 countries, 60%) than a negative impact (5 out of 12 countries, 42%). With respect to effects from decreased availability, no regional pattern could be identified.
- While some respondents feared that increased availability would be difficult to control and could lead to promotion of other drug use, others mentioned the benefit for affected patient groups. One respondent highlighted to consider differential effects of legislative changes to medical and non-medical use. Several comments report that public health impacts cannot be described due to lack of data.

3. Results: Prevalence of non-medical use

a. Non-Medical use

i. Q22

Q22: On a **national level**, is **cannabis plant (or cannabis resin)** *legally* available for non-medical use in your country?

Only 4 out of 73 (5%) countries (Armenia, Madagascar, Marshall Islands, Switzerland) indicated legal availability of cannabis plant/resin for non-medical use. In one additional country (Jamaica), personal use of a limited amount is also allowed.

ii. Q23

Q23: Is **cannabis plant/cannabis resin** used for cultural, ceremonial, or religious purposes in your country?

Out of 72 responses, 13 (18%) could not answer the question and 9 (12.5%) indicated use of cannabis plant/resin in special cultural settings. These were related to Rastafarians and other communities using cannabis products for sacramental purposes (in some countries legally, in others illegally) and certain tribes renowned for their cannabis use to boost work capacities. In some countries, cannabis use is part of festivities.

b. Public health impact of use

i. Prevalence data

1. Adults:

Q24: Does your country collect prevalence data around the use of **cannabis plant/cannabis resin**?

Out of 73 responding countries, 42 respondents (58%) reported prevalence data collection on cannabis plant / resin in their country, while 8 respondents (11%) were unsure about this question.

Q25. Prevalence of use of **cannabis plant/cannabis resin** amongst adults (over 18 years of age)?

Category	Range	Number of countries
Lifetime	<=10%	7
	>10% & <=20%	10
	>20% & <=30%	7
	>30%	7
Past year	<=5%	14
	>5% & <=10%	9
	>10% & <=15%	5
	>15%	1
Past month	<=5%	20
	>5% & <=10%	5
	>10%	1
Survey year	2016/2017	18
	2014/2015	13
	2013 or earlier	3

Prevalence by age figures is not presented in detail here due to use of incompatible age categories and reference periods (lifetime, year, month). However, cannabis use prevalence is consistently reported to peak among 18 to 34 year olds and decreases with increasing age in all countries.

2. Youth:

Q26: Prevalence of use of **cannabis plant/cannabis resin** for non-medical use amongst **young people** (below 18 years of age).

a. **<u>Question 26:</u>**

Category	Range	Number of countries
Lifetime	<=10%	9
	>10% & <=20%	9
	>20% & <=30%	8
	>30%	3
Past year	<=5%	4
	>5% & <=10%	8
	>10% & <=15%	7
	>15%	9
Past month	<=5%	10
	>5% & <=10%	5
	>10%	8
Survey year	2016/2017	13
	2014/2015	11
	2013 or earlier	4

In most surveys, youths were defined as persons aged 15 to 17 years old. In several countries, data referred to results from the ESPAD survey.

3. General trends

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

- For adults, 13 out of 39 responses (33%) indicated no recent change in cannabis use prevalence. Increasing use was reported by 23 (59%) of countries, whereas 3 (8%) countries saw a decline in non-medical cannabis use.
- As most respondents come from high-income countries (predominately Europe), a distinct regional pattern could not be identified.
- For young people, 10 out of 35 responses (29%) indicated no recent change in cannabis use prevalence. Increasing use was reported by 15 (43%) of countries, whereas 10 (29%) countries saw a decline in non-medical cannabis use.
- The comments specified sources (cross-sectional/prospective surveys, addiction treatment, seizures) and highlight that the trend is often based on longer periods than the past 3 years only (because of data availability).

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 **cannabis plant/cannabis resin**?

Out of 71 respondents, 11 (15%) were unsure in answering this question and 13 (18%) indicated data collection of cannabis plant / resin in primary health care settings.

Q29: Number of primary care presentations relating to **cannabis plant/cannabis resin**.

Several respondents provided data on presentations in **primary health care** settings:

- Belgium (study): 5% of patients using cannabis alone and 16% of patients used not only cannabis in 2013
- Bulgaria: 5 persons in relation to cannabis alone and 10 persons in relation to cannabis in combination with other substances in 2017
- Ecuador: 4232 persons in relation to cannabis alone in 2016
- Eritrea: 6 persons in relation to cannabis alone and 6 persons in relation to cannabis in combination with other substances in 2017
- Madagascar: 216 persons in relation to cannabis alone and 69 persons in relation to cannabis in combination with other substances in 2017

iii. Emergency presentations
Q30-32

Q30: Does your country collect data about presentations to **emergency care settings** due to the use of **cannabis plant/cannabis resin**?

Out of 68 respondents, 12 (18%) were unsure in answering this question and 16 (24%) indicated data collection of cannabis plant / resin in emergency care settings.

Q31: Number of individuals in the past year presenting to emergency settings relating to the use of **cannabis plant/cannabis resin**.

Several respondents provided data on presentations in **emergency care** settings:

- Czech Republic: 133 persons in relation to cannabis alone in 2016
- France: 3060 persons in relation to cannabis alone in 2015
- Greece: 51 persons in relation to cannabis alone and 5 persons in relation to cannabis in combination with other substances in 2016
- Ireland: 64 persons in relation to cannabis alone in 2015
- Mauritius: 69 persons in relation to cannabis alone and 33 persons in relation to cannabis in combination with other substances in 2017
- Mexico: 50 persons in relation to cannabis alone in 2016
- New Zealand: 155 persons with primary diagnosis (may or may not be cannabis use alone) and 452 persons with secondary diagnosis (may or may not be cannabis use alone) in 2017
- Serbia: 78 persons in relation to cannabis alone in 2016
- Slovenia: 60 persons in relation to cannabis alone in 2017
- Spain: 778 cannabis-related emergencies and 2105 cannabis- and other drug related emergencies in 2015

Q32: Please list the adverse effects presented for **cannabis plant/cannabis resin** at the emergency room/department.

Adverse effect	Number of countries	%
Injuries related to impaired driving	4	31
Injuries related to accidents/falls	4	31
Prenatal exposure	0	0
Cannabis use disorders / withdrawal	7	54
Psychiatric comorbidity	11	85
Respiratory problems	4	31
Total	13	100

iv. Drug treatment presentations

Q33

Q33: Does your country collect data about presentations to **substance misuse treatment settings** due to the use of **cannabis plant/cannabis resin**?

Out of 68 respondents, 7 (10%) were unsure in answering this question and 36 (53%) indicated data collection of cannabis plant / resin in substance misuse treatment settings.

Q34: Number of individuals in the past year presenting to **substance misuse treatment** due to **cannabis plant/cannabis resin**:

Number of persons in relation to cannabis alone:

- Australia: 34,143 in 2015-16
- Austria: 2,510 in 2016
- Colombia: 2,094 in 2016
- Czech Republic: 1,627 in 2016
- France: 26,300 in 2016
- Georgia: 13 in 2017
- Greece: 376 in 2016
- Latvia: 194 in 2016
- Mauritius: 0 in 2017
- Mozambique: 1,102 in 2017
- Netherlands: 6,889 in 2015
- New Zealand: 358 in 2016-17

- Poland: 1995 in 2016
- Slovenia: 39 in 2015
- Spain: 10,209 in 2015
- Switzerland: 948 in 2015
- United Kingdom: 13,134 in 2016
- United States of America: 213,000 in 2015

Number of persons in relation to cannabis in combination with other substances:

- Austria: 5,010 in 2016
- Colombia: 7,517 in 2016
- France: 34,160 in 2016
- Greece: 413 in 2016
- Mauritius: 500 in 2017
- Mozambique: 4,077 in 2017
- Netherlands: 8,428 in 2015
- New Zealand: 1,335 in 2016-17
- Spain: 5,467 in 2015
- United Kingdom: 31,951 in 2016
- United States of America: 516,000 in 2015

Number of persons in relation to cannabis alone and in combination with other substances:

- Mexico: 8,981 in 2016

Other definitions:

- Bulgaria: 5.1% of persons in relation to cannabis alone and 2% of persons in relation to cannabis in combination with other substances in 2017
- Belgium: 1,742 persons in relation to cannabis alone (67.5% of the sample of registered new patients to treatment) and 839 persons in relation to cannabis in combination with other substances (32.5% of the sample of registered new patients to treatment) in 2016
- Ecuador: 4,232 persons in relation to cannabis use in general in 2016
- Germany: 16,440 treatment episodes in relation to cannabis alone and 17,852 treatment episodes in relation to cannabis in combination with other substances (excluding alcohol and tobacco) in 2016
- Portugal: 10,3% as primary drug in the total population and 38,7% of all entrants into treatment in 2016

v. Poison Centres

Q35-Q36

Q35: Does your country collect data about calls to **poison centres** due to the use of **cannabis plant/cannabis resin of cannabis**?

Out of 69 respondents, 13 (19%) were unsure in answering this question and 15 (22%) indicated data collection about calls to poison centres due to the use of cannabis plant/resin.

Q36: Number of calls to **poison control centres** due to the use of **cannabis plant/cannabis resin.**

Number of persons in relation to cannabis alone:

- Brazil: 111 in 2017
- Czech Republic: 55 in 2016
- Greece: 15 in 2016
- Ecuador: 13 in 2017
- Slovenia: 60 in 2017
- Sweden: 171 in 2017
- United States of America: 2,884 in 2016

Number of persons in relation to cannabis in combination with other substances:

- Brazil: 211 in 2017
- Ecuador: 1 in 2017
- Greece: 14 in 2016
- Slovenia: 74 in 2017
- Sweden: 124 in 2017
- United States of America: 7,384 in 2016

vi. Cases of impaired driving

Q37: Does your country collect data about cases of impaired driving due to the use of **cannabis plant/cannabis resin**?

Out of 66 respondents, 17 (26%) were unsure in answering this question and 9 (14%) indicated data collection about cases of impaired driving due to the use of cannabis plant/resin.

Q38: Number of cases of **impaired driving** due to **cannabis plant/cannabis resin:**

Number of persons in relation to cannabis alone:

- Bulgaria: 15
- Eritrea: 2
- New Zealand: 133,000
- Portugal: 115

Number of persons in relation to cannabis in combination with other substances:

- Bulgaria: 20
- Portugal: 39

Other definitions

- Spain: 7.5% of roadside testing positive for cannabis
- Spain: 21% of traffic-related deaths tested positive for cannabis

c. National legislation

Q39: In the past 3 years, has your country changed its national legislation around access to **cannabis plant/cannabis resin** for non-medical use?

Out of 70 responses, the majority (65 respondents, 93%) saw no legislative changes in their country. Legislative changes were reported in 4 European and 1 American country.

Q40: If yes, what types of legislative changes has your country made for **non-medical use** of **cannabis plant/cannabis resin?**

Legislative changes with regard to non-medical use of cannabis relate to decriminalization of possession/use of small amounts or for first time offenders.

Q41: Is your country currently considering changes to its national legislation around access **cannabis plant/cannabis resin** for non-medical use?

Out of 66 responses, the majority (61 respondents, 92%) expects no legislative changes in their country. Legislative changes are anticipated in two European, one American, and one Australasian country.

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

- Many of the countries who answered indicated not to know the impact of changed legislation on public health, although this was more so for decreased availability (20 of 33: 61%) than for increased availability (21 of 45: 47%).
- As for decreased availability, 7 out of 33 countries (21%) saw/expected a substantially or slightly positive impact, 3 (9%) saw/expected no impact, and another 3 out of 33 countries (9%) saw/expected a substantially or slightly negative impact.
- As for increased availability, 22 out of 45 countries (49%) saw/expected a slight or substantially negative impact, 1 (2%) saw/expected no impact, while only 1 (2%) saw/expected slightly positive effects.

A distinct regional pattern could not be identified.
Most respondents were unable to provide a response to this question and cite no legislative changes or lack of data as reasons. Some comments indicate that higher availability is likely to lead to decreased risk perception and thus to increased use. Other argue that the impact of legislative changes need to be evaluated under consideration of accompanying measures, such as educational programs to avoid risk misperception especially among youths, or access to treatment services. On the possible positive effect, one respondent highlighted that public health might benefit from quality control of cannabis products. Further, one country explicitly aims to take a public health approach in legalizing cannabis but cannot evaluate legislative changes in their country yet.

4. Comments from countries

Many comments highlight that any cannabis product is illegal for medical as well as non-medical use in their country, which is cited as reason for lack of data.

Some justify why medical or non-medical use of cannabis products should be avoided or prohibition further enforced. One other respondent expressed concerns in rescheduling of cannabis through the WHO, who should carefully consider evidence on health and safety risks.

Others specify sources for responses given in the survey or specify definitions used for answering selected questions. Data reported for health care statistics or impaired driving should be interpreted with caution as the available data sometimes did not match the required definitions. Further, some report that data break-up by product or cannabinoids is not available, thus the presented data may not be specifically restricted to cannabis plant and resin, but may also encompass tinctures and extracts as well as combinations of various cannabinoids.

5. Conclusions

Overall, medical use of cannabis plant/resin is authorized in 12 countries to date. While medical use of cannabis is restricted to a limited number of high- or upper-middle income countries, this figure could increase rapidly as there are 15 countries considering introducing legislative changes in the near future.

With respect to non-medical cannabis use, four country representatives indicated legality in their countries (Switzerland, Madagascar, Armenia, Marshall Islands). It is likely that these responses reflect a misunderstanding of the question in some cases as the authors of this report are unaware of a legal cannabis market in Switzerland. The country representative of Marshall Islands indicated great concerns regarding cannabis legalization and refers to cannabis as an illicit drug in free text comments. Further, for all four countries, legislative changes have not occurred and are currently not planned.

Apart from this extreme example, responses presented in this report should be interpreted with caution. There are indications of insufficient understanding of questions, high rates of unsure/ don't know responses, and inconsistent responses. Some respondents highlighted that data restricted to cannabis plant / resin specifically was unavailable but they still reported some data.

Despite these limitations, the questionnaire findings indicate that cannabis use is prevalent regardless of the legal status of non-medical and/or medical use.

There are several registered trials on medical cannabis and the vast majority of registered cannabis plant products originate from the Netherlands. In several countries, prescription of cannabis plant or resin is often at the discretion of the medical doctor as in these countries there are no limitations in using cannabis for medical purposes.

Many countries provided data on use prevalence and on treatment statistics (with methodological difficulties) but there is a lack of data for other health care settings and for impaired driving.