WHO Expert Committee on Drug Dependence Pre-Review

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Cannabis plant and cannabis resin

Section 5: Epidemiology

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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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 (3), the term "cannabis use disorders" was generally used for the combined categories of "abuse" and "dependence", and in DSM-5 (1) for the unidimensional concept combining both former categories. However, in ICD-10 (2), 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. More than 183 million adults are estimated to have used cannabis in 2015 (lower estimate: 128 million; upper estimate: 238 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 North America and West and Central Africa (12.4%), followed by Oceania (10.3%) (for the definition of regions used by UNODC see (10)).

These prevalence data are based on government surveys conducted by the UNODC, and other available data, mainly from general population surveys. These data on country prevalence can be found on the website of UNODC (11). This website 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 for 121 countries. However, for the year 2015, the last year where data was available, data stems from only 21 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	**49,410**	**21,100**	**64,380**	**7.5**	**3.2**	**9.8**
East Africa	-	-	-	-	-	-
North Africa	6,280	2,500	10,380	4.3	1.7	7.1
Southern Africa	-	-	-	-	-	-
West and Central Africa	31,510	13,050	33,750	12.4	5.1	13.3
Americas	**49,220**	**48,380**	**51,320**	**7.5**	**7.3**	**7.8**
Caribbean	610	240	1,980	2.1	0.8	7.0
Central America	-	-	-	-	-	-
North America	39,780	39,580	40,000	12.4	12.3	12.4
South America	8,070	7,870	8,480	2.9	2.8	3.0
Asia	**53,660**	**29,070**	**88,780**	**1.8**	**1.0**	**3.0**
Central Asia	-	-	-	-	-	-
East and South-East Asia	-	-	-	-	-	-
Near and Middle East/South-West Asia	7,930	5,640	11,200	2.7	1.9	3.9
South Asia	-	-	-	-	-	-
Europe	**28,400**	**27,370**	**29,450**	**5.2**	**5.0**	**5.4**
Eastern and South-Eastern Europe	5,340	5,030	5,720	2.4	2.2	2.5
Western and Central Europe	23,060	22,340	23,730	7.2	7.0	7.4
Oceania	**2,620**	**2,190**	**3,730**	**10.3**	**8.7**	**14.7**
Global estimate	**183,310**	**128,110**	**237,670**	**3.8**	**2.7**	**4.9**

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.

2.2 Global and regional trends in cannabis use prevalence

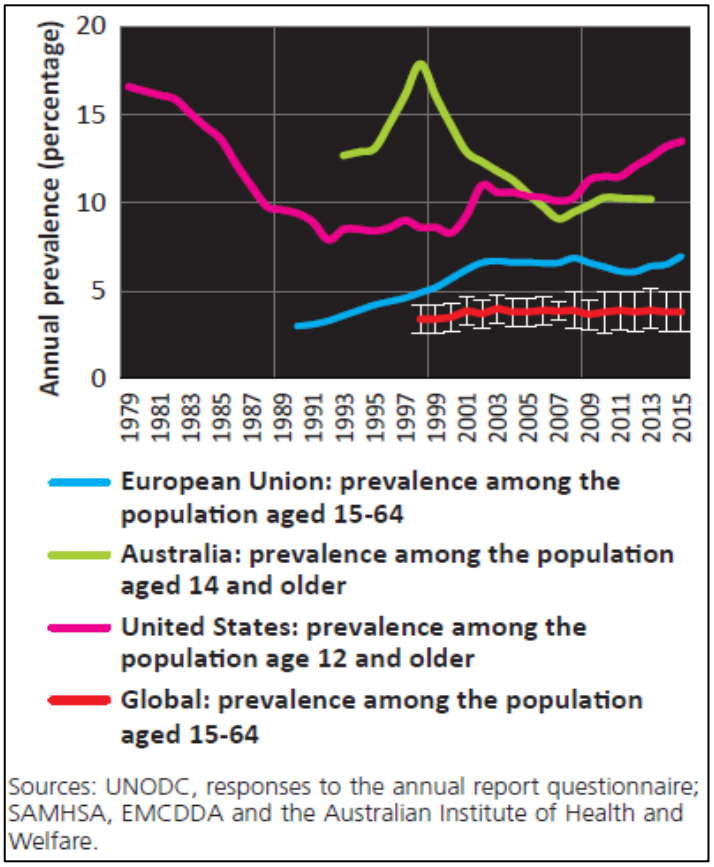


Figure 1: Annual cannabis prevalence: United States, European Union, Australia, Global level (5)

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/) (26) and the WHO funded 'Health Behaviour in School-aged Children' (HBSC, (27)), 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 (28). 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.

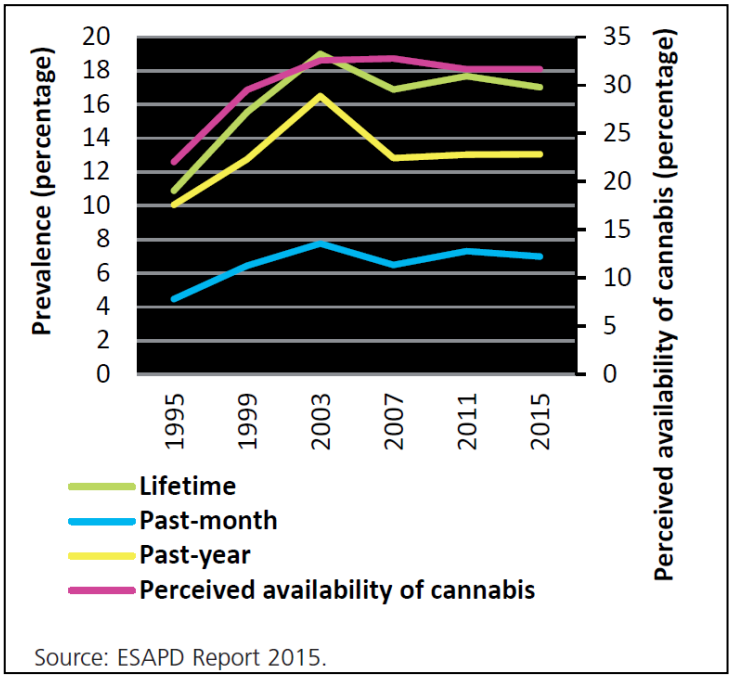


Figure 2: Cannabis prevalence among 15-16 year-olds, Europe (5)

The detailed results (not shown here but in (28)) show parallel temporal developments for boys and girls, with boys having higher prevalence on all indicators for the entire time period. ESPAD also included

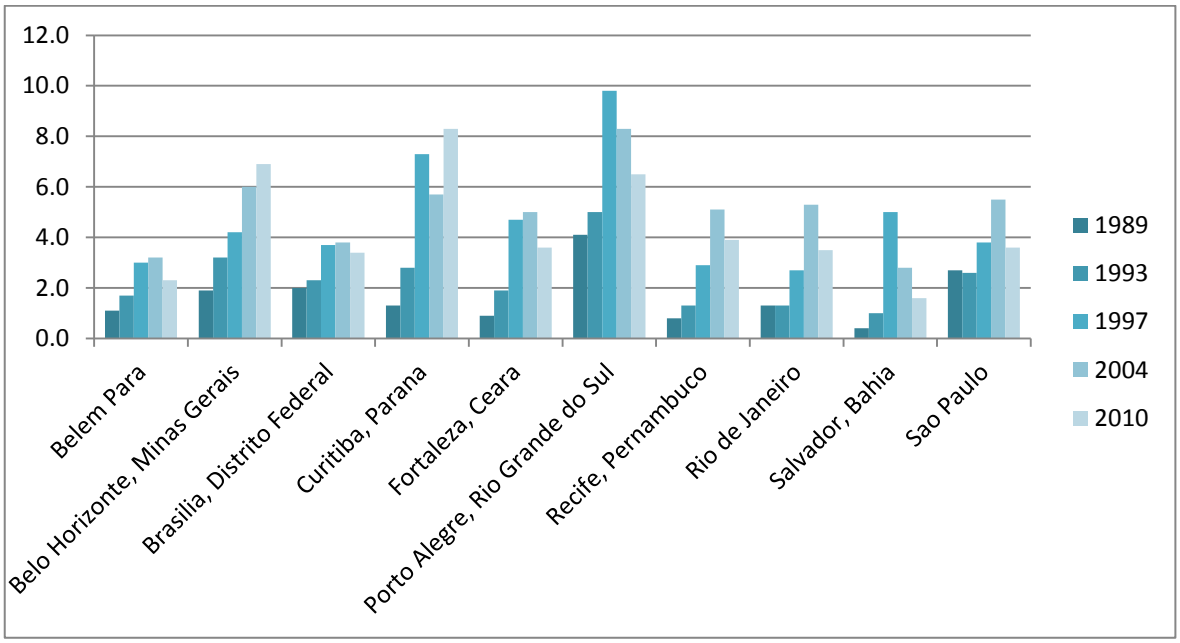
measures on the perceived availability of cannabis, which follows a similar trend curve as use (for both sexes combined and gender-specific with boys also showing higher perceived availability (28)).

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%;(29)).

According to the HSBC 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 (30). 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; (31)).

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 (32). 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%; (33)). 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 (34). In another general population survey, the rising 12-month prevalence between 2001/2002 (4.1%) and 2012/2013 (9.5%) was corroborated (35).

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 (36).

For Europe, cannabis use over time constitutes a rather heterogeneous picture when considering national or regional data. According to the 2017 EMCDDA Drug Report (37), 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% (38), which continues a rising trend of lifetime use prevalence between 1992 and 2000 (39). 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%; (40)). 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%; (41)).

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%; (42)).

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% (41, 43-65).

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 (62). 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

[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.

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 (66, 67).

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 (68). 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 (69).

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 samples, where 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) (70). 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 (71), detection via blood may become virtually impossible (72). 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% (41, 59, 61). 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 (73).

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 (41, 43, 46, 48-52, 54-59, 61, 63-65, 74, 75). 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 (76, 77).

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% (59).

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 (43)	Primary, cross-sectional	1999	964	9.8[a,b]	University students, athletes
France/11 cities (74)	Primary, case-control	2000.5	1,800	7.5[b]	Injured drivers, random roadside testing
Denmark (75)	Secondary, cross-sectional	2002	3,516	7.2[b]	Blood analysis, driving under the influence
Austria (46)	Secondary, cohort	2002	1,902	5.1[b]	Urine analysis, males, illicit drug use
Thailand/ Southern region Songkhla, Pattani, Phuket and Surat Thani (47)	Primary cohort	2003	30,011	2.3-3.4[a]	Lifetime cannabis use, high school students
Norway/ Oslo (48)	Secondary, cross-sectional	2003.5	103	13.0[b]	Acute, fatal poisonings, autopsy
Netherlands (63)	Primary, cohort	2004	7,610	2.3[a&b]	Women who delivered babies, paternal and maternal cannabis use, self-report, urine testing
Switzerland (49)	Secondary, cross-sectional	2005	4,668	27.7[b]	Blood analysis, driving under impairment
United States/ New Orleans (65)	Secondary, cross-sectional	2005	416	17.2[b]	inner city population at delivery admission, urine toxicology screen
France (50)	Secondary	2006	3,493	16.1[a & b]	Self-reported cannabis use and urine analysis, military staff
United States/	Secondary, cohort	2010	588	2.4%[b]	Unintentional ingestion of cannabis by children

Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence %	Keywords
Colorado (51)					up to age 12 visiting a hospital
Mexico/ Cuernavaca (52)	Primary, cross-sectional	2008[c]	174	1.2[b]	Drug use among college students
France/ Toulouse (69)	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 (54)	Secondary, cross-sectional	2007	13,315	22.2[b]	Driving under influence, blood analysis
Spain/Catalonia (55)	Cohort study	2007	1,026,690	4.0[b]	Wastewater analysis
Italy/ Northern region (56)	Secondary, cross-sectional study	2009.5	43,535	1.3[b] monthly prevalence	Transport-related occupations; quasi-random testing
Afghanistan/ 11 provinces (57)	Secondary, cross-sectional	2011	19,025	3.9[a&b]	Self-reported cannabis use, urine, hair and saliva testing
Norway (58)	Primary, cross-sectional	2011	2,437	0.7[b]	Saliva analysis, employees, cannabis use
Spain (64)	Cohort	2011	209	2.9[a]	Pregnant mothers, cannabis use during and before pregnancy
Italy/ 17 cities (41)	Wastewater analysis	2012	-	3.7[b]	Wastewater analysis
Switzerland/ Lausanne (59)	Wastewater analysis	2013.5	223,900	9.4[b]	Wastewater analysis in addition to self-report
United States/ Connecticut (60)	Primary, cross-sectional	2014	3,847	29.2[a]	High school students, cannabis use, e-cigarettes
Spain/Vitoria (61)	Wastewater analysis	2015	1,508,972	0.35-1.0 daily consumption[b]	Wastewater analysis
Central African Republic/ Lobaye	Primary, cross-sectional	2016[c]	379	38.6[a]	Self-report, cannabis use, indigenous

Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence %	Keywords
district (62)					

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

2.3.1 Self-medication

Up to this point, we 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, 78-81); for actual use see (82)). 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.

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 (83)	Mixed study (cross-sectional multicenter survey and retrospective chart	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

Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence (%)[a, b]	ICD Chapter, Clinical Condition	Findings
	review)					(70%).
United Kingdom (84)	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 (85)	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 (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 (86)	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,	Primary, cross-	2009	139	45.0[a]	VI, cluster	Among the 27 patients (19.4% of the total cohort) who had tried cannabis

Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence (%)[a, b]	ICD Chapter, Clinical Condition	Findings
Marseille (87)	sectional				headaches	to treat cluster headache (CH) attacks, 25.9% reported some efficacy, 51.8% variable or uncertain effects, and 22.3% negative effects.
Canada/ Halifax (88)	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 (89)	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 (90)	Primary, cohort	2005	500	11.0[b]	XVIII, chronic pain	No data on symptom relief.
Canada/ Toronto (91)	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

Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence (%)[a, b]	ICD Chapter, Clinical Condition	Findings
						questionnaire score (45.1±2.1 vs. 50.3±1.5; P=0.03).
United Kingdom/ London, Kent (92)	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.
Nether lands (93)	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 (94)	Secondary, retrospective	2010.5	2,333	10.0[b]	V, psychiatric inpatients	
United States/ Washington (95)	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 (96)	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.

Name of Country/ Sub-region	Study Type	Median Year	Sample Size (N)	Prevalence (%)[a, b]	ICD Chapter, Clinical Condition	Findings
Africa/ Uganda (97)	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 (98)	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 (99)	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 (100)	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 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 (101) 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 (102). 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 of descriptive epidemiology for cannabis use: cannabis potency is one of the key determinants between cannabis use and public health impact such as an increased risk for (93, 94) or an earlier onset of psychotic episodes ((95); for a review see (96)).

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 (103) (e.g., number of puffs, inhaled volume, the size of a standard joint; the THC content per standard joint; see (104) for future considerations on standardization) is constant; and
- the measurement procedures over time did not change.

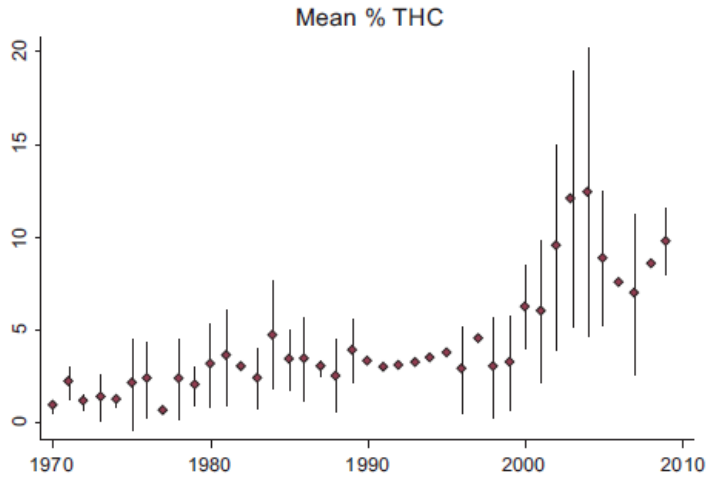
As we will see below, at least the first assumption does not hold true for the past decades, and there are reasons to believe that the other assumptions may also be problematic.

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, 38, 105-107), and increases for North America (108, 109). 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 (110) 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 (110)



Another systematic review (111) 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 (20, 21)), 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 (3)), 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., (55, 112)). One study even found wastewater analyses over several years to mirror the time trends seen in population surveys (41). However, there can also be disagreement between the two methods (113). 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 (103), and about standard size and potency of cannabis products (114, 115). 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 (112), which are four megacities in this country. This is in line with data from population surveys in mainland China (112). Consumption in Spain (61) and the Caribbean (116) were as much as five times higher than estimates for regions in Switzerland (59, 117).

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 (41). 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 (118). 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 (118). In the years 2006–2007, two analyses in Spain differed markedly by a factor of ten (55, 113); the THC consumption in Catalonia, Spain (55) 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 (113). 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 (119). 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 (119).

Boleda and colleagues (55) 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 (55). 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 (117)	2005	5,500,000	7,500
Italy/Milan (117)	2005.5	1,250,000	3,000
Switzerland/Lugano (117)	2006	120,000	6,500
Spain/Catalonia (55)	2007	1,026,690	3,466
Spain/North-Eastern (113)	2007.5	2,800,000	680
Italy/Milan (119)	2010.5	–	8,300
Italy/8 schools in 8 cities (120)	2011.5	6,126	106–1,201
China/Beijing, Shanghai, Guangzhou and Shenzhen (112)	2012	11,400,000	No detectable THC
Finland/9 cities (118)	2012	2,021,000	4,320
Italy/17 cities (41)	2012	–	4,350
France/Martinique (116)	2013	47,200	37,500
Switzerland/Western (59)	2013.5	223,900	1,600
Spain/Valencia (61)	2015	1,500,000	23,300
Costa Rica/Liberia, Puntarenas (121)	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 (41). 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) (41). Wastewater analyses of Italian schools in Rome, Turin and Verona also showed an increase in THC consumption from 2010–2013 (119). 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 (117) and another in 2010–2011 (119). Increases in THC consumption were also observed in Spain between two studies conducted in 2007–2008 (55, 113) and another in 2015 (61). On the other hand, Switzerland appears to have seen a decrease in THC consumption from approximately 6,500 mg/day/1000 people (117) to 1,600 mg/day/1000 people (59) 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 (59). 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 (115).

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 (122, 123), the Netherlands (124), France (69) and Italy (125) 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 (126), however online data from the KRIPOS section of the Norwegian police report potencies at higher levels which is more in line with other geographies (127). In The Netherlands, potency of domestically grown cannabis, whether herbal or resin, was noticeably higher than imported cannabis (128). Potency of herbal cannabis has been consistently lower than resin (69, 125, 126, 129) except for one study in which regular users provided their own supply (124).

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 (125) and France saw increases of 1-3% in just one year, as reported by the French Observatory of Drugs and Drug Addictions (69). 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 (122, 123, 130). Finally, trends in the UK were upwards as well (128, 131), whereas the THC content in the Netherlands (129) 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 (132). 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 (123). 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 (122, 123). 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 (128).

Table 5: THC content and concentration in cannabis samples

Country	Median Year	Sample Size (N)	Sample description	Average THC content (%)
United States (123)	1990	741	Herbal cannabis	3.8
United States (123)	1995	3,742	Herbal cannabis	4.0
United States (130)	1995	3,763	Herbal cannabis/resin/oil	4.0
United States (123)	2000	1,894	Herbal cannabis	5.4
United States (130)	2000	1,929	Herbal cannabis/resin/oil	5.3
Netherlands (129)	2005	110	Domestic herbal cannabis	17.8
Netherlands (129)	2005	14	Imported herbal cannabis	18.9

Netherlands (129)	2005	16	Domestic resin cannabis	6.7
Netherlands (129)	2005	55	Imported resin cannabis	20.0
United Kingdom (128)	2005	–	Herbal cannabis	16.9
United Kingdom (128)	2005	445	Resin cannabis	5.9
United Kingdom (128)	2005	–	Herbal cannabis	16.2
United States (123)	2005	2,233	Herbal cannabis	8.1
United States (130)	2005	2,295	Herbal cannabis/resin/oil	8.0
Netherlands/Alkmaar, Amsterdam, Arnhem, Nijmegen, Utrecht (124)	2008.5	70	Herbal cannabis	12.4
Netherlands/Alkmaar, Amsterdam, Arnhem, Nijmegen, Utrecht (124)	2008.5	36	Resin cannabis	12.2
Italy/Venice (125)	2010	544	Herbal cannabis	5.66
Italy/Venice (125)	2010	704	Resin cannabis	6.20
Netherlands (129)	2010	114	Domestic herbal cannabis	17.8
Netherlands (129)	2010	15	Imported herbal cannabis	7.5
Netherlands (129)	2010	9	Domestic resin cannabis	32.6
Netherlands (129)	2010	56	Imported resin cannabis	19.1
United States (123)	2010	2,023	Herbal cannabis	10.7
United States (130)	2010	2,260	Herbal cannabis/resin/oil	10.4
Australia (133)	2010.5	206	Herbal/resin Cannabis	14.9
Italy/Venice (125)	2011	581	Herbal cannabis	5.14
Italy/Venice (125)	2011	704	Resin cannabis	7.22
Australia (133)	2012	13	Indoor eradicated cannabis crop	19.2
Australia (133)	2012	13	Outdoor eradicated cannabis crop	15.5

France (69)	2012	–	Herbal cannabis	10
France (69)	2012	–	Resin cannabis	16
Italy/Venice (125)	2012	846	Herbal cannabis	7.51
Italy/Venice (125)	2012	569	Resin cannabis	10.31
France (69)	2013	–	Herbal cannabis	13
France (69)	2013	–	Resin	17.4
Norway (126)	2013.5	21	Resin	1.9
Norway (126)	2013.5	20	Herbal cannabis	3.8
United States (130)	2014	427	Herbal cannabis/resin/ cannabis oil	11.8
Netherlands (129)	2015	110	Domestic herbal cannabis	16.2
Netherlands (129)	2015	17	Imported herbal cannabis	4.8
Netherlands (129)	2015	7	Domestic resin cannabis	31.6
Netherlands (129)	2015	66	Imported resin cannabis	17.8
United States/Seattle (122)	2015	–	Cannabis flower	21.2
United States/Colorado (122)	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%; (134)).

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 (135). THC concentrations in saliva have been found to be higher than blood concentrations by a factor of 15 (136). Concentrations of THC above 25 ng/mL in saliva (58) and above 400 ng/mL in urine are indicative of recent use (43). The cannabis cut-off concentration for workplace urine

drug testing in the United States, Canada, Europe and Australia is 50 ng/mL (56) while a cut-off of 2 ng/mL has been suggested for saliva (58). The World Anti-Doping Agency lists cannabis as a prohibited substance and has a lower cut-off concentration of 15 ng/mL urine (137).

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 (62). Cannabis use was found mostly in men (62), which is in line with global trends (138). 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 (138-140). 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 (62). 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, 67, 141).

Abuse of cannabis and other illicit substances in the workplace has led to mandatory workplace drug testing by some businesses (142). 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 (58). In this study, concentrations as high as 300 ng/mL were observed (58). Not specific to cannabis, but illicit drug use was found to be higher in those employed in the restaurant and bar industry (58). As this type of profession is associated with cannabis use, it may also impact risk of cannabis dependence (58).

A systematic review revealed that cannabis is the second most common drug used by athletes and that use begins early in life (143); prevalence of 13-19% has been found in high school athletes in Europe (43). Some athletes admitted to using cannabis specifically for performance purposes (8-12.5%) (143). 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 (43). None of the students disclosed use of cannabis (43). Cannabis use for presumed performance enhancement due to its relaxing effect (137) 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 (43)	1999	964[a]	9.8[d]	[<1,000][d]	15–100[3.8][e]
Norway (58)	2011	2437[b]	0.7[e]	[0.63–300][e]	2.0–24[0.4][e]
United States/Connecticut (60)	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 (62)	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 numbers of prevalence in populations where such infestations are frequent (62). Self-medication will lead to higher prevalence (144), and to more frequent use, leading to higher THC levels for any average day tested, with details of course depending on the actual test used (70, 72). As cannabis is being perceived as positively impacting on performance in sports (145), we can expect frequent use of cannabis among highly competitive athletes, and high THC levels (122, 143). 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 (146), but there are indications that the proportion of users becoming dependent is associated with THC potency (132, 147).

2.6 Cannabis use disorders

2.6.1 Global and regional prevalence of cannabis use disorders

We refer to the GBD 2016 (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 (1)). In fact, cannabis use disorders are both a use pattern and a consequence of cannabis use (for a discussion (148, 149)), 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)

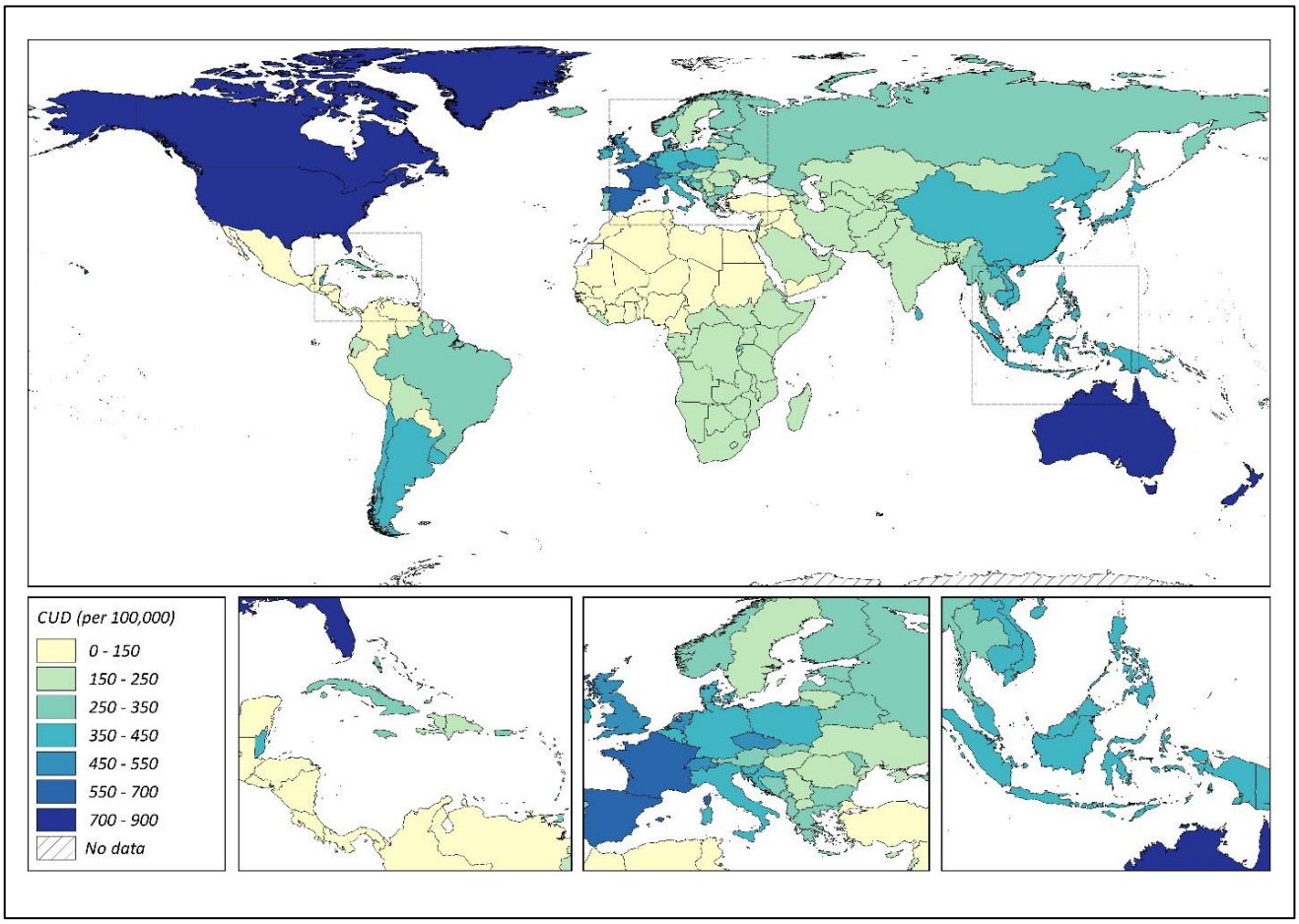
Region	**Number (95%UI)**	**Age-standardized rates (95%UI)**
Andean Latin America	96,039 (80,064, 113,733)	153.0 (128.5, 180.0)
Australasia	204,356 (173,840, 239,002)	747.9 (628.5, 882.3)
Caribbean	125,274 (104,993, 150,503)	267.6 (224.8, 321.1)
Central Asia	223,432 (183,517, 268,722)	236.4 (194.9, 286.1)
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 (150, 151). 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) (3) and the International Classification of Diseases (ICD-

10,(2)). 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 (152).

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 (150)



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 (151)).

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 (150). 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 (73). If potency is increasing and prevalence of cannabis use is stable, then prevalence 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 to use 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 allows 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 (151)) 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 (35, 153). Thus, other ratios have been mentioned.

Hall in his overview paper estimated that around one in 10 regular cannabis users develops dependence (154) . 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 (155) gives 9% or a ratio of 1:11 for dependence (for general population studies, see (156, 157)). The proportion among users developing dependence increases to 17% in adolescents and as high as 25–50% with daily consumption (155). 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 (103, 132, 158)). 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.

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 (159).

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 (160). 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 (154, 155, 161-164) and the prevalence and public health importance of the outcomes (151):

- Obviously, causality is clear for all cannabis use disorders, as they are linked to cannabis use by definition (for further mechanisms: (155)). 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 ((151); see also (165, 166)).
- 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 psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders.

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.

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 (167). 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 (165, 166). 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 (162).

In terms of harm, most harm is caused by frequent or heavy use, especially heavy use over time ((155, 161, 164); for definitions of heavy use and its relationship to use disorder, see (148, 149)). 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 (160) 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 (168). 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 (168)).

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 (103, 132, 158). However, this estimation is not possible to date, as it would require better knowledge about the dose per standard unit, or per use occasion (115). 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 (169). 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 (161, 170).

- As cannabis use impairs driving (171), 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 (122).

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 (172-174) and 31 studies on driving under the influence of cannabis (175-206).

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 (172-174)), 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 (172)	Primary, cohort	2003	974	5.3[b]	Newborn meconium analysis, prenatal cannabis exposure, gestational drug use
United States/ Iowa (173)	Secondary, cross-sectional	2009	616	4.9[b]	Children, child abuse, urine and hair analysis
Spain (174)	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.

Several other studies focused on driving and roadside testing for cannabis resin and plant (175-206). 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 (175)	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 (205)	1995.5	2,500	2.8[b]	Injured drivers, blood analysis, accidents
United States (176)	1999.5	150,010	5.2[b]	Blood analysis, driving records
Australia/ Victoria (177)	2001	436	7.6[b]	Blood analysis, injured drivers, hospital admission
Germany (178)	2001	177	5.5[b]	Driving under influence, blood analysis, suspected impaired drivers
Australia/ Victoria (179)	2004	13,176	0.7[b]	Blood or saliva testing, random screening, drivers
Brazil/ Sao Paulo (180)	2005	1,250	0.4[b]	Positive oral fluid testing, questionnaires, truck drivers
Norway (206)	2002.5	112,348	21.5[b] among suspected self-impaired drivers	Blood analysis
Sweden (182)	2002.5	22,777	21.1[b] among drivers suspected for driving under the influence of substances	Driving under the influence, blood analysis
Norway (183)	2005	676	7.2[b]	Blood findings, motor vehicle accident fatality
United Kingdom (184)	2005[c]	1,396	3.7[b]	Saliva analysis, drivers, random testing
Norway/ Southeastern region (185)	2005.5	10,816	0.6[b]	Saliva analysis, random roadside survey, drivers
Sweden (186)	2005.5	200	4.5[b]	Blood analysis, fatally injured drivers

Name of Country/ Sub-region	Median Year (field work)	Sample Size (N)	Prevalence (%) [a, b]	Keywords
Australia/ Victoria (187)	2006.5	2,638	14.5[b]	Drivers, blood analysis, motor vehicle fatalities; reanalysis of (83)
New Zealand (188)	2006.5	1,046	30.0[b]	Blood analysis, car accident fatality
Brazil, Norway (207)	2008.5	3,326	0.4[b]	Driving under influence, roadside surveys, oral fluid testing
Hungary (189)	2008.5	2,738	0.6[b]	Saliva analysis, driver random testing
Spain/Valladolid (190)	2008.5	2,632	10.8[a&b]	Oral samples, roadside survey, drivers
Australia/ Victoria (191)	2009	1,714	9.8[b]	Hospitalized drivers, motor vehicle accidents, blood testing
Belgium/Netherlands (192)	2009	535	5.6[b]	Seriously injured drivers, blood samples
Brazil/ Porto Alegre (193)	2009	609	6.9[b]	Saliva use, traffic accidents, hospital admission
Italy (194)	2009	5,592	0.2[b]	Hair testing, drivers
Afghanistan (195)	2009.5	100,518	7.2[b]	National police members, urine drug screen
Australia/ Victoria (196)	2009.5	853	42.0[b] among all the positive samples	Saliva analysis, randomly stopped drivers
Brazil/ Sao Paolo (197)	2009.5	993	0.3[a &b]	Truck drivers, urine analysis, reported use
Canada/British Columbia (198)	2011	1,097	12.6[b]	Drivers, emergency department
United States/ Washington (199)	2011	25,719	19.0[b]	Drivers, blood testing, legalization
Italy/ Milan (200)	2014	1,258	3.6[b]	Drivers, accidents, blood tests
Brazil/ Sao Paolo (201)	2014.5	762	1.0[b]	Truck drivers, cannabis use, oral analysis
Norway/Finnmark (202)	2014.5	3027	1.1[b]	Driving population
Italy/ Northern region (203)	2018[c]	3,359	3.9[b]	Urine drug testing, roadside testing

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 (171), not only to the drivers themselves, but also to other traffic participants (see point on Harm to others above).

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 (208). 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 (44, 209). Studies on culpability of drivers involved in car crashes have had contradictory findings, suggesting either no relationship (205) or a weak positive association (188) 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 (188).

Observed clinical impairment has also been associated with increasing THC concentration, whether measured by saliva (190) or blood analysis (126). Maximum THC concentrations in blood have been found to be observed minutes after smoking cannabis and to taper off in hours (210). As a result of the short half-life of THC (135), measured concentrations from mandatory blood testing may be significantly lower than concentrations while driving, thereby bypassing set legal limits (49, 199, 211).

Laboratory delays in testing samples can also lead to decreases in THC concentrations (199). 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 (54, 199). 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 (54).

The average blood concentration of THC found in positively tested drivers fall in the range of 1-8 ng/mL; Australia (191), Norway (210), Switzerland (Senna) and the United States (199) fall on the higher end of that range as compared to Sweden (186), Finland (54) and Denmark (212), while France (213) and New Zealand (188) 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 (199), however Australia had similar findings despite a zero-limit policy (191). 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% (179) and 0.6% (189) in the zero-limit countries of Australia and Hungary, respectively, whereas prevalence in random roadside testing was 3.7% in the United Kingdom (184), with one of the higher blood concentration limits of 2 ng/mL, and 10.8% in Spain (190), where the DUI thresholds are 0 but the measurement is usually set at 5 ng/ml (71, 214).

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 (44) and between 2005 and 2006 (213). In Australia, average blood THC concentrations in fatally injured and hospitalized drivers were 10.0 ng/mL across 1990–1999 (175) and 7.0 ng/mL in 2009 (191) 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 (75) 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 (212). 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 (210); another study between 2013–2014 (126) 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 (126). 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 (211), while a second study from 2005 found an average concentration of 1.1 ng/mL (186); 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 (211). 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 (49). Higher blood THC concentrations in cases with only THC detected as compared to cases with multiple substances seems to be a consistent pattern (49, 126, 211). 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 (210, 211), 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 (175)	1994.5	3398[a]	8.5[f]	10.0 [0.7–228][f]	–
Australia (205)	1995.5	2500[b]	2.8[f]	–	1.0–2.0[1.1][f]
Sweden (211)	1999.5	8794[e]	NA[f]	2.1[0.3–67][f]	<1.0[43][f]
France (44)	2003.5	2003[a]	28.9[f]	–	0.2–5.0[20.9][f]
Australia (179)	2004	13,176[c]	0.7[f,g]	[3–19][f] 81[5–6484][g]	–
Denmark (75)	2004	3516[d]	7.2[f]	5.9[0.2–79.4][f]	–
Norway (210)	2005	1748[e]	NA[f]	5.0[f]	–
Switzerland (49)	2005	4668[d]	49[f]	5.8[1.0–62][f]	>2.2[27.7][f]
United Kingdom (184)	2005*	1396[c]	3.7[g]	506[7–4538][g]	–
France (213)	2005.5	611[d]	41.6[f]	[0.1–49.9][f]	1.0–5.0[20.6][f]
Norway (183)	2005.5	676[a]	7.2[f]	–	1.3–6.5[5.9][f]
Sweden (186)	2005.5	200[a,b]	4.5[f]	1.1[0.3–5.0][f]	–
New Zealand (188)	2006.5	1046[a]	30.0[f]	–	2.0–5.0[10.7][f]
Finland (54)	2007	13315[d]	22.2[f]	3.8[1.0–60][f]	–
Denmark (212)	2008.5	840[b]	3.7[f]	1.47[0.2–6.65][f]	–

Hungary (189)	2008.5	2738[c]	0.6[g]	[1.46–433][g]	–
Spain (190)	2008.5	2632[c]	10.8[g]	–	>100[3.4][g]
Australia (191)	2009	1714[b]	9.8[f]	7.0[f]	–
United States (199)	2011	25719[d]	19.0[f]	7.4[2–90][f]	>5[10.8][f]
Norway (126)	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 (215), 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 (216). 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 (216).

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 (217).

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).

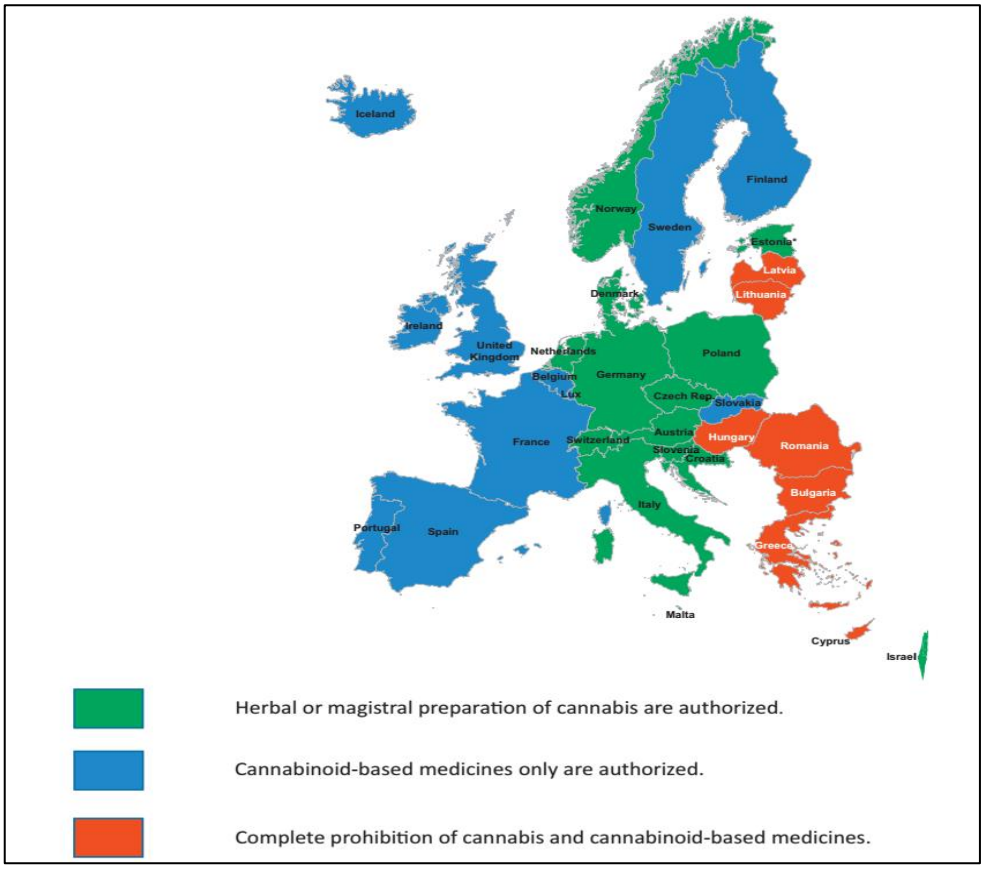
In Israel, patients can get prescriptions for natural cannabis (and cannabinoid-based medicines) from specially trained doctors and source the products from certified suppliers. In Canada, prescriptions can be made by any medical doctor or nurse practitioner with a valid license based on the Access to Cannabis for Medical Purposes Regulations (218). 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 (219) (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 (220), Colombia (221), Jamaica (222), Peru(223), 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; (224)). 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 (225), 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 (226).

Outside of these regions, very few discussions around legalizing cannabis for medical purposes are observed, with the exception of South Africa (227).

Figure 5: Medical cannabis programs in Europe



Source: (217)

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

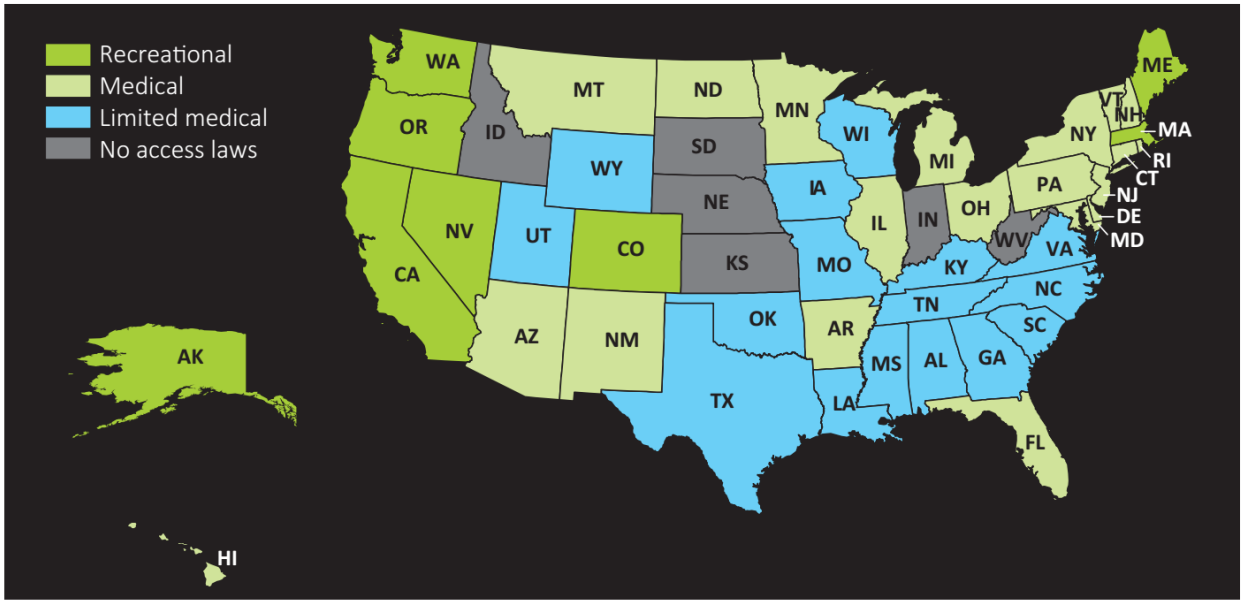
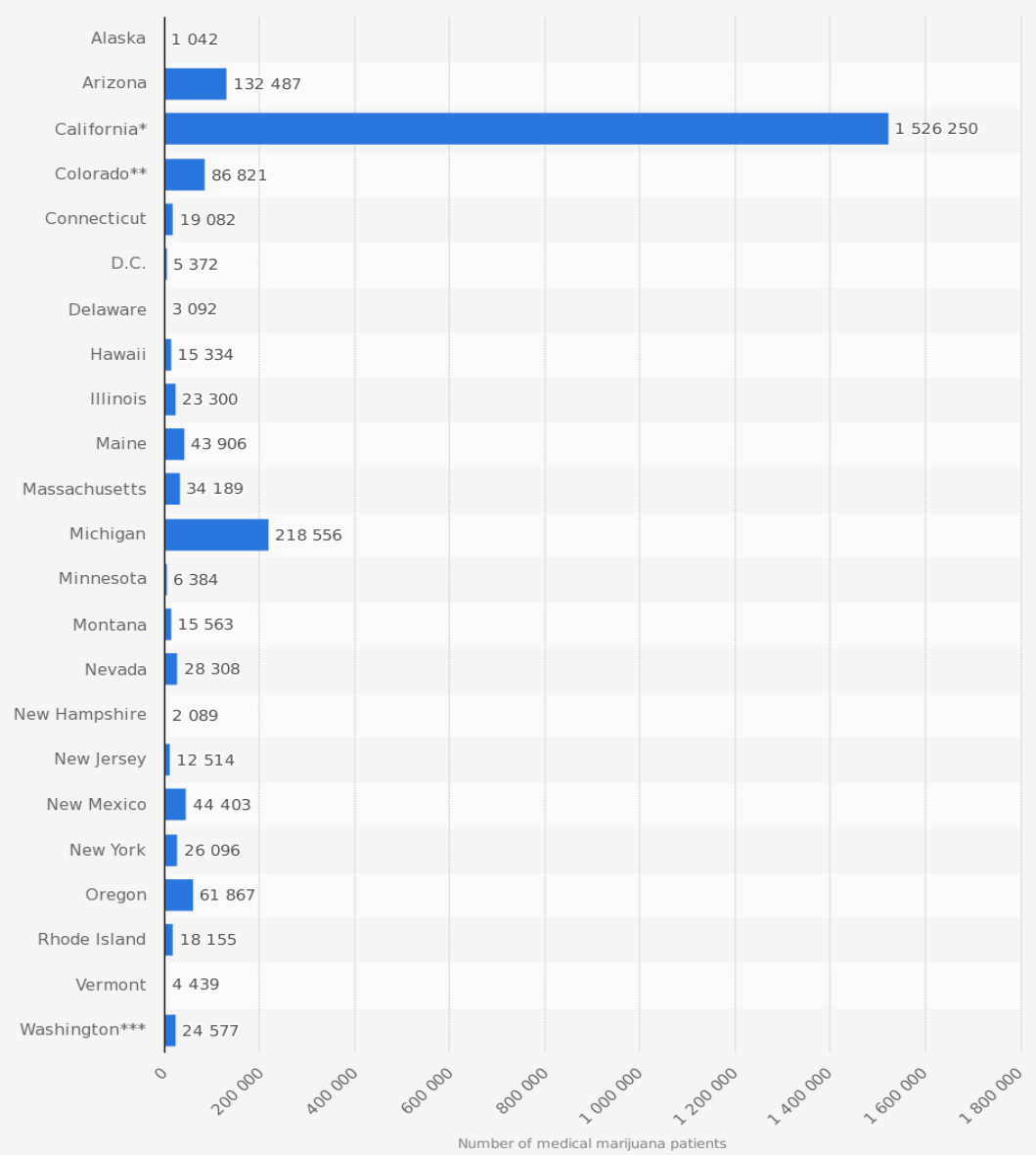


Figure 7: Number of legal medical cannabis patients in the U.S. as of August 2017, by state



Source: (228)

Due to the scheduling of cannabis as an illicit drug, there are policy implications of medical cannabis programs (229). 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 (230, 231).

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 (232-234). North America may serve as a test case for public health consequences of the recent proliferation of medical cannabis (235, 236). 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: (237); opioid prescription: (238, 239)). 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.

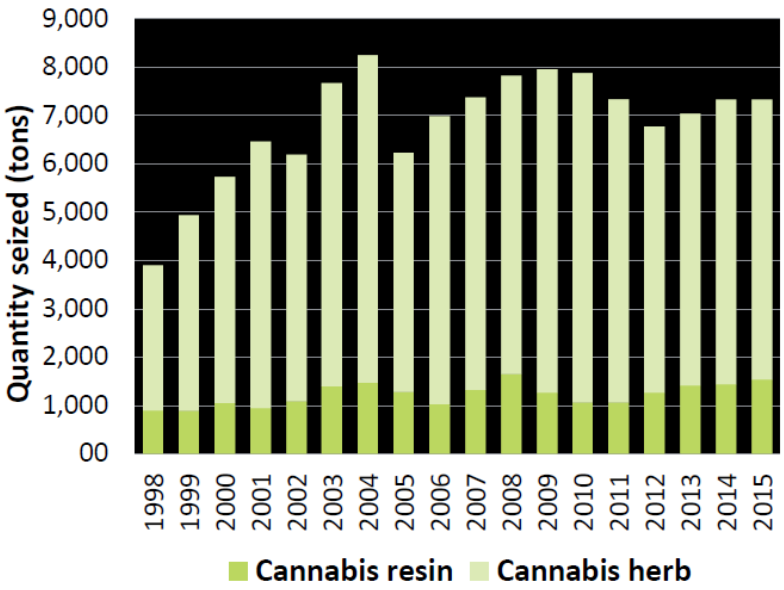
- Seizure of illicit cannabis is another policy aimed at reducing supply. Almost all countries responding to the UNODC survey reported any cannabis seizures in 2015, and cannabis seizures made up 53% of all drug seizures worldwide 2015. As noted in Figure 8 below, the amount of cannabis resin seized 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 (247, 248).

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:

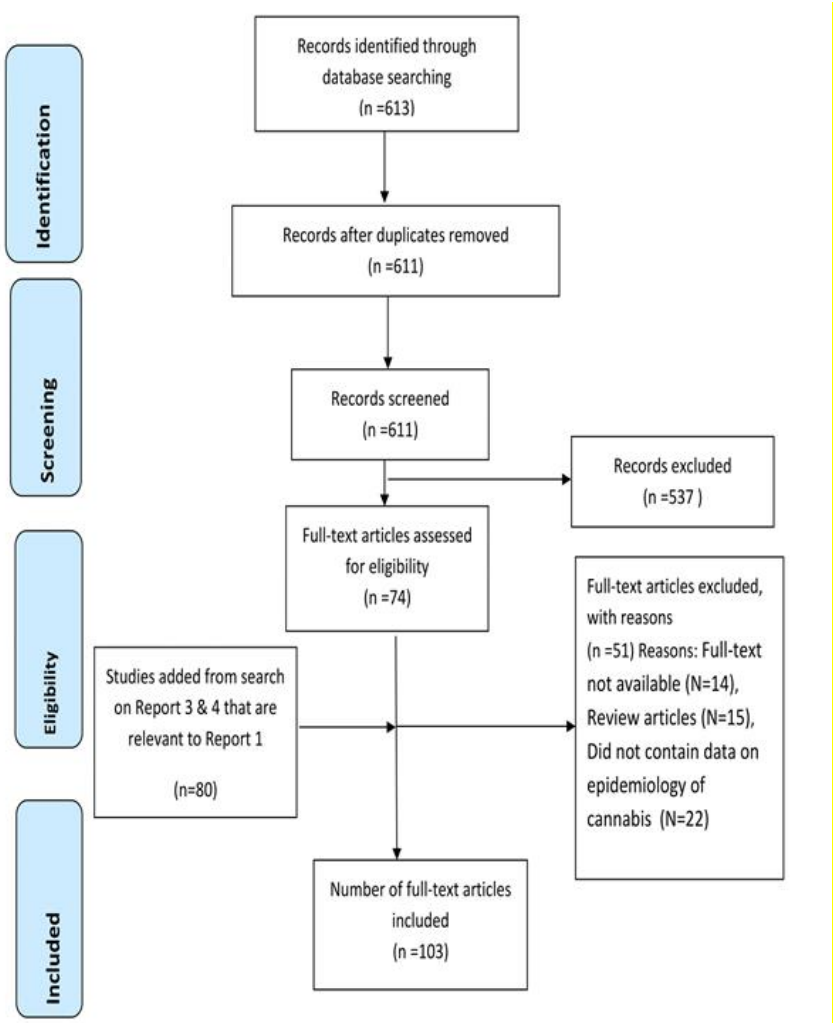
1. Based on title and abstract screening, studies with minimal uncertainty were excluded.
2. Based on full-text review of studies remaining after step 1, studies were selected for final inclusion and data was extracted.

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: (248)

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

- 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

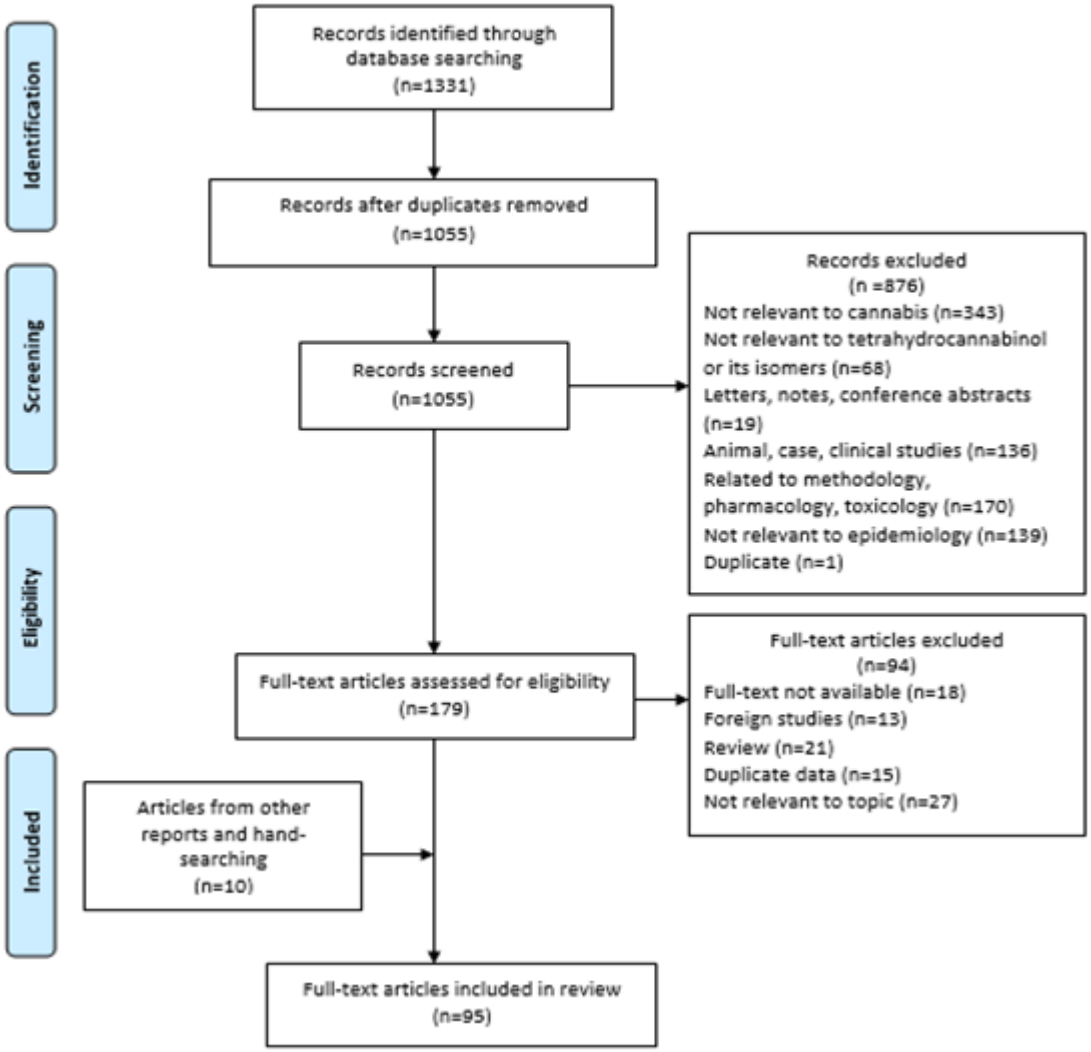
A full list of references can be found in a separate Reference Appendix document.

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 (248)



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 regards 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 (1, 2), 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 (240). A recent review, which includes epidemiology, has been conducted by Castaneto and colleagues ((241); see (242) 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 (243) and in terms of public health (244-246).

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 (249). Cannabis use may also be associated with preterm birth, particularly in chronic users (249). Respiratory problems and cognitive symptoms have been found in children through passive exposure (122). 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% (249) and has been found to be increasing with time (122).

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 (250) (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 (250). Thus, sensitivity of hair analysis is limited, especially for low exposure, and it cannot be reliably used to determine amount of consumption (251).

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 (250). However, hair concentrations found in children (250) were comparable to those found in the hair of pregnant women, 2.9% of whom self-reported cannabis use during pregnancy (64). 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 (252). In a study of 209 women, no relationship between cannabis use during pregnancy and neonatal outcomes was found (64).

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 of a combined total of 277 children did not find any cannabinoids (174) whereas in 2013 there was a drastic increase to 11.4% (250). 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 (174)	2003	277[a]	None detected	–
Spain/Vigo (64)	2011	209[c]	3.8	[0.0426–0.1972]
Spain/Barcelona (250)	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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