Reassessing the Drug Potential of Industrial Hemp

By

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Executive Summary

Industrial hemp is now grown for fiber and seeds in more than 30 countries worldwide. Of the same species as marijuana (*Cannabis sativa* L.), industrial hemp plants produce small amounts of marijuana's major psychoactive constituent delta-9-tetrahydrocannabinol (THC). This raises valid concerns over the crop's potential uncontrolled use as a medicinal or recreational drug. Major Western hemp producing countries (EU, Canada) are successfully limiting public exposure to THC by mandating exclusive use by farmers of certified low-THC varieties containing less than 0.2% (European Union) and 0.3% (Canada) of THC, licensing and reporting requirements, and field sampling and analysis for THC.

In the U.S., the perceived drug potential of industrial hemp is one of the obstacles to its re-legalization as a commercial crop. To date, there are few results from controlled studies using commercial hemp varieties to allow an assessment of this potential. This desktop study was aimed at reevaluating the potential for drug use of industrial hemp. It was also to recommend studies to experimentally verify the drug potential of industrial hemp and to suggest measures which may further reduce the potential for the drug abuse of industrial hemp, if grown in the U.S. There has been virtually no published experimental research on the drug potential of industrial hemp as a function of variety, the content of THC and the predominant cannabinoid compound cannabidiol (CBD), and the mode of consumption. Thus, any assessment of this drug potential must currently rely on anecdotal evidence and the results from clinical studies using marijuana with a very low THC content, but generally not the high CBD levels characteristic of industrial hemp varieties.

Today, the plant genus Cannabis is generally considered as a single species (*Cannabis sativa* L.) of high genetic plasticity with a wide range of morphological and chemical characteristics. The latter specifically include the relative abundance of cannabinoids, such as THC. For practical purposes, the large number of Cannabis varieties are often assigned to one of three chemotypes: drug types for production of marijuana and hashish have a THC content from 1-20% and THC/CBD ratios of greater than 2 (>2); intermediate types used for fiber, seed and potentially low-grade drug use have THC levels of 0.3-1% and THC/CBD ratios of 0.5–2; and industrial hemp varieties, the subject of this study, have a THC content of <0.2–0.3%, a high CBD/THC ratio of 2–17 and are bred for optimum fiber and seed properties.

THC levels within the industrial hemp chemotype may vary considerably. For all varieties, highest THC concentrations, corresponding to the largest drug use potential, are found in the bracts of the female flowers and upper leaves of the female plant after the onset of seed maturity. Maximum THC content varies considerably between commercial varieties depending on geographic origin of their parent races, demonstrating a strong genetic influence on THC content. Average THC levels for many EU and Canadian grown varieties

range between 0.15–0.3%. Several Ukrainian varieties contain consistently far below 0.1%. Environmental factors (temperature, precipitation, soil and nutrient conditions, latitude, environmental stress) also affect THC levels for a given variety. For example, growing a given variety at lower latitude or under stress conditions appears to increase THC levels. Finally, genetic instability of hybridized varieties is known to cause variation in THC content, possibly producing "outlier plants" with a particularly high THC content. However, the potential for finding hemp plants with such elevated THC levels appears to be low.

Most anecdotal reports from individuals who have tried to smoke industrial hemp in the EU support that these varieties are not suitable for recreational drug use by smoking. The subjective high is, if experienced at all, much weaker than desired and may be attributed to a placebo effect. Occurrence of undesirable side effects, such as headaches, has been reported but was not consistent.

Most studies agree that to experience even minimum psychotropic effects, a 70 kg person must smoke 2–3 mg of THC. For fiber hemp containing a maximum of 0.3% THC, this requires inhalation of at least 20 puffs; up to 100 puffs may be required to produce a desired "high". Several studies have indicated that the effects of smoking Cannabis with a THC content of 0.5–0.9% become indistinguishable from those of smoking a placebo. One dissenting study from the early 1970s found that smoking much lower THC doses (~0.44 mg – corresponding to Cannabis with 0.1% THC) may cause a weak high. Since this study contradicts all other findings, these results may have been caused by analytical problems when quantifying THC content, and require independent verification.

The low potency of industrial hemp in terms of its THC content is further reduced by the antagonistic action of cannabidiol (CBD). In industrial hemp, CBD is the predominant cannabinoid and often occurs in a CBD/THC ratio of more than 8:1. Several studies have shown that even CBD/THC ratios of 2:1 in both smoked and ingested Cannabis considerably reduce the subjective high rating of the same amount of pure THC, further impairing the already low psychoactive potency of industrial hemp.

These conditions and the negative side effects of heavy smoking strongly suggest that smoking industrial hemp does not realistically produce a desirable high, is readily distinguished from smoking high-grade marijuana and is not reinforcing.

Oral intake of about 10–20 mg of THC is required to produce mild psychotropic effects. This corresponds to eating 3.5–7 gram of dry matter from industrial hemp containing 0.3%. Again, the psychoactivity-suppressing effect of CBD requires that even larger amounts be eaten. The extraction of THC by cooking in butter or oil is conceivable. It appears doubtful, but requires further study, that the resulting butter could produce a weak high and be ingested in a manner acceptable to drug users. Its effectiveness will also be compromised by the high CBD content.

The chemical isomerization to THC of the CBD present in industrial hemp is possible through a relatively simple process. However, the conversion of the resulting liquid into an edible or smokable product of reasonably defined quality requires additional downstream processing. Thus, it does not appear attractive for home use. Isomerization of CBD also does not seem to provide any advantages in the illegal production of a THC containing drug, compared to the growing of high-grade marijuana.

Overall, there appears to be no realistic scenario under which industrial hemp grown in the U.S. could be used even as a weak recreational or medicinal drug, with the potential exception of individuals willing to tolerate unpleasant side effects. The impact on THC levels of growing commercial hemp varieties at low latitudes in the U.S. would have to be evaluated prior to their certification. With limited research efforts, the drug potential of industrial hemp should be determined more reliably through controlled studies in which leaves and flowers from representative commercial varieties were smoked or ingested.

1. INTRODUCTION

1.1 Background

Since the early 1990s, several countries around the world have rediscovered hemp (*Cannabis sativa* L.) as a versatile renewable raw material and a potentially viable commercial crop. In many Western countries, hemp farming had been prohibited or severely restricted after the 1930s, due to hemp's genetic proximity to marijuana (see below), or it had become economically irrelevant due to the lack of markets. In other countries, such as France, China, and many of the former Eastern Block countries, the farming of hemp had never been discontinued. Following the removal of legal barriers to hemp farming in the 1990s, farmers in about 30 countries, including most countries in the European Union (EU) (notably France, Spain, the UK, and Germany), Canada, several Eastern European countries, China and several other East Asian countries, and Australia are now cultivating hemp commercially.

In Europe, hemp processing and marketing activities have initially focused on the use of hemp fibers for a multitude of novel technical applications, particularly for interior panels in automotive applications. This development has been supported by the EU through a farming subsidy for hemp and flax and by various national R&D programs. More recently, the attractive fatty acid composition of hemp seed – botanically a tiny nut – has also created much interest in its uses for foods and cosmetics. By now, a large number of hemp nut based food and cosmetics items are on the market in Europe, the USA, Canada, and Australia. They include hemp oil, hemp breads and pastries, hemp chips, hemp granola bars, hemp chocolate and hemp ice cream, hemp soap, creams and lotions, to mention just a few.

When several Western countries considered in the mid 1990s the relegalization of hemp, the botanical proximity of hemp and marijuana raised concern that hemp may be abused as a recreational drug. What distinguishes Cannabis from all other plants is its production of resins containing a group of more than 60 related organic compounds, the so-called *cannabinoids*. Because of its psychoactive potential, delta-9-tetrahydrocannabinol (Δ^9-THC or THC) is the most relevant of these compounds. Other cannabinoids, such as the non-psychotropic cannabidiol (CBD) predominant in industrial hemp varieties are now studied for other pharmacological effects and potential therapeutic uses. The term "marijuana" summarily refers to Cannabis varieties which contain in their leaves and flower a sufficiently high concentration of THC, typically more than 2% by dry weight, to allow its use as a recreational or medicinal drug. "Industrial hemp" or "fiber hemp" varieties, on the other hand, have been bred to optimize the yield and characteristics of fiber, possibly seeds, and to minimize the amount of THC produced. However, small quantities of THC are present even in those varieties, typically much less than 1% in the most potent parts of the plant. Since Cannabis shows high genetic plasticity and the content of THC and other cannabinoids varies accordingly, authorities in these countries needed to be certain that variation in genetic and

environmental factors would not lead to the availability of drug-grade materials in easily accessible field crops.

By now, several years of experience with the controlled commercial cultivation of hemp in the EU and Canada provide conclusions on the genetic plasticity and variation of THC content in hemp varieties, as well as the effectiveness of governmental regulations to control hemp's potential for abuse as a drug. In the EU and Canada, only certified low-THC varieties may be planted by farmers. Prior to 2001, EU certified hemp varieties were not allowed to contain more than 0.3% THC in the dry matter of the upper third of the female hemp plant (leaves and bracts of flowers). Beginning with the year 2002 this limit has been lowered to 0.2% THC (Commission Regulation 2000), eliminating the use of several varieties who had been found to exceed the 0.3% limit under certain environmental conditions. Similarly, in Canada, where the maximum THC level remains at 0.3%, the list of more than 20 permitted varieties now contains varieties which rarely exceed the 0.2% level. Three Ukrainian varieties have consistently maintained THC levels of less than 0.05%. Two French varieties, which routinely exceeded the 0.3% level have since been deregistered. Four varieties that were found to exceed 0.3% under certain conditions are currently under observation, with the potential for deregistration (Health Canada 2002).

In countries with a hemp cultivation tradition, the general differentiation of Cannabis varieties into those for drug use versus the farming for fiber and seeds is generally well accepted, even by scientists who consider marijuana a drug of high toxicity and concern (*e.g.,* Nahas & Lautour 1992). Nahas, a well-known critic of considerations to decriminalize the recreational use of marijuana, stated that "...one should still distinguish two principal large groups of *Cannabis sativa* varieties, the drug type and the fiber type" (Nahas 1984). However, in all hemp producing countries with socio-agricultural conditions comparable to those in the U.S. (Canada, EU, Australia), the presence of low levels of THC in industrial hemp plants has been an issue of concern and addressed by national health, drug control and agricultural agencies. With no exception, these countries have dealt with the issue administratively and technically through the following measures: limiting the maximum acceptable THC content in certified varieties, mandating the use of certified planting seeds, adopting licensing and reporting requirements for farmers, requiring field inspections, sampling and THC analysis, and by adopting limits for the permissible THC content in hemp food items.

Overall, the governments in relevant hemp producing countries appear to be satisfied that this approach protects the general public from the intended or unintended intoxication by agricultural Cannabis. There are only few anecdotal reports of attempts to use industrial hemp as a drug or to even divert it into the drug trade, all of them having little to no success. The recent reduction in the THC limit in the EU also demonstrates that a conservative approach is taken and regulatory requirements are tightened if deemed necessary.

In the U.S. on the other hand, the commercial cultivation even of low-THC Cannabis remains in effect prohibited. One of the concerns repeatedly expressed by the federal government, represented primarily by the Drug Enforcement Administration (DEA) and the Office of National Drug Control Policy (ONDCP) is the potential for industrial hemp to be used as a recreational or medicinal drug. The control strategies chosen by other countries show that their health agencies do not share this concern, provided THC levels in hemp are effectively limited. However, this concern requires reevaluation if hemp farming is to be relegalized in the U.S. Unfortunately, the scientific literature currently does not provide conclusive, recent information on the drug potential of the industrial hemp varieties grown in the EU and Canada or likely candidates for commercial hemp farming in the U.S. Thus, when reevaluating the drug potential of industrial hemp potentially grown in the U.S., one must rely on the findings from studies of the effects of low-grade marijuana.

1.2 Objectives and Approach

This desktop study was aimed at revisiting the question of whether the leaves and flowers of industrial hemp may be used as a recreational drug. Specifically, the study was to:

- Establish, from the literature, whether THC levels present in industrial hemp can cause psychcoactivity when smoked or ingested;
- Assess whether the required patterns of consumption are realistic;
- Assess how in industrial hemp the dominance of the non-psychoactive cannabinoid CBD over THC may modifiy drug effects;
- Assess the potential for increasing the potency of leaves and flowers from industrial hemp through cannabinoid extraction or isomerization of CBD to THC;
- Recommend studies to experimentally verify the drug potential of industrial hemp and suggest measures which may further reduce the potential for the drug abuse of industrial hemp if grown in the U.S.

The following sections first review the variability of THC in common industrial hemp varieties. Relevant findings on THC uptake and metabolism are then summarized. The results from studies on the effectiveness of ingested and smoked THC at low doses and the potential interference by CBD are reviewed. Other aspects relevant to the drug abuse of industrial hemp are then discussed. Finally, recommendations for further research and a discussion on measures for THC control in industrial hemp are provided.

2. Industrial Hemp: Botany and Variation in THC Content

2.1 Botany and Classification of Hemp Varieties

Botanically, industrial hemp and marijuana (*Cannabis sativa* L.) belong, along with hops (*Humulus lupulus* and associated wild species), to the family Cannabaceae (Frohne 1992). In the past, many species of the genus Cannabis have been described, among them *C. sativa* Linnaeus, *C. chinensis* Delile, *C. indica* Lam., *C. lupulus* Scop., *C. americana* Pharm. ex Wehmer, *C. generalis* Krause, *C. ruderalis* Janischevskij, and others (Schultes et al. 1974).

Today, it is generally accepted that the genus Cannabis consists of only one species, namely *Cannabis sativa* L. of high genetic plasticity, and, accordingly, a wide range of chemical and morphological characteristics. The possible exception are several morphologically and chemically distinct races, grown exclusively for drug purposes, which may deserve separate classification as *C. afghanica* or *C. indica* (Clarke & Watson 2002). This concept of a single species encompassing all drug and "industrial hemp" varieties appears to be justified by the high variability of characteristics used for the classification of species and unlimited cross-breeding within the genus (interfertility). Other taxonomists often divide *Cannabis sativa* L. into subspecies and their respective varieties, according to their cannabinoid abundance and composition, so-called 'chemotypes', or according to appearance, so-called 'phenotypes'. Varieties used for the production of fiber and seeds are generally referred to as "sativa" (*Cannabis sativa* L. *var. sativa*), while those suitable for the production of drugs are named "indica" (Hänsel 1992).

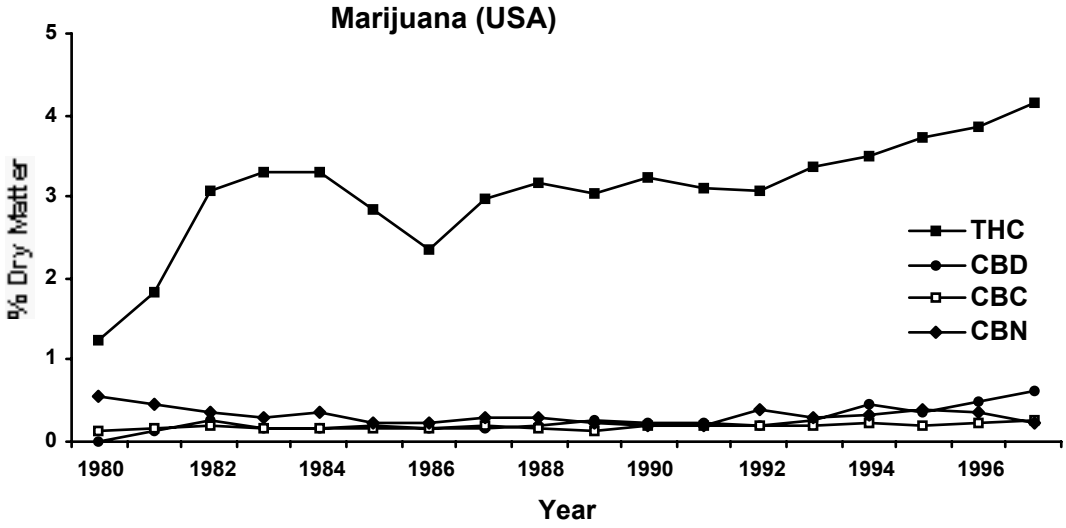
A commonly used system is the classification of varieties by "chemotype", according to their content of the most relevant psychotropic cannabinoid present, *i.e.* THC, and the relative abundance of the predominant non-psychotropic cannabinoid, cannabidiol (CBD). Proposed by Brenneisen and Kessler (1987), the system has three categories: a drug type, an intermediate type and a fiber (or industrial hemp) type. The criteria for assigning varieties to any of these three categories are listed in Table 1.

Table 1: Chemotypes of Cannabis (modified according to Brenneisen and Kessler 1987, de Meijer et al. 1992)

Chemotype	Designation – products	Predominant cannabinoids	THC content THC/CBD ratio	Psychoactivity
Drug type	marijuana, hashish – medical and recreational use	THC	>1–20% 2–12	yes
Intermediate type	Industrial hemp – fiber, oil, low-grade drug use conceivable	THC, CBD	0.3–1.0% 0.5–2	potentially
Fiber type	industrial hemp – fiber, oil	CBD	< 0.3% (EU: <0.2%) 0.06–0.5	no

THC = Δ^9-tetrahydrocannabinol; CBD = cannabidiol

In the U.S., the median THC concentration of confiscated marijuana in 1997 was 4.2% (ElSohly et al. 2000), up from less than 1.5% in 1980 (see Figure 1 top). The THC concentration in sinsemilla[1], *i.e.* seedless buds, rose from 6.33% to 11.53% during this investigation period (see Figure 1 bottom). This trend is said to be largely the result of selective breeding and crossing by Cannabis growers in Europe and North America.



[1] "Sinsemilla" marijuana is produced by eliminating the male plants from the fields before flowering, leaving only the unpollinated female plants to mature. Instead of developing seeds, female plants will continue to produce flowers covered by resin glands, thus enhancing cannabinoid production.

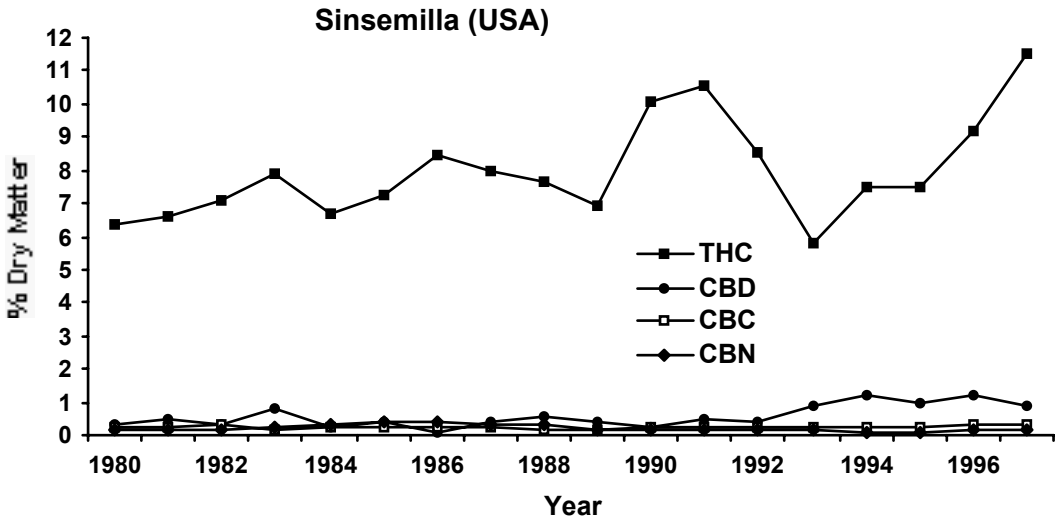


Figure 1: Median concentration of main cannabinoids (THC, CBD, CBG, CBN) in marijuana (top) and sinsemilla (bottom) (in 35,312 samples of Cannabis products confiscated in the USA 1980–1997, ditchweed samples, i.e. THC content <1%, not included (drawn after ElSohly et al. (2000)).

Cannabis products with a THC-content of less than 1% and a CBD-content higher than that of THC (CBD/THC ratio > 1) were not classified as marijuana in this analysis of 35,312 samples confiscated in the USA between 1980 and 1997, but as "ditchweed" (ElSohly et al. 2000). Ditchweed is feral hemp; wild-growing and weedy descendants of the commercial hemp once cultivated for fiber in the Midwest of the United States. The median THC content of confiscated ditchweed varied between 0.26% and 0.48% in the years 1980–1997. These samples are not included in the above graphs. Out of all samples, ditchweed samples accounted for 2.78% of the total in 1997 and 11.11% in 1991.

2.2 Variability of THC Content

Extensive studies on THC levels in hemp and their variation as a function of genetic, other botanical, and environmental factors were conducted in the 1990s in Europe and Canada. The findings demonstrate that THC levels in the flowers and leaves of Cannabis plants are primarily determined by genetic factors, *i.e.* the variety. This characteristic has allowed the selective breeding and hybridization of Cannabis, aimed at developing cultivars with a low THC content. Efforts to breed such low-THC varieties were, for example, undertaken since the 1970s in France, until recently the main supplier of hemp planting seeds in the EU, and in the Ukraine (Bócsa 1999).

Regulatory agencies in major hemp growing countries rely, in their approach to controlling THC levels in hemp, on the concept that certified seed from a given variety will

predominantly produce plants which do not exceed a specified THC limit (such as 0.2% by dry weight) even in the highest THC yielding parts of the plant. If mandatory testing of field plants shows that a given variety too frequently exceeds this limit, it may be delisted. The latter happened in recent years to French and Romanian varieties in the EU and Canada.

However, when concerned about the maximum possible THC content in a hemp plant, one must consider that the cannabinoid content of a Cannabis plant is in addition to genetic factors, highly dependent on the part of the plant collected, the plant's development stage, and environmental factors. The latter include soil type and nutrient supply, latitude, altitude, weather, particularly moisture availability during the growing season.

The mentioned European and Canadian studies, conducted both in greenhouses and in the field, show the following general trends.

2.2.1 Intra-plant Variation

Cannabinoids are produced in epidermal glands covering most of the Cannabis plant's aerial parts. The highest concentrations of cannabinoids are found in the bracts of the flowers of the female plants (or the female flowers in monoecious[2] varieties), the lowest in the roots and the seeds (Fetterman et al. 1971, Fairbairn & Liebmann 1974). Male plants have only few glandular trichomes (hairy glands) and correspondingly low cannabinoid concentrations. The highest concentrations in leaves are found in the leaves of the upper part of the female plants.

The difference in THC content between bracts and leaves is illustrated in Figure 2 (top and bottom) for the French variety Felina 34. They indicate that THC levels in bracts (thick lines) become, as the plant matures, considerably higher – typically by a factor of 2 – than those in leaves (thin lines) (Höppner & Greef 2000).

Since they carry the highest THC levels and thus the largest potential for drug use, the upper leaves and the bracts of the female flowers of a plant are used for determination of THC content in fiber hemp. The sampling and analytical methods used for the determination of THC content in the European Union is described in Commission Regulation (EC) No. 2860/2000 from December 27, 2000 (Commission Regulation 2000). Relevant excerpts can be found in Annex I. The corresponding Canadian regulations, administered by Health Canada, can be found at http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/hemp.html.

2.2.2 Variation During Plant Development

Cannabinoid content in Cannabis plants also varies over the course of plant development. A strong increase is usually observed prior to the onset of fruit maturity. Cultivation experiments in 1974–76 with Mexican marijuana varieties by Turner et al. (1982) at the

University of Mississippi found maximum THC levels 14 weeks after germination, followed by a decrease.

An extensive survey of THC and CBD levels in various hemp varieties during plant development was conducted by Höppner and Greef (2000) of the German Federal Research Institute for Agriculture (Bundesforschungsanstalt für Landwirtschaft) in Braunschweig during 1992–98.

As a typical example, Figure 2 (top, middle, bottom) shows, for the French variety Felina 34, trends in THC and CBD levels during plant development for the 1992, 1993 and 1995 growing seasons. Separate samples from bracts and leaves were collected in 1992 and 1993, while only mixed bract/leave samples were analyzed in 1995. The figures show that THC levels in both leaves and bracts strongly increased prior to the onset of fruit maturity (16–18 weeks after germination), followed by a significant decrease. The 1995 data from plants, which were left in the field through seed maturity, suggest that THC levels increased again later in the growing cycle. Figure 2 (top and middle) also indicates that CBD levels in bracts increase and decline roughly in parallel with THC levels, while CBD levels in the leaves continue to increase after the onset of seed maturity, as THC levels show their first downturn. For this variety, the CBD/THC ratio during the later stages of development typically ranged between 8–12:1.

These studies suggest that, at least for the tested varieties and growing conditions, maximum THC levels in bracts will occur at the onset of seed maturity and, in crops grown for seeds, possibly around the time of seed maturity. These findings provide guidance as to the proper timing of sampling for THC analysis since EU regulations require that THC levels are measured at the time of maximum concentration (Commission Regulation 2000).

[2] Hemp is by nature dioecious; *i.e.* there are distinctly different male and female plants. In monoecious varieties both male and female flowers are located on the same plant.

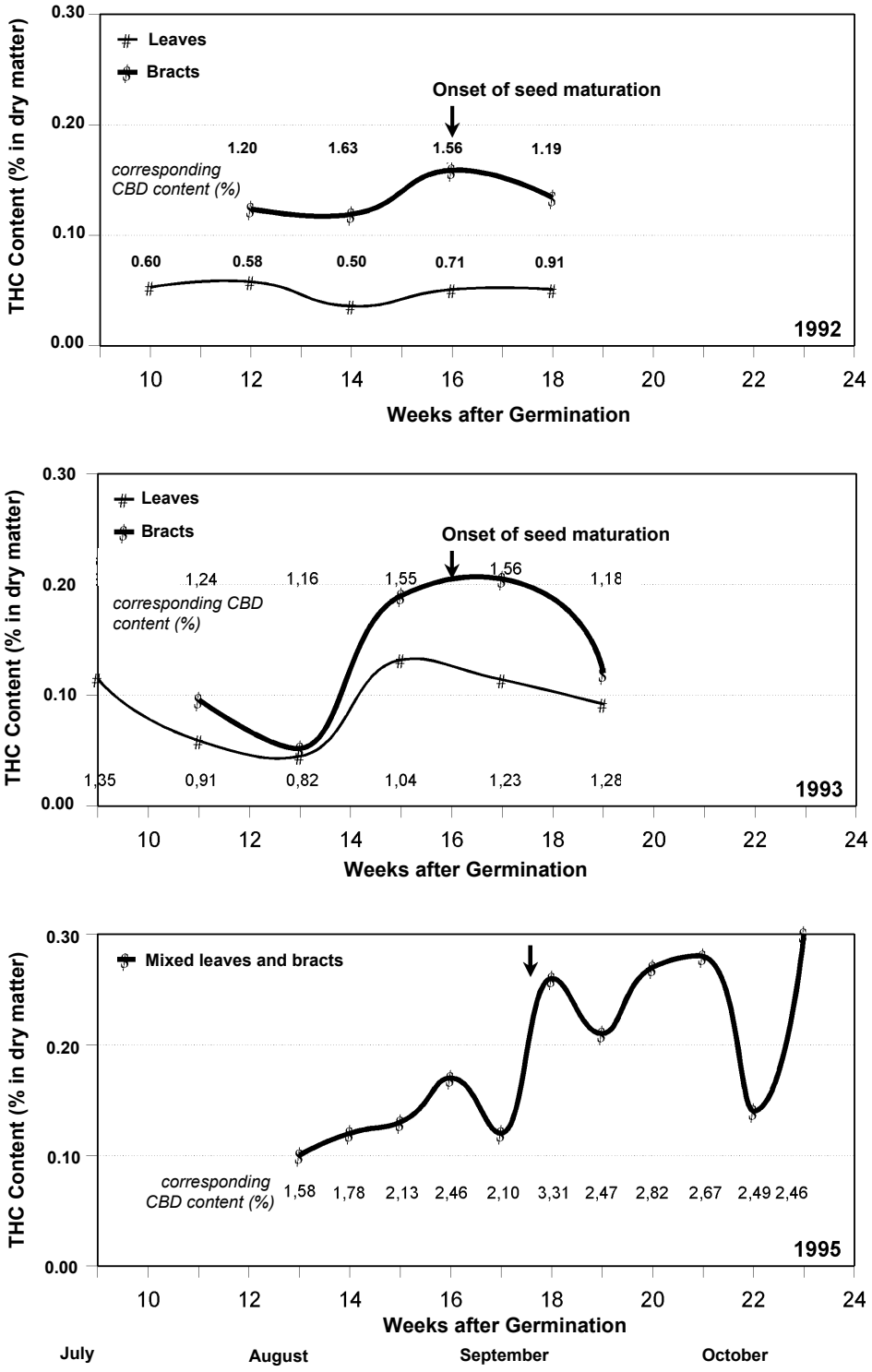


Figure 2: THC and CBD concentrations in leaves (thin lines) and bracts (thick lines) of female hemp plants (Variety: Felina 34) during plant development in 1992, 1993, and 1995 (from Höppner & Greef 2000, Figure 1). The arrow marks the onset of seed maturation.

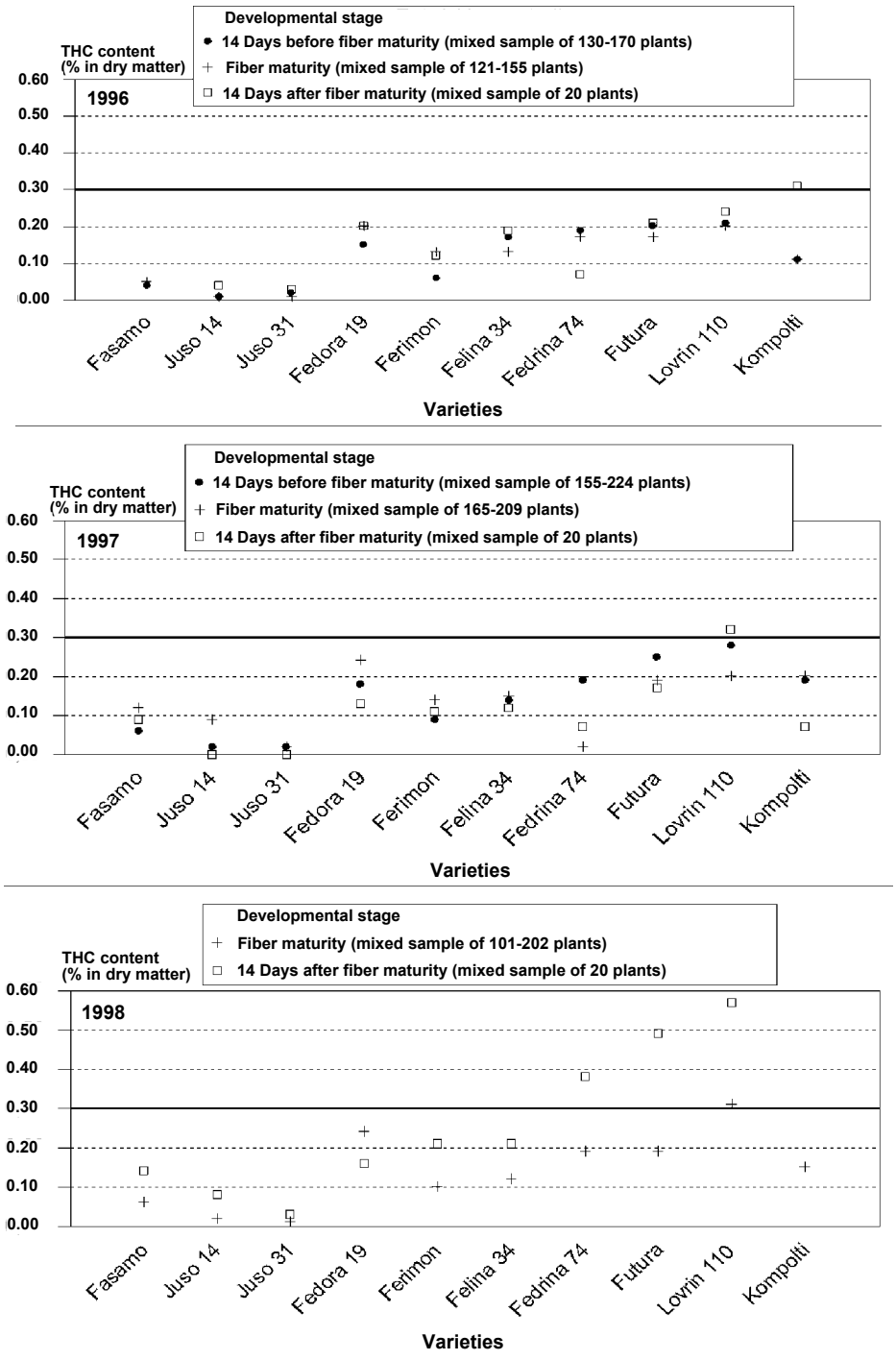


Figure 3: Median THC content in mixed samples from leaves and bracts of female plants of several hemp varieties in the years 1996–1998 as a function of plant development: 14 days before fiber maturity (•), at time of fiber maturity (+), and 14 days after fiber maturity (□). Adopted from Höppner & Greef (2000), Figure 4.

2.2.3 Environmental factors

For a given Cannabis variety, the THC content and cannabinoid composition may vary considerably with soil type and nutrient supply, latitude, altitude, weather conditions and other external factors (Fairbairn & Liebman 1974, Brenneisen & Kessler 1987, Turner et al. 1984, Pitts et al. 1992, Höppner & Greef 2000, Scheifele et al. 1999).

Brenneisen and colleagues conducted extensive cultivation experiments in Switzerland in the 1980s with Cannabis of the drug type (Brenneisen & Kessler 1987). The cannabinoid content of Cannabis remained relatively constant with elevated THC levels found in a hot summer. Leaves and flowers of the variety 'Bolivia' contained a median of 5.7% THC during the years 1981 to 1985, with a minimum of 4.0% in 1984 and a maximum of 7.1% in 1983. Fairbairn and Liebman found a variation of THC content of one variety between 2.4 and 4.4%, varying with the availability of light. In 1993–1995, Mediavilla and Brenneisen (1996) conducted analyses aimed at investigating effects of altitude on THC content in 48 samples of the French industrial hemp variety Fedora 19. No significant impact of altitude was detected. The studies by Höppner and Greef (2000) also suggested that sufficient moisture during the growing season has a positive impact on THC levels. Scheifele et al. (1999) found that plants of the same variety tend to have a lower THC content if grown at higher geographic latitude. In its presentation of results of the 2001 THC analyses, apparently contradicting the Höppner and Greef report, Health Canada (2002) suggests that some of the observed high THC levels were due to drought and other environmental stress factors.

As a rule, environmental factors seem to cause variation in THC content by no more than 50% of the average value. The work by Scheifele (1999) also shows that some varieties are more susceptible to changes in THC content as a function of environmental factors than others.

Figure 3 (top, middle, bottom) illustrates the impacts of plant genetics (variety), stage of development and weather conditions. They compare THC levels found in mixed samples of bracts and leaves of several commercially relevant varieties, grown in German trials at the same location in 1996–98. Samples were taken at 2 or 3 different stages of plant development. Particularly the Ukrainian varieties Juso (Uso) show consistently low THC levels of less than 0.1%. Most French varieties (in the center of the graph) have a "typical" THC content, which varies somewhat inconsistently with time of harvest and year. All varieties showed elevated THC levels in 1998, a year of favorable growth conditions, with some varieties routinely exceeding the then applicable regulatory 0.3% limit. Varieties characterized by a genetically determined low THC content (Fasamo, Uso 14, Uso 31) appeared to be less sensitive to external factors.

2.2.4 Inter-plant Variability

In addition to the influence of environmental factors on entire populations, there appears to be some variability in the THC content of plants of the same variety grown under identical conditions. This variation is illustrated for the Felina 34 variety in Figure 4 (top, middle, bottom). They show the THC content in mixed samples from leaves and flowers of individual plants of the variety Felina 34 at both fiber and seed maturity in 1994, 95 and 96. The THC content of all plants varied between 0.11% and 0.19%. THC levels generally increased after fiber maturity. Most significant is that the percentage of outliers (*i.e.* plants with a THC content exceeding 0.3%) varied strongly between the three crop years from 2.2% in 1995 to 12.2% in 1996. Four out of the 342 plants also contained more than 1% THC. It has been suggested by European practitioners that the subsequently observed high THC variability in the 1998 commercial Felina 34 crop and its high number of THC exceedances was caused by quality control problems during the multiplication of the planting seeds (Frank 1999). This may also explain the high variability in the 1996 crop shown here. In fact, the monoecious nature of the French and certain other hemp varieties also makes them prone to instability in other traits and requires careful quality control during seed multiplication.

Overall, the likelihood of finding industrial hemp plants with excessive THC levels appears to be low. This is confirmed by the results from Health Canada's monitoring of the 2001 commercial crop, where only a small fraction of samples from a few varieties exceeded the 0.3% levels, while the majority of samples fell often far below the 0.2% level (Health Canada 2002).

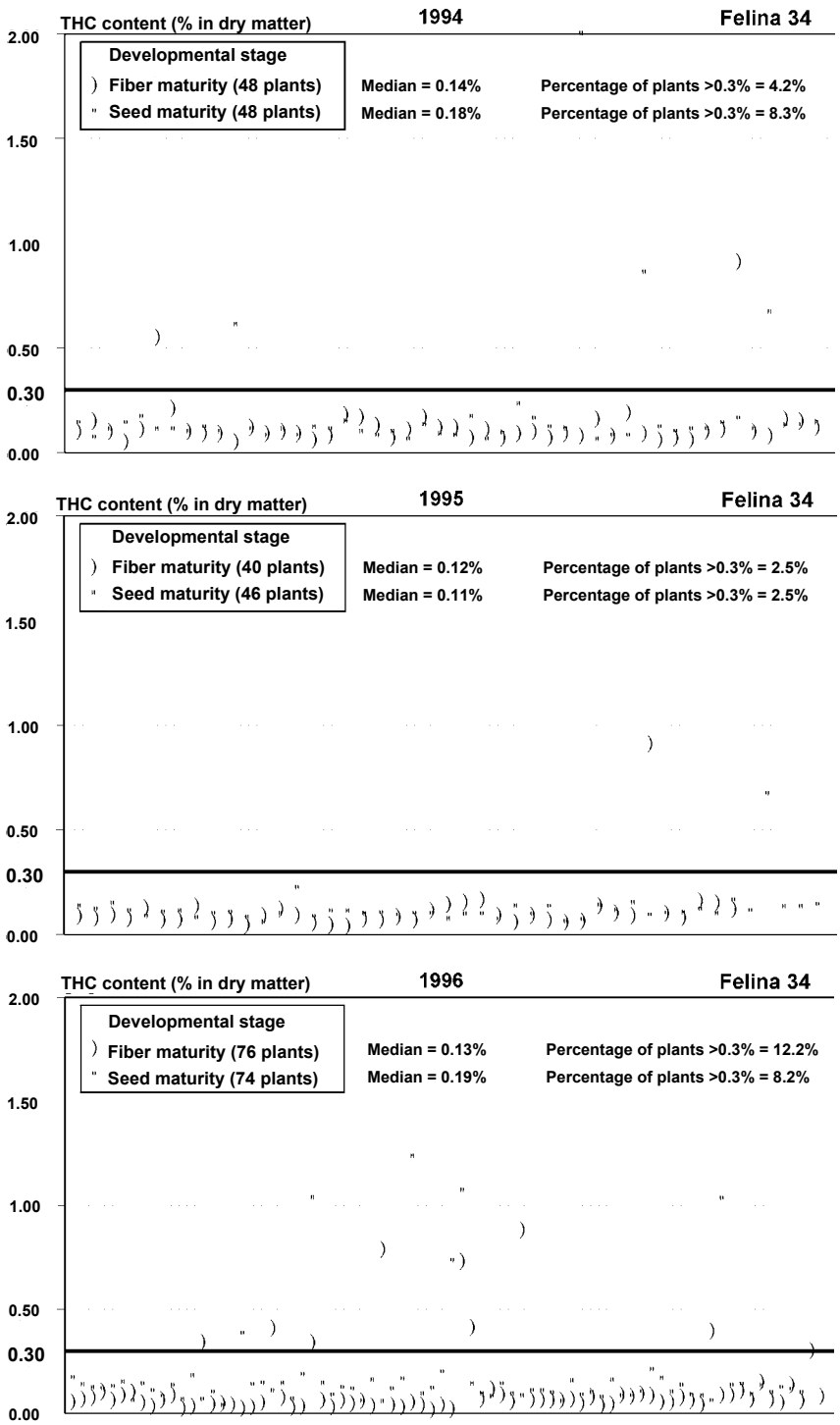


Figure 4: THC content in leaves and flowers of individual Felina 34 plants in 1994–96. About 50% of the samples were collected during fruit maturity and fiber maturity. Drawn according to Figure 3 in Höppner & Greef (2000).

In summary, commercial hemp farming, testing of field crops for THC and controlled studies have, over the last decade, demonstrated that it is possible to breed and maintain hemp varieties which consistently have THC levels in their most potent plant parts and during the time of highest THC levels of less than 0.2%, for some varieties less than 0.1%. These past achievements in reducing THC levels in a large number of commercial varieties through selection and hybridization indicate the potential for developing additional varieties adapted to specific climates and featuring both a low-THC content and desired traits related to yield and quality of fiber and seed. For varieties with "typical" THC levels of 0.1%, careful seed multiplication appears crucial to avoiding the exceedance of regulatory limits by a significant fraction of outliers. If hemp were to be grown in the U.S., the impact of the generally lower latitude on the THC level characteristic for commercial varieties used in the EU and Canada would have to be evaluated closely prior to licensing and farming.

3. Practical Experiences with Drug Use of Industrial Hemp

To our knowledge, there has not been a thorough clinical evaluation of the potential for using the leaves and flowers of industrial or fiber hemp varieties for drug purposes. However, there is anecdotal evidence of the experience by individuals. According to reports to the International Association for Cannabis as Medicine (IACM), several persons have in recent years tried to produce pharmacological effects for medicinal and recreational purposes by ingesting or smoking fiber hemp grown in the EU (IACM 2001). However, these persons experienced none of the spasmolytic, analgetic, or other cannabinoid effects caused by the ingestion of drug type Cannabis or from dronabinol (THC) prescribed by physicians. Reported antiasthmatic effects caused by the use of pillows filled with hemp leaves and sold in Switzerland may have been caused by terpenoids also present in hemp flowers or by a placebo effect.

The following report of a disappointed Cannabis grower who tried to produce psychotropic effects by consuming hemp flowers from a non-specified variety is typical. “I bought bird feed, selected the Cannabis seeds from it and planted them. I carefully cultivated and harvested them, yet, uponconsumption, they did not produce any effect”. However, there is limited anecdotal evidence that smoking of Swiss grown Cannabis, which used to contain in excess of 1% of THC, may produce mild psychoactivity (Personal reports to the authors, 2001).

Previous studies have demonstrated the importance of anticipation for the creation of psychotropic effects from low-grade marijuana (Jones 1971). This suggests the potential for individual users to experience a subjective “high” after the consumption of fiber hemp or even a placebo. These effects have to be distinguished from actual drug effects and any subjective rankings of a high must be corrected for such placebo effects. Since the reported symptoms are mild and were also produced by smoking material from plants other than hemp, this placebo effect does not justify a prohibition on hemp cultivation.

The similarity of effects caused by a placebo and a low THC dose was demonstrated in a study by Caldwell et al. (1969a). In their study on auditory and visual thresholds before and after smoking Cannabis by 20 experienced smokers, they used 300 mg Cannabis with supposed 1.3% THC (about 3.9 mg THC) provided by the U.S. National Institute of Mental Health (NIMH). In control sessions, the subjects smoked alfalfa cigarettes. Many of the subjects complained that the Cannabis used “was of poor quality or low potency” and stated, that “I could have become ‘high’ from smoking the alfalfa cigarette if I hadn’t been told what it was” (p. 758).

The complaint by volunteers caused researchers to submit samples to two independent laboratories for reanalysis, determining THC concentrations of 0.5% and 0.2% in the Cannabis used, instead of the assumed 1.3% (Caldwell et al. 1969b). Thus, the true doses smoked by the subject would have been 1.5 mg or even only 0.6 mg of THC instead of the

assumed 3.9 mg. The experience described by the citation above resembles the experiences of subjects who smoked European fiber hemp containing 0.2% THC. They could have smoked alfalfa as well. Thus, while smoking a low-THC cigarette or a placebo may produce a mild psychoactive response in some users, the results are apparently disappointing and do not reinforce consumption.

4. Pharmacokinetics

The pharmacokinetics of cannabinoids, especially of THC, have been reviewed extensively (Agurell et al. 1986, Harvey 1991, Grotenhermen 2002). The pharmacokinetics of CBD largely correspond to those of THC. For medical or recreational purposes, Cannabis products are usually smoked and inhaled, using cigarettes or pipes. Although much less prevalent, they may also be consumed orally in tea, baked goods and other foods. Recently, devices have become available which evaporate Cannabis resins for subsequent inhalation of the vapor. In the following, inhalation and ingestion of Cannabis will be considered as the two relevant conceivable consumption methods for industrial hemp.

4.1 Absorption

THC is detectable in plasma only seconds after the inhalation of the first puff from a Cannabis cigarette (Huestis et al. 1992) with peak plasma concentrations being observed 3 to 10 minutes after the onset of smoking (Hollister et al. 1981, Lindgren et al. 1981, Ohlsson et al. 1980, Chiang & Barnett 1984, Perez-Reyes et al. 1982, Huestis et al. 1992).

Systemic bioavailability of smoked THC generally ranges between about 10 and 35% of the amount present in the cigarette. Regular users achieve higher efficiencies (Lindgren et al. 1981). A systemic bioavailability of 23 ± 16% (Lindgren et al. 1981) and 27 ± 10% for heavy users (Ohlsson et al. 1982) versus 10 ± 7% and 14 ± 1% for occasional users of the drug was reported.Bioavailability varies according to depth of inhalation, puff duration and breathhold. An estimated 30% of the THC present in a cigarette is destroyed by pyrolysis. Additional THC is lost in the cigarette butt, via side-stream smoke, and by incomplete absorption in the lungs. Smoking a pipe that produces little side stream smoke may also increase effectiveness with 45% of THC transferred via the mainstream smoke in one smoker tested (Agurell and Leander 1971).

With oral use of Cannabis, THC absorption is much slower and erratic, resulting in maximum plasma concentrations usually after 60–120 minutes (Ohlsson et al. 1980, Wall et al. 1983, Timpone et al. 1997). In several studies maximum plasma levels were observed as late as 4 hours (Law et al. 1984) or even 6 hours after ingestion (Ohlsson et al. 1980, Frytak et al. 1984).

Initial degradation of Δ^9-THC is caused by digestive acids in stomach and intestine (Garrett & Hunt 1974). An extensive first pass liver metabolism further reduces oral bioavailability of THC, *i.e.* much of the THC is quickly metabolized in the liver before it reaches the sites of action. Ingestion of 20 mg THC in a chocolate cookie resulted in a systemic bioavailability of 6 ± 3% (range: 4–12%) (Ohlsson et al. 1980). Oral application of THC in sesame oil resulted in a similar bioavailability of 7 ± 3% (range: 2-14%) (Sporkert et al. 2001).

This lower bioavailability of orally consumed THC, its delayed action and the low potency of industrial hemp suggest that potential consumers will smoke rather than ingest plant matter collected from an industrial hemp plant.

4.2 Metabolism

Metabolism of THC occurs mainly in the liver by microsomal hydroxylation and oxidation. Major initial metabolites are monohydroxylated compounds. Hydroxylation results in the formation of 11-hydroxy-THC (11-OH-THC) which shows pharmacological effects qualitatively and quantitatively similar to THC. This compound is further oxidized to 11-nor-9-carboxy-THC (THC-COOH). This metabolite of THC is the major compound analyzed for in drug tests for marijuana. It does not exert psychotropic effects itself and may be further glucuronated to 11-nor-9-carboxy-THC beta-glucuronide (Agurell et al. 1986, Grotenhermen 2002).

4.3 Course of Plasma Concentration of THC and Metabolites

The course of plasma THC levels after inhalation resembles that after intravenous (i.v.) application (Perez-Reyes et al. 1982, Huestis et al. 1992). Smoking single Cannabis cigarettes containing 16 and 34 mg THC, respectively, caused average plasma peak levels of 84.3 ng/ml (range: 50.0–129.0 ng/ml) for the lower dose and 162.2 ng/ml (range: 76.0–267.0 ng/ml) for the higher dose. Levels then rapidly decreased to typically 1–4 ng/ml within 3–4 hours (Huestis et al. 1992). The maximum THC plasma level after smoking a marijuana cigarette (3.55% THC) was reported to exceed the maximal THC-COOH by threefold and the 11-OH-THC by twentyfold (Huestis et al. 1992).

After oral application, the THC plasma concentration shows a flatter profile with peaks ranging from 4.4–11 ng/ml following ingestion of 20 mg THC (Ohlsson et al. 1980), and from 2.7–6.3 ng/ml after 15 mg THC (Frytak et al. 1984). Plasma concentrations stayed relatively constant for up to 4 h. Due to the first-pass effect in the liver, much higher concentrations of 11-OH-THC are formed compared to inhalative or intravenous application (Wall et al. 1983, Frytak et al. 1984, Brenneisen et al, 1996).

4.4 Timing of THC Effects

The subjective high caused by intravenous and inhalative application peaked after 20–30 minutes, decreased to a low level after 3 hours, and to the baseline after 4 hours (Hollister et al. 1981, Lindgren et al. 1981, Chiang & Barnett 1984). Maximum increase in heart rate was noted within 1–5 minutes, decreasing to the baseline after 3 hours (Lindgren et al. 1981).

Conjunctival injection (reddening of the conjunctiva) was noted within a few minutes and lasted in some participants for up to 3 hours (Ohlsson et al. 1980).

Following inhalation, THC plasma concentrations usually have already fallen off significantly before maximum psychotropic effects are achieved (Chiang & Barnett 1984, Ohlsson et al. 1980). It has been proposed that the first hour represents the distribution phase (Sticht & Käferstein 1998) and that after one hour the central compartment, including the blood system, has reached equilibrium with the effect compartment, *i.e.* brain tissue and cannabinoid receptors (Chiang & Barnett 1984). Hence, typically 1–4 hours after smoking there is a good correlation between plasma level and effects (Chiang & Barnett 1984, Cocchetto et al. 1981).

After oral intake of 20 mg THC in a cookie, reddening of the conjunctivae occurred within 30–60 minutes, reached maximum levels from 60–180 minutes, and gradually lessened thereafter (Ohlsson et al. 1980). The pulse rate often returned to baseline or below even while the participants felt "high" (Ohlsson et al. 1980). Psychotropic effects after oral use set in after 30–90 minutes (Wall et al. 1983, Hollister et al. 1981), were at their peak between 2 to 4 hours, and declined to low levels after 6 hours (Hollister et al. 1981). Maximum psychotropic effects usually did not develop until plasma THC levels started to fall, typically 1–3 hours after ingestion (Hollister et al. 1981). The timing and intensity of effects caused by a specific oral THC dose appear highly variable, with stronger and more rapid effects produced if THC was ingested on an empty stomach and with a lipophilic carrier, such as vegetable oil.

5. THC Threshold for Psychotropic Effects

The above sections demonstrate that compared to smoking of an equal amount of THC, ingestion will result in lower utilization of THC and a much slower onset of psychotropic effects. To achieve a comparable intensity of effects, higher doses are thus required for ingestion. This observation is comparable to the differences in drug pharmacokinetics between the intravenous and oral route in everyday medications, with a faster and stronger action after injection.

To assess the drug use potential of industrial hemp via inhalation or ingestion, one must establish the minimum amounts of THC needed to achieve psychoactivity through these routes. The following paragraphs review the scientific evidence on the threshold levels for both THC inhalation and ingestion above which THC appears to achieve pharmacological effects.

5.1 Oral Use

Lucas and Laszlo (1980) found marked psychological reactions, including anxiety and visual disturbance, after oral application of single doses of about 25 mg THC in three out of nine cancer patients receiving chemotherapy. A dose of 7.5–10 mg THC caused only mild reactions. In another study, none of six patients receiving single oral doses of 15 mg THC as an antiemetic showed mood alterations (Frytak et al. 1984). Brenneisen *et al.* (1996) administered single oral doses of 10 or 15 mg THC to two patients. No changes of physiological (heart rate) or psychological parameters(concentration, mood) were noted. In a study with healthy volunteers, Chesher et al. (1990) found no difference between 5 mg of oral THC and a placebo on all measured pharmacological parameters. Single doses of 10–15 mg caused slight differences to a placebo, and 20 mg caused perceptible differences in subjective experience.

There appears to be a threshold for psychotropic effects of 0.2–0.3 mg THC per kg of body weight for a single oral dose in a lipophilic base, corresponding to 10–15 mg THC in an adult. Higher doses are required to achieve the effects desired by marijuana users. Thus, a single dose of 5 mg oral THC can be considered a placebo dose. In some clinical studies, THC doses of 5 mg or even 2.5 mg have been found to cause – usually mild – psychotropic effects (*e.g.,* Beal et al. 1995). However, the same marijuana-typical high was also caused by placebo capsules (*e.g.,* Petro & Ellenberger 1981).

5.2 Inhalation

Because of the higher systemic bioavailability and faster assimilation of smoked THC, the threshold for acute pharmacological effects after smoking is lower than for oral administration. In various studies, marijuana users smoked about 10–16 mg THC to achieve the desired effect (Ohlsson et al. 1980, Perez-Reyes 1982). In a study investigating the effects of Cannabis on driving, healthy Cannabis users were asked to smoke Cannabis until the desired effects were achieved (Robbe 1994). The medium dose smoked by volunteers was 200–300 μg/kg THC corresponding to 14–21 mg THC for a person weighing 70 kg.

Perez-Reyes et al. (1982) noted that about 24 puffs were necessary to smoke an entire standardized Cannabis cigarette from NIDA (National Institute of Drug Abuse), which weigh about 800 mg (Azorlosa et al. 1995). This corresponds to an amount of 33 mg of Cannabis smoked per puff. Others estimated a Cannabis consumption of 64 mg per puff (Liguori et al. 1998). An amount of 50 mg of Cannabis per puff thus represents a characteristic value.

These and other studies generally agree (see Table 2) that for most individuals to achieve minimum psychotropic effects, they must smoke 2–3 mg of THC. This corresponds to about 1–2 puffs from a cigarette containing Cannabis with 4% THC, assuming 50 mg of Cannabis are smoked per puff.

While several studies seem to agree on this psychotropic threshold for THC, it conflicts with the results of a study by Kiplinger et al. (1971) during which 12 out of 15 participating subjects were able to distinguish a 0.5 g Cannabis cigarette containing only about 0.4–0.5 mg THC (corresponding to a THC concentration of about 0.1%) from a placebo. This finding is remarkable since subjects in other studies had difficulties distinguishing placebos from Cannabis cigarettes containing much higher THC concentrations (Chait et al. 1988, Lukas et al. 1995, Weil et al. 1968). In those studies, “high” ratings of low-dose Cannabis cigarettes (0.1–0.3% THC) did not differ from “high” ratings produced by placebo cigarettes (Jones 1971).

It is instructive to compare the results by Kiplinger et al. (1971) to those by Dalton et al. (1976). In both studies, the Cornell Medical Index (CMI) was used to measure subjective effects of intoxication. Kiplinger et al. (1971) obtained from their subjects following inhalation of 6.25 μg/kg THC (a THC content in smoked Cannabis of about 0.1%) a CMI value similar to that found by Dalton et al. (1976) following THC inhalation of a much higher dose of 25 μg/kg (about 0.35% THC). Inhalation of 25 μg/kg THC in the study by Kiplinger et al. (1971) also caused a considerably higher CMI than in the study by Dalton et al. (1976). There is no conclusive explanation for the much stronger effects observed by Kiplinger et al. compared to Dalton et al. However, other studies conducted during that period mention their difficulties in determining the exact THC content of samples (*e.g.,* Caldwell et al. 1969a, 1969b). It is conceivable that similar problems were encountered

during the study by Kiplinger et al. (1971) and that their reported THC concentrations understated the actual THC levels.

Table 2: Comparison of psychotropic thresholds for smoked THC according to various studies (doses in parentheses refer to an individual of 70 kg body weight.)

Concentration/Dose	**Effects**	**Study**
Responses at low smoked THC doses		
50 µg/kg THC (3.5 mg)	"marijuana effects"	Isbell et al. (1967)
2 mg THC	"acceptable social high"	Jones (1971)
50 µg/kg THC (3.5 mg)	"social high"	Domino et al. (1976)
250 µg/kg THC (17.5 mg)	"hallucinogenic"	Domino et al. (1976)
12 mg THC	amount smoked in discrimination study between marijuana and placebo	Chait et al. (1988)
200–300 µg/kg THC (14–21 mg)	"desired" effects	Robbe (1994)
Discrimination of smoked Cannabis and placebo		
Cannabis (1.26% THC)	4/6 reported marijuana-like effects 3/6 reported euphoria	Lukas et al. (1995)
Cannabis (0.9% THC)	primarily placebo-appropriate response, high rating of 17	Chait et al. (1988)
Cannabis (1.4% THC)	drug appropriate response, high rating of 43	Chait et al. (1988)
4.5 mg THC in 2 cigarettes of 1 g each	3/9 reported to smoke placebo	Weil et al. (1968)
Placebo	3/12 guessed marijuana	Kiplinger et al. (1971)
6.25 µg/kg THC (0.44 mg), corresponding to about 0.1% THC content	12/15 guessed marijuana	Kiplinger et al. (1971)
Cannabis with 0.9% THC	high rating of 67 (infrequent users) high rating of 52 (frequent users)	Jones (1971)
Placebo	high rating of 22 (infrequent users) high rating of 48 (frequent users)	Jones (1971)

6. Factors Influencing the Abuse Potential of Cannabis

In addition to the THC content of industrial hemp, relative to the minimum threshold causing psychoactivity, several other factors influence the potential of industrial hemp to be used for drug purposes. Generally, marijuana users now use Cannabis with a moderate THC content (one percent and higher) and will favor it over the consumption of industrial varieties containing less than 0.3%. When smoking the latter, THC will be absorbed more slowly since more puffs have to be made. This will impair the intensity of the effects achieved by a certain dose and also result in the unpleasant sideeffects of repeated deep inhalation of smoke. Furthermore, cannabidiol (CBD), the predominant cannabinoid in industrial/fiber type Cannabis, is an antagonist to THC at the CB1 receptor and has been shown to interfere with the psychotropic effects of THC.

6.1 Impact of Cannabis Potency

The studies cited above have demonstrated the possibility of producing marijuana-like effects with low doses of THC. However, when Cannabis with a low THC content is smoked, the user's expectations may play a more important role for the subjective high than actual pharmacological effects. Even the typical marijuana taste of placebo cigarettes containing Cannabis of negligible THC content may produce some of the expected psychotropic effects (Jones & Stone 1970). As shown in the above referenced studies, this makes it difficult to distinguish placebos from Cannabis cigarettes containing 1% THC or less. Conversely, placebo cigarettes appear to be easily distinguishable from marijuana cigarettes containing 2.7% of THC, which would be classified as low to medium grade today (Chait et al. 1988).

It has been demonstrated that recreational users of the drug prefer Cannabis with a higher THC content. In a study by Chait and Burke (1994), twelve regular Cannabis smokers participated in two independent and identical choice trials in which, on separate sessions, they first sampled marijuana of two different potencies (0.63% and 1.95% THC). In a second session they were allowed to choose which of the two to smoke and how much. Subjects chose the high-potency marijuana significantly more often than the low-potency marijuana (21 out of 24 subjects).

As mentioned above, the threshold concentration for distinguishing between marijuana and placebo cigarettes for most individuals appears to be on the order of 0.5–1.0% THC. In a study by Chait et al. (1988), experienced marijuana users were trained to discriminate Cannabis cigarettes of 2.7% THC from a placebo. Cannabis containing 0.9% of THC produced primarily a response similar to that of the placebo, while Cannabis with 1.4% of THC produced a response typical to actual drug use. Users were generally able to discriminate between placebo and marijuana shortly after inhalation. Chait et al. (1988) observed drug discrimination between marijuana of 2.7% THC and placebo after 90 seconds of inhalation.

Thus, Cannabis of poor quality is quickly detected since it does not cause the anticipated psychotropic effects within an acceptable time. Potency influences the number of puffs necessary to inhale a certain amount of THC. Cannabis of medium quality (4–5% THC) will result in minor psychotropic effects (2 mg THC) after the first puff. The desired high will typically be achieved after smoking 10 mg of THC, requiring 5 puffs when using the assumptions in Chapter 5.2 (see Table 3 and Figure 5). In comparison, when smoking Cannabis with 0.3% THC content, about 13 puffs would be necessary to smoke 2 mg THC and 67 puffs to smoke 10 mg. Again, the time delay caused by the large number of puffs required and the unpleasant side effects of frequent and deep smoke inhalation are further obstacles to this mode of Cannabis consumption.

Table 3: Number of puffs necessary to inhale a certain amount of THC, as a function of THC content in Cannabis. Assumes that 50 mg of Cannabis are smoked with one puff.

THC content in Cannabis (%)	Number of puffs necessary to smoke		
	2 mg	10 mg	20 mg
10	–	2	4
5	0.8	4	8
2	2	10	20
0.5	8	40	80
0.3	13	67	133
0.2	20	100	200

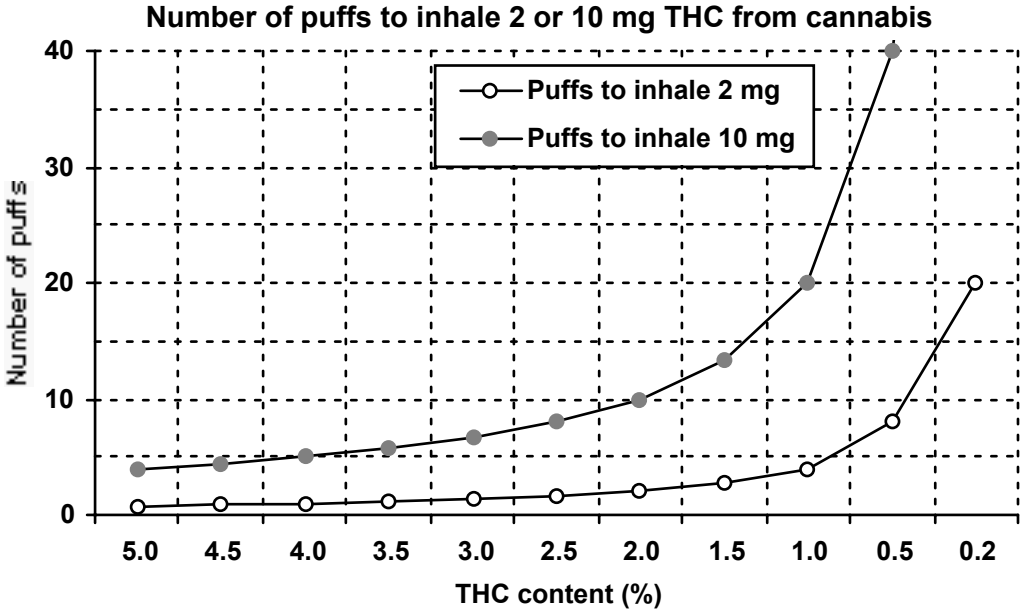


Figure 5: Number of puffs necessary to smoke a certain amount of THC as a function of THC concentration in a Cannabis cigarette.

6.2 Historic Trends in THC Content

When judging the suitability of industrial hemp for drug purposes, one must also consider the historic upward trends in the THC content of marijuana. In the late 1960s and early 1970s, researchers usually regarded Cannabis of about 1% THC as medium quality marijuana (Jones 1971, Weil et al. 1968). Jones (1971) noted: "Our experience is that marijuana smoked in San Francisco rarely contains more than 1% THC. Although a few specimens of 'good grass' given to us by our subjects for analysis contained 1.5 to 3% THC, a more typical assay was under 0.5%. A generous assumption is that marijuana generally available in the United States averages about 1.0% THC. Experienced smokers given material in this potency range judged it to be average quality" (p. 360).

There are also individual reports indicating that Cannabis of higher potency was available in the 1970s. Bowman and Phil (1973) conducted studies on cognitive performance in regular users of Cannabis. The samples provided by their subjects contained 4–5% of THC and were labeled "high potency Cannabis" by researchers. In the early 1970s, PharmChem Laboratories in Palo Alto, California tested and reported the THC content in several hundreds of anonymously submitted marijuana samples. A retrospective summary of their street-drug analysis trends from 1969 through 1975 shows that quite potent forms of Cannabis were available on the illicit U.S. market: "Early quantitative work showed a range of 1.0–2.5 percent THC for average marijuana. (...) samples in the range of 5.0–10.0 percent were not uncommon" (Perry 1977).

This is in good agreement with a statement by Tennant (1986) that Cannabis in the 1970s contained about 1–3% THC, while keeping in mind that high-grade sinsemilla with a THC content of 5–10% was already available. Today, marijuana of medium quality might contain about 3–7% THC, with higher potency of 10–20% available, according to ElSohly et al. (2000) and other sources. This trend reflects a doubling or tripling of the THC content in marijuana and sinsemilla over the last 30 years.

This rise in THC levels in street marijuana was also observed in the material used in experimental studies, reproducing the changes occurring outside of the laboratories but always lagging a little bit behind. In the early 1970s, Jones (1971) used Cannabis of 0.9% THC for his studies on the influence of expectation, experience and setting on marijuana-induced psychotropic effects. Weil et al. (1968) also used Cannabis of 0.9% THC. In the 1980s, a THC content of 0.9% was used as low-grade, 1.4% as intermediate and 2.7% as high-grade Cannabis in one study (Chait et al. 1988), and 1.2% as low-grade and 3.9% as high-grade in another investigation (Herning et al. 1986). Until the early 1990s, Cannabis of 1.0% THC was still used occasionally for studies (Perez-Reyes et al. 1991). In 1986, Cohen

noted that "the amount of THC in confiscated street samples averaged 4.1 percent THC during 1984. (...) all marijuana research to date has been done on 1 or 2 percent THC material and we may be underestimating present day smoking practices" (Cohen 1986).

In the 1990s, THC levels in marijuana used for studies increased further. In a study by Azorlosa et al. (1995), low-dose Cannabis cigarettes provided by NIDA contained 1.75% and high-dose cigarettes contained 3.55% THC. However, 3.75% THC already corresponded more to Cannabis of medium quality in the U.S. of the mid 1990s, as demonstrated by ElSohly et al. (2000).

One exception to this trend in marijuana nomenclature is a simulation study of dose-response relationships performed in the 1990s. It defined Cannabis containing 0.9% of THC as high-grade, 0.3% as medium-grade and 0.1% of THC as low-grade marijuana (Harder and Rietbrock 1997). Judging by the above, these researchers were apparently not aware of the reality outside of their laboratory, when stating that "'professionally' cultured marijuana contains up to 1% THC (…), marijuana cultured under non-optimal conditions (self-cultivated for private use) may contain up to 0.3% THC…" (p. 156).

It should also be noted that Harder and Rietbrock (1997) did *not*, as was implied in a recent document by the DEA (2001), conduct a study involving actual subjects and measurement of THC levels in plasma. Rather, they *simulated* concentration-response relationships based on data by Cocchetto et al. (1981) in a computer model. Thus, the assertion by the DEA document that "...As can be clearly seen by these data, even low doses of marijuana, containing 1%, 0.3%, and even 0.1% THC, typically referred to as 'non-active', are capable of producing subjective reports and physiological markers of being 'high'" (p. 20055) is based on a fundamental misunderstanding of the methods applied in the Harder/Rietbrock study. In light of the findings reported above, it appears doubtful that real subjects smoking Cannabis with a 0.3 or 0.1% THC content would have experienced psychotropic effects distinguishable from placebo effects.

In fact, the theoretical 'high' achieved in the simulation by Harder and Rietbrock with 0.3% and 0.1% THC Cannabis resembles the intensity of the 'high' described in studies conducted with placebo cigarettes, for example in the study by Jones (1971). Furthermore, one must question the validity of Harder and Rietbrock's extrapolation of the correlation between psychotropic intensity and THC plasma concentrations produced by Cannabis of 1% THC (Cocchetto et al. 1981) to low-grade Cannabis of 0.3% and 0.1% THC.

Today, marijuana with a THC content of 1% is considered of poor quality, containing only about half the THC of a low-dose Cannabis cigarette provided to researchers by NIDA in the study by Azorlosa et al. (1995). Cannabis with 0.5% THC, sometimes regarded as low-grade marijuana in the 1960s and 1970s, would fit today's definition of intermediate type Cannabis (Brenneisen & Kessler 1987) with a low potential for psychoactivity (see Table 1). It will generally not be accepted as marijuana by today's users. Today's industrial hemp varieties

with a THC content of generally less than 0.2% will consequently be even less suitable for intoxication.

6.3 Impact of Assimilation Rate

The comparison between the oral and inhalative routes has shown that the rate of assimilation, *i.e.* the uptake of THC, is an important factor for the intensity of effects. Due to the lower bioavailability of the ingestion route, about two to four times as much THC is needed with oral administration compared to inhalation to administer the same effective dose. In addition to dose and bioavailability, assimilation rate is the third factor determining the strength of a pharmacological effect following the intake of THC.

If the entire THC dose is inhaled within a few minutes, as is the case with high-THC Cannabis, the dose-response profile resembles the one after intravenous injection with a characteristic peak in plasma level almost immediately after inhalation (Agurell et al. 1986). Relatively little THC is needed to obtain the desired effect. On the other hand, if the entire THC dose is inhaled over a longer period of time – inevitable in the case of low-THC Cannabis – the maximum plasma peak will be much lower and will more resemble the one evident after oral administration, resulting in overall higher doses being necessary to achieve the same effects.

High THC concentrations in Cannabis allow assimilation within a shorter period of time, causing a high maximum plasma concentration within a few minutes and a correspondingly strong effect. “Thus, not only the dose of THC smoked is important, but also the time used for smoking” (Agurell et al. 1986).

Harder and Rietbrock (1997) have simulated the effects of reduced intervals between several Cannabis cigarettes of 1.0%, 0.3%, and 0.1% THC. According to their model, a dosing interval of 60 minutes between two cigarettes of 1% THC (9 mg THC) would result in a continuous high. With Cannabis of 0.3% THC, a dosing interval of 30 minutes would be necessary to achieve a prolonged plateau of effects. Their computer model also calculated a “short-term moderate response” with Cannabis of 0.1% THC if six cigarettes were smoked within three hours.

The time required for the assimilation of THC plays an important role in the intensity of the psychoactive effects. This is well known also for other drugs, such as alcohol. When drinking “non-alcoholic” beer, which contains 0.1–0.5% alcohol, intoxication is much less pronounced compared to consuming the same quantity of alcohol with “alcoholic drinks”, containing typically more than 5% alcohol.

Consequently, to achieve and sustain even mild psychoactivity requires the repeated and extensive inhalation of Cannabis with 0.3% or less THC, a consumption mode not desirable to recreational Cannabis consumers.

6.4 Impact of Smoking Patterns

A marijuana cigarette is typically smoked within 10–20 minutes, with high inter-person variability caused by individual smoking habits. To a certain degree, it is possible to compensate for a relatively low THC content through intensification of smoking patterns. Herning *et al*. (1986) studied the smoking behavior of ten experienced *Cannabis* users in response to variation in THC content. Marijuana cigarettes with 1.2 or 3.9% THC were smoked on different days. The less potent cigarettes were inhaled with longer puffs, shorter intervals between puffs and inhalation of lower volumes of dilution air.

In contrast, a study by Perez-Reyes *et al*. (1982) found only little adaptation by smokers. Six subjects were asked to smoke marijuana cigarettes containing 1.32%, 1.97% and 2.54% THC at weekly intervals in a double blind crossover design until obtaining a "high". Due to very similar smoking habits, there was a positive correlation between the potency of the cigarettes, the amount of assimilated THC, the maximum plasma concentration, and the achieved "high". The results indicate that, irrespective of the potency of the marijuana, the pattern of smoking was much the same. The extent of the subjective high, heart rate acceleration, and the plasma concentrations of THC and THC- carboxylic acid were proportional to Cannabis potency. The researchers noted that this dose response was particularly pronounced between the 1.32% and the 2.54% THC cigarettes.

Similar relationships between the THC concentration of the marijuana cigarette and the obtained effects were reported by other authors (Cappell et al. 1973, Chait 1989, Chait & Burke 1994). There is some adaptation of smoking pattern to the THC content, but there appears to be no adequate compensation for very low potency.

Studies with different marijuana-potencies have demonstrated, that "the reinforcing effects of marijuana, and possibly its abuse [sic] liability, are positively related to THC content" (Chait & Burke 1994). This observation implies that with decreasing THC content the THC-concentration in Cannabis material will eventually reach a critical threshold below which the consumption is not reinforcing, *i.e.* does not create the desire for repeated consumption.

6.5 Impact of Cannabidiol Content

The above studies focused on the effects caused by the THC present in drug type Cannabis and administered by inhalation or orally. Although many of the studies did not explicitly test for the presence of other cannabinoids, it can be assumed that the Cannabis used was of the "drug" chemotype in which THC dominates other cannabinoids, often greatly. Many of the studies used cigarettes from THC-free plant material, to which defined amounts of THC had been added, with no other cannabinoids present. The situation is different when attempting to smoke Cannabis collected from "industrial hemp" or "fiber type" varieties. Table 1, which has incorporated an analysis of 97 Cannabis populations (de Meijer 1992), shows that in these varieties, cannabidiol (CBD) is the dominant cannabinoid and CBD/THC ratios of 10

are not uncommon (see Section 2.2.2). Thus, when assessing the psychotropic potential of industrial hemp, one must examine whether the presence of CBD may enhance or interfere with the effects caused by THC alone.

A sophisticated study recently demonstrated that cannabidiol (CBD) acts as a weak antagonist at the CB1 cannabinoid receptor (Petitet et al. 1998), antagonizing the effects of THC at this receptor (see Figure 6). Antagonists block the effects at a certain receptor while agonists, such as THC at the brain (CB1) cannabinoid receptor, activate the receptor. This antagonistic action of CBD reduces the psychotropic effects caused by the low amounts of THC found in Cannabis of the intermediate and the fiber type.

The mode of action of cannabidiol is complex and not fully understood. Several mechanisms have been confirmed so far.

- It has been demonstrated that CBD acts as antagonist at the central CB1 receptor. In the study by Petitet et al. (1998), CBD considerably reduced the receptor activation by the potent classical CB1 receptor agonist CP55940. Cannabinoid receptors stimulate the binding of the GTP analog [^{35}S]GTP-γ-S. CP55940 stimulated [^{35}S]GTP-γ-S binding by about 80% with an EC_{50}[3] of 53 nM (nanomol). Cannabidiol was able to shift the concentration-response curve to the right. The C_{50} for CP55940 in the presence of 10 μM CBD was approximately 500 nM.
- CBD stimulated the vanilloid receptor type 1 with an EC_{50} of 3.2–3.5 μM and with a maximum effect similar in efficacy to that of capsaicin (Bisogno et al. 2001).
- CBD weakly inhibited the hydrolysis of the endocannabinoid anandamide, thus increasing its concentration (Bisogno et al. 2001).
- CBD increases the plasma THC level (Bornheim et al. 1995) by inhibiting hepatic microsomal THC metabolism through inactivation of the cytochrome P-450 oxidative system (Bornheim et al. 1998, Jaeger et al. 1996). Treatment of mice with CBD (120 mg/kg) resulted in changes to the metabolism of THC, administered at a dose of 12 mg/kg, a modest elevation of THC blood levels and an increase of the area under the curve (AUC) of THC by 50%. Brain levels of THC increased by nearly 3-fold (Bornheim et al. 1995). There was no or minimal effect of CBD on plasma levels of THC in man (Agurell et al. 1981, Hunt et al. 1981). Repeated administration of THC and THC metabolites (Bornheim et al. 1994, Watanabe et al. 1986), other cannabinoid receptor agonists (Costa et al. 1996) and even CBD (Bornheim et al. 1994) increased the activity of cytochrome P450 by enzyme induction.

Obviously, the interaction between CBD and THC is complex and involves several simultaneously occurring processes. While the effects caused by THC are characterized by a

[3] The EC_{50} is the effective concentration of the competitor that competes for half of the specific binding in competing binding situations at a receptor.

unique mixture of depressant and stimulant effects in the central nervous system (CNS) (Dewey 1986), CBD causes exclusively depressant effects and antagonizes the stimulant effects of THC. Yet, because of their complexity, the understanding of the effects caused by THC and CBD individually does not allow for reliable prediction of a dose-response relationship, specifically when both compounds are present. Rather, this will require controlled clinical studies.

CBD itself exerts no psychotropic effects, but several other clinically relevant effects have been observed. Among them are anticonvulsant effects in epileptic patients (Cunha et al. 1980) and antidystonic effects in movement disorders (Consroe et al. 1986). Of interest in the context of this investigation is the action of CBD on the psyche. There are sleep-inducing (Carlini & Cunha 1981), anxiolytic and anti-psychotic effects. High doses of THC can induce anxiety, panic reactions and functional psychotic states. Zuardi et al. (1997) found, when administering 300 mg of CBD, significant anxiety reduction in a model of speech simulation, comparable to that caused by 10 mg of the sedative diazepam occured. The same research group treated a young schizophrenic man who was admitted to a hospital for aggressive behavior, self-injury, incoherent thoughts and hallucinations. Over a four-week period he received daily doses of up to 1,500 mg CBD (Zuardi et al. 2002). All symptoms improved impressively.

In humans, pretreatment with 40 mg oral CBD resulted in the delayed, prolonged and slightly reinforced action of 20 mg oral THC (Hollister & Gillespie 1975) probably caused by metabolic interaction. Conversely, *simultaneous* application of CBD and THC caused significant blocking of several THC effects, among them anxiety, other subjective alterations attributed to THC (Zuardi et al. 1982), and tachycardia (acceleration of heartbeat) (Karniol et al. 1974). This blocking required that CBD and THC were given in a ratio of 1:1 or higher, presumably due to the antagonistic interaction at the CB1 receptor.

In their first study with human subjects, a Brazilian group interviewed volunteers about their emotions and sensations after ingesting THC alone and in combination with CBD (Karniol et al. 1974). 30 mg of THC provoked strong psychoactivity, rated 4 (highest) on a scale from 0–4 by four of the five subjects. CBD given simultaneously with THC considerably reduced the intensity of the psychotropic effects. For example, administering 30 mg of THC together with 60 mg CBD reduced the rating by two subjects to “1” and by the other three subject to “2” (Figure 6). The stepwise increase in the CBD/THC ratio apparently reduced to zero the number of subjects rating their experience as “4”. Thus, adding twice the amount of CBD to an oral THC dose capable of causing a pronounced high appears to reduce the effects of THC considerably. The researchers noted that the “interference of CBD on the effects of Δ^9-THC was not restricted to altering quantitatively the intensity of the psychological reactions. CBD also changed the symptoms, in such a way that the subjects receiving the mixture showed less anxiety and panic but reported more pleasurable effects” (p. 176). “The major finding of the present work is the clear interaction observed between CBD and Δ^9-THC. 15 to 60 mg CBD

were able to attenuate several effects of Δ^9-THC, such as pulse rate acceleration, time production impairment and psychological disturbances" (p. 176).

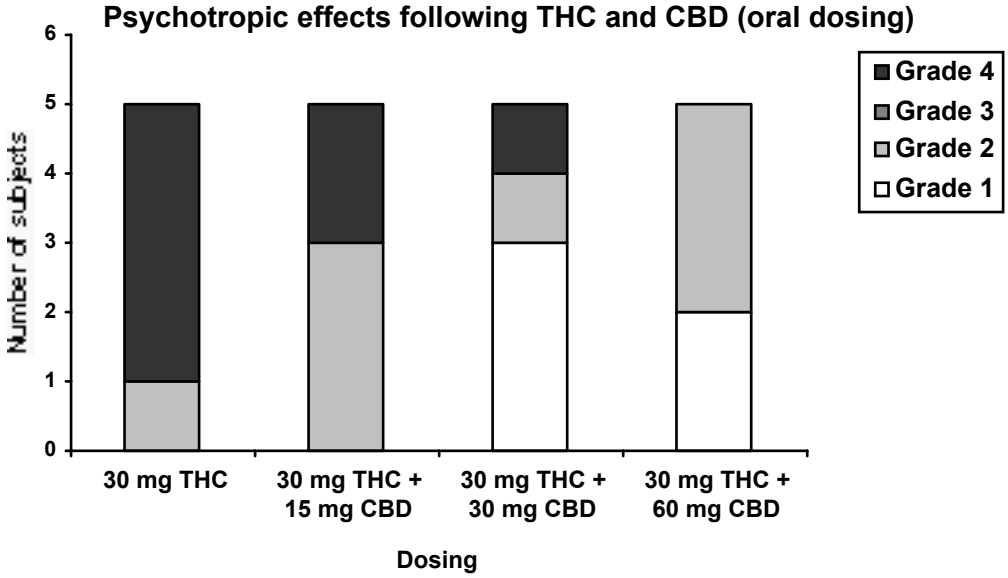


Figure 6: Intensity of psychological "high" after oral ingestion of 30 mg THC alone or together with varying doses of CBD. Drawn according to data of Karniol et al. (1974).

In the above cited DEA document (DEA 2001), the agency presented the results of this study incorrectly and misinterpreted its findings. "Karniol and colleagues (1973, 1974) have clearly demonstrated that cannabidiol (CBD) blocks some of the effects induced by THC. More importantly, CBD blocked some of the psychological effects of THC but not by altering the quantitative [sic] or intensity of the psychological reactions. CBD seemed better able to block the aversive effects of THC. CBD changed the symptoms reported by the subjects in such a way that the anxiety component produced by THC administration was actually reduced" (p. 20057). Thus, the DEA document concluded that CBD acted to "potentiate the euphorigenic and reinforcing effects of THC" (p. 20065).

In fact, the study by Karniol et al. (1974) demonstrated that CBD reduced at all doses tested the intensity of the psychological reactions caused by THC. The "more pleasurable effects" referred to by the DEA may well be attributed to a reduction in the intensity of the apparently uncomfortably strong "high" caused by the high THC dose. It is mistaken to interpret this as reinforcement of the effects of THC by CBD, especially in the context of the low quantities of THC present in fiber hemp.

In a second more detailed study, the Brazilian group compared the effects of ingesting single doses of 0.5 mg/kg THC (35 mg for a 70 kg person) and a combination of 0.5 mg/kg THC

and 1 mg/kg CBD (Zuardi et al. 1982). Again, the addition of CBD caused a significant reduction in anxiety as well as in marijuana-typical psychotropic effects. Anxiety was measured by Spielberger's State-Trait Anxiety Inventory (STAI), marijuana-typical effects by the Addiction Research Center Inventory for Marijuana Effects (ARCI-Ma).

Cannabidiol also blocks several physical effects of THC, among them tachycardia (Karniol et al. 1974). 30 mg of oral THC caused an increase in pulse rate after 50 min to a maximum of 135 beats per minute, compared to 98 beats/min for a placebo. In comparison, simultaneous ingestion of 30 mg THC and 60 mg CBD caused a maximum pulse rate of 106 beats/min (Karniol et al. 1974). In a time production task the subjects were asked to estimate the duration of a period of 60 seconds. After the ingestion of a placebo, 30 mg of THC, and simultaneous ingestion of 30 mg THC and 60 mg CBD average estimations were 58 s, 34 s, and 50 s (Karniol et al. 1974), again showing that CBD uptake significantly reduced the effect caused by THC alone.

Most relevant to the present investigation are the results from the only study investigating the interaction between *smoked* THC and CBD (Dalton et al. 1976). This study also used very low doses of THC (25 µg/kg THC) and a CBD/THC ratio of 7 which is a typical value for fiber hemp with less than 0.3% THC. Assuming an average weight of 70 kg, the 15 volunteers smoked the following: a 500 mg placebo cigarette, a cigarette containing 1.75 mg of THC (0.35% THC), a cigarette with 10.5 mg CBD, or a combination (see Figure 7). CBD significantly ($p<0.05$) reduced the psychological "high" caused by THC in the time period of maximal effects.

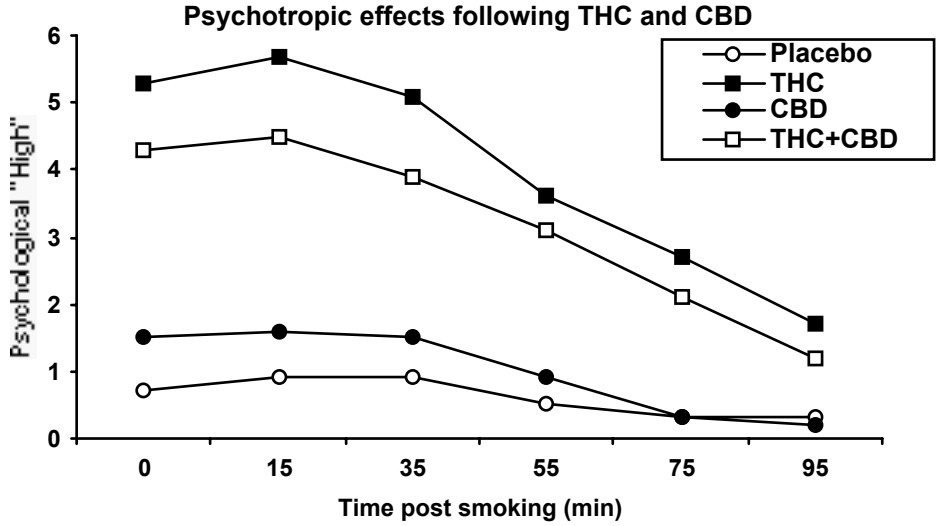


Figure 7: Intensity and duration of psychological "high" after smoking 25 µg/kg THC, 150 µg/kg CBD or a combination of both compared to placebo. Drawn according to Dalton et al. (1976).

6.6 Isomerization of CBD to THC

The above findings demonstrate that CBD, the predominant cannabinoid in industrial hemp varieties, by itself does not cause any psychotropic effects. However, it is well established that CBD can be chemically converted to THC (Mechoulam 1973). This theoretically renders industrial hemp a potent source of THC. In fact, isomerization of CBD is used by at least one European firm to produce THC for medicinal purposes. According to personal communication with Dr. Steup of THC Pharm, a German company, which produces dronabinol (THC) for medical use through isomerization of CBD, the isomerization involves the following process steps: preparation of an alcoholic extract from fiber hemp, treatment of this extract with sulfuric, hydrochloric or other acids, and removal of acid residues in a washing stage (Steup 2001). This sequence produces a THC-containing liquid for oral consumption. Note that the CBD content in fiber hemp of about 0.5–1.5% is still considerably lower than the THC content in marijuana of medium quality. Thus, even complete isomerization of CBD to THC (probably mostly the more stable and less psychotropic Δ^8-THC-isomer) will result in a THC liquid of at best low to medium quality.

Thus, it is possible to implement the DEA's concept of using isomerization to convert a "supposedly innocuous weed into a potent smoke product" (p. 20058, DEA 2001). However, in addition to the isomerization, this will require further processing to convert a liquid of unknown THC content and purity into a smokeable or edible material. This renders isomerization non-viable for domestic purposes. There are additional obstacles to the commercial illegal production of THC via isomerization. They include the limited benefits from adding to an already illegal activity, *i.e.*, the production and distribution of a controlled substance and the theft and transportation of marijuana-like material. The resulting risk likely outweighs the advantages of not having to grow a high-quality marijuana crop, which generally requires little further processing following harvest.

7. Conclusions and Recommendations

7.1 Conclusions

The evidence and considerations presented in this study allow the following major conclusions relative to the potential for drug use of industrial hemp:

- The production of albeit small quantities of THC in the leaves and flowers of low-THC "industrial hemp" varieties raises concerns over the crop's potential uncontrolled use as a medicinal or recreational drug.
- Major Western hemp producing countries (EU, Canada) are successfully limiting public exposure to THC by mandating the exclusive use by farmers of certified low-THC varieties, licensing and reporting requirements, and field sampling and analysis for THC. In the EU, certified industrial hemp varieties now may not contain more than 0.2% THC by dry weight in the most potent parts of the plant. In Canada, the limit of 0.3% still applies.
- There has been virtually no published experimental research on the drug potential of industrial hemp, as a function of variety, THC and CBD content, and mode of consumption. Thus, any assessment of this drug potential must currently rely on anecdotal evidence and the results from clinical studies using marijuana with a very low THC content, but generally not the high CBD levels characteristic of industrial hemp varieties.
- Most anecdotal reports from individuals who have tried to smoke industrial hemp in the EU and Canada support the conclusion that these varieties are not suitable for recreational drug use by smoking. The subjective high is, if experienced at all, much weaker than desired and may be attributed to a placebo effect. Occurrence of undesirable side effects, such as headaches, has been reported but was not consistent.
- To experience even mild psychotropic effects, a 70 kg person must smoke 2–3 mg of THC. For fiber hemp containing a maximum of 0.3% THC, this requires inhalation of at least 13 puffs.
- Several studies have indicated that the effects of smoking Cannabis with a THC content of 0.5–0.9% become indistinguishable from those of smoking a placebo. One dissenting study from the early 70s found that smoking much lower THC doses (~0.44 mg – corresponding to Cannabis with 0.1% THC) may cause a weak high. Since the study contradicts all other findings, these results may have been caused by analytical problems when quantifying THC content, and requires independent verification.
- In industrial hemp, CBD is the predominant cannabinoid and often occurs in a CBD/THC ratio of more than 8:1. Several studies have shown that even CBD/THC ratios of 2:1 in both smoked and ingested Cannabis considerably reduce the subjective high rating of the

same amount of pure THC, further impairing the already low psychoactive potency of industrial hemp.

- Oral intake of about 10–20 mg of THC is required to produce mild psychotropic effects. This corresponds to eating 3.5–7 gram of dry matter from industrial hemp containing 0.3% THC. Again, the psychoactivity suppressing effect of CBD present in industrial hemp requires that even larger amounts are eaten.
- The chemical isomerization to THC of the CBD present in industrial hemp is possible through a relatively basic process. However, the conversion of the resulting liquid into an edible or smokeable product of reasonably defined quality requires additional downstream processing.

These conclusions suggest three conceivable routes by which industrial hemp with a THC content of below 0.3%, and averaging 0.1%, may produce psychotropic effects:

1. *Smoking of high amounts of fiber hemp*
   Assuming an average THC content of 0.1% at least 2 grams of industrial hemp would have to be smoked to produce minimum psychoactivity. Since the intensity of effects depends on the rate of absorption the material has to be smoked within a short period of time to achieve a weak and brief effect. Actual effects will be even weaker due to the antagonistic effects of CBD. The required extensive and deep inhalation will often result in unpleasant coughs and interfere with continued smoking. Anecdotal reports from persons who tried to achieve a high from smoking fiber hemp agree on the lack of success. This further suggests that smoking of industrial hemp be only of theoretical relevance.
2. *Oral ingestion of high amounts of fiber hemp*
   Under the assumption that a minimum of 10 mg THC is needed to exceed the psychotropic threshold and 20–30 mg are needed to achieve a pleasurable high, 10 grams and 20–30 grams, respectively, of dry matter from fiber hemp with 0.1% THC are needed. Assuming that the CBD present reduces psychotropic THC effects by 50%, 20 grams and 40–60 grams of dry matter would have to be consumed to produce the respective effects. Such amounts are substantial and unlikely to be consumable over a period of 1–2 hours. Alternatively, hemp leaves and flowers could be cooked in butter or vegetable oil to extract the lipophilic THC. It is unknown whether the potency, quality, consistency and taste of such a product would make its consumption acceptable to marijuana consumers.
3. *Isomerization of CBD to THC*
   Implementation of this process even by a lay person appears to be feasible in principle. The produced liquid of unknown quality could be ingested. Assuming a CBD content of

1%, it is possible to yield 100 mg of THC (mostly Δ^8-THC) from 10 grams of dry matter. To the knowledge of the authors there have been no reports on such attempts with ditchweed found in the U.S. or with industrial hemp cultivated in Canada or the European Union.

Unlike the consumption of moderate to high-grade Cannabis, the likelihood of all these scenarios is limited by disagreeable consumption patterns and/or side effects. The latter include painful coughing, potential headaches from the smoking or ingestion of large quantities of fiber hemp, and uncontrolled dose and effects when ingesting THC-containing fat extracts and products of isomerization. Particularly the quality control problem for the latter process can apparently be solved through further purification, extraction and drying of the initial liquid. Yet, this effort appears to render isomerization non-viable for domestic purposes. There are additional obstacles to the commercial illegal production of THC via isomerization. They include the limited benefits from adding to an already illegal activity, *i.e.*, the production and distribution of a controlled substance and the theft and transportation of marijuana-like material. The resulting risk likely outweighs the advantages of not having to grow a high-quality marijuana crop, which generally requires little further processing following harvest.

In summary, our findings strongly support the notion that industrial hemp with a THC content of less than 0.3% has little to no potential for use as a crude marijuana substitute for personal consumption or the commercial illegal conversion into a high-potency drug. Based on the limited available information, it cannot be ruled out entirely that individuals may try to achieve a high through rapid and extensive smoking of industrial hemp or through the ingestion of large quantities of Cannabis plant material or oil-based extracts. Yet, the reported disappointing results by themselves appear to provide a sufficiently strong disincentive to domestic and commercial use. These findings agree with the positions of the governments in Canada and the EU that their commercial hemp programs provide sufficient protection from such use.

7.2 Recommendations

The demonstrated low abuse potential of fiber hemp will likely be relevant to the potential future re-legalization of industrial hemp in the U.S. The examples set by the EU and Canada demonstrate that a government that has the political will to allow hemp farming can control for the minimum potential for abuse. Concerns expressed by the U.S. government about the drug potential of industrial hemp could be alleviated further by the following measures.

1. The maximum acceptable THC content in industrial hemp varieties should be limited to 0.3%. Concerns over the impact of environmental factors, such as southern latitudes, on THC content should be addressed through an evaluation of the experience gained in the EU with varieties grown in Central and Southern Europe and through comparative research plots in the U.S.
2. A controlled study should address the presently insufficient evidence on the following two questions:
   - Whether the quantities of industrial hemp needed to supply a sufficiently high THC dose can realistically be smoked or ingested in a single session;
   - Whether the potentially produced high is desirable or associated with unpleasant side effects.

   Such a study would involve smoking and ingestion of realistic quantities of leaves and flowers from relevant commercial hemp varieties of known THC and CBD content.

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ANNEX I

Excerpt from ANNEX XIII of:

Commission Regulation (EC) No 2860/2000 of 27 December 2000 amending Regulation (EC) No 2316/1999 laying down detailed rules for the application of Council Regulation (EC) No 1251/1999 establishing a support system for producers of certain arable crops, to include flax and hemp grown for fibre, specifying the rules on set-aside areas and amending the base areas for Greece and Portugal *Official Journal L 332 , 28/12/2000 P. 0063 – 0075*

"(...)

Community Method for the Quantitative Determination of Δ9-THC (Tetrahydrocannabinol) Content in Hemp Varieties

1. Scope and area of application

This method seeks to determine the Δ9-tetrahydrocannabinol (THC) content of varieties of hemp (*Cannabis sativa* L.). As appropriate, the method involves applying procedure A or B herein described.

The method is based on the quantitative determination of Δ9-THC by gas chromatography (GC) after extraction with a suitable solvent.

1.1. Procedure A

Procedure A is used for checks on production as provided for in Article 5a(2) of Regulation (EC) No 1251/1999.

1.2. Procedure B

Procedure B is used in cases as referred to in the third subparagraph of Article 7b(1) of this Regulation and for checking that the conditions laid down in the second subparagraph of Article 5a(1) of Regulation (EC) No 1251/1999 are fulfilled with a view to inclusion on the list of varieties of hemp eligible for aid from the 2001/02 marketing year.

2. Sampling

2.1. Samples

- Procedure A: in a standing crop of a given variety of hemp, take a 30 cm part containing at least one female inflorescence of each plant selected. Sampling is to be carried out during the period running from 20 days after the start of flowering to 10 days after the end of flowering, during the day, following a systematic pattern to ensure that the sample is representative of the field but excluding the edges of the crop. Member States may authorise sampling to be carried out during the period from the start of flowering to 20 days after the start of flowering provided that, for each variety grown, other representative samples are taken in accordance with the above rules during the period from 20 days after the start of flowering to 10 days after the end of flowering;

- Procedure B: in a standing crop of a given variety of hemp, take the upper third of each plant selected. Sampling is to be carried out during the 10 days following the end of flowering, during the day, following a systematic pattern to ensure that the sample is representative of the field but excluding the edges of the crop. In the case of dioecious varieties, only female plants must be taken.

2.2. Sample size

- Procedure A: the sample is to comprise parts of 50 plants per field;

- Procedure B: the sample is to comprise parts of 200 plants per field.

Each sample is to be placed in a fabric or paper bag, without crushing it, and sent to the laboratory for analysis.

The Member State may provide for a second sample to be collected for counteranalysis, if required, to be kept either by the producer or by the body responsible for the analysis.

2.3. Drying and storage of the sample

(...)

3. Determination of THC content

3.1. Preparation of the test sample

(...)

3.2. Reagents and extraction solution

(...)

3.3. Extraction of Δ9-THC

3.4. Gas chromatography

(...)

4. Results

The findings are to be expressed to two decimal places in grams of Δ9-THC per 100 grams of analytical sample dried to constant weight. A tolerance of 0,03 g per 100 g applies.

- Procedure A: one determination per test sample.

However, where the result obtained is above the limit laid down in the second subparagraph of Article 5a(1) of Regulation (EEC) No 1251/1999, a second determination must be carried out per analysis sample and the mean value of the two determinations will be taken as the result.

- Procedure B: the result corresponds to the mean value of two determinations per test sample."