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Longitudinal studies have suggested that there is a relationship between adolescent cannabis use and job instability among young adults that is not explained by differences in education and other characteristics which precede cannabis use (e.g. (11). Newcomb and Bentler (23) examined the relationships between adolescent drug use and income, job instability, job satisfaction, and resort to public assistance in young adulthood, while controlling for differences between users and nonusers in social conformity, academic potential and income in adolescence. Their findings supported those of Kandel who found that adolescent drug users had a larger number of changes of job than nondrug users. Newcomb and Bentler conjectured that this reflects impaired work performance, or a failure of illicit drug users to develop responsible employment behaviour such as conscientiousness, thoroughness, and reliability.

Fergusson and Horwood (25) included unemployment for 3 months or more as one of their early outcomes in the follow up of their cohort at age 18 years. There was a relationship between how often cannabis had been used by age 16 and being unemployed for 3 months or longer. The rate of unemployment among those who had never used cannabis was 9.5% compared to rates of 18.9% and 37.5% among those who had used 1–9 times and 10 or more times respectively. After adjusting for covariates, the strength of the association was reduced but still significant (namely, 10.5%, 17.3% and 26.9% respectively). After adjustment for peer affiliations, the relationship was no longer statistically significant (12.2%, 13.4% and 14.6% respectively).

One longitudinal study (43) found more mixed evidence of an association between adolescent cannabis use in a sample of 785 young people followed from late high school in 1971–1973 until early adulthood in 1981. They found that adolescent cannabis use was weakly correlated with poor job performance, low job satisfaction or adverse job terminations. The correlations between cannabis use and these indices of job performance were 0.07, 0.07, and 0.17 respectively. These weak relationships between adolescent drug use and adult occupational performance were explained as the result of cannabis use persisting into adult life where it was associated with poor job performance, low job satisfaction, and adverse job termination.

12.8.2 Interpersonal relationships

There are good reasons for suspecting that cannabis use may adversely affect interpersonal relationships. Heavy adolescent drug use may produce a developmental lag, entrenching adolescent styles of thinking and coping which impair the ability to form adult relationships (1). There are also strong correlations between drug use and precocious sexual activity, and early marriage which in turn predicts a high rate of relationship failure (23).

Cross-sectional studies of drug use in young adults have indicated that a high degree of involvement with cannabis predicts a reduced probability of marriage, an increased rate of cohabiting, an increased risk of divorce or failed de facto relationships, and a higher rate of unplanned pregnancy and pregnancy termination (41, 42). These findings have been confirmed in analyses of the longitudinal data from a cohort of young adults (11).

Newcomb and Bentler (23) found similar relationships between drug use and early marriage in their analysis of the data from young adults in Los Angeles. Drug use in adolescence predicted an increased rate of early family formation in late adolescence and

of divorce in early adulthood. They interpreted this as evidence that: 'early drug involvement leads to early marriage and having children which then results in divorce' (p. 97). Newcomb and Bentler argued that this finding provided evidence for their theory of 'precocious development', according to which drug use accelerates development and drug users 'bypass or circumvent the typical maturational sequence of school, work and marriage and become engaged in adult roles of jobs and family prematurely without the necessary growth and development to enhance success with these roles ... [thereby developing] a pseudomaturity that ill prepares them for the real difficulties of adult life' (pp. 35–36).

12.8.3 Mental health

A number of cross-sectional studies of the association between cannabis use and poor mental health in young adults have produced mixed findings. The US National Longitudinal Alcohol Epidemiologic Survey (NLAES), a nationally representative survey of US adults (44) found that persons with DSM-IV major depression in the past 12 months were 6.4 times more likely to have DSM-IV cannabis abuse or dependence than those without major depression (6% vs. 1% respectively)(44).

A study of cannabis use and depressive symptoms did *not* find that frequency of cannabis use was associated with depression in young adult males (45). A weak association observed between early initiation of cannabis use and depression was not significant after controlling for educational attainment, marital status, and alcohol and tobacco use (45).

A study of male army draftees using cannabis but no other illicit drugs found that more problematic cannabis users had a higher rate of DSM-III-R psychiatric disorders and higher scores on the Beck Depression Inventory (BDI) (46). A study of adolescents cannabis users found that frequent users of cannabis had higher levels of depression on the Brief Symptom Inventory than abstainers or recreational users (47). 'Heavy' users were defined as those using cannabis at least 40 times *and at least one other illicit drug*.

Degenhardt et al. (48) examined relationships between cannabis use and mental health using data from the Australian National Survey of Mental Health and Well-Being (NSMHWB), a survey of a nationally representative sample of 10,641 Australian adults aged 18 years and over There was an association between cannabis use in the past 12 months and affective and anxiety disorders. Among those with cannabis dependence, 14% had an affective disorder and 17% had an anxiety disorder, compared with rates of 6% and 5% respectively in non-users. Heavier cannabis users also reported greater levels of psychological distress (as measured by Kessler's Psychological Distress scale).

The results of a number of longitudinal studies have provided more mixed evidence of the relationship between cannabis use and mental health. Kandel (41) found a cross-sectional study found an association between level of cannabis use and dissatisfaction with life, having consulted a mental health professional, and having been hospitalised for a psychiatric disorder (41). Longitudinal analyses of this cohort, however, found only weak associations between adolescent drug use and adult mental health; the strongest relationship was between cigarette smoking in adolescence and symptoms of depression in adulthood (11).

The cross sectional adult data in Newcomb and Bentler's (23) study also showed strong relationships between adolescent drug use and emotional distress, psychoticism and lack of a purpose in life. Emotional distress in adolescence predicted emotional distress in young adulthood but there were no relationships between adolescent drug use and adult emotional distress, depression and lack of a sense of purpose in life. Adolescent drug use predicted psychotic symptoms in young adulthood, and hard drug use in adolescence predicted increased suicidal ideation in young adulthood, after controlling for general drug use and earlier emotional distress. Newcomb and Bentler interpreted this as evidence that adolescent drug use 'interferes with organised cognitive functioning and increases thought disorganisation into young adulthood' (p 180).

Fergusson and Horwood (25) found a dose response relationship between frequency of cannabis use by age 16 and the likelihood of meeting DSM-IV criteria for an anxiety and depressive disorder and reporting a suicide attempt. These relationships were no longer statistically significant, however, after controlling for confounding factors.

Brook, Cohen and Brook (3) reported a longitudinal study of the relationship between alcohol, tobacco and cannabis use and mental health among 975 adolescents followed from age 13.7 years until 22.1 years in New York state. They found that early cannabis use predicted later antisocial behaviour after controlling for earlier antisocial behaviour. It did not predict an increased risk of anxiety and affective disorders. The strongest relationships between adolescent drug use and adult mental disorders were between cigarette smoking, illicit drug use (other than cannabis) and depression.

McGee, Williams, Poulton and Moffit (49) reported a longitudinal study of the relationships between cannabis use and mental health in a Dunedin, New Zealand, birth cohort between the ages of 15 and 21 years. They found that rates of cannabis use were higher among young people with mental disorders at 15, 18 and 21 years and that cannabis use was predicted by social disadvantage in childhood and low parental attachment. Cannabis use at age 15 did not predict mental health problems at age 18 but having mental health problems at age 15 (primarily alcohol dependence and conduct disorder) modestly predicted cannabis use at age 18. Cannabis use at age 18 also predicted alcohol dependence and conduct disorders at age 21. McGee et al argued that the lack of a relationship between cannabis use and anxiety and affective disorders suggests that cannabis use is not a form of 'self-medication in anxious and depressed individuals but rather reflects a 'willingness to contravene the law'.

12.8.4 Suicide

A small number of studies have examined the relationship between cannabis use and suicide among adolescents (see Hillman et al (50) for a review). Several have found an association but it remains unclear whether it is explained by other factors. An analysis of cross-sectional data from the US National Comorbidity Survey found an association between self-reported suicide attempts and the dependence on a number of drugs, including alcohol, sedatives, stimulants, cannabis, and inhalants (51). The risk for cannabis dependence was still significant after adjusting for socio-demographic factors and the presence of other psychiatric disorders, such as depression and alcohol dependence (odds ratio of 2.4,

Beautrais, Joyce and Mulder (52) reported a case-control study of the role of cannabis and other drug use in serious suicide attempts that resulted in hospitalisation. They compared rates of cannabis use among 302 consecutive hospital cases treated for serious suicide attempts with that in a random sample of 1,028 people in the community. They found that 16% of the suicide attempters had a cannabis use disorder (cannabis abuse or dependence) compared with 2% of the controls. Controlling for social disadvantage and having a diagnosis of depression or alcohol dependence substantially reduced the association but did not eliminate the association (reducing it from an odds ratio of 10 to 2).

The evidence from a small number of prospective studies is also mixed. Fergusson and Horwood (25) also found a dose response relationship between frequency of cannabis use by age 16 and the likelihood of reporting a suicide attempt, but it did not remain statistically significant after controlling for confounding factors. Patton et al (53) reported a longitudinal study on suicide attempts and self-harm in a cohort of 2066 Victorian secondary school students followed from age 15 to 16 to age 21. They found that cannabis was associated with self-harmful behaviour among females but not males, after controlling for depression and alcohol use.

Andreasen and Allebeck (54) reported an association between cannabis use and suicide deaths in their follow up of 50,465 conscripts. They found a fourfold increased risk of suicide among heavy cannabis users. A more detailed analysis of predictors of suicide in this cohort reported by Allebeck and Algulander (55) found that inpatient psychiatric hospitalisation by age 18 was the strongest predictor of suicide risk (OR = 11.3). Use of 'narcotics' (which includes cannabis) did not predict suicide independently of a psychiatric diagnosis (OR =1.3) but a diagnosis of alcohol dependence (OR = 4.3) and drug dependence (OR = 3.6) did.

12.8.5 Delinquency and crime

Cannabis and other illicit drug use are related to social nonconformity (2[illegible]6, 57) so it is unsurprising that there is a relationship between the extent of cannabis use and lifetime delinquency among adult drug users (41, 42), having been convicted of an offence, and having had a motor vehicle accident while intoxicated (41). Surveys of drug use in young people in the juvenile justice system also find high rates of regular cannabis use and a relationship between level of cannabis use and frequency of offending (58, 59).

Longitudinal studies reveal an interesting pattern of relationships between cannabis use and crime. Johnston et al. (60) analysed the relationship between drug use and delinquency in two waves of interviews of adolescent males. In their cross-sectional data, rates of delinquent activity increased steadily with increasing rates of drug use. However, analyses of changes in drug use and crime over time indicated that heavy drug users groups had much higher rates of delinquent acts *before* using drugs. The onset of illicit drug use (including cannabis) had little effect on delinquent acts, except among those who used heroin, whose rates of delinquency increased.

Newcomb and Bentler (23) reported a positive relationship between drug use and criminal involvement in adolescence, but found more mixed results in the relationship between adolescent drug use and criminal activity in young adulthood. Adolescent drug use predicted *drug* crime involvement in young adulthood; but after controlling for other

variables, it was *negatively* correlated with violent crime, and general criminal activities in young adulthood. Newcomb and Bentler argued that these negative correlations indicated that the correlation between different forms of delinquency in adolescence decreases with age, as criminal activities become differentiated into drug-related and non drug-related offences.

White (61) reported a follow up study of the relationship between cannabis use and delinquency in 1992 New Jersey youth followed from age 12 to age 18. He found modest correlations between cannabis use and delinquency at age 15 and age 18 and evidence that there were separate groups of adolescents who either engaged in cannabis use or in delinquent acts. These groups were distinguished by which of these two behaviours was most common among their immediate peers.

Fergusson and Horwood (25) included four measures of delinquency in their analysis of the consequences of adolescent cannabis use. These were: three or more violent offences, three or more property offences, arrested by police, and convicted of an offence in court by age 16. There was a dose-response relationship between each of these outcomes and frequency of cannabis use by age 16. This persisted after adjustment for covariates, suggesting that it was not wholly explained by the characteristics of adolescents who become regular cannabis users by age 16. It also persisted after adjustment for drug use and criminal behaviour in the users peer group, indicating that it was not explained by affiliating with delinquent and drug using peers.

Brook et al (29)'s longitudinal study of 695 African-American and 637 Puerto Rican youth in New York City also assessed self-reported violence towards others. They found that early cannabis use predicted a doubling of the risk of self-reported violence towards others, after adjusting for other covariates (but not for a history of delinquency and violence prior to using cannabis).

Arsenault, Moffit, Caspi and Taylor (62) reported a longitudinal study of the relationships between mental disorders and violence in a cohort of 961 youth studied from birth to age 21 in Dunedin, New Zealand. They assessed psychiatric disorders, including alcohol and cannabis dependence and asked about alcohol and other drug use prior to self-reported violence. Violence was assessed using self-report and police records of convictions for violence. They found that 7.6% of the sample reported engaging in violence in the past year and 4% had been convicted of violent offences. They found strong associations between self-reported and officially recorded violence and alcohol dependence, cannabis dependence and schizophrenia. Controlling for a history of conduct disorder in childhood (prior to using cannabis) substantially reduced the association between cannabis dependence and violence. The authors argued that the relationship reflected the heavy involvement of cannabis dependent and conduct disordered adolescents in the drug market where violence was used to resolve disputes.

12.9 Summary

Cross-sectional and prospective research indicates that young people who use cannabis are at increased risk of adverse psychosocial outcomes including criminal behaviour, poor mental health, impaired educational achievement and reduced life opportunities. The longitudinal studies suggest that a large part of these associations arise because the factors that predispose young people to use cannabis overlap with the factors that predict these outcomes. In ordinary language, the young people who are most likely to use cannabis in early adolescence are the same young people who were at greatest risk of using other drugs, engaging in delinquency, having poorer mental health, attempting suicide, and doing poorly at school *before they began to use cannabis*.

However, not all of the relationships between cannabis use and these poorer social outcomes can be wholly explained this way. There is evidence that early cannabis use further impairs the school performance of adolescents whose performance was poor before they began to use cannabis. It may also predict involvement in criminal behaviour after controlling for a history of conduct disorder, perhaps by exacerbating pre-existing anti-social behaviour. It may possibly increase the risk of suicide but this remains to be clarified by better designed studies.

Plausible mechanisms that may explain these associations have been suggested by Fergusson and Horwood (25), namely, that adolescents who are socially disadvantaged and have conduct problems as children are more likely to become early cannabis users, and early cannabis use increases the chances of an unconventional lifestyle. The latter occurs as a result of affiliating with delinquent and substance using peers and disengaging from conventional social roles such as completing education and obtaining a job. The acute effects of cannabis intoxication may also play a role by encouraging impulsive behaviour and impairing perceptions of risk among the minority of students who are daily cannabis users.

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13 Therapeutic uses of cannabis

Cannabis has had a long history of medical and therapeutic use in India and the Middle East (1–3), where it was used to treat pain, convulsions, spasm, nausea and to induce sleep. Cannabis was introduced to Britain in the mid-nineteenth century by O'Shaughnessy (4) who had used the drug while an Army surgeon in India (2, 3). He recommended its use for the relief of pain, muscle spasms, and convulsions occurring in tetanus, rabies, rheumatism and epilepsy (3). Cannabis was widely used as an analgesic, anticonvulsant and antispasmodic in Britain and the USA during the latter half of the nineteenth and the early part of the twentieth centuries.

Medical uses of cannabis declined after the turn of the twentieth century because natural cannabis preparations varied in potency and effectiveness. Cannabis was largely supplanted by pharmaceutically pure drugs, such as the opiates, aspirin, chloral hydrate, and the barbiturates, all of which could be given in standard doses to produce more predictable effects (2, 3). Many of these drugs could also be injected to provide rapid relief of symptoms whereas cannabis extracts had to be given orally (5). After the introduction of international drug control agreements in the early part of the 20th century, the medical use of cannabis preparations was discouraged by laws that treated cannabis as a 'narcotic' drug. Cannabis disappeared from the American pharmacopoeia in the early 1940s after the passage of the Marijuana Tax Act (1), although it continued to be used in Australia into the 1960s (6).

The isolation of THC in 1964 (7) occurred shortly before cannabis became widely used as a recreational drug by American youth. Its illegality and recreational use hindered pharmaceutical research, so the rediscovery of its therapeutic uses was serendipitous. Its value as an anti-emetic agent in treating nausea caused by cancer chemotherapy was discovered by young adults who had used cannabis recreationally while undergoing chemotherapy for leukemia (8).

From the mid 1970s until the early 1980s clinical research was undertaken on the therapeutic value of cannabis and cannabinoids. On the whole, however, this research was very thin and uneven, and, consequently, many of the claims for the therapeutic efficacy of cannabinoids rely on the reports of individuals who have derived medical benefit from its use (e.g. (1, 9). When cannabinoids and cannabis are advocated for medical uses it is primarily for relief of symptoms rather than to cure any underlying disease. The conditions for which cannabis is most commonly advocated are for symptomatic relief of nausea, vomiting, appetite loss, and chronic pain (10).

13.1 Cannabinoids as anti-emetic agents

Severe nausea and vomiting may prompt patients to discontinue life-saving chemotherapy and radiotherapy for cancer (10). Anti-emetic drugs (e.g. the phenothiazines) are effective in controlling nausea and vomiting in cancer patients

undergoing chemotherapy but a substantial minority of patients do not benefit from these drugs. The incomplete success of existing treatments prompted oncologists in the late 1970s and early 1980s to study the anti-emetic properties of cannabinoids (10).

One of the earliest trials studied the effects of THC on nausea and vomiting (11) in 22 patients with a variety of cancers, 20 of whose nausea and vomiting had proven resistant to existing anti-emetic drugs. Patients were randomly assigned to receive oral THC and placebo in one of four different orders. Outcome was assessed by patients' self-reports of nausea and vomiting after THC and placebo into three categories: complete response if there was vomiting after placebo but not after THC; partial response if there was a greater than 50% reduction in nausea and vomiting after THC compared to placebo; and no response if there was a less than 50% reduction in nausea and vomiting.

There were 29 trials, 14 of placebo and 15 of THC. There was no anti-emetic response in any of the 14 placebo trials. There were 5 successes, 7 partial responses, and 3 no responses in the 15 THC trials. Most patients (13/16) reported a 'high' after receiving THC, an experience which was correlated with the anti-emetic effect. The most common side-effect was sleepiness. Two patients experienced visual illusions and hallucinations and depression lasting several hours. Several patients reported that smoking cannabis had the same anti-emetic effects as oral THC.

A trial by Chang et al (12) largely supported the findings of Sallan et al (11). In this study 15 patients with osteogenic sarcoma receiving monthly high dose methotrexate therapy served as their own controls. They were assigned to receive three THC and three placebo trials in randomised order during six treatment sessions. If the patients vomited, the remaining doses of either THC or placebo were administered by smoking a cigarette. The effect of THC and placebo on vomiting and retching episodes were assessed by nursing staff who graded response into three categories: excellent (greater then 80% reduction after THC by comparison with placebo in each of these endpoints); fair (greater than 30% and less than 80% reduction), and no response (less than 30% reduction).

Eight patients had an excellent response, 6 a fair response, and one had no response. On all outcomes THC produced a statistically greater reduction in nausea and vomiting than placebo. There was a relationship between blood levels of THC and reports of nausea and feeling 'high'. Higher THC blood levels were achieved when cannabis was smoked than when THC was taken orally. There were few side effects, sedation being the most common (12/15 patients). Four patients experienced 5 dysphoric reactions in the course of 281 THC drug doses (2%). None of these lasted more than 30 minutes, and all were successfully managed by reassurance.

Since these early studies, a number of controlled clinical trials have compared the effectiveness of THC with a placebo or another anti-emetic drug (see (13–15) for reviews). Studies comparing oral THC with existing anti-emetic agents have had less consistent results than comparisons with placebo but the results have generally indicated that THC is as effective as the anti-emetic drug prochlorperazine (13, 15). The equivalence of THC and prochlorperazine was reported in one of the largest and best conducted studies (16).

Although cannabinoids showed *some* anti-emetic efficacy by comparison with prochlorperazine they typically failed to stop nausea in two thirds of patients. In one controlled study, THC produced complete control of emesis in only 13% of cases as against 47% who received metoclopramide. It achieved 'major control' of vomiting (two or fewer episodes) in 27% as against 73% in the comparator (10). The same has been true of the anti-emetic effects of nabilone and levonantradol (10).

Since these trials were conducted much more effective anti-emetic drugs than prochlorperazine have become available (10). These newer agents have dramatically reduced nausea and vomiting. The selective serotonin type 3 receptor agonists, such as ondansetron, have achieved complete control over nausea induced by cisplatin in 75% of cases and up to 90% for less emetogenic chemotherapy (10). Side effects include headache and constipation but these are generally well tolerated. These drugs have reduced the demand for THC as an anti-emetic drug.

13.2 Cannabinoids and HIV-related wasting

Cannabis has also been used therapeutically as an anti-nausea agent, an appetite stimulant and an analgesic in patients with HIV-related wasting (10). HIV/AIDS patients often experience nausea and weight loss, either while receiving antiviral drugs to suppress HIV, or as a direct effect of the AIDS-related diseases. Wasting syndrome in HIV/AIDS has been defined by the US Centers for Disease Control and Prevention as 'the involuntary loss of more than 10% of baseline average body weight in the presence of diarrhoea or fever of more that 30 days that is not attributable to other disease processes' (10).

In animal studies cannabinoids have been shown to act on brain centres that control appetite (17), supporting reports of benefits in patients with AIDS. Few controlled trials have been published on the effectiveness of cannabis or cannabinoids for this purpose. Oral THC has been shown to be of benefit in short-term trials (18, 19) and it has been registered for this purpose in the US. Some patients do not like dronabinol because of its psychoactive side effects, the difficulty in controlling their dose, the delayed onset of effects, and the prolonged effects when it is taken orally (10). There are anecdotal reports that smoked cannabis is effective for the treatment of HIV/AIDS-associated anorexia and weight loss (1, 20). There have not been any controlled studies on smoked cannabis but one is underway in California.

A major concern with HIV-infected patients smoking cannabis for medical purposes is that it might have immunosuppressive effects or infectious organisms in cannabis plant material may produce opportunistic infections. Recent epidemiological evidence does allay this concern to a degree in that a large prospective cohort study of HIV/AIDS in homosexual and bisexual men recently failed to find any relationship between cannabis use, or any other psychoactive drug use, and the development of clinical AIDS (21). Nonetheless, the immunosuppressive effects of THC and smoked cannabis need to be investigated in any research on the therapeutic uses of cannabinoids in the treatment of HIV-related wasting.

13.3 Cannabinoids as anti-glaucoma agents

Glaucoma is the leading cause of blindness in the United States, causing 300,000 new cases each year (22). It is caused by a gradual increase in pressure within the eye, intraocular pressure' (IOP). If untreated, IOP may damage the optic nerve, leading to blindness. Its incidence increases over the age of 35, especially among individuals who are short-sighted. Many drugs that reduce IOP have unwanted side-effects and patients may become tolerant to their therapeutic effects.

The effects of cannabis on IOP were discovered serendipitously by researchers and patients in the early and middle 1970s. Hepler and his colleagues (23–25) demonstrated that cannabis and oral THC substantially reduced IOP in normal volunteers and in patients with glaucoma (23–25). Subsequent research indicated that THC produced this effect (22).

Although there have been a number of case reports of the successful use of cannabis in the management of glaucoma (e.g. (1, 9), there have not been any controlled clinical studies of its effectiveness and safety. Although THC reduces IOP acutely there are doubts about its long-term effectiveness because tolerance develops to this effect (26). The US Institute of Medicine concluded that there was no evidence to support the use of THC in glaucoma (10). It argued that the effects of cannabis and THC on IOP are too short-lived, and the high oral doses that were required produced side effects that precluded its long-term use (10). The harmful effects of chronic cannabis smoking, it argued, outweighed its modest medical benefits. A cannabinoid drug with longer lasting effects on IOP and fewer psychoactive effects than THC could be of greater use (10).

13.4 Cannabinoids and epilepsy

Animal studies have provided some support for the historical use of cannabis preparations to control seizures in epilepsy, tetanus and rabies (3). Cannabidiol (CBD) appears to be a potent anticonvulsant in animals (27–29). There is very limited evidence on the therapeutic effects of cannabinoids in humans with epilepsy. There are a small number of case studies of individuals with epilepsy in which the use of cannabis appeared to enhance the anticonvulsant effects of more traditional anticonvulsant medication (e.g. (1, 30).

There is one randomised placebo controlled study of CBD in 15 patients whose epilepsy was not controlled by conventional anti-convulsants. Four of the eight patients who received CBD in addition to their usual anti-convulsant drugs were free of seizures throughout the study period, and three were improved. By contrast, only 1 out of 7 patients in the placebo condition showed any clinical improvement (31). Despite this suggestive evidence of efficacy there has been no further research on the anticonvulsant properties of CBD (3). This may be because more effective anticonvulsant drugs exist and pharmaceutical companies have no interest in marketing a naturally occurring substance that cannot be patented.

13.5 Cannabinoids and muscle spasticity

Muscle spasticity is the increased resistance to passive stretch of muscles. Involuntary contractions may occur which can be painful and debilitating. About 90% of MS patients eventually develop muscle spasticity, in the form of stiffness, spasms, cramps, aches or pain. Recent animal research has found that THC reduces both tremor and spasticity among diseased mice, suggesting that the cannabinoid system may be involved in control of these functions (32). A survey of 112 MS patients (33) supported the use of cannabis for MS, and some open studies have suggested it is of benefit (34–36).

Clinical studies have not supported the anecdotal evidence, but this may be due to the studies' limitations (10). The survey results suggest that it would be useful to investigate the potential therapeutic value of cannabinoids in relieving symptoms associated with MS (37). The regular use of *smoked* cannabis is not advisable in a chronic illness such as MS.

Muscle spasticity is also common among patients with spinal cord injuries, 60% of whom are younger than 35 years and need long-term care. As with MS, surveys of these patients suggest that cannabis reduces spasticity, nausea and insomnia. Carefully designed clinical trials of THC should be conducted, and have been proposed in the UK (38).

13.6 Cannabinoids and movement disorders

Movement disorders are caused by abnormalities in brain areas that control motor functions. They result in abnormal skeletal muscle movements in the face, limbs and trunk that may occur in patients with dystonia, Huntington's disease, Parkinson's disease and Tourette's syndrome (10). There is limited research that cannabis is useful for treating movement disorders.

There is some evidence that the muscle spasms or 'tics' experienced by patients with Gilles de la Tourette Syndrome are relieved by THC (e.g. (39). Since stress often transiently exacerbates movement disorders, the anxiety-relieving effects of cannabis or cannabinoids might help patients with movement disorders. However, regular cannabis smoking would be a risk for persons already suffering from chronic health conditions (10).

The evidence that cannabinoids have therapeutic effects in patients with movement disorders is largely anecdotal (e.g. (1, 40). Grinspoon and Bakalar (1), for example, presented four case histories of individuals with multiple sclerosis whose condition improved while they smoked cannabis, and deteriorated after they stopped smoking.

There has been one controlled study by Clifford (34) who examined the effects of THC on tremor in 8 patients (4 male and 4 female) with advanced multiple sclerosis. Five patients reported subjective benefit from THC and there was objective evidence of benefit in two of these cases. There was also evidence that their clinical condition deteriorated when they were given placebo and that it improved with the reinstatement of THC.

Grinspoon and Bakalar (1) also described several patients with paraplegia and quadriplegia who reported that cannabis use helped to reduce muscle spasm. The experiences of these individuals were supported by reports in a survey of 43 individuals with spinal cord injuries, 22 of whom reported that they used cannabis to control their muscle spasm.

One controlled trial has evaluated the effects of CBD on chorea in 19 patients with advanced Huntington's disease (41). In this study patients received CBD or placebo for six weeks under double blind conditions in a crossover design. There was no evidence of improvement in chorea on any of the clinical, self-report or motor measures.

13.7 Cannabinoids as anti-asthmatic agents

Smoked cannabis and oral THC dilate the bronchial tubes in normal persons and persons with asthma (42, 43), that is, they increase the lung's capacity to absorb oxygen. Tashkin and colleagues (43), for example, found that smoking a 2% THC cannabis cigarette produced a bronchodilator effect nearly equivalent to that of a clinical dose of isoproterenol, an anti-asthmatic medication.

A major obstacle to the therapeutic use of cannabinoids in asthma is the fact that oral THC produces a much smaller bronchodilator effect and after a substantial delay, than smoked cannabis (44). Attempts to give THC as an inhalant produce irritation and reflex bronchoconstriction (44). Smoking cannabis is the most dependable way of delivering an effective dose of THC but this is an inappropriate way to administer a drug to patients with asthma because it would also deliver other noxious substances that would nullify its therapeutic effects and increase the risk of other respiratory diseases, including cancer in the long-term (44). The unwanted psychotropic effects from cannabis smoking have also been a barrier to its use as an anti-asthmatic drug.

13.8 Cannabinoids as analgesics

Animal studies suggest that cannabinoids may be useful as analgesics. The CB_1 receptor acts on pathways that partially overlap with those affected by opioids like morphine but it acts through pharmacologically distinct mechanisms. This means that cannabinoids and opioids probably have different side effects and may have additive or synergistic analgesic effects.

The few controlled studies of the analgesic efficacy of cannabinoids in humans have been inconclusive. Three experimental pain studies in humans produced mixed results (45–47), but they were poorly controlled (10). More encouraging results have come from three clinical studies of the effects of cannabinoids in patients with severe cancer pain that was persistent and had resisted traditional analgesics (48–50). These studies, which were all double blind and placebo controlled, demonstrated that cannabinoids had analgesic effects equivalent to those of codeine, without its severe side effects, while improving mood, well–being, and appetite.

13.9 The limitations of anecdotal evidence

With the exception of its anti-emetic, anti-nausea and appetite stimulating effects, much of the case for the therapeutic uses of cannabis and cannabinoids is based upon anecdotal evidence. Such evidence is distrusted in clinical medicine. This is especially so in chronic conditions which have a fluctuating course of remission and exacerbation because it is difficult in these diseases to exclude alternative explanations of improvements in a patient's condition that follow their use of THC. It is difficult to exclude the possibility of simple coincidence: that is, THC preceded an improvement in the patient's condition that would have occurred in its absence. It is for these reasons that this review has relied upon evidence from controlled clinical trials in appraising the therapeutic uses of cannabinoids.

13.10 The risks of therapeutic cannabinoid use

For most people the primary adverse effect of acute cannabis use is impaired psychomotor performance. This makes it inadvisable for anyone under the influence of cannabis or THC to operate machinery that might put the user or others in danger, such as driving a car or operating equipment. Most people can be expected to show impaired performance of complex tasks, and a minority experience dysphoria. People who have psychiatric disorders (including substance dependence) may be vulnerable to cannabis dependence, and so sustained therapeutic cannabis use would be contraindicated for them. The short-term immuno-suppressant effects are not well established; if they exist, they are probably not large enough to preclude legitimate medical use. The US Institute of Medicine concluded that the acute effects of cannabis use were 'within the risks tolerated for many medications' (10).

The chronic effects of cannabis are of greater concern for medical use. They fall into two categories: the effects of chronic smoking, and the possibility of dependence on cannabis or THC. Cannabis smoke like tobacco smoke is a risk factor for cancer, lung damage, and poor pregnancy outcome. Smoked cannabis is therefore unlikely to be a safe medication for any chronic medical condition that requires daily use over a period of years. The risk of developing dependence on cannabis is highest in adolescents, particularly those with conduct disorders, and people with psychiatric disorders, or problems with substance abuse (10).

13.11 Obstacles to therapeutic cannabinoid use

Despite their comparative safety, and the evidence for the therapeutic effects of cannabinoids as anti-emetics and appetite stimulants, they have not been widely used clinically. Nor has pharmacological research developed synthetic cannabinoids for medical use. There are two main reasons for this. One is the lack of incentives for pharmaceutical companies to develop and market cannabinoid drugs; the other is the politics of recreational cannabis use.

13.11.1 The market outlook for therapeutic cannabinoids

The decision to develop and conduct clinical trials on a new drug is based upon a drug company's judgment that there is likely to be an adequate return on investment. The research and development costs of cannabinoids are likely to be similar to those of neuropharmaceuticals and anti-inflammatory drugs (10). In the case of the cannabinoids, there are the additional costs of meeting regulatory requirements for drugs derived from a prohibited plant.

The potential market for cannabinoids is determined by the current and projected number of patients who may use the drug, the sales of existing drugs for the indication, the availability of competing products, and the duration of disease (e.g. disease with an early age of onset and a need for long term use). Factors that affect market return include the company's ability to patent the drug, the availability of other forms of market protection, access to health insurance reimbursements, restrictions on access because of drug scheduling, social attitudes towards the drug, its adverse effect profile, and its interactions with other drugs. Naturally occurring substances such as THC cannot be patented; only newly synthesized or derived cannabinoid drugs can be patented.

13.11.2 The politics of therapeutic cannabinoids

Research on the therapeutic use of cannabinoids in the USA has become a casualty of the debate about the legal status of recreational cannabis use. For example, some of the groups advocating the therapeutic use of cannabis have also been proponents of cannabis legalisation (e.g. NORML), thereby fuelling the fears of opponents of cannabis use that success in the campaign for marijuana rescheduling will be the thin edge of a wedge to legalise cannabis. Other proponents of legalisation (e.g. 1) have argued for the legalisation of cannabis as a way of making cannabis available for therapeutic purposes.

On the other side of the argument are those opponents of cannabis use who fear that the admission that cannabis, or any of its constituents, may have a therapeutic use will send the 'wrong message' to youth. This has led to the denial that cannabinoids have any therapeutic effects, and to attempts to prevent all scientific inquiry into any such effects (Bernstein, 1989 cited (52) (p.395).

It is unfortunate that a connection has been forged between the debates about the legal status of cannabis as a recreational drug and the use of cannabinoids for therapeutic use. There is a world of difference between the use of controlled doses of a purified drug under medical supervision and the recreational use of crude preparations of a drug. In a rational world, clinical decisions about whether to use pure cannabinoid drugs should not be abrogated because crude forms of the drug may be abused by those who use it recreationally. We do not allow this type of thinking to deny us the use of opiates for analgesia. It should not deny patients access to any therapeutic uses of cannabinoids derivatives that may be revealed by pharmacological research.

13.12 Summary

The following provisional conclusions can be drawn on the therapeutic uses of cannabis. First, there is sufficient evidence that THC is an anti-emetic agent to justify it being made available in pure synthetic form to cancer and AIDS patients. In the light of the recent development of more effective anti-emetic agents, it remains to be seen how widely used THC will be for this purpose. Second, there is also reasonable evidence for the efficacy of THC in the treatment of AIDS-related wasting. Third, the suggestive evidence of the usefulness of cannabinoids as analgesic and anti-spasmodic agents warrants further pharmacological and experimental investigation, and perhaps clinical research into their effectiveness.

Despite the basic and clinical research work which was undertaken in late 1970s and early 1980s the cannabinoids have not been widely used therapeutically or extensively investigated. This seems largely attributable to the disincentives pharmaceutical companies have to develop cannabinoid drugs and the regulatory obstacles to their registration. The discouragement of therapeutic research also derives from the fact that THC, the most therapeutically effective cannabinoid, has the psychoactive effects sought by recreational users. The discovery of the cannabinoid receptor may help to overcome some of the resistance to research into the therapeutic uses of cannabinoids by holding out the prospect that the psychoactive effects of the cannabinoids can be disengaged from their other therapeutically desirable effects.

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14 A comparison of the health effects of cannabis with alcohol and tobacco

This chapter compares the most probable harms caused by cannabis use with those caused by alcohol and tobacco, two commonly used psychoactive substances in Western societies. A number of issues arise in comparing the health effects of cannabis with those of these two drugs. The first are difficulties in making causal inferences about the connections between cannabis use and the adverse health and psychological consequences which have been attributed to it (1). The second is lack of information about the risks of cannabis use for users. Both of these problems arise from the scarcity of epidemiological studies of the health risks of cannabis use by comparison with such studies of alcohol and tobacco use.

A third set of difficulties arise in measuring the public health impact of these risks. The methods used to date have typically involved comparisons of the numbers of deaths, persons years of life lost, and hospital bed days attributable to conditions caused by each type of drug (e.g. English et al, (2)). The most recent innovation has been to use a combination of Life Years Lost (YLL) and Disability Adjusted Life Years (DALYs) to estimate the total burden of disease attributable to alcohol, tobacco and illicit drug use (3, 4).

14.1 The probable adverse health effects of cannabis

The following are the major adverse health and psychological effects of acute and chronic cannabis use, classified by the degree of confidence in the relationship.

14.1.1 Acute effects

The major acute psychological and health effects of cannabis intoxication are:

- anxiety, dysphoria, panic and paranoia, especially in naive users;
- cognitive impairment, especially of attention and memory while intoxicated;
- psychomotor impairment, and probably an increased risk of accidental injury or death if an intoxicated person attempts to drive a motor vehicle or operate machinery;
- an increased risk of experiencing psychotic symptoms among those who are vulnerable because of a personal or family history of psychosis;
- an increased risk of low birth weight babies, and possibly of birth defects, if used during the first trimester of pregnancy.

14.1.1 Chronic effects

The major health and psychological effects of chronic cannabis use, especially daily use over many years, remain uncertain but the major **probable** adverse effects appear to be:

- respiratory diseases caused by smoking cannabis, such as chronic bronchitis, and changes in lung tissue that are precursors of malignancy;
- development of a cannabis dependence syndrome, characterised by an inability to abstain from or to control cannabis use;
- an increased risk of developing cancers of the aerodigestive tract, i.e. oral cavity, pharynx, and oesophagus.

The following are the major **possible** adverse effects of chronic, heavy cannabis use which remain to be confirmed by controlled research:

- subtle forms of cognitive impairment, most particularly of attention and memory, which persist while the user remains chronically intoxicated, and may or may not be reversible after prolonged abstinence from cannabis.
- a decline in occupational performance marked by underachievement in adults in occupations requiring high level cognitive skills, and impaired educational attainment in adolescents.

High risk groups

A number of groups are at increased risk of experiencing some of these adverse effects.

Adolescents

- Adolescents with a history of poor school performance whose educational achievement may be further limited by the cognitive impairments produced by chronic intoxication with cannabis;
- Adolescents who initiate cannabis use in the early teens are at higher risk of progressing to heavy cannabis use and other illicit drug use, and to the development of dependence on cannabis.

Women of childbearing age

- Babies born to women who continued to smoke cannabis may have a slightly lower birth weight.

Persons with pre-existing diseases

Persons with a number of pre-existing diseases who smoke cannabis are probably at an increased risk of exacerbating symptoms of their diseases. These include:

- individuals with cardiovascular diseases, such as coronary artery disease, cerebrovascular disease and hypertension;
- individuals with respiratory diseases, such as asthma, bronchitis, and emphysema;
- individuals with schizophrenia who are at increased risk of precipitating or of exacerbating schizophrenic symptoms;
- individuals who are or have been dependent upon alcohol and other drugs are probably at an increased risk of developing dependence on cannabis.

14.2 The implications of increased potency of cannabis

It has been claimed that a substantial increase in the average THC content of cannabis has 'made obsolete' much of what we once knew about the risks and consequences of cannabis use (5) because most of this was based on research on cannabis with low levels of THC. This argument is unconvincing for two reasons. First, as discussed in chapter 2, the evidence does not support claims that the average THC content of cannabis products has increased substantially in recent decades. Second, it is untrue that the research literature on the adverse health effects is based on studies of populations consuming cannabis with low levels of THC. The field studies in Costa Rica, Greece, Jamaica and Egypt examined very heavy, long term cannabis users and laboratory studies conducted in the USA involved subjects consuming 30 mg THC per day for periods of a month.

The claim about increased potency is popular because it appears to explain an apparent increase in the adverse effects of cannabis use. There probably has been some increase in the prevalence of some of these effects, most notably dependence, although this is uncertain because of limitations with the available data (6). There are, however, two more plausible alternative explanations for any increase in adverse effects of cannabis use: (1) cannabis markets have increased the availability of more potent forms of cannabis; and (2) changes in the patterns of cannabis use have increased the prevalence of harmful patterns of cannabis use (6).

The effect of using more potent cannabis products will depend upon the type of health effect in question, and the user's experience with cannabis. Higher average doses of THC will probably increase the risk of adverse psychological effects of cannabis use, an effect likely to be most obvious among naive or first time cannabis users. This effect may discourage further experimentation with the drug among these users. Risks of increased THC exposure among regular cannabis users possibly include an increased risk of accidents among those who drive while intoxicated, especially if cannabis use is combined with alcohol, and an increased risk of regular cannabis users developing dependence. If the THC content of the most commonly used cannabis products has increased, the net adverse effects of cannabis use may have marginally increased. Respiratory risks may be marginally decreased if cannabis smokers are able to titrate their doses of THC.

14.3 A comparison of the health risks of alcohol, cannabis and nicotine

We have used the following as authorities on the health risks of alcohol and tobacco: Anderson et al. (7); English et al (2); the Institute of Medicine (8); the International Agency for Research into Cancer (9); Mathers, Vos and Stephens (4); Roselle et al (10); and the Royal College of Physicians (11).

14.3.1 Acute effects

Alcohol

Some of the acute risks of cannabis use are similar to those of alcohol. Both drugs cause psychomotor and cognitive impairment, especially of memory and planning. In the case of alcohol these impairments increase the risks of motor vehicle and other accidents (2, 8). While cannabis intoxication probably increases the accident risks in hazardous situations, it remains to be determined whether it increases risky behaviour.

However, alcohol and cannabis differ in their relation to intentional injuries. First, alcohol intoxication is strongly associated with aggressive and violent behaviour. The relationship is complex, and the nature and extent of alcohol's causal role is controversial (12–14), but changes in the level of alcohol consumption appear to affect the incidence of violent crime (15–17). There is also increasing evidence that alcohol plays a role in suicide (18). Although cannabis and violence may be correlated among adolescents (see chapter 6), it remains to be clarified whether the relationship is causal because persons with a history of violence are more likely to become heavy cannabis users.

Second, substantial doses of alcohol taken during pregnancy can produce a Foetal Alcohol Syndrome (2). There is weak evidence that cannabis can adversely affect the development of the foetus when used during pregnancy (19), but there is no equivalent for cannabis of the foetal alcohol syndrome.

Third, acute alcohol use has one health risk that is not shared with cannabis. In large doses alcohol can cause death by asphyxiation, alcohol poisoning, cardiomyopathy and cardiac infarct. There are, by contrast, no recorded overdose fatalities from cannabis.

Tobacco

Cannabis and tobacco share acute irritant effects of smoke upon the respiratory system and THC and nicotine both stimulate the cardiovascular system. Smoking cannabis and tobacco can adversely affect persons with cardiovascular and respiratory diseases. In both cases, these effects arise from the fact that the drug is smoked.

14.3.2 Chronic effects

Alcohol

There are a number of risks of chronic alcohol use, which may be shared by chronic cannabis use. First, daily use of both increases the risk of developing dependence. There is strong evidence of such a syndrome for alcohol and reasonable evidence for cannabis. One difference is that withdrawal symptoms are mild in dependent cannabis users who abruptly stop using cannabis, whereas the abrupt cessation of alcohol use in severely dependent drinkers can produce a severe withdrawal syndrome that can be fatal in a small proportion of cases, if untreated (20).

Second, there is reasonable evidence that chronic heavy alcohol use can produce psychotic symptoms and psychoses in some individuals, either during acute intoxication or during withdrawal. There is suggestive evidence that chronic heavy cannabis use may

produce a toxic psychosis, some epidemiological evidence that heavy cannabis use may precipitate schizophrenia in individuals with a personal or a family history of psychiatric disorder, and stronger evidence that cannabis use worsens the course of schizophrenia.

Third, there is good evidence that chronic heavy alcohol use can indirectly cause brain injury—the Wernicke-Korsakov syndrome—with symptoms of severe memory defect and an impaired ability to plan and organise. With continued heavy drinking, and in the absence of vitamin supplementation, this injury may produce severe and irreversible cognitive impairment. Chronic cannabis use does not produce cognitive impairment of comparable severity. There is suggestive evidence that chronic cannabis use may produce subtle deficits in cognitive functioning that may or may not be reversed by abstinence.

Fourth, there is reasonable evidence that chronic heavy alcohol use impairs occupational performance in adults and educational achievement in adolescents. There is suggestive evidence that chronic heavy cannabis use produces similar, albeit less marked, impairments in the occupational and educational performance of adolescents and adults.

Fifth, there is good evidence that chronic, heavy alcohol use increases the risk of premature mortality from accidents, suicide and violence. There is no comparable evidence for chronic cannabis use, although it is likely that dependent cannabis users who frequently drive while intoxicated with cannabis would be at greater risk of accidental injury or death.

Sixth, alcohol use has been accepted as a contributory cause of cancer in various tissues and organs of the digestive system and breast cancer in women. There is suggestive evidence that chronic cannabis smoking may be a cause of cancers of the aerodigestive tract.

Seventh, heavy alcohol use is a major cause of liver cirrhosis and is also implicated in gastritis, high blood pressure, stroke, cardiac arrhythmias, cardiomyopathy, pancreatitis, and polyneuropathy. On the other hand, alcohol use is also associated with a reduction in the risk of heart disease that is of public health significance in societies with high rates of heart disease (18). No equivalent adverse or protective effects have been reported for cannabis. There is some evidence that THC may be therapeutically useful for appetite stimulation and as anti-emetics in patients undergoing cancer therapy.

Tobacco

The major adverse health effects shared by chronic cannabis and tobacco smokers are chronic bronchitis, and probably, cancers of the aerodigestive tract (i.e. the mouth, tongue, throat, oesophagus, lungs). The increased cancer risk is a consequence of the fact that both drugs are smoked. It is possible that chronic cannabis smoking also shares the cardiotoxic properties of tobacco smoking but this remains to be investigated. These respiratory risks could be avoided by a change to the oral route of administration which would also reduce but not eliminate the cardiovascular risks.

Tobacco smoking is associated with a wide variety of other chronic health conditions for which cannabis smoking has not so far been implicated. These include cancer of the cervix, stomach, bladder and kidney, coronary heart disease, peripheral vascular disease, and stroke, as well as cataracts and osteoporosis (2).

14.4 Comparing the magnitude of risks

Many of the quantitative risks of cannabis use can only be guessed at in the absence of studies of the dose-response relationship between cannabis use and adverse health effects. The following are guesstimates of the risks of cannabis use for the most probable adverse health effects. When in doubt we have assumed that the relative risks of cannabis use are similar to the risks of alcohol or tobacco.

Motor Vehicle Accidents: If we assume that driving while intoxicated with cannabis produces a comparable increase in the risk of accidents to that produced by driving while intoxicated with alcohol (say with a blood alcohol level of 0.05% to 0.10%), then the RR of an accident while intoxicated would be in the range of 2 to 4. The fact that alcohol and cannabis are often used in combination makes it difficult to estimate the relative risk of having an accident when using cannabis alone.

Respiratory Diseases: If we assume that a daily cannabis user who smokes 5 or more joints per day faces a comparable risk of respiratory disease to that of a 20 cigarette a day tobacco smoker, then the RR of developing chronic bronchitis would be 6 or greater for those who had ever smoked cannabis, and substantially higher among those who had been daily cannabis smokers over many years and those who also smoked tobacco (2). Recent research suggests that the risk of daily cannabis smoking is more like that of smoking 10–15 cigarettes per day (21), so the relative risks may be smaller.

Respiratory Tract Cancers: If we make the same worst case assumptions about daily cannabis smoking then the relative risks of various cancers of the respiratory tract would be of the order of: 5 for oropharyngeal cancer, 4 for oesophageal cancer, and 7 for lung cancer (2). Again these risks would be substantially higher among cannabis smokers who also smoked tobacco. The recent case control study of head and neck cancer suggested a relative risk of 2 for cannabis smoking, after adjustment for tobacco use (22).

Low Birthweight Babies: Making a worst-case assumption, a woman who smokes cannabis during pregnancy may double her chance of giving birth to a low birthweight baby (2). The average size of the effect is smaller than that for tobacco smoking (19).

Schizophrenia: This is one of the few health consequences for which there is a quantitative estimate of relative risk. If we use the estimated RR from the study by Andreasson et al (23) after adjustment for confounding variables, then an adolescent who had smoked cannabis 50 or more times by age 18 would have a 2 to 3 times higher risk of developing schizophrenia than an adolescent who had not used cannabis.

Dependence: The risk of cannabis dependence is estimated by the proportion of those who have ever used cannabis, or have had a history of daily use, who become dependent on the drug. The best estimates from US data in the late 1970s and early 1980s is that 10% of those who have ever used cannabis (24), and between 33% and 50% of those who have had a history of daily cannabis use, will become dependent on cannabis (see Hall et al (25)). The comparable risks among those who had ever used tobacco (32%), opiates (23%) and alcohol (15%) were higher than the risk for cannabis users (24).

14.5 Public health significance

14.5.1 Motor vehicle accidents

The epidemiological studies indicate that in its own right, cannabis makes at most a very small contribution to motor vehicle accidents, and so, on the whole, it may seem be a minor road safety problem by comparison with alcohol. Its public health significance for road safety may be in amplifying the adverse effects of alcohol in the majority of drivers who drive when intoxicated by alcohol and cannabis.

14.5.2 Respiratory diseases

Respiratory diseases, such as bronchitis, caused by cannabis smoking are likely to have greater public health significance than respiratory cancers. This is for two reasons. First, respiratory cancers require a greater length of exposure to cigarette smoke (15 to 20 years) than does chronic bronchitis. Second, there are very few cannabis users who use the drug for more than 5 years (26). On current patterns of use, cannabis smoking is more likely to produce respiratory disease than it is to cause premature deaths from cancers of the respiratory tract.

14.5.3 Respiratory tract cancers

Even if we make the worst case assumption that the risks of cancer are comparable among daily tobacco and cannabis smokers then cannabis smoking will make a small contribution to the occurrence of these cancers, on current patterns of use in developed societies (1). Only a minority of those who ever use cannabis become daily users, and a much smaller proportion of these use cannabis beyond their middle twenties by comparison with the high proportions of tobacco smokers who do so (26). Among this minority, concurrent cannabis and tobacco use may exacerbate the adverse respiratory effects of each.

14.5.4 Low birthweight babies

If cannabis smoking during pregnancy doubles the risks of a low birthweight baby, its public health significance will be much less than that of tobacco smoking, because the prevalence of cannabis use is much lower than that of tobacco smoking. The risks of a low birthweight baby will be higher among women who also smoke tobacco, as do many of those who smoke cannabis during pregnancy.

14.5.5 Schizophrenia

If the relationship between cannabis use and schizophrenia is causal, cannabis use would account for less than 10% of new cases of schizophrenia. Even this figure seems unlikely, however, since the incidence of schizophrenia has probably declined during the period when cannabis use among adolescents and young adults has increased (27).

14.5.6 Dependence

Cannabis dependence is potentially a more prevalent outcome than any of the other potentially adverse health effects of cannabis. On the ECA estimates, approximately 4% of the adult US population met diagnostic criteria for cannabis abuse or dependence in their lifetime and 2% in the past year. This compares with 14% who met diagnostic criteria for alcohol abuse and dependence at some time in their lives. This is a substantial proportion of the population but there may be a high rate of remission of symptoms in the absence of treatment.

14.6 Overall public health significance

Overall, the relative risks of adverse health effects for cannabis are small to moderate and the proportion of users who use regularly is much smaller than the proportions of alcohol and tobacco users who do so (28). In aggregate, then, the public health problems caused by cannabis *on current patterns of use* are modest compared with those of alcohol and tobacco.

A number of attempts have been made to directly compare the effects of alcohol, tobacco and illicit drugs on mortality, morbidity and societal costs. One of the earliest was an Australian study by Holman et al (29) which estimated the number of deaths, person years of life lost and number of hospital bed days that could be attributed to the use of alcohol, tobacco and illicit drugs. According to Holman et al, in Australia in 1986 there were 23,639 deaths attributable to these three classes of drugs. Of these 17,800 were attributed to tobacco, 5,360 to alcohol and 479 to illicit drugs, of which 289 (60%) were due to opiate use. There was a similar rank ordering of person years of life lost (92,023 for tobacco, 66,034 for alcohol and 16,438 for illicit drugs) and bed days (1,014,336 for tobacco, 1,009,591 for alcohol and 57,361 for illicit drugs). No deaths were attributed to cannabis use and cannabis made no contribution to morbidity. The authors concluded 'that apart from dependence, abuse and withdrawal, no other adverse health effect of cannabis is sufficiently substantiated or quantified to enable an analysis of resultant morbidity or mortality' (p. 377).

English et al (2) updated the Holman et al estimates of drug-caused mortality and morbidity in Australia in 1992. Unlike Holman et al, English et al included estimates of the protective effects of moderate alcohol consumption on mortality from cardiovascular disease. The inclusion of a protective effect for alcohol reduced the number of deaths attributed to alcohol from 5,360 in 1986 to 3,660 in 1992 and person years of life lost declined from 66,034 to 55,540. The contributions of tobacco and illicit drugs to mortality did not change much from the earlier estimates (18,290 and 488 respectively). Opiates were responsible for 92% of illicit drug deaths and no deaths were attributed to cannabis. Cannabis contributed to hospital bed days through treatment of cannabis dependence and abuse (1% of all bed days attributed to illicit drug use).

More recently, Ridolfo and Stevenson (30) updated the English et al estimates for Australia in 1998 using a different method to take account of the protective effect of alcohol on cardiovascular deaths. In their analysis alcohol produced a *net reduction* of 2371 deaths because the number of deaths averted by moderate alcohol use exceeded the number of deaths that alcohol caused. The number of deaths attributed to tobacco marginally increased from 18,290 to 19,019 and the number of deaths attributed to illicit drugs increased from 488 to 1,023 because of a substantial increase in the number of opioid overdose deaths.

14.6.1 Burden of disease estimates

A different approach to estimating the public health impact of alcohol, tobacco and cannabis was adopted in the Global Burden of Disease (GBD) Study (3, 33). In this study, an estimate of the years of life lost (YLL) as a result of the use of drugs was added to the disability caused by diseases to estimate the number of Disability-Adjusted Life-

Years (DALYs) for each type of drug use. This enabled an estimate of the proportion of global burden of disease that was accounted for by different types of drug use.

Murray and Lopez estimated that 3.5% of global DALYs was attributable to alcohol, 2.6% to tobacco, and 0.6% to illicit drugs (3). In six of the eight world regions, tobacco and alcohol outranked illicit drugs in DALYs. Illicit drugs outranked alcohol in the Middle Eastern region, and tobacco in the Latin American region. The authors caution that 'because of the great difficulty in reliably estimating prevalence of illicit drug use, and of reliably quantifying its health effects, the estimates for this risk factor may well be too low' (p. 310). The illicit drug that made the largest contribution to the global burden was heroin.

The Australian Burden of Disease and Injury (ABDI) (4) adapted the approach of Murray and Lopez to estimate the contribution that alcohol, tobacco and illicit drugs made to the burden of disease and injury in Australia. The ABDI study used the comprehensive data collected on mortality and morbidity in Australia which includes surveys of the health of nationally representative samples of Australians. Their findings differed from those of the GBD study in the rank ordering of alcohol and tobacco because the Australian study included an estimate of the burden of disease that was averted by moderate alcohol use. Tobacco accounted for 9.7% of the total burden of disease in Australia, alcohol accounted for 2.2% and illicit drugs for 1.8%. Among illicit drugs, the overwhelming majority of the burden was due to heroin dependence, which accounted for 1.2% of total burden. Cannabis dependence and abuse accounted for 0.2% of all disability. No deaths were attributed to cannabis use (4).

14.6.2 Summary of public health impact

Studies of mortality and morbidity and disease burden attributable to alcohol, tobacco and illicit drugs differ in their rankings of impact depending upon whether the mortality benefits of moderate alcohol use are included or not. They leave little doubt, however, that *on current patterns of use*, alcohol and tobacco are much more damaging to public health in developed societies than illicit drugs. Among illicit drugs, cannabis makes no known contribution to mortality and a minor contribution to morbidity and disability.

14.6.3 Predicting the effects of changes in the prevalence of cannabis use

These estimates of the public health impact of cannabis use are based on *current patterns of use*. They cannot be used to predict what would happen if there was a major change in the prevalence of cannabis use, as may happen if cannabis were to become as freely available and as heavily promoted as alcohol and tobacco. Although in principle, it may seem simple to predict the public health consequences of increased cannabis use (e.g. by multiplying its harms at present by the increased number of users), such a calculation would assume that the risks of cannabis use did not change with the characteristics of the user, or the legal regime under which the drug was used.

Both assumptions are questionable. Cannabis is likely to be used by a different population when its use is illegal and prevalence of use is lower than would be the case if it were legal and more people used it. This has been reported with alcohol, for example, with different patterns of alcohol consumption and alcohol-related problems in

'dry' (non-drinking) and 'wet' (high level of drinking) cultures. If adult cannabis use were legalised, it might also be easier to reduce some of these health risks, for example, by encouraging cannabis users to ingest rather than to smoke the drug, or by reducing the tar content of cannabis that is smoked. Decriminalising cannabis for adult use would probably also increase use by adolescents, the health effects of which would be very difficult to predict. Estimating the net effects of harm reduction efforts in adults and a likely increase in adolescent use is therefore difficult.

For these reasons we have not attempted to predict the health risks of cannabis use if it became as widely used as alcohol and tobacco. All that can be said with confidence is that if its rate of use increased to the levels of cigarette smoking and alcohol use, its adverse impact on public health would increase. It is impossible to say precisely by how much.

14.7 Summary

Cannabis use can harm health when it is used daily over years or decades. Considerable uncertainty remains about whether some of these effects are attributable to cannabis use alone or to tobacco and alcohol. There is too little data on the relationship between frequency, quantity and duration of cannabis use, and the risks of many of these effects. Using estimates of the known effects of alcohol and tobacco, the most probable adverse effects of chronic heavy cannabis use over a period of years are: the development of a dependence syndrome; an increased risk of motor vehicle accidents; an increased risk of chronic bronchitis; an increased risk of respiratory cancer; an increased risk of giving birth to low birth weight babies when used during pregnancy; and perhaps, an increased risk of developing schizophrenia among those who are vulnerable. Many of these risks are shared with alcohol and tobacco, which is unsurprising given that cannabis is an intoxicant, like alcohol, that is usually smoked, like tobacco.

On *current patterns of use*, cannabis poses a much less serious public health problem than alcohol and tobacco in Western societies. This is no cause for complacency as the public health significance of alcohol and tobacco are substantial, and the public health impact of cannabis would probably increase if the prevalence of heavy daily cannabis use were to approach that of heavy alcohol use, or that of daily cigarette smoking among adults.

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"An overview of cannabis potency in Europe"

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INSIGHTS

An overview of cannabis potency in Europe

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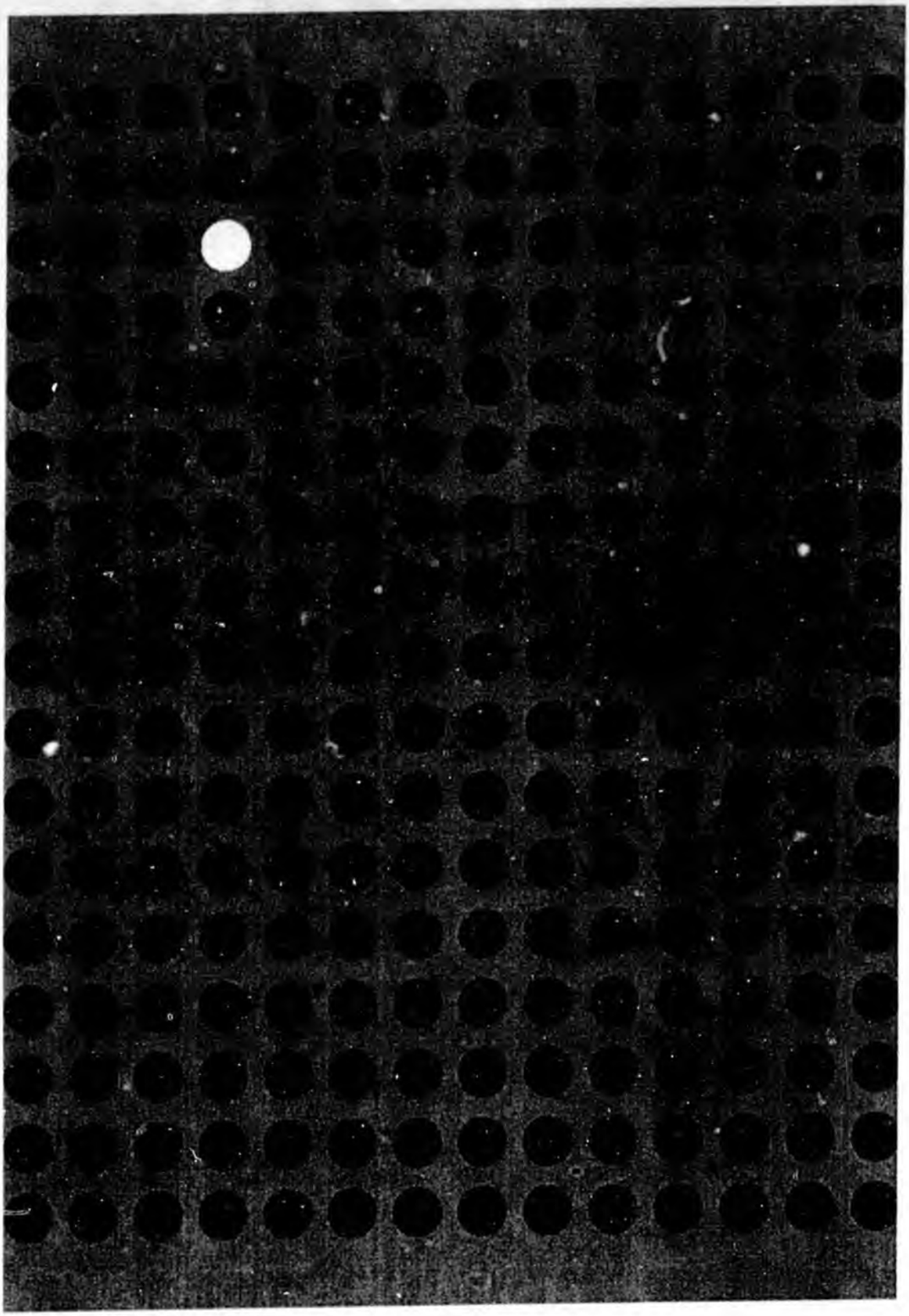

Foreword

Cannabis is the illegal substance most commonly used in all countries of the European Union, with many countries reporting lifetime experience of the drug by more than 20% of the general population.

Used mainly by young adults, but also by many schoolchildren, cannabis is a drug consumed by individuals during their formative years, at a time when they may be more vulnerable to the long-term harmful effects of drug use.

The increased use of cannabis during the past decade, during which more attention has also been given to the medicinal use of cannabis, has increased the profile of the drug. So too have legislative changes in some countries, and the more open debate on the costs and benefits of different drug control options. At the same time there is also a concern that cannabis is increasingly mentioned in connection with applications for drug treatment — and this is an issue that will be explored in detail in the Annual Report of the EMCDDA in 2004.

Comments in the media and elsewhere of a large increase in the potency of cannabis have raised concerns that the drug now available is much stronger than that available in the past. A much stronger drug might have implications for both the health and other problems resulting from the use of the drug and for the development of future policy options. However, the information on which the claims of greatly increased cannabis potency have been made is not always clear.

To establish a scientific basis on which to advise policy makers and practitioners in the drugs field, the EMCDDA commissioned an investigation into cannabis potency in Europe. The results of this study are presented here. Changes in the production and sourcing of cannabis products are documented. Information supplied through the Reitox national focal points are added to data from a wide variety of sources to enable a first overview of cannabis potency in Europe. This is discussed in the wider context of information from the United States, Australia and New Zealand, countries where there have also been media reports of increased cannabis potency.

As always when attempting to study illegal substances, the data are incomplete and the conclusions are qualified. Nevertheless, it is now possible to respond with facts and figures to questions about large increases in cannabis potency in

Europe. As the reader will discover, this is not a simple or straightforward issue. This report identifies a number of important questions that require further consideration if we are to understand the implications of changes in patterns of cannabis consumption in Europe. Nonetheless, we hope that the information and analysis contained in this edition of the EMCDDA *Insights* series will make a valuable contribution to a more informed debate about cannabis potency in Europe — and its potential impact.

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Executive Director
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Preface

The cultivation of the hemp plant (*Cannabis sativa* L.) stretches back into antiquity. Although originally produced as a source of fibre, its value as a drug also has a long history. For most of this time, it is likely that little change occurred in the methods used to manufacture the traditional drug products, namely herbal cannabis (marijuana) and cannabis resin (hashish). Yet in the last decades of the twentieth century, interest in cannabis expanded considerably. This was partly driven by the ever-increasing drug use in many countries, some of which was stimulated by new intensive methods of cultivation. But there were other developments: the licensing of commercial cultivation in the EU for fibre production; a renewed interest in medicinal uses; and legislative changes often caused by a need for law enforcement agencies to focus on more dangerous substances. There was also concern about the rising frequency with which cannabis was mentioned in the context of the treatment demand indicator (EMCDDA, 2003), and this will be the subject of a separate publication by the EMCDDA in 2004.

In parallel with these changes, there has been a greater focus on the constituents of cannabis, and in particular the main principle: Δ^9-tetrahydrocannabinol (THC). Concerns were raised that the potency of cannabis (i.e. the THC concentration) may have increased so much that the illicit drug now bears little resemblance to the cannabis that was used only thirty years ago. A widely publicised example of this is the statement by the so-called 'drug czar' in the USA, published in the Washington Post, that "Parents are often unaware that today's marijuana is different from that of a generation ago, with potency levels 10–20 times stronger than the marijuana with which they were familiar" (Walters, 2002). In a similar vein, and even more recently, Professor John Henry of St. Mary's Hospital, London, commented on the apparent increase in association between cannabis and deaths recorded as accidents and suicides. He is quoted (Henry, 2004) as saying "until the early 1990s, there was less than one per cent tetrahydrocannabinol in most cannabis. Now the most potent form, skunk, contains up to 30 per cent". As a final example of this alarm, Ashton (House of Lords, 1998) stated that "... a typical 'joint' today may contain 60–150 milligrams or more of THC". However, the potency question is not new. Nearly twenty years ago, Cohen (1986) noted that "...material ten or more times potent than the product smoked ten years

ago is being used, and the intoxicated state is more intense and lasts longer". But Mikuriya and Aldrich (1988) pointed out that the cultivation of sinsemilla and its superiority to other forms of cannabis was well known to the British Government in India in the nineteenth century.

Cannabis in its various forms remains the most commonly used illicit drug in the EU, with many countries reporting lifetime prevalence rates in excess of 20 % of the general population (EMCDDA, 2003). The purpose of the present report is to examine the evidence for changes in the potency of cannabis products in Europe and whether any such changes are a cause for public concern. Comparisons are made with the situation in the USA, New Zealand and Australia, the only non-European countries to have made serious efforts to monitor the quality of cannabis over a number of years. Published data are often in the form of national annual averages. The report examines the types of cannabis consumed and their respective origins, analytical aspects such as sampling strategies, the effect of storage, and the laboratory methods used since these could all be major factors affecting such data.

Information was collected from the published and unpublished (grey) literature and interviews with colleagues in the United Kingdom and the Netherlands. In addition, a questionnaire (available from the EMCDDA on request) was sent via the Reitox focal points to the 25 EU Member States and Norway. Replies from thirteen countries were received, but not all were able to provide data on recent trends in the potency of cannabis products.

Although this review concentrates on matters relating to potency, there is a vast scientific literature devoted to cannabis. The following is not intended to be an exhaustive list of reviews: pharmacology (Ashton, 1998, 2001; Nutt and Nash, 2002), health and psychological effects (Hall et al., 2001), effects of chronic/heavy use (Van Amsterdam et al., 1996), psychiatric illness (Johns, 1998; Rey and Tennant, 2002), therapeutic uses (British Medical Association, 1997; Baardman, 2003), production of cannabis resin (Cherniak, 1995), forensic toxicology (Huestis, 1999), historical development (Booth, 2003), medicinal products (Clarke and Watson, 2000), social and criminal aspects (Plant, 1998a), metabolism and disposition (Hawks, 1982), forensic and legislative aspects (Phillips, 1998), analysis in biological materials (Raharjo and Verpoorte, 2004), global trends in seizures and consumption (UNODC, 1997/1998, 2003) and

epidemiology (Plant, 1998b). Single sources of useful information can be found in the books by Brown (1998) and Iversen (2000) and a British Parliamentary report (House of Lords, 1998). The World Wide Web provides yet further sources of information.

To maintain consistency in this report, the phrases 'herbal cannabis' or 'herbal' are used to describe what original authors may have referred to as 'marijuana', 'grass' or even 'leaf'. Cannabis described in the literature as 'flowering tops', 'nederwiet' or 'skunk' is taken to mean 'sinsemilla', particularly when grown by intensive indoor methods or when a contrast is made by the authors with the term 'seeded', which is here defined as 'imported'. Although imported cannabis can usually be distinguished from other forms, it is possible that in some published reports either no distinction was made, or some overlap between the two occurred. The term 'cannabis resin', or simply 'resin', is used in preference to 'hashish'. 'Cannabis products' or 'cannabis' is used in a generic sense to refer to plants, herbal cannabis, cannabis resin and hash oil. This report does not include any analysis of the potency of 'hemp', that is to say plants of the 'fibre-phenotype' with little THC content, which are grown for non-drug purposes. Certain recommendations on nomenclature are discussed in Chapter 6. The Glossary provides a fuller definition of these and other terms.

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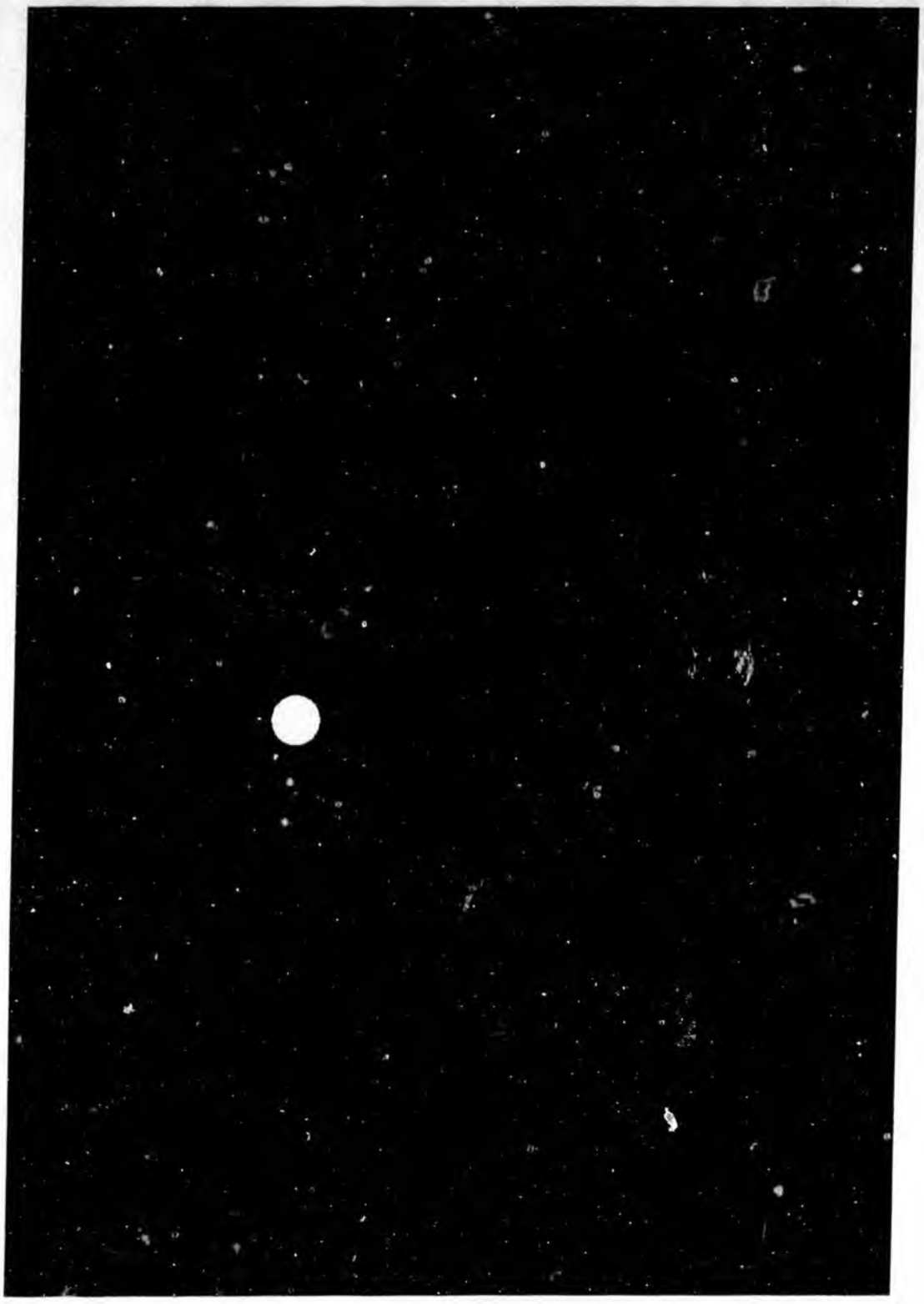


Executive summary

1. The potency of cannabis products (a term used in preference to purity) is equivalent to the Δ^9-tetrahydrocannabinol (THC) content. THC is the primary active constituent in cannabis.

2. Information on the potency of cannabis products in European countries was obtained from Standard table 14 of the EMCDDA-REITOX reporting system and by means of a questionnaire sent to experts. Information on THC levels in other countries (USA, New Zealand and Australia) was obtained from the published literature.

3. Herbal cannabis produced by intensive indoor methods (e.g. hydroponic systems with artificial lighting, propagation by cuttings and control of day length) usually has higher THC levels than imported material. Although the potency range of home-grown herbal cannabis may overlap with that of imported herbal cannabis, the average potency of home-grown herbal cannabis may be two or three times greater than that of imported herbal cannabis. The overall increases in potency that have occurred in some countries can be almost entirely attributed to the increased relative consumption of home-grown herbal cannabis.

4. Indoor cultivation of herbal cannabis occurs in all European countries. In the Netherlands, it is estimated that this product represents over half of the cannabis consumed, but for most European countries, imported products are more common.

5. The higher potency of herbal cannabis produced by indoor methods is a reflection of several factors: genetic (selected seed varieties and cultivation of female plants); environmental (cultivation technique, prevention of fertilisation and seed production); and freshness (production sites are close to the consumer and storage degradation of THC is avoided).

6. In the Netherlands, locally produced cannabis resin has particularly high THC levels, but this material is still uncommon in that country and almost unknown elsewhere.

7. Hash oil is uncommon in all countries.

8. The available data do not show any long-term marked upward trend in the potency of herbal cannabis or cannabis resin imported into Europe.

9. The countries of Europe fall into two clear groups according to whether herbal cannabis or cannabis resin is the most commonly consumed product. Of the countries for which information was available, cannabis resin was most common in Germany, Ireland, Portugal and the United Kingdom, whereas herbal cannabis was the most common product in Austria, Belgium, Estonia, Czech Republic and the Netherlands.

10. Information on potency trends and the relative consumption of different products in a particular country can be combined to give the overall trend in THC levels as perceived by the average user. Termed the effective potency, it is derived by weighting the potency of each product by its fractional share of the market and then summing the individual values. The effective potency in nearly all countries has remained quite stable for many years at around 6-8%. The only exception has been the Netherlands where, by 2001-2002, it had reached 16%.

11. In the United Kingdom, the amount of herbal cannabis or cannabis resin in cannabis cigarettes has shown no trend in the last twenty years.

12. Statements in the popular media that the potency of cannabis has increased by ten times or more in recent decades are not supported by the limited data that are available from either the USA or Europe. The greatest long-term changes in potency appear to have occurred in the USA. It should be noted here that before 1980 herbal cannabis potency in the USA was very low by European standards.

13. There are major differences in the market between the USA and Europe. In some European countries, cannabis resin, originating almost entirely from North Africa, is more common than herbal cannabis. Herbal cannabis imported into Europe originates from the Caribbean, Africa and the Far East. In the USA, herbal cannabis is either grown domestically or imported from Canada or Mexico, but cannabis resin is more rarely seen. As a consequence, direct comparisons between data in North America and Europe have questionable relevance.

14. There are major differences in the methods of consumption between the USA and Europe. In Europe, both forms are usually smoked in a mixture with tobacco. In the USA, cannabis is commonly smoked alone. These differences have important implications for the interpretation of experimental pharmacological investigations and the health effects of cannabis, particularly when comparisons are made between the USA and Europe.

15. The natural variation in the THC content between and within samples of herbal cannabis or cannabis resin at any one time and place far exceeds any long-term changes that may have occurred either in Europe or the USA. This natural variation is even greater when material from different geographical locations is examined.

16. As well as uncertainties caused by the oxidation of THC during storage and the problems of extracting (inhomogeneous) herbal or resinous material, there are analytical difficulties in the precise and accurate determination of THC. These measurement errors could also be sufficient to mask any small secular changes in potency.

17. If it is accepted that the cannabis resin imported into Europe is a fairly uniform substance that is rarely adulterated, originates mostly from North Africa and has shown no clear trend in potency for many years, then the considerable potency variations reported by different countries could suggest that there are high variations in sampling strategies and/or systematic errors in the quantitative analysis of THC in different laboratories/countries.

18. This study identifies a number of important areas that require attention if cannabis potency issues are to be properly evaluated. These include a need to:

    a. improve information gathering, analysis and dissemination;
    b. develop a consensus on nomenclature that can better identify different cannabis products;
    c. understand better the relative consumption of cannabis products in different markets and the extent and practice of domestic indoor cultivation;
    d. investigate the cannabis content of cannabis cigarettes;
    e. improve the monitoring of street prices;
    f. improve the standards of laboratory analysis, as well as data collection and data presentation at European level;

g. address information gaps that exist in understanding the relationships between potency, smoking behaviours and blood levels of THC in the European context;
h. investigate the extent to which high-potency cannabis results in increased dose exposure and any possible relationship to either chronic or acute health problems.

19. The conclusion of this report is that there have been modest changes in THC levels that are largely confined to the relatively recent appearance on the market of intensively cultivated domestically produced cannabis. Cannabis of this type is typically more potent, although it is also clear that the THC content of cannabis products in general is extremely variable and that there have always been some samples that have had a high potency. A clear need exists to develop monitoring systems that can assess the market share of different cannabis products and track changes over time. Currently this information is to a great extent lacking. This is important, as a concern exists that hydroponically produced cannabis grown in the EU may be increasing its market share.

20. An important point to note is that the possibility of additional public health problems caused by the use of high-potency cannabis as compared to cannabis products in general remains poorly understood. Nonetheless, a number of clear research questions are identifiable, that would shed light on this issue. These are discussed in the conclusions of this report.

21. This study has implications for both supply and demand side strategies, as well as to the possible costs and benefits of responding differentially to different cannabis products.

Chapter 1: Introduction

Chapter 1: Introduction

The cannabis plant and derived products

The cannabis plant (*Cannabis sativa* L.) is an annual that will grow successfully to a height of 2-3 metres in a wide range of soils in both tropical and temperate climates. The leaves are compound with up to eleven separate serrated lobes. It is dioecious (plants are either male or female), and is the only known natural source of cannabinoids (see section *Cannabinoids*). The cannabinoids are found in resinous material, produced by glandular trichomes situated mostly around the flowering parts. Although some have suggested that there is a separate species (*Cannabis indica* Lam.), most authors consider the genus to be monospecific, but that considerable genetic diversity exists leading to wide phenotypic variability. Plants grown for drug use have traditionally been cultivated outdoors in hot climates. In temperate climates, and even when grown under glass, summers may not be long enough to allow full development of the flowering parts. Apart from the fibrous stem, which was once used for rope manufacture and is still used for other purposes, the two main drug products have been herbal cannabis and cannabis resin. Herbal cannabis is the dried flowering tops with or without variable amounts of leaves, stems and seeds. Cannabis resin is obtained by sieving or otherwise separating and compressing the flowering tops. Cannabis (hash) oil is a derived product made by solvent extraction of either herbal cannabis or cannabis resin. In the past ten to twenty years, a number of horticultural developments such as propagation by cuttings, hydroponics and artificial control of 'day' length have led to the widespread development of indoor cultivation of cannabis. Recent developments in cultivation and product quality have been discussed by Szendrei (1997/1998). The situation in the United Kingdom has been described by Bone and Waldron (1997/8).

Cannabinoids

The major active principle in all cannabis products is Δ^9-tetrahydrocannabinol (THC), the structure of which is shown in Figure 1. The unsaturated bond in the cyclohexene ring is located between C_8 and C_{10} in the more common dibenzopyran ring-numbering system. Although sometimes known as dronabinol (an international non-proprietary name), naturally occurring Δ^9-tetrahydrocannabinol exists in four isomeric forms and is not chemically identical to synthetic dronabinol. Two related

substances, Δ^9-tetrahydrocannabinol-2-oic acid and Δ^9-tetrahydrocannabinol-4-oic acid (THCA) are also present, sometimes in large amounts. Figure 1 shows one of the two positional isomers of THCA. During smoking, THCA is converted to THC, although other substances are also formed (A. Hazekamp, personal communication, 2004) and some is lost by evaporation. The active isomer Δ^8-THC, where the unsaturated bond in the cyclohexene ring is located between C_8 and C_9, is found in much smaller amounts. Other closely related substances that occur in cannabis include cannabidiol (CBD; Figure 1) and, in aged samples, cannabinol (CBN; Figure 1), both of which have quite different pharmacological effects to THC. Other compounds include the cannabivarins and cannabichromenes; they are all collectively known as cannabinoids.

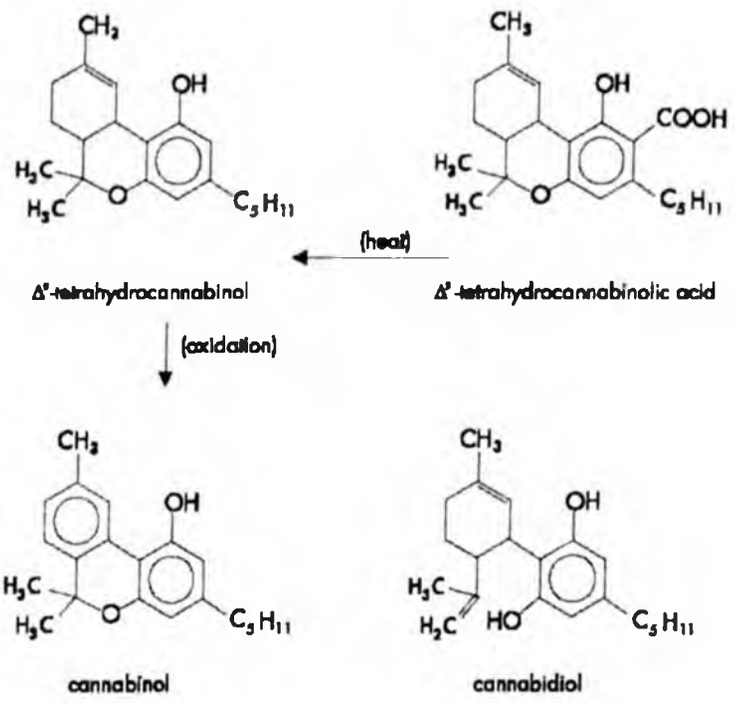


Figure 1: The structures of Δ^9-tetrahydrocannabinolic acid (THCA), Δ^9-tetrahydrocannabinol (THC), cannabinol (CBN) and cannabidiol (CBD).

The highest levels of THC occur around the floral parts of the unfertilised female plant, and this material is then described as sinsemilla (Spanish: without seeds). Fertilisation and the consequent seed production serves to reduce the level of THC. Much lower amounts are present in the leaves, and in male plants, whereas the stalk and clean seeds contain almost none. A distinction is sometimes made between cannabis plants for drug use and cannabis grown for fibre. Thus, cannabidiol is often absent in the former, but is usually found at levels exceeding 0.5% in the latter. As discussed by Maguire (2001), a useful parameter of distinction is the ratio [(% THC + % CBN)/% CBD]. If this is greater than 1.0 then the material is described as 'drug-phenotype' and if it is less than 1.0 it is 'fibre-phenotype'. In the light of the biological diversity of *Cannabis sativa*, these are simply extreme forms in a wide spectrum of different types.

Purity and potency

It is more informative, and indeed more scientifically correct, to talk of cannabis potency rather than cannabis purity. Purity is a concept that is best applied where there is a question of adulteration or dilution of an otherwise pure substance. In this sense, it is correct to refer to the purity of, say, powdered illicit drugs such as cocaine or amphetamine where cutting agents are normally added to the pure drug before it enters the retail market. Cannabis, however, does not represent a pure form of the active ingredient. The range of concentration of cannabinoids in cannabis also undermines the concept of cannabis purity. In addition, although it is alleged that cannabis resin sometimes contains inert fillers such as henna powder, herbal cannabis is rarely adulterated. For these reasons, it is not appropriate to use 'purity' when referring to cannabis. Reviews of the literature also show that 'cannabis potency', defined as the THC concentration, is the preferred term. The publication *Global Illicit Drug Trends* (UNODC, 2003) illustrates the ambiguity caused by the phrase 'purity levels' in relation to herbal cannabis and cannabis resin: values are either clustered around 1–10% and presumably reflect the THC content or they are much higher, typically above 50%, the interpretation of which is unclear, but could reflect some other concept of quality.

In the following report, the THC content of illicit herbal cannabis and cannabis resin only are considered. In the EU, cannabis (hemp) cultivated under licence for fibre contains less than 0.3% THC, and is essentially not usable as a drug. Although some data are available on the THC content of cannabis oil, the potency

is determined not only by the source material, but is also affected by its age, the efficiency of extraction and the extent to which the solvent has been removed. Furthermore, in Europe and elsewhere, hash oil accounts for a tiny fraction of the total quantity of cannabis products consumed. In the United Kingdom, the THC content of hash oil is typically in the range 25–45 % and appears to have shown no changes over the years (Baker et al., 1982; Gough, 1991; King, 2001). In the USA, during the period 1980–1997, a similar stability in the THC content of hash oil (typically 12–17 %) was reported (ElSohly et al., 2000).

A curious method of increasing the potency of cannabis was discussed by Segelman and Sofia (1973), whereby treatment of cannabis with boiling water removes unwanted soluble components, but not THC. On a weight basis, the THC concentration may be increased by around 30 %, although the absolute amount of THC has not changed.

Pharmacological aspects of high-potency cannabis

Cannabis is nearly always smoked. In Europe, it is often mixed with tobacco in a joint, also known as a reefer or spliff, but some is smoked in a water pipe (a bong). By contrast, in the USA, where little resin is consumed, cannabis is usually smoked alone. A recent trend in the USA is the smoking of 'blunts' (hollowed out cigars), which may be filled with 2–3 g of cannabis (DEA, 1999). Nearly all studies on the smoking of cannabis and its relation to potency have been carried out in North America, but it is clear that this research may not translate well into the European situation. Thus Matthias et al. (1997) found some evidence that those who smoke more potent cannabis are less exposed to noxious smoke components than those who use less potent forms. But in Europe, where a reefer cigarette typically contains only 100–260 mg of cannabis (Humphreys and Joyce, 1982; Buchanan and O'Connell, 1998; Bal and Griffin, 2001), much of the tar, carbon monoxide and other combustion products will derive from the concomitant tobacco.

Comparing the effects of marijuana cigarettes at three different potencies, Perez-Reyes et al. (1982) found no qualitative difference between the psychopharmacological effects of consuming large amounts of THC and those caused by consuming smaller amounts. Nevertheless, it is accepted that there is a dose–response curve (Miller et al., 1977). McBride and Thomas (1995) pointed out that psychosis attributed to 'skunk' (Wylie, 1995) is also common in users of 'normal' (or other types of) cannabis. If the potency of cannabis products has shown a marked increase, then it might be expected that the typical user would

need to consume less on a weight basis to achieve the desired effect. Given a choice, users preferred cigarettes with a higher THC content (Chait and Burke, 1994; Kelly et al., 1997). Ashton (1998) also argued that users would not titrate the dose of THC from cannabis in contrast to nicotine/tobacco smokers. However, Heishman et al. (1989) found that those smoking cigarettes with a higher THC content tended to have a lower inhalation rate than control subjects. Yet little research has been conducted, particularly in Europe, to answer a crucial question: Do those smoking high-potency cannabis have higher blood levels of THC?

Pharmacological studies are also compromised by a number of other factors. For example, while smoking is able to deliver a drug rapidly into the bloodstream and hence the brain, it is an inefficient process. Some THC will be destroyed by combustion or lost in the side-stream smoke, and the bioavailability of THC by this route is usually less than 50 % (Moffat et al., 2004). Based on the complete consumption of a cigarette containing 200 mg of cannabis, the amount of THC absorbed will be less than 10 mg in most cases. However, ingestion of cannabis in foods (e.g. spacecake) or infusions leads to an even lower bioavailability, largely because the gut poorly absorbs THC. Cannabis extracts do not lend themselves to injection because THC is practically insoluble in water. A further complicating factor is that some of the major metabolites of THC, such as 11-hydroxy-Δ^9-THC, have long half-lives and are themselves active.

Medicinal cannabis

In the Netherlands, herbal cannabis is available as a prescription medicine (Office of Medicinal Cannabis, 2004). Known as 'cannabis flos', one of the preparations has a nominal THC content of 18 % (±2.7 %) and is locally produced by the same intensive indoor methods that are used for illicit cultivation. It is indicated for multiple sclerosis, certain types of pain and other neurological conditions. Patients are advised to consume the cannabis by means of a hot water infusion. However, Hazekamp (personal communication, 2004) has found that, even in boiling water, the conversion of THCA to THC can take some hours and other by-products are formed. In the United Kingdom, an extract of cannabis is expected to be to licensed in 2004 to GW Pharmaceuticals Ltd. The product, to be known as Sativex, will be supplied in a nebuliser for sub-lingual application at a concentration of well below 1 % THC. Cannabis is not available for licensed therapeutic use in any other European country.

Chapter 2: Analytical aspects

Chapter 2: Analytical aspects

Quantification of THC

There are a number of problems beseting r .ıtative analysis of THC in cannabis products. Firstly, herbal cannabis, and to a esser extent cannabis resin, is an extremely inhomogeneous material. As well as the flowering tops of the female plant, where most of the THC is located, a sample may contain varying amounts of stalk, seeds and leaves, none of which contains much active drug. It is to be expected that even within a well-mixed single large batch of crude material and following removal of 'unwanted' matter, different aliquots could lead to quite different analytical results. Yet authors rarely publish information on such intra-sample variance.

Given that a suitably 'cleaned' sample has been obtained and that the THC has been efficiently extracted into a suitable solvent such as petroleum ether, then most laboratories proceed to use gas chromatography (GC), often with flame-ionisation detection (Raharjo and Verpoorte, 2004) to determine THC concentration. This has the merit that the naturally occurring precursor (THCA) is decarboxylated to THC, just as occurs during smoking. Cannabinoids can also be determined by high performance liquid chromatography (HPLC), a method suited to profiling ('chemical fingerprinting') and the separate measurement of THCA. To measure the total THC content by HPLC, the sample must be heat-treated before analysis (Kanter et al., 1979; Lehmann and Brenneisen, 1995; Rustichelli et al., 1998).

Other issues to arise in the analysis of THC concern the precision (reproducibility) and accuracy (closeness to the 'true' value) of the measurement process. Poortman van der Meer and Huizer (1999) claimed that in a series of proficiency tests organised in 1997 for 30–40 European laboratories, the relative standard deviation was about 29% whereas cocaine and amphetamine gave less than 5% and 8% respectively. This means that arourid one third of results for THC were either more than 29% greater or more than 29% below the mean value.
It is clear that even worse precision could be expected if the measurement error, caused by the sampling and extraction process noted above, were to be included.

As a reference standard, THC is usually only available from chemical suppliers in the form of an ethanolic solution and may be labelled, for example, as 'approximately 95%'. Not only could confusion arise if analysts assume the

concentration to be 100%, but Poortman-van der Meer and Huizer (1999), using the response of a flame-ionisation detector, found that one sample of a commercial THC solution had only 90% of the concentration of a different commercial solution. These authors recommended that THC quantification should be based on CBN or CBD as the internal standards and a correction made for the expected detector response from the effective carbon number of the respective substances. They claimed that this method had been used in Germany for the past ten years. It was also the method used by Maguire (2001) to study the cannabinoid content of (mostly fibre-type) cannabis in Ireland. However, as far as could be determined from the questionnaire responses, many laboratories in Europe continue to prepare standard dilutions of stock THC solution to construct calibration curves.

Finally, if precautions are not taken during analysis, THC can be lost from dilute solutions because of its propensity to adsorb onto unsilanised glass surfaces (Moffat et al., 2004). As this can affect both 'pure' reference material and extracts of cannabis products, it is a further source of error in THC determination.

Lability of THC in cannabis products and solutions

Atmospheric exposure of THC causes oxidation to CBN and other substances. In cannabis resin, Martone and Della Casa (1990) showed that, even when stored in the dark, the half-life of THC was often less than one year, and in some cases THC had disappeared almost completely within two years. In a block of resin, this could lead to variations in the THC concentration between the outside and the inside. The rate of THC decomposition in cannabis at room temperature was estimated as 17% per annum by Ross and ElSohly (1997/8). Since CBN is almost entirely absent from fresh cannabis, these authors suggest that the ratio CBN/THC could serve as a measure of the age of a sample. The relevance of this to questions of potency can be understood when it is realised that some imported products may have been harvested or manufactured many months before consumption or analysis. By contrast, and other things being equal, it is to be expected that domestic (i.e. local) production will lead to a fresher product containing more THC.

Natural variation of THC content in cannabis products

There is a wide range of variation in THC concentrations between different samples of a particular product, be that herbal cannabis or resin. Such variation is

often attributed to the quality of different geographical sources as well as the method of cultivation. Whether geographical profiling has any merit is a separate issue, but it is clear that even within a single geographical source, the potency may rise and fall in time. Figure 2 shows the variation in the THC content of herbal cannabis seized by customs in the United Kingdom in the period 1985-1986. Data were derived from Gough (1991) based on measurements at the Laboratory of the Government Chemist (LGC), and have been frequency-grouped according to the number of samples examined in that period. If this distribution had been based on the original individual THC measurements for each sample, then the spread of values would have been even greater. Thus the lowest and highest values in 1985-1986 were 0.9% and 12.2% respectively. Although not shown graphically here, the lowest and highest values found for cannabis resin in that same period were 0.5% and 26% respectively.

As a further example, the frequency distributions of the THC content of sinsemilla and imported herbal cannabis examined in the Forensic Science Service in 1996-1998 are shown in Figure 3 (King, 1998, 2000). During this period, there was no clear trend in the potency of herbal cannabis, but the inter-sample variance was large.

A difficulty faced by all sampling experiments is whether the materials examined are typical of the population. Even when samples are representative, the methods of chemical extraction are efficient and analysis is precise and accurate, it is still necessary to examine an appropriate number and derive the mean and other statistical parameters. This is particularly true of cannabis where, like many natural products, considerable diversity exists between individual samples. Thus, without knowing the lower value or the mean or even the sample size, statements such as were attributed to the situation in Switzerland (Anon, 2002), that cannabis contains up to 28% THC, are almost valueless. The comment (Henry, 2004) that "...the most potent form, skunk, contains up to 30 per cent" is equally unhelpful.

It is clear that cannabis users have constantly been exposed, in almost random fashion, to unexpectedly high and low amounts of THC in the course of their careers. Perhaps what is more significant is that the natural variation in THC content in both herbal cannabis and cannabis resin could far exceed any changes in the mean potency that may or may not have taken place over certain time-spans.

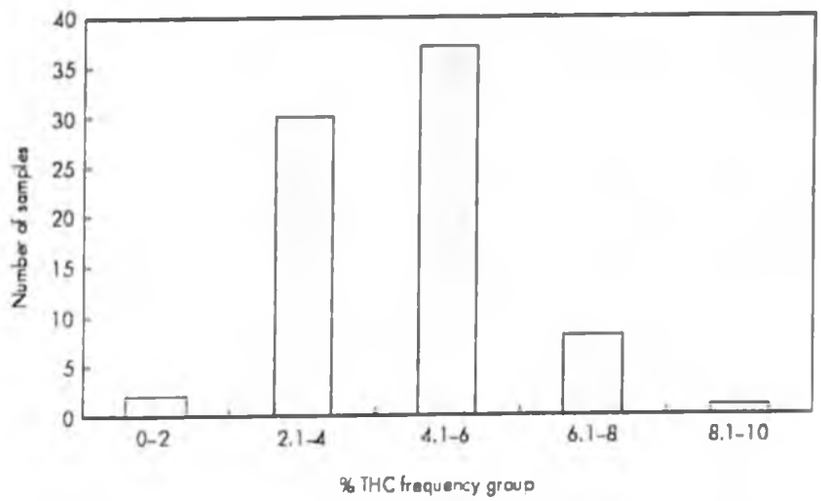


Figure 2: Variation in the mean THC content of imported herbal cannabis samples in the period 1985–1988, weighted by the number of samples from which each mean had been derived (Gough, 1991).

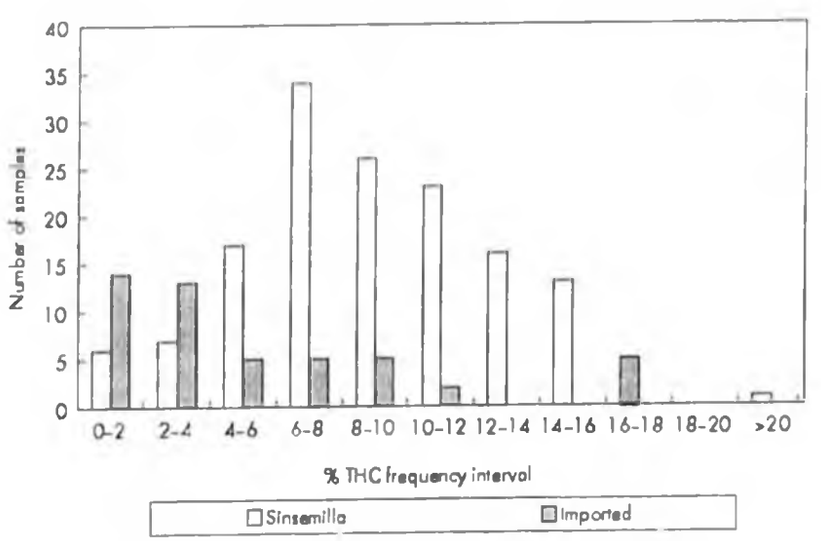
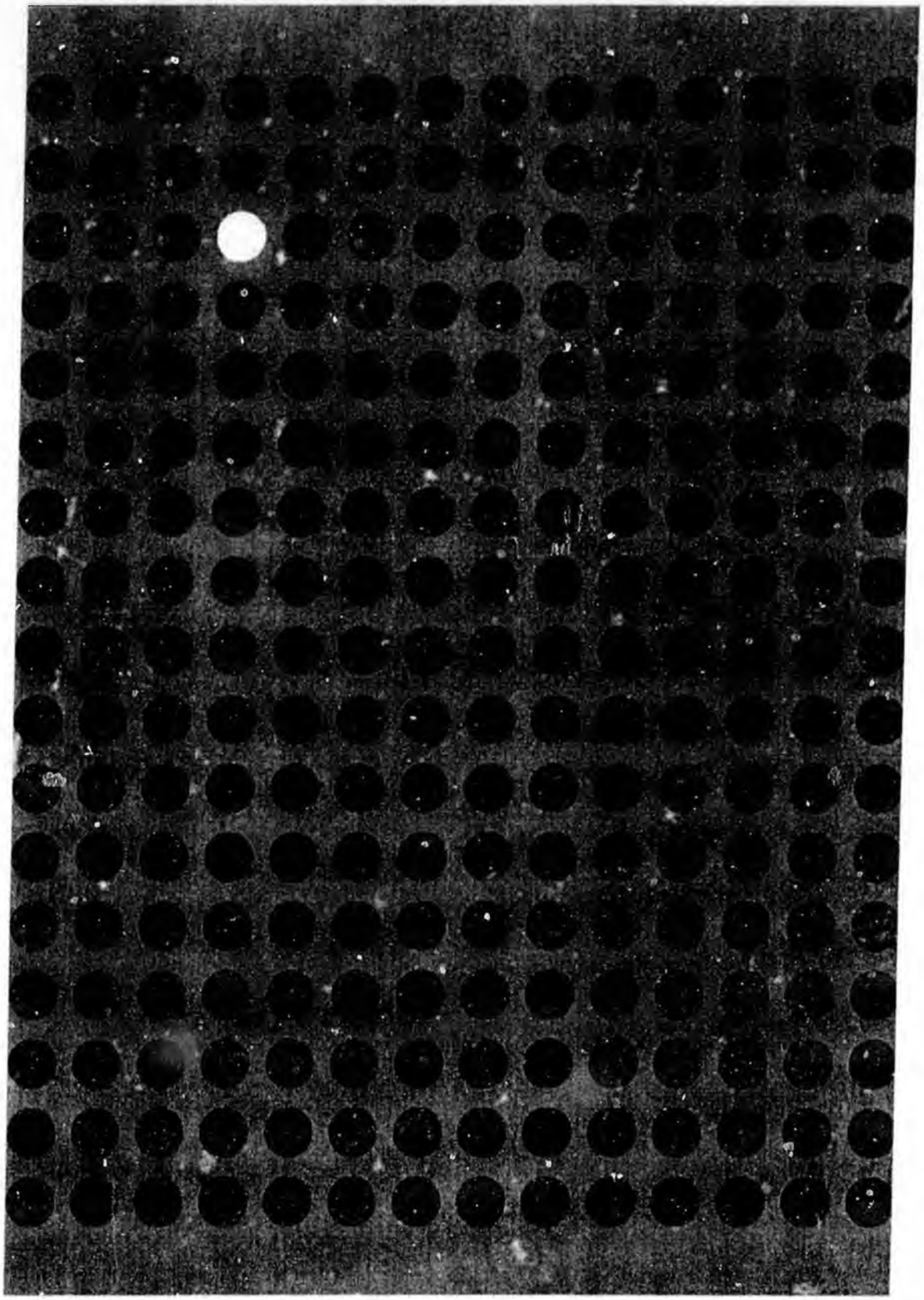


Figure 3: Frequency distributions of THC in herbal cannabis examined in the Forensic Science Service, UK (1996–1998)



Chapter 3: Trends in cannabis potency in Europe

Chapter 3: Trends in cannabis potency in Europe

National reports to EMCDDA (Standard table 14)

Tables 1 and 2 show the mean national potency of cannabis 'leaf' (taken to be herbal cannabis) and cannabis resin respectively in Member States of the European Union and Norway for the period 1996–2001 as submitted to the EMCDDA by the Reitox national focal points in Standard table 14.

Table 1: Mean national potencies (% THC) of herbal cannabis at retail level in Standard table 14 submitted to the EMCDDA (European Union and Norway)

Country	1998	1999	2000	2001	2002
Belgium (i)	–	–	10.4	6.0	6.0
Czech Republic (ii)	–	–	11	11	12
Czech Republic (iii)	–	–	–	1.6	2.65
Germany (i)	–	6.0	6.4	8.6	8.4
Finland (i)	–	–	–	–	2
France (i)	–	–	2	2	8
Hungary (iii)	–	–	–	–	1.1
Italy (i)	8.3	16.9	6.3	5.8	5.5
Latvia (i)	–	–	–	–	1.5
Luxembourg (i)	–	–	–	–	8
Netherlands (i)	–	7.5	10.1	14.6	–
Netherlands (ii)	–	8.6	11.3	15.2	–
Netherlands (iii)	–	5.0	5.1	6.6	–
Norway (i)	–	–	–	–	8
Portugal (i)	1.6	–	–	5.2	3.1
Portugal (ii)	–	–	–	14.6	13.1
UK (i)	7.9	9.5	12.0	9.5	10.7

Notes: Standard table 14 provides herbal cannabis to be reported as (i) cannabis leaves; (ii) nederwiet; (iii) other grass. Data originally listed as '0' or '–' were ignored. Some countries gave separate values for those different forms of herbal cannabis, but all data were used when calculating annual means. Values shown as '<2' by France in 2000 and 2001 were taken as 2. UK refers strictly to England and Wales only. Data for the Netherlands refer to 1999–2000, 2000–2001 and 2001–2002 instead of 1999, 2000 and 2001.

Table 2: Mean national potencies (% THC) of cannabis resin at retail level in Standard table 14 submitted to the EMCDDA (European Union and Norway)

Country	1998	1999	2000	2001	2002
Belgium		-	7.1	13.6	9.7
Czech Republic		15	11.5	11.5	6.3
Germany	-	8.4	10.5	8.6	7.9
France	-	-	7.5	7.5	8
Hungary	-	-	-	-	2.0
Italy	4.9	8.5	8.8	11.2	13.9
Latvia	-	-	-	-	4.5
Luxembourg	-	3.5	8.0	7.1	-
Netherlands	-	12.6	12.8	20.6	-
Norway	-	-	-	5	8
Portugal	4.3	3.7	2.2	5.5	2.6
UK	7.3	2.6	18.1	7.4	-

Notes: Values for resin reported by France in 2000 and 2001 as "5 to 10" are shown above as 7.5. All data were used when calculating annual means. UK refers strictly to England and Wales only. Data for the Netherlands refer to 1999–2000, 2000–2001 and 2001–2002 instead of 1999, 2000 and 2001.

The EMCDDA Standard table 14 lists mean potencies of both herbal cannabis and cannabis resin by country. The original data, upon which the country means were based, were not available. For all years and countries combined, the mean potency values of herbal cannabis and cannabis resin were 7.7% and 8.2%, respectively. Since it is likely that the sample size and sampling strategy varies between countries, these overall mean values should be treated with some caution.

Caution is also required when analysing these data as they are limited to countries where data are available (under-representation of Eastern European countries) and might, for some of them, present reliability problems (e.g. local rather than national data, data not representative of the retail level, uncertainty on the method to calculate averages).

Other national data

The Reitox national focal points were contacted in order to provide names of experts who might be in a position to answer the specific questionnaire developed

for the purpose of this study. For the United Kingdom and the Netherlands, information was obtained by interviewing a number of experts in both countries. Replies to the questionnaire were received from eleven countries: Austria (two sources), Belgium (two sources), Czech Republic (two sources), Estonia, Finland, Germany, Ireland, Luxembourg, Portugal, Slovenia and Spain, but only six countries in total were able to provide potency trend data. The data collected by these means (in 13 countries) are presented below.

Austria

Figure 4 shows the THC content of resin and herbal cannabis in Austria as provided by the Federal Ministry of the Interior. Measurements were made on seizures above 200 g. No distinction was made between imported and domestically produced cannabis, although it was stated that production of the latter was negligible. There is no clear time trend for either product.

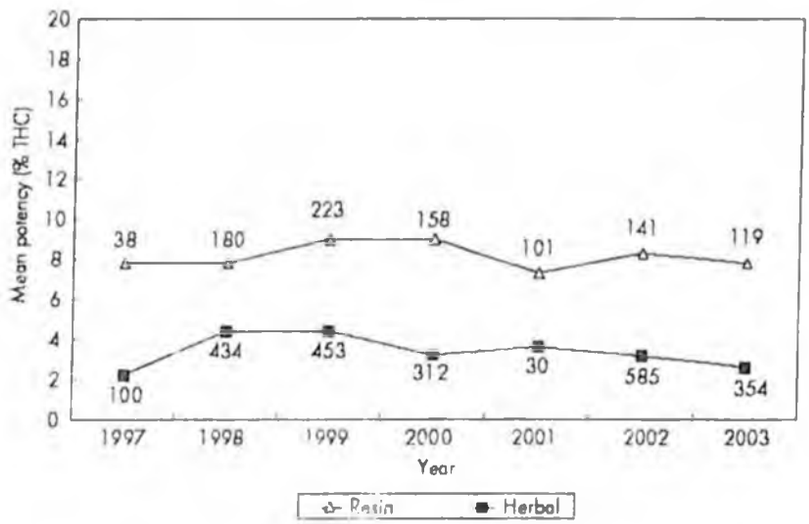


Figure 4: Mean potency (% THC) of cannabis products (1997-2003) in Austria. Values against each point represent the number of measurements.

Czech Republic

Figure 5 shows the THC content of resin and herbal cannabis in the Czech Republic as measured on police seizures and reported by the Institute of Criminalistics. In both cases, there is some evidence that the potency has increased in the period 1997-2003. However, no information was available on the sampling strategy or sample sizes and no distinction was made between imported and domestically produced cannabis.

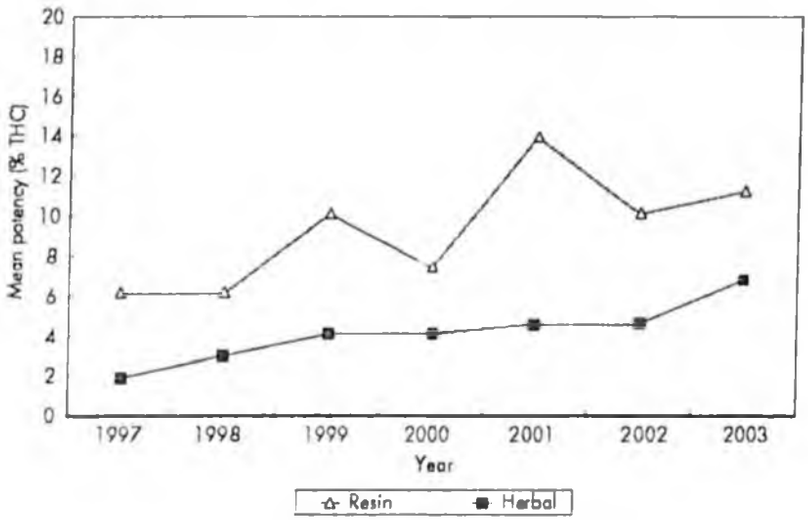


Figure 5: Mean potency (% THC) of cannabis products (1997-2003) in the Czech Republic

Germany

Figure 6 shows the THC content of resin and herbal cannabis in Germany. The potency of herbal cannabis showed an upward trend in the period 1997–2002, but no long-term trend was obvious for cannabis resin. No distinction was made between imported and domestically produced products. The samples derived from seizures by law enforcement agencies. Each year, the THC content of around 6 000 samples above a weight threshold of 7.5 g were determined by the Bundeskriminalamt, laboratories in the 16 Laender and by five customs laboratories.

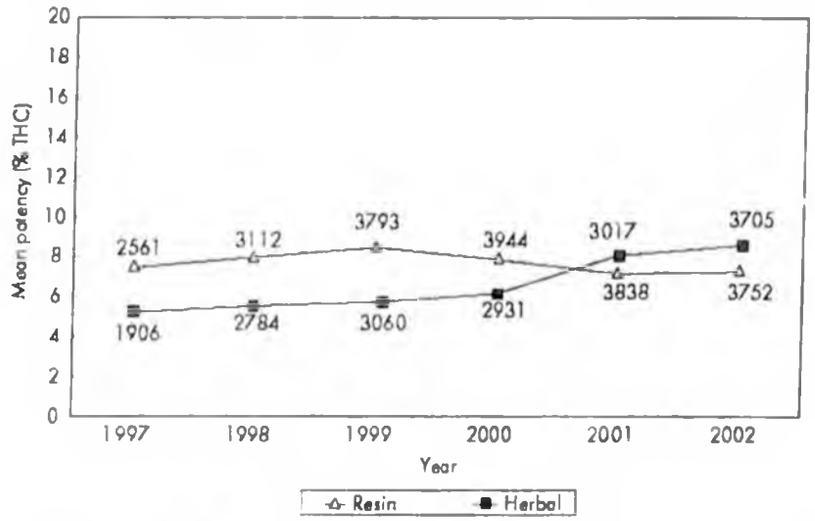


Figure 6: Mean potency (% THC) of cannabis products (1997–2002) in Germany. Values against each point represent the number of measurements.

Netherlands

The THC content of various cannabis products in the Netherlands (Niesink, 2000; Niesink et al., 2002) is shown in Figure 7. Dutch resin (nederhasj) is a locally produced material (see Glossary). Samples were obtained from 'coffee shops'. There are around 800 of these establishments where small-scale supply of cannabis products is tolerated by Dutch law. The total number of samples in the three periods was: sinsemilla = 376; imported herbal = 147; imported resin = 291; Dutch resin = 60. Apart from imported herbal cannabis, the year-on-year increases in THC level were statistically significant ($P < 0.001$).

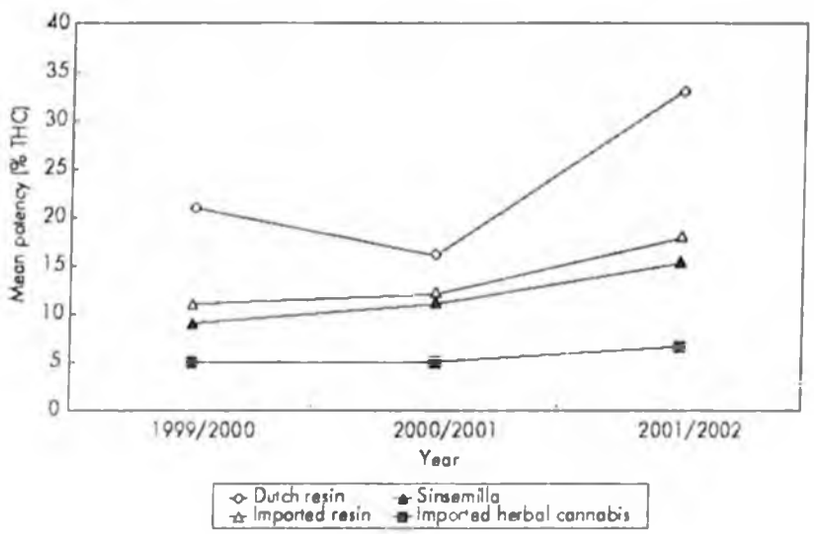


Figure 7: Mean potency (% THC) of cannabis products (1999–2002) in the Netherlands (Note that scale on the y-axis is twice that for the mean potency in other countries.)

Portugal

Figure 8 shows the THC content of resin and herbal cannabis in Portugal from 1997 to 2003. These were derived from all large seizures (>10 kg) and a random sample of smaller seizures. Although it appears that the potency of cannabis resin has increased, the trend in THC content of herbal cannabis is not clear, particularly because of the small sample size. The value for herbal cannabis in 1999 was not available.

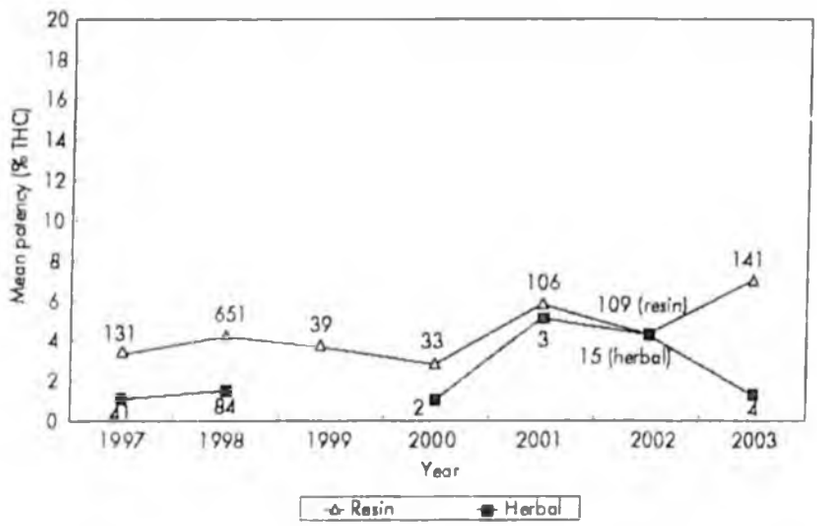


Figure 8: Mean potency (% THC) of cannabis products (1997–2003) in Portugal. Values against each point represent the number of measurements.

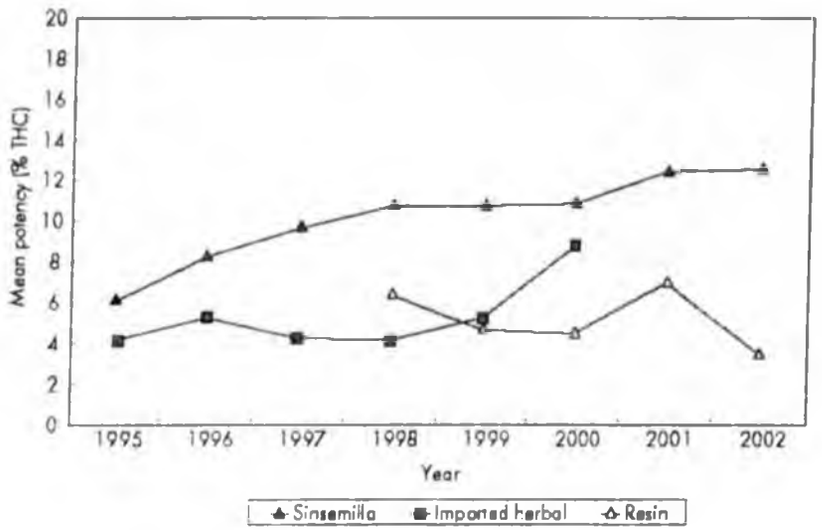


Figure 9: Mean potency (% THC) of cannabis products examined in the UK (Forensic Science Service, 1995–2002).

United Kingdom

The THC content of various cannabis products examined in the United Kingdom by the Forensic Science Service from 1995 to 2002 (Forensic Science Service, 2003) is shown in Figure 9. The samples derived mostly from police seizures and are judged to be reasonably representative of the material seized for each cannabis product. The total sample size was: sinsemilla = 938; imported herbal = 117; resin = 97. There were no data for resin before 1998 and insufficient data for imported herbal cannabis in 2001 and 2002. There has been a clear trend for an increase in the potency of sinsemilla, but little evidence that the potency of resin or imported herbal cannabis has changed.

For a number of years, the Laboratory of the Government Chemist (LGC) produced data on annual trends in cannabis potency and the variation in THC content of imported material derived from customs seizures (Baker et al., 1980, 1981, 1982; Gough, 1991). Figure 10 shows the THC content of all seized cannabis products in the period 1975–1989 as reported in the most recent publication of the series

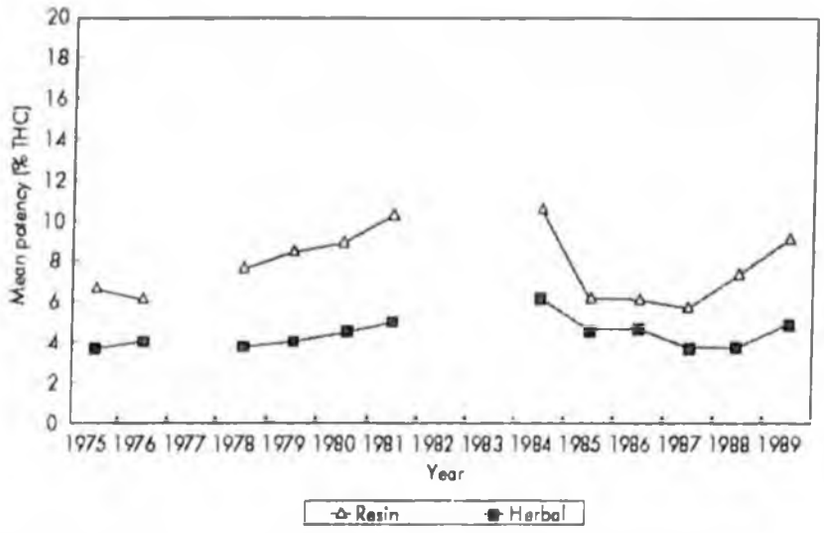


Figure 10: Mean potency (% THC) of cannabis products examined in the UK (Laboratory of the Government Chemist, 1975–1989)

(Pitts et al., 1990). There are major changes on a year-to-year basis, particularly with resin, but no clear overall trend can be discerned for either product. The mean THC content of herbal cannabis and resin was close to 4% and 8% respectively over this period. No data were published after 1989, but information provided by the LGC for 2003 showed that this situation has changed little: the mean THC content of herbal cannabis (type unspecified) was 7.0% (N = 23) and for resin was 5.1% (N = 6).

Miscellaneous data

Two replies to the questionnaire were obtained from **Belgium**: from the Institute of Public Health and from the Drugs and Toxicology Unit of the National Institute of Criminology and Criminalistics (NICC). Data for 2003 (January to October) only were provided by the Institute of Public Health on the questionnaire. These showed that the mean THC content of resin was 15.2% and herbal 14.2%. No summary of the THC data was provided by the NICC, but it stated that there had been no clear trend in the potency of herbal cannabis or cannabis resin in the period 1995–2002; that during this period both herbal cannabis and cannabis resin had

a mean THC content of around 12%, and in 2003 the mean THC content of herbal cannabis was 13.3% and that of cannabis resin 11.5%.

Although the **Estonian** Police Forensic Science Laboratory occasionally measures the THC content of cannabis products, insufficient data were available to determine trends in potency (source: reply to the questionnaire).

In **Finland**, the THC content of herbal cannabis is determined on request but no data were provided (source: reply to the questionnaire).

In **Ireland**, analysis of cannabis products for THC is carried out on an occasional basis; the limited data show that the potency of resin has increased from 2.3% in 1981 to 4.2% in 2000. For herbal cannabis, the increase in this period was from 1.4% to 6.2% (source: reply to the questionnaire).

In **Greece**, Stefanidou et al. (1998) reported that the THC content of illicit herbal cannabis seized by customs and police in two areas of Greece ranged from <1% to >4%.

Hungary did not report mean THC levels before 2002 in Standard table 14, or respond to the questionnaire, but the annual national report to the EMCDDA for 2003 notes that the highest THC level found in herbal cannabis has steadily increased since 1996, although even by 2001 this was still a modest 6%.

Analysis of cannabis products for THC is only carried out occasionally in **Luxembourg**; recent samples (type unspecified) contained up to 14% THC (source: reply to the questionnaire).

In **Spain**, the THC content of cannabis products is measured on all seizures above 4 g, but no data were provided in the questionnaire except for the comment that the mean potency of resin had increased from 5.5% in 1994 to 12% in 2002.

Older data on THC levels in European countries can be found in isolated reports, but they provide little useful information on trends. Thus Fairbairn and Liebmann (1974) planted seeds from imported cannabis and allowed them to grow outdoors in southern England. THC levels in the flowering tops ranged from <1% to >7%. The authors concluded that a warm climate with abundant sunshine was not essential to produce substantial amounts of THC. Cannabis plants growing in Jutland (Denmark) in 1988 were found to have mean total THC levels of <1%

(grown outdoors) and 1.35% (grown under glass). In the flowering tops of those grown under glass, the mean THC content was 2.13% (Kaa, 1989). Earlier, Felby and Nielsen (1985) had found mean total levels of 1.55% (range 0.1-4.2%) for plants growing on Bornholm (Denmark). The authors commented that these findings were broadly similar to THC levels of imported herbal cannabis.

Cannabis resin: variations in potency across Europe

To a large extent, and excluding the special situation of locally produced Dutch nederhasj, the cannabis resin consumed in Europe in recent years has originated mostly from North Africa, with smaller amounts coming from south-west Asia. Since resin is rarely adulterated, it could be argued that, in any given year, all laboratories have been measuring broadly similar material. As noted in the section *Natural variation of THC content in cannabis products* (Chapter 2), there is considerable natural variation in the potency of cannabis products even in a single time period. However, if laboratories made sufficient measurements, then the mean potency of cannabis resin in any year should be found to be similar for all countries. In Figure 11, the respective year-on-year trends for cannabis resin potency, already depicted by country in the section *Other national data*, are brought together. Not only is there no overall time trend, but also there is considerable variation in the reported THC levels, both against time in any one country and between countries at any one time. It is not obvious why there should be consistently less THC in cannabis resin in Portugal compared with cannabis resin in, for example, Austria or the Czech Republic. This finding raises questions about the accuracy of measurement of THC in different laboratories/countries. In other words, if all analysts had used the same THC reference standard for instrumental calibration, then these differences might not have occurred.

In the Netherlands, there has been a marked rise in the potency of cannabis resin caused by the domestic production of nederhasj. Figure 12 shows the unweighted mean potency of cannabis resin for the other countries (i.e. excluding the Netherlands). As with the data derived from Standard table 14 (Table 1), there is no clear trend. This diagram (Figure 12) only covers 1998-2002: the years for which all five countries provided data. It is not possible to derive a similar comparison for herbal cannabis in different countries since, in some cases, no distinction is made between two distinct products, i.e. imported and home-grown cannabis.

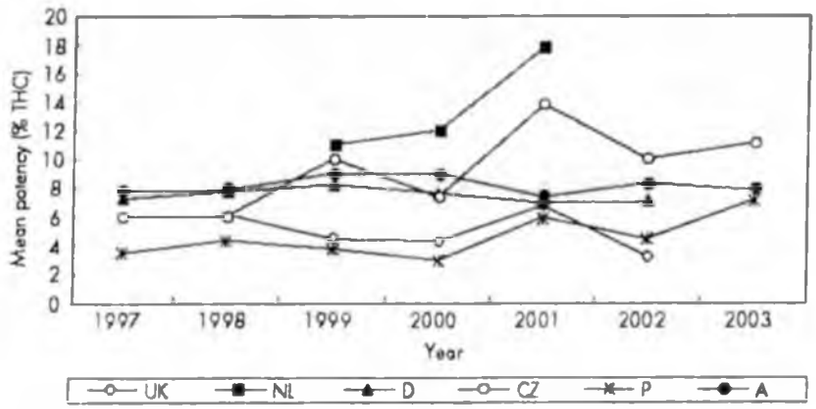


Figure 11: Mean potencies (% THC) of imported cannabis resin in Europe (1997–2003) showing the variation between different laboratories/countries. (UK = United Kingdom, NL = Netherlands, D = Germany, CZ = Czech Republic, P = Portugal, A = Austria)

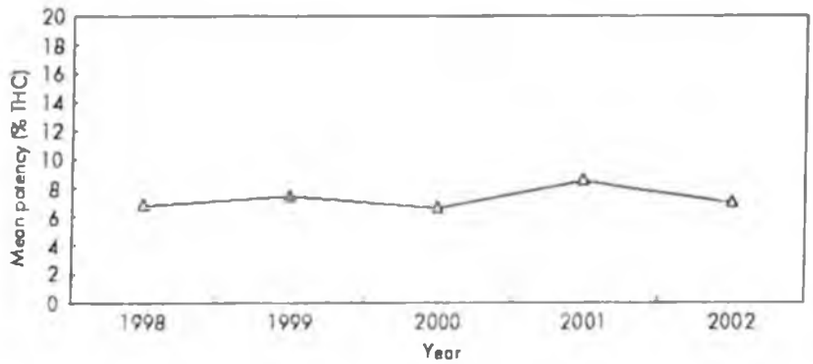
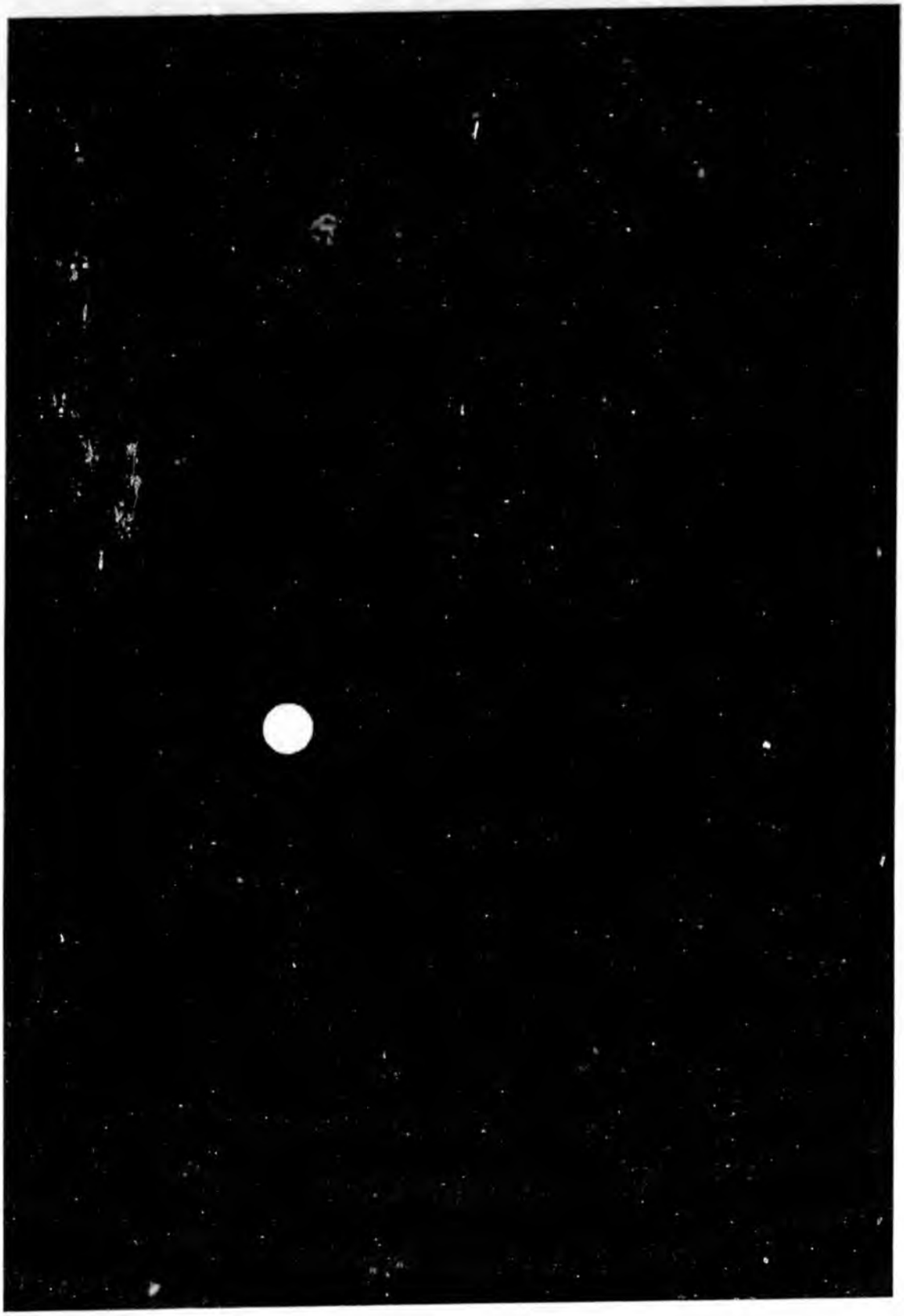


Figure 12: The overall mean potency (% THC) of cannabis resin in Europe (1998–2002) based on data supplied in the questionnaire by the countries shown in Figure 11, but excluding the Netherlands



Chapter 4: The cannabis market in Europe: potency considerations