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Commentary

Risk assessment of khat use in the Netherlands: A review based on adverse health effects, prevalence, criminal involvement and public order

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ABSTRACT

In preparing a decision about the legal status of khat in the Netherlands, the Dutch Minister of Health requested CAM (Coordination point Assessment and Monitoring new drugs) to assess the overall risk of khat in the Netherlands. The present paper is a redraft of a report which formed the scientific basis of the risk evaluation procedure (October 2007). This report reviews the scientific data about khat available in the international literature. In addition, the report contains some information specific for the Netherlands (prevalence, availability of khat and public order aspects). The main psychoactive compounds in khat leaves are cathine and cathinone, which are some 2- to 10-fold less active than amphetamine. Acute health problems are rarely seen, and are usually related with malnutrition, social and financial problems. Khat has a low addictive potential. Chronic toxicity of khat is modest when used in low amounts, whereas at high levels, khat use is associated with adverse effects, like hypertension, heart rhythm disorders, insomnia and loss of appetite. In addition, khat users show a higher prevalence of cancers in the digestive tract. At population level, khat does not lead to specific health risks in the Netherlands, as its use is confined to East-African immigrants. A relationship between khat use and psychiatric disorders has been suggested, but the reports are contradictory, and such studies are presumably heavily confounded by posttraumatic and social stress. In the Netherlands (and other countries), khat use occasionally leads to minor disturbance of civil order in the public domain (loud talking, spitting), but is not related to criminal activities. Following the assessment, CAM estimated the overall risk potential of khat use in the Netherlands as very low. A similar conclusion may be drawn for countries with a comparable prevalence of khat use and khat related public order disturbance.

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1. Introduction

Khat refers to the leaves and the young shoots of the 5–20 m high tree *Catha edulis* Forsk., a species belonging to the plant family Celastraceae. Other names of khat are qat, q'at, kat, kath, gat, chat, tschat (Ethiopia), miraa (Kenya), murungu; the dried leaves of khat are known as Abyssinian tea or Arabian tea.

In preparing a decision about the legal status of khat in the Netherlands, the Dutch Minister of Health requested experts of the CAM (Coordination point Assessment and Monitoring new drugs) to assess the overall risk of khat. Elements of the risk assessment are acute and chronic adverse health effects, the prevalence of khat use, as well as criminal behavior and disturbance of public order related to khat use. This report reviews the internationally available scientific data about these items. In addition, the report describes some more specific information about (1) the prevalence and availability of khat, (2) khat related disturbance of public order and (3) khat related criminality in the Netherlands. As such this risk assessment is applicable for countries with a similar prevalence of khat use and comparable problematic issues with respect to public order disturbance and criminality related to khat use.

2. Methods

The present review is partly based on a report of EJM Pennings from 2006. This report with the title "34th ECDD 2006/4.4 khat. Assessment of khat (*Catha edulis* Forsk.)" (Pennings, 2006) was previously made available on the internet by WHO. Recently, this report was updated using Medline literature searches with the key words catha* (truncated), cathinone, cathine, khat, chat, miraa, mairungi and qat, and the references found in the retrieved reports. Human studies were preferably cited; casuistic studies were occasionally used if no controlled studies were available.

The final assessment in October 2007 was made by a committee of experts consisting of toxicologists, representatives from customs and police forces, lawyers, policy makers, criminologists, pharmacologists, sociologists working on the field of illicit drugs. The

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assessment procedure has been evaluated and described before (van Amsterdam et al., 2004). The various items are scored on a scale of five; 'one' is low risk, whereas 'five' is very high risk.

3. Prevalence of khat use

Some authors estimate that 10 million people daily chew khat worldwide (Stefan and Mathew, 2005), and in 1990, khat consumption was estimated at about 5 million portions per day (Brenneisen et al., 1990). Usually, a person consumes 100–200 g of the leaves; young leaves are preferred because these have the highest stimulant activity. Khat leaves are chewed habitually in the south-western part of the Arabian Peninsula and in the East-African countries between Sudan and Madagascar, namely Djibouti, Ethiopia, Somalia, Kenya, Tanzania and Uganda. In addition, in Europe, Australia and the United States, khat use is seen amongst immigrants from Yemen, Somalia and Ethiopia (Browne, 1990; Goldenberg et al., 2004; Griffiths et al., 1997).

Khat chewing is deep-rooted in the Yemenite society, where khat is consumed by males and to a lesser extend by females in social gatherings with family and friends while holding conversations, smoking cigarettes and drinking tea and soft drinks. Use of by women has also been reported (Kalix, 1990).

In three urban and three rural areas in Yemen, lifetime prevalence of khat use in a sample of 800 adults (15–76 years) was 82% in men and 43% in women. In a small sample in Uganda ($N = 165$), 32% had experience with chewing khat and 20% were still using khat (Ihunwo et al., 2004). In Ethiopia, khat is freely available and its consumption has become popular in all segments of the Ethiopian population (Selassie and Gebre, 1996). In a rural Ethiopian community, the prevalence of khat use in 1997 was 32% in 1200 adults (Belew et al., 2000). Provincial studies suggested a prevalence rate among males of between 50% and 75%, with some authors suggesting higher rates based on those of neighboring countries. In rural Yemenite communities in Israel, the usage rate among 15- to 65-year-old males was 39% (Litman et al., 1986).

The prevalence and socio-demographic correlates of khat use have been determined in a large house-to-house survey carried out in the rural Ethiopian community of Butajira (Alem et al., 1999). Over 10,000 residents aged 15 years and above were interviewed. Of these, 58% were female and 74% were Muslim. Lifetime experience of khat chewing was 55.7% and the prevalence of current use was 50%. Among current chewers, 17.4% reported taking khat on a daily basis. Various reasons were given for chewing khat. Eighty percent of the chewers used it to obtain maximum concentration during prayer. There was a strong association of Muslim religion, smoking, and high educational level with daily khat chewing. The authors concluded that khat chewing affects a majority of the adult population of the Butajira district, in particular the most educated and most productive age group (Alem et al., 1999).

Somali refugees in the UK showed a higher prevalence of khat use in men (63%) than in women (17%). It is suggested that excessive khat consumption among Somalis in UK should be seen in the wider context of a people dislocated from their country of origin as facilitating a deviant pattern of drug abuse (Nabozoka and Badhadhe, 2000). Griffiths et al. studied patterns of khat use among 207 Somalis (aged 18–78 years) living in London (Griffiths et al., 1997). Life time prevalence of khat use was 78% and 67% reported khat use in the week prior to the interview. The majority (76%) used more khat in the UK than in Somali which may be related to khat use as playing a positive role in supporting the cultural identity of the Somali community (Griffiths et al., 1997). In a recent study of khat use among Somalis in four English cities, 38% of the overall sample (602 interviews) had ever used khat in their lifetime and 34% had used it in the month prior to the interview (Nabozoka and Badhadhe, 2000). The average frequency of khat use in this study was three days a week with 10% of last-month users chewing khat on a daily basis.

Out of 67 countries that answered a questionnaire sent out by WHO in October 2005 (Dr. Scholten), nine countries responded that abuse in their country exists. In 25 countries it does not exist and the remainder has no knowledge of abuse in their countries. Out of the nine countries with abuse, only Kenya has a high prevalence, estimating khat use by 20%. The other countries report that (ab-)use is confined to certain ethnic groups, in most countries to Somali, and often to adult men, although there is a tendency in several countries for use among women and adolescents. In Denmark, it is 30–40% (1350 people), in Sweden almost 100% of the adult men (2000–3000 people).

4. Chemistry

The environment and climate conditions determine the chemical profile of khat leaves. In the Yemen Arab Republic, about 44 different types of khat exist originating from different geographic areas of the country (Al Motarreb et al., 2002b; Geisshusler and Brenneisen, 1987). Fresh khat leaves may contain some 60 different cathedulins (Kite et al., 2003). Its taste varies from one kind to another and depends on the tannic acid content (up to 10% in dried material). Khat leaves have an astringent taste and have an aromatic odor. The young leaves are slightly sweet.

Compounds found in khat include alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins and minerals (Cox and Rampes, 2003; Kalix and Braenden, 1985; Nencini and Ahmed, 1989). Phenylalkylamines and the alkaloid cathedulins (basically polyesters of euonyminol) are the most important alkaloids. The phenylalkylamines in khat are structurally related to amphetamine and comprise cathinone [S-(−)-cathinone], and the two diastereoisomers cathine [1S,2S-(+)-norpseudoephedrine or (+)-norpseudoephedrine] and norephedrine [1R,2S-(−)-norephedrine]. The naturally occurring S-(−)-cathinone has the same absolute configuration as S-(+)-amphetamine. Cathinone is mainly found in the young leaves and shoots and is converted to cathine [(+)-norpseudoephedrine] and (−)-norephedrine during maturation. These latter compounds are found in the leaves in a ratio of approximately 4:1 (Kalix and Braenden, 1985).

Cathinone is unstable and undergoes decomposition to relatively inactive compounds after harvesting and during drying or extraction of the plant material (Brenneisen and Geisshusler, 1985; Kalix and Braenden, 1985; Nencini and Ahmed, 1989, WHO, 1980). As cathinone is presumably the main psychoactive component of khat, this explains why fresh leaves are preferred and why khat is wrapped up in banana leaves to preserve freshness. Phenylalkylamine alkaloids other than cathinone and cathine, found in khat leaves seem to contribute less to the stimulant effects of khat (Kalix et al., 1987b,a; Nencini and Ahmed, 1989, WHO, 1980) and will not be reviewed here.

Khat is usually chewed in a dose of 100–200 g of khat. The phenylalkylamine content of khat leaves varies within wide limits. Fresh khat from different origin contained on the average 36 mg cathinone, 120 mg cathine and 8 mg norephedrine per 100 g of leaves (Geisshusler and Brenneisen, 1987). Others (Toennes et al., 2003) found 114 mg cathinone, 83 mg cathine and 44 mg norephedrine in 100 g of khat leaves. Widler et al. (1994) found 102 mg cathinone, 86 mg cathine and 47 mg norephedrine in 100 g of fresh leaves from Kenya. Al Motarreb et al. (2002b) reported higher levels of cathinone in fresh leaves: 78–343 mg/100 g.

5. Pharmacokinetics

Chewing results in a high extraction of the alkaloids with only 9% remaining in the leaf residues. A chewing dose of 45 g khat

leaves i.e. 0.6 g/kg of body weight results in a mean absorption dose of 45 mg of cathinone. The euphoric effects of khat start after about 1 h of chewing of 60 g fresh khat leaves per subject (cathinone: 0.8–1 mg/kg body weight). Blood levels of cathinone start to rise within 1 h and peak plasma levels are obtained 1.5–3.5 h after the onset of chewing (Halket et al., 1995). Maximum plasma levels range from 40 to 140 ng/ml (mean 83 ng/ml) after 1-h chewing. In plasma, cathinone is detectable up to 24 h. The elimination half-life is some 260 min (Widler et al., 1994).

Metabolism of cathinone is rapid and occurs already during first passage through the liver. Only 2% of administered cathinone was found unchanged in the urine (Brenneisen et al., 1986; Nencini and Ahmed, 1989). In humans, after oral administration of cathinone (isomers, racemate) 22–52% was recovered in urine mainly as the aminoalcohols norephedrine and norpseudoephedrine. Metabolization of cathinone is a stereospecific keto reduction. The main metabolite of S-(−)-cathinone was R,S-(−)-norephedrine and the main metabolite of R-(+)-cathinone as R,R-(−)-norpseudoephedrine (Brenneisen et al., 1986; Toennes et al., 2003).

6. General pharmacology

The most active khat alkaloid is cathinone, which has amphetamine-like properties (Kalix, 1984; Kalix and Khan, 1984). Like amphetamine, cathinone is to be considered as an indirect dopaminergic agonistic drug. Indirect, because it is a pre-synaptic releaser and reuptake inhibitor of dopamine (Nencini and Ahmed, 1989; Giannini et al., 1986). In addition, it has a serotonergic component as (−)-cathinone also releases serotonin from its striatal stores, again similar to (+)-amphetamine although one-third as potent (Kalix, 1984). Apparently, (−)-cathinone shares important effects of (+)-amphetamine on neurotransmission, but is some 2–10 times less potent. The potency of the active compounds in khat have been estimated to range between those of caffeine and amphetamine (Halbach, 1979). The potency of cathine to stimulate central nervous system is about 7–10 times less than that of amphetamine, and cathinone is regarded as being about half as potent as amphetamine (Pantelis et al., 1989a). In general, cathinone is some 7–10 times more potent than cathine. Methcathinone is a synthetic drug, which is more potent than amphetamine (about 7-fold). Two other pharmacologically active compounds in khat are cathine (norpseudoephedrine) and norephedrine, which are less potent stimulants (WHO, 1980). Though the effects on the nervous system resemble those of amphetamine, quantitative rather than qualitative differences are present between both drugs (Cox and Rampes, 2003; Halbach, 1972; Hassan et al., 2002b; Kalix, 1990; Tariq et al., 1983).

In addition to central effects, khat use affects cardiovascular, digestive, respiratory, endocrine and genito-urinary systems. The major effects include those on the gastro-intestinal system (constipation, urine retention), acute cardiovascular effects and central effects such as increased alertness, dependence and tolerance. Adverse central effects of khat use are the induction of paranoid psychosis and hypomanic illness with grandiose delusions (Kalix, 1988).

Finally, though it has been argued that chewing a typical dose of khat leaves would be equivalent to an oral dose of 5 mg of amphetamine (ISDD, 1994), such comparisons should be made with caution, as chewing of khat differs from ingesting a dose of amphetamine (Griffiths, 1998).

7. Acute adverse health effects

7.1. Peripheral effects

The main acute toxic effects of khat use include increased blood pressure, tachycardia, insomnia, anorexia, constipation, general malaise, irritability, migraine and impaired sexual potency in men (Nencini and Ahmed, 1989).

Khat chewing induces small and transient rises in blood pressure and heart rate (Al Motarreb et al., 2002b; Hassan et al., 2000, 2005; Kalix, 1992; Nencini et al., 1986) which is mediated by β_1-adrenergic receptors (Hassan et al., 2005). Blood pressures were elevated for about 3 h after 1 h of chewing of about one quarter (0.6 g/kg) of a traditional khat session dose (Toennes et al., 2003). This dose is comparable with a mean oral dose of 45 mg cathinone. Khat induces a fall in urine flow rate in healthy men (Hassan et al., 2002b; Nasher et al., 1995) probably mediated through stimulation of α_1-adrenergic receptors by cathinone.

In white rabbits, khat leaves decreased plasma cholesterol, glucose and triglycerides (Al Habori and Al Mamary, 2004) and increased plasma alkaline phosphatase and alanine aminotransferase (Al Mamary et al., 2002). Histopathological signs of congestion of the central liver veins were observed with acute hepatocellular damage and regeneration. In addition, some kidney lesions were seen with the presence of fat droplets in the upper cortical tubules, acute cellular swelling, hyaline tubules and acute tubular nephrosis. Spleen was not affected and the histoarchitecture of the testes and cauda epididymis was normal showing, however, increased rate of spermatogenesis.

7.2. Hyperthermia

Pronounced hyperthermia has been observed in rabbits treated with 24 mg/kg (−)-cathinone (two out of three animals died). When the dose was reduced to 16 mg/kg, behavioral symptoms were less pronounced and the hyperthermic response was less (1.9 °C rise) (Kalix, 1980). Like amphetamine, (−)-cathinone induces hyperthermia. The effect of (−)-cathinone on body temperature is similar to those of (+)-amphetamine and 3,4-methylenedioxy-methamphetamine (MDMA, XTC): hyperthermia at room temperatures and above, but hypothermia in animals kept below room temperature (Kalix and Braenden, 1985).

7.3. Reduced food consumption

It has been suggested that retardation of growth rate was due to decreased absorption of food and not to decreased food consumption. In pregnant rats, however, khat reduces food consumption and maternal weight gain, and also lowers the food efficiency index (Islam et al., 1994). Khat extracts and (−)-cathinone produce anorectic effects in animal species (WHO, 1980) which is qualitatively similar to that evoked by amphetamine (Goudie, 1985; Zelger et al., 1980).

In conclusion, the health impact of the acute effects of khat is low and in nature similar to those of amphetamine.

8. Chronic adverse health effects

8.1. Cardiovascular complications

An increased incidence of acute myocardial infarction presenting between 2 PM and midnight, i.e. occurring during khat sessions, has been found (Al Motarreb et al., 2002a). Recently, it has been reported that khat chewing is associated with acute myocardial infarction (Al Motarreb et al., 2005). Khat chewing appears to be an independent dose-related risk factor for the development of acute myocardial infarction with heavy chewers having a 39-fold increased risk (Al Motarreb et al., 2005).

Two cases (Kuczkowski, 2004, 2005) described chest pain, sinus tachycardia and hypertension in two pregnant patients who had used khat in familial gatherings. The symptoms had developed after khat use only. Khat chewing has also been reported to be a

significant risk factor for acute cerebral infarction (Mujlli et al., 2005). The prevalence of high blood pressure was significantly higher in the patient group than in the control group and this higher prevalence was associated with khat chewing. Another cardiovascular complication of khat chewing is the higher incidence of hemorrhoids and hemorrhoidectomy found in chronic khat chewers (62% and 45%) as compared to non-khat users (4% and 0.5%) (Al Hadrani, 2000).

8.2. Oral and gastro-intestinal complications

As a consequence of its mode of consumption khat seems to affect the oral cavity and the digestive tract. The studies to these complications show, however, conflicting results. A high frequency of periodontal disease has been suggested as well as gastritis (Kennedy et al., 1983) and chronic recurrent subluxation and dislocation of the temperomandibular joint (Kummoona, 2001). Oral keratotic lesions at the site of chewing (Ali et al., 2004) and plasma cell gingivitis (allergic reaction to khat) (Marker and Krogdahl, 2002) have been reported. The tannins present in khat leaves are held responsible for the observed gastritis (Halbach, 1972; Pantelis et al., 1989b). Other studies rather suggested beneficial effects on the periodontium (Al Hebshi and Skaug, 2005; Hill and Gibson, 1987; Jorgensen and Kaimenyi, 1990) in stead of detrimental effects. No significant association could be found between khat chewing and oral leukoplakia (Macigo et al., 1995), and Mengel et al. (1996) found no significant role of khat chewing in periodontal disease and suggested bad oral hygiene as causal factor.

8.3. Effects on the central nervous system

Khat chewing induces a state of euphoria and elation with feelings of increased alertness, and being 'energetic' and arousal. This is followed by a stage of vivid discussions, loquacity and an excited mood. Thinking is characterized by a flight of ideas but without the ability to concentrate. However, at the end of a khat session the user may experience depressed mood, irritability, anorexia and difficulty to sleep (Al Motarreb et al., 2002b; Nencini and Ahmed, 1989). Lethargy and a sleepy state follow the next morning. Functional mood disturbances (anxiety and depression) have been reported during khat sessions, but these were temporary and had disappeared the next day (Hassan et al., 2002a). Remarkably, many Yemenite users believe that khat chewing improves their sexual desire and excitement (Al Motarreb et al., 2002b). In fact, khat reduces sexual potency. Khat chewing induced anorexia and insomnia (delayed bedtime) resulting in late wake-up next morning and low work performance the next day (Hassan et al., 2002b). Chewing 0.6 g of khat (low dose) does not affect pupil size and reaction to light, did not induce rotary nystagmus or impairment of reaction and induced no severe adverse reactions.

8.4. Physical and psychological dependence liability

In general, drugs with a fast onset of action have a high addictive potential. When using khat it takes about 2–3 h to reach maximal plasma levels and hence khat has less reinforcing properties than other stimulants such as amphetamine and cocaine. Animal studies (self-administration, drug discrimination) demonstrated that khat extracts induced a long-lasting (10–15 days) behavioral sensitization in rats, similar to cathinone and amphetamine (Banjaw et al., 2006).

In humans, khat chewing may induce moderate but often persistent psychological dependence (Kalix, 1988). It is associated with consuming khat on a daily basis (Nencini and Ahmed, 1989). Mild craving and tolerance to the effects of khat do exist but there is no definite withdrawal syndrome. A habitual user may feel hot, lethargic and gripped with the desire to chew khat in the first two days (Al Motarreb et al., 2002b). During sleep nightmares are common but these stop after a few nights. Withdrawal symptoms after prolonged use are mild and may consist of lethargy, mild depression, slight trembling and recurrent bad dreams (Kalix, 1988), but these symptoms are mild and resolve in short time (Kalix, 1990). In fact, there are very few reports on khat dependence (Giannini et al., 1992; Othieno et al., 2000; Patel, 2000) and a khat withdrawal syndrome has not been described. Nevertheless, a certain degree of tolerance seems to develop to the increases in blood pressure, heart rate, respiratory rate and body temperature, and to the insomnia (Kalix and Braenden, 1985; Kalix, 1990; Luqman and Danowski, 1976; Nencini et al., 1986). Habitual users do not show serious problems when stopping use. Discontinuation results in improvement of sleep and appetite, and fewer constipation problems (Al Motarreb et al., 2002b; Luqman and Danowski, 1976). Somalian users in UK users reported moderate dependence (Griffiths et al., 1997). A minority reported severe problems whereas medical problems associated with khat use were rarely reported. Due to its self-limiting way of administration i.e. chewing sets an upper limit to the amount of khat that can be consumed, khat was not classified as an inevitably dependence producing drug (Adam and Hasselot, 1994; Halbach, 1972). In conclusion, khat has low abuse potential in humans and khat dependence is mild.

8.5. Genotoxicity, reproduction toxicity and endocrine effects

Detailed studies on the effects of khat on human reproduction are lacking. However, the available data suggest that chronic use may cause spermatorrhoe and may lead to decreased sexual functioning and impotence (Halbach, 1972; Mwenda et al., 2003). In chronic chewers, sperm count, sperm volume and sperm motility were decreased (el Shoura et al., 1995; Hakim, 2002). Deformed spermatozoa (65% of total) have been found in Yemenite daily khat users, with different patterns including head and flagella malformations in complete spermatozoa, aflagellate heads, headless flagella and multiple heads and flagella (el Shoura et al., 1995). In pregnant women, khat consumption may have detrimental effects on uteri-placental blood flow and as a consequence, on fetal growth and development (Mwenda et al., 2003). Lower mean birth weights have been reported in khat chewing mothers compared to non-using mothers indicating an association between khat chewing and decreased birth weight (Abdul-Ghani et al., 1987).

Orally administered khat extract induced dominant lethal mutations in mice (Tariq et al., 1990), chromosomal aberrations in sperm cells in mice (Qureshi et al., 1988), and teratogenic effects in rats (Islam et al., 1994). With the micronucleus test to determine genetic damage, an 8-fold increase in micronucleated buccal mucosa cells (but not bladder mucosa cells) was seen among khat chewing individuals (Kassie et al., 2001). Here, khat, tobacco and alcohol showed additive effects, suggesting that khat consumption, especially when accompanied by alcohol and tobacco consumption increases the risk for oral malignancy (Kassie et al., 2001). In man, khat use during pregnancy is associated with lower birth weight. No teratogenic effects have been reported. The effect on the child exposed to khat constituents via breast milk is not known, but it is prudent to advise lactating mothers not to use khat.

8.6. Cancer disease

Makki (1975) stressed the importance of khat when she found that most of the oral squamous cell carcinomas of her study patients were located in the buccal mucosa and lateral sides of the tongue, which comes into direct contact with the khat during chewing. Of the 28 head and neck cancer patients in Saudi Arabia

(Soufi et al., 1991), 10 patients had a history of khat chewing. All were non-smoking chewers and all of them had used khat over a period of 25 years or longer. Eight of these 10 presented with oral cancers. In some cases, the malignant lesion occurred at exactly the same site where the khat bolus was held. The authors concluded that a strong correlation between khat chewing and oral cancer existed. In another study performed in Yemen, 30 of 36 patients suffering from squamous cell carcinoma (in the oral cavity: 17; oropharynx: 1; nasopharynx: 15; larynx: 3) were habitual khat chewers from childhood (Nasr and Khatri, 2000).

Half of khat chewers develop keratosis of the oral buccal mucosa (Hill and Gibson, 1987) which is considered as a pre-cancerous lesion that may develop into oral cancer (Goldenberg et al., 2004). Ali et al. reported that 22.4% of khat chewers had oral keratotic white lesions at the site of khat chewing, while only 0.6% of non-chewers had white lesions in the oral cavity (Ali et al., 2004). The prevalence of these lesions and its severity increased with frequency and duration of khat use. In human leukemia cell lines and in human peripheral blood leucocytes, khat extract, cathinone and cathine produced a rapid and synchronized cell death with all the morphological and biochemical features of apoptotic cell death (Dimba et al., 2004).

8.7. Khat-induced psychiatric morbidity

Khat chewing can induce two kinds of psychotic reactions. First, a manic illness with grandiose delusions and second, a paranoid or schizophreniform psychosis with persecutory delusions associated with mainly auditory hallucinations, fear and anxiety, resembling amphetamine psychosis (Cough and Cookson, 1984; Critchlow and Seifert, 1987; Dhadphale et al., 1981; McLaren, 1987; Pantelis et al., 1989a,b; Yousef et al., 1995). Both reactions are exceptional and associated with chewing large amounts of khat (Dhadphale and Omolo, 1988; Jager and Sireling, 1994). Symptoms rapidly abate when khat is withdrawn (Giannini and Castellani, 1982; Nielen et al., 2004; Pantelis et al., 1989b). In fact, khat withdrawal consistently appears to be an effective treatment of khat psychosis and antipsychotics are usually not needed for full remission (Jager and Sireling, 1994; Nielen et al., 2004; Pantelis et al., 1989a). Nevertheless, in most cases described in the literature antipsychotic medication has been used to alleviate the symptoms. Khat psychosis, however, is an infrequent phenomenon, probably due to the physical limits of the amount of khat leaves that can be chewed (Halbach, 1972; Kalix, 1987, 1990). Khat psychosis may be accompanied by depressive symptoms and sometimes by violent reactions (Pantelis et al., 1989b). It has been argued that khat chewing might exacerbate symptoms in patients with pre-existing psychiatric disorder (Hassan et al., 2002a).

Recently, a large Somalian study revealed a relationship between khat consumption and onset of psychotic reactions (Odenwald et al., 2005). The results indicated that not khat consumption *per se* but rather early onset and excessive khat chewing were related to psychotic symptoms. In most cases a pattern of binge chewing (more than two 'bundles' per day) preceded the onset of psychotic symptoms. It should, however, be noted that a positive relation was observed in this study between the number of traumatic events experienced and the averaged daily khat consumption.

Dhadphale and Omolo (1988) studied psychiatric morbidity among khat users. In moderate users there was no excess morbidity. Chewing more than two bundles per day was associated with increased psychiatric morbidity. Case reports confirm that adverse effects occur at high doses of khat (Alem and Shibre, 1997; Critchlow and Seifert, 1987; Stefan and Mathew, 2005).

Cases in the UK were characterized by the solitary use of khat by young individuals and these may represent a vulnerable group (Pantelis et al., 1989a). This may explain contradictory results sometimes obtained. For example, in a large survey among Yemenite khat users the incidence of adverse psychological symptoms was not greater than in non-users (Numan, 2004). In fact, there was a negative association between the incidence of phobic symptoms and khat use. On the other hand, a 34-year-old Somali woman living in the UK attempted suicide during a khat-induced paranoid psychosis (Critchlow and Seifert, 1987). Among Somali refugees in the UK, war-related experiences, occupational status before migration and current khat use were found to be risk factors for anxiety, depression, suicidal thinking and symptoms of psychosis (Bhui et al., 2003). Warfa et al. (2007) recently concluded that whilst khat use appears to exacerbate existing psychological problems, there is not currently, any clear evidence which indicates that khat use is a catalyst for the development of mental illness.

Hypnagogic hallucinations have been reported in chronic khat users (Granek et al., 1988). These consist of continuous visual and/or auditory dreamlike experiences that accompany daily life and are not related to khat sessions. Patients may consider them as normal and do not usually report these hallucinations unless specifically asked about.

In summary, it appears that the chronic adverse effects of khat use are generally mild in nature. Though chronic khat use is associated with an increased number of cardiovascular events like hypertension and myocard infarct, no serious khat related cardiovascular incidents have been reported by e.g. emergency units of hospitals. Some periodontal diseases and gastro-intestinal complaints seem to be associated with khat use, but the effects observed are mild and the epidemiological evidence for an association very weak. On the other hand, the high prevalence of oral, head and neck cancers in khat users is quite alarming and requires further study. The abuse potential of khat is low and khat dependence is low. Mild craving and tolerance to khat effects exists but there is no definite withdrawal syndrome. There is no strong, and even contradictory, evidence for a causal relation between khat use and psychiatric morbidity. Most studies suffer from confounding, like the presence of post traumatic stress disorder (PTSD), chronic psychotic disorders, social stress (Bhui et al., 2003; Odenwald, 2007; Odenwald et al., 2005), and personal factors such as multi illicit drug use, medication and the relatively low socio-economic background of drug users. Moreover, in psychiatric institutions khat related psychiatric disorders does not manifest very frequently.

9. Public health effects

9.1. Vulnerability of users, age group, experience in use, knowledge and setting

No quantitative data are available about the prevalence of public health problems. Except for Kenya, that reports that use of khat is associated with dependence to other drugs, there are no reports that the situation is severe. Significant associations of khat use were found with physical illness, injuries, under nutrition and mental distress. Mental distress was higher among frequent and daily users and among those who chewed khat for more than 2 years. In addition, sleep disturbances were significantly higher among khat users than among non-users. Social functioning, economic well-being and problem drinking were not associated with khat use (Belew et al., 2000).

In a recent study of khat use among Somalis in four English cities, the average frequency of khat use in this study was three days a week with 10% of last-month users chewing khat on a daily basis (Griffiths, 1998). Sleeping problems were reported by 65% (8% severe, 23% moderate, 34% mild), 51% (2% severe, 18% moderate, 14% mild) reported loss of appetite and 44% (11% severe, 11% moderate, 22% mild) reported feeling the urge to chew khat.

Several authors have argued that regular consumption of khat seriously affects the social and economic life of the user (Balint and Balint, 1994; Balint et al., 1991; Kalix, 1994). In addition to the reported health problems, the regular consumption of khat is associated with a variety of social and economic problems affecting the consumers and their families i.e. for some the daily cost of the khat habit exceeds their expenditure on food for their families.

9.2. Availability of khat and safety of the marketed product

The Dutch National Police Forces observe that Somalian inhabitants trade commercially in khat. Khat is imported in the Netherlands on a daily basis, mainly via Schiphol international airport. Khat is further distributed to other regions and town where Somalian immigrants live. No trade of khat is seen in 'coffee shops' or 'smart shops'.

Khat is an evergreen plant grown by grafting and cultivated as a bush or small tree. It is mainly found in Ethiopia, Yemen, Somali, Sudan, Madagascar and South Africa, but it is also seen in Turkestan and Afghanistan (Cox and Rampes, 2003). Khat is harvested throughout the year with two crops of a tree per year. Khat is harvested in the early morning hours and sold at markets in late morning. To preserve its freshness, khat is wrapped in banana leaves and sold as bundles (30–40 cm) of twigs, stems and leaves. For optimum activity khat has to be fresh. Outdated khat has low activity and is mostly discarded. Most retailers are refugees without work or young students.

9.3. Emergencies related to khat use

In the last decade, the Dutch National Poisoning Center received no reports about serious or fatal accidents related to the consumption of khat. One case of emergency after use of khat was reported in the USA between 1995 and 2002 by the US Federal Drug Abuse Warning Network (DAWN), whereas there were no reports by the Toxic Exposure Surveillance System (TESS) between 2001 and 2003.

10. Public order and safety

10.1. Disturbance of public disorder related to khat use

Occasionally, khat selling and consumption in the public domain (street) gives some disturbance of the civil order (hanging around, spitting of khat leaves on the street, yelling, fighting) (NND, 2007). Recently, it was prohibited in one Dutch town to use of khat within 500 m from the distribution point. Similar problems occurred in the Dutch towns Eindhoven, Rotterdam-Feijenoord, Tilburg and other cities where relative large numbers of Somali's live together. Khat is bought by small dealers near Schiphol international airport, and sold in the main towns. The merchandising of khat from the trunk of private cars gives civilians a strange, but false impression of illegal drug dealing. Some local municipal officers have proposed to regulate khat trade by arranging selling zones.

10.2. Threshold to use violence, impairment of car driving and operating machines

Both khat extract and (−)-cathinone enhance baseline aggressive behavior of isolated rats (Banjaw et al., 2006). A prevalence of khat use of 44% was found in an Ethiopian sample of 25 juvenile delinquents drawn from the national Remand Home in Addis Ababa (Meteki and Hughes, 2001). Surprisingly, the authors regarded this prevalence of 44% as relatively low, and suggested that khat is not associated with crime. No incidents have been reported about health problems or aberrant behavior following the use of khat (NND, 2007).

A study carried out in flight attendants during a standard aviation medical examination showed that khat chewing impaired perceptual-visual memory and decision-speed cognitive functions (Khattab and Amer, 1995). Toennes and Kauert investigated plasma khat alkaloid concentrations in 19 cases suspected of driving under the influence of drugs. In all cases, cathinone or cathine was found in blood and urine, but an association between alkaloid concentrations and impaired driving could not be established. Nevertheless, the authors concluded that chronic khat use might lead to a marked deterioration of psychophysical functions (Toennes and Kauert, 2004).

11. Criminal involvement

11.1. Khat and the involvement of (organized) crime

Immigrants have spread the use of the khat chewing habit to Europe and the USA. In the UK, khat is not illegal and it has been estimated that about 7000 kg of khat pass through Heathrow Airport each week from where it is distributed into the UK and into other European countries (Cox and Rampes, 2003). The countries that prohibited khat report some seizures, the highest being Sweden with 9 tons yearly. There was an increasing tendency, but this might have flattened by now.

Though a Swedish investigation from 2005 showed that the trade of khat was related with smuggling of MDMA (3,4-methylenedioxymethamphetamine), there are in the Netherlands no indications that khat trading is related to organized crime (NND, 2007), which is partly due to low profit of selling khat, because the potential buyers (Somalian refugees) have a low financial income.

According to Scholten of WHO, the import of khat into the Netherlands is considerable. Khat is mainly imported from Kenia (95%), Ethiopia and to a lesser extend from Thailand, i.e. 1.8 million kilo of khat was imported in the last 2½ years. Smaller amounts (20–50 kg) are further distributed by Somalians to Germany, Canada, France, Italy, Switzerland, Denmark, Finland, Norway, Sweden, Belgium and Ireland. Both the number of khat transports as well as the total amount of khat transported are stable or are even slightly decreasing. According to the Customs Enforcement Network the total amount of khat that was confiscated (mainly in Canada) in 2005, 2006 and 2007 averaged, respectively, 5489, 10820 and 3252 kg (in total 20 tons), where the Netherlands was the country of origin. For comparison: in these 3 years some 15 tons of khat was confiscated, where the UK was the country of origin. The absence of criminal networks related to khat was confirmed in a report of the UK (ACMD, 2006).

11.2. Current legal status of khat

At present, khat is not under international control. However, in the early 1980s all amphetamine-like substances were placed group-wise under international control including the two common khat components, cathine and cathinone. Cathinone was included in Schedule I of the UN Convention on Psychotropic Substances in 1988 (Kalix, 1992; Widler et al., 1994), and cathine was included in Schedule III of this Convention.

In the Netherlands, the trade and use of khat is legal, whereas cathine and cathinone are controlled substances and placed on list 1. Khat is illegal in France, Sweden (1998), Eritrea (1993), Finland, Jordan and Switzerland, but legal in the USA, the UK, the Netherlands and in most African countries (Adam and Hasselot, 1994). Remarkably, it is illegal in USA, if it contains cathinone (schedule I) or cathine (schedule IV) (answer to questionnaire). Anyway, trade in dried leaves is illegal in USA. In Australia only

licensed persons can import khat for personal use only up to a maximum of 5 kg (answers to questionnaire).

In 2002 the 33rd ECDD pre-reviewed khat and concluded that there was sufficient information on khat to justify a critical review (WHO, 2003). Based on this critical review, the WHO Expert Committee on Drug Dependence recommended in 2006 that the potential for abuse and dependence of khat is low. The level of abuse and threat to public health is not significantly enough to warrant international control. Therefore, the Committee did not recommend scheduling of khat. The Committee recognized that social and health problems may result from the excessive use of khat and suggested that national educational campaigns should be adopted to discourage use that may lead to these adverse consequences (Pennings, 2006).

12. Risk assessment of khat by CAM

The committee of experts who made the overall assessment consists of toxicologists, representatives from customs and police forces, lawyers, policy makers, criminologists, pharmacologists, sociologists working on the field of illicit drugs. The assessment procedure using 16 items has been described and evaluated before (van Amsterdam et al., 2004). The 16 items are scored on a scale of five; 'one' is no risk, whereas 'five' is very high risk. The score of khat on the 16 items was 1.1–2.7 (mean value 1.94; median value 1.95). For this estimation of the overall risk no weight factors for the different items were used. Following open discussions (i.e. the Delphi approach) about the data described in this review, and their own experiences in the field, the Dutch CAM expert committee estimated the risk potential of khat use. Despite the apparent association between khat use and oral cancer and psychiatric disorders, the adverse risk of khat was regarded by the committee as very low because the prevalence of khat use is very low and expected to remain limited to a subpopulation of Somalian refugees in the Netherlands. Based on this expert view of the CAM, the Dutch Minister of Health recently decided not to prohibit the use of khat in the Netherlands.

13. Discussion and overall conclusion

In summary, the adverse health effects of khat use may be regarded as very low. This view is based on its general toxicity profile, its low prevalence of use in the general population, its low consumption rate and the low criminal involvement in the Netherlands. In short, the nature of the acute effects of khat is not alarming and similar to those of amphetamine. Furthermore, chronic khat use is associated with an increased number of cardiovascular events like hypertension and myocard infarct, but serious khat related cardiovascular incidents have not been reported by e.g. emergency units of hospitals. Some periodontal diseases and gastro-intestinal complaints seem to be associated with khat use, but the effects observed are mild and the epidemiological evidence for an association very weak. The abuse potential of khat is low and khat dependence is low. Mild craving and tolerance to khat effects exists but there is no definite withdrawal syndrome. There is no strong, and even contradictory, evidence for a causal relation between khat use and psychiatric morbidity. Most studies suffer from confounding, like the presence of post traumatic stress disorder (PTSD), chronic psychotic disorders, social stress (Bhui et al., 2003; Odenwald, 2007; Odenwald et al., 2005) and personal factors such as multi illicit drug use, medication and the relatively low socio-economic background of drug users. Moreover, psychotic reactions to khat are rare and psychiatric institutions do not report a frequent admission of patients with khat related psychiatric disorders. Obviously though, like other illicit psychostimulants, the use of khat is contraindicated in subjects with an increased psychiatric susceptibility. Moreover, in the Netherlands no criminal activities and no fatal accidents related to khat use have been observed and its prevalence is stable.

Quite alarming is the high prevalence of oral, head and neck cancers in khat users. Considering the low prevalence of khat use in the Netherlands, the impact of this adverse effect is estimated as low. On the other hand, this severe disease remains a critical effect of khat use. This further implies that the adverse risk of khat use may be significantly higher in those countries where khat is used much more frequently. Similarly, this may be the case in countries where khat is used under depraving socio-economic conditions such as poverty, social isolation, state of war, high criminality and persecution.

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