

Overview of literature and information on “khat-related” mortality: a call for recognition of the issue and further research

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Summary. During the past 20 years or so, more has become known about the properties of khat, its pharmacology, physiological and psychological effects on humans. However, at the same time its reputation of social and recreational use in traditional contexts has hindered the dissemination of knowledge about its detrimental effects in terms of mortality. This paper focuses on this particular deficit and adds to the knowledge-base by reviewing the scant literature that does exist on mortality associated with the trade and use of khat. We sought all peer-reviewed papers relating to deaths associated with khat. From an initial list of 111, we identified 15 items meeting our selection criteria. Examination of these revealed 61 further relevant items. These were supplemented with published reports, newspaper and other media reports. A conceptual framework was then developed for classifying mortality associated with each stage of the plant's journey from its cultivation, transportation, consumption, to its effects on the human body. The model is demonstrated with concrete examples drawn from the above sources. These highlight a number of issues for which more substantive statistical data are needed, including population-based studies of the physiological and psychological determinants of khat-related fatalities. Khat-consuming communities, and health professionals charged with their care should be more aware of the physiological and psychological effects of khat, together with the risks for morbidity and mortality associated with its use. There is also a need for information to be collected at international and national levels on other causes of death associated with khat cultivation, transportation, and trade. Both these dimensions need to be understood.

Key words: khat, qat, *Catha edulis*, mortality, death, review.

Riassunto (*Rassegna della letteratura a delle informazioni relative alla mortalità correlata all'uso di khat; necessità di maggiore allerta e di approfondimento scientifico*). Nel corso degli ultimi 20 anni, è aumentato il livello delle conoscenze relative alle caratteristiche farmacologiche, fisiologiche e cliniche associate al consumo di khat. Nel contempo, tuttavia, i livelli elevati di disseminazione della sostanza in contesti tradizionali hanno in qualche modo limitato la diffusione delle conoscenze relative alla mortalità associata all'uso del prodotto. L'articolo prende in rassegna la scarsa letteratura dedicata all'argomento, analizzando innanzitutto i lavori pubblicati su riviste peer reviewed. Da una lista iniziale di 111 articoli, sono stati selezionati 15 lavori che soddisfacevano ai criteri di inclusione. In seguito all'esame di questi lavori, sono stati identificati altri 61 documenti di interesse, oltre ad altri report ed articoli di giornale. Viene qui proposto un approccio contestuale per la classificazione della mortalità associata ad ogni stadio del “percorso” della pianta: coltivazione, trasporto, consumo, effetti sul corpo umano. Vengono inoltre illustrati e commentati alcuni esempi che affrontano una serie di problematiche, che richiederebbero un maggiore approfondimento scientifico. Di qui la necessità di condurre studi di popolazione relativi alle determinanti sia fisiologiche che psicologiche legate alla mortalità da khat. Le comunità in cui si consuma tradizionalmente il khat, ed i professionisti della salute di queste popolazioni, dovrebbero tenere in maggiore considerazione gli effetti fisiologici e psicofarmacologici del khat, assieme ai rischi di morbilità e mortalità correlati al suo consumo. Vi è inoltre la necessità di raccogliere maggiori informazioni sia a livello nazionale che internazionale relative a queste tematiche.

Parole chiave: khat, qat, *Catha edulis*, mortalità, morti, rassegna.

INTRODUCTION

Botany and chemistry

Khat is a herbal product consisting of the leaves and shoots of the shrub *Catha edulis* Forsk, a member (genera) of the evergreen Celastraceae (moonseed or spindle-tree) family or tribe [1]. Under natural conditions, khat grows in and on the margins of dry evergreen forest and mist forest. It grows naturally at elevations of 1500-2000 m but is found at altitudes of 1200-2500 m. It is best cultivated at high elevations, with high rainfall in acidic, well-drained clay soils; but can survive long periods of drought. Khat's natural range extends throughout East Africa from Ethiopia, Eritrea and Somalia, through to South Africa; it is also found in Rwanda, Zaire, Malawi and Zimbabwe. *Catha edulis* is also found sporadically in Afghanistan, Israel, Saudi Arabia, Syria and Turkistan [2, 3]. In Arabia, it is found principally in the Yemen. Khat grows in clumps, in beds or rows; often mixed in or interspersed with other crops, such as coffee and conifers, when cultivated. The primary areas for cultivation remain Eastern Africa – mainly Ethiopia, Kenya and to a lesser extent the Comoros, Madagascar and Tanzania - and the Arabian Peninsula, especially Yemen.

Fresh leaves of khat contain the alkaloids of the phenylpropylamine type of which the two psychoactive constituents are the stimulants cathinone (S-(-)- α -aminopropiophenone) and cathine (S,S-(+)-norpseudoephedrine). The psychoactive substances in khat act on two main neurochemical pathways – dopamine and noradrenalin. It has been suggested that cathinone, like amphetamine, releases serotonin in the CNS. Both these substances induce the release of dopamine from CNS dopamine terminals thereby increasing the activity of dopaminergic pathways [4]. Cathinone is a more powerful stimulant than cathine and is generally regarded as the most important element. However, cathinone is unstable in the presence of oxygen, oxidising at room temperature, and decomposes within a few days of harvesting or if dried [5]. The stored product loses activity rapidly, becoming physiologically inactive after about 36 hours. For maximum potency, khat must be picked in the morning and chewed that afternoon [6].

Pharmacology

The psychotropic effects of khat are caused by the amphetamine-like compounds. Although amphetamine and cathinone act on different parts of the brain, they share common effects, including an interaction with the dopaminergic pathways [7]. Central stimulation by khat is manifested by euphoria, increased alertness, garrulousness, hyperactivity, excitement, aggressiveness, anxiety, elevated blood pressure, and manic behaviour. The stimulation lasts for about 3 hours [8]. A depressive phase, including insomnia, malaise, and a lack of concentration, almost always follows [9, 10]. True psychotic reactions occur with much less frequency than with amphetamines. This is most likely because of the self-limiting dose of khat, which does not permit blood vessels of the active compounds to rise high

enough for toxic psychosis to occur. However, paranoid delusions, usually persecutory, have been seen [11].

Several case studies have described *Catha edulis*-induced psychotic conditions [12-15]. Psychotic behaviour induced by khat use is sufficiently common in the khat-growing areas of eastern Ethiopia to have acquired a designated term – *jezba* [16]. In many instances, such psychoses disappear within a few days if khat consumption is stopped and/or anti-psychotic treatment initiated. However, recidivism typically results in a return of symptoms. However, the relationship between use of khat and psychiatric problems has been little explored by population-based studies.

It has been postulated that khat use can exacerbate psychotic symptoms in individuals with pre-existing conditions, and precipitate psychiatric disorders in vulnerable subjects [15]. Some commentators suggest that it is not clear whether khat use may cause a psychotic disorder in an otherwise healthy individual or trigger the onset of schizophrenia in an individual with high vulnerability to the condition [17, 18]. There have been suggestions that khat chewing exacerbates symptoms in patients with pre-existing psychiatric conditions; possibly caused by the sympathomimetic actions of cathinone on the CNS [10]. Odenwald *et al.* [19] propose that it is not khat consumption per se but specific patterns of its use are associated with the development of psychotic symptoms: early onset in life, excessive chewing (more than 2 bundles per day), and use as self-medication for war trauma-related symptoms. Other studies have found morbidity increased when daily consumption exceeds two bundles [20] or are dose-related [13, 21]. A recent review of the literature on the relationship between khat use and mental illness in general found that only clinical case studies revealed a causal connection between excessive khat use and psychosis. Such studies are unsuitable for providing evidence as to causality. A few case-control studies found an interaction between khat use and mental disorder but the findings were inconclusive. To date there have been no large-scale studies examining the relationship between dose-effect of khat and mental illness [22].

There is some debate as to whether or not *Catha edulis* can actually cause dependence. Physical dependence to khat does not occur. The available literature suggests that it is likely that khat use has the potential to develop into dependence [23]. However it seems this is much less likely than dependence on stimulants such as amphetamine and more like the type of dependence seen with caffeine. The vast majority of people who chew khat do not use in a dependent fashion and there is no evidence of more widespread drug misuse amongst khat users. Development of tolerance to the effects of cathinone is more rapid than to that of amphetamine, and there is cross-tolerance between cathinone and amphetamine [24, 25]. When a chronic khat chewer stops he feels hot, especially in the lower extremities, lethargic and with a great desire to chew khat in the first two days after cessation. Other documented withdrawal symptoms include

nightmares and slight trembling, which appear several days after ceasing to chew [26].

Context of khat use

It is important to ensure, so far as possible, that phenomena related to khat consumption are considered in the context of individuals and their environment(s). Other factors may impact on usage patterns and thus risks of both mental and physical health issues. A number of factors may be involved in the different patterns of use in the new countries of settlement of groups like Somalian refugees, especially younger generations. Economic, political, and social upheaval in such countries of origin has led to a large influx of traumatised individuals, often with little or no education. Young refugees enter an alien educational system, frequently exiting without qualifications that will afford them good employment opportunities. This leads to frustration and a lack of sense of direction. These factors make them vulnerable to the use of alcohol, tobacco and other psychoactive substances. Further, life in a new environment with different cultural and social contexts can be stressful and reinforce the need for the use of such substances [27].

Some research points to higher use amongst Somalis who are refugees or immigrants than in their native country. Bashford *et al.* [28] suggest that cultural dislocation within the Somali refugee community may play a role in initiation into drug use, and “lead individuals to seek khat as a refuge” *i.e.* as a method of self-medication to mediate stress (although also prolonging and adding to existing stress). Alcohol and drugs play a role in “killing time” for asylum seekers, and helping to forget past trauma [29]. Many start using before coming to the UK, but a significant proportion after their arrival – perhaps to help compensate for the sense of isolation, uncertainty about the future, unemployment, etc. [5, 30-35].

In the past the use of this plant was geographically limited to these areas because it loses its efficacy after a few days. However, with developments in communications and transportation, especially by air, and the migration of khat-using communities to other continents, its use has spread over the last two decades. Large shipments of khat now arrive several times a week at major airports in western Europe, including the British Isles, as well to North America and Australia.

Scientific knowledge about khat

During the past 20 years or so, more has become known about the properties of khat, its pharmacology, physiological and psychological effects on humans. However, at the same time its reputation of social and recreational use in traditional contexts has hindered the dissemination of knowledge about its detrimental effects in terms of mortality. This aspect of the potential harms of khat has received little attention in the past and no systematic treatment or discussion. This paper focuses on this particular deficit and adds to the knowledge-base by reviewing the scant literature that does exist on mortality asso-

ciated with the trade and use of khat. With khat being increasingly brought under domestic regulation in many countries, and its legal status being considered in others, it is important that such aspects are not overlooked so that balanced assessments can be taken based on evolving knowledge. It is hoped that this information will be noted by policy-makers, khat-using communities, and health professionals who deal with khat users. Deaths are associated with the trade in khat as well as from its consumption. Both these dimensions need to be understood.

This approach could also be applied to other substances, but is used here to generate awareness of the range of potential contexts in which khat cultivation, transportation, trade and consumption can lead to fatalities. This paper is not just about pharmacology, toxicology, etc. but is about the wider phenomenon of deaths linked with a particular substance – khat.

The specific aims of this paper are to: a) create a framework for discussion around the topic of khat-related death by generating a broad-based definition; b) suggest dimensions of phenomena/aspects to consider without *a priori* theoretical paradigms/mindsets; c) elucidate such dimensions by means of theoretical and actual examples.

Apart from our own paper looking at a series of 12 khat-related fatalities in the UK [36], there are no known published reviews of, or statistics on, khat-related mortality howsoever defined. This is an important gap in the knowledge-base. This paper is an overview of what has been reported.

METHODOLOGY

We undertook a literature search of all relevant databases as well as the Internet to identify relevant reports and information on “khat-related” mortality. The databases searched included: Medline, PubMed, psycINFO, Public Library of Science (PLoS), Embase, INGENTA, African Journals on Line, Web of Science Citation Index, Allied & Complementary Medicine Database (AMED), the Cumulative Index to Nursing and Allied Health Literature (CINAHL®), Science & Social Science Citation Index, Cochrane, Toxnet and Google Scholar™ (2009) search engine. As khat is known by several names, these were also included as text search terms: cat, *Catha edulis*, chat, herbal ecstasy, jaad, khat, miraa, m(a)irungi, qaad, qat, tschat. The terms for the principal psychoactive substances were also employed: cathine, cathinone, and (nor)pseudoephedrine. The search terms in relation to mortality were: chok*, death, fatal*, intoxication, lethal*, mortality, overdose, poison*, suffocat*, toxic* – where * denotes wildcards. All of these sets of terms were systematically used in combination to conduct the searches.

These terms were used in English and also translated into other major European languages (*e.g.* Dutch, French, German, Italian, and Spanish); documents that were written in English or in other major

European languages were examined, as well as abstracts written in those languages. Where necessary, on-line Internet translation engines (e.g. Babel Fish and Babylon) were employed to translate some of the search terms. Since it is possible that some reports and abstracts may not be available in non-Roman scripts, especially those relating to regions in Arabia, the search terms were converted to Arabic using *Babylon*® before conducting the research; the results were then translated back into English. This method of on-line translation appears to have identified satisfactorily many relevant sources. The resultant titles and abstracts were then verified for inclusion. The time period covered was up to April 2011.

The database searches led to 111 hits in total. Papers in peer-reviewed journals, conference abstracts/posters, and studies from governments and non-governmental organisations that contained information on a link between khat and death were all eligible for inclusion in this review: specific incidents of deaths or fatalities; proposition of explanations for factors leading to death as a result of khat trade or consumption. Items were excluded because they: related to “cell death”; concerned original laboratory experiments; matched an irrelevant text word search; items identified did not relate to the khat plant but other topics such as “khat” the ancient Egyptian concept of death, or were otherwise unconnected with the study parameters. Other reasons for ignoring items were where suggestions were vague, unsubstantiated, or misinformed. After exclusion, a final figure of 29 relevant items was obtained: of these, 14 were excluded because of duplication. Due to the paucity of relevant peer-reviewed items so identified, backward and forward citation tracking and cross-reference checking were also conducted.

Non-peer-reviewed resources were also included in the Internet searches because exploratory work revealed that data-driven literature on our search topic was very limited. However, it has to be recognised that these were “snapshots” at specific points in time, the items may be ephemeral and no longer accessible. They may also have produced hits of grey literature that were not covered by the databases searched. This additional strategy led to a further 61 relevant articles being identified. So as not to be too restrictive in our research, it was also necessary to draw on media reports identified by Internet searches to illustrate various types of deaths associated with khat trade and consumption since these are not included in the above databases. Some of these references were provided by personal contacts.

There are risks in using anecdotal sources of information, as they are not always subject to scientific rigour in terms of reporting and interpretation. This has the potential to weaken the robustness of the information presented. However, such data provide a means of filling the lacunae in knowledge until such time as more robust information is generated. For a more detailed discussion of the use of such data see Corkery *et al.* [36].

There is a range of deaths that can be directly and indirectly associated with khat, some of which can overlap. Different approaches could be employed to describe the links between khat and death, including a purely medical one concentrating on physiological, pharmacological and psychiatric issues. Since the aim of this paper is to broaden the theoretical conceptualisation of what might constitute a “death related to khat”, it is important to think outside the restricting confines of existing paradigms, especially those based on the “medical model”.

In order to assist an understanding of the different dimensions of this phenomenon it is necessary to derive themes or “motifs” emerging from the results [37]. This study looked at phenomena to describe types of deaths and their potential associations with khat, without being based on any *a priori* hypotheses or preconceptions, in order to see what emerged. Such a phenomenological approach is robust in demonstrating the presence of factors and their effects, but can only be tentative in suggesting their extent in respect of the sample population from which cases are drawn.

FINDINGS

Following the journey of khat from its start to finish, from cultivation to consumption, provides a useful vehicle to identify such themes and to derive a taxonomy. *Table 1* summarises the themes and categories that emerged from this process. The taxonomy is based on context(s) in which death occurred or was caused, e.g. its aetiology and manner of occurrence, based on the observation of reported incidences/events and *post hoc* abstraction from observed phenomena.

Trade-related cultivation / production

There is concern that people who do not wash khat before consuming it will ingest pesticides [38]. Such pesticides contribute to cancers of the digestive system and kidney failure among khat chewers [39]. Deaths have been reported that were caused by poisoning following the ingestion of pesticides/fertilisers used in the cultivation of khat [40-42].

Leaves are normally chewed fresh without any treatments (such as washing, soaking in hot water, or thermal treatments) to reduce the concentration of such chemicals, both in producing and consuming countries. For instance, an analysis of khat grown in different parts of Ethiopia in 2009 found excessive levels of pesticide residues in some producing areas [43]. Diazinon levels in Jimma were found to be 462.6 µg/kg (range 173.9-751.4 µg/kg) compared to the level of 10 µg/kg set for vegetables and fruit by the European Union (EU). The average total amount of DDT and metabolites was found to be 755.57 ± 394.0 and 709.0 ± 457.9 µg/kg respectively for Hararge and Butujera. Maximum levels found were between 240 and 1200 times the EU maximum recommended levels for foodstuffs (vegetables 10 µg/kg, cereals 50 µg/kg). The use of organochlorine

Table 1 | Taxonomy of “khat-related” mortality

Directness	Type of association	Mechanism	Example
Trade-related			
	Cultivation/production	Poisoning	Fertiliser/Pesticide not washed before consumption
		Disputes between actors	Disagreement over wages = > homicide – possibly aggravated effects of khat chewing clouding judgement and triggering aggression
	Transportation	Fatigue	Long hours and driving at high speed = > loss of concentration (can be in association with khat use to keep awake) leading to accidents
		Loss of concentration	Distraction whilst preparing khat for chewing whilst driving = > accidents
		External factors	Bad weather conditions/ mechanical failure = > plane crashes
		High speed	High speed trying to escape from law enforcement officers = > collision => fatal injuries
		High speed & mechanical failure	High speed, over-loaded vehicle, faulty brakes = > failing to negotiate bend in road = > fatal accident
	Distribution/ marketing/ wholesale	Disputes between actors	Fighting over “turf” = > violence and homicide
		Disputes between actors	Refusal to do business = > violence and homicide
		Disputes between actors/theft	Possible fighting over “turf” or theft going wrong = > homicide
	Retail	Disputes over price	Homicide – possibly aggravated effects of khat chewing clouding judgement and triggering aggression
		Violence in khat markets/terrorism	Detonation of hand grenade in khat market; militia firing guns indiscriminately into crowds; suicide bomber exploding explosives immediately after chewing khat
	Law enforcement agencies	Execution	Beheading for possession and use of khat
		Hot pursuit	Smuggler trying to escape border guards
	Drug control	Opposition to imposition of ban on khat importation	Protestors against ban fired on by militia enforcing ban
		Breach of drug controls	Trader killed by militia enforcing khat-selling restrictions
Consumption-related (medical)			
	Physiopathological	Mechanical	Choking on leaves/twigs or airway obstruction = > asphyxia or cardiac arrest
		Toxicity	Myocardial infarction = > fatal heart attack Liver failure
		Cancer related to khat use	Oral & other cancers caused by khat chewing = > death
		Endocarditis related to khat chewing	Streptococcal bacterium <i>Gemella morbillorum</i> being ingested while khat chewing = > endocarditis = > death
		Reproductive health issues	Teratogenicity/low birthweight = > perinatal & young infant mortality
	Neurological	Lack of motor co-ordination, shaking	Reduces control = > accidents
		Eye-sight problems	Impairs sight and focus = > accidents
	Psychopathological	Causing and/or exacerbating psychosis and/or depression	Suicide and/or homicide, accidental overdose
		Increases aggression and notions of personal supremacy	Violence in Somalian civil war = > homicide; fighting over khat air-freight deliveries
		Impaired judgement/ assessment of risk = > accidents	Road traffic accident
		Impaired judgement/ intoxicating effects	Misunderstanding/misinterpretation of others’ motives/actions = > offending others = > retaliation involving fatal assault Fall from height
	Other medical contributory factors	Used with other psychoactive substances and/or positive toxicology	Role may not be clear
		Cerebral haemorrhage	
		Ischaemic stroke	

Note: This is a theoretical framework based on the findings of this research, and is subject to revision as new information is reported. Its aim is to provide a starting point for debate and refinement.

pesticides has been attributed, in part, as contributing to the incidence of oral and oesophageal cancers amongst khat chewers [26, 43].

Some patients have been admitted to hospital in Yemen after chewing poisoned khat and within 3 days they have experienced jaundice, coma and sometimes death [44]. The sudden death of some previously healthy young people in Yemen while chewing khat sprayed with insecticide (such as dimethoate) may be explained by the accumulation of acetylcholine from the poison in the heart and brain involving bradycardia and cardiac arrest [45]. No such cases have been reported in the UK. Clearly, farmers and their workers applying pesticides to khat and other inter-spaced crops may also be at risk. One example cited is that of a self-inflicted poisoning where a farmer ingested the pesticide to show others that it was harmless [46]. Parasitic infections, such as fascioliasis, can also be transmitted through the consumption of contaminated khat [47, 48].

At least one violent death associated with disputes between khat-pickers over wages has been reported [49]. As is the case with other substances, khat can lead to the mind becoming overactive and exaggerating problems, with attendant misunderstanding or misinterpretation of the motives and actions of others. Chewers can become anxious, excited and display an aggressive attitude. Such effects on perception and mood during the intoxicated phase can last about three hours [8]. After this stage, a depressive phase almost always follows [9, 10]. Users come to realise in the cold light of day that what they thought or believed during the khat session was incorrect and not thought through, and they often regret what they said or did.

Drug control

There is a body of evidence that supports the suggestion that drug law enforcement activities can contribute to drug market violence and increased homicide rates [50]. For example, the imposition by Islamic militia in Somalia of bans on importation of and trading in khat has led to deaths. Opposition to the banning (by the Union of Islamic Courts) of importation of khat by air into Mogadishu in November 2006 by khat traders resulted in shots being fired to disperse protestors. At least one person was killed during the incident [51, 52]. Similarly in November 2008 when a local militia took up arms to protest against a ban on khat by radical Shehab fighters imposing Sharia law in Eldher town (350 km north of Mogadishu) the ensuing clash led to the two lives being lost by both sides [53]. Breach of controls designating where khat trading should take place resulted in a trader being shot dead by a Hizbul-Islam militiaman in Afgoye. The trader had refused to sell the product in a designated market on the town's outskirts [54].

Distribution, marketing, wholesale, retail

Deaths related to the trade in khat have occasionally been reported by the media. For example, in the UK,

several members of the Chohan family were murdered by gangsters attempting to take over an air-freight company which imported khat into the country; the gangsters sought to use the company as a front for trafficking illicit drugs within the European Union [55]. In the USA, a female vendor/dealer was killed and her money and plants stolen during a robbery [56-61]. A similar fate befell a Somali dealer in England in 2002, when he was attacked and stabbed several times and left to bleed to death by members of a rival clan who then stole his khat and sold it. However, it was unclear as to whether this was a fight over "turf" or a robbery that went wrong [62].

Deaths have occurred much nearer the source countries. In the Somali region of Ethiopia a vehicle transporting khat was attacked by members of a different clan who intended to steal the cargo; in retaliation, the khat trader's clan killed two relatives of the thieves [63]. Drug cartels in Kenya now control much of the transportation of khat from Kenya to Somalia; new entrepreneurs trying to establish themselves are permanently prevented from being in competition [64]. Even consumers of khat face danger of death for failing to share it [65-67], or to agree a price [63].

Deaths have also occurred in khat markets as a result of violence and accidents involving hand grenades [68-71]. In another incident, a suicide bomber had been chewing khat immediately before detonating explosives that killed innocent by-standers [72]. In other instances in markets, disputes over sales have led to children selling khat being killed [71].

Transportation

Fatalities have occurred whilst khat has been transported by air. For example, in May 2004 a plane flying from Nairobi, Kenya, to Mogadishu, Somalia, carrying 55 bags of khat weighing 1.5 tons collided in mid-air with another plane. It crashed in an open field in Kenya killing the two occupants [73, 74]. In August 2008, another aircraft en route with 5.4 tons of khat from Kenya to an airport 50km south-west of Mogadishu struck a telecommunications antenna during bad weather on its approach. It crashed killing all three crew members [75, 76]. More recently, a plane carrying khat from Kenya to Mogadishu crash-landed shortly after take-off from Wilson Airport in Kenya, having developed mechanical problems, killing the two co-pilots [77, 78].

The need to transport khat to markets as rapidly as possible, so that the produce arrives on time and *fresh*, leads to those transporting them in vehicles to drive at dangerous speeds, on poor roads, in over-loaded, and poorly-maintained vehicles – often with fatal results [69, 79-80]. In many countries where khat is grown and chewed, there is a lack of reliable official road traffic accident data; furthermore, there is poor appreciation of the extent and significance of road accident fatalities. For Yemen, for example, it was possible to derive a causal model for such events taking khat into consideration [79]. An examination of available data for the period 1978-95 showed that khat consumption in-

creases the risk of road traffic fatalities. The authors concluded that this was due to two factors: the anxiety and tensions that are experienced by khat chewers several hours after consumption; and, drivers consuming khat are often busy drinking water, smoking, or preparing and cleaning khat leaves whilst actually engaged in driving. These factors lead to decreased attention to driving and increased likelihood of accidents, especially on rural surfaced roads where drivers tend to drive faster.

Qualitative research from Ethiopia points to the chewing of khat as a major contributor to road traffic accidents, and hence potential fatalities. It increases driver confidence and vehicle speed, and simultaneously makes those drivers irritable and impairing concentration, with a misplaced sense of alertness [81]. Research on African/Middle Eastern drivers stopped by German police on suspicion of driving under the influence of drugs found driving ability severely reduced by khat consumption in some cases, whereas in others it had no noticeable effect [82]. However, because of concerns about the possibility of impairment, Ethiopian law implicitly makes it an offence to drive under the influence of khat [81]. There is still no clear evidence from population-based studies of a causal relationship between khat chewing and fatalities arising from road traffic accidents; however, the potential for khat to impact on driving and flying does exist.

Law enforcement agencies

In other instances, drivers have been killed in accidents trying to escape from law enforcement officers [83]. Smugglers also risk death when encountering guards at borders with countries which prohibit the possession, use and sale of khat [84]. It has been reported that in at least one country, capital punishment had been imposed in the past on a woman who was in possession of, and had used, khat [85, 86].

CONSUMPTION-RELATED

This section draws on a case-series of UK deaths associated with the use of khat, summarised in *Table 2*. Details of 13 out of the 15 cases have been previously described [36].

Mechanical

Through communication with various experts we have been informed of several mechanisms of deaths arising from khat use that are familiar to physicians and the public in Yemen, but no research has been undertaken or cases documented in the literature. The mechanisms described are: a) a very strong irritation from substances in khat that causes a laryngeal spasm; and b) whilst chewing, a piece of khat gets stuck in the trachea and cannot be dislodged by repeated coughing. Both types of incident can lead to choking and asphyxia. There have been isolated reports from Yemen of deaths resulting from individuals choking on khat. An 11-year old boy choked to death while playing soccer with a wad of khat in his mouth [87]. A male pa-

tient got khat (smuggled into the hospital by his wife) stuck in his trachea and choked to death [88].

Toxicity

We have been able to identify only one previously reported death from medical complications directly related to the use of khat in the literature or from surveys of contacts in the European Union, the eastern Mediterranean and Arabian Gulf regions. The solitary death was a case study reported over 60 years ago by Heisch [89] who described the death from poisoning by *Catha edulis* of an elderly Arab trader in Wajir, Northern Kenya, after consuming an excessive amount of miraa stalks. The man was admitted to hospital and exhibited a number of symptoms including dilation of the pupil, cold sweats, convulsions, and hyperaesthesia. He fell into a coma (clinical observation) and died after 4 days. A post-mortem showed that the stomach was full of khat. Death could not be attributed to any cause other than khat consumption. Substantial advances in toxicological and medical knowledge have been made since then, but attribution can still be difficult in some cases. However, several deaths in the UK due to medical complications following the consumption of khat have been reported to or identified by the National Programme on Substance Abuse Deaths (np-SAD). These cases, including relevant discussion of mechanism of death for these as well as psychopathological factors, are described in more detail in a complementary paper [36]. Three of these were previously briefly described [90, 91]. No deaths relating to khat toxicity as overdose have been reported, but cases due to its toxic effects are now known.

It is thought that khat produces acute myocardial infarction in some patients and triggers such events in others, leading to fatal heart attacks. Ten out of twelve male Djiboutis treated for haemorrhagic stroke between September 2005 and March 2007 were daily consumers of khat, nine of whom also smoked [92]. A clinical study of 120 Yemeni patients with myocardial infarction showed that khat chewers were three times more likely to have experienced such an event than non-chewing controls [93]. A multi-centre study of 8176 patients presenting to hospital with acute coronary syndrome in 6 Middle Eastern countries found that 11.4% were khat chewers (mostly of Yemeni origin and male). At admission, usually more than 12 hours after onset of symptoms compared to non-khat chewers, khat consumers had higher heart rate, Killip class and Global Registry of Acute Coronary Events risk scores. Khat-chewing was an independent risk factor for an in-hospital death (Odds Ratio 1.9, CI 95% 1.3-5.9, $p < 0.001$) and stroke (OR 2.7, CI 95% 1.3-5.9, $P < 0.01$) [94]. The incidence of myocardial infarction increases after chewing khat, demonstrating that it is a risk factor for this medical condition.

One mechanism suggested for this is the increased release of catecholamines triggered by the cathinone content of khat, leading to hypertension and acute myocardial infarction [9, 95-100]. Cathinone, and to a lesser extent cathine, appears to act on the beta-1

adrenoceptor causing increased systolic blood pressure and pulse rate. However, these effects can be prevented with the use of beta-blockers such as atenolol [101]. Khat use is associated with acute coronary vasospasm and myocardial infarction [9, 97]. Coronary vasospasm, induced by the cathinone in khat, causing vasoconstriction may occlude coronary arteries sufficiently to precipitate myocardial infarction.

Increased thrombogenicity could also be a key factor for myocardial infarction [102]. Differences in diurnal

patterns of acute myocardial infarction have been observed between non-khat users and khat users, with peak presentation amongst the second group shifting to the late afternoon and evening, coinciding with khat chewing sessions – 2 pm to midnight [26, 97]. It has been suggested that the cathinone content of khat is an independent dose-related risk factor for the development of acute myocardial infarction; heavy chewers having a 39-fold increased risk [98]. The risk of acute myocardial infarction is also increased when the khat “session” lasts

Table 2 | Main characteristics of np-SAD “khat-related” deaths, UK, 2004-9

Characteristic	Case				
	1	2	3	4	5
Year of death	2004	2004	2005	2005	2005
Age (years)	39.1	32.5	40.2	47.0	27.3
Gender	Male	Male	Male	Male	Male
Ethnicity	Somali	Somali	Somali	Somali	Somali
Marital status	Separated	Divorced	Married	Married	Single
Living arrangements	Alone	With sibling	With partner & children	Alone	Alone
Employment status	Unemployed	Invalidity/sickness benefits	Unemployed	Unemployed	Unemployed
UK residency (years)	11	15	Not known	11	3
Significant medical history	No	Yes	No	Yes	No
Known psychiatric history	Yes, at least 11 years	Yes	No	Yes	No
Known khat using history	Yes	Yes	Yes	Yes	Yes
Evidence of using khat prior to death	No	Yes	Yes	No	Yes
Place of death	Underground station	Car park	At home	At home	At home
Role of khat in death	Paranoid psychosis associated with history of khat use => traumatic suicide (none in body at death)	Possible suicide/accidental fall whilst judgement impaired (found in body)	Possible history of excessive use => traumatic murder and traumatic suicide	Paranoid schizophrenia exacerbated by khatting => accidental overdose	Ingestion of khat => high norephedrine levels => left ventricular failure => pulmonary oedema
Toxicology done	Yes	Yes	Yes	Yes	Yes
Toxicology results	Blood – negative; urine – negative	Blood-cathinone 104 µg/L; norephedrine/norpseudoephedrine (total) 154 µg/L; zuclopenthixol 123.8 µg/L	Blood-cathinone “low”, cathine “moderate”; consistent with “recreational use”. Urine – Cathine and cathinone detected	Blood – negative. Urine – negative	Blood-cathinone < 50 µg/L; norephedrine/norpseudoephedrine (total) 1000 µg/L. Urine-norephedrine/norpseudoephedrine detected
Cause(s) of death	1a Severe chest, abdominal and pelvic injuries	1a Multiple injuries [severe multiple injuries, impact onto a firm surface, fall from a height]	1a Hanging 1b Stab wounds to neck	1a olanzapine toxicity	1a Acute pulmonary oedema [left ventricular failure, high norephedrine levels] 1b ingestion of khat
Verdict	Act of self-harm	Open	Suicide	Accidental	Narrative
Coroner’s area	West London	Inner West London	Inner North London	Cardiff & Vale of Glamorgan	Northern London

Continues

Table 2 | (Continued)

Characteristic	Case				
	6	7	8	9	10
Year of death	2006	2006	2006	2006	2008
Age (years)	36.5	21.9	41.5	37.8	29.9
Gender	Male	Male	Male	Male	Male
Ethnicity	Somali	Eritrean	Somali	Somali	White (Polish)
Marital status	Married	Single	Not known	Not known	Not known
Living arrangements	With partner & children	Psychiatric unit	Self & children	Alone	With friends
Employment status	Unemployed	Student	Not known	Mini-cab driver	Employed (manual)
UK residency (years)	7	8	Not known	Not known	Not known
Significant medical history	Yes	No	No	Not known	Not known
Known psychiatric history	No	Yes	No	Not known	Not known
Known khat using history	Yes	Yes	Yes	Not known	Not known
Evidence of using khat prior to death	Yes	No	Yes	Yes	Yes
Place of death	Hospital	Hospital	Road	Road	At home
Role of khat in death	Long term khat use => hepatic necrosis => sub-fulminant liver failure	Drug-induced psychosis/psychosis exacerbated by use of "skunk" and khat over long period => traumatic suicide	Ingestion of khat (possibly no longer active), alcohol consumption => intoxication, impaired judgement/lack of co-ordination => traumatic road traffic accident (pedestrian)	Alcohol and khat in system => impaired judgement/co-ordination => loss of control of vehicle => traumatic road traffic accident (driver)	Overdose of injected heroin, but khat also in system
Toxicology done	No	Yes	Yes	Yes	Yes
Toxicology results	Not applicable	Blood – negative Urine – negative	Blood-ethanol 185 mg/100 mL. Urine-ethanol 235 mg/100 mL; cathinone detected; norephedrine/ norpseudoephedrine detected	Vitreous humour- alcohol 210 mg/100 mL; cathinone 110 µg/L; cathine 310 µg/L	Blood - alcohol 47 mg/100 mL; 6-MAM, morphine 0.24 mg/L; codeine 0.01 mg/L; cathinone < 25 µg/L; norephedrine/ norpseudoephedrine (total) < 50 µg/L. Urine- alcohol 79 mg/100 mL; codeine detected; cathinone detected; norephedrine/ norpseudoephedrine detected
Cause(s) of death	1a Sub fulminant liver failure 1b Hepatic necrosis 2 Khat toxicity	1a Multiple injuries	1a Chest injuries	1a Multiple injuries	1a Morphine intoxication
Verdict	Accident	Act of self-harm	Narrative	Accident	Non-dependent abuse of drugs
Coroner's area	Inner North London	West London	Southampton & New Forest	Northern London	Northern London

Continues

Table 2 | (Continued)

Characteristic	Case				
	11	12	13	14	15
Year of death	2008	2008	2008	2009	2009
Age (years)	34.5	22.2	19.3	41.0	31.9
Gender	Male	Male	Male	Male	Female
Ethnicity	Somali	Somali	Somali	Somali	Somali
Marital status	Not known	Not known	single	Not known	Married
Living arrangements	With partner	With cousin	Not known	With partner & children	With partner
Employment status	Unemployed	Unemployed	Student	Cab driver	Unemployed
UK residency (years)	Not known	15	Not known	Not known	4.5
Significant medical history	Not known	No	No	Not known	None
Known psychiatric history	Not Known	Not known	No	Not known	Depression, mental health issues, on prescribed medications but not being used
Known khat using history	Yes	Yes	Not known	Yes	Alcohol and drug abuse; chewed 2 bundles of khat, 2-4 times/week
Evidence of using khat prior to death	Yes	Yes	Yes	No	Yes
Place of death	Hospital	Hospital	Hospital	Hospital	Outside block of flats
Role of khat in death	Abused khat => jaundice, night sweats, pyrexia => sub-acute liver failure	Ingestion of alcohol & khat => intoxication => fighting => collapse => cardiovascular event. Khat may have triggered an infarction or electrical instability (arrythmia) causing death	Had consumed alcohol, cannabis & khat which may have contributed to his aggressive behaviour, leading to incident which triggered events leading to his assault and death	Excessive use of khat => fulminant hepatic necrosis => required liver transplant (failed)	Its psychotic effects or hallucinations may have led her to jump or its effects could have led to an error of judgement
Toxicology done	No	Yes	Yes	No	Yes
Toxicology results	NA	Blood-alcohol 240 mg/dL; cathine present; cathinone present. Urine-alcohol 309 mg/dL; cathine present; cathinone present; norephedrine present	Blood-alcohol 170 mg/dL; cathinone 0.019 mg/L; carboxy-THC 0.011 mg/L; phenylpropanolamine 0.1 mg/L	NA	Peripheral blood cathine 1447 ng/mL; cathinones 122 ng/mL
Cause(s) of death	1a Sub acute liver failure 1b Khat ingestion 2 Auto immune hepatitis	1a Unascertained	1a Severe head injury [consistent with impacts from heavy blunt object]	1a Pulmonary haemorrhage and multi-organ failure 1b Liver failure due to khat toxicity (orthotopic liver transplant) 2 Steatosis of the orthotopic (donor) liver transplant	1a Multiple injuries consistent with a fall whilst under the influence of khat
Verdict	Narrative	Open	Unlawful killing [attackers sentenced to life imprisonment]	Narrative	Accidental
Coroner's area	Northern London	Avon	West London	Inner North London	Northamptonshire

Note: these cases illustrate a range of deaths linked to khat consumption – from purely circumstantial to clear and unambiguous physiological causes.

more than 4 hours. Daily khat chewers are significantly more at risk, as are those whose use is recent and chronic. One study found that in those suffering from a myocardial infarction, khat use was associated with earlier age at presentation [97].

The np-SAD has been notified of the death of a young adult Somali male khat-user which was attributed by the pathologist to high norephedrine levels from khat inducing left ventricular failure with development of pulmonary oedema, which was regarded as mode of death [36]. Another young Somali male who had consumed khat and alcohol, and had assaulted another male, collapsed and had difficulty breathing. Cardio-respiratory resuscitation was started but on the way to hospital by ambulance he suffered a cardiovascular event and was pronounced dead. There was no underlying disease which could be attributed as having contributed to death. The pathologist could not exclude a contribution of khat to the cardiovascular event with either an infarction or electrical instability (arrhythmia) causing death. The positive toxicological findings for cathine, cathinone, and norephedrine meant that it was not possible to attribute death to Sudden Adult Death Syndrome. We are also aware of another, non-notified, death involving khat-induced myocardial infarction.

Khat can also produce acute myocardial infarctions by direct coronary vasoconstriction [95]. Rat studies conducted by Admassie and Engidawork suggest that frequent and chronic khat consumption may lead to transient but repetitive coronary vasoconstriction causing a reduction in blood flow and myocardial damage [103]. Myocardial oxygen demand is increased by increased heart rate, force of contractility and systolic tension which could not be associated with heightened levels of CK and AST – even though sub-chronic khat consumption, as these can lead to multi-organ damage. This is in line with findings of human liver and kidney damage reported by Chapman *et al.* [104] and Fallatah and Akbar [105]. Khat-induced ischaemic strokes have been identified in a number of case-reports [104, 106-107]. Such cardiac events can clearly lead to fatal outcomes, as evidenced by a recent study in the Middle East which found that Yemeni khat-chewing patients with Acute Coronary Syndrome had higher in-hospital complications including stroke and death [108].

Deaths and haemiplegia (paralysis of half of the body) because of meningeal haemorrhages are reported. The causal mechanism is ruptures of aneurisms following circulatory “coups de fouet” (rupture of the planteris muscle accompanied by sharp disabling pain) engendered by the use of khat [109]. A similar reported mechanism is cerebral haemorrhage, cardiac arrest and pulmonary oedema [100]. Cerebral haemorrhagic softening has also been described, although such cases are relatively rare [109]. Le Bras and Frétilière also note that when an individual is experiencing hyperthermia caused by khat consumption, death can occur following strenuous physical effort (such as playing sport) [109].

Administration of *Catha edulis* extracts has demonstrated a capacity to induce cytotoxic effects in liver and kidney cells, as well as cell death in various human leukaemia cell lines and peripheral human blood leukocytes [26]. Studies on animals have shown that khat is hepatotoxic with increases in liver enzymes and there has been histopathological evidence of acute hepato-cellular degeneration [110]. However, it has only been recently that clinical human case reports have been published [111, 112]. One case report suggested that hepatitis was probably due to right heart failure which in turn was possibly due to direct khat toxicity – as it did not respond to withdrawal of statins or proton pump inhibitors [112].

Until recently, there have been few documented cases of khat causing liver failure. However, evidence is now emerging of an association between khat consumption and liver problems, sometimes necessitating transplant, that result in death [104, 113-116].

A study of adults in Yemen with acute sporadic hepatitis with jaundice found that no viral cause was identified in half (51%) of the cases. Whilst there may be an unknown virus responsible or environmental toxins such as pesticides in khat leaves [117], liver function test abnormalities resolve when khat chewing is stopped. Young Somali males who chew khat appear to be particularly at risk of autoimmune hepatitis [113, 114], and liver disease [114].

Chapman *et al.* report that five out of six patients (four male, two female) had a history of previous unexplained hepatitis, all chewed khat and had been advised not to it all but resumed chewing before presenting a second time with liver problems [104]. Having been thoroughly screened, other causes of liver injury were excluded. All patients had multi-lobular necrosis and two had a background of chronic liver disease. These findings suggest that long-term use of khat may be associated with repeated episodes of sub-clinical hepatitis, with development over time into chronic liver disease. One patient subsequently died. There were no significant features to suggest an autoimmune or immunoallergic process in these cases, it was concluded that khat consumption was the aetiological cause of the liver injury in these individuals. Whilst the mechanism of khat-related hepatotoxicity remains uncertain, the presence of a high concentration of cathinone being detected in the liver of one patient three weeks after their last use of khat, suggests that the accumulation of the drug may be of significance.

Stuyt *et al.*, report 6 cases of long-term khat chewers who migrated from East Africa to the Netherlands that presented with liver injury [116]. Four presented with jaundice and hepatitis; one of these and two others had variceal bleeding and hepatic encephalopathy; two had clinical ascites. Three had auto-antibodies and elevated serum IgG. Other causes of liver disease were excluded. Three patients died from spontaneous bilateral peritonitis, sepsis and one case receiving a liver transplant died from pulmonary hypertension apparent during and after transplantation. These findings support the argument that long-term khat chewing can produce repeated

episodes of hepatitis (probably due to immuno-allergic or idiosyncratic) leading to fibrosis and cirrhosis.

np-SAD is aware of five deaths involving liver failure due to exposure to long-term khat consumption, three of which have been notified to np-SAD [36]. Of these, one case developed jaundice diagnosed as khat-induced hepatotoxicity which developed into recurrent khat-induced hepatitis, with pulmonary oedema and an enlarged heart; his condition developed into hepato-renal syndrome and sub-dominant liver failure [118]. A second case was admitted to hospital with jaundice, night sweats, and pyrexia which led to sub-acute liver failure; this was due to auto-immune hepatitis caused by his khat use. A third case was admitted to hospital suffering from fulminant hepatic necrosis due to khat toxicity; he had a liver transplant which was unsuccessful, and died of a pulmonary haemorrhage and multi-organ failure. Another case has been reported in the UK [114, 119]; and a further death was registered in October 2010 (personal communication to lead author from Frank Dixon, General Register Office for Scotland on 3 May 2011).

Cancer related to khat use

Keratotic white lesions are present in the mouths of about one-fifth of khat-chewers [120]. This change in pathology is recognised as pre-cancerous and may develop into oral cancer [121, 122]. Buccal epithelial cells experience genotoxic effects in a dose-related way in khat-chewers; this suggests that oral malignancies can be contributed to by khat [123].

There is an increased risk of oral carcinoma amongst khat chewers [124-126], especially when associated with alcohol and tobacco consumption [123, 125]. Khat has been found to be a significant contributory factor in the high prevalence of head and neck squamous cell carcinoma in the Yemeni population [127]. There may be a synergistic effect created by the consumption of alcohol, khat, and tobacco, leading to the development of changes in cells that can become cancerous [123].

Although oral cancers due to khat chewing occur and do lead to death, there do not appear to be any published statistics on such deaths. The few studies that have examined head and neck cancers and possible associations with khat-chewing have small sample sizes and the effects of using other substances are not controlled for. There is a need for large-scale case-control studies to gauge the strength of this possible association.

Endocarditis associated with khat chewing

A death from endocarditis caused by infection by a streptococcal bacterium *Gemella morbillorum* in a Djibouti male has been reported [128]. The bacterium had been ingested through the patient chewing khat. Despite treatment with anti-biotics, he developed pulmonary oedema requiring assisted ventilation, became asystole, and died 8 days after being hospitalised.

Reproductive health issues

The effects of khat consumption on the reproductive system, pregnancy and neonates have also been

noted. Khat is genotoxic, having teratogenic effects on the foetus if regularly consumed by pregnant mothers. Neonates have low birth weights – a risk factor for perinatal and young infant death [129-131]. Currently chewing lactating women have been found to excrete norpseudoephedrine in their breast milk, and traces were found in the urine of a breast-fed infant [132]. Cardiovascular complications amongst pregnant khat-chewing females have been reported: chest pains, tachycardia and hyperthermia [133].

Psychopathological

Khat use may be less psychogenic when integrated within its original cultural context than when taken in an unfamiliar setting after emigration. Many of the published reports relating to khat-induced psychoses concern individuals who have emigrated to Europe or North America, become culturally isolated and are in vulnerable socio-economic situations. However, this pattern may reflect a publication bias [134]. This is due to several factors. The ethnic populations in this region using khat have increased substantially over the past two decades, particularly because of the civil war in Somalia. In traditional khat producing and consuming areas, where health care services were/are lacking, those with psychotic symptoms would be confined to the home by family members [135]. Increasing reports of cases of khat-related psychosis in Europe and Australia [136] have led to more familiarity with “Khat syndrome” and consequent concern being expressed about it. In part, this may be attributable to the influx of refugees from war-torn countries such as Somalia, many of whom are suffering from trauma and who use khat [137]. It is likely that refugees from strife-torn parts of Somalia and elsewhere are likely to experience greater use of khat than previously realised [138]. This may be due to the added pressures experienced in living in a refugee community, distant from traditional patterns of life, leading to increased changes in behaviour [139]. In most European countries such individuals would be presenting to health services and their symptoms detected and they would be referred for treatment. The stressful life (and death) situations which many of these individuals had escaped have left psychological scars and damage that are self-medicated by means of khat.

Murders have been committed by individuals suffering from psychotic states aggravated or caused by khat. For example, there have been reports in the UK of individuals who, having experienced a psychotic illness as a result of khat consumption or where such consumption exacerbated an existing mental illness or depression, caused suicidal ideation, killed others and/or themselves [21, 140-143]. There has also been at least one further case of murder where the assailant was believed to be under the influence of alcohol and khat and inadvertently killed an innocent bystander instead of the intended victim [144, 145]. The use of khat can lead to aggressive behaviour [21, 142, 146-148], and impaired judgement or making mistakes [149].

Khat has had an effect on the fighting in the Somali civil war and combat related to military operations in

that country [150]. Aggression can be increased and notions of personal supremacy enhanced by khat use. Fighting over the delivery of khat at airports and children being shot over a 7kg bag of khat have been reported [151].

The np-SAD has been notified of three cases of suicide, including one following a homicide and an accidental drug overdose [36, 152-158], where the individual had a history of psychiatric problems, typically schizophrenia aggravated by khat use or a khat-induced psychosis, or was suffering from depression. The Programme is also aware of another such suicide that has not been notified.

Impaired judgement / accidents

There is concern that fatalities are high among tired lorry drivers due to accidents – especially those from Ethiopia, who chew khat to stay awake over the course of several days whilst they travel extremely long distances in Eastern Africa [159-161]. An assessment of road traffic accidents in Yemen during 1978-95 found a high correlation between road traffic fatalities and consumption of khat, as measured by the area under cultivation [79]. Although khat has a stimulatory effect during the first few hours of consumption, the study also found that its use can increase the risk of road traffic accident fatalities for two reasons. First, anxiety and tensions that occur several hours after use can affect perception and risk assessment. Second, often those taking khat whilst driving will be busy drinking water, smoking cigarettes, or preparing and cleaning the leaves. These divert the attention of the driver and are likely to cause accidents especially on rural roads where drivers tend to drive fast. Le Bras and Frétilière note the neurological effects that khat can have, particularly on gross motor co-ordination and impaired vision, leading to accidents [109]. Adverse effects on perceptual-visual memory and decision-speed have also been noted [162]. It has also been suggested that khat may have similar effects to amphetamine on driving ability, *i.e.* reduced alertness and awareness coupled with increased risk-taking [163].

The np-SAD has been notified of two cases of individuals dying in accidents involving motor vehicles. In both cases the deceased had consumed khat and alcohol [36]. One was a taxi-driver returning home after work, who lost control of his vehicle, collided with a lorry and sustained fatal injuries. The other was a pedestrian who attempted to cross a road, stumbled in the middle of the street, and was run over by a taxi [164-166]. A lack of motor co-ordination and impaired vision [109] may also have contributed to these accidents.

In these two cases, khat had been consumed with other psychoactive substances. This led to impaired judgement resulting in traumatic road traffic accidents. It may be difficult to disentangle the individual contributions of each substance, but the potential contribution of khat cannot be excluded. In a further case, the decedent died from heroin intoxication, although he had also consumed khat. This fatality may

also have involved impaired judgement or perception of risk, as well as demonstrating the possible synergistic effect of combined khat and other psychoactive substance consumption. The important feature here is not that the individual died of heroin use, but that he had also consumed khat.

The role of khat in a death reported to the np-SAD that resulted from injuries sustained in a fall from a height is unclear [36]. An adult Somali male, was found dead on a concrete surface below a fifth-floor flat at an address which he had just left after purchasing khat. The post-mortem examination showed no natural disease to account for death. There were no marks of restraint or of classical defence-type injuries. Khat was found in the mouth, oesophagus, and stomach but it is unclear as to its role, although it is possible that his khat-induced psychosis may have contributed to or influenced his fall from a height. The police could find nothing else to suggest it was anything other than suicide. Alternatively, his judgement may have been impaired by consuming khat. In 2009 a 32 year-old Somali female fell or jumped from a block of flats in an English town during a khat-chewing session with her husband and a friend. She had a history of mental health issues, as well as drug and alcohol abuse. The coroner concluded that the khat's psychotic effects or hallucinations could have led to an error of judgement by the decedent [165].

We noted earlier that violence amongst khat sellers, who were also chewing it themselves whilst retailing it, can break out and lead to death, contributed to in part by the intoxicating effects of the plant. Violence can be demonstrated not only by khat consumers but also towards them as a result of their behaviour whilst under its influence. These two aspects can be illustrated by two recent UK cases [36].

A 22-year old Somali male, who had been drinking alcohol and chewing khat, attended a party in Bristol and assaulted the host. When the latter tried to be reconciled with the young man, he was again assaulted and threatened in a restaurant where his assailant was drinking. The young man became aggressive and started acting strangely, demanding more alcohol. He suddenly lost his balance, collapsed, striking his head. He started having difficulties breathing. On the way to hospital by ambulance he suffered a cardiac event that led to death. His khat consumption could not be ruled out as a contributory factor [168].

By contrast in London, a 20-year Somali youth got on a bus with a relative, after taking alcohol, cannabis, and khat. He began spitting on the floor of the vehicle, and a passenger remonstrated with him about it. When the youth got off the bus he spat at this passenger. A short while later, the victim of the spitting turned up in two cars with family members and assaulted the youth. He received severe head injuries (consistent with impacts from heavy blunt instruments) and died in hospital. His assailants were subsequently convicted of his murder [169, 170]. It is thought that the substances the youth had consumed may have impaired his judgement and risk assessment, increased his aggressiveness,

reduced his self-control, and led to his anti-social behaviour which was sufficiently offensive for his victim to seek retaliation – with fatal results.

DISCUSSION

This paper has demonstrated that a wide range of associations can be posited legitimately to exist between khat and death. Some of these are more clear-cut and obvious, as with medical causes associated with consumption, as well as less direct or not so obvious, such as those associated with its cultivation and trade. For the purpose of this paper and its principal aim of creating a framework for discussion around the topic, a “khat-related death” is defined as meeting one or more of the following criteria (which are not necessarily mutually exclusive):

- ante- and/or post-mortem toxicology positive for cathine, cathinones, or other metabolites indicating consumption of khat;
- acute death occurring as the direct consequence of consuming khat;
- death occurring as the consequence of long-term use of khat leading to adverse physiological conditions;
- death occurring as the result of khat use aggravating a pre-existing or triggering mental health conditions leading to fatal self-harm;
- death resulting from impaired judgement caused by khat consumption;
- death associated with the cultivation, transportation or trade in khat – howsoever caused.

However, this definition is not carved in stone and is open to future refinement, as and when more objective evidence and scientific data are collected. It has to be recognised that this working definition, although based on a phenomenological approach, is nevertheless a social construction like all other drug-related deaths [171].

The contribution of khat to deaths is varied; and in some cases, can be difficult to categorise. Deaths associated with trade, marketing, wholesale and retail, can equally occur with any other illicit substance. Their inclusion here is deliberate: they are part of the wider pattern of mortality associated with the consumption of khat. The association of khat with psychiatric disorders or psychopathological factors is evident in some cases, contributing to suicide and even homicide.

Apart from poisoning from insecticide, traumatic deaths can be a feature of the cultivation, transportation, and trading activities undertaken by distributors and sellers. Violence can also occur in other settings. For example, psychopathological effects – (i) impaired judgement leading to accidents and violence, (ii) causing or exacerbating psychoses or causing depression leading to suicide and even homicide.

Physiological effects encompass: a) mechanical problems e.g., choking on pieces of the plant; and b) toxicity causing (i) heart problems leading to fatal heart attacks, and (ii) liver failure. There is now a fairly

well developed literature on the cardiac and circulatory problems caused by khat, especially with regard to myocardial infarction. There is now evidence that such consequences can be triggered by high levels of the principal psychoactive substances in khat i.e. left ventricular failure and acute pulmonary oedema.

The physiological effects of khat consumption are quite clear in a number of cases. The np-SAD cases referred to above are thought to be the first reported (as distinct from recorded) cases of death due to khat toxicity since the case reported by Heisch [89]. In one case the role of norephedrine/norpseudoephedrine producing adrenaline-like actions led to an increased likelihood of myocardial infarction [112], leading to left ventricular failure and pulmonary oedema. Khat chewing is a recognised risk factor for myocardial infarction [9, 96-100]. Khat can also cause cerebral haemorrhage [172] cerebral infarction [173], and contribute to cardiomyopathy [112]; both of which have high associated risks for morbidity and mortality.

Until recently, there have been few documented cases of khat causing liver failure. However, evidence is now emerging of an association between long-term khat consumption and liver problems, sometimes necessitating transplant, and now of death. It is possible that some deaths that are in fact attributable to khat consumption are going undetected because symptoms such as myocardial infarction and liver failure are not recognised as being associated with the substance. The cases reported here from the np-SAD of “khat-induced” liver failure [the Corkery khat liver condition] are consistent with recent findings in respect of hepatitis [111, 113, 115] and liver disease [114]. Such cases highlight that khat is a potential hepatotoxic agent and that this phenomenon needs further investigation and documentation. The determination of the aetiology of hepatitis should take into account the use of recreational drugs in all socio-cultural groups [115]. Patients presenting with such symptoms from ethnic groups associated with khat use should be asked for a full substance use history. The administration of nephrotoxic herbal remedies, including khat, should also be borne in mind when considering the origin of renal failure – again in all cultural groups. This awareness is also important in the assessment of coronary ischaemia amongst young male urban khat chewers with few other risk factors for coronary disease.

Impaired judgement or poor risk perception may play a part in fatalities [149], especially where violence may also be a factor. These factors may be made worse by the consumption of other psychoactive substances in conjunction with khat.

CONCLUSIONS

The information presented here illustrates some of the key issues related to the trade in and consumption of khat consumption. This paper is believed to be the first attempt to identify and classify mortality associated with or related to *Catha edulis*. Death can occur at any stage from cultivation to consumption. Some of

the factors can occur in combination, and it can be difficult sometimes to disentangle them. This paper not only seeks to establish potential causality between khat and death but also the type of associations that can be posited both theoretically and drawn from observation. However, this is more than a mere taxonomical exercise. A complementary paper examines in more depth causality and other associations in specific case studies and reflects on the quality of available evidence [36].

The use of case-studies and reports of individual incidents mean that the findings presented here are methodologically limited in quantitative terms, with consequent implications for analysis and interpretation. However, the research was undertaken systematically and provides a basis for the development of concepts and theories that can be refined by further, preferably population-based, research. This process could also identify other possible categories and dimensions which would need to be assimilated or incorporated into the model presented here. A similar approach to taxonomy could be applied to other substances. These would also need adaptation and refinement. For example, if applied to tobacco, it would need to take account of those manually handling the crop being poisoned by the plants because of nicotine being absorbed through the skin giving rise to toxic and even fatal results.

There are probably more deaths that have occurred in the past and which are currently happening but that are not identified as being related to the use of khat. This has meant that there is a demonstrable lack of documented cases in the literature, as well as nothing by way of quantitative data. These gaps in knowledge need to be filled employing systematic and scientifically-based approaches. This will lead to a much better understanding of the potential risks of death associated with the use of khat, based on empirical observation.

In the meantime, the dangers arising from the use of khat and its psychoactive constituents need to be brought to the attention of those in producing/growing countries, and those countries/regions that have become hosts to ever-increasing communities from these countries. This will need to be specifically focused on target groups using a variety of media, including a variety of languages. For example, khat is a major risk factor for acute heart attack [98] and needs to be considered in any ischaemic assessment of individuals from khat-consuming communities presenting to physicians with cardiac problems.

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The fatal case studies detailed above need to be borne in mind in future reviews of khat and the physiological and mental health risks associated with its use. These risks appear to be greater than previously realised. There is need for routine and systematic research of khat-using populations in respect of morbidity and mortality arising from the use of pesticides in the cultivation of the crop.

Khat research is still in its infancy, and there is little robust information on the subject [174]. Furthermore, the lack of negative health results for khat in the literature should not lead to complacency or an assumption that khat use is free from toxic consequences [175]. This absence of negative reports is due to a lack of population-based studies [19], particularly in respect of the toxicology of *Catha edulis*. Whilst anecdotal reports are informative, systematic investigations are needed to determine the incidence and prevalence of ill-effects of khat use. Only then can the best methods of supplying preventative and therapeutic interventions be considered in an informed way.

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Conflict of interest statement

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