Characteristics of deaths associated with kratom use

Authors:

John M. Corkery[1#], Peter Streete[2], Hugh Claridge[3], Christine Goodair[3], Duccio Papanti[1], Laura Orsolini[1], Fabrizio Schifano[1], Kanav Sikka[1], Sophie Körber[4], & Amy Hendricks[5]

1 Psychopharmacology, Drug Misuse, and Novel Psychoactive Substances Research Unit, Department of Clinical and Pharmaceutical Sciences, University of Hertfordshire, College Lane Campus, Hatfield, Hertfordshire, AL10 9AB, UK

2 Hampshire Scientific Service, Hyde Park Rd, Southsea, Hampshire, PO5 4LL, UK

3 National Programme on Substance Abuse Deaths, Population Health Research Institute, St George's, University of London, Cranmer Terrace, London, SW17 0RE, UK

4 Department of Pharmaceutical Science, University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland

5 Retired Forensic Pathology Technician, California, USA

Email addresses:
j.corkery@herts.ac.uk
#Corresponding author
Peter.Streete@hants.gov.uk
hclaridg@sgul.ac.uk
cgoodair@sgul.ac.uk
ducciopapanti@gmail.com
laura.orsolini@hotmail.it
f.schifano@herts.ac.uk
kanav.sikka@yahoo.com
sophie.koerber@gmx.ch
amylynnalso@gmail.com

Journal: Journal of Psychopharmacology

Abstract

Background: Kratom (*Mitragyna speciosa*) use has increased in Western countries, with a growing number of associated deaths. There is a growing debate about the involvement of kratom in these events.

Aims: This study details characteristics of such fatalities and provides a 'state-of-the-art' review.

Methods: UK cases were identified from mortality registers by searching with the terms: 'kratom', 'mitragynine', etc. Databases and online media were searched using these terms and 'death', 'fatal*', 'overdose', 'poisoning', etc. to identify additional cases; details were obtained from relevant officials. Case characteristics were extracted into an Excel spreadsheet, and analysed employing descriptive statistics and thematic analysis.

Results: Typical case characteristics (n=156): male (80%); mean age 32.3 years; White (100%); drug abuse history (95%); reasons for use - self-medication, recreation, relaxation, body-building, avoiding positive drug tests. Mitragynine alone was identified/implicated in 23% of cases. Polysubstance use was common (87%), typically controlled/recreational drugs; therapeutic drugs; alcohol. Death cause(s) included: toxic effects of kratom ± other substances; underlying health issues.

Conclusions: These findings add substantially to the knowledge-base on kratom-associated deaths; these need systematic, accurate recording. Kratom's safety profile remains only partially understood; toxic and fatal levels require quantification.

1. Introduction

Kratom (*Mitragyna speciosa* Korth) is a tree native to South-East Asia (especially Malaysia, Thailand and Indonesia), New Guinea and the Philippines. It typically grows to between 4 and 16 metres in height. (Mis)use of kratom appears to have increased in Western countries over the past decade, with a growing number of deaths (reviewed below) being reported as associated with this plant and synthetic forms of its active ingredients mitragynine and 7-Hydroxymitrgynine (Figures 1 and 2). Some context is provided, through means of a 'state-of-the-art' review (Grant and Booth, 2009), against which these deaths can be understood. This paper present outlines the principal characteristics of decedents and fatalities related to kratom use. Furthermore, it discusses the implications of the way in which these cases are identified, reported, recorded and interpreted.

< Figures 1 and 2 about here >

2. Overview of the state of knowledge of Kratom

2.1. Chemistry and pharmacology

Amongst the psychoactive ingredients found in kratom leaves are the alkaloids mitragynine and its main metabolite 7-hydroxymitragynine. Mitragynine was first isolated in Edinburgh in 1921 (Chemist & Druggist, 1930). These molecules bind to the μ (mu), κ (kappa) and δ (delta) opioid receptors (Holler et al., 2011; Prozialec et al., 2012), acting as an agonist at all three receptors, and antagonist at the δ receptor (Kruegel et al., 2016; Váradi et al., 2016). An *in vivo* mice study demonstrated that mitragynine acts as an antagonist on the serotonin and noradrenaline receptor systems (Matsumoto et al., 1996).

It is reported that 7-hydroxymitragynine has a potency 13-times higher than morphine (Takayama, 2004) and 46-times that of mitragynine (Matsumoto et al., 2004; Shellard et al., 1978). Kratom's pharmacological properties are affected by where, when and how it is cultivated. Plants from Indonesia contain higher levels of mitragynine and related alkaloids than those from Malaysia and

Thailand (Orio et al., 2012). Kratom varieties with red-veined leaves (only found in Thailand) are reported to be more sedating than those with green or white leaves which are more stimulating, according to drug user fora (Domingo et al., 2017).

The approximate mitragynine content of fresh kratom leaves is 0.86 mass % compared to 0.026 mass% for 7-hydroxymitragynine (Ponglux et al., 1994). Levels in kratom products are in the range of about 1.5 - 2 mass % and about 0.02 - 0.33 mass % respectively for these substances (Kikura-Hanajiri et al., 2009; Lydecker et al., 2016). So, the concentration of mitragynine is 50 - 100 times that of its hydroxy metabolite (Kruegel and Grundmann, 2018).

A typical dose of 8 g of raw kratom may mean that a 70 kg individual is exposed to 120 – 180 mg of mitragynine and 1.1 - 3.4 mg of 7-hydroxymitragynine (1.2 - 2.5 mg/kg and 0.015 - 0.048 mg/kg respectively) (Kruegel and Grundmann, 2018). Full effects are usually apparent 30 - 60 min after oral consumption but onset may be felt within 10 - 20 min. Kratom's effects can last 5 - 7 h, being strongest 2 - 4 h after ingestion; weak effects can be felt up to a day later (Maruyama et al., 2009; Prozialeck et al., 2012; Rosenbaum et al., 2012; Scott et al., 2014).

2.2. Metabolism and pharmacokinetics

There appears to be few human studies of mitragynine and 7-hydroxymitragynine pharmacokinetics. Trakulsrichai et al. (2015) suggest a two-compartment model of metabolism for mitragynine. Following oral consumption, the half-lives of mitragynine and 7-hydroxymitragynine are about 3.5 and 2.5 h respectively (Henningfield et al., 2018). Both are eliminated primarily in urine (Neerman et al., 2013; Prozialeck et al., 2012). Absolute bioavailability is about 3% for mitragynine (Parthasarathy et al., 2010). However, this would not appear to be explained by either a high first-pass metabolism or poor gastro-intestinal absorption (Kruegel and Grundmann, 2018). Blood levels of mitragynine of up to 191 ng/mL after consumption of tea containing 104, 166 and 192 g/mL of kratom over 7 days were recorded in 10 chronic kratom users (Trakulsrichai et al., 2015). LD_{50} levels for mitragynine in rodent studies have been reported as 200 mg/kg in a rat (Janachawee et al., 2007) and mice at 477 mg/kg (Sabetghadam et al., 2013). It appears that the LD_{50} levels for Swiss Webster male rats is similar for

intra-venous (IV) Mitragynine (27.8 mg/kg), 7-Hydroxymitragynine (24.7 mg/kg), and heroin (23.7 mg/kg), whereas the LD_{50} level for oral Mitragynine in the same animals is 547.7 mg/kg (Smith et al., 2019).

2.3. Availability, routes of administration and usage

Mitragynine is insoluble in water but can be dissolved using a range of conventional organic solvents such as acetic acid, acetone, chloroform, diethyl ether and alcohols (EMCDDA, 2015a). The dried leaves can also be consumed as a tea or smoked (Hassan et al., 2013). According to consumers, the amount of leaves that constitutes a typical dose cannot easily be smoked (Cinosi et al., 2015). Products derived from kratom are typically found as crushed or powdered leaves. Some powder preparations, green or beige-brown in colour, have additional leaf extracts added. Paste-like extracts and dark brown resin can be prepared by boiling off the water from aqueous leaf suspensions. These can be added to finely chopped palm leaves and made into pills or smoked in pipes as “madatin” (Azizi et al., 2013). Alternatively, extracts can be added to hot water and then consumed alone or added to herbal teas to make it more acceptable - “toss and wash” (Cinosi et al., 2015; Hanapi et al., 2013). Small pellets, capsules or paper ‘bombs’ filled with kratom powder are also available for oral ingestion. In the USA the most popular modes of consumption are powdered form with a beverage, pill, pure powder or as a tea (Grundmann, 2017). Other users prefer to take kratom with food, making cookies or mixing it with yoghurt to counteract its bitter taste (Cinosi et al., 2015). More recently, evidence has emerged of intravenous injecting of kratom (Lydecker et al., 2017). Kratom extracts (tinctures) are now available for use in vapourisers (Abayarathna and Jaehne, 2016; Poklis et al., 2017).

Tinctures and drinks, including alcohol and/or other psychoactive substances, can be purchased. Common additions in South-East Asia are cough syrups containing codeine or diphenhydramine to which are added a caffeine-based soft drink, and an anti-depressant, an anxiolytic or an analgesic (EMCDDA, 2015a; Tungtananuwat and Lawanprasert, 2010): an example in Thailand and Malaysia is the “4 x 100” cocktail (Tanguay, 2011; Tungtananuwat and Lawanprasert, 2010), which is believed to have more intoxicating effects (Chongrathanakon et al., 2017). In other contexts and/or regions a

variety of both ‘traditional’ recreational substances (e.g. alcohol, amphetamines, benzodiazepines, cannabis, cocaine, hallucinogens, methadone and paracetamol) and new/novel psychoactive substances (NPS) such as kava, synthetic cathinones, phenethylamines and tryptamines are also taken with kratom products/ingredients (Anwar et al., 2016; Cinosi et al., 2015).

As with other ‘herbal’ products, consumers of kratom or related derivatives, whether purchasing online or from other outlets, need to be aware that there is not only variability in the concentrations of kratom, but there is also the potential for such products to contain very dangerous/potent ingredients such as O-desmethyltramadol (Scott et al., 2014). However, Griffin et al. (2016) found that products marketed as liquid pain relief and containing mitragynine did contain kratom. Nevertheless, it is worth noting that the concentrations of 7-hydroxymitragynine found in products may be artificially made considerably higher than those found in kratom leaves (Lydecker et al., 2016).

There appears to be a dose-response effect: 1 - 5 g of leaves (low to moderate doses) generate mild stimulant effects that enable workers to stave off fatigue in Thailand and other South-East Asia regions (Cinosi et al., 2015; Prozialec et al., 2012), as well as recreational effects such as a perception of being more 'alert', “entactogenic” effects like empathy and euphoria, sometimes sexual arousal is increased (Cinosi et al., 2015); 5 - 15 g (moderate to high doses) produce opioid-like effects, and have been employed to not only manage pain, diarrhoea, and opioid withdrawal symptoms but also for euphoriant effects; over 15 g (very high doses) often give rise to sedative effects, inducing intoxication (Prozialec et al., 2012), and causing opioid-like analgesic effects, as well as causing users to be “less sensitive to physical or emotional pain, to feel and look calm, and to have a general feeling of comfortable pleasure... Others report an increase of empathy feelings” (Cinosi et al., 2015). Boyer et al. (2008) note that as early as the 1830s kratom was reported as being used as a substitute for opiates.

2.4. Addiction potential

There are case-reports of chronic kratom use leading to tolerance, cross-tolerance to both kratom and opiates, physical dependence/addiction, craving and withdrawal problems from South-East Asia,

Europe and the USA (Adkins et al., 2011; Assanangkornchai et al., 2007; Babu et al., 2008; Boyer et al., 2008; Cinosi et al., 2015; McWhirter and Morris, 2016; Roche et al., 2008; Saingam et al., 2013; Suwanlert, 1975). Whilst some users report low craving, others experience difficulty in abstaining (Ahmad and Aziz, 2012; Singh et al., 2015). Kratom tolerance develops slower than for morphine and has lower potential for addiction (Váradi et al., 2016). As with opioids, neonatal abstinence syndrome has been described in some cases (Davidson et al., 2019; Eldridge et al., 2018; Mackay and Abraham, 2018; Murthy and Clark, 2019; Trakulsrichai et al., 2013). The addiction potential of kratom and its main alkaloids is still controversial in the scientific community and on discussion websites (Hassan et al., 2012), but mitragynine probably merits further investigation in respect of its potential for use in opioid dependence (Yue et al., 2018) and chronic pain relief. It may be that mitragynine rather than 7-Hydroxymitragynine is more suited for such uses (Hemby et al., 2018) because of the former's lower abuse potential.

Withdrawal symptoms are similar to those described for traditional opioids but are milder (Singh et al., 2014, 2016) and overlap in terms of side-effects, including: decreased appetite, anorexia, weight loss, decreased sexual drive, insomnia, myalgia (muscle spasms and pain), arthralgia (aching in the muscles and bones), jerky movement of the limbs, watery eyes/nose, rhinorrhoea, dry mouth, hot flushes, hypertension, fever, nausea, frequent micturition, and diarrhoea (Burkill and Haniff, 1930; Cinosi et al., 2015; Hassan et al., 2012; Singh et al., 2014; Stanciu et al., 2019). Most of these effects appear to be dose-dependent (Grundmann, 2017; Smith and Lawson, 2017). Psychological withdrawal symptoms commonly reported are: dysphoria, nervousness, restlessness, tension, anger, hostility, irritability, aggression, and sadness (Singh et al., 2014; Suwanlert, 1975). Psychotic symptoms such as mental confusion, delusion, and hallucination are reportedly caused by regular use of kratom (Suwanlert, 1975). On the other hand, a recent small-scale study appears to show that long-term use by regular kratom users does not impair motor, memory, attention or executive function (Singh et al., 2019). One recent US study reported that about two-fifths (42.6%) of users reported some form of withdrawal symptom (Grundmann, 2017).

2.5. Adverse effects of using

Common side-effects reported include: decreased appetite, anorexia, weight loss, temporary erectile dysfunction, insomnia, sweating, hyperpigmentation, hair loss, and tremor, and constipation (Cinosi et al., 2015). The commonest symptoms reported in the USA are: tachycardia (25.0%); agitation/irritability (23.8%); drowsiness (19.4%); nausea (14.7%); and hypertension (11.7%) (Anwar et al., 2016). These symptoms, together with anxiety, are reported by other researchers (Prozialeck et al., 2012; Singh et al., 2014; Swogger et al., 2015). Kratom appears capable of raising prolactin levels leading to secondary hypogonadism (LaBryer et al., 2018). Chronic use can also cause elevated levels of transaminases (Carter et al., 2016).

Reported adverse effects, following high doses and/or the use of concentrated extracts, include: tachycardia (Lu et al., 2014); intrahepatic cholestasis (Griffiths et al., 2018; Kapp et al., 2011; Riverso et al., 2018), hepatitis (including cholestatic) and liver toxicity (Dorman et al., 2015; Drago et al., 2017; Forrester, 2013; Kupferschmidt, 2011); seizure and coma (Nelsen et al., 2010; Pantano et al., 2016; Roche et al., 2008); Adult Respiratory Distress Syndrome (Jaliawalia et al., 2018; Pathak et al., 2014); and hypothyroidism (Sheleg and Collins, 2011). Repeated kratom use can lead to generalised tonic clonic seizures and possible structural brain lesions and symptomatic focal epilepsy (Tatum et al., 2018). Cerebral haemorrhage following the use of kratom by an intravenous heroin user in remission has been reported (Liss et al., 2016).

2.6. Epidemiology

Information on the epidemiology of kratom use is scarce, due, in part, to the absence of robust metrics on typical doses, regularity of use, etc. Most information on kratom prevalence relates to its use in Thailand where it is used as a self-medicating substance to treat opiate/opioid dependence, and as an opium substitute in Malaysia (Ahmad and Aziz, 2012). In 2012, some 1.23 million individuals in Thailand reported lifetime use (ASCAN, 2012), with 76,990 having taken a “kratom cocktail”. A national survey in 2016 found lifetime use of kratom leaves at 15.1% compared to 14.5% for the cocktail; last year use was 2.1% and 0.7% respectively (Wonguppa and Kanato, 2017). The consumption of the cocktail appears to have been causing concern in official circles for several years,

especially in the Thailand/Malaysia border regions (Chang Rai Times, 2018). Facebook pages in Thai are typically positive and neutral towards kratom rather than negative in tone (Thaikla et al., 2018).

Misuse of kratom has increased in Western countries in years. Internet surveys conducted by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2008 indicated that kratom was one of the most widely offered 'legal highs' in 44% of the 27 European online shops investigated (Hillebrand et al., 2010). A more extensive EMCDDA Internet survey in July 2011 showed that kratom was the most widely offered product with 128 out of 631 (20%) of online retailers shipping it to the EU (EMCDDA, 2011). An Internet snapshot carried out in the UK in April 2009 showed that among the 346 unique products offered by 39 shops, kratom (n=30) was second only to *Salvia divinorum* (Schmidt et al., 2011). Kratom products can be bought from 'head', 'smart' and 'herbal' shops and increasingly online from overseas (Cinosi et al., 2015). The latter sources are likely to be based in Indonesia, e.g. 'Bali Kratom' where it is not controlled. The Internet is being increasingly used as a means of sourcing kratom for those using it for self-medication purposes (Boyer et al., 2008; Cinosi et al., 2015; EMCDDA, 2015a). The principal reasons for this self-medication are (a) to manage opioid withdrawal by individuals with chronic pain; (b) to alleviate symptoms associated with withdrawal from heroin, methadone and suboxone; and (c) for its ability to treat depression and anxiety.

Kratom use appears to be increasing in the United States (Warner et al., 2016), especially for self-management of opioid withdrawal and pain relief (Grundmann, 2017; Prozialeck, 2016). Pain relief appears to be the most common reason, closely followed by emotional/mental conditions such as anxiety, depression and Post Traumatic Stress Disorder (PTSD), followed by drug dependency (Grundmann, 2017). This increase appears to be reflected in the number of calls to the US National Poison Data System database. The number of calls rose from 26 in 2010 to 263 in 2015 (Anwar et al., 2016). The median age of cases was 28 years (range 2 months - 69 years); 71.7% were male. Between 2011 and 2017 about 1800 kratom exposures had been reported nationally, with two-thirds of these being during 2016-2017 (Post et al., 2019). By contrast, the Malaysian National Poison Center recorded only two cases of mitragynine poisonings between 2006 and 2009 (Daud et al., 2012). Forensic toxicology investigations in cases involving NPS in the USA also indicate an increasing proportion being attributed to mitragynine. For example, one laboratory (NMS) reports the

proportion of its NPS Blood Positive Confirmations where mitragynine was identified rising from 4.7% in 2013, to 12% in 2014, and to 15.48% in the first six months of 2016; being the second most frequently identified NPS during the latter period (Logan, 2016a, 2016b).

A survey of in-patient substance users conducted in the USA during April 2017 found that 10% had used kratom in the previous 12 months and such individuals were more likely to attend Emergency Departments (EDs), and to use it as a replacement for heroin (64%), because of a disability or chronic pain (18%). Some 43% used it because of curiosity and a similar proportion to bypass drug tests (Smith and Lawson, 2017). Commonly used drug screening methods do not detect kratom and its metabolites, and this may be another reason for its spreading use, to avoid positive opioid results in occupational or detoxification drug testing (Fuenffinger et al., 2017; Gunderson et al., 2014; Lesiak et al., 2014; Perrone et al., 2013; Prutipanlai et al., 2017; Warner et al., 2016).

2.7. Legal status of Kratom

The kratom plant, but moreover mitragynine and its other metabolites, do not appear in any of the United Nations' Drug Conventions schedules. Kratom itself is regarded by the United Nations Office for Drugs and Crime (UNODC) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) as an NPS (EMCDDA, 2015b; UNODC, 2014). However, it is controlled in Australia, Malaysia, Myanmar, New Zealand, Russia, South Korea, Thailand (but see below), Vietnam and in some US states. The US Food and Drug Administration (FDA) has not approved kratom. The Drug Enforcement Agency (DEA) became so concerned about the use of kratom in the USA that on 30 August 2016 it announced it was going to place it in Schedule I of the Controlled Substances Act 1970. However, there was such an adverse reception to this news by suppliers, consumers and politicians that on 20 October 2016 the DEA withdrew the proposal and extended a public consultation process to 1 December 2016 (Henningfield et al., 2018) – see Discussion. In October 2017, the FDA decided to look separately at Mitragynine and 7-Hydroxymitragynine (Brodwin, 2018), and has apparently recommended that both be controlled or regulated (Swetlitz, 2018). At the time of writing (February 2019), it is being reported that the Department of Health and Human Services has also recommended a ban on the chemicals to the DEA (Swetlitz, 2018). In Canada, kratom-containing

products are not authorised for sale (Wang and Walker, 2018). In Thailand the National Legislative Assembly completed its approval of a draft bill on 25 December 2018 that amends the country's Narcotic Act 1979; it came into force the day after its publication in the Government Gazette on 18 February 2019 (LawPlus Ltd, 2019). The new regulations (Narcotics Act (No. 7) B.E. 2562 (A.D. 2019)) allow the use of cannabis and kratom for government and medical benefits, the treatment of patients, research and development, agriculture, commerce, science and industry (Sattaburuth, 2018).

The amount of kratom seized globally in 2016 was in excess of 400 tons; this was seven times more than in the previous year (UNODC, 2018). Most was confiscated in Malaysia (399,139 tons), followed by Thailand (5,681 tons), Myanmar (1,413 tons), and Belgium (1 ton).

At the time of writing, kratom, mitragynine and 7-Hydroxymitragynine are controlled in 10 EU Member States and Turkey. In the UK, kratom, and its psychoactive metabolites, is regarded by the Medicines and Healthcare products Regulatory Agency (MHRA) as a medicinal herb and would require a marketing authorisation for sale as a medical treatment (personal communication to lead author from MHRA, 17 May 2018). This means it is exempted from regulation under the Psychoactive Substances Act 2016, if being used by "healthcare professionals acting in the course of their duty" or employed in approved scientific research. But, if kratom is being provided purely for its psychoactive properties prosecutions could be sought. If doctors prescribe unlicensed medicines, they need to satisfy themselves that there is sufficient safety evidence for the medicines in question. Prior to the Psychoactive Substances Act coming into force, the UK Government Chemist advised that kratom could not be considered a 'novel food' as defined in Regulation (EU) 2015/2283 (LGC, 2018). The opioid O-desmethyltramadol, which is more potent than its parent drug tramadol, was added to kratom preparations sold as 'Krypton'. This product resulted in a number of deaths (Bäckstrom et al., 2010; Kronstrand et al., 2011). As a result, O-desmethyltramadol became controlled in the UK as a Class B drug on 26 February 2013.

2.8. Deaths associated with Kratom use

Deaths associated with kratom use have been reported. Typically, the decedents had confounding health conditions and/or used other substances, whether medicines, traditional stimulants or NPS, or indeed combinations thereof. For example: propylhexedrine (Holler et al., 2011); loperamide (Bishop-Freeman et al., 2016); dextromethorphan, diphenhydramine, temazepam, clonazepam, zopiclone, citalopram, and lamotrigine (Neerman et al., 2013); venlafaxine, diphenhydramine and mirtazapine (McIntyre et al., 2015); lorazepam, triazolam, fluoxetine, quetiapine, olanzapine, pregabalin, pipamperon together with two NPS (a 'designer benzodiazepine' - etizolam, and a synthetic cathinone - probably 2-MMC) (Domingo et al., 2017); codeine, heroin, paracetamol, amphetamine, methamphetamine, MDA, MDMA and pseudoephedrine (Domingo et al., 2017); quetiapine (Hughes, 2019).

2.9. Aims of the paper

The aims of this paper are to examine the nature of deaths reported associated with the use of kratom, to profile decedents, and contribute to the literature concerning mitragynine levels in fatal cases, whether as a direct or contributory cause (Domingo et al., 2017). The purpose of doing so is to develop the existing limited knowledge-base, so as to inform policy-makers, potential and actual users, as well as those who may have to treat them or investigate their deaths.

3. Methods

3.1. Data sources and sources for UK fatalities

In the UK context, general mortality registers (GMRs) are part of the national agencies responsible for collecting and analysing vital events (births, deaths, marriages and civil partnerships). This study draws on information provided by the UK GMRs as part of two EU-funded projects.

The National Programme on Substance Abuse Deaths (NPSAD) is a special mortality register which regularly receives information from Coroners on a voluntary basis on deaths related to drugs in both

addicts and non-addicts in England, Wales, Northern Ireland, the Channel Islands and the Isle of Man. From 2004 to 2011, information was also received from the Scottish Crime and Drug Enforcement Agency. Since 1997 details of more than 35,000 deaths have been received. To be recorded in the NPSAD database as a drug-related death, at least one of the following criteria must be met: (a) presence of one or more psychoactive substances directly implicated in death; (b) history of dependence or abuse of drugs; and (c) presence of controlled drugs at post-mortem. Ethical approval is not required in the UK for studies whose subjects are deceased and solely involves retrospective reviews of death records.

A retrospective study design was employed to identify relevant cases associated with the use of kratom. Relevant cases in the UK were identified from both general and specialist mortality registers by searching the cause of death fields and post-mortem toxicological data (Scotland, Northern Ireland, NPSAD) with the following terms: ‘kratom’, ‘mitragyna’, ‘mitragynine’, ‘7-Hydroxymitragynine’, ‘O-desmethyltramadol’ and ‘Krypton’. The additional fields searched on the NPSAD database were those holding data on - verdict, accident details, and 'other relevant information'. Where cases were identified in the UK using the methods detailed in the next paragraph, further details were requested and obtained from the relevant pathologists, Coroners and Procurator Fiscals.

3.2. Data sources and sources for non-UK fatalities

In addition, regular searches were undertaken in English of literature databases and search engines (Google Scholar, PubMed), ‘grey literature’, and online media sources in Google using the above terms in conjunction with the terms ‘death’, ‘fatality’, ‘mortality’, ‘Coroner’, ‘inquest’, ‘conference’, and ‘abstract’ to identify other cases. Google Scholar alerts were also set up using these terms. Where cases outside the UK were identified, contact with those reporting the cases (e.g. media reporters, lobby/interest groups) was made by the lead author to obtain further details. Through this process, contact was made with the US co-author who had used similar methods, including freedom of information requests, to obtain copies of coroner/medical examiner reports, including autopsy reports. Some cases were already known to the authors. The sources used for identifying each case are given in the relevant tables.

3.3. Data extraction and analyses

Key characteristics of such incidents and decedents were extracted from all available sources, with a key emphasis on accessing the official documents where possible. These details were entered into a Microsoft Office Excel spreadsheet. Characteristics of decedents are examined in terms of age, gender, ethnicity, history of drug use, employment, and living arrangements. Characteristics of deaths are examined in respect of place of death, number and combinations of post-mortem drugs, role of substances in death, manner and cause(s) of death.

Data analysis were performed using Microsoft Office Excel 2016, employing descriptive statistics for quantitative information. Data on blood, urine and other tissue (e.g. vitreous humour) concentrations are presented, where available. Qualitative information was undertaken using a content/thematic analysis approach.

4. Results

This study reports on a total of 156 deaths associated with the use of kratom. So far as the authors are aware, this is the largest number of cases reported on to date in the literature. Details of these individual cases are given in the supplementary spreadsheet (available online).

A total of ten UK deaths have been identified at the time of writing (February 2019) via the methods outlined in Section 3.1 above; eight in England and two in Scotland. There have been no known deaths involving kratom or its derivatives in Northern Ireland or Wales.

Non-UK cases (n = 146) identified can be broken down into four categories (a) published academic papers/abstracts; (b) government reports; (c) media reports; and (d) reports of post-mortem toxicology casework.

The first group covering case-reports of 40 deaths comprises, in order of publication year: Tungtanauwatt and Lawanprasert (2010); Holler et al. (2011); Kronstand et al. (2011); Frost et al. (2012); Neerman et al. (2013); Anderson et al. (2014); Karinen et al. (2014); McIntyre et al. (2015); Bishop-Freeman et al., 2017; Domingo et al. (2017) (Personal communication, Olwen Domingo, University of Munich, 11 April 2017 to lead author); Ramoo et al., 2017; Fogarty et al., 2018; Wang and Walker, 2018; Hughes, 2019; Gershman et al., 2019 (Personal communication, Andrew Monte, University of Colorado, 28 January 2019 to lead author).

The second group comprises: the US Drug Enforcement Agency (DEA) gives details of 9 US cases (DEA, 2016b:23-26). The FDA (2018a, 2018b, 2018c) provides information on 44 deaths, many of which are included in the first group above.

The third group, media reports, in date order cover 1 Swedish case - Petersson (2010) - case 2 detailed in Kronstand et al. (2011); 1 Irish case - O'Halloran (2011); and numerous cases in the USA, e.g. Lystra (2013); Vigil (2014); (Personal communication 30 June 2016 Amy Martin, Chief Medical Examiner, Denver, Colorado to lead author); CBS Miami (2014); Whigham (2014a,2014b); thewatershed.com (2014); Greenfield (2015); Bruno (2016); Bhattacharjee (2016); McBride (2016); Davis (2018); Dunn and Lindstrom (2018); Main (2018); Perno (2018); Smith (2018); Vlahos (2018); Wing (2018a, 2018b); one of the US media reports (Vigil, 2014) covers a case cited by the DEA (2016b). In addition, post-mortem toxicology results have been published by Brower et al. (2015).

According to the Associate Medical Examiner in Arkansas, kratom was linked to three deaths of known kratom users in the state during 2015. In two cases kratom and other controlled substances were found in the decedents' blood. In the third case, involving a healthy male, only kratom was found in his system, the probable cause of death being ruled as kratom toxicity (Wooten, 2016). The North Carolina Medical Examiner's Office stated that 23 individuals had died with kratom in their system, and for five it was the primary cause of death; although the period covered is unknown (Toler, 2016). In addition, mitragynine was also found in 11 post-mortem cases examined in North Carolina (Brower et al., 2015). Recently, it was reported that kratom was found in the bodies of at least 27 decedents in the last 3 years in the ten most populated counties in the state of Colorado; of these, kratom was

considered as contributing to 17 overdoses, and in at least six cases it was the only drug that contributed to death (Haarer, 2018).

4.4. Trends and demographic characteristics

Apart from a single case reported from Thailand, all cases reported here occurred in North-Western Europe or North America, principally the USA (Table 1). The first documented death occurred in 2008. The number of cases appears to have had a peak in 2009-10 (mainly due to nine Krypton cases in Sweden), and from 2013 onward there has been a steady increase in cases being reported. The majority (80.1%) of victims were male. The mean age was 32.3 (range 17-64) years and, where known, all the decedents were White/Caucasian. Where known, most decedents were employed (66.7%), and lived with someone else (77.3%).

< Table 1 about here >

The reasons for using kratom were not available in all cases. However, a range of reasons were noted; the main one being self-medication, including for opiate/opioid addiction and anxiety/stress. Recreational use and body-building were also mentioned, as was using kratom to avoid positive drug tests. In the majority (95.3%) of cases it was known that the decedents had a history of drug abuse, including past or current use of Kratom or Krypton (31.4%).

4.5. Characteristics of deaths

About two-thirds (66.1%) of deaths occurred at an individual's home or that of a family member or friend, but 15.2% died in hospital or medical centre.

Tables 2a and 2b present information on the mitragynine and 7-hydroxymitragynine levels given in all published fatalities and those covered in this study. The key blood levels for mitragynine are: all cases

(n = 71) - mean 0.853, range 0.00089 - 16.000 mg/L; with other substances (n = 62) - mean 0. 0.8903, range 00089 - 16.000 mg/L; and as a sole drug (n = 3) - mean 0.398, range 0.0035 - 0.890 mg/L. The post-mortem mitragynine blood levels for four of the UK cases are above the median levels previously reported in the literature for other cases, case 3 being the highest level yet reported. The blood level for 7-hydroxymitragynine is only known for 5 cases - mean 0.66218, range 0.0009 - 2.8 mg/L. The 7-hydroxymitragynine levels for three UK cases (0.17, 0.19 and 2.8 mg/L) were all higher than the sole one (0.15 mg/L) previously reported in the literature (Karinen et al., 2014).

< Tables 2a and 2b about here >

In only six of all reported cases with toxicology information available (n = 129) was mitragynine the sole substance identified in the post-mortem toxicology; the ratio of mitragynine as sole mention to any mention in toxicology is 0.0465:1.0000. However, mitragynine was the sole drug implicated in 27 out of 117 cases where the cause of death is known (Table 3); the ratio of mitragynine as sole mention to any mention in the cause of death is 0.231:1.000. Six of these 27 cases are the same cases where mitragynine was the sole drug detected in toxicology; a ratio of 0.222:1.000. Mitragynine was detected in all but one case, i.e. in 155 cases. Of these, levels are available for 71 cases (45.8%) but unavailable/not given for 84 cases (54.2%). Mitragynine was mentioned in the cause of death for 85 (54.87%) of the 155 cases where it was detected. The substance was mentioned in the cause of death in 39/71 (54.9%) cases where levels were also stated.

The main classes of other substances found can be broadly grouped into three categories: controlled/recreational drugs; therapeutic drug classes; and alcohol. Of importance is the fact that many drugs identified in these cases are Central Nervous System (CNS) depressants; particularly O-desmethyltramdol, other opiates/opioids, benzodiazepines and alcohol. Stimulants and therapeutic drugs used to treat anxiety, depression and psychoses were commonly found. NPS including ‘designer benzodiazepines’, ‘designer opioids’, and synthetic cathinones, have also been recently reported in combination with kratom. Where known, poly-substance use was found in the majority (87.2%) of cases; the average in such cases being three or four (mean = 3.4, range 1 - 10) drugs in

addition to mitragynine/7-hydroxymitragynine. Often, combinations include opiate/opioid(s) and/or benzodiazepine(s) and/or anxiolytic(s)/anti-depressant(s)/anti-psychotic(s) and/or stimulant(s).

< Table 3 about here >

The main cause(s) of death and autopsy findings are presented in Table 4. The key issues emerging can be broadly categorised into five: (a) breathing difficulties, especially congested and/or oedematous lungs; (b) cardiac/cardio-respiratory issues; (c) brain damage/hypoxia; (d) toxic effects of kratom/Krypton (with other substances); and (e) liver/urinary problems.

< Table 4 about here >

The 27 deaths where the sole drug found reported in the post-mortem toxicology and/or implicated in deaths are summarised in Table 5. Of note in these cases are: all decedents are male and White (where ethnicity is known), with a mean age of 32 years. Where known, the majority are: employed, living with someone, and have a history of drug use, including kratom.

< Table 5 about here >

The mean blood level is about half that of all cases where levels are known, but there are only three cases where levels are available. In all cases, Mitragynine/Kratom toxicity, toxic effects, overdose or intoxication is specifically mentioned is the autopsy/cause of death. Common features are: pulmonary congestion and/or oedema, and other respiratory conditions; effects on the brain; cardiac/circulatory conditions/diseases; and liver conditions. Where manner of death is known, most deaths were regarded as accidental or misadventure.

5. Discussion

As far as the authors are aware, this paper presents the most comprehensive summary of deaths (n = 156) linked to kratom use yet published. Only 40 of these cases have been reported previously in the scientific literature.

5.1. Trends in reporting kratom-related deaths

The number of cases being reported since 2008, both in the scientific literature and the media more generally, has constantly grown. This increase in the number of deaths associated with kratom use may be due, in part, to cases being more liable to be reported due to increasing interest in its use by potential/actual users and by the media, and therefore more active surveillance, identification and official/scientific recording. This phenomenon was observed in the UK in relation to MDMA-related fatalities following the death of Leah Betts in 1994 (Schifano et al., 2006).

It is likely that more reports will occur as individual European countries and states in the USA, and the Federal government, become aware of the potentially fatal consequences of taking kratom or synthetic compounds containing mitragynine and its metabolite 7-hydroxymitragynine and introduce controls on its availability. This aspect will be important to monitor, especially since the coming into force in the UK on 26 May 2016 of the Psychoactive Substances Act 2016 which appears to capture kratom's psychoactive components, e.g. mitragynine and 7-hydroxymitragynine within its scope. The 'Krypton'-related deaths in Sweden, which also included O-desmethyltramadol in the product, led to this molecule becoming controlled in the UK (Home Office, 2013).

Increasing reports of adverse effects and toxicity including deaths associated with the use of kratom or related products led to the US Drug Enforcement Agency (DEA) to announce on 31 August 2016 a proposal to add mitragynine and 7-Hydroxymitragynine temporarily to Schedule 1 of the 1970 Controlled Substances Act (DEA, 2016a). This was met with many calls from interest groups for the DEA to reconsider its suggestion. Following much pressure, the DEA withdrew its Notice of Intent on 13 October 2016 and opened a period of public consultation which finished on 1 December 2016 (DEA, 2016c). The Agency's consideration of representations is still awaited at the time of writing. At the time of writing, some 6 states in the US have banned kratom.

There are likely to be other cases which have either not been identified or not reported in the scientific literature yet. For example, there has been justified criticism that the details of cases cited by the DEA in support of its proposal to schedule kratom (DEA, 2016b) are either not given at all, or key information such as toxicological levels and other key aspects are not presented (see below). This information needs to be published whenever and wherever possible, allowing for suitable anonymity regarding the identity of decedents.

Some claim that no deaths have occurred in South-East Asia (e.g. Singh et al., 2016), although some have been documented (e.g. Tungananuwat and Lawanprasert, 2010). However, it is very likely that other deaths have occurred or are occurring there and in other parts of the world where kratom is used as a self-medicating therapeutic agent to treat opiate/opioid dependence. There is a lack of information on drug-related poisoning deaths in Malaysia (Raj, 2017). For all the above-mentioned reasons, and probably others, such as poor identification, investigation and reporting of drug-related deaths in this region, deaths associated with kratom are likely to be unreported.

To date, there is only a single case-report from Thailand (Tungtananuwat and Lawanprasert, 2010), although mitragynine was found in the systems of two homicide victims in central Bangkok in the period 2009-2103 (Sakulsaengprapha et al., 2018). The presence of mitragynine is not a surprise, given its widespread use in Thailand.

There is a lack of detailed published information on mortality statistics in Thailand, making it impossible to know what the true nature and extent of kratom-related deaths are in that country (personal communication to lead author from Kanlayarat Karnman, 24 June 2018). The same situation would appear to hold in Malaysia and Vietnam. Even in the UK and USA there are no accurate published national figures available.

5.2. Demographics of those dying

The cases described here share many characteristics in common with the other cases so far described in academic literature, government reports and media reports. A typical decedent is White, male, aged in their early 30s, employed and lived with someone else.

The reasons for using kratom, the use of additional substances, including CNS depressants, cause of death/autopsy findings and nature of death reflect the other cases reported. Self-medication emerged as the main reason for taking kratom, especially in connection with opiate/opioid use. Such use is common in Thailand and Malaysia (Cinosi et al., 2015), and appears to be spreading to Western countries (Smith and Lawson, 2017). However, its use as a recreational drug is somewhat limited; for example, it does not appear to be used be in the clubbing or music scenes (Martinotti et al., 2017; Santacroce et al., 2017).

What is new in these cases is its link to body-building and to avoid positive opiate/opioid drug tests (at work or whilst in a drug rehabilitation programme). The type(s) of kratom products and the leaves from which they have been produced are not well reported. Where such information was given in the case reports reviewed here, it would appear that the most common products were used for relaxing/pain relief and euphoric/energising effects, often in combination.

Kratom has been added as an ingredient in an energy drink promoted at large sports gatherings. Mitragynine's role as a performance-enhancing substance was added to the repertoire to be screened for at sporting events (Guddat et al., 2016), and was added to the World Anti-Doping Agency's (WADA's) 2016 Monitoring Program in January 2016 (WADA, 2015). By the end of 2017, neither kratom nor mitragynine were listed in WADA's *Anti-Doping Testing Figures Reports* (https://www.wada-ama.org/en/resources/laboratories/anti-doping-testing-figures-report).

5.3. Toxicological analyses

Mitragynine and its metabolites are unlikely to be included in standard toxicology screens or routine drug testing (Philipp et al., 2011); although increasing awareness of the use of kratom and its products may alter this situation. Tests for kratom-derived compounds are not widely available

(Philipp et al., 2011). Most toxicology laboratories need to send their samples to specialist laboratories for identification and quantification of mitragynine and 7-hydroxymitragynine (Anderson et al., 2014; Streete, 2014). There are difficulties in obtaining reference samples for analysis (Holler et al., 2011). It may be necessary to replenish purchased reference samples of mitragynine standard solution in methanol on a regular basis, even though stored as recommended. This can be expensive.

In the UK context, Mitragynine and/or its metabolites were detected in using a Basic Drugs Screen in GC/MS and the presence and quantification of mitragynine and 7-hydroxymitragynine confirmed by LC-MS/MS. One of the authors estimates that the limit of detection for mitragynine on the GCMS is between 0.1 and 0.2 mg/L with their system/extraction technique.

According to the standard reference work, Baselt et al. (2017), the highest recorded post-mortem blood level for mitragynine is 1060 µg/L and a urine level of 3470 µg/L. there are no levels given for 7-Hydroxymitragynine. Taking into account all the cases presented here with levels, the mean post-mortem blood level for mitragynine is 0.775 (range 0.00089 – 16.000) mg/L; the mean urine level is 1.090 (range < 0.010 – 3.470) mg/L. For 7-Hydroxymitragynine the respective mean blood and urine levels are 0.66218 (range 0.0009 - 2.8) mg/L and 2.20 mg/L.; however, very few levels are available for this metabolite. Where only kratom was implicated in death and/or the only substance found in post-mortem blood samples (n = 3) the following levels have been reported: mean 0.398 (range 0.0035 – 0.890) mg/L.

There is a lack of detailed reports giving levels of mitragynine and 7-hydroxymitragynine, especially the latter, in poisoning intoxications and fatalities (Karinen et al., 2014; Neerman et al., 2013; Tungtananuwat and Lawanprasert, 2010), as well as established dosages leading to such events (Brown et al., 2017), as well as safe ceiling doses for chronic consumption in humans (Kruegel and Grundmann, 2018). Indeed, three of the known cases where 7-hydroxymitragynine levels are known were analysed by one of the present authors. Testing for 7-hydroxymitragynine testing is imperative, as it is typically not detectable in raw leaf consumption. Levels of mitragynine appear to be increasing, and when we see these increased levels, one could speculate that having detectable levels of 7-hydroxymitragynine could indicate a trend in consumption of extracted and/or artificially enhanced

products. Therefore, testing for, and detection of, quantifiable levels of 7-hydroxymitragynine would be helpful in checking out this theory. Brower (2015) suggests that the hydroxy metabolite could be identified via an organic bases screen; it elutes just before trazodone. One of the authors found that the metabolite elutes 0.4 min before mitragynine. It can be quantitated via LC/MS. Chromatography is also important in screening for the metabolite.

There is only a single case-report on driving under the influence of kratom (Wright, 2018); however, mitragynine was only qualitatively detected. Variations in the concentrations and potencies of different strains of kratom and derivatives, as well as inter-individual differences in pharmacokinetics may also be relevant factors to consider. Therefore, the publication of additional details will be of assistance to those investigating deaths where kratom was consumed. Without such information it is very difficult to define what constitute toxic/fatal doses and post-mortem levels/concentrations, especially as there is a dearth of cases where only mitragynine and/or 7-hydroxymitragynine are identified. A balanced approach to presenting information, whether based on quantitative sources or anecdotal evidence, is required, especially in relation to reporting adverse consequences associated with kratom use, as anecdotal evidence can weigh more heavily in affecting such choices (Gutierrez and Cohn, 2018).

5.4. Cause/mechanism of death

The leading issue identified from autopsy reports is that of congested and/or oedematous lungs (Table 4). However, such findings are very common in a high percentage of all autopsy reports. On its own, without histology and/or toxicology to confirm a kratom-related pathology, such a finding is inconclusive with respect to kratom causing death. Brain damage, principally due to hypoxia, is often seen in the cases described here, but this should be expected when deaths have occurred when there has been cardio-respiratory depression, the inhalation of gases, asphyxiation (including hanging), etc.

Cardiac issues also appear to be one of the key mechanisms of/contributions to death. In some cases, these appear to be already known as part of a decedent's medical history, or in some instances undiagnosed and/or triggered by the consumption of a psychoactive substance, especially

stimulants. The use of substances in this latter category appears to have been common, as reflected in prevalence surveys, as does their involvement in the cause of death (see below). Liver and urinary issues are also mentioned in the cases investigated here; for some, these conditions appear to have been chronic. However, there may be a higher incidence of such findings if the autopsy results for all cases were to be made available.

An awareness of the potential contribution that underlying medical conditions, especially undiagnosed ones, may make to the risk of death is important to convey to (potential) kratom users and those treating suspected kratom overdoses/intoxications. The principal concern here would appear be that of cardiac problems, especially cardiomegaly, coronary atherosclerosis and left ventricular hypertrophy (Table 4). Those with enlarged livers may also be at greater risk.

As with the recording and reporting of most drug-related poisoning fatalities, the actual mechanisms of death are poorly described in the cause of death fields on medical certificates of death; as indeed, are details of the substances themselves (Fugelstad et al., 2018; Jones and McAninch, 2015; Shai, 1994; Slavova et al., 2015).

This is not peculiar to any one country or geographical region of the world; and it undermines the accurate attribution of the initial underlying incident and the actual sequence of events and processes culminating in death itself, and thus accurate mortality statistics (Corkery, 2008; Shai, 1994). This issue has been known about for decades, especially amongst those responsible for instructing doctors and others completing death certificates, e.g. medical schools (Corkery, 2008; Shai, 1994). Yet, it still exists! In the UK, moves are afoot to try and mitigate these shortcomings. From April 2019 medical examiners will start checking all death certificates issued by treating doctors for accuracy and compliance with coroner notification obligations (DHSC, 2018; Luce and Smith, 2018).

5.5. Manner of death

Where known, the majority of deaths were ‘accidental’ in manner (93/131; 71%), including ‘misadventure’ cases (Table 1); for some coroners this implies that the decedent is aware that drug-

taking may involve some degree of risk-taking, for others there is no distinction between that and an 'accident' in the common-sense meaning of that term. About 9% of deaths were 'intentional', predominantly suicide, although there was one homicide. Some of the 'intentional' cases could be construed as being akin to the 'misadventure' category, whilst others where an 'open' or 'undetermined' finding was returned may be possible suicides. This spread of conclusions is broadly consistent with UK findings for drug-related deaths as a whole.

5.6. Consumption of kratom and contribution to death

The adverse, intoxicating, toxic or poisoning effects of kratom and/or other substances is the dominant theme emerging from the cause of death information provided (103/117; 88%).

In 27 cases reported here, where information was available on the cause of death (n = 117), kratom alone was implicated in the cause of death used/found on its own. In six of these case reports mitragynine and/or 7-hydroxymitragynine was the sole substance found in the toxicology. An overview of these 27 cases is given in Table 5. The key characteristics of the individuals who died are similar to those for all the deaths reported here: male; White; mean age of 32 years; employed; living with someone; and have a history of drug use, including kratom. The principal characteristics of the deaths themselves are: taking place at home address; resulting from intoxication, toxic effects, or overdose; accidental in manner; exhibiting pulmonary and/or cerebral congestion/oedema, cardiac and hepatic problems.

The majority of deaths reported here involved poly-substance consumption. This echoes the patterns observed in online fora with regard to usage (Cinosi et al., 2015). As mitragynine and its main metabolite 7-hydroxymitragynine bind to the μ and δ receptors causing an opioid-like effect at high doses and a stimulant-like effect at low doses, it is likely that they potentiate the effects of other substances consumed. The combination of kratom and stimulants (including NPS) could contribute to causing cardiac problems, whilst its use with CNS depressants (such as opioids, benzodiazepines, and alcohol mentioned in the cases reviewed here) clearly could cause potentially fatal cardio-respiratory problems. This likelihood is under-pinned by the fact that multi-substance use has been

associated with a greater risk of admission to a health care facility and/or a serious medical outcome (Post et al., 2019). The corollary is that using kratom on its own is likely to be safer than using it in combination with alcohol and/or other drugs; but underlying health conditions may still be relevant in terms of risk of dying. As mitragynine appears to have a lower lethality index than heroin (King and Corkery, 2018), its use in self-medicating for opiate/opioid dependence in countries where it is grown and produced could be seen as a *de facto* harm reduction activity.

The possibility of kratom-prescribed medication interactions is raised in some cases. For example, quetiapine's metabolism and clearance may be affected by mitragynine, possibly via its inhibitory effects on CYP2D6, CYP2C9 and other enzymes (Hughes, 2019). Sertraline also appears to be potentially affected in this way as it is metabolised via CYP2D6 (Hanapi et al., 2013).

5.7. 'At-risk' groups

The information for all cases collated in this study (see Tables 1 to 4) suggests the possibility of seven categories of kratom users at greater risk of dying, some of which overlap:

(a) those using kratom in the context of opioid use, especially heroin, fentanyl and morphine, novel opioids (such as fentanyls, U-47700), e.g. for chronic pain relief;
(b) those using kratom in the context of benzodiazepine use, including 'designer benzos' (such as etizolam);
(c) those using kratom in the context of multiple CNS depressant drugs, especially opioids and benzodiazepines (with or without alcohol);
(d) those consuming kratom in the context of recreational drug use, including stimulants (amphetamine/methamphetamine, ecstasy, cocaine), and NPS;
(e) those with cardiovascular and/or hepatic medical conditions (whether diagnosed or undiagnosed), especially where stimulants are used;
(f) those with psychiatric or mental health issues, such as anxiety and depression, including those taking prescribed psychiatric medicines (such as quetiapine or sertraline); and
(g) those taking prescribed anti-epileptics, gabapentinoids.

A limitation of this profile of users is that it is based on deaths covered by this study; many of which have limited demographic information. However, the period is sufficiently long to see the impact of emerging novel psychoactive substances, especially opioids (Schifano et al., 2015).

5.8. Strengths and limitations of this study

This is the first study to draw together information on UK kratom-related fatalities. It also presents the first comprehensive international overview and detailed analysis of cases in the public domain at the time of writing. Although most of the data are from the USA and Europe, it provides a robust dataset of nearly 160 cases from which more reliable conclusions can be drawn than hitherto. The key findings presented here echo those in a recent summary of 152 US fatalities positive for post-mortem mitragynine during July 2016-December 2017 (O'Malley Olsen et al., 2019); some of those cases may be included in our present study.

This study has, out of necessity, drawn on a wide range of data sources to collate information on as many kratom-related fatalities as possible, thereby facilitating the provision of a dataset that can be objectively analysed and appropriate scientific conclusions made. The quality of the data and their sources vary considerably, but the inclusion of less robust sources is justified in our opinion, as was done in studies looking at khat-related fatalities (Corkery, 2011; Corkery et al., 2011a, 2011b).

In terms of a hierarchy of evidence, the present investigation and similar studies probably lie towards the bottom of the evidential pyramid. For example, using a simple 4-tier approach: level 1 – generalisable studies; level 2 – conceptual studies; level 3 – descriptive studies; level 4 – single case study (Daly et al., 2007), some of the data used here come from levels 3 and 4. In a broader range of levels: Metanalysis; Systematic Reviews; Randomised Controlled Clinical Trials; Cohort studies; Case-Control Studies; Case Series/Case Reports; Editorials and Expert Opinions; *in vivo* studies; *in vitro* research studies, proposed by Sayre et al. (2017), the data employed in the present study come from levels straddling the middle of this continuum. It thereby demonstrates the need to be pragmatic in selecting approaches to research under-explored phenomena such as kratom-related fatalities. An

improved database of properly collated data, as advocated above, would help in making future studies on such deaths appear higher up the evidential pyramid.

The specific types of sources are listed against each case in the supplementary table, together with an indication of their completeness. The level of evidence for a specific case in the present study in descending order are: (a) documents relating to the incident investigation, the autopsy report and toxicology report; (b) documents relating to the incident investigation together with the autopsy report incorporating the main toxicological results; (c) summary by the coroner/medical examiner/chief investigator; (d) FDA Adverse Event Reporting System (FAERS) report; (e) published case-study; (f) published case-series; (g) media report. That said, there is some variability in the quality in terms of completeness and consistency of sources within these categories, especially the data published by the FDA.

The documents published by the FDA (2018a, 2018b, 2018c) in support of its case to include kratom into Schedule 1 of the Controlled Substances Act 1970 largely come from the FAERS. This contains entries: (a) relating to published academic papers, including many of those included in this analysis; (b) summaries of investigations by police, coroners and medical examiners that include details of autopsy and toxicology reports; as well as (c) very brief and uninformative anecdotal reports. Similar observations could be made in regard to the DEA's Three Factor Analysis (DEA, 2016b).

There is a need for measured and accurate reporting. For example, even the National Institute on Drug Abuse (NIDA) has unhelpfully concluded that "Most kratom associated deaths appear to have resulted from adulterated products (other drugs mixed in with the kratom) or taking kratom along with other potent substances (sic) …" (NIDA, 2019). Whilst the second clause is quite correct, the initial part of this sentence is very misleading. Such wording only serves to obfuscate scientific debate and progress.

The media, interest groups, and policy-makers as well as scientists need to be as accurate as possible in presenting information and making inferences, which should be evidence-based. This can only be done through comprehensive screening and identification of cases, proper collection and

accurate collation of data, especially toxicology levels, known medical history, concomitant use of other substances, and objective dissemination of information regarding deaths associated with kratom use. The exact nature of such links, if any, in terms of causality or contribution to deaths, including any caveats about interpretation, should be explicit. To do otherwise creates difficulties for investigating and understanding the epidemiology of such cases, and their future prevention. To mitigate such issues in the present paper, attempts were made to obtain copies/sight of autopsy and toxicology reports as well as police investigation reports.

Additional limitations of this paper need to be noted. Further details of cases reported in the media and conference abstracts need to be obtained to fill out the data for the cases presented here. Not all cases have been necessarily identified. However, this is believed to be the first paper where a systematic analysis of reported cases has been conducted.

6. Conclusions

The findings presented here add to the existing knowledge-base on deaths associated with kratom use. This paper confirms that a growing number of such fatalities is being reported, and it identifies that in most cases this is in association with the abuse of other psychoactive substances. Typically, CNS depressants including opiates/opioids, benzodiazepines and alcohol are found at post-mortem, along with recreational drugs such as controlled stimulants and ‘legal highs’/NPS, as well as prescribed therapeutic medications. As noted earlier, kratom was the sole drug implicated in 23.1% of cases examined here where the cause of death is known. Although the mortality data used by King and Corkery (2018) relate to England and Wales, applying their method of sole to any mention of an index in the cause of death, it would appear that kratom (mitragynine) has a higher lethality index than novel amphetamines, benzodiazepine analogues, cannabis, piperazines, and synthetic cathinones, but one that is lower than amphetamines, benzofurans, cocaine/crack, and other more potent substances. Underlying medical conditions, both already diagnosed or suspected as well as unknown at the time of death, can contribute to the way in which kratom takes or effect and vice versa. These findings support the emerging literature about the plant.

These facts need to be taken into account by: current and potential consumers of kratom; health professionals when faced with acute/chronic presentations in hospitals; and those engaged in planning prevention and treatment services. There is a need to educate health professionals, including clinicians, pathologists and medical examiners, as well as making psychiatrists and sports scientists aware of the different ways in which the plant is used.

The safety profile of *Mitragynine speciosa* still remains only partially understood, despite its increasing popularity. Further research is needed in respect of kratom on: deaths in South-East Asia where kratom is widely used; the levels of mitragynine and its metabolites consumed and possible interactions with other substances; toxic and fatal levels.

Above all, this study has demonstrated that without reliable, accurate and complete information that is correctly collated, scientifically analysed and disseminated in a timely manner, the phenomenon of what deaths can be ascribed to the use of kratom and the nature of any association(s) that can be made will remain unrealised.

Acknowledgements

The authors would like to thank the following for the provision of UK data: Her Majesty's Coroners; National Records of Scotland; and Ralph Bouhaider, pathologist in the Pathology Division of the University of Edinburgh, and Procurators Fiscal in Scotland. We also appreciate the contribution made by the staff providing analytical services in the relevant laboratories, especially Denise McKeown at the University of Glasgow. We kindly acknowledge the provision of details on individual cases by: Luke Werhan, Ohio Department of Health; Nick Wing, Huffington Post; Amy Martin, Chief Medical Examiner for Denver, Colorado; Olwen Domingo, University of Munich; Rhome Hughes, University of North Dakota; Andrew Monte, University of Colorado; and Kelly Devine, Kratom United.

Some elements of this paper have been given as oral presentations: “The characteristics of deaths involving kratom in the United Kingdom and elsewhere” at the 4th International Conference on Novel Psychoactive Substances, Budapest, 30-31 May 2016; “Deaths in the United Kingdom related to Kratom” at the UKIAFT (United Kingdom and Ireland Association of Forensic Toxicologists) Meeting, Charing Cross Hospital, London, 28 June 2018.
However, these details have not been previously published.

Conflicts of interest

Fabrizio Schifano was a full member of the UK’s Advisory Council on the Misuse of Drugs (AMCD) and its Novel Psychoactive Substances (NPS) Committee; John Corkery is a co-opted member of the ACMD’s Technical Committee, as well as having been a member of the Scottish Government’s NPS Expert Group and Hertfordshire County Community Safety Unit's NPS Working Group. Christine Goodair, Hugh Claridge and John Corkery are members of the ACMD’s Novel Psychoactive Substances Committee and Drug-Related Deaths Working Group. The views expressed here are solely those of the authors and do not necessarily reflect those of the ACMD.
Amy Hendricks has provided advice to the American Kratom Association.

None of the views or case interpretations presented here necessarily reflect that of past or current employers.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Abayarathna, S. and Jaehne, M., 2016. Electronic Vapor liquid Composition and Method of Use. 23 June. US Patent US 20160174603 A1. Available at: https://www.google.com/patents/US20160174603 Accessed on 15 May 2019.

Adkins, J.E., Boyer, E.W., McCurdy, C.R., 2011. Mitragyna speciosa, a psychoactive tree from Southeast Asia with opioid activity. Curr. Top. Med. Chem. 11, 1165-75. PubMed PMID: 21050173. https://doi.org/10.2174/156802611795371305

Ahmad, K., Aziz, Z., 2012. Mitragyna speciosa use in the northern states of Malaysia: a cross-sectional study. J. Ethnopharmacol. 141, 446-50. PubMed PMID: 22440259. http://www.ncbi.nlm.nih.gov/pubmed/22440259 https://doi.org/10.1016/j.jep.2012.03.009

Anderson, C., Duffy, I., Harre, N., Wade, N., 2014. Four odd cases in the Valley of the Sun. Abstract P-68 in Book of Abstracts of Society of Forensic Toxicologists (SOFT) 2014. 19-24 October 2014. DeVos Convention Center, Grand Rapids Michigan. Available at: http://www.soft-tox.org/files/meeting_abstracts/SOFT_2014_meeting_abstracts.pdf Accessed on 15 May 2019.

Anwar, M., Law, R., Schier, J., 2016. Notes from the Field: Kratom (Mitragyna speciosa) Exposures Reported to Poison Centers - United States, 2010-2015. MMWR Morb. Mortal. Wkly. Rep. 65, 748-9. PubMed PMID: 27466822. http://dx.doi.org/10.15585/mmwr.mm6529a4

Assanangkornchai, S., Muekthong, A., Sam-Angsri, N., Pattanasattayawong, U., 2007. The use of *Mitragynine speciosa* (“Krathom”), an addictive plant, in Thailand. Subst. Use Misuse. 42, 2145-2157. PubMed PMID 18097996. https://doi.org/10.1080/10826080701205869

Azizi, J., Ismail, S., Mansor, S.M., 2013. Mitragyna speciosa Korth leaves extracts induced the CYP450 catalyzed aminopyrine-N-demethylase (APND) and UDP-glucuronosyl transferase (UGT) activities in male Sprague-Dawley rat livers. Drug Metabol. Drug Interact. 28, 95-105. PubMed PMID: 23435185.
https://doi.org/10.1515/dmdi-2012-0039

Babu, K.M., McCurdy, C.R., Boyer, E.W., 2008. Opioid receptors and legal highs: Salvia divinorum and Kratom. Clin. Toxicol. (Phila). 46, 146-52. PubMed PMID: 18259963.
https://doi.org/10.1080/15563650701241795

Bäckstrom, B.G., Classon, G., Löwenhielm, P., Thelander, G., 2010. Krypton – ny, dödlig Internetdrog. Sedan oktober 2009 har nio unga personer dött i Sverige. [Krypton--new, deadly Internet drug. Since October 2009 nine young people have died in Sweden]. Läkartidningen. 107(50), 3196-7. PubMed PMID: 21294331.

Babin, J., 2017. Analysis of two deaths reportedly associated with Kratom use – Tupper Lake, New York, and Hillsborough County, Florida. Available at:
http://speciosa.org/analysis-of-two-deaths-reportedly-associated-with-kratom/
Accessed on 15 May 2019.

Barham, A., 2009. “My son died of an addiction to drugs bought online”. 11 February. St Albans and Harpenden Review. Available at:
http://www.stalbansreview.co.uk/news/4118138._My_son_died_of_an_addiction_to_drugs_bought_off_the_internet_/
Accessed on 15 May 2019.

Baselt, R.C., 2017. Disposition of Toxic Drugs and Chemicals in Man (11th ed.) 15 March. Biomedical Publications: Seal Beach, CA. ISBN: 978-0-692-77499-1

Bhattacharjee, B., 2016. Shawn Lucas Confirmed Dead: found lying on the bathroom floor. 5 August. Morning News USA. Available at: https://www.morningnewsusa.com/shawn-lucas-confirmed-dead-found-lying-on-the-bathroom-floor-did-democrats-kill-him-2394986.html Accessed on 15 May 2019.

Bishop-Freeman, S.C., Feaster, M.S., Beal, J., Miller, A.M., Hargrove, R.L., Brower, J.O., Winecker, R.E., 2016. Loperamide-related deaths in North Carolina. J. Anal. Toxicol., 40, 677-686. PubMed PMID: 27474361. https://doi.org/10.1093/jat/bkw069

Boyer, E.W., Babu, K.M., Adkins, J.E., McCurdy, C.R., Halpern, J.H., 2008. Self-treatment of opioid withdrawal using kratom (*Mitragynia speciosa* korth). Addiction. 103, 1048-50. PubMed PMID: 18482427; PubMed Central PMCID: PMC3670991. https://doi.org/10.1111/j.1360-0443.2008.02209.x

Brodwin, E., 2018. A ruling is imminent on the legality of a controversial drug that's used to treat addiction - but some have called it a 'dangerous opioid'. 17 November, Business Insider UK. Available at: http://uk.businessinsider.com/is-kratom-legal-government-regulators-decide-2018-11?r=US&IR=T Accessed on 15 May 2019.

Brower, J., 2015. Postmortem analysis of Kratom (Mitragynine) in North Carolina. Presentation at Society of Forensic Toxicologists (SOFT) 2015. 13-18 October 2015. Hyatt Regency Hotel, Atlanta, Georgia.

Brower, J., Hargrove, R., Winecker, R., 2015. Postmortem analysis of Kratom (Mitragynine) in North Carolina. Abstract S17 in Book of Abstracts of Society of Forensic Toxicologists (SOFT) 2015. 13-18 October 2015. Hyatt Regency Hotel, Atlanta, Georgia. Available at: http://www.soft-tox.org/files/meeting_abstracts/SOFT_2015_meeting_abstracts.pdf Accessed on 15 May 2019.

Brown, P.N., Lund, J.A., Murch, S.J., 2017. A botanical, phytochemical and ethnomedicinal review of the genus Mitragyna korth: Implications for products sold as kratom. J. Ethnopharmacol. 18, 302-325. PubMed PMID: 28330725. https://doi.org/10.1016/j.jep.2017.03.020

Bruno, J., 2016. 9 investigates Kratom: Natural herb or deadly drug? 10 March. WSOCTV. Available at: http://www.wsoctv.com/news/9-investigates/9-investigates-kratom-natural-herb-or-deadly-drug/68821730 Accessed on 15 May 2019.

Burkill, I.H., Haniff, M., 1930. Malay village medicine. The Garden's Bulletin Straits Settlement, 6, 165-207.

Carbone, A., 2017. Coroner: police sergeant died from high concentration of kratom. 12 September. Adirondack Daily Enterprise. Available at: http://www.adirondackdailyenterprise.com/news/local-news/2017/09/coroner-kratom-overdose-killed-tupper-lake-police-sergeant Accessed on 4 August 2018.

Carter, M., Wills, B., Cumpston, K., 2016. Abstract 25: Clinical effects of kratom use: a poison center observational study. NACCT Abstracts 2016, Clin Toxicol. 54, 659-811. https://doi.org/10.1080/15563650.2016.1197486

Carver, J.D., 2018. Autopsy report on Andrew Marquez. Available at: https://assets.documentcloud.org/documents/4756962/Andrew-Marquez-Autopsy.pdf Accessed on 15 May 2019.

CBS Miami., 2014. Tragic death moves Broward Commissioner to ban addictive drug. 8 October. CBS Miami. Available at: http://miami.cbslocal.com/2014/10/08/tragic-death-moves-broward-commissioner-to-ban-addictive-drug/
Accessed on 15 May 2019.

Chang Rai Times., 2012. Kratom Leaf for Drug Cocktail Adds to Thailand's Woes. 23 July, Chang Rai Times. Available at: https://www.chiangraitimes.com/kratom-leaf-for-drug-cocktail-adds-to-thailands-woes.html
Accessed on 15 May 2019.

Chapman, C., 2017. Coroner: Tupper Lake sgt died of kratom overdose. 12 September. pressrepublican.com. Available at: http://www.pressrepublican.com/news/local_news/coroner_tupper_lake_sgt_died_of_kratom_overdose/article_b583af01-1d4b-5da5-b87a-b27c67607ec7.html
Accessed on 28 July 2018.

Chemist & Druggist., 1930. Kratom Eaters. The Chemist and Druggist, 112, 702. Available at: https://archive.org/details/b19974760M2738/page/n1
Accessed on 15 May 2019.

Chongrattanakon, N., Thepthien, B-O., Hong, S.A., 2017. Prevalence and psycho-social determinants of Kratom (Mitragyna speciosa) juice cocktail consumption among youth in Surat Thani Province, Thailand. J. Substance Use. 23, 144-153. https://doi.org/10.1080/14659891.2017.1378735
https://www.tandfonline.com/doi/abs/10.1080/14659891.2017.1378735

Cinosi, E., Martinotti, G., Simonato, P., Singh, D., Demetrovics, Z., Roman-Urrestarazu, A., Bersani, F.S., Vicknasingam, B., Piazzon, G., Li, J.H., Yu, W.J., Kapitány-Fövény, M., Farkas, J., Di Giannantonio, M., Corazza, O., 2015. Following "the Roots" of Kratom (Mitragyna speciosa): The Evolution of an Enhancer from a Traditional Use to Increase Work

and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries. Biomed. Res. Int. 968786. PubMed PMID: 26640804; PubMed Central PMCID: PMC4657101.
http://dx.doi.org/10.1155/2015/968786

Cook, B.L., 2018. Caleb J. Sturgis, 25, care manager for the deaf, dies in car accident. 28 June. philly.com. Available at: http://www2.philly.com/philly/obituaries/caleb-j-sturgis-25-care-manager-for-the-deaf-dies-in-car-accident-20180628.html
Accessed on 15 May 2019.

Corkery, J., 2008. UK drug-related mortality – issues in definition and classification, Drugs and Alcohol Today, 8, 17-25.
https://doi.org/10.1108/17459265200800014

Corkery, J., 2011. Response to Commentaries on 'Bundle of fun' or 'bunch of problems'? Case series of khat-related deaths in the UK. Drugs: education, prevention and policy. 18, 431-2.
https://doi.org/10.3109/09687637.2010.504200
http://www.tandfonline.com/doi/full/10.3109/09687637.2011.604974

Corkery, J.M., Schifano, F., Oyefeso, A., Ghodse, A.H., Tonia, T., Naidoo, V., Button, J., 2011a. Review of literature and information on 'khat-related' mortality: a call for recognition of the issue and further research. Ann. Ist. Super. Sanitá, 47, 445-64. doi: 10.4415/ANN_11_04_17. PMID: 22194080.
http://www.ncbi.nlm.nih.gov/pubmed/22194080

Corkery, J.M., Schifano, F., Oyefeso, A., Ghodse, A.H., Tonia, T., Naidoo, V., Button, J., 2011b. 'Bundle of fun' or 'bunch of problems'? Case series of khat-related deaths in the UK. Drugs: education, prevention and policy, 18, 408-425.
https://doi.org/10.3109/09687637.2010.504200
http://www.tandfonline.com/doi/full/10.3109/09687637.2010.504200

Cuyahoga County Medical Examiner's Office., 2018. Drug overdose deaths. Ohio. Available at: https://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=41&ved=2ahUKEwiOzKCbt-veAhVML8AKHeKyBig4KBAWMAB6BAgJEAI&url=https%3A%2F%2Fcuyahoga-stat.demo.socrata.com%2Fapi%2Fviews%2F4taz-nm46%2Frows.pdf%3Fapp_token%3DU29jcmF0YS0td2VraWNrYXNz0&usg=AOvVaw0xeAKVVg_IfSeF5-5lKph2
Accessed on 15 May 2019.

Daly, J., Willis, K., Small, R., Green, J., Welch, N., Kealy, M., Hughes, E., 2007. A hierarchy of evidence for assessing qualitative health research. J. Clin. Epidemiol. 60, 43-9. PubMed PMID: 17161753.
https://doi.org/10.1016/j.jclinepi.2006.03.014
https://www.jclinepi.com/article/S0895-4356(06)00210-1/fulltext

Daud, A.H., Lajis, R.H., Ariff, A.M., Zyoud, S.H., Rahman, H., 2012. Toxic plants poisoning cases reported to National Poison Center (2006-2009). Poster 88. Annual Meeting Abstracts, 10th Annual Congress of Asia-Pacific Association of Medical Toxicology, Penang, Malaysia. November 2011. J. Med. Toxicol. 8, 192-237.
https://doi.org/10.1007/s13181-012-0237-z
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3550232/

Davidson, L., Rawat, M., Stojanovski, S., Chandrasekharan, P., 2019. Natural drugs, not so natural effects: Neonatal abstinence syndrome secondary to 'kratom'. J. Neonatal Perinatal Med. 12(1): 109-112. doi: 10.3233/NPM-1863. PubMed PMID: 30149482.
https://content.iospress.com/articles/journal-of-neonatal-perinatal-medicine/npm1863

Davis, K., 2018. Riverside man is charged in fentanyl sting. 25 October. Los Angeles Times. Available at: http://www.pressreader.com/usa/los-angeles-times/20181025/282321090993145

Accessed on 15 May 2019.

DEA., 2016a. Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine Into Schedule I: A Proposed Rule by the Drug Enforcement Agency. 31 August. Drug Enforcement Agency, US Department of Justice. Available at: https://www.gpo.gov/fdsys/pkg/FR-2016-08-31/pdf/2016-20803.pdf
Accessed on 15 May 2019.

DEA., 2016b. Mitragynine and 7-Hydroxymitragynine: Background Information and Evaluation of 'Three Factor Analysis' (Factors 4, 5 and 6) for Temporary Scheduling. 1 September. Drug Enforcement Agency, US Department of Justice. Available at: https://www.regulations.gov/contentStreamer?documentId=DEA-2016-0015-0004&contentType=pdf
Accessed on 15 May 2019.

DEA., 2016c. Withdrawal of Notice of Intent to Temporarily Place Mitragynine and 7-Hydroxymitragynine Into Schedule I: A Proposed Rule by the Drug Enforcement Agency. 13 October. Drug Enforcement Agency, US Department of Justice. Available at: https://www.gpo.gov/fdsys/pkg/FR-2016-10-13/pdf/2016-24659.pdf
Accessed on 15 May 2019.

DHSC., 2018. Introduction of Medical Examiners and Reforms to Death Certification in England and Wales: Government response to consultation.11 June. London: Depart of Health & Social Care. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/715224/death-certification-reforms-government-response.pdf
Accessed on 15 May 2019.

Domingo, O., Roider, G., Stöver, A., Graw, M., Musshoff, F., Sachs, H., Bicker, W., 2017. Mitragynine concentrations in two fatalities. Forensic Sci. Int. 271, e1-e7. PubMed PMID: 28089300. https://doi.org/10.1016/j.forsciint.2016.12.020

Dorman, C., Wong, M., Khan, A., 2015. Cholestatic hepatitis from prolonged kratom use: a case report. Hepatology. 61, 1086-7. PubMed PMID: 25418457. https://doi.org/10.1002/hep.27612

Drago, J.Z., Lane, B., Kochav, J., Chabner, B., 2017. The Harm in Kratom. Oncologist. Jul 24. pii: theoncologist.2017-0279. doi: 10.1634/theoncologist.2017-0279. PubMed PMID: 28739869; PubMed Central PMCID: PMC5553967. http://theoncologist.alphamedpress.org/content/22/8/1010.long

Dunn, R., Lindstrom, L., 2018. Family members question practices at Anyana-Kai following deaths of loved ones. 12 October, Toledo Blade. Available at: https://www.toledoblade.com/local/daily-log/2018/10/12/family-members-question-practices-at-west-toledo-anyana-kai-following-deaths-of-loved-ones/stories/20181003146
Accessed on 15 May 2019.

Eldridge, W.B., Foster, C., Wyble, L., 2018. Neonatal Abstinence Syndrome Due to Maternal Kratom Use. Pediatrics, 142, pii: e20181839. doi: 10.1542/peds.2018-1839. PubMed PMID: 30404789. http://pediatrics.aappublications.org/content/pediatrics/early/2018/11/05/peds.2018-1839.full.pdf

EMCDDA., 2011. Online sales of new psychoactive substances / 'legal highs': summary of results from the 2011 multilingual snapshots. Briefing paper. 15 November. Lisbon: European Monitoring Centre for Drugs and Drug Addiction. Available at: http://www.emcdda.europa.eu/system/files/publications/650/SnapshotSummary_314798.pdf
Accessed on 15 May 2019.

EMCDDA., 2015a. Kratom (*Mitragyna speciosa*) drug profile. 8 January. Available at: http://www.emcdda.europa.eu/publications/drug-profiles/kratom

Accessed on 15 May 2019.

EMCDDA., 2015b. New psychoactive substances in Europe. An update from the EU Early Warning System. Lisbon: European Monitoring Centre for Drugs and Drug Addiction. March. Available at: http://www.emcdda.europa.eu/system/files/publications/65/TD0415135ENN.pdf

Accessed on 15 May 2019.

Esch, M. 2017. Officer's death intensifies scrutiny of herbal supplement. 30 September. Apnews.com. Available at: https://www.apnews.com/e9986e318f7d4c47a3dc4189c5054bdd

Accessed on 15 May 2019.

FDA., 2018a. CFSAN Adverse Event Reporting System: Kratom Deaths (December 1, 2017). U.S. Food & Drug Administration. Available at: https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofFoods/CFSAN/CFSANFOIAElectronicReadingRoom/UCM588952.pdf

Accessed on 15 May 2019.

FDA., 2018b. FDA Adverse Event Reporting System: Kratom Deaths (February 6, 2018). U.S. Food & Drug Administration. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/CDERFOIAElectronicReadingRoom/UCM595575.pdf

Accessed on 15 May 2019.

FDA., 2018c. Kratom additional death adverse event reports. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/cderfoiaelectronicreadingroom/ucm599611.pdf

Accessed on 15 May 2019.

Fogarty, M.F., Papsun, D.M., Logan, B.K., 2018. Analysis of Fentanyl and 18 Novel Fentanyl Analogs and Metabolites by LC-MS-MS, and report of Fatalities Associated with Methoxyacetylfentanyl and Cyclopropylfentanyl. J. Anal. Toxicol. 42, 592-604. PubMed PMID: 29750250. https://doi.org/10.1093/jat/bky035 https://academic.oup.com/jat/advance-article-abstract/doi/10.1093/jat/bky035/4994607?redirectedFrom=fulltext

Forrester, M.B., 2013. Kratom exposures reported to Texas poison centers. J. Addict. Dis. 32, 396-400. PubMed PMID: 24325774. https://doi.org/10.1080/10550887.2013.854153

FOX12., 2013. Kratom investigated in Longview woman's death. 3 April. Available at: http://www.kptv.com/story/21528282/kratom-investigated-in-longview-womans-death Accessed on 29 April 2017.

Franklin, J., 2014. Winchester University student David Daniels killed by effects of Kratom coroner rules. 16 June. Southern Daily Echo. Available at: http://www.dailyecho.co.uk/news/11280190.Student__killed_by_effects_of_legal_high__Kratom_rules_coroner/ Accessed on 15 May 2019.

Frost, R.E., Deking, J., Neerman, M.F., 2012. A Drug Fatality Involving Kratom: A Case Report. Abstract S06 in Book of Abstracts of Society of Forensic Toxicologists (SOFT) 2012. 1-6 July 2012 Marriott Copley Place, Boston. Available at: http://www.soft-tox.org/files/meeting_abstracts/SOFT_2012_meeting_abstracts.pdf Accessed on 15 May 2019.

Fuenffinger, N., Ritchie, M., Ruth, A., Gryniewicz-Ruzicka, C., 2017. Evaluation of ion mobility spectrometry for the detection of mitragynine in kratom products. J. Pharm. Biomed. Anal. 134, 282-286. PubMed PMID: 27951469.

https://doi.org/10.1016/j.jpba.2016.11.055

https://www.sciencedirect.com/science/article/pii/S0731708516312705?via%3Dihub

Fugelstad, A., Ramstedt, M., Thiblin, I., Johansson, L.A., 2017. Drug-related deaths: Statistics based on death certificates miss one-third of cases. Scand. J. Public Health. Dec 1:1403494817745187. [Epub ahead of print] PubMed PMID: 29207931.

https://doi.org/10.1177%2F1403494817745187

https://journals.sagepub.com/doi/10.1177/1403494817745187

Gershman, K., Timm, K., Frank, M., Lampi, L., Melamed, J., Gerona, R., Monte, A.A., 2019. Deaths in Colorado Attributed to Kratom. N. Engl. J. Med. 380, 97-98. doi: 10.1056/NEJMc1811055. PubMed PMID: 30601742.

Grant, M.J., Booth, A., 2009. A typology of reviews: an analysis of 14 review types and associated methodologies. Health Info. Libr. J. 26, 91-108. PubMed PMID: 19490148.

https://doi.org/10.1111/j.1471-1842.2009.00848.x

https://onlinelibrary.wiley.com/doi/full/10.1111/j.1471-1842.2009.00848.x

Greenfield, B., 2015. What's Kratom? Parents claim the drug drove son to suicide. 20 May. Yahoo News. Available at: https://www.yahoo.com/news/whats-kratom-parents-speak-out-after-drug-drives-119458538452.html

Accessed on 15 May 2019.

Griffin, O.H. 3rd., Daniels, J.A., Gardner, E.A., 2016. Do You Get What You Paid For? An Examination of Products Advertised as Kratom. J. Psychoactive Drugs, 48, 330-335. PubMed PMID: 27669103.

https://doi.org/10.1080/02791072.2016.1229876

Griffiths, C.L., Gandhi, N., Olin, J.L., 2018. Possible kratom-induced hepatomegaly: A case report. J. Am. Pharm. Assoc. (2003). 58, 561-563. PubMed PMID: 30041853.

https://doi.org/10.1016/j.japh.2018.05.006

https://www.japha.org/article/S1544-3191(18)30226-7/fulltext

Grundmann, O., 2017. Patterns of Kratom use and health impact in the US-Results from an online survey. Drug Alcohol Depend. 176, 63-70. PubMed PMID: 28521200.
https://doi.org/10.1016/j.drugalcdep.2017.03.007
https://www.sciencedirect.com/science/article/pii/S0376871617301825?via%3Dihub

Guddat, S., Görgens, C., Steinhart, V., Schänzer, W., Thevis, M., 2016. Mitragynine (Kratom) - monitoring in sports drug testing. Drug Test. Anal. 8, 1114-1118.
PubMed PMID: 27001139.
https://doi.org/10.1002/dta.1970
http://www.ncbi.nlm.nih.gov/pubmed/27001139

Gummin, D.D., Mowry, J.B., Spyker, D.A., Brooks, D.E., Fraser, M.O., Banner, W., 2017. 2016 Annual Report of the American Association of Poison Control Center's National Poison Data System (NPDS): 34th Annual Report. Clin. Toxicol. 55, 1072-1254.
https://doi.org/10.1080/15563650.2017.1388087

Gunderson, E.W., Haughey, H.M., Ait-Daoud, N., Joshi, A.S., Hart, C.L., 2014. A survey of synthetic cannabinoid consumption by current cannabis users. Subst Abus. 35, 184-9. PubMed PMID: 24821356; PubMed Central PMCID: PMC4048873.
https://doi.org/10.1080/08897077.2013.846288
https://www.tandfonline.com/doi/abs/10.1080/08897077.2013.846288?journalCode=wsub20

Gutierrez, K.M., Cohn, L.D., 2018. Perceived Risk of Emerging Recreational Drugs: Impact of Anecdotal and Statistical Evidence. J. Drug Issues. 48, 435-451.
https://doi.org/10.1177/0022042618770632
http://journals.sagepub.com/doi/abs/10.1177/0022042618770632

Haarer, R., 2018. Colorado coroners link kratom to at least 23 deaths since 2016. 13 November. 9News. Available at: https://www.9news.com/article/news/health/colorado-coroners-link-kratom-to-at-least-23-deaths-since-2016/73-614063305 Accessed on 18 November 2018.

Hanapi, N.A., Ismail, S., Mansor, S.M., 2013. Inhibitory effect of mitragynine on human cytochrome P450 enzyme activities. Pharmacognosy Res. 5, 241-6. PubMed PMID: 24174816; PubMed Central PMCID: PMC3807987. https://doi.org/10.3390/pharmaceutics7020010 http://www.phcogres.com/text.asp?2013/5/4/241/118806

Hassan, Z., Muzaimi, M., Navaratnam, V., Yusoff, N.H., Suhaimi, F.W., Vadivelu, R., Vicknasingam, B.K., Amato, D., von Hörsten, S., Ismail, N.I., Jayabalan, N., Hazim, A.I., Mansor, S.M., Müller, C.P., 2013. From Kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. Neurosci. Biobehav. Rev. 37, 138-51. PubMed PMID: 23206666. https://doi.org/10.1016/j.neubiorev.2012.11.012 http://www.sciencedirect.com/science/article/pii/S0149763412002023

Hemby, S.E., McIntosh, S., Leon, F., Cutler, S.J., McCurdy, C.R., 2018. Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine. Addiction Biology. Epub 27 June. https://doi.org/10.1111/adb.12639 https://onlinelibrary.wiley.com/doi/abs/10.1111/adb.12639

Hendricks, A., 2018. There is not a scientifically proven toxic level of mitragynine, Review of CA. deaths. January. *speciosa.org. Available* at: http://speciosa.org/there-is-not-a-scientifically-proven-toxic-level-of-mitragynine-review-of-ca-deaths/ Accessed on 15 May 2019.

Hennepin County Medical Examiner., 2017. Press Release Report. 19 May. Carfentanil-related-cases-may.pdf. Available at: https://content.gov.delivery.com/accounts/MNHENNE/bulletins/196351a Accessed on 16 September 2017.

Henningfield, J.E., Fant, R.V., Wang, D.W., 2018. The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. Psychopharmacology (Berl), 235, 573-589. doi: 10.1007/s00213-017-4813-4. PubMed PMID: 29273821; PubMed Central PMCID: PMC5813050. https://link.springer.com/article/10.1007/s00213-017-4813-4

Hillebrand, J., Olszewski, D., Sedefov, R., 2010. Legal highs on the Internet. Subst. Use Misuse. 45, 330-40. PubMed PMID: 20141450. https://doi.org/10.3109/10826080903443628

Hodson, D., 2018a. Family recalls details of son's tragic death. 25 January. Mountain Democrat. Available at: https://www.mtdemocrat.com/news/family-recalls-details-of-sons-tragic-death/ Accessed on 15 May 2019.

Hodson, D., 2018b. Coroner's report on Mayes released. 18 April. Mountain Democrat. Available at: https://www.mtdemocrat.com/news/coroners-report-on-mayes-released/ Accessed on 15 May 2019.

Holler, J.M., Vorce, S.P., McDonough-Bender, P.C., Magluilo, J. Jr, Solomon, C.J., Levine, B., 2011. A drug toxicity death involving propylhexedrine and mitragynine. J. Anal. Tox. 35, 54-9. PubMed PMID: 21219704. https://doi.org/10.1093/anatox/35.1.54 http://www.ncbi.nlm.nih.gov/pubmed/21219704

Home Office., 2013. Circular 004/2013: Control of synthetic cannabinoids. 1 August 2013. London: Home Office. Available at: https://www.gov.uk/government/publications/circular-0042013-control-of-synthetic-cannabinoids Accessed on 15 May 2019.

Hughes, R.L., 2019. Fatal combination of mitragynine and quetiapine – a case report with discussion of a potential herb-drug interaction. Forensic Sci. Med. Pathol. 15, 110-113. doi: 10.1007/s12024-018-0049-9. PubMed PMID: 30498933. https://link.springer.com/article/10.1007%2Fs12024-018-0049-9

Jaliawala, H.A., Abdo, T., Carlile, P.V., 2018. Kratom: a potential cause of Acute Respiratory Distress Syndrome. American Thoracic Society 2018 International Conference D35. Drug-induced lung disease: case reports 23 May 2018, San Diego Convention Center. Am. J. Respir. Crit. Care Med. 197, A6604. https://www.atsjournals.org/doi/abs/10.1164/ajrccm_conference.2018.197.1_MeetingAbstracts.A6604

Janchawee, B., Keawpradub, N., Chittrakarn, S., Prasettho, S., Wararatananurak, P., Sawangjareon, K., 2007. A high-performance liquid chromatographic method for determination of mitragynine in serum and its application to a pharmacokinetic study in rats. Biomed. Chromatogr. 21, 176-83. PubMed PMID: 17221920. https://doi.org/10.1002/bmc.731 https://onlinelibrary.wiley.com/doi/abs/10.1002/bmc.731

Jones, C.M., McAninch, J.K., 2015. Emergency Department Visits and Overdose Deaths From Combined Use of Opioids and Benzodiazepines. Am. J. Prev. Med. 49, 493-501. PubMed PMID: 26143953. https://doi.org/10.1016/j.amepre.2015.03.040 https://www.ajpmonline.org/article/S0749-3797(15)00163-4/fulltext

Kapp, F.G., Maurer, H.H., Auwärter, V., Winkelmann, M., Hermanns-Clausen, M., 2011. Intrahepatic cholestasis following abuse of powdered kratom (Mitragyna speciosa). J. Med. Toxicol. 7, 227-31. doi: 10.1007/s13181-011-0155-5. PubMed PMID: 21528385; PubMed Central PMCID: PMC3550198. https://link.springer.com/article/10.1007%2Fs13181-011-0155-5

Karinen, R., Fosen, J.T., Rogde, S., Vindenes, V., 2014. An accidental poisoning with mitragynine. Forensic Sci. Int. 245, e29-e32. PubMed PMID: 25453780. https://doi.org/10.1016/j.forsciint.2014.10.025 http://www.ncbi.nlm.nih.gov/pubmed/25453780

Kenney, A., 2017. Colorado Kratom death: Bereaved woman says government could have saved her brother. Denverite.com. 22 November. Available at: https://denverite.com/2017/11/22/colorado-coroner-links-mans-death-controversial-kratom-denver-moves-regulate/ Accessed on 15 May 2019.

Kikura-Hanajiri, R., Kawamura, M., Maruyama, T., Kitajima, M., Takayama, H., Goda, Y., 2009. Simultaneous analysis of mitragynine, 7-hydroxymitragynine, and other alkaloids in the psychotropic plant “kratom” (Mitragyna speciosa) by LC-ESI-MS. Forensic Toxicol. 27, 67-74. https://link.springer.com/article/10.1007/s11419-009-0070-5

Kruegel, A.C., Gassaway, M.M., Kapoor, A., Váradi, A., Majumdar, S., Filizola, M., Javitch, J.A., Sames, D., 2016. Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators. J. Am. Chem. Soc. 138, 6754-64. doi: 10.1021/jacs.6b00360. PubMed PMID: 27192616; PubMed Central PMCID: PMC5189718. https://pubs.acs.org/doi/10.1021/jacs.6b00360

Kruegel, A.C., Grundmann, O., 2018. The medicinal chemistry and neuropharmacology of

kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. Neuropharmacology. 134(Pt A), 108-120. PubMed PMID: 28830758.
https://doi.org/10.1016/j.neuropharm.2017.08.026
https://www.sciencedirect.com/science/article/pii/S0028390817303933?via%3Dihub

Kronstrand, R., Roman, M., Thelander, G., Eriksson, A., 2011. Unintentional fatal intoxications with mitragynine and O-desmethyltramadol from the herbal blend Krypton. J. Anal. Toxicol. 35, 242-7. PubMed PMID: 21513619.
https://doi.org/10.1093/anatox/35.4.242
http://www.ncbi.nlm.nih.gov/pubmed/21513619

Kupferschmidt, H., 2011. Toxic hepatitis after Kratom (*Mitragyna* sp.) consumption, Abstract 39. Abstracts of the 2011 North American Congress of Clinical Toxicology Annual Meeting, September 21-26, Washington, DC, USA. Clin. Toxicol. 49, 532.
https://doi.org/10.3109/15563650.2011.598695
http://www.tandfonline.com/doi/full/10.3109/15563650.2011.598695

LaBryer, L., Sharma, R., Chaudhari, K.S., Talsania, M., Scofield, R.H., 2018. Kratom, an Emerging Drug of Abuse, Raises Prolactin and Causes Secondary Hypogonadism: Case Report. J. Investig. Med. High Impact Case Rep. 6, 2324709618765022. PubMed PMID: 29568783; PubMed Central PMCID: PMC5858613.
https://doi.org/10.1177%2F2324709618765022
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5858613/

LawPlus Ltd, 2019. Thai law on medical use of cannabis. Tweet. 23 April. Available at: https://www.facebook.com/permalink.php?id=1018177951557734&story_fbid=2672446539464192 Accessed on 16 May 2019.

Lesiak, A.D., Cody, R.B., Dane, A.J., Musah, R.A., 2014. Rapid detection by direct analysis in real time-mass spectrometry (DART-MS) of psychoactive plant drugs of abuse: the case of Mitragyna speciosa aka "Kratom". Forensic Sci. Int. 242, 210-218. PubMed PMID: 25086346. https://doi.org/10.1016/j.forsciint.2014.07.005 https://www.sciencedirect.com/science/article/pii/S0379073814002898?via%3Dihub

LGC., 2018. Government Chemist Review 2017. LGC: Teddington, Middlesex. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/739631/Government_Chemist_Review_2017.pdf
Accessed on 15 May 2019.

Lindrud, S., 2018. Waverly man found dead in Litchfield died of drug overdose. 21 March, West Central Tribune. Available at: http://www.wctrib.com/news/crime-and-courts/4421086-waverly-man-found-dead-litchfield-died-drug-overdose
Accessed on 15 May 2019.

Liss, D., Halcomb, S.L., Schwarz, E., Froelke, B., 2016. Abstract 28: Spontaneous intraparenchymal cerebral hemorrhage in a patient taking Mitragyna speciosa (Kratom). NIACCT Abstracts 2016. Clin. Toxicol. 54, 659-811. doi: 10.1080/15563650.2016.1197-486

Logan, B.K., 2016a. Designer Drug Update Summer 2016 Webinar. August. NMS Labs. Available at: https://ndews.umd.edu/sites/ndews.umd.edu/files/nms_labs_nps_webinar_august_2016.pdf
Accessed on 15 May 2019.

Logan, B.K., 2016b. NPS: Dangerous & Difficult to Detect. August. NMS Labs. Available at: http://www.nmslabs.com/uploads/PDF/Designer%20Drugs_Novel%20Psychoactive%20Substances%20(NPS)%20Trends%20Data%202016.pdf
Accessed on 29 April 2017.

Lu, J., Wei, H., Wu, J., Jamil, M.F., Tan, M.L., Adenan, M.I., Wong, P., Shim, W., 2014. Evaluation of the cardiotoxicity of mitragynine and its analogues using human induced pluripotent stem cell-derived cardiomyocytes. PLoS One. 9, e115648. PubMed PMID: 25535742; PubMed Central PMCID: PMC4275233.
https://doi.org/10.1371/journal.pone.0115648

Luce, T., Smith, J., 2018. Death certification reform in England. BMJ. 361, k2668. PubMed PMID: 29930196.
https://doi.org/10.1136/bmj.k2668
https://www.bmj.com/content/361/bmj.k2668.long

Lydecker, A.G., Sharma, A., McCurdy, C.R., Avery, B.A., Babu, K.M., Boyer, E.W., 2016. Suspected adulteration of commercial kratom products with 7-Hydroxymitragynine. J. Med. Toxicol. 12, 341-349. doi: 10.1007/s13181-016-0588-y. PubMed PMID: 27752985; PubMed Central PMCID: PMC5135684.
https://link.springer.com/article/10.1007%2Fs13181-016-0588-y

Lydecker, A.G., Zuckerman, M.D., Hack, J.B., Becker, B., Cherkes, J.K., Boyer, E.W., Babu, K.M., 2017. Intravenous Kratom Use in a Patient with Opioid Dependence. J. Toxicol. Pharmacol. 1, 003.
http://www.scientificoajournals.org/jtp.003.php

Lystra, T., 2013. Coroner: Role of kratom in Longview's mom's death undetermined. 7 May. The Daily News. Available at:
http://tdn.com/news/local/coroner-role-of-kratom-in-longview-mom-s-death-undetermined/article_0822689c-b74e-11e2-a636-0019bb2963f4.html
Accessed on 8 May 2016.

Mackay, L., Abrahams, R., 2018. Novel case of maternal and neonatal kratom dependence and withdrawal. Can. Fam. Physician. 64, 121-122. PubMed PMID: 29449242; PubMed Central PMCID: PMC5964386.
http://www.cfp.ca/content/64/2/121.long

Main, F., 2018. Kratom, health supplement targeted by FDA, linked to 9 deaths in Cook County. 5 March. *Chicago Sun Times. Available* at: https://chicago.suntimes.com/business/kratom-health-supplement-targeted-by-fda-linked-to-8-deaths-in-cook-county/
Accessed on 15 May 2019.

Marino, S., 2018. Inmate at Indian River County Jail died from Kratom overdose. 29 May. TCPalm.com. Available at: https://eu.tcpalm.com/story/news/crime/indian-river-county/2018/05/18/vero-man-arrested-and-died-next-day-found-have-died-kratom-overdose-autopsy-said/622541002/
Accessed on 15 May 2019.

Martinotti, G., Cinosi, E., Santacroce, R., Papanti, D., Pasquini, A., Mancini, V., Corbo, M., Fiori, F., Sarchione, F., Marchetti, D., Verrocchio, M.C., Di Giannantonio, M., Torrens, M., Schifano, F., Morlan Coarasa, M.J., Merino Del Villar, C., 2017. Substance-related psychopathology and aggressiveness in a nightlife holiday resort: Results from a pilot study in a psychiatric inpatient unit in Ibiza. Hum Psychopharmacol. 32(3): e2586. PubMed PMID: 28557062.
https://doi.org/10.1002/hup.2586
https://onlinelibrary.wiley.com/doi/full/10.1002/hup.2586

Maruyama, T., Kawamura, M., Kikura-Hanajiri, R., Takayama, H., Goda, Y., 2009. The botanical origin of kratom (Mitragyna speciosa; Rubiaceae) available as abused drugs in the Japanese markets. J. Nat. Med. 63, 340-4. doi: 10.1007/s11418-009-0325-9. PubMed PMID: 19294483.
https://link.springer.com/article/10.1007%2Fs11418-009-0325-9

Matsumoto, K., Mizowaki, M., Suchitra, T., Murakami, Y., Takayama, H., Sakai, S-I., Aimi, N., Watanabe, H., 1996. Central antinoceptive effects of mitragynine in mice: contributions from

noradrenergic and serotonergic systems, Eur. J. Pharmacol. 317, 75–81. doi: 10.1016/S0014-2999(96)00714-5. Available at:
Accessed on 15 May 2019.

Matsumoto, K., Horie, S., Ishikawa, H., Takayama, H., Aimi, N., Ponglux, D., Watanabe, K., 2004. Antinociceptive effect of 7-hydroxymitragynine in mice: Discovery of an orally active opioid analgesic from the Thai medicinal herb Mitragyna speciosa. Life Sci. 74, 2143-55. PubMed PMID: 14969718. https://doi.org/10.1016/j.lfs.2003.09.054

McBride, J., 2016. DNC Process Server Shawn Lucas Cause of Death Released. 1 November. Heavy.com. Available at:
http://speciosa.org/dnc-process-server-shawn-lucas-cause-of-death-released-_-kratom-is-one-of-the-reported-substances-in-his-system/
Accessed on 15 May 2019.

McIntyre, I.M., Tochta, A., Stolberg, S., Campman, S.C., 2015. Mitragynine 'Kratom' related fatality: A case report with post-mortem concentrations. J. Anal. Toxicol. 39, 152-6. PubMed PMID: 25516573. https://doi.org/10.1093/jat/bku137
http://www.ncbi.nlm.nih.gov/pubmed/25516573

McWhirter, L, Morris, S., 2010. A case report of inpatient detoxification after kratom (*Mitragyna speciosa*) dependence. Eur. Addict Res. 16, 229-31. PubMed PMID: 20798544. https://doi.org/10.1159/000320288

Michigan Office of the Medical Examiner, 2018. Department of Forensic Pathology, 2018 Q2 (April 1 – June 30) Drug Report. 29 July. Available at:
http://www.sparrow.org/upload/docs/website/2018q2drugreport.pdf
Accessed on 15 May 2019.

Mitchell-Mata, C., Thomas, B., Peterson, B., Couper, F., 2017. Two fatal intoxications involving 3-methoxyphencyclidine. J. Anal.Tox. 41, 503-507. PubMed PMID: 28830118.
https://doi.org/10.1093/jat/bkx048
https://academic.oup.com/jat/article/41/6/503/3926147

Mohr, A.L.A., Friscia, M., Papsun, D., Kacinko, S.L., Buzby, D., Logan, B.K., 2016. Analysis of Novel Synthetic Opioids U-47700, U-50488 and Furanyl Fentanyl by LC-MS/MS in Postmortem Casework. J. Anal. Toxicol. 40, 709-717. PubMed PMID: 27590036.
https://doi.org/10.1093/jat/bkw086
https://www.ncbi.nlm.nih.gov/pubmed/27590036

Mowry, J.B., Spyker, D.A., Cantilena, L.R., McMillan, N., Ford, M., 2014. 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual Report. Clin.Toxicol. 52, 1032-1283. doi: 10.3109/15563650.2014.987397

Murthy, P., Clark, D., 2019. An unusual cause for neonatal abstinence syndrome. Paediatr Child Health. 24(1):12-14. doi: 10.1093/pch/pxy084. PubMed PMID: 30792593; PubMed Central PMCID: PMC6376302.
https://doi.org/10.1093/pch/pxy084
https://academic.oup.com/pch/article/24/1/12/5047105

NBC10., 2018. Officials Link Kratom to 2 Chester County Deaths. Staff reporter, 21 August. NBC10. Available at:
https://www.nbcphiladelphia.com/news/health/Kratom-Deaths-Chester-County-Pennsylvania-Herbal-Supplement-Drug-Opioid-Alternative-Debate-491415752.html
Accessed on 15 May 2019.

Neerman, M.F., Frost, R.E., Deking, J., 2013. A drug fatality involving Kratom. J. Forensic Sciences. 58(Suppl 1), S278-9. PubMed PMID: 23082895.
https://doi.org/10.1111/1556-4029.12009

http://www.ncbi.nlm.nih.gov/pubmed/23082895

Nelsen, J.L., Lapoint, J., Hodgman, M.J., Aldous, K.M., 2010. Seizure and coma following Kratom (*Mitragynina speciosa* Korth) exposure. J. Med. Toxicol. 6, 424-426. doi: 10.1007/s13181-010-0079-5. PubMed PMID: 20411370; PubMed Central PMCID: PMC3550469.
https://link.springer.com/article/10.1007%2Fs13181-010-0079-5

NIDA., 2019. DrugFacts – What is kratom? April. National Institute on Drug Abuse, Rockville, MD. Available at: https://www.drugabuse.gov/publications/drugfacts/kratom
Accessed on 15 May 2019.

Office of the Medical Examiner, District Nineteen – Florida., 2017. ME report on Joseph Overholt (case 17-19-0941). Available at:
https://assets.documentcloud.org/documents/4756973/Joseph-Overholt-Autopsy.pdf
Accessed on 15 May 2019.

O'Halloran, G., 2011. Coroner warns on using herbal tea with other substances. 9 June. Irish Times. Available at:
http://www.irishtimes.com/news/coroner-warns-on-using-herbal-tea-with-other-substances-1.591290.
Accessed on 15 April 2019.

O'Malley Olsen, E., O'Donnell, J., Mattson, C.L., Schier, J.G., Wilson, N., 2019. Notes from the Field: Unintentional drug overdose deaths with kratom detected – 27 States, July 2016 – December 2017. MMWR Morb Mortal Wkly Rep 68:326–327.
http://dx.doi.org/10.15585/mmwr.mm6814a2

Orio, L., Alexandru, L., Cravotto, G., Mantegna, S., Barge, A., 2012. UAE, MAE, SFE-CO2 and classical methods for the extraction of Mitragyna speciosa leaves. Ultrason. Sonochem. 19, 591-5. PubMed PMID: 22054912.

https://doi.org/10.1016/j.ultsonch.2011.10.001

Paluska, M., 2017. Exclusive. Hillsborough Co. medical examiner confirms 1st death by herbal supplement kratom. 28 September. abcactionnews.com. Available at: http://www.abcactionnews.com/news/region-hillsborough/exclusive-hillsborough-confirms-first-ever-death-by-herbal-supplement-kratom-in-the-county
Accessed on 15 May 2019.

Pantano, F., Tittarelli, R., Mannocchi, G., Zaami, S., Ricci, S., Giorgetti, R., Terranova, D., Busardò, F.P., Marinelli, E., 2016. Hepatotoxicity Induced by "the 3Ks": Kava, Kratom and Khat. Int. J. Mol. Sci. 17, 580. PubMed PMID: 27092496; PubMed Central PMCID: PMC4849036. https://doi.org/10.3390/ijms17040580

Parthasarathy, S., Ramanathan, S., Ismail, S., Adenan, M.I., Mansor, S.M., Murugaiyah, V., 2010. Determination of mitragynine in plasma with solid-phase extraction and rapid HPLC-UV analysis, and its application to a pharmacokinetic study in rat. Anal. Bioanal. Chem. 397, 2023-30. doi: 10.1007/s00216-010-3707-7. PubMed PMID: 20454783. https://link.springer.com/article/10.1007%2Fs00216-010-3707-7

Pathak, V., Hahn, C., Cabellon, M., Aris, R., 2014. Adult respiratory distress syndrome secondary to the use of herbal drug kratom, in Proceedings of the American Thoracic Society International Conference Abstracts, San Diego, Calif, USA, May 2014. Am. J. Respiratory Critical Care Med. 10(2). Available at: http://www.atsjournals.org/doi/book/10.1164/ajrccm-conference.2014
Accessed on 15 May 2019.

Perno, W., 2018. Synthetic Drugs & Emerging Drug Trends. Presentation, 10 April, Camp Pendleton, San Diego. Available at: http://www.mccscp.com/mccscp/wp-content/uploads/2018/05/CAMP-PENDLETON-1.5-HOUR-SYNTHETIC-AND-OPIOIDS-PPY-10-APR-18.pdf

Accessed on 15 May 2019.

Perrone, D., Helgesen, R.D., Fischer, R.G., 2013. United States drug prohibition and legal highs: How drug testing may lead cannabis users to Spice. Drugs: Education, Prevention and Policy, 20, 216-224. https://doi.org/10.3109/09687637.2012.749392
https://www.tandfonline.com/doi/abs/10.3109/09687637.2012.749392

Petersson, C., 2010. “Nätdrogen tog min son” [“Web-drug took my son”]. 14 April. Aftonbladet. Available at: http://www.aftonbladet.se/nyheter/article12274542.ab
Accessed on 15 May 2019.

Philipp, A.A., Meyer, M.R., Wissenbach, D.K., Weber, A.A., Zoerntlein, S.W., Zweipfenning, P.G., Maurer, H.H., 2011. Monitoring of kratom or Krypton intake in urine using GC-MS in clinical and forensic toxicology. Anal. Bioanal. Chem. 400, 127-35. doi: 10.1007/s00216-010-4464-3. PubMed PMID: 21153588.
https://link.springer.com/article/10.1007%2Fs00216-010-4464-3

Poklis, J.L., Wolf II, C.E., Peace, M.R., 2017. Ethanol concentration in 56 refillable electronic cigarettes liquid formulations determined by headspace gas chromatography with flame ionization detector (HS-GC-FID). Drug Test. Anal., 9, 1637-1640). PubMed PMID: 28332307; PubMed Central PMCID: PMC5630485.
https://doi.org/10.1002/dta.2193
https://onlinelibrary.wiley.com/doi/abs/10.1002/dta.2193

Ponglux, D., Wongseripipatana, S., Takayama, H., Kikuchi, M., Kurihara, M., Kitajima, M., Aimi, N., Sakai, S., 1994. A New Indole Alkaloid, 7 alpha-Hydroxy-7H-mitragynine, from Mitragyna speciosa in Thailand. Planta Med. 60, 580-1. PubMed PMID: 17236085.
https://www.thieme-connect.com/DOI/DOI?10.1055/s-2006-959578

Post, S., Spiller, H.A., Chounthirath, T., Smith, G.A., 2019. Kratom exposures reported to United States poison control centers: 2011-2017. Clin Toxicol (Phila). Feb 20:1-8. doi: 10.1080/15563650.2019.1569236. PubMed PMID: 30786220.
https://doi.org/10.1080/15563650.2019.1569236
https://www.tandfonline.com/doi/full/10.1080/15563650.2019.1569236

Prozialeck, W.C., 2016. Update on the Pharmacology and Legal Status of Kratom. J. Am. Osteopath. Assoc. 116, 802-809. doi: 10.7556/jaoa.2016.156. PubMed PMID: 27893147.
http://jaoa.org/article.aspx?articleid=2588524

Prozialeck, W.C., Jivan, J.K., Andurkar, S.V., 2012. Pharmacology of kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. J. Am. Osteopath. Assoc. 112, 792-9. PubMed PMID: 23212430.
http://jaoa.org/article.aspx?articleid=2094342

Prutipanlai, S., Botpiboon, O., Janchawee, B., Theanchaiwattana, S., 2017. Solid phase extraction method for determination of mitragynine in urine and its application to mitragynine excretion study in rats receiving caffeine. Trp. J. Pharmaceut. Research, 16, 1675-1682.
http://dx.doi.org/10.4314/tjpr.v16i7.28
https://www.ajol.info/index.php/tjpr/article/view/159710

Raj, R., 2017. Malaysia lacks statistics on fatal drug overdoses. 6 June. The Malay Mail Online. Available at:
https://sg.news.yahoo.com/malaysia-lacks-statistics-fatal-drug-overdoses-232300605.html
Accessed on 15 May 2019.

Ramoo, B., Gary, U., Peterson, D.C., 2017. P187. A death involving mitragynine (Kratom). Society of Forensic Toxicologists (SOFT) Annual Meeting, 9-14 September 2017, Boca Raton, Florida

conference abstracts. Available at: http://www.soft-tox.org/files/meeting-abstracts/SOFT_2017_meeting_abstracts.pdf
Accessed on 15 May 2019.

Riverso, M., Change, M., Soldevila-Pico, C., Lai, J., Lui, X., 2018. Histologic characterization of Kratom use–associated liver injury. Gastroenterol. Res. 11, 79-82. doi: 10.14740/gr990e. PubMed PMID: 29511414; PubMed Central PMCID: PMC5827910.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5827910/

Roche, K.M., Hart, K., Sangali, B., Lefberg, J., Bayer, M., 2008. Kratom: a case of a legal high. Abstract 41. Abstracts of the 2008 North American Congress of Clinical Toxicology Annual Meeting, September 11–16, 2008, Toronto, Canada. Clin. Tox. 46, 598.
https://doi.org/10.1080/15563650802255033

Rosenbaum, C.D., Carreiro, S.P., Babu, K.M. 2012. Here today, gone tomorrow…and back again? A review of herbal marijuana alternatives (K2, Spice), synthetic cathinones (bath salts), kratom, Salvia divinorum, methoxetamine, and piperazines. J. Med. Toxicol. 8, 15-32. doi: 10.1007/s13181-011-0202-2. PubMed PMID: 22271566; PubMed Central PMCID: PMC3550220.
https://link.springer.com/article/10.1007%2Fs13181-011-0202-2

Sabetghadam, A., Navaratnam, V., Mansor, S.M., 2013. Dose–Response Relationship, Acute Toxicity, and Therapeutic Index between the Alkaloid Extract of Mitragyna speciosa and Its Main Active Compound Mitragynine in Mice. Drug Development Research, 74, 23-30.
https://doi.org/10.1002/ddr.21052
https://onlinelibrary.wiley.com/doi/abs/10.1002/ddr.21052

Saingam, D., Assanangkornchai, S., Geater, A.F., Balthip, Q., 2013. Pattern and consequences of krathom (*Mitragyna speciosa* Korth.) use among male villagers in southern Thailand: a qualitative study. Intl. J. Drug Policy, 24, 351-358. PubMed PMID: 23083922.
https://doi.org/10.1016/j.drugpo.2012.09.004

Sakulsaengprapha, V., Peonim, V., Worasuwanarak, W., 2018. Trends of homicide deaths in central Bangkok, Thailand: a 5-year retrospective study. Egyptian J. Forensic Sciences. 8, 14. doi: 10.1186/s41935-018-0043-0
https://ejfs.springeropen.com/articles/10.1186/s41935-018-0043-0

Samples, S., 2018a. Medical examiner: 5 deaths tied to herb. 30 June. Woodtv.com. Available at: https://www.woodtv.com/meet-the-team-/susan-samples/1001450277
Accessed 26 July 2018.

Samples, S., 2018b. The life-and-death fight over pain reliever kratom. 2 August. Woodtv.com. Available at:
https://www.woodtv.com/news/target-8/life-and-death-fight-over-pain-reliever-kratom/1343112294
Accessed 23 September 2018.

Samples, S., 2018c. Autopsy released in the 5th death tied to kratom. 22 August. Woodtv.com. Available at:
https://www.woodtv.com/new/target-8/autopsy-released-in-the-5th-death-tied-to-kratom/1389283968
Accessed 23 September 2018.

Santacroce, R., Ruiz Bennasar, C., Sancho Jaraiz, J.R., Fiori, F., Sarchione, F., Angelini, F., Catalano, G., Carenti, M.L., Corkery, J.M., Schifano, F., Di Giannantonio, M., Martinotti, G., 2017. A matter of life and death: substance-caused and substance-related fatalities in Ibiza in 2015. Hum Psychopharmacol. 32(3): e2592. PubMed PMID: 28657183.
https://doi.org/10.1002/hup.2592
https://onlinelibrary.wiley.com/doi/full/10.1002/hup.2592

Sattaburuth, A., 2018. Medical cannabis, kratom bill passed by NLA. 25 December. Bangkok Post. Available at: https://www.bangkokpost.com/news/general/1600566/medical-cannabis-kratom-bill-passed-by-nla
Accessed on 15 May 2019.

Sayre, J.W., Toklu, H.Z., Ye, F., Mazza, J., Yale, S., 2017. Case Reports, Case Series – From Clinical Practice to Evidence-Based Medicine in Graduate Medical Education. Cureus. 9, e1546. Doi: 10.7759/cureus.1546.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5630458/

Schaefer, M.A., 2018. Poisonings from kratom, sold as an herbal supplement, are rising. But no one knows how much. The Philadelphia Inquirer. 21 August. Available at: https://medicalexpress.com/news/2018-08-poisonings-kratom-sold-herbal-supplement.html
Accessed on 23 August 2018.

Schifano, F., Corkery, J., Deluca, P., Oyefeso, A., Ghodse, A.H., 2006. Ecstasy (MDMA, MDA, MDEA, MBDB) consumption, seizures, related offences, prices, dosage levels and deaths in the UK (1994-2003). J. Psychopharmacol. 20, 456-63. PubMed PMID: 16574720.
https://doi.org/10.1177%2F0269881106060147
https://journals.sagepub.com/doi/abs/10.1177/0269881106060147

Schifano, F., Orsolini, L., Papanti, G.D., Corkery, J.M., 2015. Novel psychoactive substances of interest for psychiatry. World Psychiatry, 14, 15-26. doi: 10.1002/wps.20174. PubMed PMID: 25655145; PubMed Central PMCID: PMC4329884.
https://doi.org/10.1002/wps.20174
https://onlinelibrary.wiley.com/doi/full/10.1002/wps.20174

Schmidt, M.M., Sharma, A., Schifano, F., Feinmann, C., 2011. "Legal highs" on the net-Evaluation of UK-based Websites, products and product information. Forensic Sci. Int. 206, 92-7. PubMed PMID: 20650576.

https://doi.org/10.1016/j.forsciint.2010.06.030

Schwarze, A., 2017. Carfentanil causes five more overdose-related deaths in the area. 19 May. Swnewsmedia.com. Available at: http://www.swnews.com/shakopee_valley_news/news/carfentanil-causes-five-more-overdose-related-in-the-area/article_536809d-9cfb-59e8-a48f-cfd7994778b0.html Accessed on 19 September 2017.

Scott, T.M., Yeakel, J.K., Logan, B.K., 2014. Identification of mitragynine and O-desmethyltramadol in Kratom and legal high products sold online. Drug Test. Anal. 6, 959-63. PubMed PMID: 24962931. https://doi.org/10.1002/dta.1673

Seewer, J., 2017. Family sues natural healing center after Ohio man's death. 20 October. Associated Press. Available at: https://www.foxbusiness.com/markets/family-sues-natural-healing-center-after-ohio-mans-death Accessed on 15 May 2019.

Shai, D., 1994. Problems of accuracy in official statistics on drug-related deaths. Int. J. Addict. 29, 1801-1811. PubMed PMID: 7890443. https://doi.org/10.3109/10826089409128258 https://www.tandfonline.com/doi/abs/10.3109/10826089409128258

Sharma, A., 2009. 'Herbal remedy killed my son'. 12 February. Boreham Wood and Elstree Times. Available at: http://www.borehamwoodtimes.co.uk/news/4122912._Herbal_remedy_killed_my_son_/ Accessed 15 May 2019.

Sheleg, S.V., Collins, G.B., 2011. A coincidence of addiction to "Kratom" and severe primary hypothyroidism. J. Addict. Med. 5, 300-301. doi: 10.1097/ADM.0b013e318221fbfa. PubMed PMID: 21817918.

https://journals.lww.com/journaladdictionmedicine/Abstract/2011/12000/A_Coincidence_of_Addiction_to__Kratom__and_Severe.10.aspx

Shellard, E.J., Houghton, P.J., Resha, M., 1978. The Mitragyna species of Asia: part XXXII. The distribution of alkaloids in young plants of Mitragyna speciosa Korth grown from seed obtained from Thailand, Planta Med. 34, 253-263. doi: 10.1055/s-0028-1097448.
https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0028-1097448

Singh, D., Müller, C.P., Vicknasingam, B.K., 2014. Kratom (*Mitragyna speciosa*) dependence, withdrawal symptoms and craving in regular users. Drug Alcohol Depend. 139, 132-137. PubMed PMID: 24698080.
https://doi.org/10.1016/j.drugalcdep.2014.03.017

Singh, D., Müller, C.P., Vicknasingam, B.K., Mansor, S.M., 2015. Social Functioning of Kratom (Mitragyna speciosa) Users in Malaysia. J. Psychoactive Drugs. 47, 25-31. PubMed PMID: 25950592.
https://doi.org/10.1080/02791072.2015.1012610
https://www.tandfonline.com/doi/full/10.1080/02791072.2015.1012610

Singh, D., Narayanan, S., Vicknasingam, B., 2016. Traditional and non-traditional uses of Mitragynine (Kratom): A survey of the literature. Brain Res. Bull. 126, 41-46. PubMed PMID: 27178014.
https://doi.org/10.1016/j.brainresbull.2016.05.004

Singh, D., Narayanan, S., Müller, C.P., Vicknasingam, B., Yücel, M., Ho, E.T.W., Hassan, Z., Mansor, S.M., 2019. Long-Term Cognitive Effects of Kratom (Mitragyna speciosa Korth.) Use. J. Psychoactive Drugs. 51(1): 19-27. doi: 10.1080/02791072.2018.1555345. PubMed PMID: 30556488.
https://doi.org/10.1080/02791072.2018.1555345
https://www.tandfonline.com/doi/full/10.1080/02791072.2018.1555345

Slavova, S., O'Brien, D.B., Creppage, K., Dao, D., Fondario, A., Haile, E., Hume, B., Largo, T.W., Nguyen, C., Sabel, J.C., Wright, D.; Council of State and Territorial Epidemiologists Overdose

Subcommittee., 2015. Drug Overdose Deaths: Let's Get Specific. Public Health Rep. 130, 339-42. PubMed PMID: 26345488; PubMed Central PMCID: PMC4547584.
https://doi.org/10.1177%2F003335491513000411
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4547584/
https://journals.sagepub.com/doi/abs/10.1177/003335491513000411

Smith, K.E., Lawson, T., 2017. Prevalence and motivations for kratom use in a sample of substance users enrolled in a residential treatment program. Drug Alcohol Depend. 180, 340-348. doi: 10.1016/j.drugalcdep.2017.08.034. PubMed PMID: 28950240.
https://doi.org/10.1016/j.drugalcdep.2017.08.034
https://linkinghub.elsevier.com/retrieve/pii/S0376-8716(17)30475-1

Smith, L.C., Lin, L., Hwang, C.S., Zhou, B., Kubitz, D.M., Wang, H., Janda, K.D., 2019. Chem. Res. Toxicol. 32(1): 113-121. doi: 10.1021/acs.chemrestox.8b00218. PubMed PMID: 30380840.
https://pubs.acs.org/doi/pdf/10.1021/acs.chemrestox.8b00218

Smith, T., 2018. Father tells cautionary tale of kratom. 13 November, uchealth. Available at:
https://www.uchealth.org/today/2018/11/13/father-tells-cautionary-tale-of-kratom/
Accessed on 15 May 2019.

Stanciu, C.N., Gnanasegaram, S.A., Ahmed, S., Penders, T., 2019. Kratom Withdrawal: A Systematic Review with Case Series. J Psychoactive Drugs. Jan-Mar;51(1):12-18. PubMed PMID: 30614408.
https://doi.org/10.1080/02791072.2018.1562133
https://www.tandfonline.com/doi/abs/10.1080/02791072.2018.1562133?journalCode=ujpd20

Streete, P.J., 2014. Mitragyna: should we be concerned?. Oral presentation. 2014 UKIAFT (United Kingdom and Ireland Association of Forensic Toxicologists) summer meeting. Leicester University. 28-29 August. Available at:
Accessed on 15 May 2019.

Suwanlert, S., 1975. A study of kratom eaters in Thailand. Bull. Narc. 27, 21-27. PubMed PMID: 1041694. Available at: http://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1975-01-01_3_page003.html Accessed on 15 May 2019.

Swetlitz, I., 2018. HHS recommended that the DEA make kratom a Schedule I drug, like LSD or heroin. 9 November, STAT. Available at: https://www.statnews.com/2018/11/09/hhs-recommended-dea-ban-kratom-documents-show/ Accessed on 15 May 2019.

Swogger, M.T., Hart, E., Erowid, F., Erowid, E., Trabold, N., Yee, K., Parkhurst, K.A., Priddy, B.M., Walsh, Z., 2015. Experiences of Kratom Users: A Qualitative Analysis. J. Psychoactive Drugs. 47, 360-7. PubMed PMID: 26595229. https://doi.org/10.1080/02791072.2015.1096434

Takayama, H., 2004. Chemistry and pharmacology of analgesic indole alkaloids from the rubiaceous plant, *Mitragyna speciosa*, Chem. Pharm. Bull. (Tokyo). 52, 916-928. PubMed PMID: 15304982. https://doi.org/10.1248/cpb.52.916

Tanguay, P., 2011. Kratom in Thailand, decriminalisation and community control? Series on Legislative Reform of Drug Policies, No. 13. Transnational Institute. International Drug Policy Consortium. Available at: http://speciosa.org/wp-content/uploads/2016/03/Transitional-Institutes-Analysis-Legislative-Reform-of-Drug-Policies-Addresses-Kratom-Law-Reform-in-Thailand.pdf Accessed on 15 May 2019.

Tatum, W.O., Hasan, T.F., Coonan, E.E., Smelick, C.P., 2018. Recurrent seizures from chronic kratom use, an atypical herbal opioid. Epilepsy & Behavior Case Reports. 10, 18-20. https://doi.org/10.1016/j.ebcr.2018.04.002

https://www.sciencedirect.com/science/article/pii/S2213323218300306

tdn.com., 2013. Leah 'Nikki' Waite. 11 March. tdn.com. Available at: http://tdn.com/announcements/obituaries/leah-nikki-waite/article_393fdc46-8a55-11e2-bd02-0019bb2963f4.html
Accessed on 29 April 2017.

Thaikla, K., Pinyopornpanish, K., Jiraporncharoen, W., Angkurawaranon, C., 2018. Cannabis and Kratom online information in Thailand: Facebook trends 2015-2016. Subst. Abuse Treat. Prev. Policy. 13, 15. PubMed PMID: 29743100; PubMed Central PMCID: PMC5944008. https://doi.org/10.1186/s13011-018-0155-4
https://substanceabusepolicy.biomedcentral.com/articles/10.1186/s13011-018-0155-4

thewatershed.com., 2014. Kratom addiction claimed the life of Ian Mautner. 29 September. thewatershed.com. Available at: https://www.thewatershed.com/blog/kratom-addiction-claimed-the-life-of-ian-mautner/
Accessed on 29 April 2017.

Tintner, J., 2018. Indian River County jail inmate died from kratom overdose, autopsy shows. 17 May. Wptv.com. Available at: http://amp.wptv.com/2591112804/indian-river-county-jail-inmate-died-from-kratom-overdose-autopsy-shows.html
Accessed on 15 May 2019.

Toler, W.R., 2016. Senate passes bill regulating sale of kratom. 27 June. Richmond County Daily Journal. Available at: http://yourdailyjournal.com/news/local-news-5/38753/senate-passes-bill-regulating-sale-of-kratom
Accessed on 15 May 2019.

Trakulsrichai, S., Sathirakul, K., Auparakkitanon, S., Krongvorakul, J., Sueajai, J., Noumjad, N., Sukasem, C., Wananukul, W., 2015. Pharmacokinetics of mitragynine in man. Drug Des. Devel. Ther. 9, 2421-2429. PubMed PMID: 25995615; PubMed Central PMCID: PMC4425236. https://doi.org/10.2147/DDDT.S79658 https://www.dovepress.com/pharmacokinetics-of-mitragynine-in-man-peer-reviewed-article-DDDT

Trakulsrichai, S., Tongpo, A., Sriapha, C., Wongvisawakorn, S., Rittilert, P., Kaojarern, S., Wananukul, W., 2013. Kratom abuse in Ramathibodi Poison Center, Thailand: a five-year experience. J. Psychoactive Drugs. 45, 404-408. PubMed PMID: 24592666. http://dx.doi.org/10.1080/02791072.2013.844532

Tungtananuwat, W., Lawanprasert, S., 2010. Fatal 4x100; Home-made kratom juice cocktail. J. Health Res. 24, 43-47. Available at: http://www.jhealthres.org/upload/journal/153/24%281%29_p43-47_wichian.pdf Accessed on 15 May 2019.

UNODC., 2014. Global Synthetic Drugs Assessment – Amphetamine-type stimulants and new psychoactive substances. Vienna: United Nations Office for Drugs and Crime. Available at: https://www.unodc.org/documents/scientific/2014_Global_Synthetic_Drugs_Assessment_web.pdf Accessed on 15 May 2019.

UNODC., 2018. World Drug Report 2018. Volume 2: Global overview of Drug demand and supply - Latest trends, cross-cutting issues. June. Vienna; United Nations Office on Drugs and Crime. Available at: https://www.unodc.org/wdr2018/prelaunch/WDR18_Booklet_2_GLOBAL.pdf Accessed on 15 May 2019.

Váradi, A., Marrone, G.F., Palmer, T.C., Narayan, A., Szabó, M.R., Le Rouzic, V., Grinnell, S.G., Subrath, J.J., Warner, E., Kalra, S., Hunkele, A., Pagirsky, J., Eans, S.O., Medina, J.M., Xu, J, Pan, Y.X., Borics, A., Pasternak, G.W., McLaughlin, J.P., Majumdar, S., 2016.

Mitragynine/Corynantheidine Pseudoindoxyls As Opioid Analgesics with Mu Agonism and Delta Antagonism, Which Do Not Recruit β-Arrestin-2. J. Med. Chem. 59, 8381-8397. doi: 10.1021/acs.jmedchem.6b00748. PubMed PMID: 27556704; PubMed Central PMCID: PMC5344672. https://pubs.acs.org/doi/10.1021/acs.jmedchem.6b00748

Vigil, T., 2014. Denver family warns others about dangers of legal herbal stimulant. 1 March. Kdvr.com. Available at: http://kdvr.com/2014/03/01/denver-family-warns-others-about-dangers-of-legal-herbal-stimulant/ Accessed on 8 May 2016.

Vlahos, N,. 2018. Nick in the AM: Death related to Southeast Asian drug is first in Peoria County. 19 November. Journal Star. Available at: https://www.pjstar.com/news/20181119/nick-in-am-death-related-to-southeast-asian-drug-is-first-in-peoria-county
Accessed on 25 November 2018.

WADA., 2015. The 2016 Monitoring Program. 29 September 2015. Montreal, Canada: World Anti-Doping Agency. Available at: https://www.wada-ama.org/sites/default/files/resources/files/wada-2016-monitoring-program-en.pdf Accessed on 15 May 2019.

Wales, H., 2018. Cause of a 23-year-old Bishop's Stortford student's fatal heart attack is unknown, coroner rules. 10 May, Hertfordshire Mercury. Available at: https://www.hertfordshiremercury.co.uk/news/hertfordshire-news/cause-23-year-old-bishops-1552141 Accessed on 15 May 2019.

Walsh, E.E., Shoff, E.N., Zaney, M.E., Hime, G.W., Garavan, F., Boland, D.M., 2019. To Test or Not To Test?: The Value of Toxicology in a Delayed Overdose Death. J. Forensic Sci. 64, 314-317. PubMed PMID: 29772071. https://doi.org/10.1111/1556-4029.13822

https://onlinelibrary.wiley.com/doi/abs/10.1111/1556-4029.13822

Wang, C., Walker, A.E., 2018. Fatal mitragynine-associated toxicity in Canada: a case report and review of the literature. Acad. Forensic Pathol. 8, 340-346.
https://doi.org/10.23907/2018.023

Warner, M.L., Kaufman, N.C., Grundmann, O., 2016. The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. Int. J. Legal Med. 130, 127-38.
doi: 10.1007/s00414-015-1279-y. PubMed PMID: 26511390.
https://link.springer.com/article/10.1007%2Fs00414-015-1279-y

Whigham, J., 2014a. Boynton Beach I-95 suicide victim had kratom in his system, tests confirm. 1 October. Palmbeachpost.com. Available at:
http://www.palmbeachpost.com/news/news/local/i-95-suicide-victim-had-kratom-in-his-system/nhZX9/
Accessed on 8 May 2016

Whigham, J., 2014b). Delray Beach vigil held to support families torn apart by addiction. 1 September. Palbeachpost.com. Available at:
http://www.palmbeachpost.com/news/news/local/candlelight-vigil-held-to-support-families-torn-ap/nhDRf/
Accessed on 8 May 2016.

Wing, N., 2018a. Ohio Pushes Kratom Ban with Disputed Claims About Deaths, Use Trends. 16 October, Huffington Post. Available at: https://www.huffingtonpost.co.uk/entry/ohio-kratom-ban_us_5bbe06cee4b0876edaa45ab6
Accessed on 15 May 2019.

Wing, N., 2018b. Peoria County Coroner recently reported its first kratom-related death. 21 November. Twitter thread. https://twitter.com/nickpwing/status/1065269846580056064
Accessed on 15 May 2019.

Wonguppa, R., Kanato, M., 2017. The prevalence and associated factors of new psychoactive substance use: A 2016 Thailand national household survey. Addict. Behav. Rep. 7, 111-115. doi: 10.1016/j.abrep.2017.11.001. eCollection 2018 Jun. PubMed PMID: 29892705; PubMed Central PMCID: PMC5993866. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5993866/

Wooten, T., 2016. State Crime Lab Says Kratom Linked to 3 Deaths in Arkansas. 17 February. Nwa.com. Available at: http://www.nwahomepage.com/news/state-crime-lab-says-kratom-linked-to-3-deaths-in-arkansas Accessed on 8 May 2016.

Wright, T.H., 2018. Suspected driving under the influence case involving mitragynine. J. Anal. Toxicol., 42, e65-e60. PubMed PMID: 29718282. https://doi.org/10.1093/jat/bky028 https://www.ncbi.nlm.nih.gov/pubmed/29718282 https://academic.oup.com/jat/article-abstract/42/7/e65/4989296?redirectedFrom=fulltext

Yue, K., Kopajtic, T.A., Katz, J.L., 2018. Abuse liability of mitragynine assessed with a self-administration procedure in rats. Psychopharmacology (Berl). 235, 2823-2829. doi: 10.1007/s00213-018-4974-9. PubMed PMID: 30039246. https://link.springer.com/article/10.1007%2Fs00213-018-4974-9

Zimmer, B., 2017. Mom of man killed by kratom calls for research, no ban. 23 November. Wtsp.com. Available at: https://www.wtsp.com/article/news/local/mom-of-man-killed-by-kratom-calls-for-research-not-ban/67-494110583 Accessed on 28 July 2018.

Figure 1: Chemical structure of mitragynine

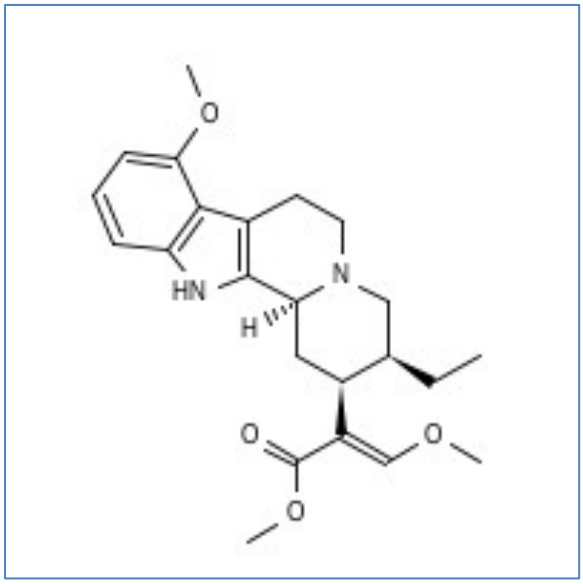

Figure 2: Chemical structure of 7-mitragynine

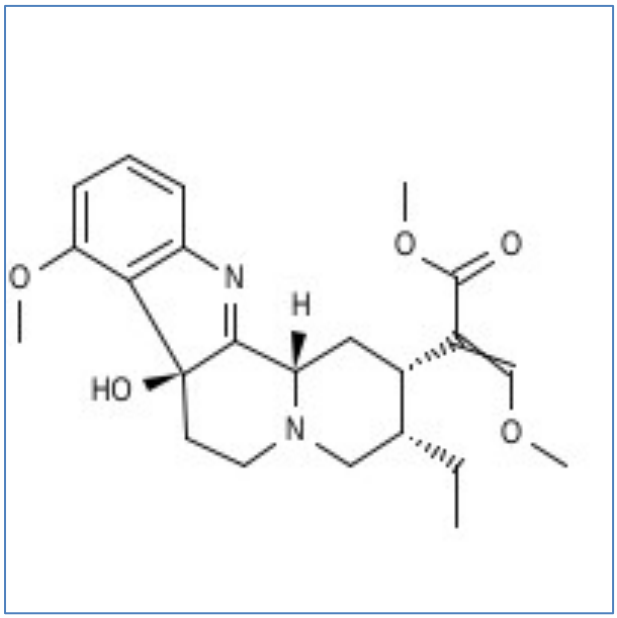

Table 1: Summary of main characteristics of case-reports of deaths associated with Kratom/Krypton use

Variable	*Characteristic*	*Frequency*
Country of death	Canada	1
	Germany	2
	Ireland	1
	Norway	1
	Sweden	9
	Thailand	1
	USA	131
	United Kingdom	10
Year of death	2008	1
	2009	3
	2010	1
	2011	0
	2012	0
	2013	6
	2014	5
	2015	17
	2016	27
	2017	43
	2018	14
	Nov 2009 – Spring 2010	8
	Pre-Oct 2011	1
	Pre- Dec 2014	1
	2012-6	14
	Not known	15
Year of first report	2008	0
	2009	1
	2010	2
	2011	10
	2012	1
	2013	1
	2014	7
	2015	17
	2016	19
	2017	35
	2018	46
	2019	17
Gender	Male	125
	Female	30
	Female (born male)/Transgender	1
Stated age (where known, n = 133)	Min	17
	Max	64
	Average (mean)	32.31
Calculated age (where known, n = 55)	Min	20.87
	Max	64.26
	Average (mean)	33.98
Ethnicity	Caucasian	5
	White	61
	White, non-Hispanic	15
	White, non-Latino	7
	White, Hispanic	1
	White, Latino	2
	Not known	65
Employment status (where known, n = 42)	Unemployed/ receiving social benefits	6
	Student	7
	Volunteer/retired	1
	Employed	28
Living arrangements (where known, n = 44)	Alone	8
	With parent(s)	12
	With son/daughter	1
	With family	12
	With partner	5
	With friend/room-mate	4
	In prison	1
	In drug treatment centre	1
Drug use (where known, n = 86)	No previous known drug use	4
	History of drug use	82
	Previous use of Kratom/Krypton	27

Reasons for using kratom (where known, n = 26) – there may be more than one reason for an individual using kratom	Body-building	3
	Recreational	3
	Self-medication	
	Anxiety/stress	5
	Depression	1
	Opiate/opioid addiction	4
	Chronic pain relief	3
	Insomnia	1
	ADHD symptoms	1
	Kratom dependence	1
	Diarrhoea	1
	Avoid positive opiate/opioid drug test	2
	To relax	2
	Experimentation	1
	Supplement to provide energy and mood enhancer	1
	As a safe stimulant	1
	In an alternative treatment centre	2
Place of death (where known, n = 112)	Home	66
	Friend's home	6
	Family member's home	2
	Hostel	1
	Hotel/motel	2
	Living quarters	1
	Outside home address	1
	Hospital/medical centre	15
	Vehicle	4
	Drug treatment centre	2
	Alternative treatment centre	2
	Fuel/gas station	1
	Highway	1
	Lake	1
	Water treatment plant	1
	Rural location	1
	Open space	1
	Pig-sty	1
	Playing sports	2
	Work	1
Nature of death – verdict/conclusion/manner	Accidental	71
	Accidental drug intoxication/overdose/poisoning	19
	Drug-related	2
	Drug and Alcohol related	3
	Misadventure	4
	Intentional	2
	Intentional – misuse of drugs	1
	Intention unclear	1
	Open verdict	1
	Suspected suicide	2
	Suicide	6
	Homicide	1
	Undetermined	2
	Natural	1
	Not known	25
N		156

Table 2a: Mitragynine and 7-hydroxymitragynine levels in human fatalities – individual cases

Source	*Source case number*	*Other substances present*	*Mitragynine*	*7-hydroxymitragynine*
Holler et al., 2011 [n = 11]		Y	Heart [central] bl 0.39 mg/L Liver 0.12 mg/kg Kidney 0.16 mg/L Vitreous 0.15 mg/L Urine 1.20 mg/L	
Kronstrand et al., 2011	1	Y	Femoral bl 0.07 mg/L	
	2	Y	Femoral bl 0.16 mg/L	
	3	Y	Bl 0.04 mg/L	
	4	Y	Femoral bl 0.05 mg/L	
	5	Y	Femoral bl 0.18 mg/L	
	6	Y	Femoral bl 0.05 mg/L	
	7	Y	Femoral bl 0.03 mg/L	
	8	Y	Femoral bl 0.02 mg/L	
	9	Y	Femoral bl 0.05 mg/L	
Frost et al., 2012; Neerman et al., 2013		Y	Femoral bl 0.60 mg/L	
Karinen et al., 2014		Y	Femoral bl 1.06 mg/L Urine 3.47 mg/L	Femoral bl 0.15 mg/L Urine 2.20 mg/L
McIntyre et al., 2015		Y	Peripheral bl 0.23 mg/L Central bl 0.19 mg/L Liver 0.43 mg/kg Vitreous <0.05 mg/L Urine 0.37 mg/L	
Brower, 2015 (cases 3 and 4 are included below in Bishop-Freeman et al., 2016)	1	NK	Bl 0.42 mg/L; liver >8.0 mg/kg	
	2	NK	Bl 2.0 mg/L; liver >8.0 mg/kg	
	5	Y	Bl 0.18 mg/L; liver 0.71 mg/kg	
	6	Y	Bl 0.35 mg/L; liver 0.48 mg/kg	
	7	Y	Bl 0.88 mg/L; liver 3.8 mg/kg	
	8	Y	Bl 0.075mg/L	
	9	Y	Bl < 0.050 mg/L	
	10	NK	Bl 0.36 mg/L; liver 3.3 mg/kg	
	11	Y	Bl 0.21 mg/L; liver 0.60 mg/kg	
	12	Y	Bl 0.031 mg/L	
	13	NK	Bl 1.1 mg/L; liver 6.2 mg/kg	
	14	NK	Bl 0.30 mg/L; liver 1.4 mg/kg	
	15	Y	Bl 2.0 mg/L; liver > 8.0 mg/kg	
Brower et al., 2015			Peripheral [femoral?] bl median 0.27, range 0.021-3.8 mg/L (n=8) Central [heart] bl median 0.60, range 0.60-0.60 mg/L (n=2) Liver 1.8 range 0.48-3.8 mg/kg (n=5) Vitreous 0.16 mg/L (n=1) Urine 0.92, range 0.05-1.8 mg/L (n=2)	
Bishop-Freeman et al., 2016	12	Y	Peripheral bl < 0.050 mg/L	
	19	Y	Peripheral bl 0.60 mg/L Liver 0.68 mg/kg	
	20	Y	Liver 3.5 mg/kg	
Domingo et al., 2017	1	Y	Femoral bl 0.790 mg/L Urine > 0.400 mg/L	
	2	Y	Femoral bl 0.010 mg/L Urine < 0.010 mg/L	
Ramoo et al., 2017	P. 187	Y	Sub-clavian bl 980 ng/mL	
Fogarty et al., 2018	1	Y	Iliac bl 0.890 ng/mL	
Wang and Walker, 2018		Y	Femoral venous bl 2500 ng/mL	
Gershman et al., 2019;	5	Y	16 ng/mL	
	7	Y	140 ng/mL	
	8	Y	2100 ng/mL	
	9	Y	1400 ng/mL	
	10	Y	1000 ng/mL	
	11	Y	170 ng/mL	
	12	Y	2700 ng/mL	
	13	Y	4800 ng/mL	
	14	Y	250 ng/mL	
	15	Y	747 ng /mL	

Additional cases from current study	2	Y	Fem bl 1.6 mg/L	Bl 0.19 mg/L
	3	Y	Fem bl 16.0 mg/L	Bl 2.8 mg/L
	4	Y	Fem bl 2.3 mg/L	Fem bl 0.17 mg/L
	5	Y	Fem bl 0.42 mg/L	
	7	Y	Bl 0.051 mg/L	Bl 0.0009 mg/L
	35	N	Liver - 86mg/Kg	
	36	Y	Peripheral bl 1.7 mg/L	
	37	Y	Peripheral bl 0.50 mg/L	
	47	N	Bl 3500 ng/mL	
	48	Y	Peripheral bl 1.8 mg/L	
	50	Y	Bl - 920 ng/mL	
	52	Y	Peripheral bl 0.13 mg/L	
	53	Y	Peripheral bl 0.50 mg/L	
	54	Y	Peripheral bl 1.7 mg/L	
	55	Y	Peripheral bl 0.68 mg/L	
	56	Y	Peripheral bl 0.68 mg/L; liver 0.51 mg/kg	
	60	Y	Femoral bl 92 ng/mL	
	67	Y	Peripheral bl - 0.74 mg/L	
	68	Y	Peripheral bl - 0.46 mg/L	
	69	NK	Serum 4200 ng/mL	
	87	Y	Bl - 40 ng/mL	
	88	N	Iliac bl - 300 ng/mL	
	89	Y	Bl - 24 ng/mL	
	93	Y	6.2 mg/kg	
	100	Y	Chest fluid - 13 ng/mL	
	101	Y	AM peripheral bl 1600 ng/mL	
	102	Y	290 ng/mL	
	103	Y	Bl - 720 ng/mL	
	104	Y	Femoral bl - 830ng/mL	
	111	N	Bl - 890 ng/mL	
	138	Y	Iliac bl 2300 ng/mL	
	140	Y	Bl – 0.15 mg/L	

Table 2b: Mitragynine and 7-hydroxymitragynine levels in human fatalities

Mitragynine	7-hydroxymitragynine
Blood: **All cases** **Mean 0.853, range 0.00089 – 16.000 mg/L (n=71)** **Sole drug** **Mean 0.398, range 0.0035 – 0.890 mg/L (n=3)** **With other substances** **Mean 0.8903, range 0.00089 – 16.000 mg/L (n=62)** **Presence of other drugs unknown** **Mean 0.697, range 0.0042 - 2.000 mg/L (n=6)**	**Blood:** **Mean 0.66218, range 0.0009 - 2.8 mg/L (n=5)** **Urine:** **2.20 mg/L (n= 1)** **All cases had other substances present**
Liver: **All cases** **Mean 8.233, range 0.120 – 86.000 mg/kg (n=16)** **Sole drug** **86 mg/kg (n=1)** **With other substances** **Mean 1.883, range 0.120 - > 8.000 mg/kg (n=10)** **Presence of other drug unknown** **Mean 5.380, range 1.400 - > 8.000 mg/kg (n=5)**	
Urine: **With other substances** **Mean 1.090, range < 0.010 – 3.470 mg/L (n=5)**	
Vitreous humour: **With other substances** **Mean 0.100, range < 0.050 – 0.150 mg/L (n=2)**	
Kidney: **With other substances** **0.160 mg/L (n=1)**	

Table 3: Main classes of other substances noted in post-mortem toxicology and cause of death for human fatalities associated with Kratom/Krypton use

Class of substance	***Frequency***	
	Toxicology	Cause of death
Only mitragynine/7-hydroxymitragynine	6	26
'Legal high'/NPS	25	13
of which, Synthetic opioid (5 U-47700; 12 novel fentanyls)	18	12
Synthetic cathinone (4 bupropion)	5	1
Benzodiazepine	8	2
PCP-like	1	0
Stimulant (e.g. cocaine, MDMA, etc.)	25	11
of which, Amphetamine/Methamphetamine	9	3
Cocaine	10	5
MDMA, MDA, ephedrine, pseudoephedrine	7	4
DMAA	1	0
2,4,5 TMA	1	0
THC/cannabis/cannabinoid	11	0
GHB	1	1
Anxiolytic	18	4
Anti-depressant (excluding benzodiazepine)	15	3
Anti-epileptic (excluding gabapentin, pregabalin)	9	1
Gabapentinoid	13	6
Anti-histamine	21	10
Anti-psychotic	16	2
Benzodiazepine	50	18
Any opiate/opioid	77	44
O-Desmethyltramadol (9 Krypton cases)	10	1
Heroin	21	12
Fentanyl	22	16
Morphine	13	8
Codeine	8	7
Tramadol	6	1
Methadone	3	2
Other opiates/opioids	24	11
Non-opioid pain-killer	8	1
Loperamide	5	0
Dextromethorphan	4	1
Muscle relaxant	3	1
Alcohol	22	8
Caffeine	12	0
Helium	0	2
Inhalant	2	0
Naloxone	2	0
Other	15	1
Multiple substances	1	8
Not stated/unascertained	19	53
No Kratom/Mitragynine	1	1

Notes Rows may sum to more than the total as more than one class of substance may have been identified; the true number of specific substances implicated in the cause of death may be higher as they have been included in cases involving "multiple drugs", etc.

Table 4: Main causes of death/autopsy findings in fatalities associated with Kratom/Krypton use

Cause of death/autopsy findings	***Frequency***			
	Role of Kratom unclear	Kratom only	Combination of substances	Total
Head				
Cerebral oedema	6		7	13
[Anoxic/Hypoxic] brain injury	1	1	1	3
Hypoxic encephalopathy		3	1	4
Infarct cranial pressure			2	2
Heart & circulatory system				
Cardiac arrythmia			1	1
Cardiomegaly	3		5	8
Cardiomyopathy			1	1
Coronary atherosclerosis		2	5	7
Focal band necrosis in myocardium			1	1
Heart attack	1	1		2
Heart condition		1		1
Hypertensive cardiovascular disease		2	1	3
Left ventricular hypertrophy		3	3	6
Myocardial ischaemia	1			1
Myocarditis			1	1
Respiratory system				
Adult Respiratory Distress Syndrome	1			1
Aspiration of gastric contents	1	2	1	4
Bronchopneumonia	1		2	3
Cardio-respiratory failure/arrest		1	1	2
Central Nervous System depression			2	2
Central Nervous System & respiratory depression	1		1	2
Chronic Obstructive Pulmonary Disease			1	1
Congested and/or oedematous/ heavy wet lungs	6	5	15	26
Congested larynx, trachea & bronchi	1	1		2
Influenza pneumonia		1		1
Pulmonary oedema	5	5	6	16
Pulmonary thrombo-emboli			1	1
Intoxication/overdose/toxicity				
Kratom overdose/toxicity, toxic effects of mitragynine/7-hydroxymitragynine		27		27
Multidrug intoxication/toxicity			62	62
Additive/combined/synergistic effect of drugs			4	4
Polypharmacy overdose			1	1
Combined adverse effects of drugs			1	1
Poisoning	8			8
Alcoholism		1	1	2
Hepato/Renal/Urinary system				
Congested kidney	1			1
Congested liver	1	1	1	3
Distended bladder/urinary retention		1	3	4
Enlarged liver/hepatomegaly	1	1	1	3
Fatty change in liver/Liver steatosis	2	1	2	5
Kidney stones		1		1
Nephritis	1			1
Liver fibrosis	1			1
Trauma				
Asphyxia (hanging/mechanical)	1		2	3
Blunt force head trauma, broken ribs	1			1
Drowning	2			2
Firearm discharge, intraoral => head defect	1			1
Gunshot wound	1			1
Gunshot wound to head	1			1
Haematoma & fracture of left humerus			1	1
Multiple injuries	1			
Plastic bag asphyxia with helium gas inhalation	2			2
Thermal injuries, inhalation of products of combustion	1			1
Other				
Deep vein thrombosis			1	1
Diabetic ketosis			1	1

Epilepsy			1	1
Metastatic breast carcinoma			1	1
Obesity			1	1
Oedema in lower extremities			2	2
Seizures		1		1
Thyroid disease		1		1
Neither autopsy nor cause of death stated	24			24

Note: More than one cause can be relevant to an individual case.

Table 5: Cases involving Mitragynine/7-Hydroxymitragynine/Kratom alone in cause of death

Key characteristic	Number (n = 27)
Decedents	
Male	27 (100.0%)
Age at death (years)	Mean = 32.16; Range = 17 - 64
Ethnicity	Caucasian/White/White Hispanic = 20 (74.1%); Not known =7 (25.9%)
Employment status	Employed = 6 (22.2%); Unemployed, student, retired, on benefits = 3 (11.1%); Not known = 18 (66.7%)
Living arrangements	With someone = 7 (25.9%); Alone/in treatment centre/prison = 5 (18.5%); Not known = 15 (55.6%)
History of drug use	Yes = 18 (66.7%); No = 1 (3.7%); Not known = 8 (29.6%)
Known to have previously used kratom	Yes = 13 (48.1%); Not known = 14 (51.9%)
Place of death	At home = 16 (59.3%); Hospital/medical centre = 4 (14.8%); Alternative health/ treatment centre = 2 (7.4%); Not known = 5 (18.5%)
Deaths	
Mitragynine blood level	Mean 2.128 (range 0.016 – 16.000) mg/L (n=15)
Main autopsy findings/cause of death	Cerebral oedema = 2; Hypoxic encephalopathy = 2; Seizures = 2; Anoxic brain injury = 1; Underlying heart condition = 1; Atherosclerosis = 1; Severe atherosclerosis = 1; Cardiomegaly = 1; Left ventricular hypertrophy = 3; Hypertensive cardiovascular disease = 1; Cardio-respiratory arrest = 2; Pulmonary oedema/congestion = 9; Pulmonary emboli = 1; Congested larynx, trachea & bronchi = 1; Aspiration of gastric contents = 2; Haemophilus influenzae & Haemophilus parainfluenzae pneumonia = 1; Enlarged liver = 1; Fatty change of liver = 2; Congested liver = 1; Renal calculi = 1; Distended bladder = 1; Thyroid disease = 1; Ulcerative colitis = 1; Chronic alcoholism = 1; Mitragynine/Kratom toxicity/toxic effects = 18; Mitragynine/Kratom intoxication = 6; Kratom overdose = 2; Combined effects of Mitragynine & 7-Hydroxymitragynine = 1
Nature of death	Accidental = 18 (66.7%); Misadventure = 2 (7.4%); Undetermined = 1 (3.7%); Not known = 6 (22.2%)