An index of fatal toxicity for new psychoactive substances

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Abstract

An index of fatal toxicity for new psychoactive substances (NPS) has been developed based solely on information provided on death certificates. An updated index of fatal toxicity (T_f), as first described in 2010 (King and Corkery, 2010), was calculated based on the ratio of deaths to prevalence and seizures for the original five substances (amphetamine, cannabis, cocaine/crack, heroin and MDMA)[1]. These correlated well with the 2010 index. Deaths were then examined both for cases where the substance was and was not found in association with other substances. This ratio (Sole to All mentions; S/A) was then calculated for deaths in the period 1993 to 2016.

This new measure of fatal toxicity, expressed by S/A, was well-correlated with the index $Ln(T_f)$ of the original reference compounds. The calculation of S/A was then extended to a group of NPS where insufficient prevalence or seizure data were available to directly determine a value of T_f. by interpolation of a graph of T_f versus S/A.

Benzodiazepine analogues (BZD) had particularly low values of S/A and hence T_f. By contrast, γ-hydroxybutyrate/γ-butyrolactone (GHB/GBL), AMT, synthetic cannabinoid receptor agonists (SCRAs) and benzofurans had a higher fatal toxicity.

[1] Although mortality data were available for many substances over the period 1993 to 2016, prevalence data from the British Crime Survey, later the Crime Survey for England and Wales, were only available from 2001/2. Currently, seizure data are only available for drugs once they are controlled under the Misuse of Drugs Act 1971.

Abbreviations (see also Table 1)

5F-ADB: aka 5F-MDMB-PINACA:

5F-AKB-48: *N*-(1-Adamantyl)-1-(5-fluoropentyl)-1*H*-indazole-3 –carboxamide

5F-PB-22: Quinolin-8-yl 1-pentyfluoro-1*H*-indole-3-8-carboxylate

AB-CHMINACA: *N*-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide

AH-7921: 3,4-Dichloro-*N*-[[1-(dimethylamino)cyclohexyl]methyl]benzamide

AMT: α-Methyltryptamine

APB: Aminopropylbenzofuran aka 1-(1-Benzofuran-2-yl)propan-2-amine

APDB: 5-(2-Aminopropyl)-2,3-dihydrobenzofuran

BCS: British Crime Survey

BZP:1-Benzylpiperazine

CSEW: Crime Survey for England and Wales

5-EAPB: 1-(1-Benzofuran-5-yl)-*N*-ethylpropan-2-amine

GHB/GBL: γ-Hydroxybutyrate/γ-butyrolactone

MDDA: aka MDDM and MDDMA; 3,4-Methylenedioxy-*N*,*N*-dimethylamphetamine

MDMA: 3,4-Methylenedioxymethamphetamine

MDMB-CHMICA: *N*-[[1-(Cyclohexylmethyl)-1*H*-indol-3-yl]carbonyl]-3-methyl-valine, methyl ester

MPA: Methiopropamine

NBOMe derivatives: *N*-(Methoxybenzyl) phenethylamine derivatives (e.g. 25I-NBOMe)

NPS: New Psychoactive Substance

ONS: Office for National Statistics

PMA: *para*-Methoxyamphetamine

PMMA: *para*-Methoxy-*N*-methylamphetamine

SCRA: Synthetic cannabinoid receptor agonists

TFMPP: 1-(3-Trifluoromethylphenyl)piperazine

U-47700: 3,4-Dichloro-*N*-[2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide

Introduction

New psychoactive substances (NPS) have been associated with a range of serious harms in Europe including deaths (EMCDDA, 2017). The number of fatalities associated with NPS appears to be increasing across the United Kingdom (NISRA, 2016; NRS, 2017; ONS, 2017a). This raises the question of how we might determine their lethal toxicity compared with better-known drugs. The intrinsic fatal toxicity of a substance cannot simply be equated to the number of deaths associated with that substance; a suitable denominator of the extent of use or availability is usually required. With licensed medicines, it was found over thirty years ago that an index of fatal toxicity (T) could be created by relating the number of deaths associated with a certain substance to its availability measured by the number of prescriptions issued (King and Moffat, 1981; King and Moffat, 1983). Since that method is not appropriate for illicit substances, a different approach is needed. Measures of availability such as law enforcement seizures, estimates of market size and prevalence, as judged by household surveys, were used to provide an alternative index of fatal toxicity (King and Corkery, 2010). However, for many NPS there is almost no information on prevalence. There are many reasons for this, including: users can purchase them through internet websites and largely avoid interception by law enforcement agencies; new substances are not immediately included in household or other surveys of drug use in the population, in some cases because their prevalence is so low; and many users of NPS may not know exactly what it is that they are consuming.

During the collection of data for that original index of fatal toxicity (T) based on deaths related to prescriptions (King and Moffat, 1983) it was noted that: *"… the mortality statistics provide a second, albeit crude, measure of drug toxicity. The index T is found to be related to the proportion of deaths involving a given drug where that drug was not in association with other drugs. For example, 72 per cent of deaths associated with pentobarbitone (T = 65.8) were not associated with other drugs whereas only 23 per cent of deaths associated with diazepam (T = 1.8) did not involve other drugs."*

If we imagine a substance that has an extremely low fatal toxicity, then amongst a population of suspected fatal poisonings it will occur rarely and will mostly be associated with other more toxic substances that are the direct cause of death. If we determine the number of cases where it is the sole mention (S) on death certificates and those where it is mentioned alongside other substances (A), then the ratio S/A will be low. On the other hand, if we have a substance that is highly toxic, then its mere presence will often be associated with the direct cause of death, and the ratio S/A will be higher. Thus S/A should be a measure of the intrinsic fatal toxicity of a substance.

It could be argued that the detection of a substance in post mortem tissues is subject to many distorting factors. This is particularly true with new drugs where a toxicology laboratory may not be able to detect certain substances perhaps because there are no suitable pure reference standards. Secondly, the toxicological examination may not be exhaustive, but allows analysis to be halted once one or more likely candidates have been found. However, by taking the ratio S/A, such selection effects should be reduced. The mention of a drug in the "cause of death" field on a death certificate does not necessarily indicate that substance was a

direct cause of death; it may have been a contributory factor, or it may have been a combination of substances that led to death. Some of the fatal cases recorded by the Office for National Statistics (ONS) may not have been poisonings in the normal sense because their definition includes cases of intoxication, dependence, drug withdrawal, etc. (ONS, 2017a). In other words, in this paper, lethal toxicity needs to be interpreted in a broad sense. This is particularly true for cannabis, which has only rarely been the direct cause of any death, but nevertheless features in a number of deaths where no other substance was mentioned (Ghodse et al., 2007). Furthermore, these figures do not include cases where drugs may have been involved in other ways, such as impairing judgement or perception of risk (e.g. drowning, fall from height, hyperthermia, road traffic accidents), or causing psychiatric problems (e.g. suicide using mechanical means), or even homicide. The numbers of deaths attributed to specific substances are likely to be under-estimates since about 10% of UK drug poisoning deaths are recorded in ambiguous terms such as "multiple drug overdose" without specifying the substances actually implicated in or contributing to death. A further difficulty, experienced in respect of NPS, is that the name of the specific molecule may not be properly communicated to ONS (see Table 1).

Table 1 about here

The advantage of using the ratio S/A is that it relies solely on the information on death certificates, and does not require any knowledge of availability. It could therefore be useful for evaluating the fatal toxicity of NPS. The purpose of this paper is to test that hypothesis.

Methods

Data related to deaths registered in England and Wales between 1993 and 2016 were either extracted from the mortality statistics published by ONS (2017a) or extracted specifically for this study (ONS, 2015, 2016a, 2016b, 2016c, 2017b), where the selected substances were implicated in the cause of death. The principal substances examined were: amphetamine; cannabis; cocaine/crack; ecstasy; heroin; ketamine; and mephedrone. Table 1 lists those drugs that come under the ONS definition of NPS. Table 2 lists the number of deaths classified as 'sole mentions' (S), while Table 3 lists the 'any mentions' (A). In respect of deaths involving 'any mention', other substances present may or may not have been psychoactive. In both Tables 2 and 3, substances are included where sufficient data were available (minimum of 10 deaths). Amongst NPS, this included AMT (α-methyltryptamine), benzodiazepine analogues, benzofurans, GHB/GBL (γ-hydroxybutyric acid/γ-butyrolactone), MPA (methiopropamine), novel amphetamines, piperazines, PMA (*para*-methoxyamphetamine; 4-MA; 4-methoxyamphetamine)/ PMMA (*para*-methoxy-*N*-methylamphetamine), synthetic cathinones (other than mephedrone) and synthetic cannabinoids. There were insufficient data to examine the fatal toxicity of specific synthetic cannabinoids. The term 'amphetamines' mostly relates to amphetamine (α-methylbenzeneethanamine) itself. Although the word 'ecstasy' may be used rather broadly, it is taken here to mean 3,4-methylenedioxymethylamphetamine (MDMA). The mortality statistics refer to 'heroin and morphine' as a category. Since heroin is rapidly metabolised to morphine, post mortem analysis will rarely differentiate the two. Nevertheless, most of these deaths will have followed use of (illicit) heroin rather than (pharmaceutical) morphine, so in the present paper this is listed as 'heroin'. Mephedrone and other synthetic cathinones as a wider class are both examined.

Deaths associated with ketamine or GHB/GBL are believed to be almost entirely a consequence of the use of illicit preparations rather than prescription medicines. Finally, crack cocaine is not usually distinguished from powder cocaine on death certificates, so figures for deaths comprise both substances. For the period in question, the number of users of crack cocaine was less than 10% of all cocaine users (Broadfield, 2017).

Table 4 shows the estimated number of last year users (aged 16-59 years) of the 7 principal substances as derived from the British Crime Survey Drug Misuse Declared (BCS), now known as the Crime Survey for England and Wales (CSEW; Broadfield, 2017). In Table 4, the use of cocaine is taken as any use of cocaine and/or crack. The mean estimated number of amphetamine users excludes the minor contribution of methylamphetamine, which was only recorded since 2008. In the case of ketamine, although mortality data were available for the period 1993-2016, prevalence data only started in 2006. For this reason, analysis was based on the 11 years from 2006. With mephedrone and synthetic cathinones more generally, mortality and prevalence estimates only related to the seven years 2010-2016. For piperazines and GHB/GBL, prevalence data were available only for one or two years (2010/11 and 2011/12; and 2011/12 respectively).

Seizures of selected substances made by law enforcement agencies in England and Wales for the period 2000-2015/6 (Hargreaves and Smith, 2016) are given in Table 5. Most of the data are derived from published sources, but some were specially extracted for this study. It should be noted that the statistics moved from a calendar year to a financial year in 2006/7, hence the change in date format.

Although the earlier index (King and Corkery, 2010) made use of other measures of availability, in the present study it was found that prevalence in the form of household surveys as summarised in the BCS/CSEW, and law enforcement seizures were the best measures. Furthermore, there are no recent estimates of market size for most of the drugs examined in this study; the estimates used here can be found in King and Corkery (2010).

Tables 2 - 5 about here

The index of fatal toxicity as defined by King and Corkery (2010), here named as T_f, was recalculated for each substance where data were available. The index of fatal toxicity (T_f) was defined as the mean number of deaths per annum (sole mentions) divided by the availability of that drug, where availability could be the mean number of users, the mean number of seizures per annum, or the market size.

The calculation of T_f proceeds as follows:

If T_f (H) is the fatal toxicity of heroin, which will be defined as 1000, then

$$T_f (H) = [D(H) \times F]/A(H) = 1000$$

where D(H) is the number of deaths associated with heroin (sole mentions), A(H) is the availability of heroin, measured either by the number of users, the number of seizures or some other metric, and F is a numerical factor that is unique to the particular type of availability measure.

The fatal toxicity of some other substance (Z) is then given by

$T_f(Z) = [D(Z) \times F]/A(Z)$

where D(Z) is the number of deaths associated with substance Z (sole mentions) and A(Z) is the appropriate availability measure of Z.

Prevalence data in the BCS/CSEW were only available from 2001/2, so values of T_f were calculated using the average number of deaths in the 16 year period 2001 to 2016 or, where appropriate, for shorter periods as noted above. As before, the index was then normalised such that heroin = 1000.. A Napierian logarithmic (L_n) transform was then used. This was necessary for graphical purposes because of the wide range in values of the index T_f. However, this was quite arbitrary since using the cube root of the index, for example, produced broadly similar scale compression T_f values for seizures and market size were calculated in a similar way. For combined parameters T_f values were calculated by obtaining the mean of the indices for the individual parameters (King and Corkery, 2010), then the Naperian logarithmic transforms were applied.

Results and Discussion

Tables 6(a) to 6(e) show the index T_f for the original five substances (amphetamine, cannabis, cocaine/crack, heroin, and MDMA) based on: (a) prevalence; (b) number of seizures; (c) a combination of prevalence and number of seizures; (d) market size and finally (e) a combination of prevalence, number of seizures and market size. When

compared to the original (King and Corkery, 2010) values of LnT_f , the Pearson product moment correlation coefficients (r) for each of these five measures of the index (as LnT_f) were all greater than 0.96, and values of P, the probability of the null hypothesis, were less than 0.01 in all cases. For all subsequent analyses, values of T_f were based on deaths related to the combination of prevalence and number of seizures.

Table 6 about here

Table 7 lists values of Sole (S) and Any (A) deaths as well as the ratio S/A for the period 1993-2016, or as otherwise indicated, for the reference compounds and NPS or groups of NPS (α-methyltryptamine, benzodiazepine analogues, benzofurans, GHB/GBL, ketamine, mephedrone, methiopropamine, novel amphetamines, *para*-methoxyamphetamine/*para*-methoxy-*N*-methylamphetamine, piperazines, synthetic cathinones (other than mephedrone) and synthetic cannabinoids).

Table 7 about here

Figure 1 shows the relationship between the updated index T_f [based on a combination of prevalence and number of seizures; see Table 6(c)] and values of S/A (see Table 8) ($r = 0.922$; $P < 0.01$) for the seven reference compounds (amphetamine, cannabis, cocaine, heroin, ketamine, MDMA and mephedrone). The straight line is the least squares fit [$LnT_f = 11.12(S/A) - 0.48$].

Figure 1 about here

Since sufficient data had been available to calculate values of T_f for ketamine and mephedrone, their inclusion in this group provides a cross-check on the indirect calculation of T_f from their S/A values using the above linear relationship. Thus, for ketamine the value of LnT_f calculated from deaths / (prevalence + seizures) was 3.47 whereas the value interpolated from Figure 1 was 4.13. For mephedrone, the value of LnT_f calculated from deaths /(prevalence + seizures) was 3.52 whereas the value interpolated from Figure 1 was 1.73. As will be seen from Figure 1, the high value of LnT_f for mephedrone appears anomalous, whereas the value interpolated from S/A seems more consistent with other substances, and particularly with synthetic cathinones (other than mephedrone) where the interpolated value of LnT_f was 1.95 (Table 7).

The results shown in Figure 1 confirm the original hypothesis that the ratio S/A is a measure of the fatal toxicity of a substance. Because of limitations in the data, as discussed below, values of S/A, as shown in Table 7, should not be over-interpreted. Many NPS are based on what might be termed ‘amphetamine-type drugs’. It was found that substituted phenylisopropylamines had broadly similar fatal toxicities (i.e. S/A) compared to MDMA and amphetamine, but the fatal toxicity of ‘novel amphetamines’ was low. However, small differences in the estimated fatal toxicity of this group may not be significant. However, benzodiazepine analogues (BZD) had particularly low values of S/A. By contrast GHB/GBL and synthetic cannabinoid receptor agonists (SCRAs) had higher toxicities.

There are a number of limitations in the original data. For example, it is believed that prevalence, as assessed by BCS/CSEW, may underestimate the number of users of heroin and crack cocaine as well as those who do not live in normal domestic premises. For GHB/GBL and piperazine derivatives, prevalence data were only available for one or two years respectively, but as more data accumulate a future analysis should enable estimates of T_f to be made for these substances. In respect of NPS, and despite the public concern about their toxicity, there have still been relatively few fatal poisonings, especially for 'sole mentions', when compared with more established drugs of misuse. The role of alcohol as a contributory factor in some of the deaths is unknown, and has not been taken into account here. (The ONS only recently started publishing data for deaths involving alcohol but no other substance (ONS, 2017a)). Finally, the fatality index treats all users of a drug as an equivalent point. That is to say, the index relates to an 'average' user. Those who regularly consume more of a drug on each occasion compared to another user are probably at greater risk of a fatal outcome, but there is no reliable information on what constitutes occasional/regular or heavy/light use for most of the substances considered here.

Conclusions

This analysis supports the hypothesis that the ratio S/A is a meaningful measure of fatal toxicity. Bearing in mind the limited mortality and prevalence data available for some new substances, it is suggested that the fatal toxicity of benzodiazepine analogues (BZD) was particularly low. By contrast GHB/GBL, synthetic cannabinoid receptor agonists (SCRAs), benzofurans and AMT had higher toxicities. It is expected that the analysis shown here could be improved as more mortality and prevalence data become available.

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Declaration of Conflicting Interests

The authors are unaware of any potential conflicts of interest. However, LK is a former head of the Home Office Forensic Science Drugs Intelligence Unit (1992 - 2001), and a former member of the Home Office Advisory Council on the Misuse of Drugs (ACMD). JC was responsible for producing drug statistics for the Home Office (1994 - 2002), acted as the UK Focal Point on Drugs' expert on drug-related deaths and mortality related to drug use (2000 - 2015), was a member of the ACMD's Working Groups on Drug-related deaths (1999-2000 and 2016-7), and is currently a co-opted member of the Technical Committee (2016 to date) and NPS Committee (2009 to date). No funding was received for the preparation of this article.

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Table 1. ONS definitions of NPS categories

NPS category	Substances
Benzodiazepine analogues	Diclazepam, Etizolam, Flubromazepam, Flubromazolam, Phenazepam, Pyrazolam,
Benzofurans	1-(Benzofuran-5-yl)-*N*-methylpropan-2-amine, 1-(Benzofuran-5-yl)-propan-2-amine, 1-(Benzofuran-6-yl)-propan-2-amine, APB(1), APDB(2), 5-EAPB
Cathinones	Butylone, Cathine, Cathinone, Fluoromethcathinone, 4- Mephedrone, Methoxymethcathinone, Methylenedioxypyrovalerone, Methylethcathinone, Methylone
NBOMes	25B-NBOMe, 25C-NBOMe, 25I-NBOMe
Novel amphetamines	2-Aminoindane, Fluoromethamphetamine, 4-MDDA(3), Methylamphetamine
Novel opiates	Acetylfentanyl, AH-7921, U-47700
Piperazines	BZP, Piperazine(4), TFMPP
Synthetic cannabinoids	5F-ADB(5), 5F-AKB-48, 5F-PB-22(6), AB-CHMINACA, MDMB-CHMICA, Synthetic cannabinoid

Notes:
There was uncertainty in some cases as to which specific molecule was meant as ONS did not receive toxicological information and relied solely on the text give in the cause of death field on the death certificate or in any supplementary information given by the coroner, e.g. in their findings or 'verdict'.

(1) "Aminopropyl Benzofuran" was stated in the majority of cases, but some just stated APB. The specific isomer was unknown.
(2) "APDB" was all that was mentioned on the death certificate. The specific isomer was unknown.
(3) "MDDA" was all that was written on the death certificate. This is presumed to mean MDDM aka MDDMA
(4) The term "piperazine" almost certainly referred to a substituted piperazine.
(5) "5F-ADB" aka "5F-MDMB-PINACA".
(6) In all cases, all that was on the death certificate was "5F-PB-22". This was presumed to refer to the indole analogue.

Source: Personal communication to JC from Mortality Team, Office for National Statistics, 14 and 31 August 2017

Table 2. Deaths registered in England and Wales for the period 1993 - 2016 where selected substances were implicated in the cause of death (sole mentions).

Substance/ Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total	Years of exposure	Mean
Amphetamine	5	4	5	5	4	3	4	14	12	17	16	21	27	19	27	29	22	28	26	22	18	33	41	44	446	24	18.58
AMT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	4	3	4	0	14	24	0.58
Benzodiazepine analogues	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	2	8	0.25
Benzofurans	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	4	1	0	7	6	1.17
Cannabis	5	5	5	4	6	2	4	0	0	0	1	1	2	2	1	2	1	2	1	0	1	7	4	3	59	24	2.46
Cocaine/crack	0	3	3	4	5	12	15	40	40	41	44	49	54	71	84	86	73	59	34	39	46	74	88	108	1,072	24	44.67
GHB/GBL	0	0	0	1	0	0	2	1	0	2	2	0	2	4	3	13	12	6	10	8	10	12	10	20	118	23	5.13
Heroin	110	138	185	216	233	277	345	663	725	621	481	492	566	497	588	587	562	487	332	305	424	492	603	588	10,517	24	438.21
Ketamine	0	0	0	0	0	0	1	1	1	1	0	0	0	1	3	4	7	4	7	3	2	5	1	7	48	18	2.67
MDMA	9	10	10	8	8	10	6	10	26	24	29	24	33	27	28	15	13	5	7	13	28	25	24	32	424	24	17.67
Mephedrone	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0	2	1	4	1	2	12	2	24	8	3.00
MPA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3	1	1	6	5	1.20
Novel amphetamines	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0	0	0	0	0	0	1	0	0	0	0	1	11	0.09
Piperazines	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	1	2	1	0	4	0	0	0	0	8	9	0.89
PMA/PMMA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11	14	12	6	2	45	24	1.88
Synthetic cannabinoids	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	6	14	22	8	2.75
Synthetic cathinones	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0	2	2	7	5	2	12	4	34	8	4.25

Note: n/a = not available

Sources: ONS (2015, 2016a, 2016b, 2016c, 2017a, 2017b)

Table 3. Deaths registered in England and Wales for the period 1993 - 2016 where selected substances were implicated in the cause of death (any mentions).

Substance/ Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total	Years of exposure	Mean
Amphetamine	37	19	35	33	41	48	67	40	28	51	33	43	50	49	50	59	50	48	46	49	56	85	90	96	1,203	24	50.13
AMT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	7	6	5	0	22	24	0.92
Benzodiazepine analogues	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	4	3	14	11	10	44	8	5.50
Benzofurans	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	7	5	2	3	20	6	3.33
Cannabis	13	19	16	9	14	10	8	9	16	13	11	19	19	17	12	19	22	11	7	14	11	28	21	24	362	24	15.08
Cocaine/crack	11	24	22	13	27	65	88	83	97	128	129	154	176	190	196	235	202	144	112	139	169	247	320	371	3,342	24	139.25
GHB/GBL	0	0	0	1	0	0	3	3	1	5	6	1	4	7	9	20	16	12	20	13	18	20	26	30	215	23	9.35
Heroin	155	270	331	440	444	609	755	851	981	865	696	751	842	713	829	897	880	791	596	579	765	952	1,201	1,209	17,402	24	725.08
Ketamine	0	0	0	0	0	0	1	2	2	1	3	1	0	2	6	8	15	6	11	12	9	19	7	12	117	18	6.50
MDMA	12	20	17	16	15	17	21	28	55	56	50	43	58	48	47	44	27	8	13	31	43	50	57	63	839	24	34.96
Mephedrone	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0	6	5	12	18	22	44	15	122	8	15.25
MPA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	4	7	6	10	29	5	5.80
Novel amphetamines	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0	0	0	0	0	0	1	3	4	1	1	10	11	0.91
Piperazines	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	5	9	6	2	9	1	2	0	0	34	9	3.78
PMA/PMMA	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	20	29	24	10	3	88	24	3.67
Synthetic cannabinoids	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	8	27	38	8	4.75
Synthetic cathinones	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0	6	6	18	26	27	49	25	157	8	19.63

Note: n/a = not available

Sources: ONS (2015, 2016a, 2016b, 2016c, 2017a, 2017b)

Table 4. Estimated number (thousands) of individuals aged 16-59 who had used selected substances in the last year in England and Wales, 2001/2-2016/7

Substance/Year	2001/2	2002/3	2003/4	2004/5	2005/6	2006/7	2007/8	2008/9	2009/10	2010/1	2011/2	2012/3	2013/4	2014/5	2015/6	2016/7	Mean
Amphetamines	460	475	470	426	423	421	327	376	297	323	247	205	246	193	198	145	327.00
Cannabis	3185	3281	3271	2984	2732	2597	2367	2471	2077	2147	2191	2038	2144	2174	2121	2177	2497.31
Cocaine/crack	634	687	788	660	817	891	782	995	827	721	731	659	816	790	756	779	770.81
Any cocaine	587	635	754	638	770	840	743	949	786	682	699	628	777	756	738	764	734.13
GHB/GBL	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	47	n/a	n/a	n/a	n/a	n/a	47.00
Heroin	44	44	42	38	39	42	35	29	33	34	46	27	34	21	27	15	34.38
Ketamine	n/a	n/a	n/a	n/a	n/a	93	112	178	151	197	185	117	195	159	94	116	145.18
MDMA	634	596	595	549	499	567	470	567	496	434	445	403	516	545	492	439	515.44
Mephedrone	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	345	375	167	211	162	89	48	199.57
Piperazines	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	34	47	n/a	n/a	n/a	n/a	n/a	40.50

Notes: n/a = not available; no earlier data available for this age-range.

Sources: Home Office, 2012; Broadfield, 2017

Table 5. Total seizures of selected substances made by police forces and Customs & Excise/Border Force in England and Wales for the period 2000 – 2015/6.

Substance/ Year	2000	2001	2002	2003	2004	2005	2006/7	2007/8	2008/9	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	Total	Years of exposure	Mean
Cocaine	5,582	6,797	6,015	7,251	8,279	12,512	16,917	21,346	24,659	21,377	17,710	17,596	16,758	16,825	15,815	15,588	231,027	16	14,439
MDMA	8,337	9,080	7,044	6,475	6,256	6,688	8,184	7,173	5,218	3,724	2,537	3,200	3,224	3,237	3,018	2,906	86,300	16	5,394
Heroin	13,713	15,447	13,357	11,195	11,668	14,072	13,942	14,186	13,302	12,836	10,821	9,182	8,573	8,579	7,892	8,050	186,813	16	11,676
Total cannabis	85,087	80,654	82,519	87,512	81,517	120,427	144,599	173,589	186,147	176,830	167,410	175,264	157,208	149,087	124,408	109,527	2,101,786	16	131,362
Amphetamine	6,390	6,348	6,181	6,208	6,504	7,837	8,477	8,863	7,760	7,302	7,185	6,773	5,934	6,067	5,530	4,418	107,778	16	6,736
GHB only	n/a	n/a	n/a	29	21	29	61	63	47	59	66	45	61	41	75	64	661	13	51
Ketamine	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	1,269	1,612	1,793	1,543	1,527	1,621	485	530	10,380	8	1,298
Piperazines (substituted)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	157	830	398	142	194	92	42	1,855	7	265
Mephedrone	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	35	2,002	2,461	3,850	3073	2,325	1,031	14,777	7	2,111

Notes: n/a = not controlled

Sources: Smith (2008); Hargreaves and Smith (2016); personal communication to JC from J. Hargreaves, Home Office Crime and Policing Analysis Unit, 24 November 2016

Table 6. Overall Index (T_f) of fatal toxicity for the period 2001/2 to 2016

(a) [Prevalence only]

Substance	Index (any mention)	Index (sole mention)	Overall Index	Ln (Overall Index)
Heroin	1000.00	1000.00	1000.00	6.91
Cocaine & crack	9.91	5.29	7.60	2.03
Amphetamine	6.85	5.06	5.96	1.79
MDMA	3.41	2.82	3.12	1.14
Cannabis	0.27	0.05	0.16	-1.83
GHB/GBL	11.23	9.99	10.61	2.36
Ketamine	1.99	1.30	1.65	0.50
Piperazines	3.79	1.45	2.62	0.96
Mephedrone	3.10	0.99	2.05	0.72

Note: The Overall index is the mean of the ‘sole’ and ‘any’ mention indices

(b) [Seizures]

Substance	Index (any mention)	Index (sole mention)	Overall Index	Ln (Overall Index)
Heroin	1000.00	1000.00	1000.00	6.91
Cocaine & crack	132.29	70.62	101.46	4.62
Amphetamine	112.98	83.45	98.22	4.59
MDMA	110.74	91.51	101.13	4.62
Cannabis	1.73	0.30	1.02	0.02
GHB/GBL	3527.96	3137.06	3332.51	8.11
Ketamine	75.73	49.57	62.65	4.14
Piperazines	196.59	75.05	135.82	4.91
Mephedrone	99.62	31.79	65.17	4.18

(c) [Prevalence & Seizures]

Substance	Index (any mention)	Index (sole mention)	Overall Index	Ln (Overall Index)
Heroin	1000.00	1000.00	1000.00	6.91
Cocaine & crack	71.10	37.95	54.53	4.00
Amphetamine	59.92	44.25	52.09	3.95
MDMA	57.07	47.17	52.12	3.95
Cannabis	1.00	0.17	0.59	-0.53
GHB/GBL	1969.59	1573.52	1771.56	7.48
Ketamine	38.86	25.44	32.15	3.47
Piperazines	100.19	38.25	69.22	4.24
Mephedrone	51.36	16.39	33.88	3.52

(d) [Market size]

Substance	Index (any mention)	Index (sole mention)	Overall Index	Ln (Overall Index)
Heroin	1000.00	1000.00	1000.00	6.91
Cocaine & crack	93.02	49.65	71.34	4.27
Amphetamine	127.46	94.15	110.81	4.71
MDMA	78.80	65.12	71.96	4.28
Cannabis	0.38	0.07	0.23	-1.47

(e) [Prevalence, Seizures & Market size]

Substance	Index (any mention)	Index (sole mention)	Overall Index	Ln (Overall Index)
Heroin	1000.00	1000.00	1000.00	6.91
Cocaine & crack	51.13	26.53	38.83	3.66
Amphetamine	45.05	31.83	38.44	3.65
MDMA	41.21	33.05	37.13	3.61
Cannabis	0.68	0.12	0.40	-0.92

Table 7. Mean values of Sole (S) and Any (A) mentions, and S/A where selected substances were implicated in the cause of death registered in England and Wales for the period 1993 - 2016 or as otherwise shown. Values of LnT_f have been interpolated from Figure 1 for those substances where LnT_f was unavailable directly because of lack of prevalence/seizure data. Substances with high interpolated values of LnT_f (>4) are shown emboldened, whereas substances with low values (<2) are shown in italics.

Substance	**Years of exposure**	**S**	**A**	**S/A**	LnT_f
Amphetamine	24	18.58	50.13	0.371	-
AMT	24	0.58	0.92	0.630	**6.59**
Benzodiazepine analogues	8	0.25	5.50	0.045	*-0.02*
Benzofurans	6	1.17	3.33	0.351	3.46
Cannabis	24	2.46	15.08	0.163	-
Cocaine/crack	24	44.67	139.25	0.321	
GHB/GBL	23	5.13	9.35	0.549	**5.68**
Heroin	24	438.21	725.08	0.604	-
Ketamine	18	2.67	6.50	0.411	-
MDMA	24	17.67	34.96	0.505	-
Mephedrone	8	3.00	15.25	0.197	-
MPA	5	1.20	5.80	0.207	1.84
Novel amphetamines	11	0.09	0.91	0.100	*0.64*
Piperazines	9	0.89	3.78	0.235	2.16
PMA/PMMA	24	1.88	3.67	0.497	**5.09**
Synthetic cannabinoids	8	2.75	4.75	0.579	**6.02**
Synthetic cathinones	8	4.25	19.63	0.217	*1.95*

Figure 1. The relationship between the updated index LnT_f [based on a combination of prevalence and number of seizures; see Table 6 (c)] and values of S/A (see Table 7) ($r = 0.923$; $P < 0.01$) for the seven reference compounds (amphetamine, cannabis, cocaine, heroin, ketamine, MDMA and mephedrone). The straight line is the least squares fit [$LnT_f = 11.22(S/A) - 0.48$].