# Comparison of acute lethal toxicity of commonly abused psychoactive substances

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Submitted 15 September 2003;
initial review completed 22 November 2003;
final version accepted 12 February 2004

## ABSTRACT

**Aims** To determine the acute lethal toxicity of a range of psychoactive substances in terms of the dose customarily used as a single substance for non-medical purposes.

**Design and method** A structured English-language literature search was conducted to identify experimental studies and clinical reports that documented human and non-human lethal doses of 20 abused substances that are distributed widely in Europe and North America. Four inclusion criteria were specified for the reports, and approximately 3000 relevant records were retrieved from search engines at Biosis, Science Citation Index, Google and the National Library of Medicine's Gateway. In order to account for different drug potencies, a 'safety ratio' was computed for each substance by comparing its reported acute lethal dose with the dose most commonly used for non-medical purposes.

**Findings** The majority of published reports of acute lethal toxicity indicate that the decedent used a co-intoxicant (most often alcohol). The calculated safety ratios varied between substances by more than a factor of 100. Intravenous heroin appeared to have the greatest direct physiological toxicity; several hallucinogens appeared to have the least direct physiological toxicity.

**Conclusions** Despite residual uncertainties, the substantial difference in safety ratios suggests that abused substances can be rank-ordered on the basis of their potential acute lethality.

**KEYWORDS** Acute toxicity, lethality, positive subjective effects, safety ratio, therapeutic index.

## INTRODUCTION

It is commonly assumed that abused substances differ with respect to their acute physical toxicity. However, public opinion and public policies are often based on anecdotal reports and statistical information that is not adjusted for factors such as prevalence of use. The present study addressed this issue by undertaking a comparison of the toxicity of abused substances based on reports of experimental human and non-human animal research and on published toxicological analyses of overdose fatalities.

Most substances have multiple mechanisms of toxicity and multiple target organs, each with its own vulnerability to the administered compound. Because detailed toxicological evaluation is time-consuming and expensive, drug concentrations in plasma or whole blood are used routinely as surrogate measures in overdose cases. Several well-known compilations of cases have listed the lethal human blood concentrations for a range of hazardous substances and drugs: Druid & Holmgren (1997), Repetto & Repetto (1997) Schulz & Schmoldt (1997), Ekwall *et al.* (1998), National Toxicology Program (2001) and Baselt (2002). Blood analysis of a decedent is not, however, without measurement complications. Different substances have varying patterns of postmortem redistribution from organ tissue to the bloodstream (Pounder & Jones 1990; Leikin & Watson 2003).

 doi:10.1111/j.1360-0443.2004.00744.x 

Furthermore, a drug such as heroin might not be detected at all in postmortem blood samples because it has an arterial half-life of only about 3 minutes (Rentsch *et al*. 2001) and its metabolite morphine-3-glucuronide has a half-life of approximately 90 minutes. Once a blood sample has been obtained, factors of storage and measurement techniques may also affect the result. Cocaine, for example, is notoriously susceptible to decomposition in storage.

Fortunately, non-human animal models can provide supplementary and detailed descriptions of toxic processes. The median lethal dose ($LD_{50}$) of a new compound is often the first estimate of toxicity that is established in pre-clinical research within a rodent population (Gad & Chengelis 1998). Specifically, the dose–response relationship is documented by plotting the number of deaths occurring among the group of experimental animals against the range of drug doses administered. The $LD_{50}$ is simply the dosage at which 50% of the animals die within a specified interval of time. Several governmental organizations (cf. Interagency Coordinating Committee 2002; OECD 2002) have promulgated guidelines for experimentally establishing $LD_{50}$s, and a list of lethal oral starting doses of 347 chemicals has been published by the National Toxicology Program (2001). In order to reduce animal suffering, vigorous efforts have been made to develop alternative methods of toxicity assessment (cf. Gad 2000).

The $LD_{50}$ is just one data-point along an entire range of potential responses, and therefore it does not provide information about the *shape* of a dose–response curve. Two drugs might have the same $LD_{50}$, but in practice present a different degree of health hazard. A drug with a relatively 'flat' dose–response curve might have a low threshold of lethality but require large changes in dosage before 50% of the animals die. In contrast, a drug with a 'steep' dose–response curve might have a much higher initial lethal threshold, but need only small additional quantities of the chemical to reach the 50% level of fatalities. The second drug would be safer in most applications, unless users were unwilling or unable to measure dosages accurately (a condition that frequently occurs in social situations). Despite limitations, the $LD_{50}$ remains an important benchmark. In terms of 'generating the most information per animal, the $LD_{50}$ is the most simple single summary statistic to measure on the dose–response curve' (Interagency Coordinating Committee 2002, Addendum III, p. 1).

Similar to dose–response curves for acute lethality, dose–response curves for desired effects can be plotted in order to establish the median effective dose ($ED_{50}$) of a substance. A well-established tradition of assessing abuse liability in diverse settings and among diverse populations provides a substantial database of controlled studies (e.g. Balster & Bigelow 2003). Several research strategies are particularly relevant to documenting preferred dosages by including variables such as positive subjective effects (e.g. rates of drug self-administration, experimental choice procedures and user responses on standardized questionnaires such as the Addiction Research Center Inventory, Profile of Mood States or Single-Dose Questionnaire (cf. Jasinski & Henningfield 1989).

A notable series of studies by Brady *et al*. (1987) demonstrated the feasibility of rank-ordering the abuse liability of anorectic drugs in terms of a ratio between a dose that produces an anorectic/therapeutic effect and a dose that produces a reinforcing/toxic effect. The authors noted that such comparison is similar to the 'therapeutic index' or 'therapeutic ratio' used commonly to assess the relative toxicity of medications. A few studies (e.g. Buckley *et al*. 1995; Whyte *et al*. 2003) have rank-ordered substances within a specific class of drugs based on the traditional therapeutic ratio which compares the therapeutic dose to the *lethal* dose. The present review can be distinguished from this previous work in two respects: (1) the 'therapeutic ratio' was calculated by comparing the customary *non-medical* dose of a substance to its lethal dose and (2) the rank-ordering covered *multiple classes* of drugs. (The term 'safety ratio' rather than 'therapeutic index' or 'therapeutic ratio' will be used hereafter with reference to abused substances because the intended application is not therapeutic.)

## METHODS

In order to ensure that a range of psychoactive substances would be represented, 20 drugs were identified from seven broadly defined categories of drug action: narcotic analgesics, psychomotor stimulants, central nervous system depressants, anti-anxiety agents, sedative/hypnotics, hallucinogens/psychedelics and cannabis. The selection focused on substances that are distributed most widely in Europe and North America and that are known to have abuse potential.

A simple inductive search procedure was used to locate relevant English-language sources. The current edition of standard reference works was consulted initially to provide an overview of relative toxicities (e.g. Gangolli 1999; Hardman & Limbird 2001; Baselt 2002). Concurrently, a structured literature search was conducted using the National Library of Medicine's (NLM) Gateway (including Medline, Oldmedline and Pubmed). The generic or popular trade name of each the 20 substances was keyed into the NLM *Gateway* search engine as a means of locating journal articles or conference papers in which the substance appeared, during the years 1953–2003, in conjunction with one of the following medical subject headings: 'fatal overdose', 'lethal dose

50' or 'LD 50'. The same procedure was followed using Scifinder to access Biosis Previews covering serial publications between 1969 and 2003. The Google search engine was also used to locate creditable toxicological reports in its extensive database and to access material safety data sheets.

Estimates of commonly used non-medical doses for the 20 substances were derived in the same manner as described previously. However, the search procedure used the descriptors 'positive subjective effects', 'effective dose', 'therapeutic index' and 'safety index'. In addition, publications focusing on the pharmacology of non-medical drug use (e.g. Julien 2001; Stafford 1992) were scanned manually for references to non-medical drug dose quantities.

An item retrieved from NLM Gateway, Biosis, Science Citation Index or Google was considered potentially relevant if it met four criteria: (1) the abstract made reference to the quantification of a lethal or non-medical effective dose of one of the target substances; (2) the substance was not used in combination with another substance; (3) the source appeared to be technical or scholarly in nature; and (4) the target substance was administered to a human or non-human animal presumed to be in normal health. Thus, popular or non-technical sources that appeared to be unsubstantiated or secondary in nature (e.g. newspapers, magazines, website commentary) were excluded. Articles citing data generated from special situations or populations (e.g. extremes of age, metabolic or genetic anomalies, adherence to abnormal diets) were similarly excluded. Various types of empirical evidence (e.g. controlled clinical trials, laboratory experiments, case studies, meta-analyses) were acceptable if the data appeared to be from a reputable original source.

## RESULTS

### Identification of reports

The large majority of retrieved documents focused on topics of pharmacokinetics, drug interactions, drug synthesis, pharmacogenetics, research methodology, overdose management or epidemiology. When 'lethal dose 50' or '$LD_{50}$' was cross-indexed with the 20 target substances, the NLM Gateway search resulted in a total of 765 records; the Biosis search resulted in 307 records. The term 'fatal overdose' resulted in 294 and 51 records for Gateway and Biosis, respectively. Approximately 70% of the cited items had abstracts. (No articles in Medline prior to 1975 or in Oldmedline have abstracts.) The abstracted articles were screened on the basis of the four previously mentioned criteria. If an electronic version of the entire article was not available immediately, the abstract was printed in order to facilitate subsequent retrieval of a hard copy. Manual searches were conducted to locate relevant references cited in the retrieved articles. The most relevant research or review papers were keyed into the Science Citation Index in order to scan the titles of subsequent publications citing that paper.

Because the Google search engine retrieves pages on the basis of the number of websites that use the chosen descriptors, there were numerous secondary citations and much unsubstantiated commentary. More than 31 000 records were retrieved by Google when the 20 substances were cross-indexed with 'LD50'; therefore, a systematic search was abandoned. Citation tracking within European and North American literature was undoubtedly incomplete, but the reported $LD_{50}$ values from experimental studies with rodents seldom varied by more than a factor of 2. Case study data from human fatalities showed more variability.

When the descriptor 'positive subjective effects' was combined with each of the 20 substances, a total of 195 records was generated from Gateway but only 25 from Biosis. Separate searches in Biosis were conducted subsequently using the terms 'positive effects' and 'subjective effects', which resulted in a total of 475 citations for the 20 substances. The term 'effective dose' resulted in 3457 citations from Gateway and 320 from Biosis. 'Therapeutic index' retrieved 1071 items from Gateway and 70 items from Biosis. Gateway and Biosis citations showed considerable redundancy with respect to articles citing doses for medical purposes, but relatively few citations and little redundancy of articles citing non-medical doses. *Google* listed 158 items for 'positive subjective effects', 52 800 for 'effective dose', 15 712 for 'therapeutic index' and 14 700 for 'safety index'. Again, systematic screening of Google records was discontinued.

In addition to experimental studies of abuse liability, several dozen reasonably detailed self-reports (e.g. Mitchell 1896, cited in Metzer 1989; Bennett 1960; Gelpke 1981) and other creditable publications (e.g. *Heffter Review* 1998/2001; Shulgin & Shulgin 1991, 1997; Strassman 2001) were useful in estimating effective dose levels. When all the lethal and effective dose search terms were combined with all 20 substances, a grand total of approximately 6500 records was retrieved from Gateway and Biosis. Approximately 3000 articles survived screening, and were printed and filed between 1995 and 2003. Due to space limitations, only two references for each substance are cited in Table 1. Unfortunately, this leaves much original and detailed research work unacknowledged in this review.

### Safety ratio estimates

Lethality and effective-dose data for each of the 20 substances are summarized in Table 1. The number of fatal

**Table 1** Estimated lethal and effective doses of abused psychoactive substances.[a]

| *Common, generic or trade name* | *Principal active component* | *Non-human median lethal dose (mg/kg)* | *No. of fatal human cases selected* | *Usual lethal concentration (and range) in blood (mg/l)* | *Usual lethal dose (and range) reportedly administered* | *Usual effective dose (and range) for non-medical purposes* | *Safety ratio* | *References* | *Comments* |
|---|---|---|---|---|---|---|---|---|---|
| Alcohol (or)[b] | Ethanol | mouse (or) 6800; rat (or) 10 300 | 894 | 3600 (2200–5000) | 330 g (276–455) | 33 g (22–40) | 10 | Jones & Holmgren 2003), Ekwall & Clemedson (1997) | Ethanol most common substance in multidrug fatalities |
| Cocaine (in) | Cocaine hydrochloride | mouse (ip) 91; dog (iv) 21 | 21 | 5 (1–20) | 1200 mg (20–2000) | 80 mg (40–90) | 15 | Mittleman & Wetli (1984), Smart & Anglin (1987) | |
| Codeine (or) | Codeine phosphate | mouse (or) 250; rat (or) 266 | 32[c] | 2.3 (0.7–11) | 800 mg (500–1000) | 40 mg (30–60) | 20 | Baselt (2002), La Barre 1959) | |
| DMT (or) | N,N-dimethyl-tryptamine | mouse (or) 280; mouse (ip) 47 | 0 | – | 2 g (extrapolated) | 40 mg (34–70) | 50 (?) | Gillin *et al.* (1976), Callaway *et al.* (1999) | |
| DXM (or) | Dextro-methorphan | mouse (or) 210, rat (or) 350 | 7 | 3 (1.1–18) | 1.5 g (–) | 150 mg (100–300) | 10 | Dalpe-Scott *et al.* (1995), Rammer *et al.* (1988) | |
| GHB (or) (GBL/BD)[d] | Gamma-hydroxybutyrate | mouse (or) 1720; rat (or) 1540 | 11 | 300 (140–489) | 16 g (5.44–24 g) | 2 g (1.4–3 g) | 8 | Hornfeldt *et al.* (2002), Kalasinsky *et al.* 2001) | |
| Heroin (iv) | Diacetylmorphine | mouse (iv) 22; rat (iv) 23 | 178 | 0.30[e] (0.1–2.8) | 50 mg (12–180) | 8 mg (5–10) | 6 | Meissner *et al.* (2002), Goldberger *et al.* 1994) | |
| Isobutyl nitrite (inh) | Isobutyl nitrite and metabolites | mouse (inh) 1346 p.p.m.; rat (inh) 1000 p.p.m. | 3 | 60% methe-moglobin[f] (23–95%) | 1.5 ml of vaporized liquid | 0.2 ml of vaporized liquid | 8 | Bradberry *et al.* (1994) Horne *et al.* (1979) | Doses are rate-of-loss from container by inhalation |
| Ketamine (in) | Ketamine hydrochloride | mouse (ip) 400; guinea pig (im) 361 | 0 | – | 2.7 g (extrapolated) | 70 mg (20–150) | 38 (?) | Green *et al.* (1999), Moore *et al.* (1997) | Reported deaths only IV, IM or with co-intoxicant |
| LSD (or) | d-Lysergic acid diethylamine | mouse (iv) 46; rat (iv) 17 | 2 | 4.8 μg/L (–) | 100 mg[g] (extrapolated) | 100 μg (25–200) | 1000 (?) | Fysh *et al.* (1985), Klock *et al.* 1975) | |
| Marijuana (sm) | Δ9-tetrahydro-cannabinol | mouse (or) 22; monkey (iv) 130 | 2 | – (180–315 μg/L) | > 15 g (extrapolated) | 15 mg (12–22) | > 1000 (?) | Kalant *et al.* (1999), Heyndrickx *et al.* (1969) | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| MDMA (or) | Methylenedioxy-methamphetamine | rat (or) 160; guinea pig (ip) 26 | 27 | 3 (0.04–8.5) | 2 g (150–1250)[l] | 125 mg (15–150) | 16 | Kalant (2001), Garcia-Repetto *et al.* (2003) | Variability linked to environmental factors |
| Mescaline (or) | Trimethoxy-phenethylamine | mouse (or) 880; rat (im) 330 | 1 | 0.48 (–) | 8.4 g (extrapolated) | 350 mg (200–450) | 24 (?) | Henry *et al.* (2003), Nolte & Zumwalt (1999) | Rare deaths from related violent trauma |
| Methadone (or) | Di-methadone hydrochloride | mouse (or) 124; rat (or) 30 | 206[c] | 0.70 (0.06–3.1) | 100 mg (20–420) | 5 mg (3–10) | 20 | Seymour *et al.* (2003), Worm *et al.* (1993) | Long half-life of methadoneis a risk factor |
| Methamphet-amine (or) | Meth-amphetamine hydrochloride | mouse (ip) 43; dog (or) 10 | 20 | 2 (?) (1–43) | > 150 mg (140–1650) | 15 mg (10–25) | 10 | Logan *et al.* (1998), Wallace & Squires (2000) | Widely divergent reactions to high doses |
| Nitrous oxide (inh) | Nitrous oxide | rat (or) 505; rat (inh) 1274 | 9 | 100 ml/l (46–180) | > 525 l[j] (–) | 3.5 l (1.75–7) | >150 | Garriot & Petty (1980) Winek *et al.* (1995) | |
| Phenobarbital (or) | Phenobarbital | mouse (or) 137; rat (or) 162 | 32 | 95 (55–230) | 5 g (1.5–8) | 100 mg (60–120) | 50 | Druid & Holmgren (1997), Ekwall *et al.* (1998) | |
| Prozac/ Sarafen (or) | Fluoxetine | mouse (or) 248; rat (or) 452 | 11 | 3.8 (1.3–6.8) | > 2 g (1.2–3.0) | 20 mg (10–80) | 100 | Goeringer *et al.* (2000), Kincaid *et al.* 1990) | |
| Psilocybin (or) | Psilocybin | mouse (ip) 285; rat (ip) 280 | 1[k] | 4 (–) | 6 g (extrapolated) | 6 mg (–) | 1000 (?) | Allen *et al.* (1991), Gerault & Picart (1996) | Wild mushrooms commonly misidentified |
| Rohypnol (or) | Flunitrazepam (benzodiazepine) | mouse (or) 700; rat (or) 1000 | 43 | 0.06 (0.01–0.25) | 30 mg[l] | 1 mg (0.5–2) | 30 | Druid *et al.* (2001), Robertson & Drummer (1998) | |

[a]The doses indicated are the estimated quantity for an average healthy 70-kg adult human who has not developed tolerance to the substance, and who does not have residues of the substance in the body from previous administrations. Note, however, that individuals vary greatly in terms of physical and psychological vulnerability; therefore, the information in this table should not be used as a dosage guide. [b]im = intramuscular, inh = inhaled, in = intranasal, ip = intraperitoneal, iv = intravenous, or = oral, sm = smoked. [c]The degree of opiate/opioid tolerance was unknown at the time of drug administration for some decedents. [d]Gamma-butyrolactone (GBL) and 1,4-butanediol (BD) are metabolized to GHB. [e]Measured as free (rather than total) morphine. An individual's tolerance and rate of metabolism are apparently among critical factors leading to a significant overlap in observed blood morphine concentrations between survivors and non-survivors. [f]Parent compound is not detectable in blood; thus, methemoglobin is used as a marker for exposure. Inhalation fatalities are possibly under-reported. [g]One of the two reports of a fatality (with only liver tissue LSD concentration indicated) asserted that the quantity of LSD ingested was equivalent to 800–1600 times the usual 'street' dose (Griggs & Ward 1977). [h]Range is based on cases of non-lethal but severe toxicity. Scattered, incomplete reports of deaths by oral and i.v. administration. [i]Survival is reported after a calculated dose of 6.25 g (Ramcharan *et al.* 1998). [j]Calculated from a non-lethal case. $N_2O$ when used with adequate oxygen is not lethal. Non-medical doses (e.g. in a balloon) are usually 100% $N_2O$, and death is due to anoxia. [k]For a critique of this case, see Gartz, Samorini & Festi (1996). [l]Flunitrazepam is rapidly metabolized. The metabolites that are chosen for postmortem analysis often lead to differing assessments of fllunitrazepam toxicity.

human cases listed in Table 1 reflects, for most substances, a notable reduction in the total number of cases reported in clinical and research literature. A documented fatality was not included in Table 1 when the decedent was reported to have used a significant amount of a co-intoxicant or died as a result of accidental trauma. For example, in an exceptionally detailed summary of 168 fatal cases involving four selective serotinin reuptake inhibitor (SSRI) drugs (Goeringer *et al.* 2000), only one case was verified for this review as having been caused exclusively by a fluoxetine overdose.

The range of concentrations and doses in Table 1 incorporate the findings of individual case studies as well as compilations that reported aggregated data. Most of the toxicological compilations did not present descriptive statistics beyond either a mean or a median. Thus, the present review favored the somewhat colloquial terms 'usual' and 'customary' to describe concentrations or doses so that a precise measure of central tendency would not be implied. Furthermore, so few cases were located for several substances (e.g. isobutyl nitrite, LSD) that any measure of central tendency would not be meaningfully robust.

The $LD_{50}$ values cited in Table 1 are the estimates of a customary dose for a normally healthy 70-kg adult who has not developed tolerance to the substance in question, and who does not have residues of the substance in the body from previous administrations. The estimates do not take into account factors such as environmental stressors or individual differences with respect to sex or ethnicity.

Phenobarbital can be used to illustrate the nature of the data sources and some of the challenges involved in specifying a lethal dose. This class of drugs is generally cited as having a therapeutic (safety) index of about 10 times the hypnotic dose (Harrison, Mendelson & de Wit 1995; Charney, Mihic & Harris 2001). Phenobarbital, in particular, can be expected to have a higher safety ratio than most barbiturates because gastrointestinal absorption of phenobarbital is slower and its capacity to produce respiratory depression is less. Although one handbook has cited the average human lethal dose of phenobarbital as 1.5 g (True & Dreisbach 2002), a small compilation of cases by Ekwall, Wallum & Bondesson (1998) cited a lethal range of 4.8–7.8 g. Non-human animal studies reported oral $LD_{50}$ doses of mice at 168 and 137 mg/kg, and rats at 162 mg/kg (National Toxicology Program 1991). An unadjusted extrapolation of the rodent average of 156 mg/kg would put the median lethal dose of phenobarbital for a 70-kg person (who has not developed tolerance) at approximately 11 g. However, in order to allow for interspecies variation, some toxicologists (e.g. Neubert 1999) and regulatory agencies (e.g. UN International Programme on Chemical Safety, US Food and Drug Administration) routinely lower a rodent $LD_{50}$ by a factor of 10, based on body weight, when generalizing results to humans. Thus, we can be reasonably confident that the human lethal dose lies somewhere between 1 and 8 g.

In an effort to be more specific, an $LD_{50}$ estimate was calculated from pharmacokinetic information about blood concentrations of phenobarbital. In adults, single oral doses of 30 mg and 100 mg have produced peak serum concentrations of 0.7 and 2.3 mg/l, respectively (Viswanathan, Booker & Welling 1979; Yska *et al.* 2000). A compilation of nine fatalities by Druid & Holmgren (1997) reported a median postmortem femoral blood concentration of 75 mg/l. A series of 15 fatalities summarized by Crafoord & Ekwall (1997) reported an average lethal blood concentration of 114 mg/l. Assuming a normal distribution of lethal concentrations among these 24 cases, the median lethal blood level of phenobarbital would be approximately 95 mg/l. At a constant rate of drug absorption, a 95-mg/l concentration would require a minimal dose of 4 g. Baselt (2002, p. 613) noted that acute human fatalities have occurred 'after ingestion of as little as 6 g of phenobarbital' with a resulting blood concentration between 78 and 116 mg/l. Table 1 lists the lethal dose of oral phenobarbital as 5 g. (Only a small minority of reviewed studies cited both the lethal drug dose that was presumably administered and the associated blood concentration.)

The estimated human lethal dose of all substances was corroborated by non-human animal studies; however, for six of the substances (DMT, ketamine, LSD, marijuana, mescaline and psilocybin) fewer than three reports of human fatality were located. In this situation, the lethal dose in Table 1 is extrapolated from the animal studies. The extrapolated value, reduced by a factor of 10, is noted in the table, and a question-mark follows the related safety ratio. The clinical validity of animal models is always suspect, but the data probably provide a justifiable estimate in the absence of direct evidence (cf. Gad & Chengelis 1998). It should be noted that, for all 20 substances, there were 'survivor' or 'near-fatal' human cases, not referenced in Table 1, that helped set the parameters of a lethal dose.

For a few substances such as intranasal cocaine hydrochloride, human fatalities were rarely reported for the route of administration specified in Table 1 unless another substance was co-administered by the decedent. In this circumstance, a dose–response relationship was inferred from typical blood concentrations of the specified drug when research participants reported psychoactive effects (e.g. Javaid *et al.* 1983) and from blood concentrations of the drug in overdose fatalities where a variety of administration routes may have been used (e.g. Cravey 1990). This interpolation necessarily ignores changes in pharmacokinetics that are impacted by different dosage routes, drug quantities and postmortem redistribution.

Substantially more data were available for estimating the effective dose than the lethal dose of most substances. Information from a few well-documented self-reports (e.g. Blofeld 1966; Gelpke 1981; Shulgin & Shulgin 1997) was augmented by data from pharmacodynamic and drug preference studies (e.g. Hetem *et al.* 2000; Hart *et al.* 2001). For example, studies administering intranasal hydrochloride cocaine of 25–30 mg have produced mixed results with respect to ratings of 'high' and 'pleasantness' (Resnick *et al.* 1977; Van Dyke *et al.* 1982), while 50 mg could be discriminated from placebo on the basis of peripheral effects other than anesthesia of the nasal passage (Schuh, Schubiner & Johanson 2000). Doses of 53, 64, 96 and 105 mg have generally shown a consistent increase in both cocaine plasma concentrations and ratings of 'high' (Yang *et al.* 1982; Javaid *et al.* 1983). Pharmacokinetic and drug treatment studies have occasionally employed doses as large as 2 mg/kg (140 mg for a 170-kg person) as an experimental dose (Lange *et al.* 1989; Tuncel *et al.* 2002). Assuming that a 70-kg non-medical user will insufflate two or three 'lines' of cocaine containing between 20 and 30 mg each (Fischman 1984), the dosage range would be 40–90 mg, with the associated subjective effects ranging from pleasant excitement to moderate elation. Because a notable characteristic of cocaine use is the strong urge to repeat the experience and escalate the dosage, the higher end of this range, 80 mg, was listed in Table 1 as the estimated effective dose for a non-tolerant user.

The results of the present review disclosed substantial differences in the safety ratio of abused substances. The most toxic substances appear to have a lethal dose less than 10 times the effective dose. These substances include: GHB (oral), heroin (intravenous) and isobutyl nitrite (inhaled). Less acutely toxic substances, with safety ratios from 10 to 20, include: alcohol (oral), cocaine (intranasal), codeine (oral), dextromethorphan (oral), MDMA (oral), methadone (oral) and methamphetamine (oral). A diverse group of drugs have still wider ratios, ranging from above 20–80: DMT (oral), flunitrazepam (oral), ketamine (inhaled), mescaline (oral) and phenobarbital (oral). Five substances have ratios of 100 or above: fluoxetine (oral), LSD (oral), marijuana (oral), nitrous oxide (inhaled) and psilocybin (oral). These safety ratio estimates should be interpreted with caution. Because they are based on aggregated data, none of the ratios in Table 1 is applicable to any particular individual.

## DISCUSSION

The findings of this review indicate that abused drugs are substantially dissimilar with respect to their acute lethal toxicity. Due to inherent imprecision in toxicity assessments, it would be a flagrant misinterpretation of the numbers in Table 1 to assume that they could be mathematically manipulated. None the less, the range of safety ratios is so wide that the data appear to have the attributes of an ordinal scale. For example, we can be reasonably sure that the safety ratio of nitrous oxide is larger than the safety ratio of GHB. We need not assert that the safety ratio of nitrous oxide is 20 times greater than GHB in order to make a valid ranking.

The practice of ordinally ranking drugs and substances is a widely accepted element of risk assessment and management. For example, the Canadian National Pollutant Release Inventory lists 230 substances that have been ranked into eight categories on the basis of specified health threats (Olewiler & Dawson 1998). The US Environmental Protection Agency (2001) has classified all pesticide products into four categories based on studies of relative acute toxicity. With respect to psychotropic substances, probably the most challenging task has been fulfilling legislative requirements to assign substances to (partially rank-ordered) drug-control schedules (cf. Australian Drugs, Poisons, and Controlled Substances Act; UK Misuse of Drugs Regulations). Although the toxicity of a substance may be comparatively low, other lethal and non-lethal factors (e.g. neurological complications, pulmonary disease, chemical dependence) must be considered and may ultimately determine the assignment of the substance to a particular schedule. The US Drug Enforcement Administration (2001, p. 20041) noted, for example, that 'marijuana has a low level of toxicity when compared to other drugs of abuse', but the agency denied a petition to reclassify marijuana, citing other pharmacological and behavioral risks.

The present paper has focused narrowly on acute, single-dose systemic toxicity. For this reason, the data presented have varied applicability. A rank-ordering of substances with respect to their acute toxicity might contribute to drug education programs utilizing evidence-based prevention messages that 'discuss the risks associated with initial use of alcohol, marijuana and cocaine' (NIDA 2003, np, see also NAC 2003). However, the findings of the present review probably have less application to treatment programs where participants tend to be chronic users.

A broader and more ecologically valid review of drug toxicity must take into account several common characteristics of non-medical drug use:

**1** The probability of adverse effects is increased substantially when more than one substance is administered. Tanaka (2002) reported a substantial increase in fatalities among humans when alcohol was ingested with a benzodiazepine, despite the relatively wide therapeutic index of benzodiazepines. Darke *et al.* (2002) found that among 42 deaths from heroin overdose, postmortem

tests revealed that substances other than morphine were detected in over 80% of the cases.

**2** The risk of overdose is increased when the user repeats administration of the drug. A user may believe mistakenly that the initial dose is ineffective or no longer present in the body. After oral administration of MDMA, for example, plasma concentration does not peak for about 2 hours (Mas *et al*. 1999). A life-threatening situation may also arise from administering seemingly modest daily doses of methadone because the drug has a long elimination half-life (averaging 22 hours, with a reported range of 5–130 hours), thus allowing a toxic level of methadone to accumulate gradually (cf. Drummer *et al*. 1992; Eap, Buclin & Baumann 2002).

**3** Acute effects do not, by definition, take into account the health effects of chronic use. Direct acute lethality from alcohol or nicotine is quite rare, given prevalence of use. However, alcohol and tobacco use, along with obesity, are among the leading long-term causes of preventable death (WHO 2002).

**4** The safety ratios in Table 1 do not reflect metabolic or functional tolerance that a user might have developed. In situations where tolerance to the reinforcing effects of the drug increases more rapidly than to the metabolic effects of the same or a concomitant drug, the safety ratio will narrow.

**5** Non-drug variables can significantly alter toxic reactions. The psychophysiological effects of environment, diet, physical exertion, expectation and stress are known to have a significant impact on drug reactions (see, e.g. Gomita *et al*. 1983; Marzuk *et al*. 1998).

**6** A safety ratio does not reflect serious non-lethal sequelae that may burden the user and society. At relatively low non-toxic levels, psychoactive substances may induce dangerous performance decrements. LSD has a larger safety ratio than codeine, but it would certainly not be the drug-of-choice while operating machinery.

Millions of people have risked arrest and their health for the positive subjective effects of psychoactive substances. Hence, no catalog of toxicity—regardless of how complete—can account adequately for the continuing, and often troubling, human attraction to chemical alteration of consciousness. However, by taking into account the customary non-medical dosages of these substances, we can more realistically assess their hazards to public health.

## Acknowledgements

Data collection was supported, in part, by the Life Science Research Group, Inc. I thank Evan Claudeanos for manuscript assistance and Scot Johnson of the Kaiser Permanente Medical Group for his review. I also wish to acknowledge the help of Michael Yost, Supervising Coroner Investigator, Alameda County, California, as well as the foresight and guidance of Cristina Campbell, Chief Librarian, Public Health Library, University of California, Berkeley.

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