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# Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach

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**A comparative risk assessment of drugs including alcohol and tobacco using the margin of exposure (MOE) approach was conducted. The MOE is defined as ratio between toxicological threshold (benchmark dose) and estimated human intake. Median lethal dose values from animal experiments were used to derive the benchmark dose. The human intake was calculated for individual scenarios and population-based scenarios. The MOE was calculated using probabilistic Monte Carlo simulations. The benchmark dose values ranged from 2 mg/kg bodyweight for heroin to 531 mg/kg bodyweight for alcohol (ethanol). For individual exposure the four substances alcohol, nicotine, cocaine and heroin fall into the "high risk" category with MOE < 10, the rest of the compounds except THC fall into the "risk" category with MOE < 100. On a population scale, only alcohol would fall into the "high risk" category, and cigarette smoking would fall into the "risk" category, while all other agents (opiates, cocaine, amphetamine-type stimulants, ecstasy, and benzodiazepines) had MOEs > 100, and cannabis had a MOE > 10,000. The toxicological MOE approach validates epidemiological and social science-based drug ranking approaches especially in regard to the positions of alcohol and tobacco (high risk) and cannabis (low risk).**

Compared to medicinal products or other consumer products, risk assessment of drugs of abuse has been characterised as deficient, much of this is based on historical attribution and emotive reasoning[1]. The available data are often a matter of educated guesses supplemented by some reasonably reliable survey data from the developed nations[2]. Only in the past decade, have there been some approaches to qualitatively and quantitatively classify the risk of drugs of abuse. These efforts tried to overcome legislative classifications, which were often found to lack a scientific basis[3]. UNODC suggested the establishment of a so-called Illicit Drug Index (IDI), which contained a combination of a dose index (the ratio between the typical dose and a lethal dose) and a toxicology index (concentration levels in the blood of people who died from overdose compared with the concentration levels in persons who had been given the drug for therapeutic use)[4]. King and Corkery[5] suggested an index of fatal toxicity for drugs of misuse that was calculated as the ratio of the number of deaths associated with a substance to its availability. Availability was determined by three separate proxy measures (number of users as determined by household surveys, number of seizures by law enforcement agencies and estimates of the market size). Gable[6] provided one of the earliest toxicologically founded approaches in a comparative overview of psychoactive substances. The methodology was based on comparing the "therapeutic index" of the substances, which was defined as the ratio of the median lethal dose (LD50) to the median effective dose (ED50). The results were expressed in a qualitative score as safety margin from "very small" (e.g. heroin) to "very large" (e.g. cannabis). In a follow-up study, Gable[7] refined the approach and now provided a numerical safety ratio, which allowed a rank-ordering of abused substances.

Despite these early efforts for toxicology-based risk assessments, the most common methods are still based on expert panel rankings on harm indicators such as acute and chronic toxicity, addictive potency and social harm, e.g. the approaches of Nutt et al.[8,9] in the UK and of van Amsterdam et al.[3] in the Netherlands. The rankings of the two countries correlated very well[3,8]. Similar studies were conducted by questioning drug users, resulting in a high correlation to the previous expert judgements[10–12]. The major criticism that was raised about these "panel" based approaches was the necessity of value judgements, which might depend upon subjective personal criteria and not

Table 1 | Toxicological thresholds selected for calculating the margin of exposure

| Agent | Route | LD50 [mg/kg bw][a] | Average animal BMDL10[b] [mg/kg bw] | Human thresholds for sensitivity analysis |
|---|---|---|---|---|
| Heroin (RN: 561-27-3) | Intravenous | 21.8 (mouse)<br>22.5 (rat) | 2 | - |
| Cocaine (RN: 50-36-2) | Intravenous | 13 (dog)<br>16 (mouse)<br>17 (rabbit)<br>20 (rabbit)<br>17.5 (rat) | 2 | - |
| Tetrahydrocannabinol (THC) (RN: 1972-08-3) | Oral | 482 (rat)<br>666 (rat) | 56 | LOEL = 0.04 mg/kg bw (psychotropic effects)[55] |
| Nicotine (RN: 54-11-5) | Oral | 17.8 (bird)<br>9.2 (dog)<br>3.34 (mouse)<br>50 (rat) | 3 | LOAEL = 0.008 mg/kg bw/day (heart rate acceleration)[56,57] |
| Alcohol (ethanol) (RN: 64-17-5) | Oral | 5560 (guinea pig)<br>3450 (mouse)<br>6300 (rabbit)<br>7060 (rat) | 531 | BMDL1.5 = 0.4 g/kg bw (liver cirrhosis mortality)[21] |
| Methadone (RN: 76-99-3) | Oral | 70 (mouse)<br>86 (rat) | 8 | - |
| Amphetamine (RN: 300-62-9) | Oral | 135 (unspecified)<br>21 (mouse)<br>30 (rat) | 7 | - |
| Methamphetamine (RN: 537-46-2) | Unreported | 82 (mouse) | 8 | - |
| 3,4-Methylenedioxymethamphetamine (MDMA) (RN: 42542-10-9) | Oral | 325 (rat) | 32 | - |
| Diazepam (RN: 439-14-5) | Oral | 500 (mammal)<br>48 (mouse)<br>328 (rabbit)<br>249 (rat) | 27 | - |

[a]LD50 values were obtained from tabulations in ChemIDplus Advanced (United States National Library of Medicine; http://chem.sis.nlm.nih.gov/chemidplus) except for MDMA, for which the value was taken from Shulgin[24].
[b]An estimate of BMDL10 is obtained from LD50 by division by 10.2 using method B of Gold et al.[25]. See Supplementary Table S1 online for distribution functions used for calculation.

only upon scientific facts[13]. The methodology was also criticized because a normalization to either the total number of users or the frequency of drug use was not conducted, which might have biased the result toward the harms of opiate use[14] and may have under-represented the harms of tobacco[15]. Problematic may also have been the nomenclature applied in previous studies, mixing up "hazard" and "risk" into the term "drug harm". In chemical and toxicological risk assessment, the term "harm" is not typically used, while hazard is the "inherent property of an agent or situation having the potential to cause adverse effects when an organism, system, or (sub)population is exposed to that agent". Risk is defined as "the probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent"[16].

In the context of the European research project "Addiction and Lifestyles in Contemporary Europe – Reframing Addictions Project", the aim of this research was to provide a comparative risk assessment of drugs using a novel risk assessment methodology, namely the "Margin of Exposure" (MOE) method. The Margin of Exposure (MOE) is a novel approach to compare the health risk of different compounds and to prioritize risk management actions. The MOE is defined as the ratio between the point on the dose response curve, which characterizes adverse effects in epidemiological or animal studies (the so-called benchmark dose (BMD)), and the estimated human intake of the same compound. Clearly, the lower the MOE, the larger the risk for humans. The BMD approach was first suggested by Crump[17], and was later refined by the US EPA for quantitative risk assessment[18]. In Europe, the MOE was introduced in 2005 as the preferred method for risk assessment of carcinogenic and genotoxic compounds[19]. In the addiction field, the MOE method was never used, aside from evaluating substances in alcoholic beverages[20,21] or tobacco products[22,23]. This study is the first to calculate and compare MOEs for other addiction-related substances.

## Results

The only toxicological threshold available in the literature for all of the compounds under study was the LD50. The LD50 values taken from the ChemIDplus database of the US National Library of Medicine and from Shulgin[24] are shown in table 1. Using the method of Gold et al.[25], the LD50 values were extrapolated assuming linear behaviour (as no other information on dose-response is available) to BMDL10 values. As shown in Supplementary Table S1 online, the full range of available LD50 values in different animal species is taken into account as a risk function assuming a normal distribution for BMDL10 rather than that a single value is entered into the calculation (except methamphetamine and MDMA for which only one value was available in the literature). The mean values of BMDL10 range from 2 mg/kg bodyweight (bw) for heroin and cocaine up to 531 mg/kg bw for ethanol.

To determine the typical range of individual daily dosage, various textbook and internet sources[21,26–41] were evaluated (Table 2). As no information about the most likely function for dosage distribution is available, a uniform probability distribution was entered into the calculation in this case (Supplementary Table S1).

The data used for calculation of population-based exposure is shown in Table 2. Prevalence data was available for all drugs except methadone; and amphetamine and methamphetamine were grouped together. For a sub-group of drugs, exposure estimation based on sewage analysis is available (Table 2) (not all drugs are available in sewage analysis due to different stabilities/degradation rates of the compounds, for details see Ref. 26). The corresponding risk functions are shown in Supplementary Table S1 online. Except for eth-

Table 2 | Exposure data selected for calculating the margin of exposure (see Supplementary Table S1 online for distribution functions used for calculation)

| Agent | Range of individual daily dosage (low, high) [mg] | Ratio between no-tolerance and high tolerance dosage [authors' estimation based on cited literature] | Prevalence Europe (lower, upper) for drugs [%]/Per capita consumption for alcohol in Europe [L] | Exposure based on sewage analysis (min/max)[26] [mg/day/1000 population] |
|---|---|---|---|---|
| Heroin | 5–300[27] | 10[27] | Opiates: 0.5–0.6[28] | (no data available) |
| Cocaine | 20–100[29] | 4[42] | 0.8–0.9[28] | 2–1998 |
| THC | 10–60[30,31] | 4[43,44] | Cannabis: 5.4–5.7[28] | 14–192 |
| Nicotine | 1.65–1.89 mg/cigarette[32] 10–20 cigarettes/smoker/day[33] | 3[45,46] | 13–52[34] | (no data available) |
| Alcohol | 13.6 g–54.4 g (1–4 standard drinks[21]) | 1.5[47,48] | 2.0–17.5 L/year[41] | (no data available) |
| Methadone | 10–40[35] | 5[49–51] | (no data available) | (no data available) |
| Amphetamine | 5–50[36] | No data available | ATS excl. ecstasy: 0.5–0.6[28] | 33–3040 |
| Methamphetamine | 5–150[37] | 3[37] | (see amphetamine) | 3–376 |
| MDMA | 50–700[38] | 10[52,53] | Ecstasy: 0.6–0.7[28] | 32–615 |
| Diazepam | 5–40[39] | 2[54] | 42 daily doses per 1000 population per day (benzodiazepines)[40] | (no data available) |

ATS (amphetamine-type stimulant) excluding ecstasy comprises synthetic stimulants from the group of substances called amphetamines, which includes amphetamine, methamphetamine, and methcathinone; "ecstasy"-group substances include methylenedioxymethamphetamine (MDMA) and its analogues.

anol and nicotine, for which certain distributions could be fitted to the data for the European countries, uniform probability distributions were chosen in all other cases as only minimum/maximum prevalence values for Europe in total were available. The detailed calculation formulae chosen for probabilistic risk assessment are shown in Supplementary Table S2 online.

The margin of exposure values were calculated for individual exposure (Figure 1), population-based exposure calculated from prevalence data (Figure 2) and population-based exposure calculated from sewage analysis (Figure 3). The full numerical results of the MOE distributions are presented in Supplementary Table S3 online. For both individual and population-based scenarios, alcohol consumption was found to have the lowest margin of exposure. For individual exposure, heroin has the second lowest margin of exposure. However, considering worst-case scenarios (e.g. 5$^{th}$ percentile), heroin may have a lower MOE than alcohol (compare standard deviation bars in Figure 1). On the other end of the scale, THC or cannabis can be consistently found to have high MOE values, as well as amphetamine-type stimulants and benzodiazepines. Cocaine and nicotine/tobacco were found to have intermediary MOE values.

For sensitivity analysis, three different methods were applied: convergence testing during the probabilistic simulation, application of a factor to consider drug tolerance, and comparison with human toxicological thresholds for some of the agents.

Convergence was achieved for all calculated output MOE values. This means that the generated output distributions are stable and reliable. The estimated means change less than 5% as additional iterations are run during the simulation. From the model input variables, the highest influence (as expressed by rank of regression coefficients) on the results is caused by the exposure, rather than the toxicological thresholds or the bodyweights.

The sensitivity analysis data for tolerant users are additionally shown in Figure 1–3 based on the ratio between no-tolerance and high tolerance dosage as shown in Table 2[27,37,42–54]. Even though the

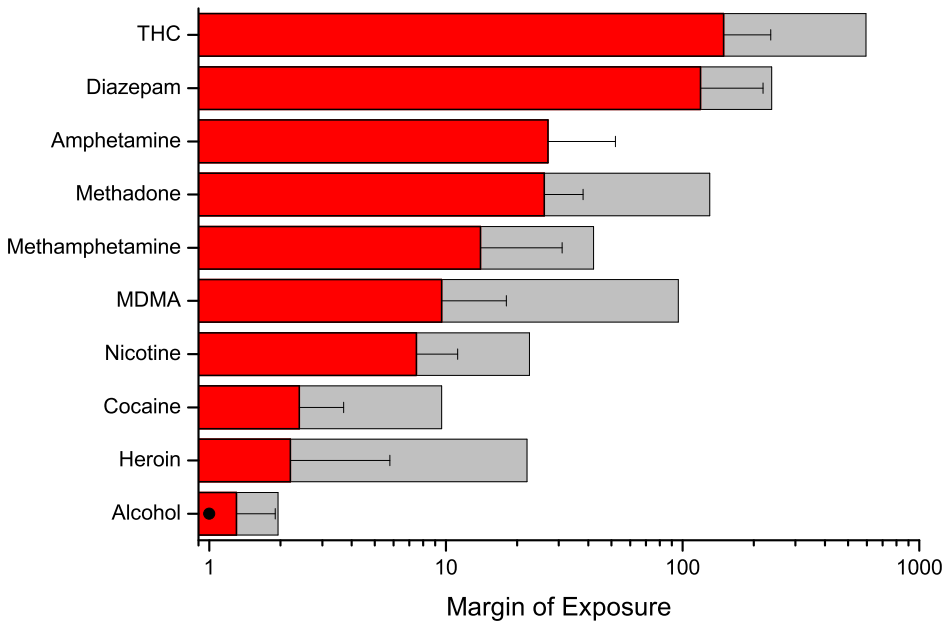


**Figure 1 | Margin of exposure for daily drug use estimated using probabilistic analysis (left red bar: average; error bar: standard deviation; right gray bar: tolerant user; circle symbol (for alcohol): value based on human data).**

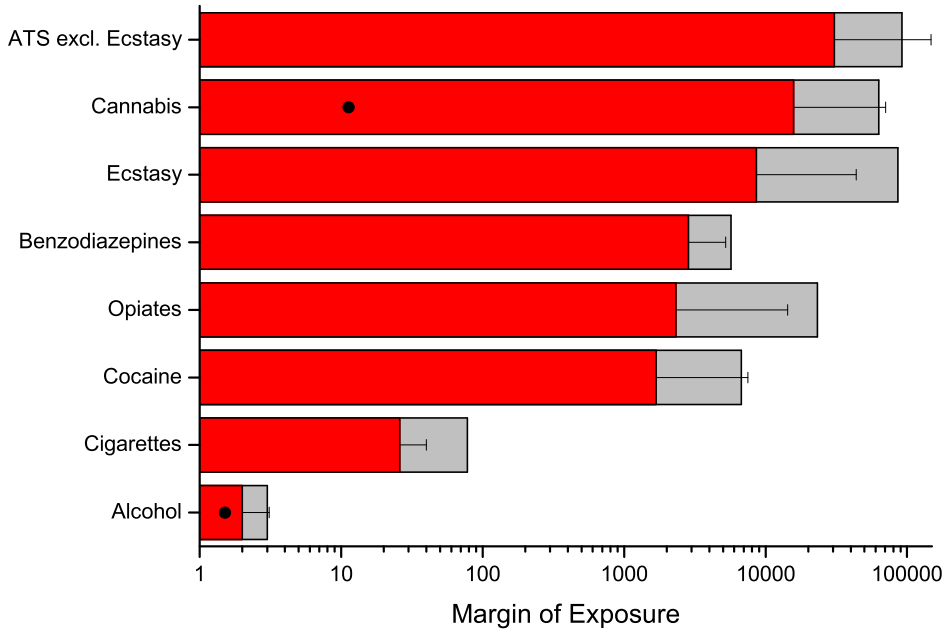


**Figure 2 | Margin of exposure for the whole population based on prevalence data estimated using probabilistic analysis (left red bar: average; error bar: standard deviation; right gray bar: tolerant user; circle symbol (for alcohol and cannabis): value based on human data).**

general results remain stable (i.e. especially alcohol at the top position), the ranks between opiates and cocaine change due to the high tolerance to extreme dosages that was reported for opiates. However, as the percentage of tolerant users is generally unknown, the most probable value of MOE would lie in the range between non-tolerant and tolerant users (the gray-marked area in Figures 1–3).

Finally, the sensitivity analysis results from application of human toxicity data for some of the compounds (alcohol, nicotine and THC[21,55–57]) are shown in Supplementary Table S3 online and marked in Figures 1–3. For alcohol, the human MOE results correspond closely to the ones calculated from animal LD50. For the other compounds, a discrepancy between animal and human data was detected (see discussion).

## Discussion

Many governments in Europe have favoured more restrictive policies with respect to illicit drugs than for alcohol or tobacco, on the grounds that they regard both illicit drug abuse and related problems as a significantly larger problem for society[58]. Drug rankings can therefore be useful to inform policy makers and the public about the relative importance of licit drugs (including prescription drugs) and illicit drugs for various types of harm[58].

Our MOE results confirm previous drug rankings based on other approaches. Specifically, the results confirm that the risk of cannabis may have been overestimated in the past. At least for the endpoint of mortality, the MOE for THC/cannabis in both individual and population-based assessments would be above safety thresholds (e.g. 100

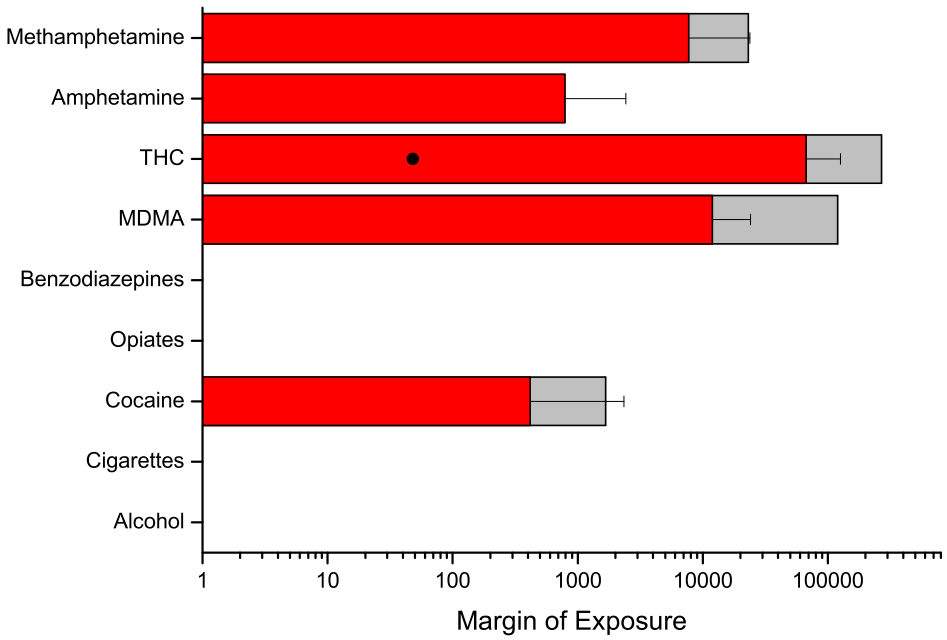


**Figure 3 | Margin of exposure for the whole population based on sewage analysis estimated using probabilistic analysis (left red bar: average; error bar: standard deviation; right gray bar: tolerant user; circle symbol (for THC): value based on human.**

for data based on animal experiments). In contrast, the risk of alcohol may have been commonly underestimated.

Our results confirm the early study of Gable[6] who found that the margin of safety (defined as therapeutic index) varied dramatically between substances. In contrast, our approach is not based on a therapeutic index, which is not necessarily associated with risk, but uses the most recent guidelines for risk assessment of chemical substances, which also takes the population-based exposure into account.

A major finding of our study is the result that the risk of drugs varies extremely, so that a logarithmic scale is needed in data presentation of MOE (e.g. Figures 1–3). Therefore, we think that previous expert-based approaches which often applied a linear scale of 0–3 or 0–100[3,9], might have led to a form of "egalitarianism", in which the public health impact of drugs appears more similar than it is in reality (i.e. more than 10.000-fold different as shown in our results on a population basis, e.g. Fig. 2 and 3). As expected, for an individual the difference between the impact of different drugs is not as large as for the whole society (i.e. only up to 100 fold, Fig. 1).

According to the typical interpretation of MOEs derived from animal experiments, for individual exposure the four substances alcohol, nicotine, cocaine and heroin fall into the "high risk" category with MOE $< 10$, the rest of the compounds except THC fall into the "risk" category with MOE $< 100$. On a population scale, only alcohol would fall into the "high risk" category, and cigarette smoking would fall into the "risk" category. A difference between individual and whole population MOE was confirmed by the lack of correlation between average values (linear fit: $R = 0.25$, $p = 0.53$). This result is different to the previous expert-based surveys, for which the ranking performed at the population and individual level generally led to the same ranking ($R = 0.98$)[3]. Nevertheless, we judge our results as more plausible. For an individual heavy consumer of either heroin or alcohol, the risk of dying from a heroin overdose or from alcoholic cirrhosis increased considerably in each case. However for the society as a whole, the several ten-thousands of alcohol-related deaths considerably outnumber drug overdose deaths. Hence, it is plausible that the MOE for alcohol can be lower than the one for heroin, purely because of the high exposure to alcohol in the European society (see also Rehm et al.[59]).

Nevertheless, as previously stressed, our findings should not be interpreted that moderate alcohol consumption poses a higher risk to an individual and their close contacts than regular heroin use[14]. Much of the harm from drug use is not inherently related to consumption, but is heavily influenced by the environmental conditions of the drug use[2], and this additional hazard is not included in a drug ranking based on (animal) toxicology.

The first major problem of the approach is the lack of toxicological dose-response data for all compounds except alcohol and tobacco. No human dose-response data are available; also no dose-response data in animals, only LD50 values are published. Furthermore, no chronic-toxicity data (long-term experiments) are available, which are usually used for such kinds of risk assessment. Therefore, we can assess only in regards to mortality but not carcinogenicity or other long-term effects. The absence of such data is specifically relevant for compounds with low acute toxicity (such as cannabis), the risk of which may therefore be underestimated.

Additionally, the available toxicological thresholds (i.e. LD50 values) have considerable uncertainty (for example, more than a factor of 10 for diazepam in different species). However it has been previously shown that the animal LD50 is closely related to fatal drug toxicity in humans[60]. The sensitivity analysis based on human data for ethanol shows that the average MOE result is similar to the result based on animal LD50. Our results for ethanol are also consistent with previous MOE studies of ethanol[20,21]. For cannabis and nicotine, the discrepancy in the sensitivity analysis can be explained in the chosen endpoints (no dose response data on mortality in humans were identifiable in the literature). For example, the only available human toxicological endpoint for cannabis as chosen by EFSA[55] was "psychotropic effects". The rationale for choosing this endpoint was the exclusion of risk for the inadvertent and indirect ingestion of THC when hemp products are used as animal feed[55]. We were unable to identify dose-response information for other endpoints of cannabis (e.g. mental health problems, chronic risk, or other cannabis-constituents besides THC). We think that while it is clear that different endpoints may yield quite different results, the human MOE for cannabis based on the endpoint "psychotropic effects" can be seen as general validation of the MOE concept, because the resulting values below 1 are expected as the psychotropic effect is the desired endpoint (and hence the psychotropic threshold dose is exceeded by drug users). Similar to cannabis, the sensitivity analysis for nicotine based on human data resulted in much lower MOE values. This again is based on a different endpoint (increase of blood pressure in this case, which is expected to be more sensitive than mortality). We nevertheless think that the risks of cigarettes could have been underestimated in our modelling, because in contrast to the other agents, tobacco contains a multicomponent mixture of toxicants. Previous risk assessment of tobacco (both financed and co-authored by the tobacco industry) have looked at various compounds but not included nicotine itself[22,23]. From the variety of investigated compounds in tobacco smoke, the lowest MOEs were found for hydrogen cyanide (MOE 15)[22] and acrolein (MOE range 2–11)[23]. These values are reasonably consistent with our MOE for nicotine of 7.5 (individual exposure). However, it would be advisable for future risk assessments of tobacco smoking to include modelling of a combined MOE, which considers all toxic compounds.

The second major problem is the uncertainty in data about individual and population-wide exposure due to the illegal markets. There is a scarcity of epidemiological studies of cannabis use by comparison with epidemiological studies of alcohol and tobacco use[61]. If population data are available, they are usually provided as "% prevalence", but for risk assessment we need a population-wide per-capita dosage in "mg compound/person/day".

Due to both problems (or in other words the large uncertainty in input data of exposure), we cannot calculate with point estimates. To overcome this, we are using a probabilistic calculation methodology that takes the whole distribution of the input variables into account. For example, for the exposure a random sample of the number of days of annual drug use is combined with a random sample in the range of the usual dosages of the drug to provide an estimate for dosage.

The downside of the probabilistic approach is that the output also is not a single numerical value but rather a likelihood distribution. Nevertheless, using graphical approaches (Figs. 1–3) the results for all drugs under study can be quickly compared. On the other hand, this may be an advantage, as we did not try to establish a single value "to be written in stone". The utility of "single figure index harm rankings" has also been questioned in general[62].

Our approach contains some further limitations: Drug interactions cannot be taken into account as we just do not have any toxicological data on such effects (e.g. by co-administration in animals). However, polydrug use in humans is common, especially of illicit drugs with ethanol or benzodiazepines[63]. Addiction potential and risk of use (e.g. unclean syringes leading to increased infection risk) are also not considered by the model, because adequate dose-response data could not be identified for these endpoints.

Aside from the limitations in data, our results should be treated carefully particularly in regard to dissemination to lay people. For example, tabloids have reported that "alcohol is worse than hard drugs" following the publication of previous drug rankings. Such statements taken out of context may be misinterpreted, especially considering the differences of risks between individual and the whole population.

A main finding of our study is the qualitative validation of previous expert-based approaches on drug-ranking (e.g. Nutt et al.[9]),

especially in regard to the positions of alcohol (highest) and cannabis (lowest). Currently, the MOE results must be treated as preliminary due to the high uncertainty in data. The analyses may be refined when better dose-response data and exposure estimates become available. As the problem is multidimensional[15], it would also make sense to establish some form of harm or risk matrix[64] that may be more suitable than a single indicator. Our MOE could be one piece in the puzzle that constitutes to the establishment of a "holistic drug risk".

Currently, the MOE results point to risk management prioritization towards alcohol and tobacco rather than illicit drugs. The high MOE values of cannabis, which are in a low-risk range, suggest a strict legal regulatory approach rather than the current prohibition approach.

## Methods

The methodology for comparative quantitative risk assessment was based on a previous study conducted for compounds in alcoholic beverages[20] with the exception that probabilistic exposure estimation was conducted[65–67]. The MOE approach was used for risk assessment[18,19]. The MOE is defined as the ratio between the lower one-sided confidence limit of the BMD (BMDL) and estimated human intake of the same compound. If the BMD as preferred toxicological threshold for MOE assessment is unavailable, no observed effect levels (NOEL), no observed adverse effect levels (NOAEL) or lowest observed adverse effect levels (LOAEL) may be applied. As none of these thresholds (neither human data nor animal data) was available for the illicit drugs, LD50 values from animal experiments were selected instead and extrapolated to BMDL. The exposure was calculated for individual scenarios of daily drug use, as well as for population based scenarios using drug prevalence data and sewage analysis data for Europe, which is a promising complementary approach for estimating the drug use in the general population.

The MOE was calculated using the software package @Risk for Excel Version 5.5.0 (Palisade Corporation, Ithaca, NY, USA). Monte Carlo simulations were performed with 100,000 iterations using Latin Hypercube sampling and Mersenne Twister random number generator. Convergence was tested with a tolerance of 5% and a confidence level of 95%. The distribution functions and detailed calculation methodology is specified in Supplementary Tables S1–S2 online.


1. Coomber, R. Assessing the real dangers of illicit drugs - Risk analysis as the way forward? *Addict. Res.* **7**, 85–90 (1999).
2. Fischer, B., Kendall, P., Rehm, J. & Room, R. Charting WHO-goals for licit and illicit drugs for the year 2000: are we 'on track'? *Public Health* **111**, 271–275 (1997).
3. van Amsterdam, J., Opperhuizen, A., Koeter, M. & van den Brink, W. Ranking the harm of alcohol, tobacco and illicit drugs for the individual and the population. *Eur. Addict. Res.* **16**, 202–207 (2010).
4. UNODC. Towards the Creation of an Illicit Drug Index. *World drug report 2005. Volume 1: Analysis* [165–174] (United Nations Office on Drugs and Crime, Vienna, Austria, 2005).
5. King, L. A. & Corkery, J. M. An index of fatal toxicity for drugs of misuse. *Hum. Psychopharmacol.* **25**, 162–166 (2010).
6. Gable, R. S. Toward a comparative overview of dependence potential and acute toxicity of psychoactive substances used nonmedically. *Am. J. Drug Alcohol Abuse* **19**, 263–281 (1993).
7. Gable, R. S. Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction* **99**, 686–696 (2004).
8. Nutt, D., King, L. A., Saulsbury, W. & Blakemore, C. Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet* **369**, 1047–1053 (2007).
9. Nutt, D. J., King, L. A. & Phillips, L. D. Drug harms in the UK: a multicriteria decision analysis. *Lancet* **376**, 1558–1565 (2010).
10. Morgan, C. J., Noronha, L. A., Muetzelfeldt, M., Fielding, A. & Curran, H. V. Harms and benefits associated with psychoactive drugs: findings of an international survey of active drug users. *J. Psychopharmacol.* **27**, 497–506 (2013).
11. Morgan, C. J., Muetzelfeldt, L., Muetzelfeldt, M., Nutt, D. J. & Curran, H. V. Harms associated with psychoactive substances: findings of the UK National Drug Survey. *J. Psychopharmacol.* **24**, 147–153 (2010).
12. Carhart-Harris, R. L. & Nutt, D. J. User perceptions of the benefits and harms of hallucinogenic drug use: A web-based questionnaire study. *J. Substance Use* **15**, 283–300 (2010).
13. Kalant, H. Drug classification: science, politics, both or neither? *Addiction* **105**, 1146–1149 (2010).
14. Claridge, L. C. Drugs and harm to society. *Lancet* **377**, 552 (2011).
15. Caulkins, J. P., Reuter, P. & Coulson, C. Basing drug scheduling decisions on scientific ranking of harmfulness: false promise from false premises. *Addiction* **106**, 1886–1890 (2011).
16. IPCS. *IPCS Risk Assessment Terminology* (World Health Organization, Geneva, 2004).
17. Crump, K. S. A new method for determining allowable daily intakes. *Fundam. Appl. Toxicol.* **4**, 854–871 (1984).
18. U.S.EPA. *The use of the benchmark dose approach in health risk assessment. EPA/630/R-94/007* (Office of Research and Development. US Environmental Protection Agency, Washington, DC, 1995).
19. EFSA. Opinion of the Scientific Committee on a request from EFSA related to a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic. *EFSA J.* **282**, 1–31 (2005).
20. Lachenmeier, D. W., Przybylski, M. C. & Rehm, J. Comparative risk assessment of carcinogens in alcoholic beverages using the margin of exposure approach. *Int. J. Cancer* **131**, E995–E1003 (2012).
21. Lachenmeier, D. W., Kanteres, F. & Rehm, J. Epidemiology-based risk assessment using the benchmark dose/margin of exposure approach: the example of ethanol and liver cirrhosis. *Int. J. Epidemiol.* **40**, 210–218 (2011).
22. Xie, J. *et al.* A probabilistic risk assessment approach used to prioritize chemical constituents in mainstream smoke of cigarettes sold in China. *Regul. Toxicol. Pharmacol.* **62**, 355–362 (2012).
23. Cunningham, F. H., Fiebelkorn, S., Johnson, M. & Meredith, C. A novel application of the Margin of Exposure approach: Segregation of tobacco smoke toxicants. *Food Chem. Toxicol.* **49**, 2921–2933 (2011).
24. Shulgin, A. T. The background and chemistry of MDMA. *J. Psychoactive Drugs* **18**, 291–304 (1986).
25. Gold, L. S., Gaylor, D. W. & Slone, T. H. Comparison of cancer risk estimates based on a variety of risk assessment methodologies. *Regul. Toxicol. Pharmacol.* **37**, 45–53 (2003).
26. Thomas, K. V. *et al.* Comparing illicit drug use in 19 European cities through sewage analysis. *Sci. Total Environ.* **432**, 432–439 (2012).
27. Erowid. *Notes on heroin dosage and tolerance* (http://www.erowid.org/chemicals/heroin/heroin_dose1.shtml, (2001), Date of access: 2014/04/13).
28. UNODC. *World Drug Report 2013* (United Nations Office on Drugs and Crime, Vienna, Austria, 2013).
29. Musshoff, F., Lachenmeier, D. W. & Madea, B. Cocain Und Cocainmetaboliten. *Haaranalytik-Technik und Interpretation in Medizin und Recht* [Madea, B. & Musshoff, F. (eds.)] [163–178] (Deutscher Ärzte-Verlag, Cologne, Germany, 2004).
30. Musshoff, F., Lachenmeier, D. W. & Madea, B. Cannabinoide. *Haaranalytik-Technik und Interpretation in Medizin und Recht* [Madea, B. & Musshoff, F. (eds.)] [179–188] (Deutscher Ärzte-Verlag, Cologne, Germany, 2004).
31. Hunault, C. C. *et al.* Delta-9-tetrahydrocannabinol (THC) serum concentrations and pharmacological effects in males after smoking a combination of tobacco and cannabis containing up to 69 mg THC. *Psychopharmacol. (Berl.)* **201**, 171–181 (2008).
32. Land, T. *et al.* Recent increases in efficiency in cigarette nicotine delivery: Implications for tobacco control. *Nicotine Tob. Res.* **16**, 753–758 (2014).
33. OECD. *OECD.Stat Extracts. Non-Medical Determinants of Health. MetaData. Tobacco consumption.* http://stats.oecd.org/index.aspx?queryid=30127, (2014), Date of access: 2014/04/13.
34. WHO. *Global Health Observatory Data Repository. Tobacco control. Monitor: Prevalence - adult age-standardized. Data by country* (World Health Organization, Geneva, Switzerland. http://apps.who.int/gho/data/node.main.1250?lang=en, (2014), Date of access: 2014-04-24).
35. Leavitt, S. B. Methadone dosing & safety in the treatment of opioid addiction. *Addiction Treatment Forum* **12**, 1–8 (2003).
36. Musshoff, F., Lachenmeier, D. W. & Madea, B. Amphetamine. *Haaranalytik-Technik und Interpretation in Medizin und Recht* [Madea, B. & Musshoff, F. (eds.)] [189–205] (Deutscher Ärzte-Verlag, Cologne, Germany, 2004).
37. Erowid. *Methamphetamine dosage* (http://www.erowid.org/chemicals/meth/meth_dose.shtml, (2003), Date of access: 2014/04/23).
38. NHTSA. *Drugs and human performance fact sheets. Methylenedioxymethamphetamine (MDMA, Ecstasy)* (http://www.nhtsa.gov/people/injury/research/job185drugs/methylenedioxymethamphetamine.htm, (2014), Date of access: 2014/04/23).
39. NHTSA. *Drugs and human performance fact sheets. Diazepam* (http://www.nhtsa.gov/people/injury/research/job185drugs/diazepam.htm, (2014), Date of access: 2014/04/23).
40. EMCDDA. *Benzodiazepines. European Monitoring Centre for Drugs and Drug Addiction* (http://www.emcdda.europa.eu/publications/drug-profiles/benzodiazepine, (2013), Date of access: 2014/04/24).
41. WHO. *Global status report on alcohol and health - 2014 ed.* (World Health Organization, Geneva, Switzerland, 2014).
42. EMCDDA. *Cocaine and crack. European Monitoring Centre for Drugs and Drug Addiction* (http://www.emcdda.europa.eu/publications/drug-profiles/cocaine, (2013), Date of access: 2014/06/12).
43. Jones, R. T., Benowitz, N. L. & Herning, R. I. Clinical relevance of cannabis tolerance and dependence. *J. Clin. Pharmacol.* **21**, 143S–152S (1981).
44. Haney, M., Ward, A. S., Comer, S. D., Foltin, R. W. & Fischman, M. W. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology (Berl.)* **141**, 385–394 (1999).
45. Mayer, B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. *Arch. Toxicol.* **88**, 5–7 (2014).

46. Stolerman, I. P., Bunker, P. & Jarvik, M. E. Nicotine tolerance in rats; role of dose and dose interval. *Psychopharmacologia (Berl.)* **34**, 317–324 (1974).
47. Minion, G. E., Slovis, C. M. & Boutiette, L. Severe alcohol intoxication: a study of 204 consecutive patients. *J. Toxicol. Clin. Toxicol.* **27**, 375–384 (1989).
48. Vonghia, L. *et al.* Acute alcohol intoxication. *Eur. J. Intern. Med.* **19**, 561–567 (2008).
49. Farrell, M. *et al.* Methadone maintenance treatment in opiate dependence: a review. *BMJ* **309**, 997–1001 (1994).
50. Modesto-Lowe, V., Brooks, D. & Petry, N. Methadone deaths: risk factors in pain and addicted populations. *J. Gen. Intern. Med.* **25**, 305–309 (2010).
51. Musshoff, F., Lachenmeier, K., Lachenmeier, D. W., Wollersen, H. & Madea, B. Dose-concentration relationships of methadone and EDDP in hair of patients on a methadone-maintenance program. *Forensic Sci. Med. Pathol.* **1**, 97–103 (2005).
52. Parrott, A. C. Chronic tolerance to recreational MDMA (3,4-methylenedioxymethamphetamine) or Ecstasy. *J. Psychopharmacol.* **19**, 71–83 (2005).
53. Schifano, F. A bitter pill. Overview of ecstasy (MDMA, MDA) related fatalities. *Psychopharmacology (Berl.)* **173**, 242–248 (2004).
54. Cook, P. J., Flanagan, R. & James, I. M. Diazepam tolerance: effect of age, regular sedation, and alcohol. *Br. Med. J. (Clin. Res. Ed.)* **289**, 351–353 (1984).
55. EFSA. Scientific opinion on the safety of hemp (Cannabis genus) for use as animal feed. *EFSA J.* **9**, 2011 (2011).
56. EFSA. Potential risks for public health due to the presence of nicotine in wild mushrooms. *EFSA J.* **RN-286**, 1–47 (2009).
57. Lindgren, M., Molander, L., Verbaan, C., Lunell, E. & Rosen, I. Electroencephalographic effects of intravenous nicotine–a dose-response study. *Psychopharmacol. (Berl.)* **145**, 342–350 (1999).
58. Rossow, I. Can harm ratings be useful? *Addiction* **106**, 1893–1894 (2011).
59. Rehm, J., Lachenmeier, D. W. & Room, R. Why does society accept a higher risk for alcohol than for other voluntary or involuntary risks? *BMC Med.* **12**, 189 (2014).
60. King, L. A. & Moffat, A. C. A possible index of fatal drug toxicity in humans. *Med. Sci. Law.* **23**, 193–198 (1983).
61. Hall, W., Room, R. & Bondy, S. Comparing the Health and Psychological Risks of Alcohol, Cannabis, Nicotine and Opiate Use. *The Health Effects of Cannabis* [Kalant, H., Corrigal, W., Hall, W. & Smart, R. (eds.)] [477-506] (Addiction Research Foundation, Toronto, , Canada, 1999).
62. Rolles, S. & Measham, F. Questioning the method and utility of ranking drug harms in drug policy. *Int. J. Drug Policy* **22**, 243–246 (2011).
63. Musshoff, F., Lachenmeier, D. W. & Madea, B. Methadone substitution: medicolegal problems in Germany. *Forensic Sci. Int.* **133**, 118–124 (2003).
64. Fischer, B. & Kendall, P. Nutt *et al.*'s harm scales for drugs–room for improvement but better policy based on science with limitations than no science at all. *Addiction* **106**, 1891–1892 (2011).
65. Lachenmeier, D. W. & Rehm, J. Unrecorded Alcohol - No Worries Besides Ethanol: a Population-Based Probabilistic Risk Assessment. *Alcohol policy in Europe: Evidence from AMPHORA. 2nd ed.* [Anderson, P., Braddick, F., Reynolds, J. & Gual, A. (eds.)] [118–130] (Alcohol Measures for Public Health Research Alliance (AMPHORA), Barcelona, Spain, 2013).
66. Lachenmeier, D. W., Godelmann, R., Witt, B., Riedel, K. & Rehm, J. Can resveratrol in wine protect against the carcinogenicity of ethanol? A probabilistic dose-response assessment. *Int. J. Cancer* **134**, 144–153 (2014).
67. Lachenmeier, D. W. *et al.* Caffeine intake from beverages in German children, adolescents, and adults. *J. Caffeine Res.* **3**, 47–53 (2013).


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## Author contributions

D.W.L. conceived of the study, conceptualized the data analyses and performed the calculations. J.R. collected the data from WHO and provided additional data for sensitivity analysis. All authors have been involved in the drafting of the article and the interpretation of the data and in critical revisions of the content. All authors have given final approval of the version to be published.

## Additional information

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