Addiction and Lifestyles in Contemporary Europe: Reframing Addictions Project (ALICE RAP)

Classification of addictions: Addendum Analyses of margins of exposure

Deliverable 4.1-Addendum, Work Package 4

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Abstract

Risk assessment of illicit drugs has often been based on historical attribution, emotive reasoning or educated guesses. This research aims for a comparative risk assessment of drugs including alcohol and tobacco based on a toxicological methodology.

The margin of exposure (MOE) approach was used as methodology. The MOE is defined as ratio between toxicological threshold (benchmark dose) and estimated human intake. Median lethal dose (LD50) values from animal experiments were used to derive the benchmark dose. The human intake was calculated for individual scenarios of daily drug use and population-based scenarios (drug prevalence and sewage analysis data). The MOE was calculated using probabilistic Monte Carlo simulations taking into account the full variability of the input data because of their high uncertainty.

Results show that 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.

In conclusion, the toxicological MOE approach validates science-based drug ranking approaches especially in regard to the positions of alcohol and tobacco (high risk) and cannabis (low risk).

1. Introduction

1.1 Prior approaches for risk assessment of illicit drugs

Compared to medicinal products or other consumer products, risk assessment of drugs of abuse has been deficient, much 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, there have 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 only upon scientific facts [13]. The methodology was 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 underrepresented 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].

1.2 Aims of ALICE-RAP WP4 on “Analyses of Margins of Exposure”

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 state-of-the-art 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 preferred method for risk assessment of carcinogenic and genotoxic compounds [19]. In the addiction field, the MOE method was never used, with the exception of 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.

2. 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 [24-26]. 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. 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 Tables 2.1 and 2.2.

Table 2.1. Distribution functions as input for probabilistic analysis

Agent	**Risk function [a] for BMDL10 [b] [mg/kg bw]**	**Risk function for individual daily dosage [c] [mg/day; g/day for alcohol]**	**Risk function for prevalence in %) [d] (per capita consumption for alcohol in L)**	**Risk function for population-based exposure based on sewage analysis [mg/day/1000 population]**
Heroin	RiskNormal(22;0.4);RiskTruncate(21.8;22.5)/10.2	RiskUniform(5;300)	RiskUniform(0.5;0.6)	(no data available)
Cocaine	RiskNormal(17;2);RiskTruncate(13;20)/10.2	RiskUniform(20;100)	RiskUniform(0.8;0.9)	RiskUniform(2;1998)
THC	RiskNormal(574;92);RiskTruncate(482;666)/10.2	RiskUniform(10;60)	RiskUniform(5.4;5.7)	RiskUniform(14;192)
Nicotine	RiskNormal(20;18);RiskTruncate(9.2;50)/10.2	RiskUniform(1.65;1.89)*RiskUniform(10;20)	RiskLoLogistic(30.4642;3.8963;RiskTruncate(13;52)	(no data available)
Alcohol (ethanol)	RiskNormal(5593;1346);RiskTruncate(3450;7060)/10.2	RiskUniform(13.6;54.4)	RiskLoLogistic(10.2833;2.1567;RiskTruncate(2;17.5)	(no data available)
Methadone	RiskNormal(78;8);RiskTruncate(70;86)/10.2	RiskUniform(10;40)	(no data available)	(no data available)
Amphetamine	RiskNormal(62;52);RiskTruncate(21;135)/10.2	RiskUniform(5;50)	ATS excl. ecstasy: RiskUniform(0.5;0.6)	RiskUniform(33;3040)
Methamphetamine	82/10.2	RiskUniform(5;150)	(see amphetamine)	RiskUniform(3;376)
MDMA	325/10.2	RiskUniform(50;700)	Ecstasy: RiskUniform(0.6;0.7)	RiskUniform(32;615)
Diazepam	RiskNormal(281;162);RiskTruncate(48;500)/10.2	RiskUniform(5;40)	42 doses/1000 population/day (no distribution available)	(no data available)

[a] RiskNormal(mean;standard deviation) specifies a normal distribution with the entered mean and standard deviation. RiskTruncate(minimum;maximum) truncates the input distribution. Truncating distribution restricts samples drawn from the distribution to values within the entered minimum-maximum range.
[b] An estimate of BMDL10 is obtained from LD50 by division by 10.2 using method B of Gold et al. [28]
[c] RiskUniform(minimum;maximum) specifies a uniform probability distribution with the entered minimum and maximum values. Every value across the range has an equal likelihood of occurrence (“no knowledge” distribution).
[d] RiskLogistic(alpha;beta) specifies a logistic distribution with the entered alpha and beta values

Table 2.2. Detailed calculation methodology for probabilistic comparative risk assessment of alcohol, tobacco and illicit drugs

Parameter	**Calculation formula for the software package @Risk for Excel Version 5.5.0 (Palisade, Corporation, Ithaca, NY, USA)** [a]
MOE for individual drug user	= Risk function for BMDL10 / (Risk function for individual daily dosage / Risk function for body weight)
Population-based exposure based on prevalence data for all drugs except nicotine and alcohol	= Risk function for days of drug use per year * Risk function for individual daily dosage * Risk function for prevalence / 100 / 365
Population-based exposure based on prevalence data for nicotine	= Risk function for individual daily dosage * Risk function for prevalence / 100
Population-based exposure based on per capita consumption data for alcohol	= Risk function for per capita consumption * 0.789 * 1000 / 365
MOE for population (based on prevalence data)	= Risk function for BMDL10 / (Population-based exposure / Risk function for body weight)

[a] Further input distributions: Risk function for bodyweight (kg) = RiskNormal(73.9;12). Risk function for days of drug use per year = RiskUniform(1;365).

3. Results

3.1 Toxicological thresholds

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 [27] are shown in table 3.1. Using the method of Gold et al. [28], the LD50 values were extrapolated assuming linear behaviour (as no other information on dose-response is available) to BMDL10 values. As shown in table 3.1, 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.

Table 3.1. 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) 22.5 (rat)	2	-
Cocaine (RN: 50-36-2)	Intravenous	13 (dog) 16 (mouse) 17 (rabbit) 20 (rabbit) 17.5 (rat)	2	-
Tetrahydrocannabinol (THC) (RN: 1972-08-3)	Oral	482 (rat) 666 (rat)	56	LOEL = 0.04 mg/kg bw (psychotropic effects) [58]
Nicotine (RN: 54-11-5)	Oral	17.8 (bird) 9.2 (dog) 3.34 (mouse) 50 (rat)	3	LOAEL = 0.008 mg/kg bw/day (heart rate acceleration) [59,60]
Alcohol (ethanol) (RN: 64-17-5)	Oral	5560 (guinea pig) 3450 (mouse) 6300 (rabbit) 7060 (rat)	531	BMDL1.5 = 0.4 g/kg bw (liver cirrhosis mortality) [21]
Methadone (RN: 76-99-3)	Oral	70 (mouse) 86 (rat)	8	-
Amphetamine (RN: 300-62-9)	Oral	135 (unspecified) 21 (mouse) 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) 48 (mouse) 328 (rabbit) 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 [27]
[b] An estimate of BMDL10 is obtained from LD50 by division by 10.2 using method B of Gold et al. [28]. See Table 2.1 for distribution functions used for calculation.

3.2 Drug intake and exposure

To determine the typical range of individual daily dosage, various textbook and internet sources [21,29-44] were evaluated (Table 3.2). 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 (Table 2.1).

The data used for calculation of population-based exposure is shown in table 3.2. 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 3.2). The corresponding risk functions are shown in table 2.1. Except for ethanol 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 above in table 2.2.

Table 3.2. Exposure data selected for calculating the margin of exposure (see Table 2.1 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) [29] [mg/day/1000 population]
Heroin	5-300 [30]	10 [30]	Opiates: 0.5-0.6 [31]	(no data available)
Cocaine	20-100 [32]	4 [45]	0.8-0.9 [31]	2-1998
THC	10-60 [33,34]	4 [46,47]	Cannabis: 5.4-5.7 [31]	14-192
Nicotine	1.65-1.89 mg/cigarette [35] 10-20 cigarettes/smoker/day [36]	3 [48,49]	13-52 [37]	(no data available)
Alcohol	13.6 g-54.4 g (1-4 standard drinks [21])	1.5 [50,51]	2.0-17.5 L/year [44]	(no data available)
Methadone	10-40 [38]	5 [52-54]	(no data available)	(no data available)
Amphetamine	5-50 [39]	No data available	ATS excl. ecstasy: 0.5-0.6 [31]	33-3040
Methamphetamine	5-150 [40]	3 [40]	(see amphetamine)	3-376
MDMA	50-700 [41]	10 [55,56]	Ecstasy: 0.6-0.7 [31]	32-615
Diazepam	5-40 [42]	2 [57]	42 daily doses per 1000 population per day (benzodiazepines) [43]	(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.

3.3 Margin of Exposure and sensitivity analysis

The margin of exposure values were calculated for individual exposure (Figure 3.1), population-based exposure calculated from prevalence data (Figure 3.2) and population-based exposure calculated from sewage analysis (Figure 3.3). The full numerical results of the MOE distributions are presented in table 3.3. 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. 5th percentile), heroin may have a lower MOE than alcohol (compare standard deviation bars in Figure 3.1). 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 3.1-3.3 based on the ratio between no-tolerance and high tolerance dosage as shown in Table 3.2 [30,40,45-57]. While the general results remain stable (i.e. especially alcohol at the top position), the ranks between opiates and cocaine change because of 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 grey-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 [21,58-60]) are shown in table 3.3 and marked in Figures 3.1-3.3. 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).

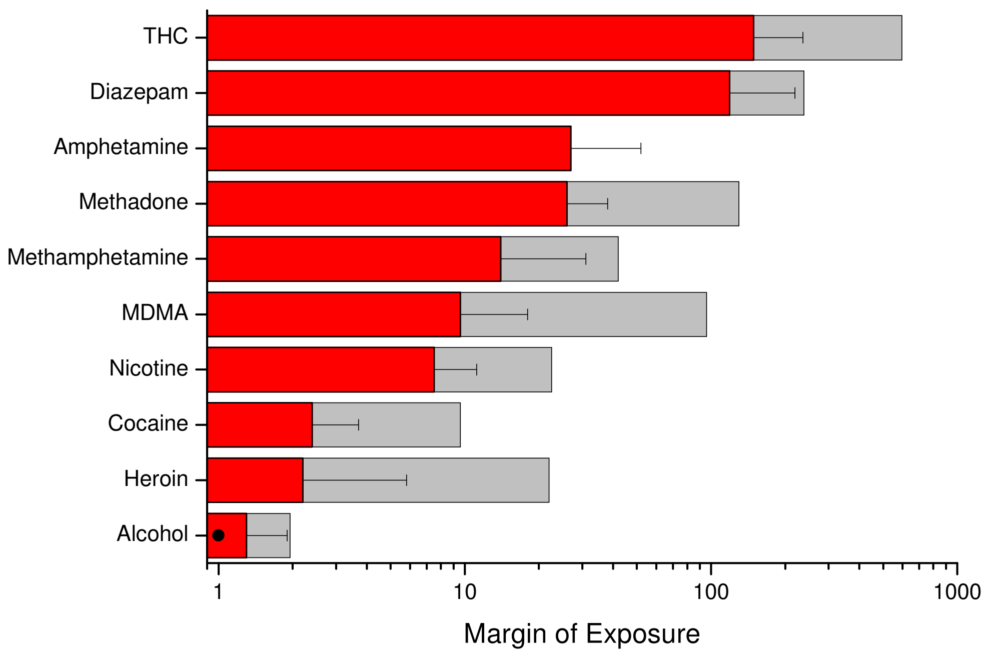

Figure 3.1. Margin of exposure for daily drug use estimated using probabilistic analysis (left red bar: average; error bar: standard deviation; right grey bar: tolerant user; circle symbol (for alcohol): value based on human data)

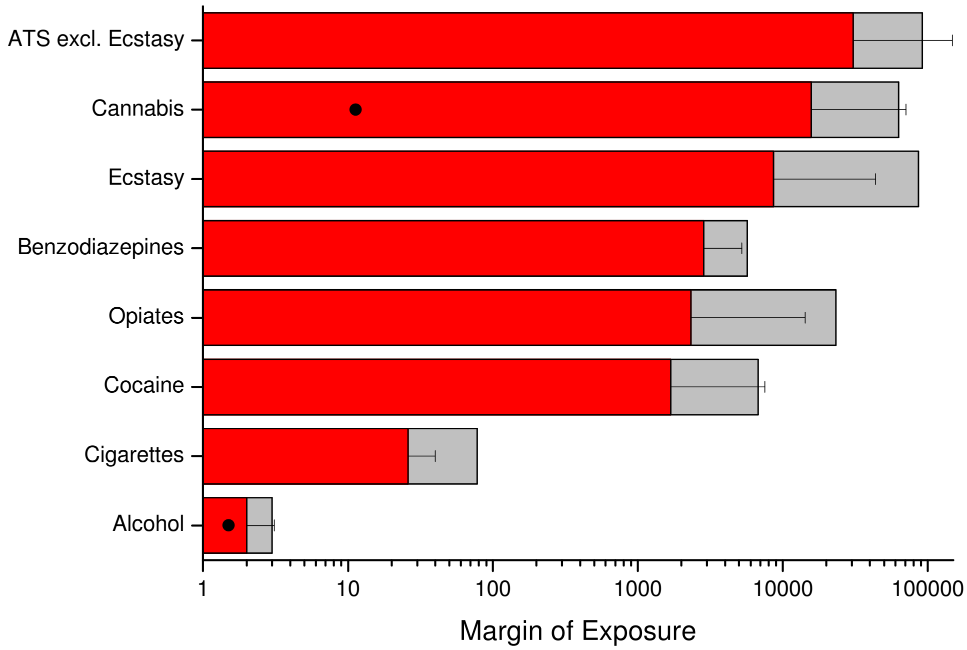

Figure 3.2. Margin of exposure for the whole population based on prevalence data estimated using probabilistic analysis (left red bar: average; error bar: standard deviation; right grey bar: tolerant user; circle symbol (for alcohol and cannabis): value based on human data)

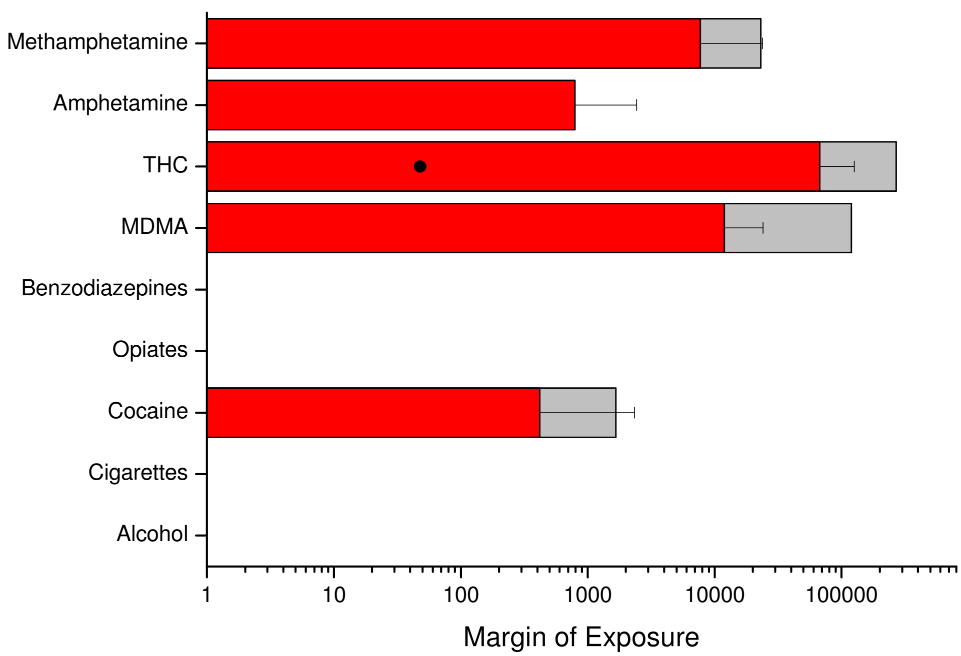

Figure 3.3. Margin of exposure for the whole population based on sewage analysis estimated using probabilistic analysis (left red bar: average; error bar: standard deviation; right grey bar: tolerant user; circle symbol (for THC): value based on human data)

Table 3.3 Raw results of probabilistic estimation of margin of exposure (MOE) using 100,000 iterations

[a] MOEs marked „individual“ refer to individual daily drug use. MOEs marked „population“ refer to data based on drug prevalence data. MOEs marked „sewage“ are based on exposure analysis from sewage analysis

Name [a]	Minimum	Maximum	Mean	Std Deviation	5% Perc	25% Perc	50% Perc	75% Perc	90% Perc	95% Perc
MOE Heroin (Individual)	0.2	43	2.2	3.6	0.5	0.7	1.1	2.0	4.7	8.2
MOE Cocaine (Individual)	0.5	10	2.4	1.3	1.1	1.5	2.0	3.0	4.3	5.1
MOE THC (Individual)	28	697	149	87	64	87	119	185	278	336
MOE Nicotine (Individual)	1.1	27	7.5	3.7	2.7	4.6	6.8	9.6	12	14
MOE Alcohol (Individual)	0.2	5.0	1.3	0.6	0.6	0.9	1.2	1.7	2.3	2.7
MOE Methadone (Individual)	5.6	87	26	12	13	17	23	32	44	50
MOE Amphetamine (Individual)	1.8	242	27	25	6	12	19	32	57	78
MOE Methamphetamine (Individual)	1.7	166	14	17	3.8	5.2	7.7	14	30	48
MOE MDMA (Individual)	1.1	68	9.6	8.4	3.2	4.4	6.3	11	21	29
MOE Diazepam (Individual)	5.3	914	119	100	25	56	89	147	246	327
MOE Opiates (Population)	41	1090117	2325	11992	133	250	505	1327	3873	7661
MOE Cocaine (Population)	77	219044	1688	5827	181	315	552	1123	2794	5442
MOE Cannabis (Population)	615	2431803	15738	54976	1623	2861	5100	10674	26116	50406
MOE Cigarette smoking (Population)	2.8	177	26	14	9	15	23	33	44	53
MOE Alcohol (Population)	0.3	14.3	2.0	1.1	1.0	1.4	1.8	2.4	3.2	4.1
MOE ATS excl. Ecstasy (Population)	853	5454089	30619	117268	2544	4768	9119	20647	50880	99383
MOE Ecstasy (Populaton)	293	1977266	8622	35067	696	1270	2458	5765	14365	28183
MOE Benzodiazepines (Population)	127	21752	2843	2374	594	1322	2111	3508	5861	7779
MOE Cocaine (Sewage)	22	86482	417	1917	56	80	120	240	596	1175
MOE THC (Sewage)	7821	478345	66986	58933	22094	30747	44183	78083	142864	199263
MOE Amphetamine (Sewage)	22	34565	790	1639	98	203	341	671	1580	2868
MOE Methamphetamine (Sewage)	692	264870	7700	16136	1518	2096	3134	6177	14783	27625
MOE MDMA (Sewage)	1446	101362	11934	12105	3669	5004	7278	13263	26109	38385
Sensitivity analysis (based on human data: psychotropic effects for THC; liver cirrhosis for alcohol; heart rate acceleration for nicotine)										
MOE THC (Individual)	0.02	0.4	0.1	0.1	0.05	0.06	0.08	0.13	0.20	0.24
MOE Nicotine (Individual)	0.01	0.1	0.02	0.01	0.01	0.02	0.02	0.03	0.03	0.03
MOE Alcohol (Individual)	0.2	3.6	1.0	0.5	0.5	0.7	0.9	1.2	1.7	1.9
MOE Cannabis (Population)	0.4	1655	11.3	39.8	1.2	2.0	3.7	7.6	19	36
MOE Cigarette smoking (Population)	0.01	0.3	0.08	0.03	0.04	0.06	0.07	0.09	0.12	0.13
MOE Alcohol (Population)	0.3	9.3	1.5	0.8	0.8	1.1	1.3	1.7	2.4	3.0
MOE THC (Sewage)	5.8	334	48	42	16	22	32	55	102	141

4. Discussion

4.1 The usefulness of the MOE approach for drug ranking

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 [61]. 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 [61].

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 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 3.1-3.3). 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 to die from a heroin overdose or from alcoholic cirrhosis is considerably increased 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.

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.

4.2 Limitations of the MOE approach for drug ranking

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. 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 [62]. 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 [58] 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 [58]. We think that while it is clear that these different endpoints may yield quite different results, the human MOE for cannabis based on this endpoint 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 [46]. 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 do 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 [63].

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 [64]. Addiction potential and risk of use (e.g. unclean syringes) are also not considered by the model.

Not only due to the limitations in data, our results should be treated carefully especially 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 out of context may be misinterpreted, especially considering the differences of risks between individual and the whole population.

5. Conclusions and recommendations for policy/future research

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 [65] that may be better suitable than a single indicator. Nevertheless, 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.

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