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Methanol in unrecorded fruit spirits. Does it pose a health risk to consumers in the European Union? A probabilistic toxicological approach

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HIGHLIGHTS

- Data on the concentration of methanol in unrecorded fruit spirits were collected.
- Methanol intakes from unrecorded fruit spirits were estimated.
- Blood methanol levels arising from drinking unrecorded fruit spirits were estimated.
- Daily methanol intake from unrecorded fruit spirits can exceed the reference dose.
- Actions should be taken to reduce exposure to methanol from unrecorded fruit spirits.

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ABSTRACT

Methanol is present at high concentrations in unrecorded fruit spirits, placing consumers of these beverages at risk of exposure at high levels. When assessing any health risk it is necessary to consider blood methanol levels (BMLs), reference dose (RfD), and maximum tolerable blood methanol level (MTBML). The aim of our study was to estimate daily methanol intake and related BMLs attributable to drinking unrecorded fruit spirits in the European population using a probabilistic Monte Carlo simulation. Data on the concentration of methanol in unrecorded fruit spirits in European Union member states were collected and the health risk posed by consumption of unrecorded fruit spirits was estimated. We found that drinking unrecorded fruit spirits containing methanol at a concentration higher than 8598.1 mg/litre of pure alcohol (p.a.) or 6382.1 mg/litre of p.a. and also at least 10 g ethanol can result in a methanol intake above the RfD by men and women, respectively. We confirmed that consumption of unrecorded fruit spirits containing methanol does not result in BMLs higher than the MTBML. Further studies are required to assess whether there is any health risk from chronic exposure to methanol above the RfD from unrecorded fruit spirits.

1. Introduction

Methanol is a commonly occurring toxic contaminant of alcoholic beverages (Blumenthal et al., 2021; Ohimain, 2016; World Health Organisation, 2014). Because of its similarity to ethanol and lower price, methanol has long been used to fortify informally and illicitly produced alcoholic drinks (Blumenthal et al., 2021; Everstine et al., 2013; Ohimain, 2016; World Health Organisation, 2014). These adulterated beverages are sold illegally and there are many accounts of methanol poisoning worldwide,

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with examples in numerous African (Gambia, Kenya, Libya, Nigeria, Sudan, Uganda), American (Costa Rica, Ecuador, Mexico, Nicaragua), Asian (Cambodia, India, Indonesia, Iran, Malaysia, Pakistan, Turkey), and European (Czech Republic, Estonia, Norway, Romania) countries (AbdulRahim and Shiekh, 2012; Adil et al., 2019; Doreen et al., 2020; Hassanian-Moghaddam et al., 2015; Hovda et al., 2005; Lachenmeier et al., 2021; Levy et al., 2003; Ohimain, 2016; Paasma et al., 2007; Pressman et al., 2020; Rostrup et al., 2016; World Health Organisation, 2014, 2020; Zakharov et al., 2014; for more details on these acute methanol poisonings see Supplementary Table 1). Many reports relate to mass poisonings, with numbers affected ranging from 20 to 800, but it can be assumed that these are only a small fraction of all cases (World Health Organisation, 2014; Okaru et al., 2011). These reports suggest that about 30 % of those who ingest alcoholic drinks adulterated with methanol die (World Health Organisation, 2014).

While the risks of drinking methanol in adulterated beverages are widely recognised, it is rather less well known that methanol is also present naturally in traditional alcoholic beverages produced in different parts of the world (Ohimain, 2016). These are made from fermentation of products grown locally, such as sap of raffia and oil palms, sorghum, millet, maize, rice and banana in Africa and Asia, sugarcane and agave in Central and South America (Ohimain, 2016), and grains and fruits, including wheat, barley, apple, apricot, cherry, grape, mirabelle, peach, pear, and plum in Europe (Blumenthal et al., 2021). Methanol is derived from pectin in the raw materials (Ohimain, 2016). Enzymatic degradation of pectins takes place during the fermentation process by pectinases such as pectin methylesterase produced by bacteria, fungi, and yeast (Ohimahin, 2016). In addition, pectinases may be added exogenously to the mash to increase the ethanol yield, which can also lead to increased methanol formation (McKee et al., 2012; Pang et al., 2017). As a consequence, levels of methanol can vary considerably in alcoholic beverages depending on the raw material used, the means of fermentation and distillation, and the type of alcoholic drink (Millán et al., 1990; Ohimain, 2016). For illustration, it has been detected at concentrations of 6–27 mg/litre of pure alcohol (p.a.) in beer and 96–321 mg/litre of p.a. in wine (Fishbein,

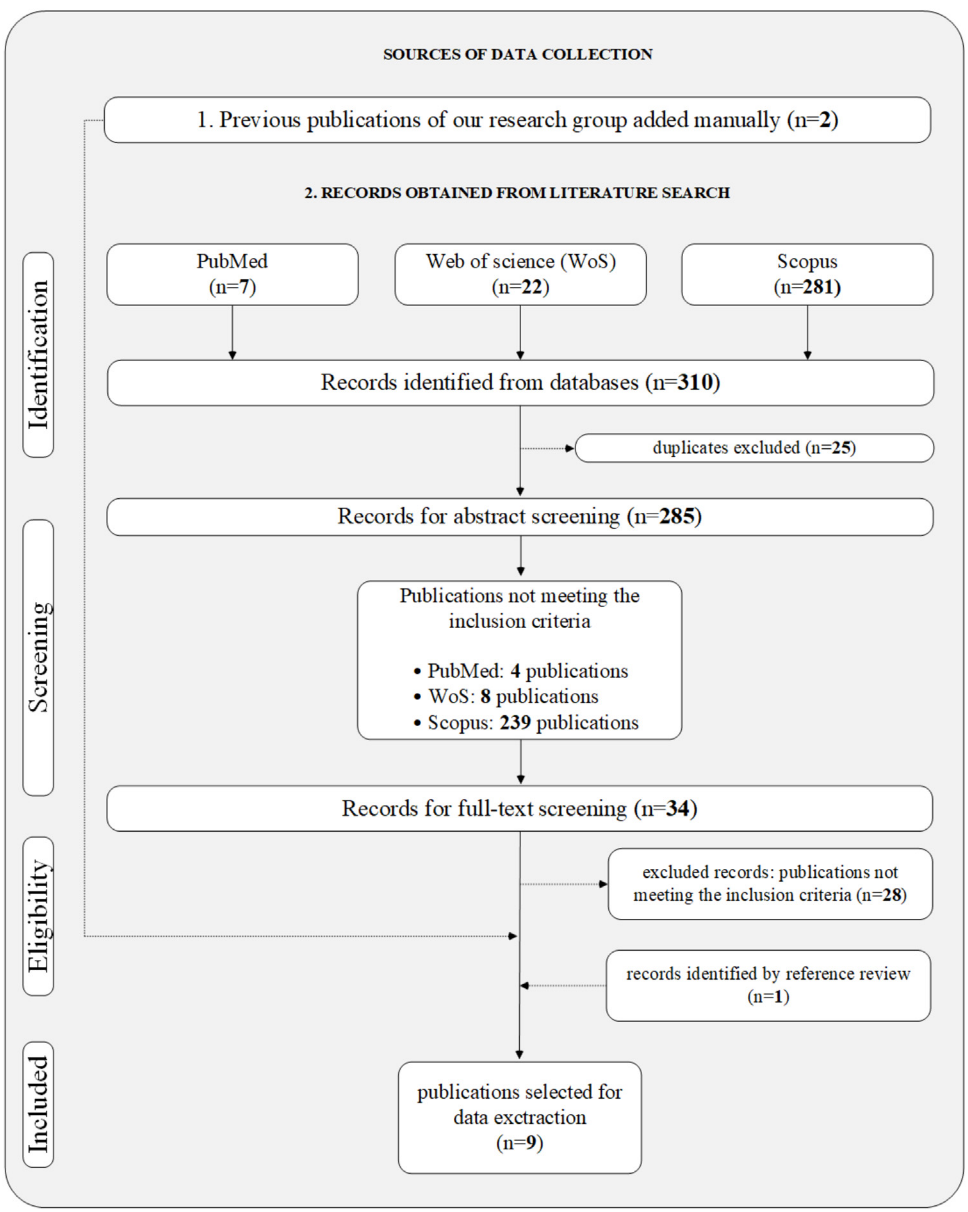

Fig. 1. Flowchart of computer-assisted literature search.

1997). In legally manufactured and marketed (henceforth "recorded") vodka, rum, whiskey, and brandy methanol has been found at levels in the ranges of 0–64 mg/litre of p.a., 0–73 mg/litre of p.a., 21–67 mg/litre of p.a., and 128–388 mg/litre of p.a., respectively (Lachenmeier and Musshoff, 2004). However, the highest methanol concentrations are typically found in recorded and unrecorded spirits prepared from fruits (Blumenthal et al., 2021). The latter deserve particular attention as, by definition, unrecorded fruit spirits are not captured by official production and sale statistics and so escape the gaze of fiscal authorities (McKee et al., 2012; World Health Organisation, 2018). The concentration of methanol can be significantly higher [median: 6347.3 mg/litre of p.a., interquartile range (IQR): 4095.9–8514.5 mg/litre of p.a.] than those of measured in their recorded counterparts [median: 1086.6 mg/litre of p.a., IQR: 204.3–4697.3 mg/litre of p.a.]. (The median and IQR values were calculated from the results of our previous measurements, Bujdosó et al., 2019).

Because of its toxicity, maximum levels (MLs) of methanol in spirits have been set in many countries of the world including Australia, Canada, China, New Zealand, and the United States of America (Pang et al., 2017). In the European Union (EU) these depend on the raw material used for production and are set at between 50.0 and 15 000.0 mg/litre of p.a., for London gin and fruit marc spirits, respectively (European Commission, 2008). The maximum level permitted in fruit spirits is 10 000.0 mg/litre of p.a. (European Commission, 2008). The same limit has been proposed for methanol in unrecorded fruit spirits by the Alcohol Measures for Public Health Research Alliance (AMPHORA) project (Lachenmeier et al., 2011a). Generally, the concentrations of methanol in recorded fruit spirits do not exceed MLs because they are manufactured under controlled conditions and their methanol content is monitored by the spirit producers and official food control laboratories in the EU (Botelho et al., 2020; Teipel et al., 2020). In contrast, unrecorded fruit spirits are usually produced using rudimentary or sub-standard distillation equipment in conditions lacking any meaningful quality control, so that their methanol levels can be above recommended limits placing consumers at a potential risk (Ohimain, 2016; Lachenmeier et al., 2011a; Pál et al., 2020; Tatarková et al., 2019; McKee et al., 2012). However, in determining any risk to health it is necessary to look beyond the concentration of methanol to consider the amount of methanol ingested, the consequent blood methanol levels (BMLs), the reference dose (RfD), also known as acceptable daily intake (ADI), and the maximum tolerable blood methanol level (MTBML). The MTBML has been assessed at 5.0 mg/decilitre and blood methanol concentrations above that may increase the risk of acute methanol toxicity (Paine and Dayan, 2001). The United States Environmental Protection Agency (United States Environmental Protection Agency, 2013) has defined a RfD of 2.0 mg/kg body weight/day for chronic oral exposure to methanol below which the health risk attributable to chronic exposure is minimized (United States Environmental Protection Agency, 2013).

Consumers of unrecorded fruit spirits, especially episodic heavy drinkers, can be exposed to potentially hazardous levels of methanol, and their methanol intake and related BMLs can be higher than 2.0 mg/kg body weight kg/day and 5.0 mg/decilitre, respectively. However, we are unaware of any studies that estimated the daily intake of methanol and BMLs associated with drinking unrecorded fruit spirits at a population level. To fill this gap we estimate the daily intake of methanol and BMLs attributable to drinking unrecorded fruit spirits in the European population using a probabilistic Monte Carlo simulation, looking separately at men and women with different consumption levels. For this assessment, we collected published data on the concentration of methanol in unrecorded fruit spirits from EU member states. Finally, we estimated the health risk posed by consumption of unrecorded fruit spirits by comparing the daily methanol intakes and related BMLs to their threshold values.

2. Data and methods

2.1. Sources of data on the concentration of methanol in unrecorded fruit spirits

Data on the concentration of methanol in unrecorded fruit spirits were obtained from two sources, our previous research (Szűcs et al., 2005; Bujdosó et al., 2019) and literature searches were conducted using the PubMed (US National Library of Medicine, Bethesda, MD, USA), Web of Science (Thompson Reuters, Philadelphia, PA, USA) and Scopus (Elsevier B.V., Amsterdam, the Netherlands) databases. For the latter we used the following keywords: unrecorded, fruit, distillate, spirits, illegal, illicit, methanol, traditional, home-made. The specific search strings are reported in Supplement 1. Articles retrieved from the databases were reviewed by two researchers independently. The inclusion criteria were as follows: articles published after 2000 that contain

Table 1
Studies selected for data extraction. Data on the concentration of methanol in unrecorded fruit spirits were obtained from the studies meeting the following inclusion criteria: articles published after 2000 that contain individual data on the concentration of methanol in at least 10 samples of unrecorded fruit spirit collected in the EU and written in English or German. (see details in Section 2.1).

studies selected	name of fruit spirit	raw materials	place of sample collection	number of samples analysed
Hanousek-Čiča et al., 2019	wine-derived spirit	*grape*	Croatia	13
Huckenbeck et al., 2003	schnapps	*apple, apricot, cherry, peach, pear, plum, quinces*	Germany	50
Soufleros et al., 2004	mouro	*mulberry tree fruit*	Greece	10
Soufleros et al., 2005	koumaro	*strawberry tree fruit*	Greece	19
Huckenbeck et al., 2003	pálinka	*apple, apricot, cherry, peach, pear, plum*	Hungary	25
Szűcs et al., 2005	pálinka	*apple, apricot, grape, pear, plum*	Hungary	34
Lachenmeier et al., 2009	pálinka	*apricot, cherry, plum*	Hungary	11
Bujdosó et al., 2019	pálinka	*apple, apricot, grape, pear, plum, sour cherry*	Hungary	87
Levy et al., 2003	ţuică	*apple, apricots, cherry, orange, pears, plum*	Romania	26
Rusu Coldea et al., 2011	brandy	*apple, pear, plum*	Romania	25

individual data on the concentration of methanol in at least 10 samples of unrecorded fruit spirit collected in the EU and written in English or German. The reference list of each included article was also hand searched for further relevant papers. The flow chart of the literature search and the list of the studies meeting the inclusion criteria are reported in Fig. 1 and Table 1, respectively.

2.2. Compliance of methanol concentrations with the threshold value

The AMPHORA project has designated 10 000.0 mg/litre of p.a. as the ML for methanol in unrecorded fruit spirits (Lachenmeier et al., 2011a) and concentrations reported in the selected studies were compared with this value. The number of samples containing methanol above the AMPHORA threshold value of 10 g methanol/litre was determined and their proportion within the total number of samples was calculated. The individual methanol concentrations are shown in Supplementary Table 2.

2.3. Estimation of methanol intake and associated blood methanol levels at different consumption levels

To estimate daily methanol intake and BMLs associated with the consumption of unrecorded fruit spirits at population level, we carried out probabilistic Monte Carlo simulations with @Risk for Excel software, version 8.1 (Palisade Corporation, Ithaca, NY, USA) using 10 000 iterations, Latin Hypercube sampling, and a Mersenne Twister random number generator (Bujdosó et al., 2019). Daily methanol intakes were calculated by taking into account the volume of 40 V/V % unrecorded fruit spirit consumed and its methanol and ethanol content. First, the probability density functions were determined separately for the concentrations of methanol reported in the studies retrieved from the literature search. The best fit distributions were selected using the Akaike information criterion test with a lower limit fixed at zero. To compare the estimated daily methanol intakes (EDMIs) with the RfD (2.0 mg/kg body weight/day), chronic exposure to methanol was defined by assuming the consumption of unrecorded fruit spirits containing methanol at levels reported in the studies selected and also 10 g, 20 g, 40 g, 60 g, and 80 g of ethanol/day over a lifetime (United States Environmental Protection Agency, 2013). The corresponding volumes of unrecorded fruit spirits containing 40 % ethanol are shown in Table 2. RfD is an estimate of a daily oral exposure to an agent that is assumed to confer no appreciable risk of adverse health effects over a human lifetime (Faustman and Omenn, 1975). The distributions of EDMIs (mg/day) were determined by considering the probability density functions of methanol at different consumption levels. Then, the distributions of EDMIs were calculated based on a body weight of 82.0 ± 13.1 kg for men and 67.2 ± 12.8 kg for women, supposing a normal distribution. For each consumption level, the distributions of EDMIs were calculated as follows:

$$\mathrm{EDMI} = \frac{\mathrm{Cmx}\ \mathit{DCUFS}}{\mathrm{DBW}}$$

where C_m is the probability density functions of methanol concentrations extracted from the studies retrieved from the literature search (mg/mL), DCUFS is the daily consumption of 40 V/V % unrecorded fruit spirits containing 10 g, 20 g, 40 g, 60 g, and 80 g of ethanol (ml/day; see the corresponding volumes of unrecorded fruit spirits containing 40 % ethanol in Table 2), DBW is the distribution of body weight (kg). EDMIs were expressed in mg/kg body weight/day. The corresponding distributions of estimated daily ethanol intakes (EDEIs) were calculated in the same way as follows:

$$\mathrm{EDEI} = \frac{\mathrm{Ce\ x}\ \mathit{DCUFS}}{\mathrm{DBW}}$$

where C_e is the concentration of ethanol in 40 V/V % unrecorded fruit spirits (mg/mL), DCUFS is the daily consumption of 40 V/V % unrecorded fruit spirits containing 10 g, 20 g, 40 g, 60 g, and 80 g of ethanol (ml/day; see the volumes of unrecorded fruit spirits containing 40 % ethanol in Table 2), DBW is the distribution of body weight (kg). EDEIs were expressed in mg/kg body weight/day.

Methanol concentrations in unrecorded fruit spirits required to reach the RfD at different consumption levels were calculated in the following sequence. First, to obtain the amount of methanol that need to be consumed to reach the RfD, the distribution of body weight of the consumers was multiplied by the RfD of methanol. Second, to calculate the methanol concentration in unrecorded fruit spirits expressed in mg/litre, the distribution of methanol amount obtained was multiplied by the ratio of 1000 mL/x ml where x is the volume of 40 V/V% unrecorded fruit spirit containing 10 g, 20 g, 40 g, 60 g, and 80 g of ethanol. Third, the methanol concentrations obtained were converted to mg/litre of p.a. using a conversion factor of 2.5. The results are presented in Table 4.

Acute exposure to methanol was defined assuming a single consumption of unrecorded fruit spirits containing methanol at levels published in the studies selected and also 10 g, 20 g, 40 g, 60 g, and 80 g of ethanol. The corresponding volumes of unrecorded fruit spirits containing 40 % ethanol are shown in Table 2. The distributions of estimated intakes of methanol (grams) were also determined by considering the probability density functions of methanol at different consumption levels. The distributions of BMLs were calculated using Widmark's equation as follows:

$$C_{bm} = \frac{A_m}{r_m \ \times W}$$

where, A_m is the distribution of the amount of methanol consumed (gram), C_{bm} is the distribution of blood methanol concentration (gram/litre), W is the body weight (kg), distributed as described above, r_m is Widmark's factor replaced with volume of distribution of methanol (0.6–0.7 litre/kg for men and women supposing an

Table 2
Volume of 40 V/V% unrecorded fruit spirit that needs to be consumed to ingest 10 g, 20 g, 40 g, 60 g, and 80 g of pure ethanol. The table shows the mass and volume of pure ethanol as well as the volume of 40 V/V % unrecorded fruit spirits that needs to be consumed to ingest 10 g, 20 g, 40 g, 60 g, and 80 g of pure ethanol. The volumes of pure ethanol (expressed in ml) were calculated by dividing the mass of ethanol (10 g, 20 g, 40 g, 60 g, 80 g) with its density of 0.789 g/mL. The volumes of 40 V/V % unrecorded fruit spirits (expressed in ml) were calculated by multiplying the volume of pure ethanol with a conversion factor of 2.5 (100/40). The volumes of 40 V/V % unrecorded fruit spirits that needs to be consumed to ingest 10 g, 20 g, 40 g, 60 g, and 80 g of pure ethanol were taken into account for the estimation of daily methanol intake and related blood methanol levels.

pure ethanol consumption [g]	pure ethanol consumption [ml]	volume of unrecorded fruit spirit containing 40 V/V% ethanol [ml]
10	12.7	31.7
20	25.4	63.4
40	50.7	126.7
60	76.1	190.1
80	101.4	253.5

Table 3
Number and characteristics of unrecorded fruit spirit samples analysed in the studies from which data were extracted. Publications meeting the following inclusion criteria were selected: articles published after 2000 that contain individual data on the concentration of methanol in at least 10 samples of unrecorded fruit spirit collected in the EU and written in English or German (see details in Section 2.1). Articles meeting these criteria were retrieved from the PubMed, Web of Science, and Scopus databases. Individual data on the concentrations of methanol in unrecorded fruit spirits were collected and their medians as well as related interquartile ranges were calculated. Then the number of samples containing methanol above the AMPHORA threshold value of 10 g methanol/litre was determined and their proportion within the total number of samples was calculated.

reference	number of samples analysed	median concentration of methanol and IQR* [mg/litre of pure alcohol]		proportion of samples containing methanol above the AMPHORA threshold value [%]
Bujdosó et al., 2019	87	6347.3	4166.3−8435.2	11
Hanousek-Čiča et al., 2019	13	539.0	426−1046	0
Huckenbeck et al., 2003	50**	4674.6	2343.9-6348.3	2
	25***	6408.0	3087.1-8178.3	12
Lachenmeier et al., 2009	12	3075.0	475−4950	0
Levy et al., 2003	25	2000.0	1000−4000	4
Rusu Coldea et al., 2011	26	9542.2	8634.5−10766.1	35
Soufleros et al., 2004	10	1323.0	1102.7−1848.6	0
Soufleros et al., 2005	19	8436.0	7682−9504.5	11
Szűcs et al., 2005	34	4994.4	1267.7−6740.1	9

* Interquartile Range.
** Place of sample collection: Germany.
*** Place of sample collection: Hungary.

Table 4
Methanol concentrations in unrecorded fruit spirits required to reach the reference dose (RfD) at different consumption levels. Methanol concentrations in unrecorded fruit spirits required to reach the RfD at different consumption levels were calculated in the following sequence. First, to obtain the amount of methanol that need to be consumed to reach the RfD, the distribution the body weight of the consumers was multiplied by the RfD of methanol. Second, to calculate the methanol concentration in unrecorded fruit spirits expressed in mg/litre, the distribution of methanol amount obtained was multiplied by the ratio of 1000 mL/x ml where x is the volume of 40 V/V% unrecorded fruit spirit containing 10 g, 20 g, 40 g, 60 g, and 80 g of ethanol. Third, the methanol concentrations obtained were converted to mg/litre of pure alcohol using a conversion factor of 2.5.

percentiles	body weight distribution of men	methanol concentration* in unrecorded fruit spirits required to reach the reference dose of 2.0 mg/kg body weight/day at different ethanol consumption levels					body weight distribution of women	methanol concentration* in unrecorded fruit spirits required to reach the reference dose of 2.0 mg/kg body weight/day at different ethanol consumption levels				
		10 g ethanol (31.7 mL+)	20 g ethanol (63.4 mL+)	40 g ethanol (126.7 mL+)	60 g ethanol (190.1 mL+)	80 g ethanol (253.5 mL+)		10 g ethanol (31.7 mL+)	20 g ethanol (63.4 mL+)	40 g ethanol (126.7 mL+)	60 g ethanol (190.1 mL+)	80 g ethanol (253.5 mL+)
1%	55.0 kg	8 598.10	4 367.29	2 166.45	1 448.10	1 087.51	40.8 kg	6 382.12	3 241.71	1 608.09	1 074.88	807.22
25%	73.4 kg	11 463.66	5 822.81	2 888.48	1 930.72	1 449.95	58.8 kg	9 182.05	4 663.90	2 313.59	1 546.45	1 161.37
50%	82.0 kg	12 812.16	6 507.76	3 228.26	2 157.84	1 620.51	67.2 kg	10 499.67	5 333.16	2 645.59	1 768.37	1 328.02
75%	90.6 kg	14 160.57	7 192.67	3 568.02	2 384.94	1 791.06	75.6 kg	11 817.19	6 002.38	2 977.56	1 990.26	1 494.66
99%	108.9 kg	17 022.89	8 646.55	4 289.23	2 867.01	2 153.09	93.6 kg	14 613.97	7 422.97	3 682.26	2 461.30	1 848.41

* in mg/litre of pure alcohol; + The values in brackets show the volume of unrecorded fruit spirit containing 40.0 V/V % ethanol.

uniform distribution) [European Food Safety Authority (EFSA), 2012; Fishbein, 1997; Posey and Mozayani, 2007]. For each consumption level, BMLs were converted to mg/decilitre. The corresponding distributions of blood ethanol levels (BELs) were also determined via Widmark's equation as follows:

$$C_{be} = \frac{A_e}{r_e \times W}$$

where A_e is the amount of ethanol consumed (10 g, 20 g, 40 g, 60 g, and 80 g on a single occasion), C_{be} is the distribution of BELs (gram/litre), W is the body weight (kg), distributed as described above, r_e is Widmark's factor (0.68 ± 0.085 L/kg for men and 0.55 ± 0.050 L/kg for women supposing a uniform distribution) [European Food Safety Authority (EFSA), 2012; Flanagan et al., 2020; Posey and Mozayani, 2007]. For each consumption level, BELs were also converted to mg/decilitre. Methanol concentrations in unrecorded fruit spirits (C_m) required to reach the MTBML at different consumption levels were calculated as follows:

$$C_m = MTBML \times r \times W \times R \times CF$$

where MTBML is the maximum tolerable blood methanol level (0.05 g/litre), r is Widmark's factor and W is the body weight (kg), 82.0 ± 13.1 kg for men and 67.2 ± 12.8 kg for women, supposing a normal distribution, R is the ratio of 1000 mL/x ml where x is the volume of 40 V/V% unrecorded fruit spirit containing 10 g, 20 g, 40 g, 60 g, and 80 g of ethanol, and the CF is the conversion factor of 2.5 to p.a. The methanol concentrations were obtained in g/litre and converted to mg/litre of p.a. The results are reported in Table 5 .

2.4. Statistical analysis

The distributions of data on the concentration of methanol in unrecorded fruit spirits were tested for normality using the Shapiro-Wilk test. The distributions of BMLs and EDMIs associated

Table 5
Methanol concentrations in unrecorded fruit spirits required to reach the maximum tolerable blood methanol level at different consumption levels. Methanol concentrations in unrecorded fruit spirits (Cm) required to reach the maximum tolerable blood methanol level (MTBML) at different consumption levels were calculated as follows: $Cm = MTBML \times r \times W \times R \times CF$ where MTBML is the maximum tolerable blood methanol level (0.05 g/litre), r is Widmark's factor and W is the distribution of body weight of the consumers (kg), R is the ratio of 1000 mL/x ml where x is the volume of 40 V/V% unrecorded fruit spirit containing 10 g, 20 g, 40 g, 60 g, and 80 g of ethanol, and the CF is the conversion factor of 2.5 to pure alcohol (p.a). The methanol concentrations were obtained in g/litre and converted to mg/litre of p.a. Calculations are also described in Section 2.3.

		methanol concentration* in unrecorded fruit spirits required to reach the maximum tolerable blood methanol level of 5.0 mg/dl at different ethanol consumption levels						methanol concentration* in unrecorded fruit spirits required to reach the maximum tolerable blood methanol level of 5.0 mg/dl at different ethanol consumption levels				
percentiles	body weight distribution of men	10 g ethanol (31.7 mL^{+})	20 g ethanol (63.4 mL^{+})	40 g ethanol (126.7 mL^{+})	60 g ethanol (190.1 mL^{+})	80 g ethanol (253.5 mL^{+})	body weight distribution of women	10 g ethanol (31.7 mL^{+})	20 g ethanol (63.4 mL^{+})	40 g ethanol (126.7 mL^{+})	60 g ethanol (190.1 mL^{+})	80 g ethanol (253.5 mL^{+})
1%	55.0 kg	–	69 904.4	34 952.2	23 301.5	17 476.1	40.8 kg	–	52 152.5	26 076.3	17 384.2	13 038.1
25%	73.4 kg	–	–	46 758.6	31 172.4	23379.3	58.8 kg	–	74 987.2	37 493.6	24 995.7	18 047.9
50%	82.0 kg	–	–	52 412.7	34 941.8	26 206.3	67.2 kg	–	–	42 958.3	28 638.9	21 479.1
75%	90.6 kg	–	–	58 240.1	38 826.7	29 120.0	75.6 kg	–	–	48 619.2	32 412.8	24 309.6
99%	108.9 kg	–	–	71 4740	47 649.3	35 737.0	93.6 kg	–	–	61 002.9	40 668.6	30 501.5

* Only methanol concentrations possible at the given consumption levels are shown in mg/litre of pure alcohol. + The values in brackets show the volume of unrecorded fruit spirit containing 40.0 V/V % ethanol.

with consumption of unrecorded fruit spirits were compared with the distribution of BMLs and EDMIs, respectively, when drinking a hypothetical fruit spirit (HFS) containing methanol at the maximum level of 10 000.0 mg/litre of p.a. as defined by the AMPHORA project. Significance was assessed using the Kruskal-Wallis test with Dunn-Bonferroni post hoc test. Statistical analyses were carried out using IBM SPSS statistics 25.0 software (IBM Inc, Armonk, New York, USA). Values of $p < 0.05$ were considered statistically significant. Median EDMIs, EDEIs, BMLs, and BELs, their interquartile ranges, and 1st and 99th percentiles are shown in Figs. 1–6.

3. Results

Table 3 presents the characteristics of unrecorded fruit spirit samples analysed in the included studies. As shown, the median methanol concentrations in unrecorded fruit spirits varied between 539.0 mg/litre and 9542.2 mg/litre. Furthermore, 2%, 4%, 9%, 11 %, 11 %, 12 %, and 35 % of the schnapps (Huckenbeck et al., 2003), ţuică (Levy et al., 2003), pálinka (Szűcs et al., 2005), pálinka (Bujdosó et al., 2019), koumaro (Soufleros et al., 2005), pálinka (Huckenbeck et al., 2003), and brandy (Rusu Coldea et al., 2011) samples contained methanol above the AMPHORA threshold value of 10 g/litre, respectively.

The distributions of the population-based EDMIs are reported in Fig. 2 using the methanol concentration detected in wine-derived spirits (panels A1-A2), schnapps (panels B1-B2), mouro (panels C1-C2), and koumaro (panels D1-D2) separately for men and women. As shown, the distribution of EDMIs exceeded the RfD when consuming koumaro (panel D1), schnapps (panel B1), mouro (panel C1), and wine-derived spirits (panel A1) containing methanol and also at least 10 g, 20 g, 60 g, and 80 g ethanol for men, respectively. For women, the distribution of EDMIs were above the RfD when drinking schnapps (panel B2), koumaro (panel D2), mouro (panel C2), and wine-derived spirit (panel A2) containing methanol and also no less than 10 g, 10 g, 40 g, and 60 g of ethanol, respectively. Fig. 3 presents the distributions of EDMIs using the methanol concentrations in pálinka samples (panels E1-H2) separately for men and women. As depicted, the distribution of EDMIs exceeded the RfD when consuming pálinka containing methanol and also at least 10 g (panels E1, F1, and H1), and 20 g ethanol (panel G1) for men. For women, the distribution of EDMIs were above the RfD when drinking the same type of unrecorded fruit spirit containing methanol and also no less than 10 g (panels E2, F2, and H2), and 20 g of ethanol (panel G2). Fig. 4 reports the distributions of EDMIs using the methanol concentration detected in ţuică (panels I1-I2), brandy (panels J1-J2), and a HFS containing methanol at the maximum concentration defined by the AMPHORA project (panels K1-K2) separately for men and women. The figure shows that the distribution of EDMIs exceeded the RfD when consuming ţuică, brandy, and HFS containing methanol and also at least 10 g ethanol (panels I1, J1, and K1 for men and panels I2, J2, and K2 for women).

The distributions of EDMI values associated with consumption of unrecorded fruit spirits included in our study differed significantly from those associated with drinking HFS at each consumption level both for men and women ($p < 0.001$). Table 4 reports the methanol concentrations in unrecorded fruit spirits required to reach the reference dose at different consumption levels. As presented, drinking unrecorded fruit spirits containing methanol at a minimum concentration of 8598.1 mg/litre or 6382.1 mg/litre of p.a. and also at least 10 g ethanol (corresponding to 31.5 mL of unrecorded fruit spirits containing 40 % ethanol) can result in a methanol intake equal to the RfD by men and women, respectively.

The distributions of the population-based BMLs are presented in Figs. 5,6 and 7 using the methanol concentration detected in wine-derived spirit (Fig. 5, panels A1-A2), schnapps (Fig. 5, panels B1-B2), mouro (Fig. 5, panels C1-C2), koumaro (Fig. 5, panels D1-D2), pálinka samples (Fig. 6, panels E1-H2), ţuică (Fig. 7, panels I1-I2), brandy (Fig. 7, panels J1-J2), and a HFS (Fig. 7, panels K1-K2) separately for men and women. As shown, the distribution of BMLs exceeded the MTBML when consuming ţuică (Fig. 7, panels J1-J2) containing methanol and also at least 80 g and 60 g ethanol for men and women, respectively. The distributions of BMLs associated with consumption of unrecorded fruit spirits included in our study

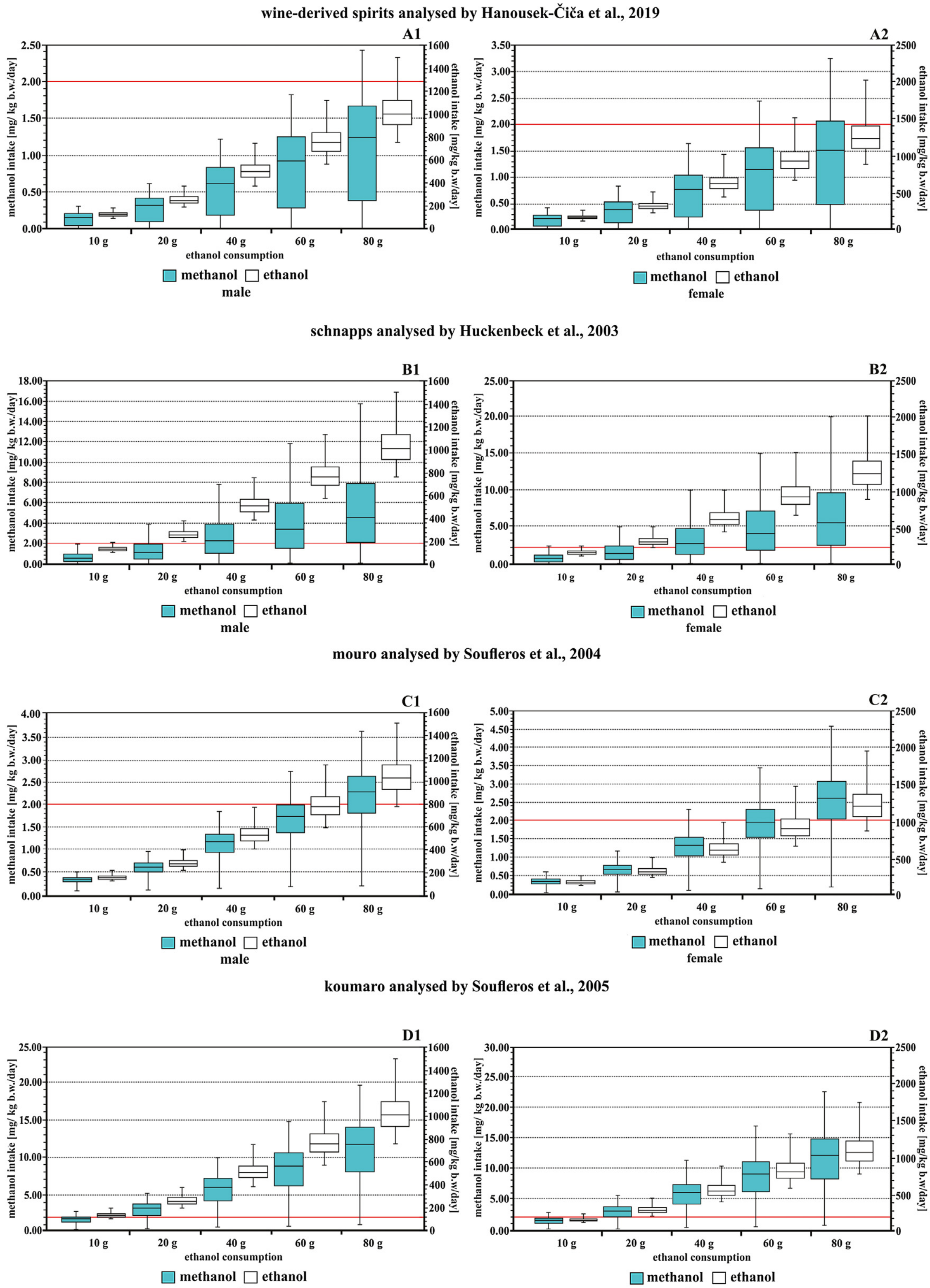

Fig. 2. Estimated daily methanol and ethanol intakes by males and females when drinking unrecorded fruit spirits containing methanol. The left and right y axes show the distribution of methanol and ethanol intakes (mg/kg body weight/day), respectively. Panels: A1-A2 wine-derived spirits, B1-B2 schnapps, C1-C2 mouro, D1-D2 koumaro. Median values, their interquartile ranges, 1st and 99th percentiles are presented. The red line indicates the reference dose of methanol.

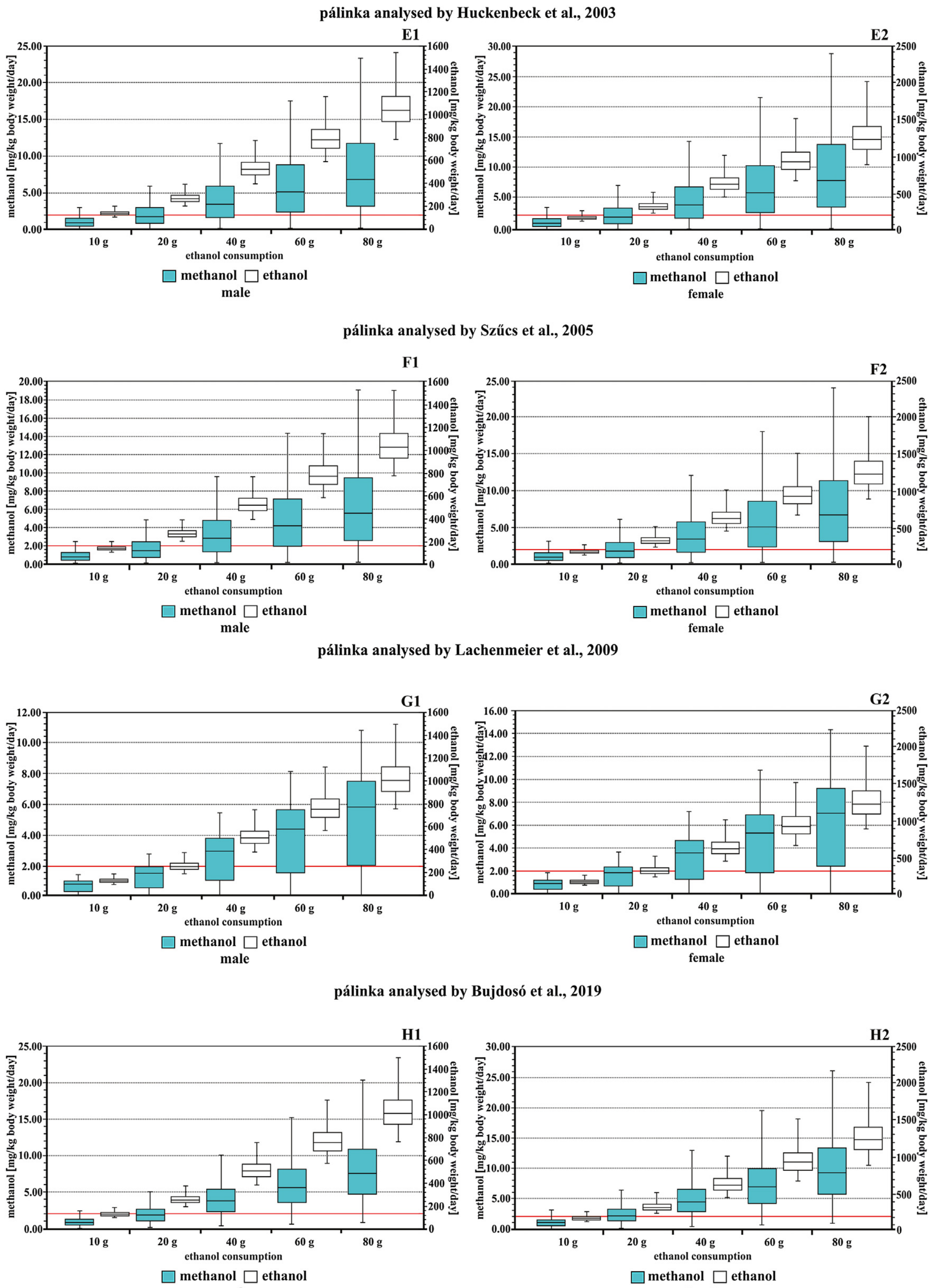

Fig. 3. Estimated daily methanol and ethanol intakes by males and females when consuming unrecorded fruit spirits containing methanol. The left and right y axes show the distribution of methanol and ethanol intakes (mg/kg body weight/day), respectively. Panels: E1-E2 pálinka, F1-F2 pálinka, G1-G2 pálinka, H1-H2 pálinka. Median values, their interquartile ranges, 1st and 99th percentiles are depicted. The red line indicates the reference dose of methanol.

differed significantly from those associated with drinking HFS at each consumption level both for men and women ($p < 0.001$). Table 5 shows the methanol concentrations in unrecorded fruit spirits required to reach the MTBML at different consumption levels. As demonstrated, drinking unrecorded fruit spirits containing methanol at a concentration of 17, 476.1 mg/litre of p.a. or 17,384.2 mg/litre of p.a. and also at least 80 g (corresponding to 253.4 mL of fruit spirit containing 40 % ethanol) and 60 g ethanol

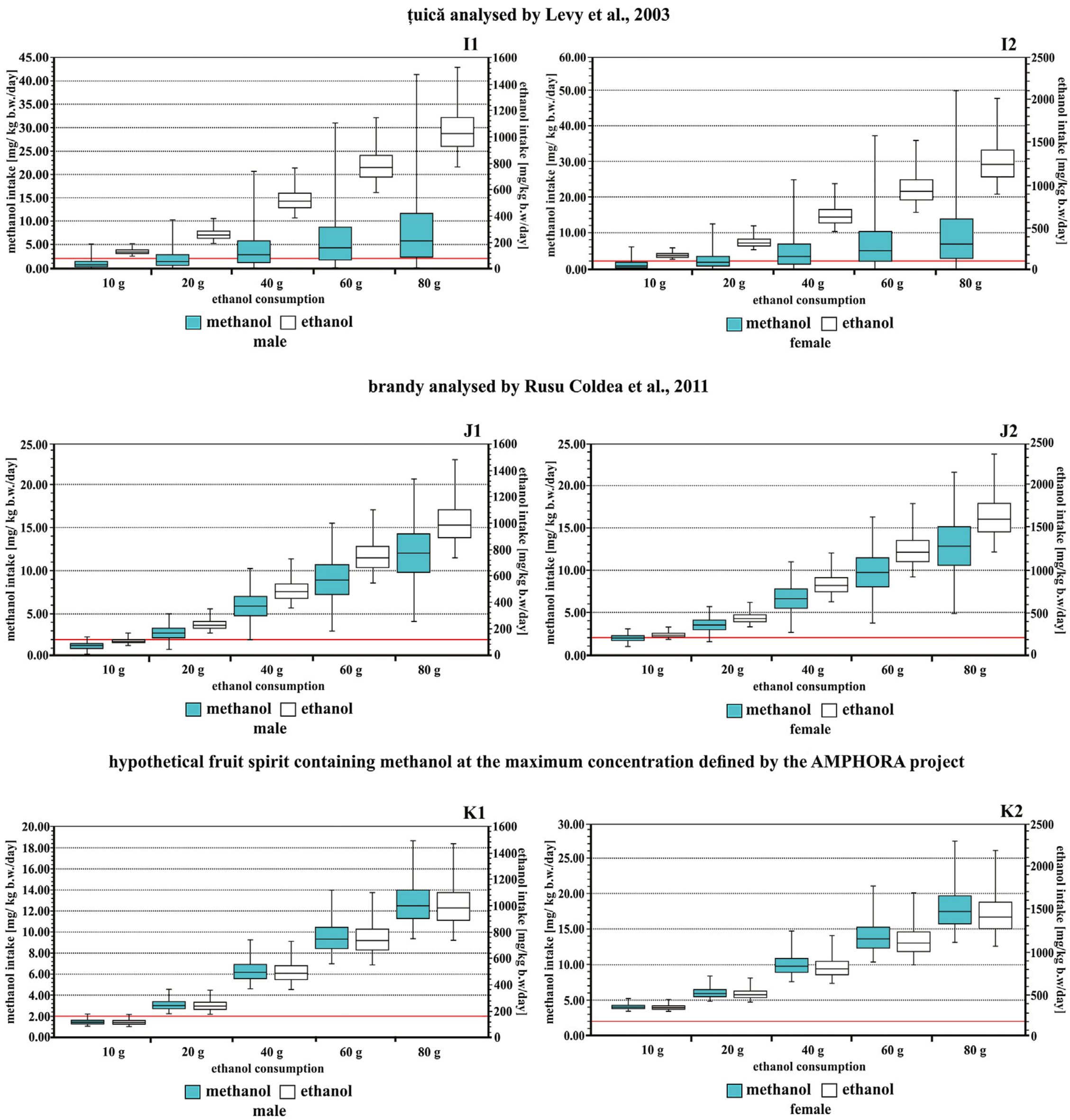

Fig. 4. Estimated daily methanol and ethanol intakes by males and females when drinking unrecorded fruit spirits containing methanol. The left and right y axes show the distribution of methanol and ethanol intakes (mg/kg body weight/day), respectively. Panels: I1-I2 țuică, J1-J2 brandy, K1-K2 hypothetical fruit spirit. Median values, their interquartile ranges and whiskers, 1st and 99th percentiles are shown. The red line indicates the reference dose of methanol.

(corresponding to 190.1 mL of fruit spirit containing 40 % ethanol) can result in a methanol intake equal to the MTBML by men and women, respectively.

4. Discussion

Unrecorded alcohols are consumed in many parts of the world (World Health Organisation, 2018). According to the latest available data published by the World Health Organisation, their share in worldwide alcohol per capita (APC) consumption among adults was 25.5 % in 2016 (World Health Organisation, 2018). As shown in Supplementary Table 3, 13.74 % of overall APC consumption in the EU was in the form of unrecorded alcohols (World Health Organisation, 2018). Estimated proportions of unrecorded alcohol consumption in the countries included in our study varied from 10.4 % in Germany, 13.1 % in Hungary and 15.7 % in Croatia through 17.4 % in Romania to 41.3 % in Greece (World Health Organisation, 2018). Considering the share of regular drinkers in the adult population in these countries, the total numbers potentially exposed to methanol from unrecorded alcohols was calculated to be 80.6 million (see Supplementary Table 3). The majority of this exposure originated from the Central and Eastern European (CEE) countries including Hungary, Croatia, and Romania, where unrecorded fruit spirits comprise a large share of unrecorded alcohols (Popova et al., 2007). Importantly, many heavy drinkers experience financial hardship and, given that unrecorded alcoholic beverages tend to be cheap, they can be expected to consume relatively high levels of unrecorded fruit spirits compared to the general population (Babor, 2010). Therefore, it was reasonable to determine the consumption level at which the daily methanol intake from unrecorded fruit spirits might exceed the threshold values.

Unrecorded fruit spirits are frequently consumed in those countries where the samples included in our study were analysed so, given the potential for methanol contamination, there is potential cause for public health concern beyond the adverse effect of ethanol. The results reported in 6 out of 9 studies showed that 2 % to 35 % of unrecorded fruit spirit samples contained methanol

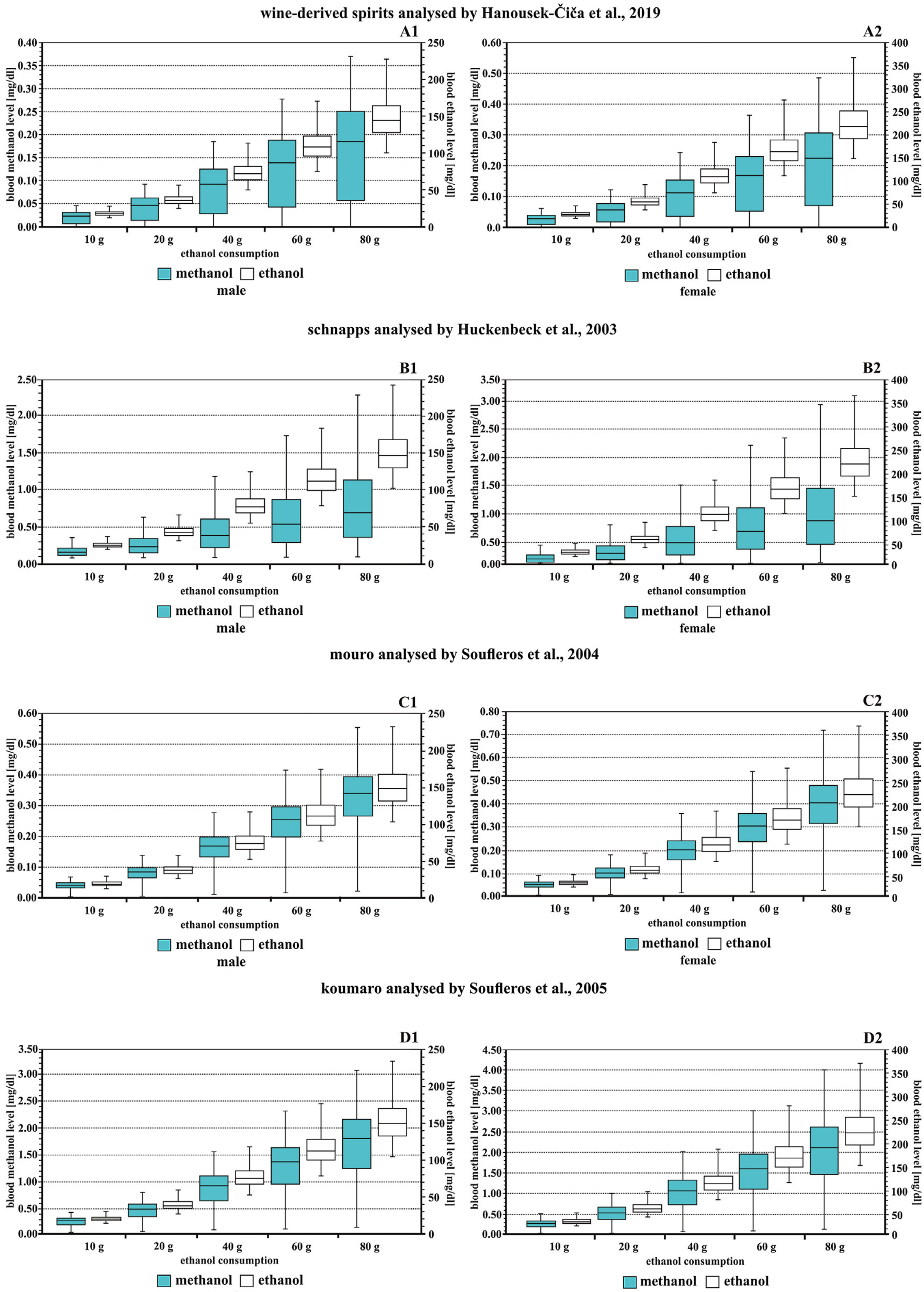

Fig. 5. Estimated blood methanol and ethanol concentrations in males and females when consuming unrecorded fruit spirits containing methanol. The left and right y axes show the distribution of blood methanol and ethanol levels (mg/dl), respectively. Panels: A1-A2 wine-derived spirits, B1-B2 schnapps, C1-C2 mouro, D1-D2 koumaro. Median values, their interquartile ranges, 1st and 99th percentiles are depicted.

above the AMPHORA limit (see Table 3). Consequently, those consuming these alcoholic beverages may be exposed to potentially hazardous levels of methanol, with methanol intakes potentially exceeding the RfD. Our population-based estimation indicated that drinking koumaro, pálinka, ţuică, and brandy containing methanol at a minimum concentration of 8598.1 mg/litre of p.a. and at least 10 g ethanol (corresponding to 31.5 mL of unrecorded fruit spirits containing 40 % ethanol) can result in a

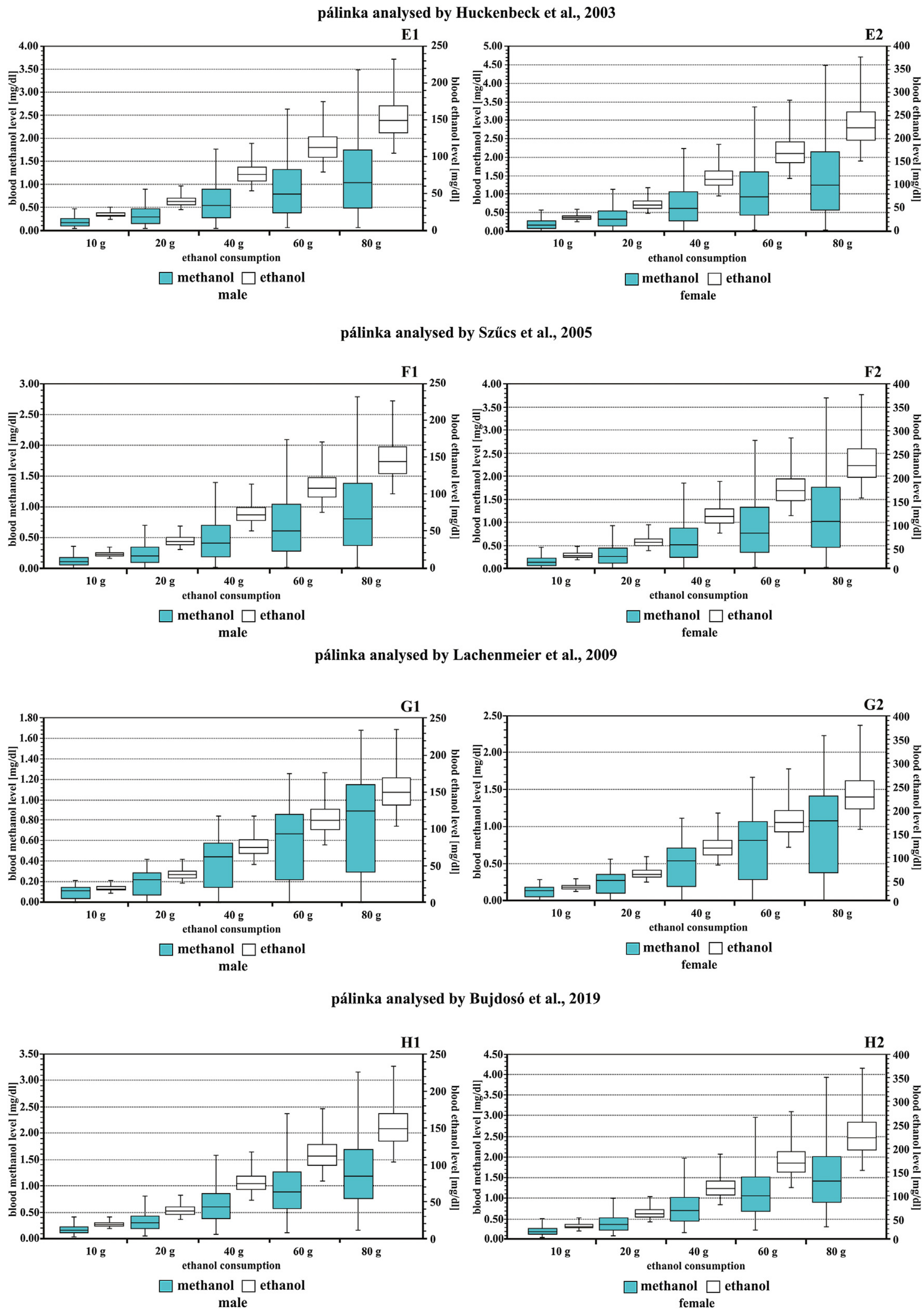

Fig. 6. Estimated blood methanol and ethanol concentrations in males and females when drinking unrecorded fruit spirits containing methanol. The left and right y axes show the distribution of blood methanol and ethanol levels (mg/dl), respectively. Panels: E1-E2 pálinka, F1-F2 pálinka, G1-G2 pálinka, H1-H2 pálinka. Median values, their interquartile ranges, 1st and 99th percentiles are shown.

methanol intake by men equal to the RfD (see Table 4). For women, in addition to consumption of the above mentioned unrecorded fruit spirits, drinking schnapps containing methanol at a minimum concentration of 6382.1 mg/litre of p.a. and no less than 10 g ethanol can also contribute to a methanol intake equal to the RfD (see Table 4).

This finding suggests that long term consumption of these alcoholic drinks might lead to chronic methanol toxicity even if

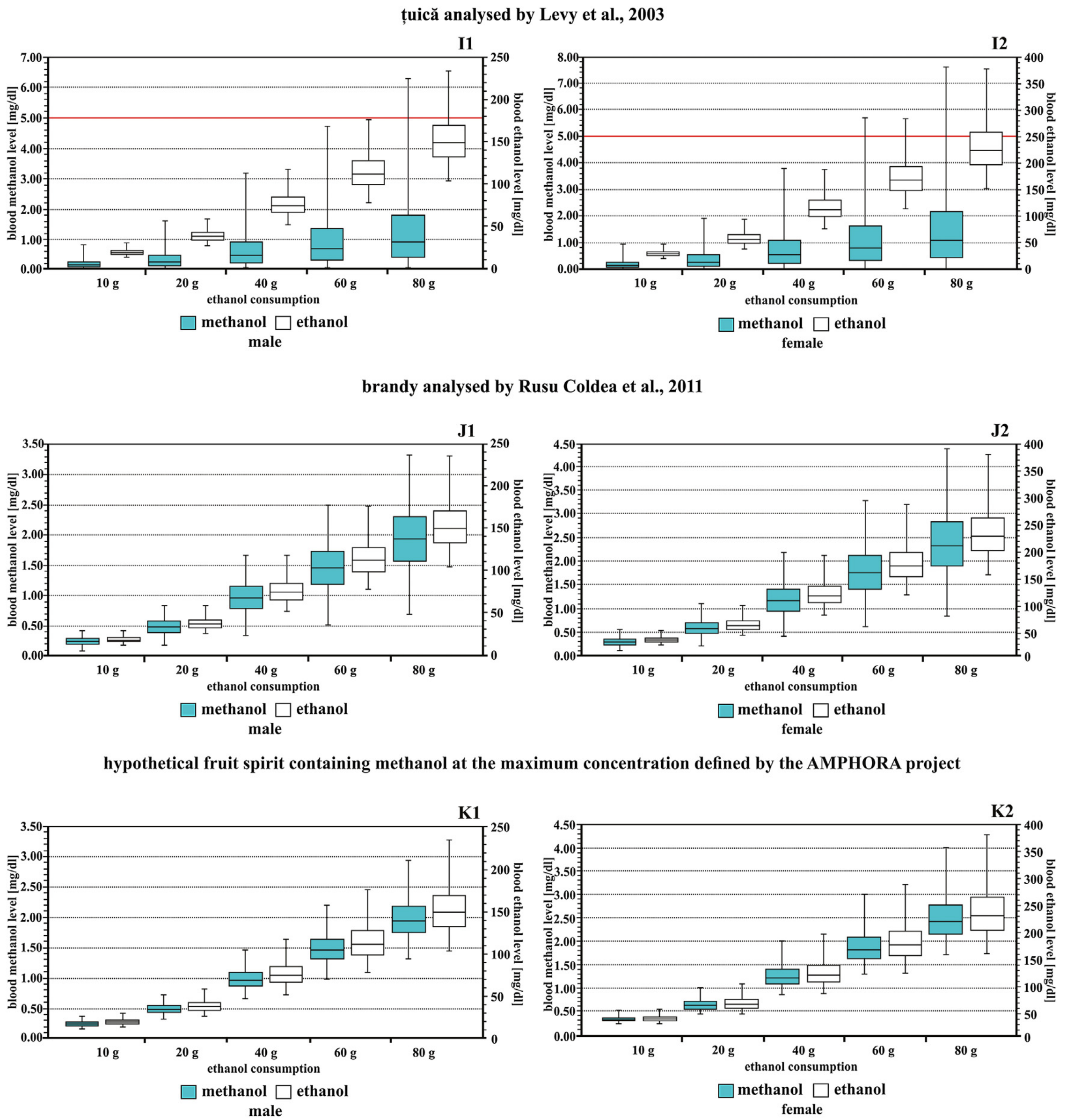

Fig. 7. Estimated blood methanol and ethanol concentrations in males and females when consuming unrecorded fruit spirits containing methanol. The left and right y axes show the distribution of blood methanol and ethanol levels (mg/dl), respectively. Panels: I1-I2 ţuică, J1-J2 brandy, K1-K2 hypothetical fruit spirit. Median values, their interquartile ranges, 1st and 99th percentiles are demonstrated. The red line indicates the maximum tolerable blood methanol level.

methanol concentrations are less than 10 000.0 mg/litre of p.a. However, this is an area where there is considerable uncertainty because there is very limited information about the chronic effects of low level oral exposure to methanol (Yang et al., 2014a, b). The little research that exists includes animal experiments that have linked chronic exposure to methanol to development of Alzheimer's like disease (Yang et al., 2014a, b). However, the methodological challenges of assessing any possible adverse health effects of long-term intake of methanol from unrecorded fruit spirits at a level exceeding the RfD of 2.0 mg/kg body weight/day are considerable, given that any effects are likely to be masked by those of the much higher levels of ethanol, while those drinking large amounts of these products are likely to have other health-damaging characteristics (Shiffman and Balabanis, 1996).

The proposed limit of 10 000.0 mg/litre of p.a. for methanol concentration in unrecorded spirits was calculated by considering a former RfD of 20.0 mg/kg body weight/day (Fishbein, 1997; Lachenmeier et al., 2011a). However, the RfD of 2.0 mg/kg body weight/day published later by the United States Environmental Agency was taken into account in our study (United States Environmental Protection Agency, 2013). If this RfD is used, the current limit for methanol levels in unrecorded spirits should be re-evaluated.

Having shown that the methanol concentration in unrecorded fruit spirits and its intake can be above the AMPHORA limit and the RfD, respectively, it is important to determine whether the BML of those consuming these alcoholic drinks can reach or exceed the MTBML of 5.0 mg/decilitre? We found that BMLs can be above the MTBML when consuming unrecorded fruit spirits containing methanol at a concentration of 17,476.1 mg/litre of p.a. or 17,384.2 mg/litre of p.a. and also at least 80 g (corresponding to 253.4 mL of fruit spirit containing 40 % ethanol) and 60 g ethanol (corresponding to 190.1 mL of fruit spirit containing 40 % ethanol) by men and women, respectively (see Table 5). Consequently, consuming unrecorded fruit spirits containing methanol at these levels and above can give rise to acute toxicity. A BML above 50.0

mg/decilitre has been reported to produce severe acute toxic effects (World Health Organisation, 2014). Such high BMLs are usually observed in acute methanol poisoning. Therefore, our results confirm that consumption of unrecorded fruit spirits containing methanol at concentrations described in the studies selected is unlikely to cause any acute toxic effects (Lachenmeier et al., 2021).

Although several actions have been taken by EU decision makers and manufacturers of alcoholic beverages to reduce the methanol content of recorded fruit spirits well below the EU limit of 10 000.0 mg/litre of p.a., less attention has been paid to methanol levels in unrecorded fruit spirits (Botelho et al., 2020; Lachenmeier et al., 2021). Since our population-based estimation suggests that long-term methanol intake from unrecorded fruit spirits can reach or exceed the RfD, posing a health risk to the consumers, health policy makers in the EU, especially in the countries that provided studies identified in our literature search, should also consider measures to reduce exposure to methanol from these alcoholic beverages. Previous studies have recommended potential interventions to decrease the possible adverse effects of consumption of non-ethanol alcohols in unrecorded fruit spirits (Lachenmeier et al., 2021, 2011b). They include stricter control of their production by fiscal authorities, monitoring the quality of unrecorded alcohols by national food safety laboratories, increasing the incentives for small-scale producers to register their products, and requiring quality control (Lachenmeier et al., 2021; Ohimain, 2016). There may also be benefits from increasing public awareness of the presence of methanol and other alcohols in unrecorded alcohols and their potential adverse effects.

5. Strengths and limitations

Our study is the first to investigate the intake of methanol from various unrecorded fruit spirits and related BMLs at population level. It also benefits from considering differences by sex and amount of alcohol consumption. Our probabilistic toxicological approach was based on internationally accepted RfD and an MTBML used most frequently to evaluate chronic and acute methanol toxicity, respectively. This is also the first research to assess the lowest methanol concentrations in unrecorded fruit spirits that would reach the RfD and MTBML over the distribution of body weight in the population. A limitation is that although we reviewed over 300 publications, only a few published data on methanol concentrations in unrecorded fruit spirits and most only reported average levels. As we included only studies with 10 or more unrecorded fruit spirit samples, some smaller ones were excluded. Individual data on methanol concentrations required for our Monte Carlo Simulations were available only from 5 EU countries, which limits the generalizability of our results to other EU countries. Therefore, further studies are required that determine and report individual data on the methanol levels in large number of unrecorded fruit samples collected in each EU member state allowing more precise probabilistic toxicological assessments.

6. Conclusions

The risks of drinking alcoholic beverages adulterated with methanol are well known. However, it may not be so widely known that certain spirit beverages distilled from fruit also contain it. Methanol is especially likely to be found in beverages that are home-produced, especially pálinka and brandy, products consumed in appreciable quantities in some parts of Europe. While these amounts of methanol are unlikely to cause harm to drinkers whose consumption is low, they could pose a risk to those who consume larger quantities. By modelling the effects of ingestion of these products, with concentrations of methanol deduced from a systematic assessment of evidence on its concentration in spirits consumed in Europe, we were able to estimate the likely distribution of blood methanol levels in individuals drinking up to 80 g of ethanol per day. Although some of these products do contain appreciable quantities of methanol, often at levels much higher than in commercially produced spirits, we are reassured that the blood methanol levels achieved will not be sufficient to cause acute toxicity. However, this does not exclude the possibility of so far unknown adverse consequences of chronic consumption.

Data availability

Data used for this research are available in the supplementary material related to this article.

Author contributions

Teuta Muhollari: data curation, visualization, writing - original draft; **Sándor Szűcs:** conceptualization, investigation, supervision, writing - original draft; **Róza Ádány:** resources, writing - review & editing; **János Sándor:** resources, writing - review & editing; **Martin McKee**: writing - review & editing; **László Pál:** conceptualization, investigation, methodology, project administration, supervision, writing - original draft

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.toxlet.2021.12.019.

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