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Short communication

The total margin of exposure of ethanol and acetaldehyde for heavy drinkers consuming cider or vodka

Dirk W. Lachenmeier [a,b,*], Jan S. Gill [c], Jonathan Chick [c,d], Jürgen Rehm [b,e,f,g,h]

[a] *Chemisches und Veterinäruntersuchungsamt (CVUA) Karlsruhe, Weissenburger Strasse 3, D-76187 Karlsruhe, Germany*
[b] *Epidemiological Research Unit, Institute for Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany*
[c] *School of Nursing, Midwifery and Social Care, Edinburgh Napier University, Sighthill Campus, Edinburgh EH11 4BN, Scotland, UK*
[d] *Castle Craig Hospital, Blyth Bridge, West Linton, EH46 7DH Scotland, UK*
[e] *Social and Epidemiological Research (SER) Department, Centre for Addiction and Mental Health, Toronto, Canada*
[f] *Addiction Policy, Dalla Lana School of Public Health, University of Toronto (UofT), Canada*
[g] *PAHO/WHO Collaborating Centre for Mental Health & Addiction, Toronto, Canada*
[h] *Institute of Medical Science, UofT, Canada*

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ABSTRACT

Heavy drinkers in Scotland may consume 1600 g ethanol per week. Due to its low price, cider may be preferred over other beverages. Anecdotal evidence has linked cider to specific health hazards beyond other alcoholic beverages. To examine this hypothesis, nine apple and pear cider samples were chemically analysed for constituents and contaminants. None of the products exceeded regulatory or toxicological thresholds, but the regular occurrence of acetaldehyde in cider was detected. To provide a quantitative risk assessment, two collectives of exclusive drinkers of cider and vodka were compared and the intake of acetaldehyde was estimated using probabilistic Monte–Carlo type analysis. The cider consumers were found to ingest more than 200-times the amount of acetaldehyde consumed by vodka consumers. The margins of exposure (MOE) of acetaldehyde were 224 for the cider and over 220,000 for vodka consumers. However, if the effects of ethanol were considered in a cumulative assessment of the combined MOE, the effect of acetaldehyde was minor and the combined MOE for both groups was 0.3. We suggest that alcohol policy priority should be given on reducing ethanol intake by measures such as minimum pricing, rather than to focus on acetaldehyde.

1. Introduction

Previous research has surveyed heavy drinkers in Scotland, who consume 200 UK units and more per week (1 UK unit being 8 g of ethanol), i.e. 1600 g ethanol per week. White cider made an important contribution to the weekly intake, likely facilitated by its low price per unit (ppu) of alcohol (Black et al., 2014). Because some ciders are among the cheapest forms of alcohol sold within the UK, some drinkers were observed who exclusively consumed white cider. During the survey, many drinkers confirmed that white cider represented their first choice of drink when funds are low (Black et al., 2014). Cider may also be consumed in more risky locations than other beverage types (Forsyth and Barnard, 2000).

Anecdotal evidence has linked cider consumption to gastric complaints (Black et al., 2014) and "Alcohol Concern" in England produced a recent report also providing anecdotal evidence of certain harmful effects of cider (Goodall, 2011). A study about the antioxidant potential of alcoholic beverages has indeed suggested that its low values in white drinks such as cider may pose an extra risk for liver cirrhosis (Gill et al., 2010).

Other reports (without substantiating evidence) suggested that "ciders have traditionally been regarded as high in 'fusel alcohols',

* Corresponding author. Chemisches und Veterinäruntersuchungsamt (CVUA) Karlsruhe, Weissenburger Strasse 3, D-76187 Karlsruhe, Germany.
E-mail address: Lachenmeier@web.de (D.W. Lachenmeier).

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particularly 2-phenyl ethanol, which has often been attributed to their low nutrient status" (Lea, 2004). A French study in the 1970s detected increased relative risks for oesophageal cancer for consumers of cider compared to other alcoholic beverages. The extra risk was speculated as being due to the presence of carcinogens in cider (Tuyns et al., 1979). However, the literature so far lacks any evidence that cider may be different in its content of "carcinogens" from other beverages (see e.g. Lachenmeier et al. (2012) for review about carcinogens in alcoholic beverages).

White cider's low price alone may promote high doses and this will have an impact on health. However, given the weight of anecdotal evidence, it seemed important to explore whether or not cider consumption may contain constituents or contaminants other than ethanol, which are potentially pathogenic. An official Scottish Government publication has suggested there is a need for more drink-specific data (Beeston et al., 2014). For this reason, we have analysed a collective of cider samples from Scotland for health-relevant constituents and contaminants, and provide a risk assessment for the cumulative effects using the combined margin of exposure (MOE_T) procedure (for background information on the margin of exposure approach see EFSA (2005) and US EPA (1995), the MOE_T procedure has been reviewed by US EPA (2001) and Wilkinson et al. (2000)).

2. Materials and methods

Nine samples (7 apple and 2 pear ciders) were obtained from supermarkets during May 2014 in Scotland. The type and brands of cider were chosen to be typical of those reported as consumed by the participants of the Black et al. (2014) study including the different cider categories based on alcoholic strength. Details on sample type and purchase price are provided in Table 1. The samples were screened using Fourier transform infrared (FTIR) spectroscopy (Lachenmeier, 2007) and nuclear magnetic resonance (NMR) spectroscopy (Godelmann et al., 2013) for constituents and contaminants. A standard enzymatic assay was applied to determine total SO_2. Volatiles including acetaldehyde were analysed using gas chromatography (for details on parameter selection and chemical methodology, see Lachenmeier et al. (2011b)). For comparison, data on acetaldehyde content of vodka were taken from the literature (Lachenmeier and Sohnius, 2008) and additional data of vodka sampling and analysis in Germany between 2010 and 2014 ($n = 106$). Results for volatiles are reported in grams per hectolitre of pure (100%) alcohol (g/hl pa). The remaining results are reported in mg/L of the original beverage.

Alcohol consumption data were taken from two collectives of heavy drinkers, who exclusively consumed cider or vodka. In the sample of 639 participants, 161 reported white cider consumption and within those 72 drank it exclusively in the week recorded (=last week or in a typical week). 147 reported vodka consumption, from which 95 were exclusive vodka consumers. Briefly, in addition to demographic data participants responded to a questionnaire which documented a 'typical' or 'last week' alcohol consumption (type, brand, volume, price, place of purchase). Details on the epidemiologic study were previously published (Black et al., 2014). Average body weights for male and female adults were obtained from EFSA (2012).

The data of the chemical analysis and alcohol consumption were combined to estimate the exposure of the drinkers to the compounds ethanol and acetaldehyde. The methodology for quantitative risk assessment using the margin of exposure (MOE) approach (EFSA, 2005; US EPA, 1995) was based on a previous study conducted for compounds in alcoholic beverages (Lachenmeier et al., 2012) with the exception that probabilistic exposure estimation was conducted (Lachenmeier et al., 2014; Lachenmeier and Rehm, 2013b; Lachenmeier et al., 2013). The MOE is defined as the ratio between the lower one-sided confidence limit of the benchmark dose (BMDL) and estimated human intake of the same compound. BMDL values for acetaldehyde (Lachenmeier et al. (2009) based on Soffritti et al. (2002)) and ethanol (Lachenmeier et al. (2011a) based on NTP (2004) and Beland et al. (2005)) were taken from the literature.

In addition to the individual MOE values for ethanol and acetaldehyde, the combined margin of exposure (MOE_T) was calculated

Table 1
Sample description, purchase price and selected analytical results[a] of cider samples from Scotland.

Sample number	1	2	3	4	5	6	7	8	9
Cider type	White	White	Pear	Pear	Cheap amber	Cheap amber	Cheap amber	Amber "quality cider"	Amber "quality cider"
Purchase price (pence per UK unit)	15.3	29	21.6	33.3	18.8	23.8	25	32.5	31.9
Alcoholic strength (% vol) (labelling)	7.5	7.5	5.3	4.5	5.3	4.2	4	5	4.7
Alcoholic strength (% vol) (analysis)	7.4	7.3	5.2	4.2	5.2	4.2	4.1	5.0	4.8
Total sugar (g/L)	11	3	46	46	10	16	15	16	31
Energy (kJ/L)	1940	1750	2050	1810	1410	1240	1180	1410	1690
Total SO_2 (mg/L)	59	74	56	63	65	66	55	42	76
Acetic acid (mg/L)	180	168	123	177	131	114	229	<100	112
Fumaric acid (mg/L)	17	n.d. (<5)	32	34	24	24	16	25	10
HMF (mg/L)	n.d. (<5)	n.d. (<5)	n.d. (<5)	n.d. (<5)	14	6	8	n.d. (<5)	n.d. (<5)
Furfural (mg/L)	n.d. (<2)	n.d. (<2)	n.d. (<2)	n.d. (<2)	3	3	n.d. (<2)	n.d. (<2)	n.d. (<2)
Malic acid (g/L)	3.3	0.8	4.4	4.4	3.8	3.6	2.5	3.2	2.3
Lactic acid (mg/L)	n.d. (<200)	n.d. (<200)	n.d. (<200)	n.d. (<200)	n.d. (<200)	n.d. (<200)	256	319	n.d. (<200)
Acetaldehyde (g/hl pa)	10	20	31	14	16	20	22	12	27
Methanol (g/hl pa)	n.d. (<4)	6	4	5	n.d. (<4)	n.d. (<4)	6	5	18
1-Propanol (g/hl pa)	9	12	11	8	10	10	8	34	7
Iso-butanol (g/hl pa)	41	17	27	42	25	14	32	9	21
Amyl alcohols (g/hl pa)	200	96	143	225	131	120	166	132	170
2-Phenyl ethanol (g/hl pa)	5	n.d. (<2)	5	8	4	5	7	4	7
Ethyl acetate (g/hl pa)	28	33	29	24	26	25	37	32	22
Ethyl lactate (g/hl pa)	n.d. (<6)	n.d. (<6)	n.d. (<6)	n.d. (<6)	n.d. (<6)	n.d. (<6)	12	11	n.d. (<6)

[a] Not detectable (n.d.) in all samples (detection limit in mg/L in brackets): citric acid (200 mg/L), tartaric acid (0.5 mg/L), acetoine (10 mg/L), formic acid (5 mg/L), gluconic acid (400 mg/L), putrescine (50 mg/L), cadaverine (50 mg/L), pyruvic acid (20 mg/L), 4-aminobutanoic acid (120 mg/L), alanine (35 mg/L), arginine (150 mg/L), proline (150 mg/L), caftaric acid (15 mg/L), epicatechin (30 mg/L), gallic acid (25 mg/L), shikimic acid (20 mg/L), trigonelline (10 mg/L), benzoic acid (10 mg/L), sorbic acid (10 mg/L), salicylic acid (10 mg/L), 1-butanol (2 g/hl pa), 2-butanol (2 g/hl pa), 1-hexanol (2 g/hl pa), benzyl alcohol (2 g/hl pa), methyl acetate (6 g/hl pa), benzyl acetate (1 g/hl pa), ethyl benzoate (1 g/hl pa), and benzaldehyde (1 g/hl pa).

using the following formula assuming additive risk due to similar mechanism (US EPA, 2001; Wilkinson et al., 2000):

$$MOE_T = \frac{1}{\frac{1}{MOE_{Ethanol}} + \frac{1}{MOE_{Acetaldehyde}}}$$

Similar to the approach of Medeiros Vinci et al. (2012) for probabilistic human exposure assessment of food contaminants, best fit distributions were applied to the alcohol consumption data as well as to the data on acetaldehyde contents in the beverages and the resulting risk functions were entered into the probabilistic analysis. All risk functions were truncated at zero because negative values are factually impossible. All calculations were conducted using the software package @Risk for Excel Version 5.5.0 (Palisade Corporation, Ithaca, NY, USA). Monte–Carlo simulations were performed with 50,000 iterations using Latin Hypercube sampling and Mersenne Twister random number generator. The distribution functions and detailed calculation methodology is specified in Supplementary Tables S1–S2 online.

3. Results

The results of the chemical analysis of cider samples are reported in Table 1. The alcoholic strengths of the products varied between 4.1% and 7.4% vol. All alcoholic strengths of all samples were within the legal tolerance of plus/minus 1% vol according to EU regulation 1169/2011 (annex XII). All samples did contain total SO_2 (sulphur dioxide and sulphites) above 10 mg/L, but did include the mandatory labelling “contains sulphites” according to article 21 of EU regulation 1169/2011. The maximum sulphur dioxide limit of 200 mg/L according to EU regulation 1333/2008 (annex II, part E, food category 14.2.3) was not exceeded in any of the samples.

Except ethanol and acetaldehyde, the compounds with health relevance (e.g. methanol, HMF, and higher alcohols) were within normal ranges for this product category and below toxicological thresholds (for limits including toxicological assessment see Lachenmeier et al. (2011b, 2008) and Monakhova and Lachenmeier (2012)).

Besides ethanol, which obviously is the toxic principle of any alcoholic beverage, acetaldehyde was selected for further risk assessment, because it is currently unclear if its mechanisms of toxicity and carcinogenicity have a threshold (Lachenmeier et al., 2009).

Using probabilistic Monte–Carlo type analysis, the distribution of the alcohol and acetaldehyde intakes was estimated for exclusive cider and exclusive vodka consumers in Scotland (Table 2). The average alcohol intake was higher for the cider consumers (277 g/day) than for the vodka consumers (243 g/day). However considering the standard deviation of more than 100 g/day, the distributions were similar for both beverages, with some extreme cases reaching intakes of 500 g/day and more.

In contrast to alcohol intake, a pronounced significant difference between the two groups was found for the acetaldehyde intake. The cider consumers (average acetaldehyde intake: 0.866 mg/kg bw/day) ingested more than 200-times that of the vodka consumers (average acetaldehyde intake: 0.004 mg/kg bw/day).

The average margins of exposure for ethanol were similar for the two groups (about 0.3), reflecting similar average ethanol intake per week, while the average margins of exposure for acetaldehyde were 224 for the cider group and 227,019 for the vodka group. However, on the combined margin of exposure, the influence of acetaldehyde was minor in both groups, while the influence of ethanol predominates. The MOE_T of both compounds is similar to the MOE of ethanol (about 0.3). Even in the cider group, the MOE_T changes only on the third decimal compared to the MOE of ethanol (0.286–0.285). This means that more than 99.7% of the combined effect would be caused by ethanol. The normalized regression coefficients for the probabilistic MOE_T calculation show that the values are influenced primarily by the alcohol intake (coefficient: −0.64), and the bodyweights (coefficients: +0.15 for male bodyweight and +0.03 for female bodyweight), while the acetaldehyde content in cider has only a very minor influence (coefficient: −0.01). Thus, even while the acetaldehyde content in cider is high compared to vodka, its influence on the MOE_T is still 64 times lower than the influence of ethanol and – at least mathematically – is almost completely masked by ethanol.

Nevertheless, the MOEs for genotoxic carcinogens in foods should be above 10,000 according to EFSA (2005). For acetaldehyde, vodka is considerably above this threshold with a MOE of over 220,000, but cider is considerably below (MOE 224). Clearly, ethanol is for both cases in a high risk-range with MOE <1.

4. Discussion

Our research was not able to corroborate claims that cider was of “low” quality (quality is a rather vague term (Lachenmeier and

Table 2
Results of probabilistic estimation of alcohol and acetaldehyde intake, margin of exposure (MOE) and combined margin of exposure (MOE_T) for exclusive cider and vodka consumers.

Name	Minimum	Maximum	Mean	Std deviation	5% Perc	25% Perc	50% Perc	75% Perc	90% Perc	95% Perc
Exclusive Cider consumers (n = 72)										
Alcohol (ethanol) intake (g/day); original distribution of raw data	42	960	277	153	60	180	240	360	480	540
Alcohol (ethanol) intake (g/day); distribution from risk function	4.8	1417	277	151	83	166	250	359	480	563
Acetaldehyde intake (mg/kg bw/day)	1.1E-05	8.651	0.866	0.611	0.177	0.433	0.723	1.140	1.650	2.025
MOE ethanol	0.022	8.895	0.286	0.246	0.094	0.152	0.221	0.337	0.516	0.681
MOE acetaldehyde	6	5.0E+06	224	22197	28	49	77	129	219	316
MOE_T (ethanol & acetaldehyde)	0.022	8.873	0.285	0.245	0.094	0.152	0.221	0.336	0.514	0.679
Exclusive vodka consumers (n = 95)										
Alcohol (ethanol) intake (g/day); original distribution of raw data	22	900	243	137	70	142	210	300	420	480
Alcohol (ethanol) intake (g/day); distribution from risk function	3.4	1205	243	133	72	146	220	315	422	495
Acetaldehyde intake (mg/kg bw/day)	4.8E-08	0.124	0.004	0.005	1.5E-04	0.001	0.002	0.005	0.010	0.014
MOE ethanol	0.038	11	0.308	0.280	0.102	0.163	0.237	0.359	0.551	0.732
MOE acetaldehyde	453	1.2E+09	227019	6.9E+06	4017	10715	24223	63852	182867	383261
MOE_T (ethanol & acetaldehyde)	0.038	11	0.308	0.280	0.102	0.163	0.237	0.359	0.551	0.732

Rehm, 2013a)) or contained certain constituents or contaminants posing additional health risk to the consumer over and above ethanol. From an organoleptic standpoint, it may be debatable whether the taste of the cheap cider products would be considered inferior to other alcoholic beverages, but the chemical composition of the ciders under study was typical for this class of products. Several other alcoholic beverages (e.g. beer or grape wine) have comparable concentrations of the analysed compounds, and some spirits (e.g. fruit spirits) may have considerably higher concentrations of methanol and higher alcohols. The claim, that cider may have extreme contents in higher alcohols and specifically 2-phenyl ethanol (Lea, 2004), was not corroborated in our sample collective, which had rather low contents of this compound compared to other wines and spirits. Even the acetaldehyde content was not unusual for fermented beverages. Normal grape wines contain an average acetaldehyde content of 28 g/hl pa (Lachenmeier and Sohnius, 2008), which corresponds to the contents found in the ciders from Scotland (range 10–31 g/hl pa). Apple wines and ciders from Germany and France had much higher acetaldehyde contents (average 97 g/hl pa) (Lachenmeier and Sohnius, 2008). The lower contents in Scotland can probably be explained by chaptalization (i.e., an addition of sugar prior to fermentation to increase the alcoholic strength), which generally lowers the content of other volatiles besides ethanol.

Interestingly, the EU food law does not provide limits for most of the compounds occurring in cider. The existing legal standards, e.g. regarding alcohol labelling and SO_2 content, were observed by all products. From the aspects of general food safety standards (ciders are regulated as “food” in the EU), we currently cannot see any problems with food quality or food information that may restrict the sales of the ciders analysed.

Nevertheless, we were concerned about the extreme intakes that have been reported for cider consumers, which were much higher than what we have used in our previous risk assessment of acetaldehyde (Lachenmeier et al., 2009) or the average of people with alcohol dependence in primary care (Rehm et al., 2015a) or in specialized care in Europe (Rehm et al., 2015b). Indeed, the calculated average acetaldehyde intake from cider of 0.866 mg/kg bw/day by far exceeds our estimations on average acetaldehyde intake in the EU from all alcoholic beverages (0.112 mg/kg bw/day) (Lachenmeier et al., 2009). To make a judgement about the influence of acetaldehyde compared to ethanol, the MOE_T was calculated. The results show that the risk of acetaldehyde would be minor compared to ethanol. Considering both ethanol and acetaldehyde, this group of heavy cider drinkers is certainly exposed to a very high risk (MOE <1), which is currently not exceeded by any drug in Europe except alcohol (Lachenmeier and Rehm, 2015).

5. Conclusions

The possibility was investigated that not all alcoholic drinks have the same health risk. However, we were unable to find a specific hazard within samples of ciders sold in Scotland. The conclusion for the consumer is that the contents of acetaldehyde in cider do not make any appreciable difference to the cumulative risk, because the risk of ethanol itself is already so high and predominant, particularly for the heavy drinkers described above.

One difference may be that ethanol is intentionally and voluntarily ingested, and acetaldehyde is (probably) unintentionally ingested. The intentional risk (i.e., risk because of consumer choice) probably demands other thresholds for acceptable risk than the unintentional risk (compare: skiing and water contamination) (Rehm et al., 2014). Therefore, we could still demand some mitigation measures to reduce acetaldehyde in cider (it must be considered, however, that its content is natural and cannot be easily minimized below certain levels, see Lachenmeier and Sohnius (2008) for a review discussing mitigation measures).

However, in relation to reducing risk to the consumer, the first priority of alcohol policy should focus on reducing the ethanol intake *per se*, for which some measures such as increase in price or introduction of a minimum price have been discussed (Babor et al., 2010; Black et al., 2014), the latter specifically addressed to heavy drinkers.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

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Transparency document

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Supplementary Table S1. Distribution functions and inputs for probabilistic analysis

Input	Value or distribution risk function for the software package @Risk for Excel Version 5.5.0 (Palisade, Corporation, Ithaca, NY, USA) [a]	Origin of data
Alcohol intake (exclusive cider consumers) [g/day]	RiskGamma(3.3457;82.748;RiskTruncate(0;))	This study, best-fit distribution selected with @Risk Software
Alcohol intake (exclusive vodka consumers) [g/day]	RiskGamma(3.4173;71.926;RiskShift(-2.4269);RiskTruncate(0;))	This study, best-fit distribution selected with @Risk Software
Acetaldehyde content in cider [g/hl pa]	RiskNormal(19.1556;6.9318;RiskTruncate(0;))	This study, best-fit distribution selected with @Risk Software
Acetaldehyde content in vodka [g/hl pa]	RiskExpon(0.10258)	This study, best-fit distribution selected with @Risk Software
Bodyweight males [kg]	RiskNormal(82;13.1)	Bodyweight statistics for adults (18-64) of the EFSA Comprehensive database (EFSA 2012)
Bodyweight females [kg]	RiskNormal(67.2;12.8)	Bodyweight statistics for adults (18-64) of the EFSA Comprehensive database (EFSA 2012)
BMDL_Acetaldehyde [mg/kg bw/day]	56	(Lachenmeier et al. 2009; Soffritti et al. 2002)
BMDL_Ethanol [g/kg bw/day]	0.7	(Beland et al. 2005; Lachenmeier et al. 2011a; NTP 2004)

[a] RiskGamma(alpha,beta) specifies a gamma distribution using the shape parameter alpha and the scale parameter beta. RiskShift(shift amount) shifts the domain of the distribution in which it is used by the entered shift amount. This function is automatically entered when a fit result includes a shift factor. 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 (in the current calculation this avoids negative values that are physically impossible). RiskExpon(beta) specifies an exponential distribution with the entered beta value. The mean of the distribution equals beta.

Supplementary Table S2. Detailed calculation methodology for probabilistic risk assessment of ethanol and acetaldehyde for consumers of cider and vodka

Parameter	Calculation formula for the software package @Risk for Excel Version 5.5.0 (Palisade, Corporation, Ithaca, NY, USA) [a]
Acetaldehyde intake (mg/kg bw/day)	Risk function for alcohol intake (g/day) / 0.789 (g/ml) * Risk function for acetaldehyde content in cider or vodka (g/hl pa) / 100 / [(Percentage males in collective/100 * Risk function for bodyweight males (kg) + Percentage females in collective/100 * Risk function for bodyweight females (kg)]
MOE_Acetaldehyde	BMDL_Acetaldehyde (mg/kg bw/day) / Acetaldehyde intake (mg/kg bw/day)
MOE_Ethanol	BMDL_Ethanol (g/kg bw/day) / Risk function for alcohol intake (g/day) / [(Percentage males in collective/100 * Risk function for bodyweight males (kg) + Percentage females in collective/100 * Risk function for bodyweight females (kg)]
MOE_T	1 / [(1 / MOE_Acetaldehyde) + (1 / MOE_Ethanol)]

[a] The density of alcohol (0.789 g/ml) is used to correct from volume to mass in the formula for acetaldehyde intake