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Comparative risk assessment of carcinogens in alcoholic beverages using the margin of exposure approach

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Brief statement about novelty and impact:

This study is the first to apply a quantitative approach for comparative risk assessment of different carcinogens in alcoholic beverages. Ethanol was found to be the most important ingredient leading to substantial cancer risk. This result clarifies misinformation that other contaminants are predominantly responsible for the carcinogenicity, e.g., claims by industry about carcinogenic contaminants, which are not contained in certain brand products. Until now, the scientific basis was lacking to refute such misleading advertisement claims. The developed methodology can also be transferred to other ingredients or to comparative risk assessment of other substances.

Abstract

Alcoholic beverages have been classified as carcinogenic to humans. As alcoholic beverages are multi-component mixtures containing several carcinogenic compounds, a quantitative approach is necessary to compare the risks.

Fifteen carcinogenic compounds (acetaldehyde, acrylamide, aflatoxins, arsenic, benzene, cadmium, ethanol, ethyl carbamate, formaldehyde, furan, lead, 4-methylimidazole, *N*-nitrosodimethylamine, ochratoxin A, and safrole) occurring in alcoholic beverages were identified based on monograph reviews by the International Agency for Research on Cancer. The margin of exposure (MOE) approach was used for comparative risk assessment. MOEs were calculated for different drinking scenarios (low risk and heavy drinking) and different levels of contamination for four beverage groups (beer, wine, spirits, unrecorded alcohol).

The lowest MOEs were found for ethanol (3.1 for low risk and 0.8 for heavy drinking). Lead and arsenic have average MOEs between 10 and 300, followed by acetaldehyde, cadmium and ethyl carbamate between 1,000 and 10,000. All other compounds had average MOEs above 10,000 independent of beverage type.

Ethanol was identified as the important carcinogen in alcoholic beverages, with a clear dose-response curve. Some other compounds (lead, arsenic, ethyl carbamate, acetaldehyde) may pose risks below thresholds normally tolerated for food contaminants, but from a cost-effectiveness point of view, the focus should be on reducing alcohol consumption in general than on mitigative measures for some contaminants that contribute only in minor fashion (if at all) to the total health risk.

Introduction

Since the first observation in France in the beginning of the last century that the consumption of absinthe was related to oesophageal cancer,¹ epidemiology has established a causal relationship between alcohol consumption in general (i.e. independent of beverage type) and the occurrence of cancer. Moreover, in 1988, the International Agency for Research on Cancer (IARC) classified alcoholic beverages into group 1 as "carcinogenic to humans".² At this time, a causal relationship between alcohol consumption and the occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus and liver was established. In the following IARC evaluations, colorectum cancer and female breast cancer were added to the list of cancer sites with causal relationship, while only limited evidence points to stomach and pancreas as further sites.³⁻⁵ While the epidemiological evidence on the carcinogenicity of alcoholic beverages had been sufficiently established for several decades, the principal mechanism underlying this relationship has been a matter of debate. For a long time it was assumed that ethanol itself was not a direct carcinogen. The 1988 IARC monograph, for example, stated that there is inadequate evidence for the carcinogenicity of ethanol in experimental animals.² However, this statement was based on lack of well-controlled and designed experimental studies rather than on a clear absence of effect. Since then, two adequately designed long-term animal studies have clearly demonstrated that ethanol causes dose-related cancer in mice and rats at sites similar to those observed in humans (liver and oral cavity).^{6,7} As a result of this new evidence, the 2007 IARC evaluation concluded that there is sufficient evidence in experimental animals for the carcinogenicity of ethanol.^{3,5} Furthermore, substantial mechanistic evidence has become available in humans who are deficient in aldehyde dehydrogenase that acetaldehyde derived from the metabolism of ethanol in alcoholic beverages contributes to the causation of malignant oesophageal tumours. Acetaldehyde reacts

with DNA to form various DNA adducts, and elevated levels of acetaldehyde-derived DNA adducts have been detected in white blood cells of individuals who are heavy alcoholic beverage drinkers. Some of the DNA adducts that are increased after alcoholic beverage consumption are mutagenic in human cells. In addition, these adducts can undergo rearrangements in double-stranded DNA, which can result in the formation of DNA–protein cross-links and DNA interstrand cross-links, which are mechanistically consistent with the generation of chromosomal aberrations. Elevated levels of chromosomal aberrations have been observed in human cells in culture after exposure to acetaldehyde as well as *in vivo* in human alcoholics.³ This mechanistic evidence combined with the results in experimental animals and the epidemiological observation that all alcoholic beverages cause cancer demonstrate that ethanol is an important carcinogenic compound in alcoholic beverages. In their most recent evaluation, IARC has therefore classified both "ethanol in alcoholic beverages" as well as "acetaldehyde associated with alcohol consumption" into group 1 as "human carcinogens".⁴

Nevertheless, misinformation is still spread that ethanol is not a carcinogen at all or that alcohol-related cancer is exclusively caused by something else. For example, promotional material on an ethanol-containing mouthwash states that "ethanol is not a carcinogen; however, alcoholic beverages contain numerous carcinogenic compounds such as urethane, nitrosamines, polycyclic hydrocarbons and aflatoxins".⁸ While there is certainly ample evidence pointing to the fact that ethanol is the major carcinogenic compound in alcoholic beverages, the assumption about other carcinogens cannot be directly negated. Alcoholic beverages are multi compound mixtures and (similar to tobacco) may regularly contain various carcinogens such as those mentioned in the promotional material. The IARC also remarked that identification of ethanol as a known carcinogenic agent in alcoholic beverages does not rule out the possibility that other components may also contribute to their carcinogenicity.³ A summary of carcinogens typically occurring in

alcoholic beverages is provided in table 1. In fact some of these carcinogens in alcoholic beverages, and specifically ethyl carbamate (urethane), are seen by international bodies such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA) or the European Food Safety Authority (EFSA) as public health risk independent of ethanol.^{9,10} For this reason, the European Commission has advised the member states to monitor the ethyl carbamate contamination in certain alcoholic beverages.¹¹ Another example is *N*-nitrosodimethylamine (NDMA), which was first found in German beers in 1978,¹² when concentrations of up to 68 µg/L caused worldwide concern. A change in the target organ specificity of NDMA by co-administration of ethanol was observed: when NDMA was given in combination with ethanol, rats and mice developed tumours in the nasal cavity, which is not a target site for this nitrosamine. This suggests that ethanol may influence the initiation of carcinogenesis in some manner, but it is also possible that the process is enhanced due to some mechanistic events: the facilitation of entry into the target cell by ethanol, a change in intracellular metabolism or suppression of DNA repair. The hypothesis of competitive inhibition of hepatic metabolism of the carcinogen, which allows it to reach the target organs, has also been proposed.³ The questions about the risk posed by other substances other than ethanol is especially important for unrecorded (i.e. illicitly or home-produced) alcohol, which is assumed to potentially contain higher concentrations of contaminants, especially ethyl carbamate and acetaldehyde.^{13,14}

The literature currently offers no quantitative information if and how much other carcinogenic constituents or contaminants of alcoholic beverages compare with and contribute to the risk generated by ethanol. Such information is necessary especially to inform risk management to prioritize cancer prevention.

Several approaches were suggested in the past for quantitative risk assessment of carcinogens.¹⁵ From these, the so-called margin of exposure (MOE) approach is currently preferred by

118 international bodies such as WHO¹⁶ or EFSA¹⁷, for recent review see Benford et al.¹⁸. This study
119 will therefore apply the MOE approach to provide a comparative risk assessment of carcinogens
120 occurring in alcoholic beverages. The results will be used to point out options for alcohol policy.

121 **Methods**

122 The selection of carcinogens and their occurrence in alcoholic beverages was based on the most
123 recent detailed IARC review,³ for exceptions see remarks in results section. The assessment of
124 toxicological endpoints and benchmark doses (BMD) for the selected carcinogens was generally
125 based on literature data, as own dose-response modelling would have gone beyond the scope of
126 this study. Suitable risk assessment studies including endpoints and dose-response modelling
127 results were typically identified in monographs of national and international risk assessments
128 bodies such as WHO International Programme on Chemical Safety (IPCS), JECFA, US
129 Environmental Protection Agency (EPA) and EFSA. For substances without available
130 monographs or with missing data on dose-response modelling results, the scientific literature in
131 general was searched for such data. Searches were carried out in September 2011 in the following
132 databases: PubMed (U.S. National Library of Medicine, Bethesda, MD), Web of Science
133 (Thomson Reuters, Philadelphia, PA), Scopus (Elsevier B.V., Amsterdam, the Netherlands), and
134 Google Scholar (Google Inc., Mountain View, CA).

135 The BMD/MOE approach was used for risk assessment.^{17,19,20} Based on dose-response
136 modelling, the BMD is the point on the dose response curve, which characterizes adverse effects.
137 This value can then be used in combination with exposure data to calculate a MOE for
138 quantitative risk assessment. The MOE is defined as the ratio between the lower one-sided
139 confidence limit of the BMD (BMDL) and estimated human intake of the same compound. It can
140 be used to compare the health risk of different compounds and in turn prioritize risk management

actions. By definition, the lower the MOE, the larger the risk for humans; generally a value under 10,000 used to define public health risks.²¹

If BMDL values were unavailable in the literature, no observed effect level (NOEL) or no observed adverse effect level (NOAEL) values were identified as surrogate thresholds instead. The MOEs were then calculated by dividing the NO(A)EL by the estimated human intake.

For each beverage group (i.e. beer, wine, spirits and unrecorded alcohol), the human intakes were calculated for two different drinking scenarios (low risk drinking and heavy drinking) based on the drinking guidelines for Canada, which consider that 13.6 g pure alcohol constitute a standard drink.²² For both drinking scenarios, MOEs for average contamination as well as maximum contamination with the different carcinogens were additionally calculated to estimate a range for average and worst case contamination scenarios.

Results

Alcoholic beverages may contain more than 1,000 different components,² from which several are potentially carcinogenic. In the first step of the comparative risk assessment, a selection of compounds for further evaluation has to occur. The IARC Monographs Working Group Vol. 96³ compared the complete IARC list of carcinogens with the list of compounds regularly occurring in alcoholic beverages (appendix 1 in the IARC 1988 monograph²) and provided a summary of carcinogens that may be present in alcoholic beverages (see table 1.14, p. 113 in the IARC 2010 monograph³). From this summary, we have chosen the compounds set into IARC group 1 (carcinogenic to humans), IARC group 2A (probably carcinogenic to humans) and IARC group 2B (possibly carcinogenic to humans) to be included in our evaluation. Compounds set into IARC group 3 (not classifiable as to its carcinogenicity to humans) such as deoxynivalenol,

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3 163 nivalenol, organolead compounds and patulin were excluded from our evaluation. The remaining
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6 164 compounds in groups 1, 2A and 2B were acetaldehyde, acrylamide, aflatoxins, arsenic, benzene,
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8 165 cadmium, ethanol, ethyl carbamate, furan, lead, NDMA, and ochratoxin A (Table 1). Since the
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10 166 writing of the exposure section in the IARC Monograph Vol. 96 in 2007 (two of the authors of
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12 167 this article, DWL and JR, were members of this working group and contributed to the initial
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14 168 evaluation), additional evidence for some compounds has become available. For example, the
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16 169 regular occurrence of formaldehyde, an IARC group 1 carcinogen, in alcoholic beverages was
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18 170 detected.²³ Furthermore, 4-methylimidazole a contaminant of caramel colours with known use in
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20 171 certain alcoholic beverages,^{24,25} was newly evaluated by IARC in 2011 and set into group 2B.²⁶
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22 172 Safrole, another group 2B substance, may also potentially occur in alcoholic beverages.²⁷ Safrole
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24 173 is a flavour compound with a comparably high ranking in the Berkeley carcinogenic potency
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26 174 project due to its occurrence in spices.²⁸ Therefore, formaldehyde, 4-methylimidazole and safrole
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28 175 were added to our list (Table 1).
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33 176 The data on occurrence of the chosen compounds in alcoholic beverages are summarized in Table
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35 177 2. Data on recorded alcohol (i.e. commercial wine, beer and spirits) were predominantly based on
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37 178 the summaries in the IARC 2010 monograph³. In some instance, actualized data from
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39 179 international surveys (e.g. from EFSA) were available (see details in Table 2²⁹⁻³³). Less data on
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41 180 unrecorded alcohol is generally available.^{13,34} The data were therefore taken from an own survey
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43 181 recently conducted in the European Union.¹⁴
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48 182 In general, the contamination of alcoholic beverages with the selected compounds is subject to a
49
50 183 wide variation depending on product category, raw material, or diligence during manufacturing.
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52 184 The substances typically occur at ppb-levels or below, e.g. for aflatoxins, cadmium, or ochratoxin
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55 185 A. The exception are ethyl carbamate and formaldehyde, which may reach ppm-levels but only in
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57 186 certain products, while acetaldehyde typically occurs in ppm-levels in all product categories
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(besides vodka and neutral alcohol-based products), and may even exceed 1 g/L in certain highly contaminated products. No clear difference between commercial and unrecorded alcoholic beverages was detected with the exception of lead that may exceed 1 mg/L in highly contaminated unrecorded alcohol.

The toxicological endpoints used for dose-response modelling and the chosen points of departure for MOE assessment are shown in Table 3.^{6,10,21,35-62} According to international guidelines for risk assessment using the MOE approach,^{16-18,20} the most sensitive toxicological endpoint was chosen, when several endpoints were available. For some agents such as formaldehyde, benzene or lead, non-cancer endpoints were more sensitive than cancer endpoints or cancer endpoints were unavailable. To provide a conservative assessment, we decided to use these non-cancer endpoints in these cases. For a third of the compounds, human epidemiological data were available suitable for dose-response modelling. For the rest of the compounds, the assessments have to be based on animal data. The effective doses of the compounds as expressed by BMDL vary over a very wide range, from 0.00087 mg/kg bw/day for aflatoxin B₁ to 700 mg/kg bw/day for ethanol.

Table 4 shows the corresponding MOEs for several scenarios and alcoholic beverage groups. An average over all groups is provided in Figure 1. The lowest MOEs were calculated for ethanol, with 3.1 for low risk drinking and 0.8 for heavy drinking. Lead and arsenic have average MOEs between 10 and 300, followed by acetaldehyde, cadmium and ethyl carbamate between 1,000 and 10,000. Safrole, ochratoxin A, NDMA, 4-methylimidazole, furan, formaldehyde, aflatoxin B₁ and acrylamide have average MOEs above 10,000, even in the heavy drinking scenario.

Discussion

Our study provides the first comprehensive comparison of the risk related to compounds in alcoholic beverages. It is interesting to note that from all evaluated agents, ethanol exhibits the lowest potency in terms of BMDL in mg/kg bw/day required to produce an effect. Nevertheless, due to its very high exposure as a major constituent of alcoholic beverages, this situation is completely reversed in terms of MOE, where now ethanol has the highest potency, as all other substances occur at considerably lower concentrations in order to produce the same effect. The observation that the MOE of ethanol is already in an effective dose range for the low risk drinking guideline for females is absolutely in line with epidemiological observations. For breast cancer, as an example, the largest pooled study on breast cancer shows significant effects for lower than one drink daily.⁶³

Interestingly, a similar comparative risk assessment that was recently conducted for tobacco carcinogens⁶⁴ did not detect a single compound responsible for the carcinogenic effect as it was in our case for ethanol in alcoholic beverages. In tobacco, acrolein, formaldehyde, and cadmium all had MOEs down to below 10 and several other compounds had MOEs below 1000.⁶⁴

Our result for ethanol (MOE of 3.1 for one drink per day) is in excellent agreement with the result from the Berkeley Carcinogenic Potency Database (CPDB) project,²⁸ which reported a MOE of 3 for moderate daily drinking (based on ethanol exposure of 326 mg/kg/day). It is of note that the CPDB project uses different methodology to calculate MOE (based on adjusted TD₅₀ values from older animal experiments⁶⁵ and not BMDL₁₀ from the most recent NTP study as in our case²¹). As the results are almost the same, this independently validates our approach.

The CPDB project also reported data on NDMA in beer before 1979 (MOE of 1,000) and NDMA in beer 1994-1995 (MOE of 50,000), which is also in agreement with our MOE results and the

231 general observation that NDMA in beer is nowadays of negligible risk due to changes in
232 production technology.⁶⁶
233 A limitation of our study is the fact that the MOE estimations for several of the other compounds
234 are not as robust as those for ethanol. For ethanol, not only the BMDL₁₀ from animal experiments
235 is available but also human BMD modelling data for several endpoints including liver cirrhosis ²¹
236 as well as liver markers and blood pressure,^{67,68} all of which are in the same order of magnitude
237 confirming the validity and inter-species transferability of the animal data. As no BMDL for
238 cancer effect of ethanol was available in the literature, we used the animal BMDL for this study.
239 For several of the other compounds, no epidemiological data was available or it was inconclusive
240 (signified by classification into IARC groups 2A and 2B). Two major problems of such
241 assessments remain: extrapolating between species as well as extrapolating from high-doses in
242 animals to low-doses in humans.⁶⁹ Our approach would therefore rather overestimate the risks of
243 these agents compared to ethanol, for which these problems do not arise. A second limitation of
244 the study would also lead to overestimation of the risks of all compounds besides ethanol: the
245 limited database on occurrence data of these compounds in alcoholic beverages. For most of the
246 compounds large international surveys are missing, which would be necessary to provide more
247 robust exposure estimations. The exception of this is ethyl carbamate, for which large
248 international and EU-wide surveys have been conducted.^{9,10} Such data are especially lacking for
249 aflatoxins, cadmium, lead, and ochratoxin A. Several compounds also occur in only one category
250 of beverages (e.g., acrylamide and furan are only expected in beer, while 4-methylimidazole may
251 only occur in caramel-coloured products). In these cases, the absence of data can be explained by
252 the unlikelihood of occurrence, which explains that some groups of beverages were not studied at
253 all in the context of risk-oriented monitoring programs (see, e.g. Roth et al.⁷⁰). We also assume
254 that there is a publication bias favouring positive results.⁷¹ From own experience in our research

projects about unrecorded alcohol we know that it is much more problematic to publish survey results indicating no public health relevance rather than alarmist reports of methanol deaths, for example. From the typical lack of studies reporting absence of contamination in alcoholic beverages, along with own experience as alcohol control authority (that routinely tests for chemical contamination), we think that the occurrence data reported in table 2 are most likely biased towards higher levels. This observation even strengthens our argumentation that ethanol is the real risk factor in alcoholic beverages, as even with the available (most likely biased) occurrence data, the MOEs of all other compounds are considerably higher than the MOE of ethanol.

Conclusion

There are two main conclusions. First, the MOE approach is excellently suitable to provide comparative risk assessments for lifestyle factors that are mixtures of several toxic compounds such as alcoholic beverages. Second, ethanol was confirmed as by far the most important carcinogen in alcoholic beverages. This confirms deductions by other approaches (such as genetic epidemiology and mechanistic considerations, see introduction). This observation ultimately leads to the question if mitigation measures for the other carcinogens (e.g. as currently conducted for ethyl carbamate) are an adequate policy or if the money should not rather be spent on reducing alcohol consumption per se, for which several cost-effective measures are already available.⁷² The focus on alcohol policy would also not only reduce alcohol-related cancer but alcohol-related harm in general. The German Federal Institute for Risk Assessment, for example, holds the view in their assessment of acetaldehyde as contaminant of alcoholic beverages that mitigation measures are not required in this case, as alcoholic beverages are health damaging anyway.⁷³ On the one hand, we agree of course with this statement as alcoholic beverages per se

278 certainly pose inherent health risks. However, it also disregards the obligation of the regulating
279 agency to provide the safest possible environment. In modern societies we accept the fact that
280 citizens take risks, including risks, which are potentially lethal (e.g., by drinking alcohol or
281 exercising risky sports). However, within this risk taking the regulating agencies have to make
282 sure that the environment in which individual risk taking occurs is the safest possible (see
283 Refs.^{74,75} for further elaboration of these arguments). We would not argue to tolerate not closing a
284 ski slope with present danger of avalanche based on the reasoning that skiing is dangerous
285 anyway. In other words, reducing directly contained acetaldehyde in alcoholic beverages, which
286 is technically possible,^{35,76} should be targeted by regulating agencies, as it would reduce risk of
287 cancer independent of any individual risk decision. Our society cannot on the one hand tolerate
288 the use of alcoholic beverages and regulate them within food laws (as is the case in the European
289 Union) but then allow an exception regarding quality and safety. The individual drinker would
290 also most certainly select uncontaminated alcohol over contaminated alcohol.

291 In this context, it is noteworthy that for many of the mentioned contaminants, no maximum limits
292 are set by legislation that would allow adequate control and enforcement of quality standards.³⁴

293 At least for one of the compounds, ethyl carbamate, mitigative risk management approaches are
294 ongoing but only on a "recommendation" basis.¹¹ Inorganic compounds such as lead or arsenic
295 could be relevant for future research as was previously suggested in an analysis focused on
296 wine.⁷⁷ However, the problem of lead is not restricted to alcoholic beverages, which contribute
297 only about 7% to the total lead exposure from foods and beverages.⁵¹ As the MOEs for total lead
298 exposure may reach down to 1,⁵¹ risk management strategies outside of alcohol policy appear to
299 be necessary for this metal.

300 A final conclusion is the interesting observation that there is basically no substantial difference in
301 risk between unrecorded and recorded alcohol as it was sometimes differently purported by the

alcohol industry.⁷⁸ We also see no scientific basis for advertising claims that certain alcoholic beverages are more or less carcinogenic than others (e.g. red wine less than spirits).

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References

1. Lamy L. Étude de statistique clinique de 134 cas de cancer de l'œsophage et du cardia. *Arch Mal Appar Digest* 1910;**4**:451-75.

2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Alcohol Drinking. *IARC Monogr Eval Carcinog Risks Hum* 1988;**44**:1-416.

3. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Alcohol consumption and ethyl carbamate. *IARC Monogr Eval Carcinog Risks Hum* 2010;**96**:1-1428.

4. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Coglianò V. A review of human carcinogens - Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol* 2009;**10**:1033-4.

5. Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Altieri A, Coglianò V, WHO International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of alcoholic beverages. *Lancet Oncol* 2007;**8**:292-3.

6. Beland FA, Benson RW, Mellick PW, Kovatch RM, Roberts DW, Fang JL, Doerge DR. Effect of ethanol on the tumorigenicity of urethane (ethyl carbamate) in B6C3F1 mice. *Food Chem Toxicol* 2005;**43**:1-19.

7. Soffritti M, Belpoggi F, Cevolani D, Guarino M, Padovani M, Maltoni C. Results of long-term experimental studies on the carcinogenicity of methyl alcohol and ethyl alcohol in rats. *Ann N Y Acad Sci* 2002;**982**:46-69.

8. Johnson & Johnson. *Listerine - FAQs for Professionals*. URL:<http://www.listerine.com.sg/faqs-for-professionals.html>. Accessed: 2011-10-18. (Archived by WebCite® at <http://www.webcitation.org/62Wfznhct>): Johnson & Johnson Pte. Ltd., 2011.

9. EFSA. Ethyl carbamate and hydrocyanic acid in food and beverages. *EFSA J* 2007;**551**:1-44.

10. Vavasour E, Renwick AG, Engeli B, Barlow S, Castle L, DiNovi M, Slob W, Schlatter J, Bolger M. Ethyl carbamate. *WHO Food Additives Series 55. Safety evaluation of certain contaminants in food. Prepared by the sixty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)*. Geneva, Switzerland: WHO and FAO, 2006:205-316.

11. European Commission. Commission Recommendation of 2 March 2010 on the prevention and reduction of ethyl carbamate contamination in stone fruit spirits and stone fruit marc spirits and on the monitoring of ethyl carbamate levels in these beverages. *Off J Europ Union* 2010;**L52**:53-7.

12. Spiegelhalter B, Eisenbrand G, Preussmann R. Contamination of beer with trace quantities of *N*-nitrosodimethylamine. *Food Cosmet Toxicol* 1979;**17**:29-31.
13. Rehm J, Kanteres F, Lachenmeier DW. Unrecorded consumption, quality of alcohol and health consequences. *Drug Alcohol Rev* 2010;**29**:426-36.
14. Lachenmeier DW, Leitz J, Schoeberl K, Kuballa T, Straub I, Rehm J. Quality of illegally and informally produced alcohol in Europe: Results from the AMPHORA project. *Adicciones* 2011;**23**:133-40.
15. Barlow S, Renwick AG, Kleiner J, Bridges JW, Busk L, Dybing E, Edler L, Eisenbrand G, Fink-Gremmels J, Knaap A, Kroes R, Liem D, et al. Risk assessment of substances that are both genotoxic and carcinogenic. Report of an International Conference organized by EFSA and WHO with support of ILSI Europe. *Food Chem Toxicol* 2006;**44**:1636-50.
16. IPCS. *Environmental Health Criteria 240: Principles and Methods for the Risk Assessment of Chemicals in Food*. Geneva: World Health Organization, 2009.
17. EFSA. Opinion of the Scientific Committee on a request from EFSA related to a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic. *EFSA J* 2005;**282**:1-31.
18. Benford D, Bolger PM, Carthew P, Coulet M, DiNovi M, Leblanc JC, Renwick AG, Setzer W, Schlatter J, Smith B, Slob W, Williams G, et al. Application of the Margin of Exposure (MOE) approach to substances in food that are genotoxic and carcinogenic. *Food Chem Toxicol* 2010;**48**:S2-S24.
19. Crump KS. A new method for determining allowable daily intakes. *Fundam Appl Toxicol* 1984;**4**:854-71.
20. U.S.EPA. *The use of the benchmark dose approach in health risk assessment*. EPA/630/R-94/007. Washington, DC.: Office of Research and Development. US Environmental Protection Agency, 1995.
21. Lachenmeier DW, Kanteres F, Rehm J. Epidemiology-based risk assessment using the benchmark dose/margin of exposure approach: the example of ethanol and liver cirrhosis. *Int J Epidemiol* 2011;**40**:210-8.
22. CAMH. *Low-risk drinking guidelines [pamphlet]*. Toronto, Canada: Centre for Addiction and Mental Health, 2005.
23. Jendral JA, Monakhova YB, Lachenmeier DW. Formaldehyde in alcoholic beverages: large chemical survey using purpald screening followed by chromotropic acid spectrophotometry with multivariate curve resolution. *Int J Anal Chem* 2011;**2011**:Article ID 797604.
24. Klejdus B, Moravcová J, Lojková L, Vacek J, Kubán V. Solid phase extraction of 4(5)-methylimidazole (4MeI) and 2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)-imidazole (THI)

- from foods and beverages with subsequent liquid chromatographic electrospray mass spectrometric quantification. *J Sep Sci* 2006;**29**:378-84.
25. Yoshikawa S, Fujiwara M. Determination of 4(5)-methylimidazole in food by thin layer chromatography. *J Food Hyg Soc Jap* 1981;**22**:189-96.
26. Grosse Y, Baan R, Secretan-Laubay B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Islami F, Galichet L, Straif K. Carcinogenicity of chemicals in industrial and consumer products, food contaminants and flavourings, and water chlorination byproducts. *Lancet Oncol* 2011;**12**:328-9.
27. Curro P, Micali G, Lanuzza F. Determination of beta-asarone, safrole, isosafrole and anethole in alcoholic drinks by high-performance liquid chromatography. *J Chromatogr* 1987;**404**:273-8.
28. Gold LS, Ames BN, Slone TH. *How Many Fold Lower Is Human Exposure Than the Dose That Gave Rodents Cancer: Margin of Exposure, MOE (Rodent Cancer Dose/Human Exposure)*. Berkeley, CA. URL:<http://potency.berkeley.edu/MOEtable.html>. Accessed: 2009-08-11. (Archived by WebCite® at <http://www.webcitation.org/5ix20tFMx>): Carcinogenic Potency Project, University of California, Berkeley, 2008.
29. Mabry M, Mankotia M, Cavlovic P, Tam J, Wong L, Pantazopoulos P, Calway P, Scott PM. Survey of aflatoxins in beer sold in Canada. *Food Addit Contam* 2005;**22**:1252-7.
30. EFSA. Update on furan levels in food from monitoring years 2004-2010 and exposure assessment. *EFSA J* 2011;**9**:2347.
31. Donhauser S, Wagner D, Jacob F. Critical Trace-Elements in Brewing Technology. 2. Occurrence of Arsenic, Lead, Cadmium, Chromium, Mercury and Selenium in Beer. *Monatsschr Brauwissensch* 1987;**40**:328-33.
32. Andrey D, Beuggert H, Ceschi M, Corvi C, de Rossa M, Herrmann A, Klein B, Probst-Hensch N. Monitoring-Programm 'Schwermetalle in Lebensmitteln'. IV. Blei, Cadmium, Kupfer und Zink in Weinen auf dem Schweizer Markt. Teil B: Vorgehen, Resultate und Diskussion. [Monitoring programme for heavy metals in food. IV. Lead, cadmium, copper and zinc in wine on the Swiss market. Part B: methods, results and discussion.]. *Mitt Geb Lebensm Hyg* 1992;**83**:711-36.
33. Gutsche B, Weisshaar R, Buhlert J. Acrylamide in food - screening results from food control in Baden-Württemberg. *Deut Lebensm Rundsch* 2002;**98**:437-43.
34. Lachenmeier DW, Schoeberl K, Kanteres F, Kuballa T, Sohnius E-M, Rehm J. Is contaminated alcohol a health problem in the European Union? A review of existing and methodological outline for future studies. *Addiction* 2011;**106** (Suppl.1):20-30.
35. Lachenmeier DW, Kanteres F, Rehm J. Carcinogenicity of acetaldehyde in alcoholic beverages: Risk assessment outside ethanol metabolism. *Addiction* 2009;**104**:533-50.

36. Soffritti M, Belpoggi F, Lambertin L, Lauriola M, Padovani M, Maltoni C. Results of long-term experimental studies on the carcinogenicity of formaldehyde and acetaldehyde in rats. *Ann N Y Acad Sci* 2002;**982**:87-105.
37. Mueller U, Agudo A, Carrington C, Doerge D, Hellenäs KE, Leblanc JC, Rao M, Renwick A, Slob W, Wu Y. Acrylamide (Addendum). *WHO Food Additives Series 63. Safety evaluation of certain contaminants in food. Prepared by the seventy-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)*. Geneva, Switzerland: WHO and FAO, 2011:1-151.
38. NTP. NTP technical report on the toxicology and carcinogenesis. Studies of acrylamide (CAS No. 79-06-1) in F344/N rats and B6C3F1 mice (drinking water study). *Natl Toxicol Program Tech Rep Ser* 2011;**in press**.
39. EFSA. Opinion of the scientific panel on contaminants in the food chain on a request from the commission related to the potential increase of consumer health risk by a possible increase of the existing maximum levels for aflatoxins in almonds, hazelnuts and pistachios and derived products. *EFSA J* 2007;**446**:1-127.
40. Yeh FS, Yu MC, Mo CC, Luo S, Tong MJ, Henderson BE. Hepatitis B virus, aflatoxins, and hepatocellular carcinoma in southern Guangxi, China. *Cancer Res* 1989;**49**:2506-9.
41. Benford DJ, Alexander J, Baines J, Bellinger DC, Carrington C, Devesa i Pérez VA, uxbury J, Fawell J, Hailemariam K, Montoro R, Ng J, Slob W, et al. Arsenic (Addendum). *WHO Food Additives Series 63. Safety evaluation of certain contaminants in food. Prepared by the seventy-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)*. Geneva, Switzerland: WHO and FAO, 2011:153-316.
42. Chen CL, Chiou HY, Hsu LI, Hsueh YM, Wu MM, Chen CJ. Ingested arsenic, characteristics of well water consumption and risk of different histological types of lung cancer in northeastern Taiwan. *Environ Res* 2010;**110**:455-62.
43. U.S.EPA. *Benzene (CASRN 71-43-2). Integrated Risk Information System. Document 0276*. Washington, DC: U.S. Environmental Protection Agency, 2003.
44. Rothman N, Li GL, Dosemeci M, Bechtold WE, Marti GE, Wang YZ, Linet M, Xi LQ, Lu W, Smith MT, Titenko-Holland N, Zhang LP, et al. Hematotoxicity among Chinese workers heavily exposed to benzene. *Am J Ind Med* 1996;**29**:236-46.
45. U.S.EPA. *Cadmium (CASRN 7440-43-9). Integrated Risk Information System. Document 0141*. Washington, DC: U.S. Environmental Protection Agency, 1998.
46. NTP. NTP technical report on the toxicology and carcinogenesis. Studies of urethane, ethanol, and urethane/ethanol (urethane, CAS No. 51-79-6; ethanol, CAS No. 64-17-5) in B6C3F1 mice (drinking water studies). *Natl Toxicol Program Tech Rep Ser* 2004;**510**:1-346.

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55
56
57
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59
60

461 47. IPCS. *Formaldehyde. Concise international chemical assessment document 40*. Geneva:
462 World Health Organization, 2002.

463 48. Til HP, Woutersen RA, Feron VJ, Hollanders VH, Falke HE, Clary JJ. Two-year
464 drinking-water study of formaldehyde in rats. *Food Chem Toxicol* 1989;**27**:77-87.

465 49. Williams GM, Ariseto AP, Baines J, DiNovi M, Feeley M, Schlatter J, Slob W, Toledo
466 MCF, Vavasour E. Furan. *WHO Food Additives Series 63. Safety evaluation of certain*
467 *contaminants in food. Prepared by the seventy-second meeting of the Joint FAO/WHO*
468 *Expert Committee on Food Additives (JECFA)*. Geneva, Switzerland: WHO and FAO,
469 2011:487-603.

470 50. Moser GJ, Foley J, Burnett M, Goldsworthy TL, Maronpot R. Furan-induced dose-
471 response relationships for liver cytotoxicity, cell proliferation, and tumorigenicity (furan-
472 induced liver tumorigenicity). *Exp Toxicol Pathol* 2009;**61**:101-11.

473 51. EFSA. Scientific opinion on lead in food. *EFSA J* 2010;**8**:1570.

474 52. Navas-Acien A, Tellez-Plaza M, Guallar E, Muntner P, Silbergeld E, Jaar B, Weaver V.
475 Blood cadmium and lead and chronic kidney disease in US adults: a joint analysis. *Am J*
476 *Epidemiol* 2009;**170**:1156-64.

477 53. EFSA. Scientific opinion on the re-evaluation of caramel colours (E 150 a,b,c,d) as food
478 additives. *EFSA J* 2011;**9**:2004.

479 54. NTP. Toxicology and carcinogenesis studies of 4-methylimidazole (Cas No. 822-36-6) in
480 F344/N rats and B6C3F1 mice (feed studies). *Natl Toxicol Program Tech Rep Ser*
481 2007;**535**:1-274.

482 55. Zeilmaker MJ, Bakker MI, Schothorst R, Slob W. Risk assessment of N-
483 nitrosodimethylamine formed endogenously after fish-with-vegetable meals. *Toxicol Sci*
484 2010;**116**:323-35.

485 56. Peto R, Gray R, Brantom P, Grasso P. Dose and time relationships for tumor induction in
486 the liver and esophagus of 4080 inbred rats by chronic ingestion of N-nitrosodiethylamine
487 or N-nitrosodimethylamine. *Cancer Res* 1991;**51**:6452-69.

488 57. Peto R, Gray R, Brantom P, Grasso P. Effects on 4080 rats of chronic ingestion of N-
489 nitrosodiethylamine or N-nitrosodimethylamine: a detailed dose-response study. *Cancer*
490 *Res* 1991;**51**:6415-51.

491 58. Barlow S, Bolger M, Pitt JJ, Verger P. Ochratoxin A (addendum). *WHO Food Additives*
492 *Series 59. Safety evaluation of certain contaminants in food. Prepared by the sixty-eighth*
493 *meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)*. Geneva,
494 Switzerland: WHO and FAO, 2008:357-429.

495 59. NTP. *Toxicology and carcinogenesis studies of ochratoxin A (CAS No. 303-47-9)*
496 *in F344/N rats (gavage studies)*. *Natl Toxicol Program Tech Rep Ser* 1989;**358**:1-142.

- 497 60. Martati E, Boersma MG, Spenkeliink A, Khadka DB, Punt A, Vervoort J, van Bladeren
498 PJ, Rietjens IM. Physiologically based biokinetic (PBBK) model for safrole bioactivation
499 and detoxification in rats. *Chem Res Toxicol* 2011;**24**:818-34.
- 500 61. Boberg EW, Miller EC, Miller JA, Poland A, Liem A. Strong evidence from studies with
501 brachymorphic mice and pentachlorophenol that 1'-sulfoxysafrole is the major ultimate
502 electrophilic and carcinogenic metabolite of 1'-hydroxysafrole in mouse liver. *Cancer Res*
503 1983;**43**:5163-73.
- 504 62. Miller EC, Swanson AB, Phillips DH, Fletcher TL, Liem A, Miller JA. Structure-activity
505 studies of the carcinogenicities in the mouse and rat of some naturally occurring and
506 synthetic alkenylbenzene derivatives related to safrole and estragole. *Cancer Res*
507 1983;**43**:1124-34.
- 508 63. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW, Jr., Coates RJ, Liff
509 JM, Talamini R, Chantarakul N, Koetsawang S, Rachawat D, et al. Alcohol, tobacco and
510 breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies,
511 including 58,515 women with breast cancer and 95,067 women without the disease. *Br J*
512 *Cancer* 2002;**87**:1234-45.
- 513 64. Cunningham FH, Fiebelkorn S, Johnson M, Meredith C. A novel application of the
514 Margin of Exposure approach: Segregation of tobacco smoke toxicants. *Food Chem*
515 *Toxicol* 2011;**49**:2921-33.
- 516 65. Gold LS, Slone TH, Bernstein L. Summary of carcinogenic potency and positivity for 492
517 rodent carcinogens in the carcinogenic potency database. *Environ Health Perspect*
518 1989;**79**:259-72.
- 519 66. Lachenmeier DW, FÜgel D. Reduction of Nitrosamines in Beer - Review of a Success
520 Story. *Brewing Science* 2007;**60**:84-9.
- 521 67. Dakeishi M, Iwata T, Ishii N, Murata K. Effects of alcohol consumption on hepatocellular
522 injury in Japanese men. *Tohoku J Exp Med* 2004;**202**:31-9.
- 523 68. Dakeishi M, Murata K, Tamura A, Iwata T. Relation between benchmark dose and no-
524 observed-adverse-effect level in clinical research: effects of daily alcohol intake on blood
525 pressure in Japanese salesmen. *Risk Anal* 2006;**26**:115-23.
- 526 69. Gold LS, Slone TH, Manley NB, Ames BN. *Misconceptions about the causes of cancer*.
527 Vancouver, British Columbia, Canada: The Fraser Institute, 2002.
- 528 70. Roth M, Hartmann S, Renner R, Hörtig W. Sampling on a risk basis in the context of
529 official control in the German federal state Baden-Württemberg. *Deut Lebensm Rundsch*
530 2007;**103**:45-52.
- 531 71. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, Decullier E, Easterbrook
532 PJ, Von Elm E, Gamble C, Ghera D, Ioannidis JP, et al. Systematic review of the

1
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51
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53
54
55
56
57
58
59
60

533 empirical evidence of study publication bias and outcome reporting bias. *PLoS One*
534 2008;**3**:e3081.

535 72. Babor T, Caetano R, Casswell S, Edwards G, Giesbrecht N, Graham K, Grube J, Hill L,
536 Holder H, Homel R, Livingstone M, Österberg E, et al. *Alcohol: No ordinary commodity. Research and public policy. 2nd edition.* Oxford, UK: Oxford University Press, 2010.
537

538 73. BfR. *Gesundheitliche Bewertung von Acetaldehyd in alkoholischen Getränken. Aktualisierte Stellungnahme Nr. 022/2010 des BfR vom 04. Mai 2010.* Berlin:
539 Bundesinstitut für Risikobewertung, 2010.
540

541 74. Rehm J, Patra J. Different guidelines for different countries? On the scientific basis of
542 low-risk drinking guidelines and their implications. *Drug Alcohol Rev* 2011;**in press**,
543 DOI: 10.1111/j.1465-3362.2011.00395.x.

544 75. Room R, Rehm J. Clear criteria based on absolute risk: Reforming the basis of guidelines
545 on low-risk drinking. *Drug Alcohol Rev* 2011;**in press**, DOI: 10.1111/j.1465-
546 3362.2011.00398.x.

547 76. Lachenmeier DW, Sohnius E-M. The role of acetaldehyde outside ethanol metabolism in
548 the carcinogenicity of alcoholic beverages: Evidence from a large chemical survey. *Food*
549 *Chem Toxicol* 2008;**46**:2903-11.

550 77. Naughton DP, Petróczi A. Heavy metal ions in wines: meta-analysis of target hazard
551 quotients reveal health risks. *Chem Cent J* 2008;**2**:22.

552 78. Lachenmeier DW, Rehm J. Unrecorded alcohol: A threat to public health? *Addiction*
553 2009;**104**:875-7.
554
555

Table 1. Summary of WHO International Agency for Research on Cancer (IARC) evaluation of carcinogenicity of substances that may be present in alcoholic beverages (updated from IARC³)

Agent	IARC Monographs evaluation of Carcinogenicity			IARC Monographs (Volume Number)
	In animals	In humans	IARC group ^a	
Acetaldehyde associated with consumption of alcoholic beverages	Sufficient	Sufficient	1	36, Sup 7, 71, 100E
Acrylamide	Sufficient	Inadequate	2A	60
Aflatoxins	Sufficient	Sufficient	1	56, 82, 100F
Arsenic	Sufficient	Sufficient	1	23, Sup 7, 100C
Benzene	Sufficient	Sufficient	1	29, Sup 7, 100F
Cadmium	Sufficient	Sufficient	1	58, 100C
Ethanol in alcoholic beverages	Sufficient	Sufficient	1	44, 96, 100E
Ethyl carbamate (urethane)	Sufficient	Inadequate	2A	7, Sup 7, 96
Formaldehyde	Sufficient	Sufficient	1	88, 100F
Furan	Sufficient	Inadequate	2B	63
Lead compounds, inorganic	Sufficient	Limited	2A	87
4-Methylimidazole	Sufficient	Inadequate	2B	101
N-Nitrosodimethylamine	Sufficient	Inadequate	2A	17, Sup 7
Ochratoxin A	Sufficient	Inadequate	2B	56
Safrole	Sufficient	Inadequate	2B	10, Sup 7

^a Group 1: Carcinogenic to humans; Group 2A: Probably carcinogenic to humans; Group 2B: Possibly carcinogenic to humans (for definitions of groups, see monographs.iarc.fr).

Table 2. Occurrence of WHO International Agency for Research on Cancer (IARC) carcinogens in alcoholic beverages

Agent	Amount in alcoholic beverages (Average/Maximum) ^a	Amount in unrecorded alcohol (Average/Maximum) ^b
Acetaldehyde associated with consumption of alcoholic beverages	9/63 mg/l (beer); 34/211 mg/l (wine); 66/1159 mg/l (spirits) ⁷⁶	90/822 mg/l
Acrylamide	0-72 µg/kg (beer) ^c	(no data)
Aflatoxins	0.002/0.230 µg/L (beer) ²⁹	(not detectable in all samples)
Arsenic	0/102.4 µg/L (beer); 4/14.6 µg/L (wine); 13/27 µg/L (spirits)	(not detectable in all samples)
Benzene	10/20 µg/L in beer produced with contaminated CO ₂	(no data)
Cadmium	0.9/14.3 µg/L (beer); 1.0/30 µg/L (wine); 6/40 µg/L (spirits)	0/0.04 mg/L
Ethanol in alcoholic beverages	(2-80% vol)	(10-89% vol)
Ethyl carbamate (urethane)	0/33 µg/kg (beer); 5/180 µg/kg (wine); 93/6730 µg/kg (spirits); 744/22000 µg/kg (fruit spirits) ⁹	0.5/5.4 mg/L
Formaldehyde	0 mg/L (beer); 0.13/1.15 mg/L (wine); 0.50/14.37 mg/L (spirits) ²³	0.22/6.71 mg/L ²³
Furan	3.3/28 µg/kg (beer) ³⁰	(no data)
Lead compounds, inorganic	2/15 µg/L (beer) ³¹ ; 57/326 µg/L (wine) ³² ; 31/600 µg/L (spirits)	0.03/1.4 mg/L
4-Methylimidazole	Caramel colored products: 9/28 µg/L in dark beer ²⁴ ; 0/0.14 mg/L in whisky ²⁵	(no data)
N-Nitrosodimethylamine	0.1/1.3 µg/kg (beer)	(no data)
Ochratoxin A	0.05/1.5 µg/L (beer); 0.23/7.0 µg/L (wine)	(no data)
Safrole	0/6.6 mg/l (bitters/liqueurs/aperitifs) ²⁷	(no data)

^a If no other source is stated, the data are taken from the IARC literature review³ by calculating the average over all studies. Historical data (i.e. prior to implementation of mitigation measures) was not included.

^b If no other source is stated, the data are taken from an European sample of unrecorded alcohol¹⁴

^c Few surveys on acrylamide in alcoholic beverages are available. The majority of analyzed samples contained levels below the detection limit. The level of 72 µg/kg was reported in a single sample of wheat beer.³³

Table 3. Dose response modelling results of WHO International Agency for Research on Cancer (IARC) carcinogens occurring in alcoholic beverages

Agent	Toxicological Endpoint for Modelling ^a	Reference for Dose-Response Modelling Study	Reference for Original Data used for Modelling	BMDL ₁₀ ^b [mg/kg bw/day]
Acetaldehyde	Tumour-bearing animals in male rats	³⁵	³⁶	56
Acrylamide	Harderian gland tumours in mice	³⁷	³⁸	0.18
Aflatoxin B ₁	Liver cancer in humans	³⁹	⁴⁰	0.00087
Arsenic	Lung cancer in humans	⁴¹	⁴²	BMDL _{0.5} : 0.003
Benzene	Lymphocyte count in humans	⁴³	⁴⁴	1.2
Cadmium	Human studies involving chronic exposures	⁴⁵	⁴⁵	NOAEL: 0.01 ^c
Ethanol	Hepatocellular adenoma or carcinoma in rats	²¹	⁴⁶	700
Ethyl carbamate (urethane)	Alveolar and bronchiolar neoplasms in mice	⁴⁰	⁴⁶	0.3
Formaldehyde	Histological changes in the aerodigestive tract, including oral and gastrointestinal mucosa of rats	⁴⁷	⁴⁸	NOEL: 15 ^c
Furan	Hepatocellular adenomas and carcinomas in female mice	⁴⁹	⁵⁰	0.96
Lead	Cardiovascular effects in humans	⁵¹	⁵²	BMDL ₀₁ : 0.0015
4-Methylimidazole	Cancer of the lung in mice	⁵³	⁵⁴	NOAEL: 80 ^c
N-Nitrosodimethylamine	Total liver tumors	⁵⁵	^{56,57}	0.029
Ochratoxin A	Kidney adenoma and carcinoma in male rats	⁵⁸	⁵⁹	0.025
Safrole	Hepatic tumors in mice	⁶⁰	^{61,62}	3 ^d

^a Human data was preferred over animal data, if available. Non-cancer endpoints were chosen if dose-response modelling for cancer effects was unavailable (such as in the case of lead). The most sensitive endpoint was chosen if dose-response data for several organ sites were available.

^b BMDL_x: lower one-sided confidence limit of the benchmark dose (BMD) for a x% incidence of health effect.

^c No usable BMD-modelling for oral exposure was identified in the literature. The No Effect Level (NOEL) or No Observed Adverse Effect Level (NOAEL) are used in these cases instead.

^d A range of "approximately 3-29 mg/kg bw/day" was provided as BMDL₁₀ for safrole⁶⁰. As no further rationale was provided in the study, we chose the minimum of this range to provide a conservative assessment.

Table 4. Margin of Exposure (MOE) of WHO International Agency for Research on Cancer (IARC) carcinogens occurring in alcoholic beverages calculated for different drinking and contamination scenarios (MOE = BMDL or NO(A)EL / Exposure)

Agent	Type of alcohol	Scenario 1: One standard drink per day (low risk drinking guideline for females) ^a		Scenario 2: Heavy drinker (4 standard drinks per day, own categorization) ^a	
		MOE for average contamination	MOE for maximum contamination (Worst case)	MOE for average contamination	MOE for maximum contamination (Worst case)
Acetaldehyde ^b	Beer	1095	156	274	39
	Wine	696	112	174	28
	Spirits	1184	67	296	17
	Unrecorded	868	95	217	24
Acrylamide	Beer	∞ ^c	440	∞	110
Aflatoxin B ₁	Beer	76540	666	19135	166
Arsenic	Beer	∞	5	∞	1
	Wine	317	87	79	22
	Spirits	322	155	81	39
Benzene	Beer	21114	10557	5279	2639
Cadmium	Beer	1955	123	489	31
	Wine	4225	141	1056	35
	Spirits	2326	349	581	87
	Unrecorded	∞	349	∞	87
Ethanol	All	3.1	-	0.8	-
Ethyl carbamate (urethane)	Beer	∞	1600	∞	400
	Wine	25352	704	6338	176
	Spirits	4501	62	1125	16
	Fruit spirits	563	19	141	5
	Unrecorded	837	78	209	19
Formaldehyde	Beer	∞	∞	∞	∞
	Wine	48754	5511	12189	1378
	Spirits	41860	1457	10465	364
	Unrecorded	95137	3119	23784	780
Furan	Beer	51186	6033	12797	1508
Lead	Beer	132	17.6	33	4.4
	Wine	11	1.9	2.8	0.5
	Spirits	68	3.5	17	0.9
	Unrecorded	70	1.5	17	0.4
4-Methylimidazole	Caramel-coloured Beer	1564027	502723	391007	125681
	Caramel-coloured Whisky	∞	797342	∞	199336
N-Nitrosodimethylamine	Beer	51026	3925	12757	981
Ochratoxin A	Beer	87977	2933	21994	733
	Wine	45928	1509	11482	377
Safrole	Bitters/Liqueurs/Aperitifs	∞	634	∞	159

^b A standard drink in Canada is considered to have a total of 13.6 grams of alcohol²². To recalculate the amount of contaminants per L or per kg to standard drink, portions of 341 ml (beer), 142 ml (wine), 43 ml (spirits and unrecorded) were chosen²². As no density was given in any of the contamination studies, 1 kg was set to equal 1 L for recalculation to volume if necessary. The exposure was estimated for the different drinking scenarios based on the occurrence data in Table 2 and a body weight of 60 kg.

594 ^b Acetaldehyde directly contained in the beverages excluding metabolically formed acetaldehyde.
595 ^c The lemniscate symbol indicates that the MOE was not calculable as the exposure was zero (i.e.
596 below the detection limit of the applied analytical methodology)

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Figure 1. Margin of Exposure (MOE) for carcinogens occurring in alcoholic beverages for heavy drinking scenario (averages based on data from table 4; error bar indicates worst case contamination).