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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, colo-rectum 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

international bodies such as WHO[16] or EFSA[17], for recent review see Benford et al.[18]. This study will therefore apply the MOE approach to provide a comparative risk assessment of carcinogens occurring in alcoholic beverages. The results will be used to point out options for alcohol policy.

# Methods

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

The BMD/MOE approach was used for risk assessment.[17,19,20] Based on dose-response modelling, the BMD is the point on the dose response curve, which characterizes adverse effects. This value can then be used in combination with exposure data to calculate a MOE for quantitative risk assessment. The MOE is defined as the ratio between the lower one-sided confidence limit of the BMD (BMDL) and estimated human intake of the same compound. It can 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. 96[3] compared the complete IARC list of carcinogens with the list of compounds regularly occurring in alcoholic beverages (appendix 1 in the IARC 1988 monograph[2]) and provided a summary of carcinogens that may be present in alcoholic beverages (see table 1.14, p. 113 in the IARC 2010 monograph[3]). 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,

nivalenol, organolead compounds and patulin were excluded from our evaluation. The remaining compounds in groups 1, 2A and 2B were acetaldehyde, acrylamide, aflatoxins, arsenic, benzene, cadmium, ethanol, ethyl carbamate, furan, lead, NDMA, and ochratoxin A (Table 1). Since the writing of the exposure section in the IARC Monograph Vol. 96 in 2007 (two of the authors of this article, DWL and JR, were members of this working group and contributed to the initial evaluation), additional evidence for some compounds has become available. For example, the regular occurrence of formaldehyde, an IARC group 1 carcinogen, in alcoholic beverages was detected.[23] Furthermore, 4-methylimidazole a contaminant of caramel colours with known use in certain alcoholic beverages,[24,25] was newly evaluated by IARC in 2011 and set into group 2B.[26] Safrole, another group 2B substance, may also potentially occur in alcoholic beverages.[27] Safrole is a flavour compound with a comparably high ranking in the Berkeley carcinogenic potency project due to its occurrence in spices.[28] Therefore, formaldehyde, 4-methylimidazole and safrole were added to our list (Table 1).

The data on occurrence of the chosen compounds in alcoholic beverages are summarized in Table 2. Data on recorded alcohol (i.e. commercial wine, beer and spirits) were predominantly based on the summaries in the IARC 2010 monograph[3]. In some instance, actualized data from international surveys (e.g. from EFSA) were available (see details in Table 2[29-33]). Less data on unrecorded alcohol is generally available.[13,34] The data were therefore taken from an own survey recently conducted in the European Union.[14]

In general, the contamination of alcoholic beverages with the selected compounds is subject to a wide variation depending on product category, raw material, or diligence during manufacturing. The substances typically occur at ppb-levels or below, e.g. for aflatoxins, cadmium, or ochratoxin A. The exception are ethyl carbamate and formaldehyde, which may reach ppm-levels but only in certain products, while acetaldehyde typically occurs in ppm-levels in all product categories

(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 $B_1$ 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 carcinogens[64] 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 $TD_{50}$ values from older animal experiments[65] and not $BMDL_{10}$ from the most recent NTP study as in our case[21]). 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

general observation that NDMA in beer is nowadays of negligible risk due to changes in production technology.[66]

A limitation of our study is the fact that the MOE estimations for several of the other compounds are not as robust as those for ethanol. For ethanol, not only the $BMDL_{10}$ from animal experiments is available but also human BMD modelling data for several endpoints including liver cirrhosis [21] as well as liver markers and blood pressure,[67,68] all of which are in the same order of magnitude confirming the validity and inter-species transferability of the animal data. As no BMDL for cancer effect of ethanol was available in the literature, we used the animal BMDL for this study. For several of the other compounds, no epidemiological data was available or it was inconclusive (signified by classification into IARC groups 2A and 2B). Two major problems of such assessments remain: extrapolating between species as well as extrapolating from high-doses in animals to low-doses in humans.[69] Our approach would therefore rather overestimate the risks of these agents compared to ethanol, for which these problems do not arise. A second limitation of the study would also lead to overestimation of the risks of all compounds besides ethanol: the limited database on occurrence data of these compounds in alcoholic beverages. For most of the compounds large international surveys are missing, which would be necessary to provide more robust exposure estimations. The exception of this is ethyl carbamate, for which large international and EU-wide surveys have been conducted.[9,10] Such data are especially lacking for aflatoxins, cadmium, lead, and ochratoxin A. Several compounds also occur in only one category of beverages (e.g., acrylamide and furan are only expected in beer, while 4-methylimidazole may only occur in caramel-coloured products). In these cases, the absence of data can be explained by the unlikelihood of occurrence, which explains that some groups of beverages were not studied at all in the context of risk-oriented monitoring programs (see, e.g. Roth et al.[70]). We also assume 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

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

In this context, it is noteworthy that for many of the mentioned contaminants, no maximum limits are set by legislation that would allow adequate control and enforcement of quality standards.[34] At least for one of the compounds, ethyl carbamate, mitigative risk management approaches are ongoing but only on a "recommendation" basis.[11] Inorganic compounds such as lead or arsenic could be relevant for future research as was previously suggested in an analysis focused on wine.[77] However, the problem of lead is not restricted to alcoholic beverages, which contribute only about 7% to the total lead exposure from foods and beverages.[51] As the MOEs for total lead exposure may reach down to 1,[51] risk management strategies outside of alcohol policy appear to be necessary for this metal.

A final conclusion is the interesting observation that there is basically no substantial difference in 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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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 IARC[3])

| 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 review[3] 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 alcohol[14]

[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] | [6,46] | 700 |
| Ethyl carbamate (urethane) | Alveolar and bronchiolar neoplasms in mice | [10] | [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 $BMDL_{10}$ for safrole [60]. 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 alcohol [22]. 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 chosen [22]. 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.

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

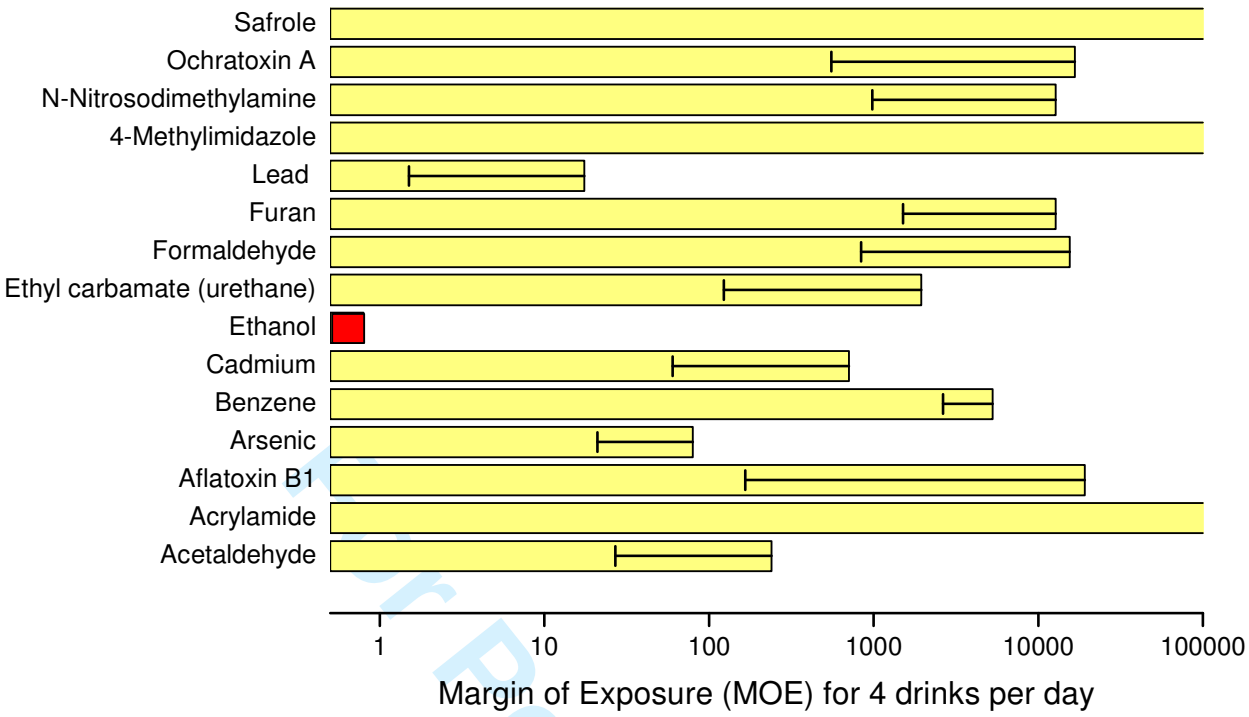


**Figure 1.** Margin of Exposure (MOE) for carcinogens occurring in alcoholic beverages for heavy drinking scenario (averages based on data from table 4; error bar indicates worst case contamination).