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REVIEW ARTICLE

Carcinogenic compounds in alcoholic beverages: an update

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Abstract The consumption of alcoholic beverages has been classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC) since 1988. More recently, in 2010, ethanol as the major constituent of alcoholic beverages and its metabolite acetaldehyde were also classified as carcinogenic to humans. Alcoholic beverages as multi-component mixtures may additionally contain further known or suspected human carcinogens as constituent or contaminant. This review will discuss the occurrence and toxicology of eighteen carcinogenic compounds (acetaldehyde, acrylamide, aflatoxins, arsenic, benzene, cadmium, ethanol, ethyl carbamate, formaldehyde, furan, glyphosate, lead, 3-MCPD, 4-methylimidazole, *N*-nitrosodimethylamine, pulegone, ochratoxin A, safrole) occurring in alcoholic beverages as identified based on monograph reviews by the IARC. For most of the compounds of alcoholic beverages, quantitative risk assessment provided evidence for only a very low risk (such as margins of exposure above 10,000). The highest risk was found for ethanol, which may reach exposures in ranges known to increase the cancer risk even at moderate drinking (margin of exposure around 1). Other constituents that could pose a risk to the drinker were inorganic lead, arsenic, acetaldehyde, cadmium and ethyl carbamate, for most of which mitigation by good manufacturing practices is possible. Nevertheless, due to the major effect of ethanol, the cancer burden due to alcohol consumption can only be reduced by reducing alcohol consumption in general or by lowering the alcoholic strength of beverages.

Keywords Alcoholic beverages · Risk assessment · Cancer risk · Ethanol · Acetaldehyde · Lead

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Introduction

The carcinogenicity of alcoholic beverages has been a "hot topic" for over a century. The earliest epidemiological observations were provided in 1910 in France, when 80 % of the patients diagnosed with oesophageal cancer were heavy drinkers of absinthe, a spirit with high alcoholic strength (Lamy 1910). The epidemiological evidence about a causality between the lifestyle choice of alcohol consumption and cancer of several sites (oral cavity, pharynx, larynx, oesophagus and liver) was corroborated in numerous studies during the twentieth century, which led the WHO International Agency for Research on Cancer (IARC) to classify "alcohol drinking" as carcinogenic to humans (group 1) in 1988 (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 1988).

While the epidemiology was convincing, the causative factors for the carcinogenicity of alcoholic beverages were still a matter of debate. This was aggravated because early animal experiments suffered from various limitations and were interpreted either that the studies "could not be used for an evaluation of carcinogenicity" (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 1988) or that "ethanol is not carcinogenic" (Seitz et al. 1982). Well-designed long-term experiments have later disproven this view and found both ethanol (Beland et al. 2005; Holmberg and Ekström 1995; NTP 2004; Soffritti et al. 2002a) and acetaldehyde as the first metabolite of ethanol as carcinogenic for animals (Soffritti et al. 2002b; Woutersen et al. 1986). Based on this evidence and further contributing evidence from genetic epidemiology, the IARC determined in their reassessment of alcoholic beverages that "ethanol in alcoholic beverages" is carcinogenic to humans (group 1, indicating sufficient evidence) (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010), and in a further reassessment "acetaldehyde associated with alcohol consumption" was also upgraded into group 1 (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012g). Colo-rectal cancer and female breast cancer were added to the list of cancer sites caused by alcohol consumption.

Still, there remains the fact that any alcoholic beverage is a multi-component mixture, which may contain one or several more carcinogenic compounds besides ethanol and acetaldehyde, so that the question arises if these compounds may have additional or synergistic effects on the carcinogenicity of the beverages. In a first comparative quantitative risk assessment, all compounds likely to occur in alcoholic beverages that were evaluated by IARC as group 1 (carcinogenic to humans), group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) were evaluated by the margin of exposure method (Lachenmeier et al. 2012). The research basically showed that only ethanol may reach margins of exposure in magnitudes that may explain the carcinogenic risk of alcoholic beverages detected in epidemiological studies. However, several other compounds such as lead or ethyl carbamate were also contained in levels above typical thresholds acceptable for carcinogens in foods and beverages. The IARC also noted that identification of ethanol as a known carcinogenic agent in alcoholic beverages does not exclude the possibility that other compounds may also contribute to the carcinogenicity of alcoholic beverages (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010).

Since this evaluation, IARC has evaluated several further carcinogens that were not included in the previous quantitative risk assessments of alcoholic beverages. This article therefore will update the evidence about the currently known or suspected carcinogens in alcoholic beverages. First and foremost, glyphosate was included in the assessment, which recently led to a large outcry of German media and consumer groups, when all major German beer brands were allegedly found to contain glyphosate. Besides glyphosate, 3-MCPD and pulegone were additionally included. The full list of compounds to be evaluated in this article is shown in Table 1. The review will first point out the toxicological evidence of each compound and summarise the occurrence and exposure due to alcohol consumption. The discussion will provide an updated comparative quantitative risk assessment and point out some conclusions for food control and policy.

Ethanol and acetaldehyde

As mentioned in introduction, ethanol and its first metabolite acetaldehyde were both evaluated by IARC as group 1 carcinogens and are the two compounds from all the carcinogens occurring in alcoholic beverages, for which the most comprehensive evidence on epidemiology and mechanisms of carcinogenesis is available. Based on this evidence, alcohol has been estimated to have caused 770 thousand new cancer occurrences in the year 2012 [5.5 % of all cancer occurrences: 3.5 % in women and 7.2 % in men (Praud et al. 2016)]. In the same year, 480 thousand people were estimated to have died of alcohol-attributable cancer [5.8 % of all cancer deaths: 3.3 % in women and 7.8 % in men (Praud et al. 2016)] (Fig. 1). The risk relations between alcohol consumption and the attributable cancer sites are monotonous: the more alcohol consumed, the higher the risk for cancer (Parry et al. 2011; Shield et al. 2013), with no lower threshold. In other words, even light or moderate drinking has been shown to cause cancer (Bagnardi et al. 2013).

For comprehensive reviews on the carcinogenicity of ethanol and acetaldehyde, see the recent IARC monographs (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010, 2012g) and Seitz and Stickel (2007).

There are several mechanisms discussed how ethanol and acetaldehyde may cause or contribute to carcinogenesis (Fig. 2). The major mechanism is believed to be due to the metabolism of ethanol by alcohol dehydrogenase (ADH) to acetaldehyde, which is carcinogenic and binds to DNA (Seitz and Stickel 2007). The most striking evidence about the causality of alcohol consumption and cancer has become available in humans who are deficient in aldehyde dehydrogenase, which leads to accumulation of the compound and an increased risk of developing malignant oesophageal tumours (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010).

Additionally, ethanol may also be metabolised by cytochrome P450 2E1 to acetaldehyde, a process which produces reactive oxygen species (ROS) that may lead to lipid peroxidation and mutagenic adducts. During

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 Working Group on the Evaluation of Carcinogenic Risks to Humans (2010) and Lachenmeier et al. (2012) with permission from John Wiley and Sons)

Agent[a]	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
Glyphosate	Sufficient	Limited	2A	112
Lead compounds, inorganic	Sufficient	Limited	2A	87
3-MCPD	Sufficient	No data	2B	101
4-Methylimidazole	Sufficient	Inadequate	2B	101
N-Nitrosodimethylamine	Sufficient	Inadequate	2A	17, Sup 7
Ochratoxin A	Sufficient	Inadequate	2B	56
Pulegone	Sufficient	Inadequate	2B	108
Safrole	Sufficient	Inadequate	2B	10, Sup 7

[a] The compounds were selected as follows: the complete IARC list of known and suspected human carcinogens was compared with the list of compounds regularly occurring in alcoholic beverages (see Table 1.14, p. 113 in IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010). From this summary, 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) were chosen to be included. Compounds set into IARC group 3 (not classifiable as to its carcinogenicity to humans) such as deoxynivalenol, nivalenol, organolead compounds and patulin were excluded. The list was updated to reflect the most recent IARC evaluations available in May 2016

cancer promotion, ethanol and acetaldehyde may also lead to DNA hypomethylation, which changes the expression of oncogenes and tumour-suppression genes. Mechanisms with less evidence include decreases in levels of retinoic acid, increases in oestrogen levels and induction of gastroesophageal reflux disease (GERD) resulting in hyperproliferation of the oesophageal mucosa (Seitz and Stickel 2007). Finally, ethanol may act as a solvent for various carcinogens or pro-carcinogens found in alcoholic beverages or other co-ingested products such as tobacco, which facilitates the entering of these compounds into the cells, especially into the mucosa of the upper aerodigestive tract (Seitz and Stickel 2007) (for further details on ethanol as penetration enhancer, see review in Lachenmeier 2008).

Regarding exposure, excellent data are available for alcohol itself. For example, the WHO Global Information System on Alcohol and Health (WHO 2016) lists data on alcohol per capita consumption including data on consumption per type of beverage and patterns of drinking. In 2010, the worldwide total consumption was equal to 6.2 l of pure alcohol per person 15 years and older.

Regarding acetaldehyde, it is interesting to note that the compound may not only be formed as metabolite of ethanol following ingestion, but is also directly contained in alcoholic beverages to an extremely varying degree depending on beverage type. On average, acetaldehyde is lowest in beer (9 mg/l) and wine (34 mg/l). Higher levels may be found in certain spirits (66 mg/l) but especially in fortified wines (118 mg/l) (Lachenmeier and Sohnius 2008). The average exposure of the European population to acetaldehyde directly contained in beverages was estimated to be 0.1 mg/kg bodyweight/day. However, cumulative risk assessment has shown that the risk of ethanol and metabolically formed acetaldehyde would considerably outweigh the risk of acetaldehyde directly contained in the beverages (Lachenmeier et al. 2015).

Acrylamide

Acrylamide is classified as probably carcinogenic to humans (group 2A). This classification relates to the last review of the subject in 1994 (IARC Working Group on

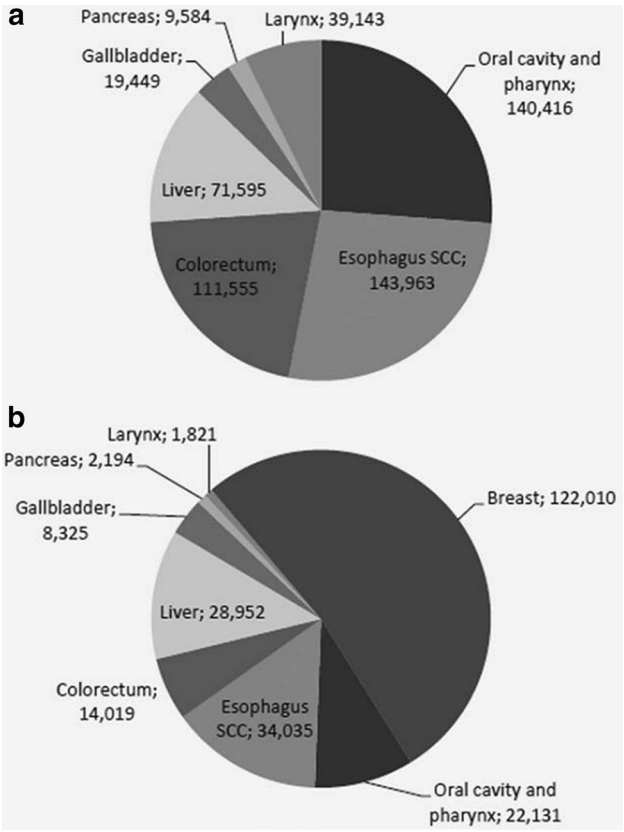

Fig. 1 Distribution of the number of cancer cases attributable to alcohol in men (**a**) and women (**b**) by cancer site, worldwide, 2012. Reprinted with permission from John Wiley and Sons from Praud et al. (2016)

the Evaluation of Carcinogenic Risks to Humans 1994). In the National Toxicology Program Report on Carcinogens, acrylamide is classified as "reasonably anticipated to be a human carcinogen" (NTP 2014a). Although there is no evidence that acrylamide causes cancer in humans, the risks for selected cancers were slightly elevated in a few instances (Marsh et al. 2007).

The carcinogenic character of acrylamide can be explained by the fact that glycidamide is a metabolite of acrylamide in the human body (Boettcher et al. 2005). Glycidamide as reactive electrophile can bind to the DNA by forming adducts which are inefficiently repairable and lead, therefore, to errors in the DNA sequence. In a study of glycidamide, it was shown that this metabolite is carcinogenic to mice (NTP 2014b).

In an investigation of 201 samples of rice wine, maximum amounts of 22 µg/kg of acrylamide were found (Mo et al. 2014). However, the highest levels of acrylamide were found in beer. The formation of acrylamide is strongly associated with the Maillard reactions that occur at two main stages during the malting (roasting) and brewing process. Nevertheless, there are only few reports on acrylamide contents in beer and rice wine. Tareke et al. (2002) analysed three beer samples from the Swedish market, which all had acrylamide concentrations below the detection limit of 5 µg/kg. In the sample set of 11 German beers analysed by Gutsche et al. (2002), only one wheat beer had a detectable acrylamide concentration of 72 µg/kg. The report of Dupire (Dupire 2003) shows that acrylamide in beer is in much lower concentrations than in other foods. Dupire (2003) also determined that there is an association between the concentration of acrylamide and beer colour. The highest amounts of acrylamide were found in beers of intermediate colour. Since there was no acrylamide detected in very dark roasted barley or malts, it seems that acrylamide may be degraded or lost at higher roasting temperatures.

Aflatoxins

Aflatoxins are mycotoxins primarily produced by two species of mould, *Aspergillus flavus* and *Aspergillus parasiticus*. They mainly occur in maize and peanuts, but they can also be present in other types of nuts and cereals. Aflatoxins B1, B2, G1, G2 and M1 are the most common aflatoxins. *A. flavus* produces only B aflatoxins, whereas *A. parasiticus* produces both B and G aflatoxins. Aflatoxin M1 is a metabolite of aflatoxin B1 and can be present in milk and milk products from animals fed with aflatoxin-containing feed (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012c). Naturally occurring aflatoxins are carcinogenic to humans (group 1) and can cause liver cancer in humans (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012c). Different studies have independently found statistically significant effects of exposure to aflatoxins on the development of hepatocellular carcinoma (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012c). There is strong evidence that the carcinogenetic of aflatoxins is based on a mechanism that includes metabolic activation to a genotoxic epoxide metabolite, formation of DNA adducts and modification of the TP53 gene, whereby aflatoxin B1 is considered the most harmful of the aflatoxins (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012c). Moreover, a synergistic interaction between hepatitis B virus and aflatoxin exposure was found (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012c).

Aflatoxins can find their way into beer due to the use of contaminated grain. They have been found as natural contaminants in barley, maize and sorghum malts (Odhav and Naicker 2002; Scott 1996). Nakajima et al. (1999) conducted a survey of aflatoxins in beers from all over the world. In 13 out of 116 beer samples, aflatoxins were detected (concentrations 0.0005–0.0831 µg/L). They were found in beer samples from warm countries such as

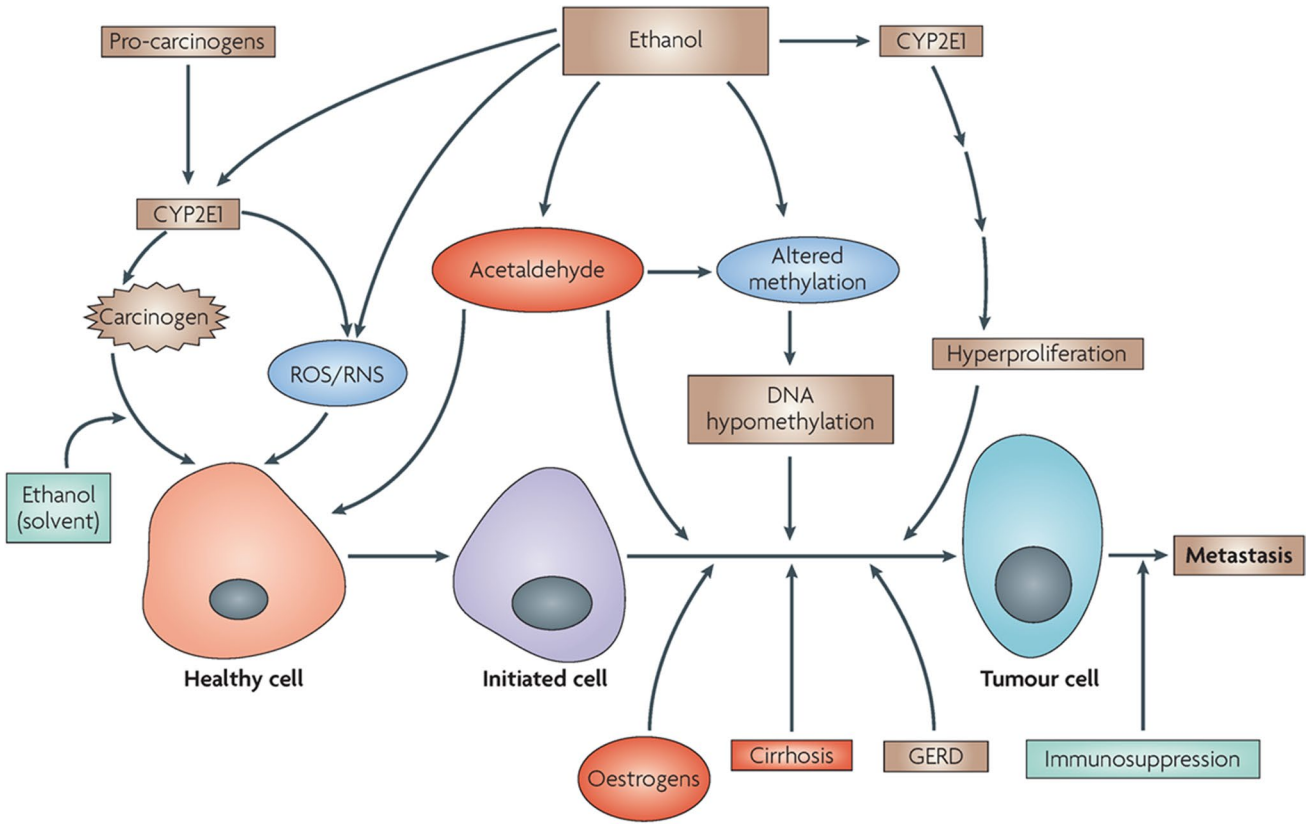

Fig. 2 A simplified scheme of the mechanisms by which alcohol may affect carcinogenesis. Mechanisms with strong evidence are shown in *red*, with moderate evidence in *blue* and with weak evidence in *green*. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Cancer (Seitz and Stickel 2007), copyright 2007

Mexico, Bolivia, Brazil, Peru, Kenya, India and the Philippines, where the occurrence of a contamination with aflatoxins might be expected due to the warm climate. Mably et al. (2005) confirmed in a large worldwide survey that beers from warmer countries such as Mexico and India contain a higher median concentration of aflatoxin B1. The highest incidence and concentrations (up to 0.23 µg/L) of aflatoxin B1 were detected in beer from India.

Arsenic

The IARC classifies the semimetal arsenic and inorganic arsenic compounds in group 1 as known human carcinogens. Inorganic arsenic compounds can cause cancer of the lung, skin and urinary bladder. Moreover, a positive association has been observed between exposure to arsenic and inorganic arsenic compounds and cancer of the liver, kidney and prostate (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012d). Long-term, low-dose exposure to inorganic arsenic compounds is likely to cause increased mutagenesis as a secondary effect of genomic instability. The underlying mechanisms observed at low concentrations include the rapid induction of oxidative DNA damage and DNA repair inhibition, as well as slower changes in DNA methylation patterns, aneuploidy and gene amplification, which lead to altered gene expression and genomic instability (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012d).

Arsenic is ubiquitous in the environment. As a result of volcanic activity and industrial activities, arsenic is emitted to the environment and can be detected in water, air and living organisms. In the agricultural industry, for example, arsenic has historically been used in a wide range of applications, including herbicides and insecticides (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012d). For the general population, the primary route of exposure to arsenic is via the ingestion of contaminated water and food (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012d). Low levels of arsenic have been found in most foodstuffs (typical concentrations are less than 0.25 mg/kg). Arsenic has also been detected in beer (0–102.4 µg/L), spirits (0–27 µg/L) and wine (0–14.6 µg/L) (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010). The mean arsenic content of red wines was found to be significantly

lower than that of rosé and white wines (Barbaste et al. 2003). These differences can be due to the different methods of vinification (Aguilar et al. 1987).

Benzene

Benzene is classified as carcinogenic to humans (group 1) and can cause various types of leukaemia (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012e). There is strong evidence that multiple genotoxic effects at the level of the pluripotent haematopoietic stem cell are induced by benzene metabolites. These effects lead to chromosomal changes in humans consistent with those observed in haematopoietic cancer (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012e).

Benzene has become an environmental contaminant due to industrial sources, fuel evaporation from gasoline filling stations and car exhaust fumes (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012e). The general population is mainly exposed to benzene via the ambient air; however, benzene may also be present in drinking water and food (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012e). Comparably high concentrations of benzene can occur in alcohol-free beverages containing benzoic acid, in heat-treated carrot products (especially in carrot juices intended for infants) and in cherry-flavoured beverages. In these product groups, benzene may be formed from precursors as benzoic acid (used as a preservative) and benzaldehyde (typically contained in cherry flavours) in the presence of ascorbic acid, or in the case of heat-treated carrot products from precursors as beta-carotene, phenylalanine or flavour compounds (Gardner and Lawrence 1993; Hileman 2006; Lachenmeier et al. 2008, 2010a; Loch et al. 2016; Steinbrenner et al. 2010). Furthermore, benzene may be present in soft drinks and beer due to the carbonation with contaminated industrial carbon dioxide (Long 1999; Wu et al. 2006). However, the average level of benzene found in beers carbonated with contaminated carbon dioxide was below 10 µg/L and samples did not exceed 20 µg/L, as the carbonation levels of beer are relatively low and a large part of the carbon dioxide is produced during the fermentation process (Long 1999). Wu et al. (2006) analysed 77 beers from China and 7 beers from other countries for benzene. Detectable amounts of benzene were only found in 6 Chinese beers (1.9–7.1 µg/L, mean of 4.0 µg/L). Moreover, contamination with benzene might occur in mixtures of alcoholic beverages and soft drinks. Lachenmeier et al. (2008) found low concentrations of benzene in alcopops (in 11 out of 12 samples, maximum of 0.44 µg/L) and beer-mixed drinks (in 2 out of 13 samples, maximum of 0.09 µg/L).

Cadmium

Based on "sufficient evidence" for carcinogenicity to humans, cadmium and cadmium compounds are classified into group 1 (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012f). The evaluation of IARC is a result of the fact that cadmium and its compounds cause lung cancer and its observed association between exposure and kidney and prostate cancer.

A scientific report of EFSA (EFSA 2012a) showed an overview of cadmium levels in different food categories. In the category of alcoholic beverages, the middle bound mean (MB) occurrence results varied between 0.5 µg/kg for fortified and liqueur wines and 6.0 µg/kg for liqueur. Wines including white and red varieties showed an MB of 1.2 µg/kg, and beer and similar products had an MB of 1.8 µg/kg. These mean contents of cadmium in red and white wines are similar to those already published by Kim (2004); here, values ranged from <0.1 to 3 µg/L, which were in accordance with those reported previously. Also, there was no significant difference in cadmium contents of wines with different state of origin (Kim 2004). Differences in the mean cadmium content among the types of wine were reported by Barbaste et al. (2003) with the lowest content for red and the highest mean content for white wines. These differences may be attributed to the wine-making process as well as a result from both natural and exogenous factors. Natural factors include grape variety and soil composition. Exogenous factors are, for instance, the wine-making system, the fermentation process, processing aids (filter materials) or diverse types of contamination (Kim 2004). High concentration of cadmium found in the 1990s in wine samples reported by Mena et al. (1996) and Illuminati et al. (2014) could be due to the use of contaminated pesticides or fertilisers with this metal.

Beer samples analysed by Mena et al. (1996) showed a mean concentration of 0.21 µg/L cadmium. The highest levels were found in canned beers, with values that varied from 0.50 to 0.80 µg/L probably due to the fact that low-quality cans had been used, and lower concentrations with a mean value of 0.20 µg/L were found in draft beers.

The highest concentration of cadmium in other alcoholic beverages was found in brandy (5.31 µg/L) and whisky (3.20 µg/L) (Mena et al. 1996).

Ethyl carbamate (urethane)

Ethyl carbamate is classified as probably carcinogenic to humans (group 2A) (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010). Although ethyl carbamate has been detected in many types of fermented foods, the highest amounts are found in alcoholic beverages. While the levels in wine and beer are in the

microgram per litre range (Dennis et al. 1997; Uthurry et al. 2004), the highest levels have been found in spirits, especially stone-fruit spirits, with concentrations up to milligrams per litre (Lachenmeier et al. 2005; Vahl 1993).

In the metabolic pathway, ethyl carbamate is oxidised to the electrophilic vinyl carbamate epoxide, which reacts with the DNA and therefore has strong mutagenic and carcinogenic properties (Barbin 2000; Guengerich and Kim 1991; Park et al. 1993).

In the past 20 years, major research has been carried out to identify the precursors of ethyl carbamate formation and develop methods for its reduction. Urea is one of the most established precursors of ethyl carbamate, which may be formed during the degradation of arginine by yeast. After hydrolyses of L-arginine to L-ornithine and urea by arginase (Schehl et al. 2007), urea reacts with ethanol to form ethyl carbamate (An and Ough 1993; Kitamoto et al. 1991; Ough et al. 1988). The addition of urease has been shown to reduce the amount of ethyl carbamate in fermented products, such as wine (Kim et al. 1995; Kobashi et al. 1988; Kodama and Yotsuzuka 1996; Ough and Trioli 1988; Tegmo-Larsson and Henick-Kling 1990). Another possible precursor for ethyl carbamate is cyanide. This may also explain the fact that ethyl carbamate is found in its highest amounts in stone-fruit spirits and cachaça (Lachenmeier et al. 2010b). In these plants, cyanide is released by enzymatic reaction from cyanogenic glycosides (Lachenmeier et al. 2005). After oxidation to cyanate, it reacts with ethanol to form ethyl carbamate (Aresta et al. 2001; Battaglia et al. 1990; MacKenzie et al. 1990; Taki et al. 1992; Wucherpfennig et al. 1987). Because of the fact that the concentration of ethyl carbamate varies over a broad range in stone-fruit spirits, a light- and time-dependent formation after distillation and storage can be assumed (Andrey 1987; Baumann and Zimmerli 1988; Lachenmeier et al. 2005; Mildau et al. 1987; Schehl et al. 2005; Suzuki et al. 2001; Zimmerli and Schlatter 1991).

For the reason that ethyl carbamate is seen as public health risk by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) or the European Food Safety Authority (EFSA) (EFSA 2007a; Vavasour et al. 2006), the European Commission has advised the member states to monitor the ethyl carbamate contamination in certain alcoholic beverages (European Commission 2010).

Formaldehyde

Formaldehyde is classified by IARC as carcinogenic to humans (group 1) (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2006a). In 2012, IARC evaluated formaldehyde as a causative agent of leukaemia as well as nasopharyngeal cancer in humans (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012h). The US EPA stated a reference dose for chronic oral exposure (RfD) of 0.2 mg/kg bodyweight/day (US EPA 1998a, b). The WHO IPCS (IPCS 2002) defined a tolerable concentration (TC) of 2.6 mg/L in ingested products based on animal experiments (Til et al. 1988). Feron et al. (1991) estimated that the formaldehyde intake by food may range between 1.5 and 14 mg/person/day, which could, therefore, exceed the RfD in a worst-case scenario. Formaldehyde is a natural ingredient of a variety of fruits, vegetables, meat, milk products and fish. Relatively high concentrations of formaldehyde were found in alcoholic beverages (Monakhova et al. 2012). In an earlier survey of about 500 products of wine, beer, spirits and unrecorded alcohol, it was shown that only 1.8 % of the samples had formaldehyde levels above the WHO IPCS tolerable concentration. A 60-kg person would need to consume 0.8 L of alcohol at 14.37 mg/L daily to exceed the US EPA RfD of 0.2 mg/kg bodyweight/day, which is extremely unlikely even in this worst-case scenario (Jendral et al. 2011). Monakhova et al. (2012) estimated the human dietary intake of formaldehyde via alcoholic beverages in the European Union based on WHO alcohol consumption data and the literature on formaldehyde contents of beer, wine, spirits and unrecorded alcohol. The estimated human exposure to formaldehyde from alcoholic beverages averages 8×10^{-5} mg/kg bodyweight/day, which was suggested as being below the threshold for public health concern (Monakhova et al. 2012).

Furan

Furan, a very volatile and colourless liquid, has been classified by the IARC as possibly carcinogenic to humans (group 2B) (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 1995). According to the IARC, there are no data on carcinogenic effects relating to humans available.

Furan with its low polarity can pass easily through membranes and is mainly enriched in the liver and is metabolised to different species (Burka et al. 1991). Burka et al. (1991) also determined that these metabolites, including furan itself, were not binding to DNA, but can react with protein. In further studies, it was found out that furan is metabolised by cytochrome P-450 to the dialdehyde, *cis*-2-butene-1,4-dial, which can interact directly with DNA (Chen et al. 1995; Peterson et al. 2005).

In a study of surveys conducted between 2004 and 2010 (EFSA 2011b), furan was found in 102 beer samples with concentrations up to 28 µg/kg. In 20 wine and liqueur samples, furan concentrations up to 6.5 and 28 µg/kg were found. In view of low levels of furan in beer, compared to maximum concentrations of 360 µg/kg in brewed coffee, it seems that most of furan from raw materials is lost during

the long brewing process due to its high volatility. Baxter et al. (2005) observed that furan in beer could, despite its relatively low concentrations, still make a significant contribution to dietary exposure because of the high volume of its consumption. The same is true for the consumption of wine, albeit to a lesser extent.

Glyphosate

Glyphosate is a broad-spectrum herbicide, which is the most heavily used herbicide in the world. Exposure of the general population may occur mainly through the diet (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2015a). Glyphosate was only recently evaluated in 2015 by IARC and included into group 2A as "probably carcinogenic to humans". The evaluation was based on limited evidence in humans about a positive association for non-Hodgkin lymphoma, and sufficient evidence for the carcinogenicity of glyphosate in experimental animals (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2015a). The IARC evaluation of glyphosate as carcinogenic was controversially discussed by industry and other regulatory agencies (see, for example, Portier et al. 2016).

There are no systematic data available about the occurrence and exposure of consumers with glyphosate due to alcoholic beverage consumption. According to the German Federal Institute for Risk Assessment (BfR 2016), residues of glyphosate in beer are plausible and can be expected, because glyphosate is an authorised herbicide for use on cereals. Nagatomi et al. (2013) analysed 15 commercial canned beers from Japan. Glyphosate was not quantifiable in any of the samples (limit of quantification 10 µg/L) but found in traces in four of the samples.

The BfR reported about non-peer reviewed data from the media that suggested glyphosate levels in German beer of up to 30 µg/L. However, consumption of 1000 L of beer per day would be necessary to exceed the acceptable daily intakes even when the media claims could be confirmed (BfR 2016).

Lead

Inorganic lead and lead compounds are in general considered to be "probably carcinogenic" (group 2A) (IARC 1987), whereas organic lead compounds "are not classifiable as to their carcinogenicity to humans" (group 3) (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2006b). The potential risk is due to the long half life in the human body and its chronic toxicity. In particular, the central nervous system, the kidney and various biosynthetic pathways are affected (EFSA 2012b). An EFSA report showed an overview of lead dietary exposure from different food categories. In the wine category, the mean middle bound (MB) occurrence for red wine was 22 µg/kg and for white wine 29 µg/kg. Beer and beer-like beverages had a mean MB occurrence of 12 µg/kg (EFSA 2012b).

The mean values of lead reported by Kim (2004) in red and white wines (29 µg/L) are in good agreement with the EFSA report, and there was no significant difference in lead content between red and white wines (Kim 2004). Tahvonen (1998) found means of 33 µg/L in white wines and 34 µg/L in red wines. Significant differences between red (65.7 µg/L), rosé (49.5 µg/L) and white (38 µg/L) wines were determined by Andrey et al. (1992). The main sources of lead contamination in wine are attributed to winery equipment (Kaufmann 1998; Rosman et al. 1998), lead capsules and atmospheric pollution (Lobinski et al. 1994; Médina et al. 2000; Teissedre et al. 1994). Also pesticide treatment raised the levels of lead significantly (Salvo et al. 2003). The Codex alimentarius recommends a maximum level of 0.20 mg/kg lead in wine (Codex alimentarius 2003); the International Organisation of Vine and Wine (OIV) has even a lower standard with 150 µg/L (for overview of regulations, see Lachenmeier et al. (2011b)). Comparing the results reported in previous studies (Sherlock et al. 1986) with more recent ones (Illuminati et al. 2014; Kim 2004) displays a decrease in lead contamination over the last few decades. Eschnauer and Ostapczuk (1992), Kaufmann (1998) Médina et al. (2000) and Illuminati et al. (2014) detected a reduction in the content of lead in wines of various vintages between different periods of time. The average wine in vintage 1990 contained 55 µg/L lead, while the concentration in vintage 1980 was 109 µg/L (Kaufmann 1998). Illuminati et al. (2014) reported a decrease in lead around 74 % from 1995 to 2010. This reported reduction is a result of change in production practice and winery equipment, like the replacement of lead–tin foil bottle capsules with aluminium or other material capsules. Winery apparatuses made of brass and alloys, which were widely used in traditional wine cellars (Kaufmann 1998), are now substituted with stainless steel products (Illuminati et al. 2014). Also the atmospheric deposition, due to leaded gasoline, before being banned in the 1990s, was a considerable source of lead in wines (Médina et al. 2000; Teissedre et al. 1994). Nowadays, the contribution of lead emission is much smaller than in the past (Kim 2004). Nevertheless, wines produced at present are not free of lead; therefore, it is important to know all the sources of this metal to enable their removal or minimisation (Kim 2004).

Low lead content in beer is shown in earlier studies of Tahvonen (1998) or Donhauser et al. (1987), which reported a mean content of 1.6 µg/L in 100 beer samples. With the exception of some beers which had higher lead values of up to 15 µg/L most likely due to damage of the tinplate cans, tin coating of welded and also old equipment

may be also a source of lead in beer samples (Smart et al. 1990). The MB occurrence of lead reported by the EFSA (2012b) is higher than the previous reported contents (Donhauser et al. 1987; Tahvonen 1998) but still less compared to wine. Nevertheless, beer and beer-like beverages are rated as high lead contributors due to their large consumption quantities (EFSA 2012b).

3-Monochloro-1,2-propanediol (3-MCPD)

3-Monochloropropane-1,2-diol (3-MCPD) is a so-called food-borne contaminant, which may be formed due to thermal processing in a number of food ingredients including malt used for brewing (Wenzl et al. 2007). 3-MCPD exhibits nephrotoxicity and may cause renal tubule carcinoma and adenoma in experimental animals. The mechanistic data for carcinogenicity are weak. Earlier authors suggested that 3-MCPD is genotoxic in vitro, but that there is no evidence of its genotoxicity in vivo (Lynch et al. 1998). However, IARC (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012a) was unable to exclude a genotoxic mechanism based on the sparsity of available data, especially because the target tissues of 3-MCPD were not tested in vivo. 3-MCPD was evaluated as possibly carcinogenic to humans (group 2B) (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012a).

There are several studies available that detected 3-MCPD in some raw products (dark specialty malts) used for beer production (Breitling-Utzmann et al. 2003; Dupire 2003; Hamlet et al. 2002; Muller et al. 2005; Svejkovská et al. 2004). However, because of the relatively small applied proportions of specialty malt products, most beers do not contain detectable levels of 3-MCPD. Breitling-Utzmann et al. (2003) analysed a series of German lightly or darkly coloured types of beer, and 3-MCPD was not found at levels above 10 µg/kg. Baxter et al. (2005) found no 3-MCPD in 55 beers in the UK, with a quantification limit of 10 µg/L.

4-Methylimidazole

4-Methylimidazole is carcinogenic in animal experiments (NTP 2007) and is classified by the IARC as group 2B carcinogen ("possibly carcinogenic to humans") (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012b). Human exposure to substituted imidazoles may originate from the use of ammonia caramel colour (E150c) and ammonium sulphite caramel colour (E150d) as additive in foods and beverages. During the production process, sugar degradation products (such as methylglyoxal) are ammonolysed into amides and amino aldehydes, which condensate into 2-, 4- or 5-substituted imidazoles (Moon and Shibamoto 2011). So substituted imidazoles may end up as contaminants of caramel colour in foods, non-alcoholic beverages, e.g. coffee, and alcoholic beverages, e.g. dark beer (Klejdus et al. 2006; Yoshikawa and Fujiwara 1981). In another survey, 4-methylimidazole, 2-methylimidazole and THI (2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)-imidazole) were analyzed in 97 cola samples from Germany and France (Schlee et al. 2013). The results showed that commercial colas never exceed 0.6 mg/L of 4-MI and do not contain the two other imidazoles. In a worst-case scenario, when the complete soft drink consumption would be cola containing 0.6 mg/L of 4-MI, the exposure would be in the range of 2–5 g/kg bodyweight/day. This exposure was judged as a low risk for public health (Schlee et al. 2013), and it may be deduced that the risk of alcoholic beverage consumption is even lower because lower levels (if any at all) of 4-methylimidazole occur in alcohol than in cola beverages.

N-Nitrosodimethylamine

The nitrosamine *N*-nitrosodimethylamine (NDMA) is classified by the IARC as group 2A carcinogen (IARC 1987; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 1978). NDMA is a hepatotoxic agent. A change in the target organ specificity of NDMA was observed in animal studies by co-administration of ethanol: 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 indicates that ethanol may influence the initiation of carcinogenesis. But it is also possible that the process is enhanced due to some mechanistic events, e.g. the facilitation of entry into the target cell by ethanol, a change in intracellular metabolism or suppression of DNA repair (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010).

N-nitroso compounds may occur and be formed during the manufacturing process or storage of foods and beverages (Lijinsky 1999; Tricker and Kubacki 1992). In 1978, NDMA was first found in German beers (Spiegelhalder et al. 1979). It turned out that NDMA is a contaminant of malt and formed by direct firing, the predominant production method at that time. Once the source and the mechanism of its formation had been elucidated, reduction in NDMA in beer was achieved by switching to indirect firing of the malt kiln from concentrations of 68 µg/L up to nearly zero.

In a survey from southern Germany during the years 1992–2006, NDMA was detectable in 29 malt samples (43 %) and in 81 beer samples (7 %). The technical threshold value was exceeded by 49 of 1242 German beers (4 %) (Lachenmeier and Fügel 2007). From the large number of negative samples in this survey, it was concluded that nowadays, beer may be nearly neglected as source of NDMA intake in human

nutrition. NDMA occurs also as a contaminant in drinking water resulting from reactions during chlorination or via direct industrial contamination (Mitch et al. 2003).

Ochratoxin A

Ochratoxin A is a mycotoxin which has been classified into group 2B as possibly carcinogenic to humans (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 1993). Creppy (1999) has reviewed the toxic effects, especially the nephrotoxicity. During fermentation, ochratoxin A (OTA) can be partially detoxified (Esti et al. 2012), but it is stable in wine for at least 1 year (Lopez de Cerain et al. 2002). Location of the vineyard and the weather had more influence on the levels of OTA, than the variety of grape (Kozakiewicz et al. 2004); also the period of harvest, pesticide treatment and the brewing technique are crucial (Bellver et al. 2014). It was indicated that OTA-producing fungi are already present on grapes before the harvest (Kozakiewicz et al. 2004). A study of Spanish wines by Lopez de Cerain et al. (2002) showed very different levels of OTA contamination between 2 years of harvest: 85 % of 1997 wine samples versus 15 % of 1998 wine samples. The storage conditions and subsequent processing steps of grapes were very similar in both cases, so the differences are most likely due to weather conditions during the summer in 1997 which led to lower production and sanitary problems like contamination with fungi. These results confirm the belief that fungi producing OTA are already present on the grapes before the wine is processed and demonstrate the great importance of processing techniques and of climate, which depends on the latitude and especially on the particular circumstances in any given year (Lopez de Cerain et al. 2002). Otteneder and Majerus (2000) reported the results of an evaluation of more than 850 wines which indicates that the detected amount of OTA is much more common and its concentration is remarkably higher in red wines (54 %) than in rosé (40 %) and white wines (25 %). Also dry wines showed lower OTA concentrations than sweet (Bellver et al. 2014). The differences can be explained by the wine-making procedures itself which are totally different with respect to red/white and sweet/dry wines. For instance, white grapes are pressed out directly, whereas red grapes are left mashed for a certain length of time, which is likely to permit fungal growth and therefore production of the toxin (Höhler 1998).

The presence of OTA in beer is much lower than the reported amounts in wine; contamination comes here from prime material like barley, malt or cereal derivatives. The fungi strains are stable throughout the cooking process, but OTA undergoes a partial elimination during the fermentation process. In recent years, the reported incidences of OTA have increased in European beers. The EU has not established a limit for OTA in beer; on the contrary, the maximum limit in wine is 2 µg/kg (Bellver et al. 2014).

Pulegone

Pulegone is a monoterpene ketone present in the leaves and flowering tops of several members of the mint family (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2015b). Studies in humans and rodents indicated that some of the pulegone metabolites deplete hepatic levels of glutathione and can bind to cellular proteins. This may result in chronic regenerative cell proliferation, which may be related to the carcinogenicity observed in the liver and urinary bladder in experimental animals. Pulegone was classified as possibly carcinogenic to humans (group 2B) (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2015b).

Pulegone may be introduced into alcoholic beverages flavoured with mint or peppermint with a maximum limit in the EU of 100 mg/kg (European Parliament and Council 2008). There are some limited data about analytical methods to determine pulegone in alcoholic beverages (Galli et al. 1984; Przyborski and Bandion 1992), but occurrence or exposure data on this compound are sparse. The NTP reported that the average level of pulegone in alcoholic beverages might be 10.5 ppm (NTP 2011b).

Safrole

Safrole was evaluated by the WHO International Agency for Research on Cancer (IARC) as "possibly carcinogenic to humans" (group 2B) (IARC 1987). Safrole has been demonstrated to be carcinogenic in animal studies and genotoxic in vitro. Safrole is a natural constituent of a number of spices such as nutmeg, mace, cinnamon, anise, black pepper and sweet basil and in food and beverages used as flavour compound (SCF 2002). The most important dietary sources are nutmeg, mace and their essential oils (SCF 2002). Safrole may be present in cola drinks (SCF 2002) and may also potentially occur in alcoholic beverages (Curro et al. 1987). The estimated average intake amounts to 0.3 mg/day and the 97.5th percentile to 0.5 mg/day. In an evaluation from the Council of Europe in 1995, the intake of safrole was assumed to be 1 mg/person/day from food and spices and 1 mg/person/day from essential oils.

Comparative risk assessment of compounds in alcoholic beverages

Alcoholic beverages may contain more than 1000 different components (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 1988) of which the 18

Table 2 Occurrence of WHO International Agency for Research on Cancer (IARC) known and suspected human carcinogens in alcoholic beverages (updated from Lachenmeier et al. (2012) with permission from John Wiley and Sons)

Agent	Amount in alcoholic beverages (average/maximum)[a]
Acetaldehyde associated with consumption of alcoholic beverages	9/63 mg/L (beer); 34/211 mg/L (wine); 66/1159 mg/L (spirits), Lachenmeier and Sohnius (2008)
Acrylamide	0–72 µg/kg (beer)[b]
Aflatoxins	0.002/0.230 µg/L (beer), Mably et al. (2005)
Arsenic	0/102.4 µg/L (beer); 4/14.6 µg/L (wine); 13/27 µg/L (spirits)
Benzene	10/20 µg/L in beer produced with contaminated CO_2
Cadmium	0.9/14.3 µg/L (beer); 1.0/30 µg/L (wine); 6/40 µg/L (spirits)
Ethanol in alcoholic beverages	(2–80 % vol)
Ethyl carbamate (urethane)	0/33 µg/kg (beer); 5/180 µg/kg (wine); 93/6730 µg/kg (spirits); 744/22,000 µg/kg (fruit spirits), EFSA (2007a)
Formaldehyde	0 mg/L (beer); 0.13/1.15 mg/L (wine); 0.50/14.37 mg/L (spirits), Jendral et al. (2011)
Furan	3.3/28 µg/kg (beer), EFSA (2011b)
Glyphosate	0–30 µg/L (beer)[c], BfR (2016)
Lead compounds, inorganic	2/15 µg/L (beer), Donhauser et al. (1987); 57/326 µg/L (wine), Andrey et al. (1992); 31/600 µg/L (spirits)
3-MCPD	0–10 µg/kg (beer)[d], Breitling-Utzmann et al. (2003)
4-Methylimidazole	Caramel coloured products: 9/28 µg/L in dark beer, Klejdus et al. (2006); 0/0.14 mg/L in whisky, Yoshikawa and Fujiwara (1981)
N-Nitrosodimethylamine	0.1/1.3 µg/kg (beer)
Ochratoxin A	0.05/1.5 µg/L (beer); 0.23/7.0 µg/L (wine)
Pulegone	10.5 mg/kg NTP (2011b)/100 mg/kg, European Parliament and Council (2008)[e]
Safrole	0/6.6 mg/L (bitters/liqueurs/aperitifs), Curro et al. (1987)

[a] If no other source is stated, the data are taken from the IARC literature review (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010) by calculating the average over all studies. Historical data (i.e. prior to implementation of mitigation measures) were not included

[b] Few surveys on acrylamide in alcoholic beverages are available. The majority of analysed samples contained levels below the detection limit. The level of 72 µg/kg was reported in a single sample of wheat beer (Gutsche et al. 2002)

[c] No systematic data were available on glyphosate in beer. The upper level of 30 µg/L can be seen as "worst-case" scenario (BfR 2016)

[d] Very few studies on 3-MCPD occurrence in alcoholic beverages were available. Levels of less than 10 µg/L were reported in beer, so that this level was chosen as maximum (Breitling-Utzmann et al. 2003)

[e] No systematic data were available on pulegone in alcoholic beverages. An average level of 10.5 mg/kg was reported for alcoholic beverages in the USA (NTP 2011b). 100 mg/kg has been chosen as maximum level in the European flavouring legislation (European Parliament and Council 2008)

compounds pointed out in Table 1 are potentially carcinogenic with different levels of evidence. Only a subgroup of 7 compounds (acetaldehyde, aflatoxins, arsenic, benzene, cadmium, ethanol and formaldehyde) is clearly known to cause cancer in humans (group 1).

The occurrence of the compounds in alcoholic beverages is summarised in Table 2. It is interesting to note that not all substances occur in all groups of alcoholic beverages. Some of the compounds, such as 3-MCPD, furan and *N*-nitrosodimethylamine, were only detected in beer. Safrole may only occur in certain flavoured liqueurs, and very high concentrations of ethyl carbamate are restricted to fruit spirits. Nevertheless, a number of compounds including obviously ethanol, but also acetaldehyde, formaldehyde and some metals may regularly occur in any type of alcoholic beverage. 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 (Lachenmeier et al. 2012). For many of the compounds besides ethanol, a lack of systematic and representative survey data was detected.

The substances besides ethanol typically occur at sub-ppb levels, e.g. aflatoxins, cadmium or ochratoxin A. The exception is ethyl carbamate and formaldehyde, which may reach ppm levels 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 (Lachenmeier et al. 2012).

As the IARC groups are hazard categories, the occurrence alone does not directly equate with an actual risk of these compounds for drinkers of alcoholic beverages. For

this reason, we have conducted a quantitative comparative risk assessment using the margin of exposure (MOE) methodology (Lachenmeier et al. 2012). The toxicological endpoints used for dose–response modelling and the chosen points of departure for MOE assessment are shown in Table 3. The full methodology for the comparative assessment is available in Lachenmeier et al. (2012). For this review, the new IARC-evaluated carcinogens glyphosate, 3-MCPD and pulegone were included using exactly the same methodology.

Figure 3 shows the corresponding MOEs for average and worst-case scenarios for daily drinkers of 4 standard drinks per day. The lowest MOE (0.8) was calculated for ethanol. This MOE for ethanol is consistent with the MOE range (average 1.3, P5–P95:0.6–2.7) calculated using a more refined probabilistic methodology for daily drinking of 1–4 drinks (Lachenmeier and Rehm 2015). The result is also consistent with an older estimation found in the Berkeley Carcinogenic Potency Database (CPDB) project (Gold et al. 2008), which reported a MOE of 3 for moderate daily drinking (based on ethanol exposure of 326 mg/kg/day). This is despite the fact that the CPDB project used an adjusted TD_{50} (median toxic dose) value from older animal experiments (Gold et al. 1989) to calculate MOE, and not the $BMDL_{10}$ from the most recent National Toxicology Program (NTP) long-term study as in our case (Lachenmeier et al. 2011a).

From the other compounds, inorganic lead and arsenic have average MOEs between 10 and 300, followed by acetaldehyde, cadmium, ethyl carbamate and pulegone between 1000 and 10,000. Safrole, ochratoxin A, NDMA, 4-methylimidazole, 3-MCPD, glyphosate, furan, formaldehyde, aflatoxin B1 and acrylamide have average MOEs above 10,000, even in this heavy drinking scenario.

The update of this risk assessment by inclusion of further compounds did not change our original assessment: ethanol itself has by far the highest risk of all carcinogenic compounds in alcoholic beverages. Our results for glyphosate (MOE > 70,000) are also an independent validation of the provisional assessment of the BfR, suggesting that it is impossible to ingest glyphosate with beer in quantities that would pose a health risk.

Conclusion

Ethanol was confirmed using comparative risk assessment as quantitatively the most important carcinogen in alcoholic beverages. This not only confirms deductions by other approaches (such as genetic epidemiology and mechanistic considerations, see introduction), but also corroborates the evaluation by IARC that ethanol itself is carcinogenic to humans. It is also plausible because ethanol is the only common element between all alcoholic beverages, and epidemiological studies point to an increased risk from alcohol consumption independent of type (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010).

As stated by the WHO International Programme on Chemical Safety in their manual for the risk assessment of chemicals, the primary use of calculated margins of exposure is priority setting by the risk manager (IPCS 2009). Regarding the results from our comparative study, the first priority should therefore be to reduce alcohol intake per se (for effective measures see overview in Babor et al. 2010). Besides classical alcohol policy measures, such as—for example—increasing prices/taxes or decreasing availability, the aim to reduce alcohol intake can also potentially be achieved by reducing the alcoholic strength (Rehm et al. 2016). For example, the consumption of 4 bottles of conventional beer with 5.5 % vol would lead to a MOE of 0.5, while the consumption of the same volume of light beer with 1.5 % vol would lead to a MOE of 1.9. There is some research available that consumers are typically not able to discriminate between regular and low-strength beer (Cox and Klinger 1983; McLaughlin 1988; Milner 1979; Segal and Stockwell 2009), nor that it leads to higher drinking volumes (Geller et al. 1991).

Regarding the other carcinogens besides ethanol, there is clearly a necessity for mitigation measures as well. On the one hand, the international and national food standards or laws (e.g. Codex alimentarius (1997) or European Council (1993) demand that contaminant levels should be kept as low as can reasonably be achieved by following good practices (ALARA principle). On the other hand, consumers may demand the absence of contaminants even when the exposure falls below virtually safe doses by several orders of magnitude as in the case of glyphosate (see, for example, the recent public outcry following the findings of this herbicide in traces in German beers with over 1000 Google news hits on the keywords glyphosate and beer). The glyphosate example also corroborates our previous finding that society may accept a higher risk for alcohol drinking (which is a voluntary behaviour) than for contaminants in alcohol (which are involuntary risks) (Rehm et al. 2014).

The authors also believe that it is the obligation of the regulating agency to provide the safest possible environment (Lachenmeier et al. 2012). Mitigation measures for several of the carcinogens such as acetaldehyde or ethyl carbamate are available and should be implemented (European Commission 2010; Jayakody et al. 2016; Lachenmeier et al. 2009; Lachenmeier and Sohnius 2008). To improve control and enforcement, it would be preferable to set maximum limits for the compounds that are currently unregulated (Lachenmeier et al. 2011c), especially for

Table 3 Dose–response modelling results of WHO International Agency for Research on Cancer (IARC) known and suspected human carcinogens occurring in alcoholic beverages (updated from Lachenmeier et al. (2012) with permission from John Wiley and Sons)

Agent	Toxicological endpoint for modelling (route of exposure)[a]	Reference for dose–response modelling study	$BMDL_{10}$[b] (mg/kg bw/day)	Reference for original data used for dose–response modelling
Acetaldehyde	Tumour-bearing animals in male rats (oral)	Lachenmeier et al. (2009)	56	Soffritti et al. (2002b)
Acrylamide	Harderian gland tumours in mice (oral)	Mueller et al. (2011)	0.18	NTP (2011a)
Aflatoxin B_1	Liver cancer in humans (food)	EFSA (2007b)	0.00087	Yeh et al. (1989)
Arsenic	Lung cancer in humans (water)	Benford et al. (2011)	$BMDL_{0.5}$: 0.003	Chen et al. (2010)
Benzene	Lymphocyte count in humans (inhalation extrapolated to oral)	US EPA (2003)	1.2[c]	Rothman et al. (1996)
Cadmium	Human studies involving chronic exposures (food)	US EPA (1998)	NOAEL: 0.01[d]	US EPA (1998)
Ethanol	Hepatocellular adenoma or carcinoma in rats (oral)	Lachenmeier et al. (2011a)	700	Beland et al. (2005), NTP (2004)
Ethyl carbamate (urethane)	Alveolar and bronchiolar neoplasms in mice (oral)	Vavasour et al. (2006)	0.3	NTP (2004)
Formaldehyde	Histological changes in the aerodigestive tract, including oral and gastrointestinal mucosa of rats (oral)	IPCS (2002)	NOEL: 15[d]	Til et al. (1989)
Furan	Hepatocellular adenomas and carcinomas in female mice (oral)	Williams et al. (2011)	0.96	Moser et al. (2009)
Glyphosate	No dose–response data for cancer endpoint available. NOAEL for developmental toxicity study in rabbits used instead	EFSA (2015)	NOAEL: 50[d]	EFSA (2015)
Lead	Cardiovascular effects in humans (dietary exposure based on blood lead levels)	EFSA (2010)	$BMDL_{01}$: 0.0015[f]	Navas-Acien et al. (2009)
3-MCPD	Renal tubular hyperplasia in rats (oral)[g]	Abraham et al. (2012)	0.27	Cho et al. (2008)
4-Methylimidazole	Cancer of the lung in mice (oral)	EFSA (2011a)	NOAEL: 80[d]	NTP (2007)
N-Nitrosodimethylamine	Total liver tumours (oral)	Zeilmaker et al. (2010)	0.029	Peto et al. (1991a, b)
Ochratoxin A	Kidney adenoma and carcinoma in male rats (oral)	Barlow et al. (2008)	0.025	NTP (1989)
Pulegone	Urinary bladder tumours in rats (oral)	EMA (2014)	LOAEL: 20[d]	NTP (2011b)
Safrole	Hepatic tumours in mice (oral)	Martati et al. (2011)	3[e]	Boberg et al. (1983), Miller et al. (1983)

[a] Human data were 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. To provide a conservative assessment, non-cancer endpoints were used in cases when they were more sensitive than cancer endpoints

[b] $BMDL_x$ lower one-sided confidence limit of the benchmark dose (BMD) for a x % incidence of health effect

[c] The original endpoint was based on inhalation exposure. BMDL for oral exposure was derived by route-to-route extrapolation (US EPA 2003)

[d] No usable BMD modelling for oral exposure was identified in the literature. The no effect level (NOEL), no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) are used in these cases instead

[e] A range of "approximately 3–29 mg/kg bw/day" was provided as $BMDL_{10}$ for safrole (Martati et al. 2011). As no further rationale was provided in the study, we chose the minimum of this range to provide a conservative assessment

[f] The values are based on total exposure determined by blood lead levels. The used BMDL was calculated for dietary exposure (EFSA 2010)

[g] Renal tubular hyperplasia was a more sensitive endpoint than renal tubule adenoma and carcinoma

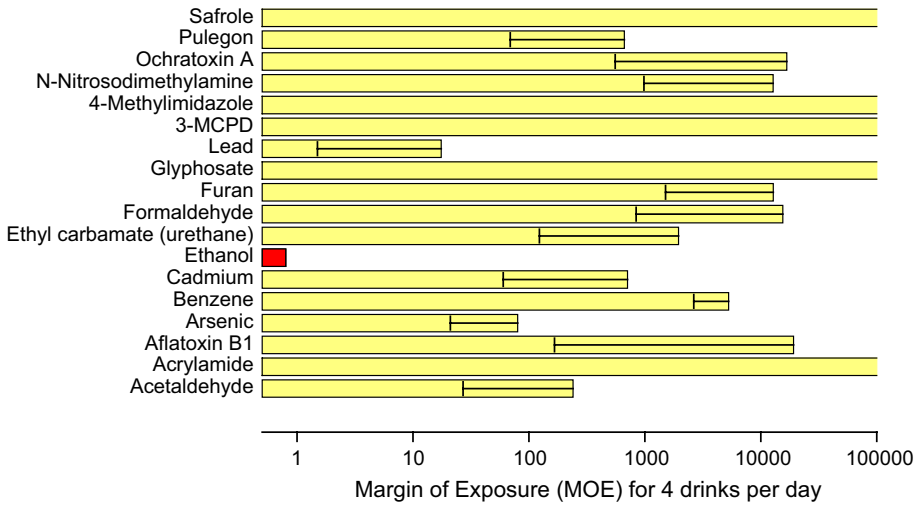

Fig. 3 Margin of exposure (MOE) for carcinogens occurring in alcoholic beverages for four standard drinks per day (averages based on data from Table 2; *error bar* indicates worst-case scenario with maximum amount from Table 2) updated from Lachenmeier et al. (2012) with permission from John Wiley and Sons

those with MOE below 10,000 such as lead, ethyl carbamate, cadmium, benzene, arsenic and acetaldehyde.

Finally, 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). Similar to the toxic levels of adverse compounds besides ethanol, effective levels of compounds with positive effects such as resveratrol cannot be reached by drinking alcohol (Lachenmeier et al. 2014).

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Compliance with ethical standards

Conflict of interest None declared.

Ethical standards This manuscript does not contain clinical studies or patient data.

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