Review

THE MARGIN OF EXPOSURE TO FORMALDEHYDE IN ALCOHOLIC BEVERAGES

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Formaldehyde has been classified as carcinogenic to humans (WHO IARC group 1). It causes leukaemia and nasopharyngeal cancer, and was described to regularly occur in alcoholic beverages. However, its risk associated with consumption of alcohol has not been systematically studied, so this study will provide the first risk assessment of formaldehyde for consumers of alcoholic beverages.

Human dietary intake of formaldehyde via alcoholic beverages in the European Union was estimated based on WHO alcohol consumption data and literature on formaldehyde contents of different beverage groups (beer, wine, spirits, and unrecorded alcohol). The risk assessment was conducted using the margin of exposure (MOE) approach with benchmark doses (BMD) for 10 % effect obtained from dose-response modelling of animal experiments.

For tumours in male rats, a BMD of 30 mg kg^{-1} body weight per day and a "BMD lower confidence limit" (BMDL) of 23 mg kg^{-1} d^{-1} were calculated from available long-term animal experiments. The average human exposure to formaldehyde from alcoholic beverages was estimated at 8·10^{-5} mg kg^{-1} d^{-1}. Comparing the human exposure with BMDL, the resulting MOE was above 200,000 for average scenarios. Even in the worst-case scenarios, the MOE was never below 10,000, which is considered to be the threshold for public health concerns.

The risk assessment shows that the cancer risk from formaldehyde to the alcohol-consuming population is negligible and the priority for risk management (e.g. to reduce the contamination) is very low. The major risk in alcoholic beverages derives from ethanol and acetaldehyde.

KEY WORDS: *alcohol, alcohol consumption, aldehydes, cancer, risk assessment*

Formaldehyde (methanal, CH$_2$O, CAS # 50-00-0) is a colourless substance, which is widely present in foods, industry, and in the environment (1, 2) and may also be endogenously produced in humans and animals (3). The industrial use includes mainly the production of various types of resin, the use as intermediate in the manufacture of industrial chemicals, and the direct use in aqueous solutions (formalin) as a disinfectant and preservative (1-3). Epidemiological studies have demonstrated a causal relationship between formaldehyde and cancer in humans (3). Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and myeloid leukaemia among individuals with high exposure to formaldehyde. The findings are based on case-control studies of industrial workers and other professional groups in inhalatory contact with formaldehyde such as pathologists, funeral directors or embalmers (3). Biological mechanisms associated with formaldehyde-induced cancer are not completely understood, but potential carcinogenic modes of actions for formaldehyde include DNA reactivity (covalent

binding), gene mutation, chromosomal breakage, aneuploidy, and epigenetic effects (3). However, the biological plausibility of an association between formaldehyde exposure and leukaemia was questioned, because formaldehyde is rapidly metabolised, and it would not be expected to enter the systemic circulation (3). No studies in humans are available for the oral route of exposure, but animal feeding experiments have demonstrated that formaldehyde may also be carcinogenic after ingestion (4, 5).

The hazard of formaldehyde has been confirmed by the International Agency for Research on Cancer (IARC), which found sufficient evidence for the carcinogenicity of formaldehyde both for humans and experimental animals. The IARC cancer classification was upgraded in 2006 and formaldehyde was assigned to group 1 ("carcinogenic to humans") with clear evidence for cancer in humans (5, 6).

Formaldehyde is a natural constituent in a variety of fruits, vegetables, meat, milk products, and fish (1). Feron et al. (1) estimated that the formaldehyde intake from food ranges between 1.5 mg and 14 mg per person per day, which may already reach the reference dose (RfD) for chronic oral exposure of 0.2 mg kg^{-1} d^{-1} (approximately 12 mg d^{-1} for a 60-kg adult) postulated by the US Environmental Protection Agency (EPA) (7). Relatively high concentrations of formaldehyde were found in alcoholic beverages; for example, in sugar cane spirits (mean 4.13 mg L^{-1}, maximum 10.90 mg L^{-1}) (8) and rum (mean 2.42 mg L^{-1}, maximum 10.07 mg L^{-1}) (9). In our on-going investigation of the composition and global public health impact of alcoholic beverages, including unrecorded alcohol (10), we have also detected high formaldehyde concentrations in a number of products (11). Thus, the natural occurrence of formaldehyde from methanol oxidation in alcohol products, together with contamination from other sources (e.g. the usage of formaldehyde-containing or formaldehyde-releasing disinfectants), could therefore be a potential problem on a worldwide scale.

In contrast to other constituents of alcoholic beverages (e.g. methanol, higher alcohols, acetaldehyde or ethyl carbamate), for which excellent risk assessments are available in the literature (12-15), we found a major knowledge gap regarding information about the potential public health impact of formaldehyde, resulting in an inability to adequately ascertain the risk for consumers of the alcoholic beverages researched. In this study, applying the harmonised approach of the European Food Safety Authority (EFSA) (16), we present for the first time, a quantitative risk assessment for formaldehyde in alcoholic beverages.

METHODS

Data on formaldehyde were obtained by a computer-assisted literature search. Searches were carried out in the following databases: PubMed, Toxnet, and ChemIDplus (US National Library of Medicine, Bethesda, MD), Web of Science (Thomson Scientific, Philadelphia, PA), and IPCS/INCHEM (International Programme on Chemical Safety/ Chemical Safety Information from Intergovernmental Organizations, WHO, Geneva, Switzerland). We specifically aimed to identify long-term animal studies that would be usable for dose-response modelling as well as studies on the occurrence of formaldehyde in alcoholic beverages.

Analysis was conducted according to the harmonised approach of EFSA (16) and similar to our previous acetaldehyde cancer risk assessment (14). This includes an approach known as the margin of exposure (MOE). MOE is defined as the ratio between the benchmark dose (BMD) and the estimated human intake of the same compound. MOE can be used to compare the health risk of different compounds and prioritise risk management actions. By definition, the lower the MOE, the larger the risk for humans; generally a value under 10,000 is used to define public health risks (16). The benchmark dose (BMD), derived from animal data by mathematical modelling within the observed range of experimental data, was used as a reference point. To obtain MOE, the Benchmark Dose Lower Confidence Limit (BMDL) for a 10 % effect was taken (MOE = BMDL / Exposure). BMDL is an estimate of the lowest dose that is 95 % certain to cause no more than a 10 % effect (e.g. cancer incidence) in rodents. The BMD and BMDL values were calculated using the US EPA's BMDS 2.2 software (available at the US Environmental Protection Agency website: http://www.epa.gov/ncea/bmds/ index.html).

RESULTS

Toxicity of orally ingested formaldehyde in animal studies

There is adequate evidence for the carcinogenicity of formaldehyde in animal experimental studies (6).

Several studies have proved that long-term inhalation exposure to formaldehyde causes both benign and malignant nasal tumours in male and female rats (17-19). As the focus on the specific effects of orally administered formaldehyde is relatively new, there are not many studies on this subject. The following two are considered to be the most significant ones: Soffriti et al. (4) conducted a long-term study of rat groups exposed to formaldehyde that resulted in a carcinogenic effect; Til et al. (20) observed severe damage to the gastric mucosa, renal papillary necrosis, and irregular mucosal thickening in the forestomach and/or glandular stomach in rats given top doses of formaldehyde. These studies are discussed in more detail in the section "dose response analysis".

Besides these two pivotal studies, some further studies were identified. In the paper of Tobe et al. (21), groups of 20 male and 20 female Wistar rats were given formaldehyde in their drinking water at four concentrations (0.50, 0.10, 0.02, and 0) % for 24 months. Various non-neoplastic lesions, erosions, and ulcers were found both in the forestomach and glandular stomach mostly in the 0.50 % group. There were no significant differences in the incidence of any tumours among groups of both sexes. Based on their results, the no observable effect level of formaldehyde was 0.02 % in drinking water (10 mg kg^{-1} d^{-1}). Another valuable oral study is that of Takahasi et al. (22), in which Wistar rats were given formaldehyde during a 32-week period at a single concentration level (0.5 % - about 300 mg kg^{-1} bw per day). Due to the single dose level and/or limited number of animals, these studies were not included in our dose-response-modelling. However, it is important to mention that although no tumours were observed, papillomas in the forestomach and non-neoplastic changes in glandular stomach were reported (22). The finding suggests that formaldehyde could exert pre-carcinogenic activity in the rat glandular stomach. Long-term or lifetime studies above certain concentration threshold are necessary for detecting tumours (4).

Dose-response analysis

There is no adequate human study available for a dose-response analysis. From the animal experiments mentioned above, two long-term studies of the oral route of exposure to formaldehyde appear to be suitable for dose-response modelling.

Til et al. (20) examined the oral toxicity of formaldehyde in rats in a two-year drinking-water study at dose levels of (0, 1.2, 15, and 82) mg kg^{-1} d^{-1} for males and (0, 1.8, 21, and 109) mg kg^{-1} d^{-1} for females. The study did not provide any evidence of carcinogenicity of formaldehyde after oral consumption. Thickening and raising of the limiting ridge of the forestomach, irregular mucosal thickenings, histopathological gastric changes (papillary epithelial hyperplasia, hyperkeratosis, focal ulceration, and focal chronic atrophic gastritis) were observed mostly in the high-dose group. In a more recent 104-week study of carcinogenicity by Soffritti et al. (4), male and female Sprague-Dawley rats were given drinking water containing formaldehyde at concentrations of about (0, 1, 5, 10, 51, 102, and 153) mg kg^{-1} d^{-1} [own calculations based on formaldehyde concentrations in drinking water (0, 10, 50, 100, 500, 1000, and 1500) mg L^{-1} and data about average body weight and drinking volume]. Treatment with formaldehyde resulted in an increase in total malignant tumours and showed specific carcinogenic effects on various organs and tissues.

Due to the lower number of animal subjects and smaller doses, Til et al. (20) provided only limited applicable evidence for dose-response assessments, especially as carcinogenic effects were not detectable. However, we modelled this study for comparison purposes, as irregular thickenings in the forestomach and glandular stomach, chronic atrophic gastritis, and histopathological changes (papillary epithelial hyperplasia accompanied by hyperkeratosis) could be pre-carcinogenic lesions. A large number of oncological lesions of the intestine and the stomach were detected in the study of Soffritti et al. (4), especially at the highest doses (which were higher than the ones used in Til et al. (20)). The study by Soffritti et al. (4) is, therefore, the only study adequately designed to be used for a dose-response assessment of carcinogenic effects of orally administered formaldehyde.

The best-fitting models for different end-points are listed in Table 1. It can be seen that the values for different end-points calculated from the Til et al. (20) study are consistent: the BMD and BMDL values are in the range of (22 to 50) mg kg^{-1} d^{-1} and (12 to 45) mg kg^{-1} d^{-1}, respectively. Regarding the Soffritti et al. data (4), significant models were reached for both sexes when the total number of tumour-bearing animals was modelled. An adequate model for hemolymphoreticular neoplasias (females) was also observed (Table 1). Overall, BMDs and BMDLs of models from both studies (4, 20) are in the same order of magnitude, which is indicative of an overall adequacy of the calculated values, as even between

Table 1 *Summary of own dose response modelling results for formaldehyde in different animal experiments conducted by Til et al. (20) and Soffritti et al. (4)*

End-point		Model[a]	p-value[b]	BMD[c] / mg kg[1] d^{-1}	BMDL[d] / mg kg[1] d^{-1}
Til et al. (20)					
Focal papillary epithelial hyperplasia	Male	Gamma	0.77	41	18
	Female	Multistage	0.42	29	22
	Combined	Dichotomous-Hill	0.49	25	21
Focal hyperkeratosis	Male	Multistage-Cancer	0.28	34	12
	Female	Multistage-Cancer	0.43	34	21
	Combined	Multistage	0.55	45	26
Chronic atrophic gastritis	Male	Gamma	(1)[e]	(38)	(21)
	Female	Gamma	(1)[e]	(38)	(24)
	Combined	Gamma	(1)[e]	(38)	(28)
Focal ulceration	Male	Gamma	(1)[e]	(70)	(38)
	Female	Gamma	(1)[e]	(95)	(55)
	Combined	LogProbit	0.85	62	45
Gradular hyperplasia	Male	Multistage-Cancer	0.24	37	25
	Female	Gamma	(1)[e]	(90)	(49)
	Combined	Dichotomous-Hill	0.78	41	23
Papillary necrosis	Male	Logistic	0.38	36	29
	Female	Multistage-Cancer	0.24	50	36
	Combined	Quantal Linear	0.11	22	17
Soffritti et al. (4)					
Tumour-bearing animals	Male	Probit	0.13	30	23
	Female	Logistic	0.59	67	38
Hemolymphoreticular neoplasias	Male	Quantal Linear	(0.036)[f]	(40)	(28)
	Female	Multistage-Cancer	0.63	111	61

[a] *Data from best-fitting models selected with BMDS 2.2-software according to US EPA criteria are presented*
[b] *A p-value greater than 0.1 indicates that the model fits the data (p-value 1.0 = perfect fit).*
[c] *BMD: benchmark dose for a 10% incidence of health effect*
[d] *BMDL: lower one-sided confidence limit of the BMD*
[e] *Only the highest dose-level exhibited effects. No clear dose-response established. Values are shown in brackets for information*
[f] *Not significant dose-response. Values are shown in brackets for information*

different models differences up to factors of five are accepted as typical and would allow for an averaging of the values (23). To be conservative, we decided to take the model for male tumour-bearing animals with a BMD of 30 mg kg^{-1} d^{-1} and a BMDL of 23 mg kg^{-1} d^{-1} for our further calculations (Figure 1). Notably, these values are expectedly smaller than what we calculated for acetaldehyde from the same Soffritti et al. (4) study (BMD=114 mg kg^{-1} d^{-1} and BMDL=56 mg kg^{-1} d^{-1}) (14). This is consistent with previous assumptions that the toxicity of aldehydes decreases with chain length (24).

Exposure assessment

In this study we used the EFSA guidelines (16), which recommend that risk assessments provide different exposure scenarios (e.g. for entire, or specific groups of populations) along with their inherent uncertainties. Other than the mean and median, intakes from highly exposed individuals (due to high consumption of average contaminated foods or to average consumption of highly contaminated foods) should be considered as represented by the 90th, 95th, 97.5th, and 99th percentiles.

To provide estimates on the dietary intake of formaldehyde, data on the consumption of alcoholic
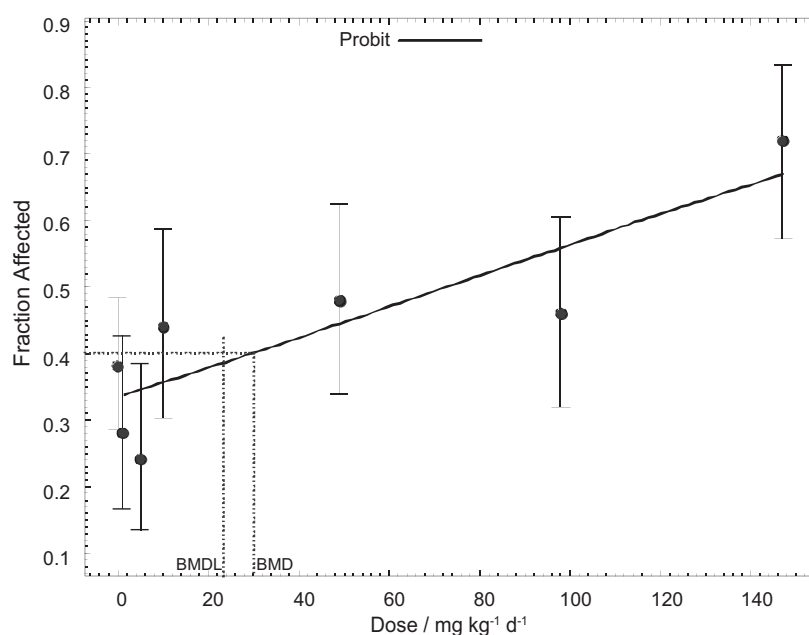
Figure 1 *Benchmark dose modelling for oral formaldehyde administration with male tumour-bearing animals as endpoint. Probit model with 0.95 confidence level. BMD: benchmark dose for a 10 % incidence of health effect; BMDL: lower one-side confidence limit of the BMD. Original data from Soffritti et al. (4).*

beverages and their content of formaldehyde is needed. Currently, there are not enough systematic data on formaldehyde content of alcoholic beverages or indeed of most foods in general. Although formaldehyde is a natural component of a variety of foodstuffs (1), with the highest concentrations in fruits (25), vegetables

(25), and fish (26-28), monitoring has generally been sporadic and inconsistent.

Nevertheless, there are some studies where the actual formaldehyde content in different alcoholic beverages was determined (8, 9, 11, 29-48). The investigation of alcoholic beverages for formaldehyde

Table 2 *Formaldehyde concentration in alcoholic beverages*

Category [a]	Sample size	Formaldehyde / mg L^{-1} (data summarised from Refs. 8, 9, 11, 29-48)						>2.6 mg L^{-1} [b] / %
		Mean	**Median**	**90th percentile**	**95th percentile**	**97.5th percentile**	**99th percentile**	**Maximum**	
Rum/cane	86	0.42	0.06	0.48	2.20	3.08	7.33	10.90	6.98
Whiskey	29	0.26	0.08	0.72	1.19	1.43	1.54	1.62	0.00
White spirits	139	0.01	0.00	0.01	0.01	0.06	0.11	0.80	0.00
White spirits incl. tequila	177	0.27	0.00	0.83	1.72	2.69	3.24	6.06	5.08
Flavoured spirits	106	0.24	0.00	0.45	0.95	1.43	2.70	5.39	1.89
Asian products	43	1.23	0.03	1.54	9.75	13.44	14.06	14.37	9.30
Brandy	19	0.69	0.18	2.06	2.24	2.62	2.86	3.01	15.79
Beer	93	0.02	0.00	0.05	0.17	0.21	0.23	0.27	0.00
Wine	39	0.2	0.02	0.72	0.82	0.89	1.05	1.15	0.00
Unrecorded and others	116	0.32	0.00	1.04	1.53	3.05	3.47	6.71	4.31
Total spirits	417	0.31	0.01	0.82	1.70	2.84	3.32	10.90	4.80
Total all alcoholic beverages	708	0.32	0	0.74	1.54	2.93	6.01	14.37	4.10

[a] *The categories were chosen based on available consumption data (see Lachenmeier et al. (14) for details)*
[b] *A tolerable concentration of 2.6 mg L^{-1} was suggested by WHO IPCS (2) based on non-cancer endpoints*

content started as early as in 1983 with the measurement of a limited number (n=9) of beer samples (29). From then, formaldehyde has also been detected in wine, spirits, and unrecorded alcohol. However, most of the studies evaluated only a limited number of samples. Up to now, the only study on a large sample of alcoholic beverages was provided by Jendral et al. (n=488) (11). The formaldehyde concentrations of the corresponding beverage groups for all mentioned studies are summarised in Table 2. Mean concentrations of formaldehyde in a variety of alcoholic beverages ranged from 0.01 mg L^{-1} in white spirits to 0.69 mg L^{-1} in brandies. The highest concentrations were typically detected in spirits from Asia (mean 1.23 mg L^{-1}).

Annual consumption of different types of alcoholic beverages for the population older than 15 can be easily obtained from the WHO databases. This can be done for most countries around the world. However, as studies about formaldehyde concentrations in alcoholic beverages other than European-style beverages are unavailable (especially the knowledge about Asian beverages is based on only very few analytical results), we decided to limit the whole population dietary intake estimate to the European Union (EU). The formaldehyde exposure due to alcoholic beverage consumption was calculated from Table 2 combined with values of annual per capita consumption of alcoholic beverages in the EU (see Lachenmeier et al. (14) for details on annual consumption of different beverage groups). Table 3 summarises the exposure for different scenarios.

Risk characterisation

The exposure data from Table 3 was used to characterise the risk using the margin of exposure (MOE) calculated from BMDL (Table 4). MOEs can be used by risk managers for setting priorities; small MOE represents a higher risk and vice versa. In general, an MOE of 10,000 or higher, if based on a BMDL from an animal study, would be considered a low public health concern and subsequently a low priority for risk management actions (16). In the case of formaldehyde, MOEs were in all scenarios above this 10,000 threshold, demonstrating that, in general, formaldehyde in alcoholic beverages appears not to be a public health concern.

This evaluation is in line with previous risk assessments that have considered only non-cancer end-points. For example, the WHO IPCS (2) has established a tolerable concentration (TC) of 2.6 mg L^{-1} in ingested products based on the experiments of Til et al. (20). In this respect, some brandies, rum, and Asian spirits are problematic, as these products can contain formaldehyde concentrations above the threshold of 2.6 mg L^{-1} (see Table 2). However, a 60 kg person would need to daily consume 0.8 L of alcohol at 14.37 mg L^{-1} (the highest concentration found in alcoholic beverages so far) (11) to exceed the US EPA RfD of 0.2 mg kg^{-1} d^{-1} (7), which is extremely unlikely even in this worst-case scenario. None of our population-based exposure estimations exceed the US EPA RfD.

Table 3 *Population-based exposure scenarios for the European Union. The table shows the formaldehyde exposure due to all types of alcoholic beverages (beer, wine, spirits, unrecorded) calculated as mg kg^{-1} d^{-1} (calculated for a 60 kg person)*

Formaldehyde exposure / mg kg^{-1} d^{-1}		Exposure scenarios for different formaldehyde concentrations in the beverages					
		Mean	Median	90th percentile	95th percentile	97.5th percentile	99th percentile
Exposure scenarios for different amounts of alcoholic beverage consumption in Europe	Mean	8.0E-05	7.8E-06	2.6E-04	3.6E-04	4.3E-04	5.3E-04
	Median	5.3E-05	4.9E-06	1.7E-04	2.4E-04	2.9E-04	3.5E-04
	90th percentile	1.7E-04	1.7E-05	5.5E-04	7.7E-04	9.2E-04	1.1E-03
	95th percentile	2.0E-04	2.1E-05	6.5E-04	9.1E-04	1.1E-03	1.3E-03
	97.5th percentile	2.5E-04	2.5E-05	7.7E-04	1.1E-03	1.3E-03	1.6E-03
	99th percentile	2.8E-04	2.8E-05	8.7E-04	1.2E-03	1.5E-03	1.8E-03

Table 4 *Margin of exposure (MOE) for formaldehyde in different exposure scenarios. Calculated with BMDL of 23 mg kg^{-1} d^{-1} (MOE = BMDL / exposure)*

MOE		Exposure scenarios for different formaldehyde concentrations in the beverages					
		Mean	Median	90th percentile	95th percentile	97.5th percentile	99th percentile
Exposure scenarios for different amounts of alcoholic beverage consumption in Europe	Mean	287,500	2,948,718	88,462	63,889	53,488	43,396
	Median	433,962	4,693,878	135,294	95,833	79,310	65,714
	90th percentile	135,294	1,352,941	41,818	29,870	25,000	20,909
	95th percentile	115,000	1,095,238	35,385	25,275	20,909	17,692
	97.5th percentile	92,000	920,000	29,870	20,909	17,692	14,375
	99th percentile	82,143	821,429	26,437	19,167	15,333	12,778

DISCUSSION

In contrast to the risk assessment of another carcinogenic aldehyde - acetaldehyde - for which a considerably lager database about human carcinogenicity and genetic epidemiology exists (14, 49), our formaldehyde assessment contains several limitations:

1. The assessment is based on only one oral animal study where formaldehyde showed specific carcinogenic effects on various tissues and organs. Some problems with the modelling of these data existed. In particular, the modelling of the data was complicated, as the background levels were relatively high. In addition, the incidence of certain carcinomas was increased in the treated groups, but the statistical power was insufficient to allow the modelling of any specific cancer site besides hemolymphoreticular neoplasias in females (see also (14) about discussion of the same problems in dose-response modelling of acetaldehyde). Additionally, there are no other estimates for BMDL and BMD values in the literature. However, as the values obtained for different end-points corresponded well to each other and also to non-cancer endpoints from another study, we believe that the chosen BMDL value is certainly in the right order of magnitude and could be used for quantitative risk assessment.

2. The second important limitation is the fact that we assumed a uniform distribution of formaldehyde in the whole body. However, the tissues that are in direct contact with an alcoholic beverage are exposed at considerably higher levels than other organs. For example, the risk for gastrointestinal tract cancer could be higher, as stomach and intestine lesions have been reported in the animal experiments (4). On the other hand, some recent research has suggested that formaldehyde might enter the systemic circulation of humans exposed to formaldehyde (3), which would justify the application of this assumption to provide a conservative assessment until the mechanism of action has been fully elucidated.

3. The whole population evaluation may under-estimate the risk for heavy drinkers and the risk for drinkers that drink predominantly formaldehyde-rich beverages.

Besides alcoholic beverages, humans could be exposed to formaldehyde from other sources. However, the current data only allow rough estimations. Formaldehyde appears in almost all common foods at (1 to 100) mg kg^{-1} (1) and adult dietary intake is estimated in the range from (1.5 to 14) mg per person per day [(0.022 to 0.23) mg kg^{-1} d^{-1}] (1). Drinking water is expected to contain less than 0.1 mg L^{-1} (2), resulting in a daily intake of less than 0.2 mg per person (0.003 mg kg^{-1} d^{-1}) (2). The endogenous levels in human blood were estimated at about 2 mg L^{-1} to 3 mg L^{-1} (6). However, all of these estimates are comparably old and possibly outdated (due to regulatory changes and inadequate analytical methodologies in older studies). Migration of formaldehyde monomers from tableware was pointed

out as a further source of food contamination with formaldehyde (50-52). This migration was estimated at ppm (mg kg^{-1}) levels.

An important source of formaldehyde intake is cigarette smoke (2). Formaldehyde levels in mainstream smoke were reported at 45 µg to 283 µg per cigarette (2, 53). This equals a maximum exposure of 0.094 mg kg^{-1} d^{-1} for a 60 kg person smoking 20 cigarettes per day.

Compared with these other exposures, the average exposure via alcoholic beverages of $8 \cdot 10^{-5}$ mg kg^{-1} d^{-1} appears to be negligible. Nevertheless, data on cumulative formaldehyde exposure (especially for foods and beverages) are sparse and should be updated in the future.

CONCLUSIONS

The overall conclusion is that the occurrence of trace levels of formaldehyde in alcoholic beverages does not constitute an additional cancer risk for humans. Our data showed that even in worst-case scenarios, the exposure (0.0018 mg kg^{-1} d^{-1}) is lower than thresholds of toxicity (if a threshold-based mechanism is assumed for this carcinogen, which is still a matter of debate) (54).

Our calculation has revealed that formaldehyde in alcoholic beverages shows MOEs in a magnitude that is not considered a high priority for regulatory measures. For other compounds of alcoholic beverages, such as acetaldehyde or ethyl carbamate, MOEs have been found in considerably lower ranges (below 1000) according to EFSA and Lachenmeier et al. (14, 15). The major risk, however, certainly comes from ethanol with a MOE of 1 or even smaller (55). Ethanol was also identified as the most important carcinogen in alcoholic beverages in a comparative quantitative assessment of 15 carcinogenic compounds (56). This study fully confirms this finding and suggests prioritising general alcohol policy measures over more specific measures such as mitigative efforts to reduce the content of trace contaminants such as formaldehyde.

Conflicts of interest statement

All authors declare that they have no direct financial interest in the subject matter or materials discussed that could inappropriately influence the manuscript.

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Sažetak

GRANICA IZLAGANJA FORMALDEHIDU U ALKOHOLNIM PIĆIMA

Formaldehid je kancerogen za ljude te je klasificiran u skupinu 1 prema WHO IARC-u. Uzrokuje leukemiju i nazofaringealni karcinom, a navodi se i kao redoviti sastojak alkoholnih pića. Međutim, rizik od izlaganja formaldehidu konzumacijom alkoholnih pića nije sustavno istražen pa će ovo istraživanje pružiti prvu takvu procjenu rizika. Količina formaldehida koju ljudi unose alkoholnim pićima u Europskoj je uniji procijenjena temeljem podataka Svjetske zdravstvene organizacije o konzumaciji alkohola i literature o sadržaju formaldehida u različitim skupinama alkoholnih pića (pivo, vino, jaka alkoholna pića i neregistrirani alkohol). Procjena rizika obavljena je korištenjem pristupa granice izlaganja (eng. *margin of exposure*, MOE) i graničnih doza (eng. *benchmark doses*, BMD) za 10 %-tni učinak koji se postiže modeliranjem odnosa doza-odgovor u ispitivanjima provedenima na životinjama. BMD od 30 mg kg^{-1} tjelesne težine na dan i BMD s nižom granicom pouzdanosti (BMDL) od 23 mg kg^{-1} d^{-1} izračunati su za tumore kod mužjaka štakora temeljem raspoloživih dugotrajnih ispitivanja provedenih na životinjama. Prosječno izlaganje ljudi formaldehidu u alkoholnim pićima procijenjeno je na 8·10^{-5} mg kg^{-1} d^{-1}. U usporedbi s BMDL vrijednošću krajnji MOE je iznosio više od 200.000 u prosječnim situacijama. Čak i u najlošijim situacijama MOE nije nikada bio niži od 10.000, što se smatra graničnom vrijednošću za zdravlje ljudi. Procjena rizika pokazuje da je rizik od nastanka karcinoma uslijed izlaganja formaldehidu iz alkoholnih pića zanemariv te da je prioritet upravljanja rizikom u takvim slučajevima (npr. kako bi se smanjila kontaminacija) vrlo nizak. Najveći rizik proizlazi iz etanola i acetaldehida koji se također nalaze u alkoholnim pićima.

KLJUČNE RIJEČI: *alkohol, aldehidi, karcinom, konzumacija alkohola, procjena rizika*

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