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Short Communication

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Estimates of Ethanol Exposure in Children from Food not Labeled as Alcohol-Containing

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Abstract

Ethanol is widely used in herbal medicines, e.g., for children. Furthermore, alcohol is a constituent of fermented food such as bread or yogurt and "non-fermented" food such as fruit juices. At the same time, exposure to very low levels of ethanol in children is discussed as possibly having adverse effects on psychomotoric functions. Here, we have analyzed alcohol levels in different food products from the German market. It was found that orange, apple and grape juice contain substantial amounts of ethanol (up to 0.77 g/L). Furthermore, certain packed bakery products such as burger rolls or sweet milk rolls contained more than 1.2 g ethanol/100 g. We designed a scenario for average ethanol exposure by a 6-year-old child. Consumption data for the "categories" bananas, bread and bakery products and apple juice were derived from US and German surveys. An average daily exposure of 10.3 mg ethanol/kg body weight (b.w.) was estimated. If a high (acute) consumption level was assumed for one of the "categories," exposure rose to 12.5–23.3 mg/kg b.w. This amount is almost 2-fold (average) or up to 4-fold (high) higher than the lowest exposure from herbal medicines (6 mg/kg b.w.) suggested to require warning hints for the use in children.

Introduction

There is currently no harmonized approach in Europe to assess the safety of ingestion of ethanol in low amounts. Ethanol occurs as a natural constituent in food including food items not labeled as alcohol-containing (1). Furthermore, ethanol is used as an extraction solvent or a diluent in herbal preparations and herbal medicinal products (2). This fact has been causing toxicological concerns, in particular, related to the exposure of children, with respect to both short-term and prolonged use of ethanol-containing herbal medicinal products that are mainly authorized and marketed on a nonprescription basis.

Acute, subchronic or chronic exposure to ethanol for recreational purposes in inadequate amounts can lead to the well-known adverse effects including neuropsychiatric conditions, gastrointestinal diseases, cancers, cardiovascular diseases, immune suppression, etc. (3). Pregnant women, children and adolescents or patients suffering from psychotic or psycho-organic central nervous system (CNS) disturbances are considered to be particularly vulnerable to ethanol (4–6).

In this context, the relevant issue is about an acceptable, i.e., toxicologically safe dose. For ethanol, no tolerable daily intake value has been derived so far. The reasons for this are manifold including (i) ethanol is a natural constituent of the human diet, even if no alcoholic beverages are consumed, (ii) ethanol occurs in very minor amounts in human blood, even if controlled studies guarantee that no alcoholic beverages have been consumed and (iii) there is good evidence that the regular consumption of small amounts of ethanol may be beneficial, at least in healthy adults, for health and life expectancy (7).

In a reflection paper (2) and recent "Questions and Answers" (8) the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA) made a couple of statements/comments related to the presence of ethanol in a number of phytomedicinal drugs including those used in the treatment of children. For example, the Committee derived an acceptable maximum dose per intake (minimum dose interval 4 h) of 1.5 g absolute ethanol for a 6-year-old child (b.w. 20 kg). These publications led us to further investigate the issue of exposure of consumers, in particular of children, to ethanol via food items, which are not labeled as alcohol-containing.

It has been reported that even the small amounts of ethanol ingested by infants of alcohol-consuming mothers during breastfeeding could be detrimental for the child's psychomotor development at the age of 1 year (9). However, in a later study the same group was unable to replicate the finding in 18-month-old toddlers (10).

Available acute and chronic toxicity data of ethanol in children is limited. Current knowledge on the metabolism of ethanol in children is based mainly on cases of acute poisonings or has been extrapolated from data produced in adults or from animal studies. Based on these studies, it can be estimated that the rate of serum ethanol clearance in children and adolescents is comparable to that reported in adults or somewhat faster (11). This is the case despite that the major ethanol-metabolizing hepatic enzyme, alcohol dehydrogenase, in children has been reported to be low and may reach adult levels only after the age of 5 years (12).

It was supposed that ethanol exerts symptoms of acute toxicity in children at a dose level in the range of 0.3 g/kg b.w. (13). Furthermore, it was assumed that ethanol blood concentrations in the range of 0.01–1 g/L (14) are associated with adverse effects of the CNS such as dizziness (15). It has been stated that ingestion of ethanol with medicinal products should not result in blood concentrations eventually leading to such effects. The CHMP further stated that herbal medicinal products should not be used in neonates and infants younger than 2 years. Furthermore, a single dose of an ethanol-containing medicinal drug should not lead to a blood ethanol concentration exceeding 125 mg/L. For a 6-year-old child of 20 kg b.w., the CHMP calculated a maximum (per treatment) acceptable dose of 1.5 g ethanol.

In a Questions and Answers statement published later, the CHMP (16) stated that in its opinion it seems reasonable to accept amounts that raise blood ethanol levels by no greater than the endogenous 1.5 mg/L. The latter value was based on the assumption by CHMP that ethanol is present as an endogenous substance in the blood of man, probably produced in the intestinal tract, at an average level of 1.5 mg/L (17). Furthermore, it is stated that according to Jones *et al.* (18), endogenous ethanol reaches low concentrations of 0.39 ± 0.45 µg/mL (0.039 mg/dL) in the blood of sober people. Where exposure to ethanol from a medicine is higher than 6 mg/kg b.w. per day, consideration should be given to restricting supply to the patient under the supervision of a physician (prescription-only), in order to control repeated short-term use. Furthermore, the package leaflet should contain information referring to the ethanol content of the product and the possible neurophysiological hazards related to its use.

It was the aim of this study to assess scenarios of ethanol exposure of children via conventional food items in order to make data on the exposure by food available for the current discussion in the field of phytomedicine regulation.

The available information in the international literature on ethanol levels in food items is extraordinarily limited and focused on the forensic implications of such sources of exposure (1). Therefore, we have analyzed a broad spectrum of food items purchased from major German retailers. The food items had been selected under the aspect of their suspected or reported ethanol content. Major criteria were the use of ethanol-forming yeast or other microorganisms in the production process (bread, yogurt, etc.) or descriptions about ethanol formation in fruit during the ripening process (banana, pear). Furthermore, fruit juices that are known to contain ethanol as a consequence of yeast infections between harvest and heat treatment of the juice were also analyzed.

Based on these findings, we have estimated exposure for various scenarios for a 6-year-old child of a b.w. of 20 kg to get a better insight in the relative contribution of food to the overall ethanol exposure in this age group.

Experimental

Selection of samples and determination of ethanol levels

The selection of food items was focused on fermented products such as bread, yogurt, kefir or vinegar and on fruit juices, which are prone to intermediate fermentation before and during manufacturing. The limit of quantification (LOQ) was at 0.0019 g per 1 L. This corresponds to 19 mg ethanol per 100 g food. The samples were purchased randomly from various German retail/discounter stores and mostly if not exclusively represented brands prepared for the nationwide market.

All chemicals used for the analysis were of reagent grade. Potassium hexacyanoferrate (II) and zinc sulfate × 7 H_2O were from Merck (Darmstadt, Germany), methanol and ethanol (purity >99.8%) were from Sigma (Taufkirchen, Germany).

Bread, bakery products or fruits were mashed in a blender. An aliquot was weighed and stirred in an ice water bath after addition of another aliquot of pure water over 10 minutes. In order to analyze recovery, a certain amount of methanol was added before stirring. The sample was transferred to a 100-mL flask and, in case of protein-containing food items, 1 mL each of Carrez I (15% potassium hexacyanoferrate (II) solution in water) and Carrez II solution (30% zinc sulfate × 7 H_2O solution in water) were added. Then, the flasks were filled to a total volume of 100 mL and filtered through a Macherey-Nagel (Düren, Germany) 615 MN filter.

Clear juices were analyzed directly, malt beer, cloudy juices or juices with fruit flesh (orange juices) were filtered through a Macherey-Nagel 615 MN filter and then filtered through Membrane Nylon filter 45 µm (LLG Labware, Meckenheim, Germany).

Samples were analyzed in an Agilent 7890 A gas chromatograph (Agilent, Waldbronn, Germany) on a 30 m/0.25 mm Optima 225–0.25 µm column. The injection volume was 1 µL, the temperature program was as follows: 3 minutes at 50°C, then rising by 10°C/minute to 140°C, hold for 3 minutes, then rise by 35°C/minutes to 220°C, hold for 1 minute. Under these conditions, ethanol eluted after 3.27 minutes and methanol after 2.87 minutes. The lowest standard ethanol concentration used was 0.0025% (v/v) equivalent to 0.01975 g/L (LOQ). For a sample size of 10 g or 100 mL, this corresponds to a concentration of 0.019 g ethanol per 100 g or per 1 L, respectively. The analysis was started with three different but exactly determined amounts from each sample. In each of these preparations, the ethanol content was analyzed in triplicate. In very ripe bananas, brown regions of the edible fruit were cut out and discarded.

For each sample the arithmetic mean and standard deviation were calculated from $n = 3$ independent determinations.

Exposure scenarios

In order to estimate the probable average daily ethanol exposure of a 6-year-old child of 20 kg b.w., we based our assumptions with respect to the food items most relevantly contributing to the ethanol uptake, like apple juice, bread and bakery products and bananas on the following data. The amount of fruit juice consumed daily (162 mL) was taken from a survey published by Dennison *et al.* (19) on the average daily consumption of fruit juices by preschool children in the USA. This number was used as a default value for apple juice. A (partial) replacement of apple juice by orange or grape juice would not change the picture substantially, since all three food items contained ethanol in the same range. Furthermore, it was assumed that a high consumer of apple juice is unlikely to be a high consumer of orange juice at the same time. Thus, apple juice was considered as a reasonable surrogate for the consumption of fruit juice. For the daily intake of bananas, an average of 23.5 g/day was taken from a survey on food consumption by German preschool children (20). From the same survey, the average consumption of bakery products made from wheat flour (62.5 g/day) and rye flour (12.3 g/day) resulting in a total of 74.8 g/day were used. It was assumed that this distribution between wheat and rye flour can be applied to the overall consumption of bakery products. The level in milk rolls was used as the highest level since burger rolls in American style are unlikely to be consumed on a regular daily basis. The average and high consumption of data were multiplied with the mean ethanol contents of the three food categories.

For high (acute) consumption, published data for the 89th percentile for fruit juice consumption among preschool children in the USA of 356 mL (19), and the 97.5th percentile for the daily intake of bananas (239.2 g) was taken from a survey on food consumption by German preschool children (20). From the same survey, the 97.5 percentile for consumption of bakery products made from wheat flour (190.9 g/day) was used as a surrogate for the consumption of bakery products. For these (three different) scenarios (Table III), it was assumed that only one of these food items ("category") was consumed at the high consumption level, while the others were consumed at the average level. This method is in accordance to a recent EFSA Food Additive Intake Model (21) using the single highest 95th percentile for consumers only from one food combined with the population average from the rest of the diet in order to avoid overestimates of exposure.

Results and discussion

Ethanol levels in various food items

It was found that all brands tested of apple juice, grape juice and orange juice contained detectable amounts of ethanol (Table I). The highest levels were found in grape juice (0.29–0.86 g/L), while apple juice samples differed by more than 10-fold (0.06–0.66 g/L) in their ethanol content. The data for orange juice seemed to be more consistent (0.16–0.73 g/L) although the number of samples ($n = 5$) was rather limited. The tested samples of malt beer, a specialty made from non-fermented beer broth, differed enormously in their ethanol contents (<LOQ – 2.15 g/L), which may reflect fundamental differences in the manufacturing process. In a sample of vinegar (made from fermented wine), the highest ethanol levels among all liquid food items were found.

In bread and bakery products, it was obvious that the highest ethanol levels were present in two packed roll products, i.e., American style burger rolls (1.28 g/L) and French style milk rolls (1.21 g/L). In other types of bakery products such as regular bread and rolls, lower but detectable levels (0.14–0.29 g/L) were found. In dry products packed in paper/cardboard packaging such as Scandinavian style crispbread or zwieback, the levels were below the LOQ. In one sample of apple pie in dried fruit and in fermented dairy products such as yogurt or kefir, the levels were very low, some even below LOQ. In banana, the ethanol content was relatively low when compared, e.g., to certain bakery products.

Table I. Ethanol contents in various food items[a]

	Mean	SD
Grape juice (g/L)		
Brand 1 (red)	0.77	±0.05
Brand 2 (rose)	0.29	±0.02
Brand 3 (red)	0.86	±0.10
Apple juice (g/L)		
Brand 1	0.24	±0.01
Brand 2	0.06	±0.01
Brand 3	0.66	±0.05
Brand 4	0.10	±0.02
Brand 5	0.26	±0.05
Mean	0.26	
Orange juice (g/L)		
Brand 1	0.72	±0.05
Brand 2	0.73	±0.03
Brand 3	0.30	±0.02
Brand 4	0.16	±0.01
Brand 5	0.20	±0.01
Malt beer (g/L)		
Brand 1	2.15	± 0,2
Brand 2	<LOQ	
Brand 3	0.44	±0.02
Vinegar (g/L)		
Vinegar (white, from wine)	2.64	±0.09
Bread and bakery products, packed (g/100 g)		
Wheat toast	0.18	±0.01
Wheat rolls	0.14	±0.01
Burger rolls, American style	1.28	±0.08
Wheat and rye bread	0.29	±0.02
Crispbread, Scandinavian style	<LOQ	
Zwieback	<LOQ	
Rye bread	0.18	±0.01
Pumpernickel, rye	0.03	±0.01
Rye bread, traditional	0.20	±0.01
Rye bread, organic	0.17	±0.01
Apple pie, traditional, packed	<LOQ	
Sweet milk rolls, French style	1.21	±0.02
Mean (without burger rolls, American style)	0.22	
Bread, loose (g/100 g)		
Wheat bread	0.12	±0.01
Bananas		
Banana, green peel	<LOQ	
Banana, ripe	0.02	±0.01
Banana, very ripe, peel with dark zones	0.04	±0.01
Mean	0.02	
Other fruit (g/100 g)		
Pear, ripe	0.04	±0.01
Mango, ripe	<LOQ	
Apple sauce, ready to eat	<LOQ	
Fruit salad, ready to eat	0.01	±0.01
Dried fruit		
Prunes, soft	<LOQ	
Figs, soft	<LOQ	
Dairy products (g/100 g)		
Kefir 1	0.02	±0.01
Kefir 2	<LOQ	
Kefir 3	<LOQ	
Yogurt, cherry	0.02	±0.01
Yogurt, with Bircher muesli	<LOQ	

[a]Data represent mean values (g/L or g/100 g) and standard deviations (SD) of three independent measurements/samples.

Furthermore, there was a good correlation between the degree of ripeness of the banana and the ethanol content, i.e., very ripe banana had the highest level with 0.04 g/L.

Based on these data, we designed a scenario for a daily consumption of three major food items ("categories"), i.e., bananas, bread and bakery products (without burger rolls, American style), and apple juice by a 6-year-old child of 20 kg b.w. For this purpose, published consumption data for preschool children from the USA and Germany were used as described under "Experimental" (Table II). Next, the average ethanol level in each of the three categories was multiplied by the assumptions for daily consumption. Thus the scenario resulted in an estimate of ~0.21 g ethanol consumed per day equivalent to a relative daily exposure of ~10.3 mg ethanol/kg b.w. for a child of 20 kg b.w. This scenario does not consider the consumption of any other food item probably also containing ethanol such as yogurt, vinegar, fruit salad, etc.

In the next step, scenarios were focused on high (acute) exposure. It was assumed that only one of the three food items ("categories") was consumed at the high (89th or 97.5th percentile, respectively) level, as reported by Dennison *et al.* (19) and BfR (20), while the others were consumed at the average level. It was found that under these conditions, an acute daily exposure of 12.5–23.3 mg/kg b.w. in preschool children may occur (Table III).

Consequences for risk assessment

There are a few reports on ethanol levels in food not labeled as alcohol-containing, while the possible consequences for human exposure were estimated in one publication only (22). Fruit juices like apple juice play a major role as one of those food items being among the most popular beverages for children. In apple juices (by various vendors), ethanol levels varied between 0.1 and 0.4 g/L (23). Ethanol levels were also recently reported by Gros (24) to be in the range of 0.041–0.184 g/L. Our findings for apple juice are in the same range with the exception of one brand (among five) showing a much higher level, i.e., 0.66 g/L. According to the German "Deutsches Lebensmittelbuch" (German Book of Food Standards), fruit juices may contain up to 0.38% (v/v) ethanol (25) equivalent to 3 g/L. Thus, all apple juice brands analyzed were within the range legally permitted. For orange juice, surprisingly no

Table II. Scenario on estimated span of average daily (mg/kg b.w.) and mean average daily exposure to ethanol from food for a 6-year-old child of 20 kg b.w. for the three food categories apple juice, bread and bakery products, and banana

Food item	Ethanol content (g/L[a]) or (g/100 g[b])	Daily consumption	Ethanol consumption (g)	Arithmetic mean of exposure (g)	Relative ethanol consumption (mg/kg b.w.)	Arithmetic mean of exposure (mg/kg b.w.)
Apple juice[a]	0.06–0.66	162.8 mL[b]	0.01–0.11	0.04	0.5–5.5	2.0
Bread and bakery products[c]	0.009[d]–1.21[e]	74.8 g[f]	0.007–0.91	0.16	0.35–4.6	8.0
Banana, edible portion[c]	0.009[d]–0.04	23.5 g[f]	0.002–0.009	0.005	0.1–0.45	0.3
Total (sum of means)				0.21		10.3

[a]g/L.
[b]According to Reference (19).
[c]g/100 g.
[d]0.5 × LOQ = 0.009 g/100 g; 0.5 × LOQ = 0.009 g/L.
[e]Without burger rolls, American style.
[f]Modified from Reference (20).

Table III. Scenarios on estimated span of high daily (mg/kg b.w.) and mean high daily exposure to ethanol from food for a 6-year-old child of 20 kg b.w. for the sum of the three categories: apple juice, bread and bakery products, and banana. it is assumed that one category is highly consumed, while the others are consumed at an average level

Food item	Ethanol content (g/L[a]) or (g/100 g[b])	Daily consumption	Ethanol consumption (g)	Arithmetic mean of exposure (g)	Relative ethanol consumption (mg/kg b.w.)	Arithmetic mean of exposure (mg/kg b.w.)
Apple juice[a]	0.06–0.66	355.2 mL[c]	0.02–0.23	0.09	1.0–11.5	4.5
All others[d]				0.17		8.3
Total (sum of means)				0.33		12.8
Bread and bakery products[b]	0.009[e]–1.28[f]	190.9 g[g]	0.02–2.31	0.42	1.0–115.5	21.0
All others[d]				0.05		2.3
Total (sum of means)				0.35		23.3
Banana, edible portion[b]	0.009[e]–0.040	239.2 g[g]	0.021–0.096	0.05	1.05–4.8	2.5
All others[d]				0.20		10.0
Total (sum of means)				0.38		12.5

[a]g/L.
[b]g/100 g.
[c]89th percentile according to Reference (19).
[d]Sum of others (average consumption), taken from Table 1.
[e]0.5 × LOQ = 0.009 g/100 g; 0.5 × LOQ = 0.009 g/L.
[f]Including burger rolls, American style.
[g]97.5th percentile, modified from Reference (20).

data were found in the literature. We found substantial levels of ethanol in all brands tested with two brands showing even higher levels than in any apple juice brand analyzed.

Grape juice, with an alcohol content of up to 1% (v/v) can be marketed in the EU (26). In freshly opened commercially available grape juices, the ethanol concentrations were reportedly between 0.3 and 1.8 g/L and increased significantly in two cases during 7 days in storage at room temperature from 0.3 to 0.9 and 0.5 to 1.2 g/L, respectively (23). We found ethanol levels between 0.29 and 0.86 g/L confirming that grape juice, in addition to malt beer, is a non-labeled beverage that regularly shows a relatively high alcohol content. In sauerkraut, the ethanol concentration was measured at 2 g/kg. Bananas were stored for 9 days at room temperature and protected from direct sunlight. On the day of consumption, the matured peeled bananas had an ethanol concentration of 0.5 g/100 g (23). Our findings of 0.4 g/100 g in ripe bananas are thus realistic. In our samples of ripe banana, brown zones of the fruit were removed/cut out, since many consumers including children handle the fruit in the same way.

In bread and bakery products, a wide range of ethanol levels was found. The highest levels with 1.21 and 1.28 g/100 g were detected in a packaged fine bakery product (milk rolls, French style) and in burger rolls, American style. Very similar levels were reported by Logan and Distefano (1) in certain bakery products from the US market such as apple walnut rolls, rosemary onion bread or raisin bread.

In our samples of bread and regular rolls, lower levels were found while certain other types of bakery products, e.g., zwieback or crispbread, which are dried extensively and packed in gas permeable package materials such as paper contained no ethanol above the LOQ. Thus, for bakery products, manufacturing and packaging procedures seem to have a marked influence on ethanol levels.

The low levels in yogurt or kefir suggest that these products were fermented under controlled conditions allowing the growth of *Lactobacteria* only but excluding the growth of other microorganisms that form much higher amounts of ethanol.

Based on these data, we have designed a scenario for the daily consumption of ethanol-containing food items by a 6-year-old child of 20 kg b.w. We consider our assumptions to be realistic since they are in agreement with reports by others. The amount of fruit juice consumed daily (162 mL) was taken from a survey published by Dennison *et al.* (19) on the average daily consumption of fruit juice by preschool children in the USA. A (partial) replacement of apple juice by orange or grape juice would not change the picture substantially since all three food items contained ethanol in the same range. High (acute) consumption was assumed, based on 89th or 97.5th percentiles reported by Dennison *et al.* (19) or BfR (20). In these calculations, only one food category was assumed to be consumed at this high level, while the two others contributed at average. These scenarios revealed that acute ethanol exposure can be in the range of 12.5–23.3 mg/kg b.w. per day. This is up to 4-fold higher than the "signal" value of 6.0 mg/kg b.w. suggested for phytomedicines by the CHMP.

Conclusion

Taken together, our data suggest that a variety of food items consumed by preschool children contain substantial amounts of ethanol. The main contributors seem to be bread and bakery products, fruit juices and bananas. For these three categories, an average exposure scenario was derived from the average ethanol levels found and on published consumption data for preschool children in the USA and Germany. An average daily exposure of 10.3 mg ethanol/kg b.w. can be estimated under these assumptions. This amount is almost 2-fold higher than the lowest exposure level from herbal medicines recently suggested to lead to a mandatory list of warning hints with respect to the use in children. For high (acute) consumption of one of the three categories, with the two other categories consumed at the average level, an even higher exposure of 12.5–23.3 mg/kg b.w. was calculated. This indicates that acute exposure from food can exceed by far the "signal" value of 6.0 mg/kg b.w. suggested for herbal drugs anticipated for the use in children. An exceedance of this value was suggested to require warning hints on phytomedicines with respect to the child's performance, e.g., at school, and recommendations to the health care professional to avoid chronic use. This suggestion seems not to take into account the scientific information on the factual and commonly accepted exposure of children to low levels of ethanol via food. It is noteworthy that such precautionary regulatory attempts tend to regulate medicinal drugs in a considerably more strict way than food. The benefit of such regulatory interventions for the consumer/patient remains questionable.

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