

Commentary

ACETALDEHYDE: A CUMULATIVE CARCINOGEN IN HUMANS

Lachenmeier *et al.* are to be congratulated. Their risk assessment of acetaldehyde present as a congener in alcoholic beverages touches the tip of the iceberg [1]. The world-wide annual incidence of lung, upper aerodigestive tract and stomach cancers is close to 3 million (25% of all cancers), and it is these organs that are exposed to acetaldehyde derived from various environmental sources, as well as from microbial and mucosal oxidation of ethanol to acetaldehyde [2]. The extension of the European Food Safety Authority's margin of exposure (MOE) approach to cover the total acetaldehyde exposure of humans with different drinking, smoking and eating habits, and with varying genetic and/or other risk factors, could thus have an enormous impact on cancer prevention world-wide.

The ethanol molecule itself is not carcinogenic. However, acetaldehyde is carcinogenic in animals and furthermore, some gene mutations affecting hundreds of millions of people provide an exceptional human model for long-term acetaldehyde exposure in man. These gene polymorphisms have a profound effect on the concentration or presence of acetaldehyde in saliva produced from ethanol by oral microbes or parotid glands and oral mucosa [3–7]. Most importantly, the same mutations associate among alcohol drinkers and/or smokers dose-dependently with a particularly high cancer risk of the upper digestive tract [8–10]. Alcohol, tobacco and poor oral hygiene are other important risk factors associated with increased exposure to acetaldehyde derived either from microbial metabolism of ethanol or from tobacco smoke [11–14]. The greatest risk for gastric carcinoma due to severe atrophic gastritis has been found in Japanese alcoholics, who are heterozygous for an inactive aldehyde dehydrogenase (ALDH2) genotype [15]. In achlorhydric atrophic gastritis, bacterial overgrowth results in the presence of glucose in formation of minor concentrations of endogenous ethanol and acetaldehyde in the gastric juice, and after administration of a small amount of alcohol intragastric acetaldehyde production increases 6.5-fold compared to healthy controls [16].

In addition to alcohol and tobacco, poor oral hygiene and some nutritional and environmental factors are important risk factors for upper digestive tracts cancers in undeveloped countries. It is well known that most of the beverages and foodstuffs produced or preserved by fermentation and considered to be non-alcoholic may, in fact, contain small amounts of ethanol and mutagenic (>100 µM) concentrations of acetaldehyde. These

include dairy products (e.g. yogurts), fermented soy products (e.g. soy sauces), tofu products, fermented vegetables (e.g. Chinese pickles and kimchi), vinegar and home-made beers and meads. Many fruits, e.g. some apples, may have their own metabolic pathways for acetaldehyde production [17]. All these foods have been used for centuries world-wide. In addition, acetaldehyde is used widely as a food additive and aroma agent. In the products mentioned above we have measured acetaldehyde concentrations ranging from 0 to more than 3500 µM and ethanol from 1 mM to 300 mM. It should be emphasized that during mastication ethanol in food is metabolized immediately to acetaldehyde by oral microbes.

As discussed by Lachenmeier *et al.* [1], and presented in Table 1, acetaldehyde exposure in man is indisputably cumulative. This concept is also supported by a recent large-scale epidemiological survey demonstrating a supra-multiplicative combined risk for oesophageal cancer among alcohol and tobacco consumers, who are low ADH1B and ALDH2-deficient carriers, the highest adjusted odds ratio being as high as 382.3 [10].

As shown in Table 1, the cumulative cancer risk of acetaldehyde strongly suggests world-wide screening of acetaldehyde levels in thousands of beverages and foodstuffs, as well as giving high priority to regulatory measures and consumer guidance. The good news is that there are several means for the minimization of acetaldehyde exposure. The ALARA principle ('as low as reasonably achievable') to acetaldehyde levels of alcoholic beverages, tobacco smoke and also to other beverages and foods produced by fermentation can be applied. Oral hygiene can be improved. Risk groups with gene polymorphisms and hypochlorhydric atrophic gastritis associated with enhanced acetaldehyde exposure can be screened and informed. Acetaldehyde exposure can be decreased or even totally abolished by using special medical devices that slowly release L-cysteine [18,19]. Equally important will be the re-evaluation of the 'generally recognized as safe' (GRAS) status of acetaldehyde and the upgrading of the carcinogen classification of acetaldehyde, as suggested by Lachenmeier *et al.* [1].

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Table 1 Examples of cumulative acetaldehyde exposure in humans (estimates based on referred publications and own pilot samples; margin of exposure (MOE) was calculated according to Lachenmeier *et al.* [1]; MOE > 10 000 considered to be of low concern for public health).

Source of exposure (Ach = acetaldehyde) (secretion of saliva assumed to be about 1 ml/min, weight 60 kg)	Exposure mg/kg bw/day	MOE
Acetaldehyde as a congener [1]	0.1–1.6	560–35
Heavy drinking (120 g pure alcohol/day = 10 doses/day)		
Normal ALDH2: Ach 100 µM in saliva for 17 hours [11]	0.078	718
ALDH2-deficient: Ach 250 µM in saliva for 17 hours [3,8]	0.194	289
Combined ALDH2-deficiency and low ADH1B: ACH 250 µM in saliva for 24 hours (?) [3,8,9]	0.275	204
30 cigarettes/day, Ach exposure via saliva (400 µM/150 min) [14]	0.044	1 273
Rest of 0.45 Ach exposure via inhalation [1]	0.406	138
150 ml yogurt/day (Ach 400 µM)	0.044	1 273
150 ml homemade beer (Ach 1200 µM)	0.132	424
150 ml apple, Golden Delicious (Ach 1400 µM)	0.152	368
150 ml apple Jonagold (Ach 22 µM)	0.002	28 000
Worst scenario: ALDH2-deficiency, low ADH1B, heavy drinking and smoking, and one yogurt, one apple (Golden Delicious) and one glass of homemade beer/day (does not include acetaldehyde present in consumed alcoholic beverages as a congener)	1.053	53
Worst scenario + acetaldehyde as a congener [1]	1.153–2.653	49–21

Declaration of interest

The author is a board member of Biohit Oyj.

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