

ACETALDEHYDE

Specific class 1 carcinogen associating with the use of alcoholic beverages

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Key issue in cancer prevention is the identification of specific etiologic factors. Alcohol drinking and tobacco smoking are major risk factors for upper digestive tract cancers. The ethanol molecule itself is not carcinogenic. However, its first metabolite - **acetaldehyde** - is carcinogenic both in animals and man. Some gene mutations affecting hundreds of millions of people provide an exceptional human model for long term acetaldehyde exposure in man. Epidemiological and biochemical studies including alcohol using individuals with these mutations provide undisputable evidence for the local carcinogenic action of acetaldehyde in humans. On this basis acetaldehyde associated with alcoholic beverages was recently classified by the International Agency for Research on Cancer (WHO/IARC) as Group 1 carcinogen to humans. Mutagenic concentrations ($>100\mu\text{M}$) of acetaldehyde are found as a congener in many alcoholic beverages. The most important source of acetaldehyde exposure, however, is the local microbial production of carcinogenic acetaldehyde from ethanol and its accumulation in the oral cavity and saliva.

Ethanol is readily distributed to the water phase of oral cavity after each sip of alcoholic beverage. Some microbes representing normal oral flora instantly metabolize ethanol locally to acetaldehyde. This instant acetaldehyde production lasts for up to ten minutes. High ethanol concentration of an alcoholic beverage results in a higher peak acetaldehyde level ($100\text{-}200\mu\text{M}$) and as well in a longer exposure time. After its ingestion alcohol is evenly distributed to the whole water phase of human body. Depending on the amount of alcohol used ethanol stays in the human body and saliva for hours. This results in long-term exposure to acetaldehyde produced by oral microbes. Some alcoholic beverages, especially sherry and some strong fruit spirits, may contain very high acetaldehyde concentrations. After sipping of these beverages peak salivary acetaldehyde levels are at least doubled for up to 2 minutes.

Tobacco and alcohol are independent and multiplicative risk factors for upper digestive tract cancers. With increasing tobacco consumption the risk increases linearly. On the other hand, alcohol and tobacco have also a synergistic effect on acetaldehyde exposure via saliva. The concentration of acetaldehyde is more than 1000 times greater than that of any other carcinogenic compound present in the cigarette smoke. Most importantly, acetaldehyde of tobacco smoke - as a very water soluble agent - becomes dissolved in saliva during smoking. Smoking results in mean $250\mu\text{M}$ salivary acetaldehyde concentration that lasts as long as active smoking continues i.e. 5-7 minutes. Because chronic smoking modifies the oral flora to produce more acetaldehyde from ethanol, the concomitant smoking and drinking has a synergistic i.e. 7-fold effect on the exposure of the oral cavity and oesophagus to acetaldehyde. Chronic smoking, heavy drinking and poor oral hygiene are established risk factors for oral and oesophageal cancers; as well they appear to increase microbial acetaldehyde production from ethanol.

In conclusion, all known risk factors for upper digestive tract cancer are associated with enhanced exposure to carcinogenic acetaldehyde. The cumulative cancer risk associating with increasing levels of acetaldehyde exposure suggests world-wide screening of acetaldehyde levels of alcoholic beverages and as well of ethanol and acetaldehyde levels of fermented food. The GRAS (Generally Regarded As Safe) status of acetaldehyde should be re-evaluated. The ALARA principle (As Low As Reasonably Achievable) should be applied to acetaldehyde of alcoholic and non-alcoholic beverages and food stuffs produced by fermentation.

Positive news is that there are many ways to reduce acetaldehyde exposure both at population and individual level. These include the moderation of alcohol consumption and quitting from smoking, since these are the major sources of acetaldehyde exposure. One should avoid drinking to intoxication, since high salivary ethanol levels lead to higher acetaldehyde concentrations in the saliva. Light alcoholic beverages should be preferred, since local microbial acetaldehyde production in the mouth is higher after sipping of strong alcoholic beverages. Measures improving oral hygiene should be encouraged. Alcoholic beverages containing high acetaldehyde levels e.g. sherry, port wine and strong fruit beverages should be avoided. Acetaldehyde levels of alcoholic beverages and food stuffs should be informed to the consumers. Risk groups with ADH- and ALDH2 gene polymorphisms, *H. pylori* infection and or achlorhydric atrophic gastritis should be screened and informed about the possibilities for the minimization of acetaldehyde exposure. Medical devices releasing slowly L-cysteine provide new means for the reduction of local acetaldehyde exposure and as well for future intervention studies.

Key references

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