

## **Volume 96: Alcoholic Beverage Consumption and Ethyl Carbamate (Urethane) 6–13 February 2007**

An *IARC Monographs* Working Group of 26 scientific experts from 15 countries met in Lyon to re-evaluate the potential carcinogenic hazards to humans from consumption of alcoholic beverages. A separate evaluation was made for ethyl carbamate (urethane), a frequent contaminant of fermented foods and beverages. These evaluations will be published in Volume 96 of the *IARC Monographs*. The previous evaluation of alcohol drinking had been undertaken in 1988 (Monograph volume 44), and that of urethane in 1974 (Monograph volume 7).

### **Alcoholic beverage consumption**

Although moderate alcohol consumption has some health benefits, in particular with respect to cardiovascular problems, the WHO identified the consumption of alcohol as one of the top-10 risks contributing to the worldwide burden of disease. In 2002, more than 1900 million people ( $\geq 15$  years of age) around the world were estimated to be regular consumers of alcoholic beverages, with an average daily consumption of 13 g of ethanol (about one drink). In general, men drink alcohol more often and in larger quantities than women do. On the basis of production data, per-capita consumption is highest in eastern Europe and the Russian Federation. In Africa, South America, and Asia, alcohol consumption is comparatively lower, but in those regions a large proportion of alcohol is produced locally and remains unrecorded. Over the past 40 years, alcohol consumption has remained stable in most regions of the world, except in the western Pacific region — predominantly China — where it has increased about five times during that period. In addition to ethanol and water, alcoholic beverages can contain many different substances derived from fermentation — e.g., ethyl carbamate or urethane; see below) — contamination, and from the use of additives or flavours.

#### *Studies of cancer in humans*

The Working Group reviewed the epidemiological evidence on the possible association between alcohol consumption and cancer at 27 anatomical sites.

##### – Cancer of the upper digestive tract

Many studies of different design and in different populations around the world have consistently shown that regular alcohol consumption is associated with an increased risk for cancers of the oral cavity, pharynx, larynx, and the esophagus. Daily consumption of around 50 g of ethanol increases the risk for these cancers two to three times, compared with the risk in non-drinkers. In addition, for these cancer types the effects of drinking and smoking seem to be multiplicative.

##### – Liver cancer

A large number of cohort and case-control studies provide strong evidence that the consumption of alcohol is an independent risk factor for primary liver cancer. Cirrhosis and other liver diseases often occur before the cancer becomes manifest and patients with these disorders generally reduce their alcohol intake. Therefore, the effect of alcohol consumption on the risk for liver cancer is difficult to quantify.

##### – Breast cancer

More than 100 epidemiological studies that assessed the association between alcohol consumption and breast cancer in women consistently found an increased risk with increasing alcohol intake. A pooled analysis of 53 studies on more than 58 000 women with breast cancer showed that daily consumption of about 50 g of alcohol is associated with a relative risk of about 1.5 (95% confidence interval 1.3–

1.6), compared with that in non-drinkers. Even for regular consumption of about 18 g of alcohol per day, the increase in relative risk is statistically significant.

– Colorectal cancer

The association between alcohol consumption and colorectal cancer has been investigated in more than 50 prospective and case–control studies. Pooled results from eight cohort studies and data from recent meta-analyses provide evidence for an increased relative risk of about 1.4 for colorectal cancer with regular consumption of about 50 g of alcohol per day, compared with that in non-drinkers. This association seems to be similar for colon cancer and for rectal cancer.

– Kidney cancer

There is consistent evidence, both from cohort and case–control studies, of no increase in risk for renal-cell cancer with increasing alcohol consumption. In several studies, increasing alcohol intake was associated with a significantly lower risk for renal-cell cancer. This inverse trend was seen in both men and women.

– Non-Hodgkin lymphoma

Two prospective cohort studies and several large case–control studies showed an inverse association or no association between alcohol consumption and non-Hodgkin lymphoma; most studies showed a lower risk in drinkers than in non-drinkers.

– Lung cancer

In most populations, there is a strong correlation between the use of tobacco and the consumption of alcohol. Many studies have reported an increased risk for lung cancer associated with alcohol drinking, but it is not generally possible to exclude residual confounding by smoking, by far the most important cause of lung cancer. The findings from some of the studies that presented separate data on the risk for lung cancer in non-smokers suggest an increased risk with consumption of alcoholic beverages, but others do not.

– Stomach cancer

Epidemiological studies on the risk for stomach cancer associated with the consumption of alcoholic beverages show inconsistent results, with significantly increased risks being reported in some studies, but not in others. Potential confounding by *Helicobacter pylori* infection, the most important known cause of non-cardia stomach cancer, does not seem to be a major concern, because the vast majority of the population in areas where an association was seen had probably been infected by the bacteria. However, alcohol drinking may have been accompanied by dietary deficiencies and other unfavourable lifestyle factors. Since insufficient allowance was made for these factors, the interpretation of the findings is not clear.

For other cancers, the evidence of an association between alcohol consumption and cancer risk was generally sparse or inconsistent.

The Working Group confirmed the previous conclusion (Volume 44, 1988) that cancers of the oral cavity, pharynx, larynx, esophagus and liver are causally related to the consumption of alcoholic beverages. In addition, there is *sufficient evidence* to conclude that breast cancer in women and colorectal cancer also belong in this list.

### *Genetic susceptibility*

The major alcohol-metabolising enzymes in humans are the alcohol dehydrogenases (ADH) that oxidise ethanol to acetaldehyde, and the aldehyde dehydrogenases (ALDH) that detoxify acetaldehyde to acetate. The variant allele ALDH2\*2, which encodes an inactive subunit of the enzyme ALDH2, is dominant and highly prevalent in certain eastern-Asian populations (28–45%), but rare in other ethnic groups. Most homozygous carriers of this allele (ALDH2\*2/\*2) are abstainers or infrequent drinkers, because the enzyme deficiency would cause a strong facial flushing response, physical discomfort, and severe toxic reactions. In heterozygous carriers (ALDH2\*1/\*2, with about 10% residual ALDH2 activity) these acute adverse effects are less severe, but when they consume alcohol these carriers are at high risk for several alcohol-related aerodigestive cancers. For example, genetic epidemiological studies provide strong evidence that the heterozygous *ALDH2\*1/\*2* genotype contributes substantially to the development of esophageal cancer related to alcohol consumption, with relative risks — compared with carriers of the homozygous ALDH2\*1/\*1 genotype, which encodes the active enzyme — of up to 12 for heavy drinkers. Compared with those with the ALDH2\*1/\*1 genotype, the heterozygous carriers have higher levels of acetaldehyde in blood and saliva after alcohol drinking, and in a recent study higher levels of acetaldehyde-related DNA adducts have been measured in their lymphocytes.

### *Cancer in experimental animals*

Since the previous evaluation, the evidence of the carcinogenicity of ethanol in experimental animals has become stronger. Administration of ethanol in the drinking-water caused a dose-related increase in the incidence of hepatocellular adenomas and carcinomas in male mice, an increased incidence of head and neck carcinomas in male and female rats, an increased incidence of fore-stomach carcinomas, testicular interstitial-cell adenomas, and osteosarcomas of the head, neck, and other sites in male rats, and of mammary adenocarcinomas in female rats. In most of the studies in which it was co-administered with known carcinogens, ethanol enhanced the carcinogenic effect. The Working Group concluded that there is *sufficient evidence* of the carcinogenicity of ethanol in experimental animals.

### **Overall evaluation**

Overall, the Working Group confirmed that alcoholic beverages are *carcinogenic to humans* (Group 1) and concluded that the occurrence of malignant tumours of the oral cavity, pharynx, larynx, esophagus, liver, colorectum, and female breast is causally related to alcohol consumption. For renal-cell cancer and non-Hodgkin lymphoma the Working Group concluded that there is *evidence suggesting lack of carcinogenicity*.

Because the positive associations were generally noted with different types of alcoholic beverage, and in view of the carcinogenicity of ethanol in animals, the Working Group also classified ethanol in alcoholic beverages as *carcinogenic to humans* (Group 1).

The Working Group further agreed that the substantial mechanistic evidence in humans deficient in aldehyde dehydrogenase indicates that acetaldehyde derived from the metabolism of ethanol in alcoholic beverages contributes to causing malignant esophageal tumours.

## Ethyl carbamate (urethane)

### *Exposure data*

Ethyl carbamate has been used as an antineoplastic agent, especially in the treatment of multiple myeloma, and as a co-solvent of drugs commonly used parenterally in humans. While human exposure may have been extensive in the past, the use of ethyl carbamate was largely reduced during the 30 years since the previous IARC evaluation (Volume 7, 1974). Nowadays, it is used as an anaesthetic in veterinary medicine. Ethyl carbamate may be formed naturally as a result of fermentation, and it has been detected in a variety of fermented foods and beverages. The concentrations in wine and beer are usually below 100 microgram per litre, whereas higher levels (in the milligram per litre range) have been found in some spirits. The concentration of ethyl carbamate in foods has been regulated and significantly reduced during the last 20 years.

### *Cancer in humans*

Despite the large-scale use of ethyl carbamate in patients during 1950–1975, there are no epidemiological data available on its potential carcinogenicity in humans.

### *Cancer in experimental animals*

Ethyl carbamate and its metabolites vinyl carbamate and vinyl carbamate epoxide have been tested for carcinogenicity in numerous studies in experimental animals.

*Mice* treated orally with ethyl carbamate demonstrated an increased incidence of lung adenomas, carcinomas and squamous-cell tumours, lymphomas (mainly lymphosarcomas), mammary gland adenocarcinomas, carcinomas and adenoacanthomas, leukaemias, forestomach squamous-cell papillomas or carcinomas, heart haemangiosarcomas, liver haemangiosarcomas, Harderian gland adenomas or carcinomas and angiomas. Subcutaneous administration of ethyl carbamate to adult and newborn mice induced significant increases, respectively, in the incidence of lung adenomas and hepatomas. Topical application of ethyl carbamate to mice resulted in a significant increase in the incidence of lung adenomas and mammary gland carcinomas. Mice exposed by inhalation to ethyl carbamate had an increased incidence of lung adenocarcinomas, leukaemias and uterine haemangiomas. Intraperitoneal administration of ethyl carbamate to adult mice resulted in a significant increase in lung adenomas, hepatomas and skin papillomas. Similar treatment in newborn mice induced lymphomas, lung adenomas, hepatomas, Harderian gland tumours and stromal and epithelial tumours of the ovary. Mice exposed transplacentally to ethyl carbamate developed an increased incidence of lung tumours, hepatomas and ovarian tumours. Mice born after pre-conceptual exposure of the fathers to ethyl carbamate had an increased incidence of pheochromocytomas and adrenal gland tumours.

*Rats* treated orally with ethyl carbamate had an increased incidence of Zymbal gland carcinomas and mammary gland carcinomas.

*Hamsters* treated orally with ethyl carbamate showed an increased incidence of skin melanotic tumours, forestomach papillomas, mammary gland adenocarcinomas, liver hepatomas, liver and spleen haemangiomas, and thyroid, ovarian and vaginal carcinomas.

*Monkeys* treated orally with ethyl carbamate developed hepatocellular adenomas and carcinomas and adenocarcinomas of the lung, in one study.

Intraperitoneal injection of vinyl carbamate or vinyl carbamate epoxide induced lung adenomas in female A/J mice and liver tumours (hepatomas) in male B6C3F<sub>1</sub> mice. Intramuscular injection of vinyl carbamate or vinyl carbamate epoxide into female rats caused sarcomas at the injection site. In both cases, vinyl carbamate epoxide was more active than vinyl carbamate.

The Working Group concluded that there is *sufficient evidence* for the carcinogenicity of ethyl carbamate and its metabolites vinyl carbamate and vinyl carbamate epoxide in experimental animals.

#### *Other relevant data*

Ethyl carbamate is metabolized predominantly by the enzyme CYP2E1, which generates the metabolites vinyl carbamate and vinyl carbamate epoxide, which are likely to be proximate carcinogens. The pathways for the metabolism of ethyl carbamate are similar in rodents and humans. Interactions between ethanol and ethyl carbamate are complex: co-administration of ethanol has been shown to inhibit the metabolism of ethyl carbamate, while sequential dosing had in some cases an enhancing effect. The enzyme CYP2E1 is strongly induced by ethanol in rats, mice and humans. Chronic exposure to ethanol may thus increase the oxidation of urethane to its reactive epoxide derivative. At high doses, urethane exhibits toxic effects on the central nervous system, the gastro-intestinal tract, the spleen and the thymus in experimental animals. Lower doses lead to long-term effects on the spleen and the thymus. Ethyl carbamate is teratogenic in experimental animals when administered during gestation. The teratogenic effects are evident in the offspring when either male or female rodents are exposed prior to mating or pregnancy. Effects of ethyl carbamate on the reproductive system in mice and rats are minimal and occur only at high doses. Ethyl carbamate is genotoxic, mutagenic and clastogenic, especially in the presence of metabolic activation.

#### **Overall evaluation**

Ethyl carbamate (urethane) is *probably carcinogenic to humans (Group 2A)*.

In making this evaluation, the Working Group noted that (i) experimental evidence suggests great similarities in the metabolic pathways of the activation of ethyl carbamate in rodents and humans; and (ii) the formation of proximate carcinogens that are DNA-reactive and are thought to play a major role in ethyl carbamate-induced carcinogenesis in rodents probably also occurs in human cells.