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Summary of Data Reported and Evaluation

Alcohol drinking

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ALCOHOL DRINKING
(Group 1)

For definition of Groups, see Preamble Evaluation.

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Chem. Abstr. Name: Ethanol

5. Summary of Data Reported and Evaluation

5.1 Chemical composition, consumption and trends

Alcoholic beverages are produced from raw materials by fermentation. The predominant types of commercially produced alcoholic beverages are beer, wine and spirits. The main components of all alcoholic beverages are ethanol and water; beers also contain substantial amounts of carbohydrates. Many compounds that have been identified as common to all alcoholic beverages are present in different quantities depending on the beverage. Some components and occasional contaminants include known and suspected carcinogens. Beers and wines also contain vitamins and other nutrients which are usually absent from distilled spirits. Despite the differences in concentration, the average intake of ethanol per drink is approximately constant across beverage types.

Alcoholic beverages, both home-made and commercially produced, have long been consumed in most parts of the world. Recorded consumption tends to be higher in societies with populations of European origin and lower in Muslim societies. In most of the developed countries, a majority of adults consume alcoholic beverages at least occasionally.

Since 1950, consumption per head has increased substantially in most parts of the world, although since the mid-1970s a reduction in the rate of increase and, in some countries, a decline in consumption have occurred. Drinking patterns - overall level of alcohol consumption, choice of alcoholic beverages, differences by sex and age and temporal variations - differ among and within societies.

5.2 Experimental carcinogenicity data

Ethanol and some alcoholic beverages were tested for carcinogenicity in five studies in mice by oral administration. Ethanol was also tested in one experiment by transplacental exposure or exposure *via* mother's milk. Due to severe limitations in experimental design or conduct, these studies could not be used for an evaluation of carcinogenicity.

Two studies involved oral administration of ethanol and of one alcoholic beverage to rats. One study was inadequate for evaluation, and in the other no difference in the incidence of tumours was found.

In seven studies, ethanol or an alcoholic beverage was administered to rats as a control in studies of combined effects with a known carcinogen. In one of these, involving male animals only, ethanol administered in water as the drinking fluid significantly increased the incidences of hepatocellular carcinomas and of tumours of the pituitary gland, of the adrenal gland and of pancreatic islet cells, but neither isocaloric nor isonutrient diets were used. All of these studies, however, suffered from various limitations and could not be used for evaluation.

Ethanol and certain alcoholic beverages were administered to hamsters by oral administration in four studies, three of which were designed to ascertain combined effects with known carcinogens. All of these studies suffered from various limitations and could not be evaluated. One study in mice involving application of ethanol

or residues of alcoholic beverages to the skin could also not be evaluated.

In experiments in which various carcinogens were administered orally with ethanol as a vehicle, ethanol enhanced the incidence of nasal cavity tumours induced in mice by *N*-nitrosodimethylamine and enhanced the incidences of oesophageal/forestomach tumours and lung tumours induced in mice by *N*-nitrosodiethylamine or *N*-nitrosodi-*n*-propylamine.

In further studies, various carcinogens were administered by different routes simultaneously with ethanol in water as the drinking fluid or in liquid diets. Ethanol enhanced the incidence of benign tumours of the nasal cavity induced in rats by *N'*-nitrosonornicotine given in a liquid diet, and enhanced the incidences of nasal cavity and tracheal tumours and of neoplastic nodules of the liver induced in hamsters by *N*-nitrosopyrrolidine given by intraperitoneal injection. Administration of ethanol in the drinking-water enhanced the incidences of hepatocellular carcinomas and of liver angiosarcomas induced in rats by inhalation of vinyl chloride.

In a number of other experiments, ethanol had no modifying effect on the overall incidence of tumours in mice, rats or hamsters given *N*-nitrosomethylbenzylamine, *N*-nitrosobis(2-oxopropyl)amine, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, 7,12-dimethylbenz[*a*]anthracene or 1,2-dimethylhydrazine by various routes of administration.

There is *sufficient evidence* for the carcinogenicity of acetaldehyde (the major metabolite of ethanol) in experimental animals.

5.3 Human carcinogenicity data

Cancers of the oral cavity and pharynx

In six retrospective cohort studies of persons with an intake of alcoholic beverages higher than that of the reference population and including alcoholics and brewery workers, the risk for cancers of the oral cavity and pharynx (effectively excluding the nasopharynx) has been examined. In five studies of alcoholics, the mortality or incidence ratio was significantly increased by between two and five fold.

In two prospective cohort studies, the risk for cancers of the oral cavity, pharynx, larynx and oesophagus combined and for cancers of the oral cavity, pharynx and oesophagus combined increased with the daily number of drinks.

Case-control studies have been performed of cancers of the oral cavity (11 studies), pharynx (ten studies), and oral cavity and pharynx combined (two studies). In all but two of the studies, the risk increased significantly with increasing level of consumption of alcoholic beverages; in two studies, nonsignificant increases were observed. These results persisted after adjustment for tobacco smoking. The risk increased with daily intake of alcoholic beverages at any level of tobacco smoking in six studies in which this was examined, and the risk for cancer increased with amount drunk by nonsmokers in three out of four studies in which this aspect was examined.

Epidemiological studies clearly indicate that drinking of alcoholic beverages is causally related to cancers of the oral cavity and pharynx (excluding the nasopharynx). There is no indication that the effect is dependent on type of beverage.

Cancer of the larynx

Data on laryngeal cancer were provided by six retrospective cohort studies - five of alcoholics and one of brewery workers. The risk for laryngeal cancer was significantly increased by two to five fold in four of the studies.

Fourteen case-control studies in North America and Europe all showed that the relative risk increased with level of intake of alcoholic beverages.Three large studies indicated that the risk associated with intake of alcoholic beverages was stronger for cancer at sites at the junction between the larynx and pharynx than for cancer of the endolarynx. These results persisted after adjustment for tobacco smoking. In nine of the studies in which this was examined, it was reported that the association with drinking of alcoholic beverages was seen at any level of smoking. Three studies have been carried out on small groups of lifetime nonsmokers; the relative risk increased with amount of drinking in one, but no difference was seen in the proportion of drinkers and nondrinkers in the two others.

Epidemiological studies clearly indicate that drinking of alcoholic beverages is causally related to laryngeal cancer. There is no indication that the effect is dependent on type of beverage.

Cancer of the oesophagus

Seven of eight retrospective cohort studies of alcoholics and brewery workers showed two- to four-fold increased risks of cancer of the oesophagus, although this was nonsignificant in two. Of 13 case-control studies, 11 showed significantly increased relative risks with level of intake of alcoholic beverages. The increased risk persisted after adjustment for tobacco smoking and was seen at all levels of tobacco smoking in the two studies in which this was examined. The risk increased with intake of alcoholic beverages in a small number of persons who had never smoked in the only study in which this aspect was examined.

Epidemiological studies clearly indicate that drinking of alcoholic beverages is causally related to cancer of the oesophagus. There is no indication that the effect is dependent on type of beverage.

Cancer of the stomach

In three of 13 cohort studies, stomach cancer risk was increased in association with consumption of alcoholic beverages, but in only one was this statistically significant. Summation of observed and expected number of cases of stomach cancer in the eight retrospective cohorts of persons with above-average consumption of alcoholic beverages indicates a slight deficit in risk.

Data have been reported from 12 case-control studies on the relationship between drinking of alcoholic beverages and stomach cancer. In two studies, the risk for stomach cancer was positively and significantly associated with consumption of alcoholic beverages. In another study, a significant increase in risk was found with one specific drinking practice. One study reported a nonsignificant reduction in the risk for stomach cancer associated with drinking of alcoholic beverages.

In most epidemiological studies of alcoholic beverages and stomach cancer, including all nine retrospective cohort studies, there was no adjustment for any possible confounding effect of diet.

In view of the overall lack of excess risk for stomach cancer in the cohort studies, the inconsistent results of the case-control studies, and the inadequate control for dietary and socioeconomic factors, there is little in the aggregate data to suggest a causal role for drinking of alcoholic beverages in stomach cancer.

Cancer of the large bowel

Two of 13 cohort studies of colon cancer showed an increase in risk, while another showed a nonsignificantly decreased risk associated with raised consumption of alcoholic beverages. Summation of observed and expected numbers of cases of colon cancer in the nine retrospective cohorts of persons with above-average consumption of alcoholic beverages indicates no overall shift in the risk.

For rectal cancer, the risk was increased in association with drinking of alcoholic beverages in four of nine cohort studies. In two of these four studies, a significant increase was seen in relation to beer consumption, including one study in which there was evidence of a dose-response relationship up to a three-fold increase in

risk. In the two others, nonsignificant, two- to three-fold increases in the risk for rectal cancer in alcoholics were reported. Summation of observed and expected numbers of cases of rectal cancer in the seven retrospective cohorts of persons with above-average consumption of alcoholic beverages indicates a slight (15%) excess of cases.

Of the four cohort studies in which data were reported on colon and rectal cancers combined, one showed a significant, two-fold increase, while two others showed a nonsignificant increase in risk with raised consumption of alcoholic beverages.

In four of eight case-control studies of colon cancer, a significant positive relationship was evident with drinking of specific beverages: with beer consumption in two studies, and with spirits consumption in three studies.

In six of nine case-control studies of rectal cancer, a significant positive relationship with drinkingof alcoholic beverages was reported. In three studies, beer consumption wassignificantly associated with rectal cancer in men only; in one study, this association was significant for men and women combined. Of the other two studies with significant positive results, one showed an association with consumption of spirits, the other with total ethanol consumption. A case-control analysis within one of the studies of brewery workers showed a positive relationship between drinking of stout and rectal cancer risk.

In most epidemiological studies of consumption of alcoholic beverages and large-bowel cancer, including all nine retrospective cohort studies, there was no adjustment for any possible confounding effect of diet.

In view of the inconsistent findings from epidemiological studies and the probability of uncontrolled confounding by dietary factors, no conclusion can be drawn about the role of consumption of alcoholic beverages in the causation of colon cancer.

Overall, some of the epidemiological studies provide suggestive but inconclusive data for a causal role of drinking of alcoholic beverages, most often beer consumption, in rectal cancer.

Cancer of the liver

Of four cohort studies of the general population, two showed a significantly increased risk for liver cancer among drinkers of alcoholic beverages, whereas in a third study an increased risk was found only among a subgroup of drinkers in one of the two populations studied. Three of ten cohort studies of persons with high intake of alcoholic beverages showed a significant association between consumption of alcoholic beverages and liver cancer, whereas in five other studies the association was positive but nonsignificant. Summation of observed and expected numbers of cases of liver cancer in these ten studies on special cohorts indicate a significant 50% increase in risk.

Six of ten case-control studies showed significant associations at the two- to three-fold level between consumption of alcoholic beverages and primary liver cancer.

A particularly strong association between consumption of alcoholic beverages and primary liver cancer was demonstrated in a cohort study of hepatitis B surface antigen-positive volunteer blood donors. The results of one case-control and one cohort study suggest that the risk for liver cancer is particularly high among people who both drink alcoholic beverages and smoke cigarettes.

Potential confounding due to hepatitis B virus, tobacco smoking and aflatoxin was not explored in all the studies; whenever it was, it did not alter the findings qualitatively. The available results, taken together, indicate that drinking of alcoholic beverages is causally related to liver cancer.

Cancer of the pancreas

Of five cohort studies of the general population, only one showed a significantly increased incidence of cancer of the pancreas among regular drinkers of alcoholic beverages; of ten cohort studies of persons with high intake, none showed a significant association between consumption of alcoholic beverages and pancreatic cancer risk. Of 14 case-control studies, only one has indicated an increased pancreatic cancer risk among regular drinkers of alcoholic beverages. Taken together, the results of these 29 studies suggest that consumption of alcoholic beverages is unlikely to be causally related to cancer of the pancreas.

Cancer of the breast

A significant positive association between intake of alcoholic beverages and breast cancer incidence was seen in each of four large prospective studies and in seven of 13 case-control studies. Nonsignificant positive associations of similar magnitude were observed in two of the case-control studies, in which there were relatively few persons. A dose-response relationship, generally with up to 1.5- to two-fold risks, has been observed. The consistency of this positive association makes it unlikely that the relationship is due to chance or methodological bias. There is no indication that the association is dependent on type of beverage.

Confounding due to currently recognized risk factors for breast cancer was controlled for in most studies; in no instance did adjustment for these factors appreciably alter the estimated risk. In view of the modest elevations in relative risks observed, the possibility of confounding by an unrecognized factor cannot be ruled out entirely, especially since much of the etiology of breast cancer remains unexplained. In order that such a factor be sufficient to explain the observed associations with the drinking of alcoholic beverages, however, it would have to be much more strongly associated with the occurrence of breast cancer than the known common risk indicators and, also, highly correlated with consumption of alcoholic beverages.

The modest elevation in relative risk that has been observed is potentially important because of the high incidence of breast cancer in many countries. Although the available data indicate a positive association between drinking of alcoholic beverages and breast cancer in women, a firm conclusion about a causal relationship cannot be made at present.

Cancer of the lung

Fifteen cohort studies of alcoholics, of persons with higher than average consumption of alcoholic beverages and of the general population have yielded inconsistent results on an association between drinking of alcoholic beverages and the risk for lung cancer. Smoking was taken into account in only five of these studies. In five case-control studies, there was no association between risk for lung cancer and consumption of alcoholic beverages. In view of the lack of excess risk in case-control studies and the inconsistent results of cohort studies, there is no indication that drinking of alcoholic beverages has a causal role in lung cancer.

Cancers at other sites

Overall, studies on cancers of the urinary bladder, kidney, ovary, prostate and lymphatic and haematopoietic system show no association with consumption of alcoholic beverages. The sparsity of the observations on cancers of the skin, corpus and cervix uteri, vulva, testis, brain, thyroid and soft tissues precludes an evaluation.

5.4 Other relevant data

Toxic effects and metabolism

The concentrations of ethanol attained in humans in the upper gastrointestinal tract after consumption of alcoholic beverages can cause local irritation. Long-term, excessive drinking of alcoholic beverages can also cause fatty liver, alcoholic hepatitis, cell necrosis, fibrosis and cirrhosis in the liver.

In humans and experimental animals, ethanol metabolism generates acetaldehyde, predominantly in the liver,

and low concentrations of acetaldehyde are found in the blood. In alcoholics, the rate of ethanol oxidation is enhanced, resulting in increased levels of acetaldehyde in the liver and blood. In some ethnic groups, the absence of a specific form of aldehyde dehydrogenase leads to elevated acetaldehyde concentrations in tissues and blood after ingestion of alcohol.

An acute effect of ethanol is the inhibition of the metabolism of xenobiotics in humans and experimental systems. In rodents, administration of nitrosamines together with ethanol results in increased DNA alkylation in some extrahepatic tissues such as oesophagus and kidney. Long-term ingestion of ethanol by humans and experimental animals increases levels of cytochrome P450 in the liver, resulting in enhanced metabolism of a wide variety of xenobiotics.

Alterations in hormonal status have been described after either acute or chronic ingestion of ethanol in some studies in humans and experimental animals.

Effects on reproduction

In humans, ethanol is a developmental toxin, and various effects have been associated with ethanol intake. Excessive consumption of alcoholic beverages during pregnancy is associated with the development of a syndrome of physical and mental manifestations in the offspring - the fetal alcohol syndrome; it may also cause defects in the central nervous system, heart, kidney and limbs. Moderate consumption can be associated with reduced birthweight and behavioural deficits, but effects generally have not been observed with an intake of about one drink per day.

Ethanol at high blood levels affects the structure of the reproductive organs and causes significant reductions in fetal body weight, increased resorptions and teratogenic effects in a number of species. Behavioural development of mice and rats was affected by exposure to ethanol *in utero* in some, but not all, studies; exposure *in utero* or during lactation reduced postnatal growth.

Ethanol crosses the placenta in a variety of species, and both ethanol and acetaldehyde have been found in fetal tissues after dosage of pregnant rodents with ethanol. Both ethanol and acetaldehyde can cause embryonal developmental abnormalities *in vitro*.

Genetic and related effects

Increased frequencies of chromosomal aberrations, sister chromatid exchanges and aneuploidies were found in the peripheral lymphocytes of alcoholics.

In rodents exposed *in vivo*, ethanol induced dominant lethal mutations in mice and rats and aneuploidy in germ cells of mice, but did not induce chromosomal aberrations in rats or Chinese hamsters. It induced sister chromatid exchanges in mice and rats but not in Chinese hamsters. It did not induce micronuclei in mice, but conflicting results were obtained in rats. It induced sister chromatid exchanges in mouse embryos exposed *in vivo* and, in one study, chromosomal aberrations in rat embryos exposed *in vivo*.

In most studies of human cells *in vitro*, ethanol did not induce chromosomal aberrations in the absence of an exogenous metabolic system or sister chromatid exchanges in the presence or absence of an exogenous metabolic system. In limited studies, ethanol gave positive results in tests for morphological cell transformation in mouse C3H 10T1/2 cells but not in Syrian hamster embryo cells. In rodent cells *in vitro*, sister chromatid exchanges were induced in the presence, but generally not in the absence, of an exogenous metabolic system. Neither micronuclei nor chromosomal aberrations were induced in the absence of an exogenous metabolic system. Ethanol did not induce DNA damage or mutation in rodent cells *in vitro*. It did not induce mutation or recombination in *Drosophila*.

In plant roots, ethanol induced chromosomal aberrations and sister chromatid exchanges and, in one study, micronuclei in tetrads. In fungi, it induced mutations and nondisjunction; in single studies, it induced mitotic

crossing-over but not gene conversion. Ethanol did not induce mutation or DNA damage in bacteria.

Ethanol-free extracts of some alcoholic beverages induced sister chromatid exchanges in human cells *in vitro* and mutation in bacteria.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity of ethanol and of alcoholic beverages in experimental animals.

There is *sufficient evidence* for the carcinogenicity of alcoholic beverages in humans.

The occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus and liver is causally related to the consumption of alcoholic beverages.

Alcoholic beverages are *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

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