NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT for ALCOHOLIC BEVERAGE CONSUMPTION

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TABLE OF CONTENTS

NTP Report on Carcinogens Listing for Alcoholic Beverage Consumption

Carcinogenicity

Consumption of alcoholic beverages is *known to be carcinogenic to humans* based on human studies that indicate a causal relationship between consumption of alcoholic beverages and an increased risk of cancer in humans (reviewed in IARC, 1988; Longnecker and Enger, 1996). Studies indicate that the risk is most pronounced among smokers and at the highest levels of consumption.

Consumption of alcoholic beverages is causally related to cancers of the mouth, pharynx, larynx, and esophagus. Cohort and case control studies in a variety of human populations are notable for their consistency in reporting the presence of moderate to strong associations with dose-response relationships for these four sites. Evidence also supports a weaker but possibly causal relation between alcoholic beverage consumption and increased risk of cancers of the liver and breast (Longnecker, 1994). The effect of a given level of alcoholic beverage intake on absolute risks of cancer of the mouth, pharynx, larynx, and esophagus is influenced by other factors, especially smoking. However, smoking does not explain the observed increased risk of cancers associated with increased alcoholic beverage consumption.

No adequate experimental animal carcinogenicity studies of alcoholic beverages have been reported in the literature. Studies specifically examining the carcinogenicity of ethanol in animals have not yielded results that would suggest that the ethanol component of alcoholic beverages is solely responsible for the increases in cancer observed in people consuming alcoholic beverages.

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

Increased frequencies of chromosomal aberrations, sister chromatid exchanges, and aneuploidies have been found in the peripheral lymphocytes of alcoholics. Ethanol-free extracts of some alcoholic beverages induced sister chromatid exchanges in human cells *in vitro* and mutations in bacteria (IARC, 1988).

The mechanism by which consumption of alcoholic beverages can cause cancers in humans is not established.

Listing Criteria from the Report on Carcinogens, Eighth Edition

Known To Be A Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated To Be A Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded, or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either a known to be human carcinogen or reasonably anticipated to be human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

1.0 CHEMICAL COMPOSITION

The chemical composition of alcohol beverages was addressed by IARC (1988). Ethanol and water are the main constituents of most alcoholic beverages. The amount of ethanol consumed in a standard measure of most drinks is similar for beer, wine, and spirits (10-14 g). The ethanol in these beverages comes from the fermentation of carbohydrates by yeast. Although ethanol can be chemically synthesized from ethylene, alcohol synthesis for use in beverages is not employed by the alcoholic beverage industry because of the presence of impurities from the synthetic process.

1.1 Physical-Chemical Properties of Ethanol

Property	Information	Reference
Color	clear, colorless liquid	IARC (1988)
Boiling Point	78.5 °C	IARC (1988)
Melting Point	-114.1 °C	IARC (1988)
Density	d_4^{20} 0.789	IARC (1988)

Beer, wine, and spirits also contain volatile and nonvolatile flavor compounds that originate from raw materials, fermentation, wooden casks used for maturation, and synthetic substances added to specially flavored beverages. The exact composition of many beverages is confidential business information, though much published data defines the organic compounds usually present at low levels. Components and contaminants identified in beer, wine, and spirits were noted by IARC (1988) and several of these are known or suspected animal or human carcinogens, including acetaldehyde, nitrosamines, aflatoxins, ethyl carbamate, asbestos, and arsenic compounds (Table 1-1).

1.2 Beer

Carbonyl compounds have been identified in beer produced in the United States, Germany and Norway; acetaldehyde was found to be the most common carbonyl compound with reported levels as high as 37.2 mg/L (Nykänen and Suomalainen, 1983; cited by IARC, 1988). Formaldehyde was also detected at lower levels.

Several nitrosamines have been identified in beer, including *N*-nitrosodimethylamine (NDMA), *N*-nitrosodiethylamine (NDEA), *N*-nitrosodipropylamine (NDPA), *N*-nitrosopyrrolidine, and *N*-nitrosoproline (Klein, 1981; cited by IARC, 1988).

Aflatoxins have been detected in Kenyan beer samples at concentrations of 1-2.5 μg/L; the source was believed to be rejected maize (Peers and Linsell, 1973; cited by IARC, 1988). Ochratoxin A and zearalenone were found in Kenyan beer made from contaminated barley (IARC 1983; cited by IARC, 1988).

Ethyl carbamate (urethan), a product of the reaction of ethanol and carbamyl phosphate, has been detected in commercial ales (Ough, 1984; cited by IARC, 1988).

Asbestos fibers have been identified in Canadian and U.S. beers (Cunningham and Pontefract, 1971; cited by IARC, 1988). The fibers in Canadian beer were described as

chrysotile and the fiber concentrations in Canadian and U.S. beers were reported as 1.1-6.6 million fibers/L.

1.3 Wine

Acetaldehyde has been detected at 50-160 mg/L in wines produced in different countries (Nykänen and Suomalainen, 1983; Postel et al., 1972b; both cited by IARC, 1988). All aldehydes can be chemically bound to ethanol, higher alcohols, and the additive sulfur dioxide (IARC, 1988).

The nitrosamine NDMA was identified in 33 wine samples at concentrations of < 0.05-0.6 μg/L (Klein, 1981; cited by IARC, 1988). NDEA was detected in one sample at a concentration of 0.3 μg/L, but NDPA was not detected.

The fungi that produce aflatoxins may occur on grapes, since a wide variety of molds normally inhabit grapes. Consequently, wine samples were analyzed for the presence of aflatoxins (IARC, 1988). Aflatoxin B_1 was detected in two of 33 German wines at concentrations of < 1 μg/L (Schuller et al., 1967; cited by IARC, 1988). Aflatoxins were also identified in 16 of 22 wines from different countries at concentrations of < 1-2.6 μg/L (Lehtonen, 1973; cited by IARC, 1988). Using improved methods in later studies, aflatoxins were not detected in samples of French red wine, Spanish sherry, madeira and port wine (Drawert and Barton, 1974; Lemperle et al., 1975; both cited by IARC, 1988).

Since ethyl carbamate is expected to be present in most fermented beverages, some wine samples were analyzed for this compound (IARC, 1988). Ethyl carbamate was reported by Ough (1984; cited by IARC, 1988) to have been found in experimental wine (0.6-4.3 μg/L) and commercial wines (0.3-5.4 μg/L).

Asbestos fibers may be present in alcoholic beverages from filters used for clarification, water used during production processes, and from asbestos-cement water pipes (IARC, 1988). Asbestos fibers have been identified in European and Canadian wine, but concentrations were not reported (Cunningham and Pontefract, 1971; cited by IARC, 1988).

Arsenic was analyzed in wine samples because of the use of arsenic-containing fungicides (IARC, 1988). Arsenic was reported in nine U.S. wines at concentrations from 0.02-0.11 mg/L (Noble et al., 1976; cited by IARC, 1988). Arsenic concentrations in Spanish wine were shown to decrease after processing (Aguilar et al., 1987; cited by IARC, 1988), and the arsenic content of German wines has been ~0.009 mg/L since 1970 (Eschnauer, 1982; cited by IARC, 1988).

1.4 Spirits

Acetaldehyde occurs in all spirits because it is easily distilled with water; greater than 90% of the total aldehyde content is acetaldehyde (IARC, 1988). Concentrations reported in several whiskeys ranged from 20-220 mg/L, and the concentration in brandy has been found to be as high as 600 mg/L (Nykänen and Suomalainen, 1983; cited by IARC, 1988).

Many investigations have determined nitrosamine occurrence in alcoholic beverages (IARC, 1988). The nitrosamines NDMA, NDEA, and NDPA were detected in white alcohol, whiskey, rum, and cognac, with concentrations ranging from < 0.05 μg/L-4.8 μg/L (Klein, 1981; cited by IARC, 1988).

Because of the high concentration of urethan detected in some fruit brandies (0.1-7.0 mg/L), this substance was analyzed in other distilled spirits (IARC, 1988). Whisky, rum, cognac, sherry, and liqueur were reported to contain ethyl carbamate at concentrations ranging from 0.02-0.16 mg/L (Mildau et al., 1987; cited by IARC, 1988).

Table 1-1. Potential Carcinogens Identified in Alcoholic Beverages

Beverage	Components	Reference
Beer	acetaldehyde, nitrosamines, aflatoxins, ethyl carbamate, asbestos fibers	IARC (1988)
Wine	acetaldehyde, nitrosamines, aflatoxins, ethyl carbamate, asbestos fibers, arsenic compounds	IARC (1988)
Spirits	acetaldehyde, nitrosamines, ethyl carbamate	IARC (1988)

2.0 HUMAN EXPOSURE

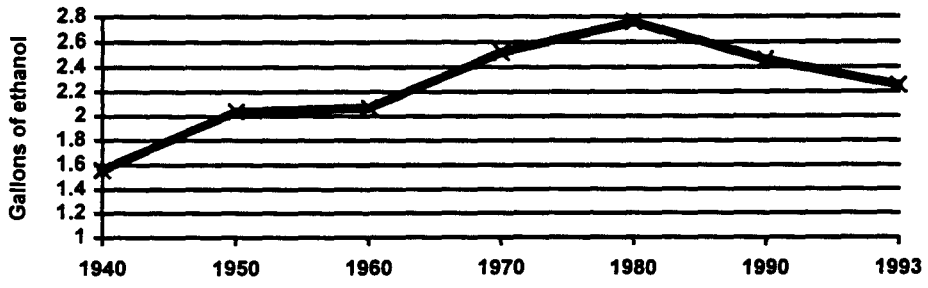
2.1 Use

IARC (1988) describes in detail the use of alcoholic beverages (Appendix B). Consumption trends, including overall level of alcohol consumption, beverage choice, age and sex differences, and temporal variations, differ among and within societies. Patterns of alcohol consumption have been observed to vary on a global scale, largely independent of regional differences or economic and social changes (IARC, 1988).

A downward trend in alcohol consumption was observed in the United States and many European countries from the turn of the twentieth century until the period between the world wars. Alcohol consumption then increased, approaching the peak levels of the nineteenth century, until the 1970s and 1980s when consumption rates slowed, leveled off or, in some countries (including the United States, Canada, Germany, Italy, Spain, France, Australia, and New Zealand), decreased. Overall increases in consumption were observed in some other countries (Denmark, Finland, Great Britain, Japan, and Luxembourg) over the same period. The authors note that alcohol consumption in these countries was initially (in 1970) very low in comparison to the other countries studied (NIAAA, 1997).

Alcohol consumption in the United States increased from the 1940s until the early 1980s, then began to steadily decrease; by 1993, consumption had declined to the lowest level since 1964 (Table 2-1). Per capita consumption figures for Table 2-1 were derived by estimating total alcohol use, based on sales and shipment data, of the U.S. population aged 14-years or older. Apparent per capita consumption is expressed in gallons of pure alcohol (NIAAA, 1997).

Table 2-1. Total per capita alcohol consumption United States, 1940-1993



Source: Williams et al. (1995); cited by NIAA (1997)

A 1990 National Alcohol Survey gathered data regarding the demographic distribution of drinking patterns in the United States (Midanik and Clark, 1994). Respondents were classified as current drinkers (any use of alcohol beverages in the preceding year), weekly drinkers (any alcoholic beverage use at least weekly during the preceding year), and drinkers of five or more drinks (drinking five or more drinks on one occasion weekly or more often during the preceding year).

Of the men surveyed, 71.2% were current drinkers, 40.0% were weekly drinkers, and 6.5% were in the five drinks group. In the group reporting the highest alcohol consumption, men aged 18-29, 76.5% were current drinkers, 44.4% were weekly drinkers, and 11.0% were in the five drinks group. The same age group reported the highest consumption among women: 69.7% were current drinkers, 19.7% were weekly drinkers, and 3.0% were in the five drinks group. When data from all age groups of women were combined, 59.4% were current drinkers, 18.8% were weekly drinkers, and 1.4% were in the five drinks group. These figures all represent decreases in alcohol consumption as measured by a similar survey conducted in 1984 (Midanik and Clark, 1994).

Respondents were grouped by ethnicity and religious affiliation (Table 2-2). The survey found no statistically significant differences in alcohol use among ethnic groups, but conservative Protestants reported significantly lower alcohol consumption in all three categories.

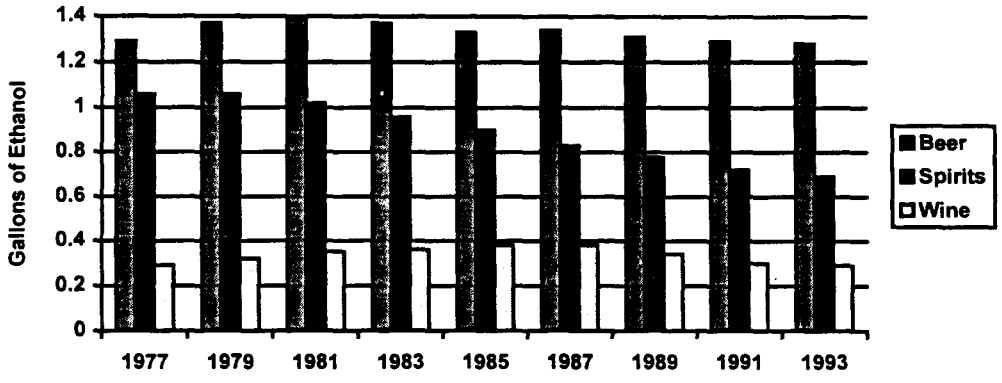
Table 2-2. Demographic Characteristics of U.S. Drinkers 1990: Ethnicity and Religion—Percentage of Drinkers in Groups

	Current Drinkers	Weekly Drinkers	Drinkers of Five or More Drinks
Race			
Black	61.6	25.8	3.5
White	65.9	30.2	3.5
Hispanic	66.6	26.5	8.9
Other	57.0	21.6	1.4
Religion			
Catholic	78.6	37.3	6.7
Jewish	91.8	30.2	0.0
Liberal Protestant (excessive alcohol use discouraged)	72.6	36.1	1.0
Conserv. Protestant (all alcohol use discouraged)	51.1	19.3	2.2
Other	75.4	37.1	9.3

Source: Midanik and Clark (1994)

Per capita consumption of wine and beer in the United States was relatively stable over the period beginning in the early 1980s and continuing into the 1990s when overall alcohol consumption was falling (Williams et al., 1995; cited by NIAAA, 1997). Most of the decrease in U.S. alcohol consumption can be attributed to decreased consumption of spirits. Though wine has made much less of a contribution to the total volume of U.S. alcohol consumption than beer or spirits, per capita consumption of wine was the same in 1993 as it was in 1977, while consumption of spirits fell by almost 35% over the same period. Per capita consumption of beer decreased from 1981 to 1985, fluctuated thereafter, and in 1993 was one percent below 1977 consumption levels (NIAAA, 1997) (Table 2-3).

Table 2-3. Per capita alcohol consumption by beverage type United States, 1977-1993



Source: Williams et al. (1995); cited by NIAAA (1997)

Per capita consumption of absolute alcohol is highest in Europe. Based on data for 1982-1991, France had the highest average per capita consumption at 13.1 liters (3.4 gallons) (ARF, 1994). In other parts of the world, especially in countries where Islam is the major religion, per capita consumption of alcohol is well below this level, although increases have been noted in some countries in recent years.

2.2 Production

IARC (1988) summarized data on worldwide production of alcoholic beverages including kinds of beverage, and production methods (Walsh and Grant, 1985; cited by IARC, 1988). All alcoholic beverages are produced by the fermentation of fruit or other vegetable matter. Most commercial and home production involves fermented beverages that are classified, based on raw materials and production methods used, as beer, wine, or spirits, although smaller quantities of other kinds of fermented beverages (cider, rice wine, palm wine, etc.) are also produced. Beer is produced by fermentation of malted barley or other cereals with the addition of hops. Wine is made from fermentation of grape juice or crushed grapes; fortified wines include additional distilled spirits. Distilled spirits, so named because of liquid distillation after sugar fermentation to increase the alcohol content, originate from sources of starch or sugar, including cereals, molasses from sugar beets, grapes, potatoes, cherries, plums, and other fruits.

Estimates of alcoholic beverage production in each region of the world in 1990 are listed in Table 2-4. Totals in this table may not match due to rounding of original data.

Table 2-4. World Alcoholic Beverage Production, 1990

	Africa	America	Asia	Europe	Oceania	World Total
Wine (in thousand metric tons)	1070	4520	254	22673	494	29010
Beer (in thousand hectoliters)	57265	374529	165955	466739	24254	1088742
Spirits (in thousand hectoliters)	1203	18454	14284	22992	823	57756

Source: ARF (1994)

2.3 Regulations

A March 1999 search of the most recent editions of the *Code of Federal Regulations* found no regulations requiring warnings on alcoholic beverage labels of an increased risk of cancer due to alcoholic beverage consumption. (Labels on saccharin-containing wines, distilled spirits, and malt beverages, however, must warn of a cancer risk from saccharin consumption [27 CFR 4.32, 5.32, and 7.22, respectively, enforced by the Bureau of Alcohol, Tobacco and Firearms, Department of the Treasury]).

FDA regulates health claims information on food labels. Thus, labels on low fat foods may make the health claim that diets low in fat "may" or "might" reduce the risk of some cancers with several provisions (21 CFR 100.73 Health claims: dietary lipids and cancer). Optional

information allowed includes identification of risk factors for development of cancer. Alcohol consumption is one of the risk factors that FDA lists. The same optional information may be added to labels stating there is a reduced risk of cancer for diets high in fiber-containing grain products, fruits, and vegetables (21 CFR 101.76, 21 CFR 101.78).

3.0 HUMAN STUDIES

Recent investigations, including a review of new epidemiological data (Longnecker and Enger, 1996), reinforce previous reports of a causal relationship between alcoholic beverage consumption and cancers of the oral cavity, pharynx, larynx, esophagus, and liver (IARC, 1988). Estimated relative risks were significantly higher for cancers of the mouth, pharynx, larynx, esophagus, breast, and liver among consumers of alcoholic beverages, particularly among heavy drinkers. An association between increased risk of breast cancer and alcohol intake has been established, but conclusions regarding causality cannot be drawn in the absence of an established mechanism (Longnecker and Tseng, 1999). The effect of all defined levels of alcohol intake on absolute risks cancers of the mouth, pharynx, larynx, and esophagus was influenced by other risk factors, especially smoking. Large bowel cancers had a weak association with alcoholic beverage consumption, while melanoma and cancers of the bladder, stomach, ovary, and endometrium were not consistently related to alcohol intake (Longnecker and Enger, 1996; Westerdahl et al., 1996).

Results of 59 of the largest (defined by number of cases) case-control and cohort studies of the relationship between alcohol consumption and risk of oral and pharyngeal, esophageal, laryngeal, breast, and liver cancers are summarized below. Study details are presented in Table 3-1.

3.1 Oral and Pharyngeal Cancer

Nine case-control studies, each with more than 100 cases, support a strong association of alcohol drinking and oropharyngeal cancer (Elwood et al., 1984; cited by IARC, 1988; Martinez, 1969; Bross and Coombs, 1976; Brugere et al., 1986; Notani, 1988; Tuyns et al., 1988; Barra et al., 1990; Franceschi et al., 1990; Day et al., 1994), consistent with conclusions in a recent review (Longnecker and Enger, 1996). All risk estimates were adjusted for smoking which is a known risk factor for oropharyngeal cancer. The cohort studies reviewed are not included in this report because the risk estimates were not adjusted for smoking or because studies combined analysis of oropharyngeal cancer with cancer of the larynx and esophagus. However, in five retrospective cohort studies of alcoholics, the relative risk of oral and pharyngeal cancer was significantly increased (IARC, 1988).

3.2 Esophageal Cancer

Nine case-control studies with cases in excess of 100 show a strong dose-response relationship between alcohol intake and esophageal cancer (Tuyns et al., 1977; cited by IARC, 1988; Tuyns et al., 1979; Vassallo et al., 1985; De Stefani et al., 1990; Cheng et al., 1992; Franceschi et al., 1994; Gao et al., 1994; Hanaoka et al., 1994; Brown et al., 1997). As with studies of oropharyngeal cancer, risk estimates were adjusted for smoking and other potential confounders. The cohort studies reviewed are not presented because the risk estimates were not adjusted for smoking. However, seven of eight retrospective cohort studies indicate a two- to four-fold increase in esophageal cancer risk (IARC, 1988).

3.3 Breast Cancer

Six of nine case-control studies with greater than 1000 cases indicate a modest, but significant, dose-response relationship between alcohol consumption and breast cancer (Williams and Horm, 1977; Rosenberg et al., 1982; Lê et al., 1984; Harvey et al., 1987; La Vecchia et al., 1989.; Longnecker et al., 1995). All five of the cohort studies of more than 100 cases (Hiatt and Bawol, 1984; Hiatt et al., 1987; Schatzkin et al., 1987; Garfinkel et al., 1988, Smith-Warner, 1997) showed a positive association between breast cancer and alcohol consumption. Most of these studies controlled for factors known to contribute to the risk of breast cancer (e.g., reproductive factors and family history of breast cancer). The association of breast cancer and alcohol consumption is also supported by a recent meta-analysis of 38 studies (Longnecker, 1994).

3.4 Laryngeal Cancer

Ten case-control studies with more than 90 cases each support an association between alcohol drinking and laryngeal cancer (Wynder et al., 1956, 1976; Burch et al., 1981; Elwood et al., 1984; all cited by IARC, 1988; Olsen et al., 1985; Brugere et al., 1986; Tuyns et al., 1988; Choi and Kayho, 1991; Franceschi et al., 1994; Dosemeci et al., 1997). All risk estimates from these case control studies were adjusted for smoking, a known risk factor for laryngeal cancer. The cohort studies reviewed are not included in this report because information on smoking habits was not obtained. However, the risk of laryngeal cancer was significantly increased in four of six retrospective cohort studies (IARC, 1988).

3.5 Liver Cancer

Seven of ten case-control studies with 60 or more cases (Bulatao-Jayme et al., 1982; Stemhagen et al., 1983; Hardell et al., 1984; Austin et al., 1986; Yu et al., 1988; Tsukuma et al., 1990) and four cohort studies with greater than 20 cases (Jensen et al., 1980; cited by IARC, 1988; Hakulinen et al., 1974; Kono et al., 1986; Shibata et al., 1986) showed an association between liver cancer and heavy drinking. Most of these studies indicate a dose-response gradient.

3.6 Type of Alcoholic Beverage as Risk Factor

Although a number of studies compare the cancer risk associated with specific types of alcohol, the data do not support general conclusions regarding beverage specific differences.

3.7 Dose-Response Relationships

The studies summarized in Table 3-1 generally show a dose-response between alcohol beverage intake and cancer incidence at certain sites. This relationship is also apparent from qualitative analyses of published results (Longnecker and Tseng, 1999). Variations in dose-response occur among and within different countries, possibly due to differences in beverage preferences, drinking patterns, reporting of alcoholic beverage consumption, and study design.

3.8 Beneficial Effects of Low to Moderate Alcohol Consumption

Potential health benefits of low alcoholic beverage consumption should be recognized as well as the detrimental effects of heavy consumption. Light-to-moderate intake of alcoholic beverages (defined by the authors as up to 2 drinks/day) has been repeatedly associated with a reduced risk of coronary artery disease (Klatsky, 1994). Thun et al. (1997) found an association between moderate alcohol consumption (defined by the authors as ~1 drink/day) and a slightly reduced overall mortality rate in a recent study of middle-aged and elderly U.S. adults.

Table 3-1. Human Studies of Alcohol

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
Oral and Pharyngeal Cancer Case-Control Studies						
population-based case-control	**Cases:** 921 males and females (black and white) with primary oral cancer **Controls:** 900 persons identified by random digit dialing or rosters provided by the Health Care Financing Administration cases and controls from four areas in U.S. less than half of controls reported ≥1drinks of wine or beer or >4 drinks of liquor per week	**Evaluation**: personal interviews with participants or next of kin (24% of cases, 2% of controls)	**Estimation**: calculation of OR for oropharyngeal cancer OR (95% CI) 13.2 (5.2-33.5) for heavy drinkers of light colored liquors 4.6 (2.7-7.9) for heavy drinkers of dark colored liquors 'heavy' defined by authors as 30+ drinks/wk	Adjustment was made for multiple potentially confounding factors, including smoking and other types of alcohol.	This analysis used data from a U.S. case-control study of oral-pharyngeal cancer. The original study was large and population-based.	Day et al. (1994)
case-control	**Cases:** 281 with cancer of the hypopharynx **Controls:** 3057 from general population in six areas considered (selected from census lists, electoral lists, population registries) cases and controls from Italy, Spain, Switzerland, France; average adult lifetime daily alcohol consumption was computed for cases and controls	**Evaluation:** interviews	**Estimation:** Calculated OR of hypopharynx cancer using logistic regression OR (95% CI) 1.57 (0.72-3.42) for 21-40 g alcohol/day 3.15 (1.58-6.24) for 41-80 g alcohol/day 5.59 (2.79-11.21) for 81-120 g alcohol/day 12.54 (6.29-25.00) for 121+ g alcohol/day	OR adjusted for smoking, age, location	alcohol effect in lowest smoke category	Tuyns et al. (1988)
case-control	**Cases:** 145 white females with cancer of the mouth and tongue **Controls:** 1973 white females with non-neoplastic diseases	**Evaluation:** interviews	**Estimation:** calculation of RR for mouth and tongue cancer RR (95% CI) 1.3 (0.8-2.2) for < 30 drinks/mo. 3.4 (1.7-6.6) for ≥ 30 drinks/mo.	RRs presented were adjusted for age and smoking by IARC (1988)		Bross and Coombs (1976)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 278 males with oral cavity cancers **Controls:** 392 males from hospital and general population	**Evaluation:** interviews	**Estimation:** calculated RR (95% CI) for cancer according to alcohol consumption RR for cancer of oral cavity 1.2 (0.7-1.9) for 1.9+ g/day RR for cancer of the pharynx 1.4 (0.9-2.4) for 1.9+ g/day *results for <1.9 g/day not given	adjusted for age and smoking	no dose-response evaluation	Notani (1988)
case-control	**Cases:** 305 males with cancer of oral cavity and pharynx **Controls:** 1621 males in the hospital for acute nonneoplastic conditions unrelated to alcohol consumption	**Evaluation**: reported consumption of alcoholic beverages	**Estimation**: calculation of OR for oral and pharyngeal cancer OR (95% CI) Wine, beer, and spirits 0.8 (0.3-2.3) for ≤ 55 drinks/wk) 1.8 (0.8-4.4) for 56-83 drinks/wk 4.1 (2.0-8.2) for ≥ 84 drinks/wk	OR adjusted for cigarette smoking, age, residence, occupation	Heavy alcohol consumption even in lowest exposure groups	Barra et al. (1990)
case-control	**Cases:** 108 males with oral cancer **Controls:** 108 males from same hospital or neighborhood as cases	**Evaluation:** interviews	**Estimation:** calculated RR for cancers of the lip, floor of mouth, tongue, other parts of the mouth RR (95% CI) 0.5 (0.2-1.5) for ≤ 1 unit/day 1.7 (0.7-3.9) for 2-4 units/day 2.8 (1.1-7.0) for ≥ 5 units/day unit = 2 oz. Liquor 18 oz. Beer 8 oz. Wine	Pairs matched for age and smoking	ORs shown were calculated by IARC (1988)	Martinez (1969)
case-control	**Cases:** 634 males with oropharynx cancer **Controls:** unknown number from national survey (~4000 males)	**Evaluation:** hospital chart records of alcohol and tobacco consumption compared to consumption by general population	**Estimation:** calculated RR for oropharynx cancer RR (95% CI) 1.0 for 0-39 g ethanol/day 2.6 (1.6-4.2) for 40-99 g ethanol/day 15.2 (9.2-25.1) for 100-159 g ethanol/day 70.3 (41.2-120) for 160+ g ethanol/day	RR adjusted for smoking Controls may have underreported their alcohol consumption, leading to an overestimation of the RR for alcohol.	IARC (1988) noted that information on tobacco and alcohol use was obtained by different methods and situations	Brugere et al. (1986)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 366 males with hypopharynx cancer **Controls:** unknown number from national survey (~4000 males)	**Evaluation:** hospital chart records of alcohol and tobacco consumption compared to consumption by general population	**Estimation:** calculated RR for hypopharynx cancer RR (95% CI) 1.0 for 0-39 g ethanol/day 3.3 (1.4-7.9) for 40-99 g ethanol/day 28.6 (12.5-65.1) for 100-159 g ethanol/day 143.1 (61.9-330.5) for 160+ g ethanol/day	RR adjusted for smoking The authors note that the controls may have underreported their alcohol consumption, leading to an overestimation of the RR for alcohol.	IARC (1988) noted that information on tobacco and alcohol use was obtained by different methods and in different interview situations for cases and controls.	Brugere et al. (1986)
case-control	**Cases:** 133 males and females with cancer of the tongue, gum, floor of mouth, and other cancers of the oral cavity **Controls:** 133 hospital controls other cancers presumed by the authors to be unrelated to tobacco or alcohol use	**Evaluation:** interviews	**Estimation:** calculated RR of oral cancers based on alcohol consumption per week RR (95% CI not calculated) 1.0 for < 24 g 1.1 for 24-96 g 1.4 for 120-216 g 1.8 for 240-480 g 4.5 for > 480 g	RR adjusted for smoking		Elwood et al. (1984; cited by IARC, 1988)
case-control	**Cases:** 157 males with histologically confirmed oral cancer **Controls:** 1272 males in same hospitals as cases and without alcohol-related disease	**Evaluation:** personal interviews by trained interviewers	**Estimation:** calculation of OR for oral cancer using logistic regression OR (95% CI) 1 for ≤ 19 drinks/wk 1.1 (0.5-2.5) for 20-34 drinks/wk 3.2 (1.6-6.2) for 35-59 drinks/wk 3.4 (1.7-7.1) for 60+ drinks/wk significant positive trend	OR adjusted for age, area of residence, years of education, occupation, and smoking		Franceschi et al. (1990)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
Esophageal Cancer Case-Control Studies						
population-based case-control	**Cases:** 373 males (124 white, 249 black) diagnosed with squamous-cell esophageal cancer; aged 30-79 **Controls:** 1364 males (750 white, 614 black) from three geographic areas in the U.S. Response Rate = 68% cases 76% controls	**Evaluation:** interviews	**Estimation:** calculated esophageal cancer OR for black men OR (95% CI) black men 1.0 for never drank 1.7 (0.8-3.6) for < 8 liquor drinks/wk 3.8 (1.9-7.7) for 8-14.9 liquor drinks/wk 8.2 (4.2-16.3) for 15-28.9 liquor drinks/wk 10.0 (5.0-19.9) for 29+ liquor drinks/wk $p < 0.001$ also significant ($p < 0.001$) increase in OR with increasing intake of wine among black men and beer and liquor among white men	OR adjusted for age, area, smoking, income, and each type of alcoholic beverage is adjusted for amount of the other two. Other analyses adjusted for total alcohol.		Brown et al. (1997)
case-control	**Cases:** 196 males with esophageal cancer **Controls:** 1064 males in hospital without cancer	**Evaluation:** interviews	**Estimation:** calculated RR for esophageal cancer risk RR (95% CI) 1.0 for never consuming alcohol 1.0 (0.6-1.8) for ever consuming alcohol	RR adjusted for smoking, calculated by IARC (1988)		Bradshaw and Schonland (1974)
case-control	**Cases:** 200 males with esophageal cancer; all cases in the population between 1972-1974 **Controls:** 778 males selected randomly from same population	**Evaluation**: interviews	**Estimation:** calculated RR for esophageal cancer RR (95% CI could not be calculated) 1.0 for 0-20 g ethanol/day 1.2 for 21-40 g ethanol/day 3.4 for 41-60 g ethanol/day 6.1 for 61-80 g ethanol/day 6.6 for 81-100 g ethanol/day 18.3 for > 101 g ethanol/day	RR adjusted for smoking, but adjustment did not affect crude RR		Tuyns et al. (1977)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 312 males with esophageal cancer **Controls:** 869 hospital-based male controls matched by age	**Evaluation:** interviews	**Estimation:** calculated RR for esophageal cancer RR (95% CI not given) 1.0 for 0-20 g ethanol/day 1.11 for 21-40 g ethanol/day 2.54 for 41-60 g ethanol/day 3.59 for 61-80 g ethanol/day 9.83 for 81-100 g ethanol/day 10.90 for 101-120 g ethanol/day 11.28 for 121-140 g ethanol/day 23.36 for 141+ g ethanol/day	RR adjusted for smoking		Tuyns et al. (1979)
case-control	**Cases:** 199 males in Uruguay with esophageal cancer **Controls:** 398 hospital-matched without alcohol or tobacco-related diseases and resident of Uruguay for at least 5 yr	**Evaluation:** interviews	**Estimation:** calculated RR for esophageal cancer RR (95% CI; no. cases/no. controls) 1 (26/100) for 0 mL alcohol/day 0.85 (0.4-1.8; 16/61) for 1-24 mL alcohol/day 0.71 (0.3-1.6; 12/51) for 25-49 mL alcohol/day 1.37 (0.8-2.4; 50/117) for 50-149 mL alcohol/day 3.57 (1.9-6.7; 46/38) for 150-249 mL alcohol/day 5.27 (2.7-10.2; 49/31) for 250+ mL alcohol/day trend test significant $\chi^2 = 4.9$, 1 d.f.	RR adjusted for cigarette smoking, age, residence		De Stefani et al. (1990)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
hospital-based case-control	**Cases:** 400 males and females with esophageal cancer **Controls:** 1598 (800 from hospital and 798 from general clinics) without alcohol or tobacco-related diseases	**Evaluation:** interviews	**Estimation:** calculated OR for esophageal cancer using conditional logistic regression OR (95% CI) 1.00 for never drinker 1.07 (0.66-1.75) for < 50 g alcohol/wk 1.36 (0.67-2.74) for 50-99 g alcohol/wk 1.82 (0.99-3.35) for 100-199 g alcohol/wk 3.40 (1.92-6.01) for 200-399 g alcohol/wk 5.05 (2.72-9.39) for 400-599 g alcohol/wk 11.11 (5.40-22.85) for 600-799 g alcohol/wk 18.07 (7.40-44.13) for 800-999 g alcohol/wk 9.93 (5.27-18.74) for > 1000 g alcohol/wk	adjusted for tobacco smoking and several other factors including dietary factors		Cheng et al. (1992)
population-based case-control	**Cases:** males (624) and females (278) in Shanghai, China with esophageal cancer **Controls:** 1552 randomly selected from urban Shanghai population and matched to cases by age and sex	**Evaluation:** interviews	**Estimation:** calculated OR for esophageal cancer using unconditional logistic regression OR (95% CI; no. cases/controls) in men 1.2 (0.8-1.8; 61/103) for 1-249 g ethanol/wk 0.9 (0.6-1.3; 95/147) for 250-749 g ethanol/wk 4.0 (2.6-6.3; 134/44) for 750+ g ethanol/wk	adjusted for several factors including smoking		Gao et al. (1994)
hospital-based case-control	**Cases:** 337 males with esophageal cancer **Controls:** 1706 male inpatients with acute conditions unrelated to alcohol and tobacco consumption	**Evaluation:** interviews	**Estimation:** calculated OR using unconditional logistic regression OR (95% CI) 1 for 0 drinks/wk (reference category) 0.6 (0.27-1.29) for 1-13 drinks/wk 0.45 (0.25-0.81) for 14-27 drinks/wk 1.03 (0.60-1.76) for 28-41 drinks/wk 2.25 (1.29-3.93) for 42-55 drinks/wk 3.69 (2.19-6.22) for ≥ 56 drinks/wk	adjusted for smoking		Franceschi et al. (1994)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
hospital-based case-control	**Cases:** 185 males with esophageal cancer **Controls:** 386 males with other neoplastic conditions	**Evaluation:** interviews	**Estimation:** calculated RR of esophageal cancer RR (95% CI) 1.0 for 0-49 mL ethanol/day 4.1 (2.0-8.1) for 50-99 mL ethanol/day 7.1 (3.8-13.2) for ≥ 100 mL ethanol/day significant positive trend	adjusted for smoking		Vassallo et al. (1985)
multicenter hospital-based case-control	**Cases:** 141 patients with confirmed esophageal cancer **Controls:** 141; one control per case among patients in same hospital all cases and controls patients in surgical departments of seven hospitals	**Evaluation:** interviews	**Estimation:** calculated esophageal cancer risk using conditional logistic regression analyses OR (95% CI) 1.00 for ≤ 53 g alcohol/wk 2.19 (0.92-5.18) for > 53 g alcohol/wk 5.17 (2.13-12.55) for > 242 g alcohol/wk 5.86 (2.43-14.17) for > 414 g alcohol/wk significant ($p < 0.0001$) positive trend	OR adjusted for tobacco consumption		Hanaoka et al. (1994)
Breast Cancer Case-Control Studies						
population-based case-control	**Cases:** 6662 breast cancer patients, average age 58.7 yr, reported to one of four statewide cancer registries in the northeastern United States; response rate = 80% **Controls:** 9163 selected from state driver's license lists and Health Care Financing Administration lists of Medicare beneficiaries; response rate = 84%	**Evaluation:** telephone interviews; reliability of questionnaire assessed by reinterview after 6-12 mo. (similar responses; Spearman correlation coefficients at least 0.75)	**Estimation:** calculated RRs for breast cancer and adjusted for various factors using unconditional logistic regression RR (95% CI) 1 for 0 g ethanol/day 1.08 (0.98-1.19) for 0-5 g ethanol/day 1.09 (0.96-1.23) for 6-11 g ethanol/day 1.17 (1.01-1.37) for 12-18 g ethanol/day 1.49 (1.24-1.79) for 19-32 g ethanol/day 1.95 (1.42-2.66) for 33-45 g ethanol/day 1.96 (1.43-2.67) for > 46 g ethanol/day p for trend <0.0001	RR adjusted for age, state, age at first full-term pregnancy, parity, body mass index, age at menarche, education, benign breast disease, and family history of breast cancer		Longnecker et al. (1995)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 1010 females with breast cancer who attended private surgical clinics in France **Controls:** 1950 females selected from same clinics	**Evaluation:** interviews	**Estimation:** calculated RR RR (CI not provided; no. cases/no. controls) 1.0 (473/1105) for no alcohol with meals 1.47 (537/845; p = 0.0001) for total alcohol with meals 1.50 (20/36) for cider with meals 2.44 (14/16; p = 0.05) for beer with meals 1.44 (495/778; p = 0.001) for wine with meals	controlled for reproductive factors and dairy products		Lê et al. (1984)
case-control	**Cases:** 2402 females with histologically confirmed breast cancer Response = > 97% **Controls:** 2220 females with acute conditions unrelated to risk factors for breast cancer Response = > 97%	**Evaluation:** interviews	**Estimation:** calculated adjusted RR for breast cancer using logistic regression RR (95% CI) 1.3 (1.1-1.6) for < 1 drink/day 1.3 (1.1-1.5) for 1 to < 2 drinks/day 1.4 (1.2-1.7) for 2-3 drinks/day 2.2 (1.7-2.7) for > 3 drinks/day positive trend (p < 0.001)	RR adjusted for age, geographic area, socio-demographic variables, smoking, family history of breast cancer, nutrition and diet indicators, menstrual, reproductive, and hormonal risk factors		La Vecchia et al. (1989)
case-control	**Cases:** 1152 females with breast cancer **Controls:** 2702 females with nonmalignant disorders used data from a large drug-surveillance program in Canada, Israel, and the United States	**Evaluation:** interviews	**Estimation:** calculated RR for breast cancer with Mantel-Haenszel and multiple logistic regression RR (95% CI) 1.9 (1.5-2.4) for alcohol consumed < 4 days/wk 2.5 (1.9-3.4) for alcohol consumed ≥ 4 days/wk	RR adjusted for age and geographic area		Rosenberg et al. (1982)
case-control	**Cases:** 1314 females with breast cancer in a New York hospital **Controls:** 770 patients with nonneoplastic conditions	**Evaluation:** interviews	**Estimation:** calculated RR of breast cancer RR (95% CI not reported) 1.0 for 0 drinks/mo. (never) 0.6 for 0 drinks/mo. (ex) 1.1 for < 3 drinks/mo. 1.0 for 3-8 drinks/mo. 1.1 for 9-25 drinks/mo. 1.1 for ≥ 26 drinks/mo.	RR adjusted for age		Byers and Funch (1982)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases**: 1226 females with breast cancer identified through eight U.S. cancer registries Response Rate = 82% **Controls**: 1279 females identified through random digit phone dialing Response Rate = 85%. IARC (1988) noted that the number of controls not contacted is never known.	**Evaluation**: interviews	**Estimation:** calculated RR for breast cancer RR (95% CI) 1.0 for 0 g ethanol/wk (referent) 0.9 (0.7-1.2) for < 50 g ethanol/wk 0.9 (0.7-1.2) for 50-149 g ethanol/wk 1.1 (0.7-1.7) for 150-199 g ethanol/wk 1.1 (0.7-1.9) for 200-249 g ethanol/wk 1.0 (0.5-1.7) for 250-299 g ethanol/wk 1.1 (0.6-1.8) for ≥ 300 g ethanol/wk	RR adjusted for family history, reproductive factors, age, smoking, body mass index	IARC (1988) noted that alcohol questions were not clearly related to period before diagnosis. Both cases and controls reported intakes that were higher than in national surveys (reported by study authors).	Webster et al. (1983)
nested case-control	**Cases**: 1524 females with breast cancer who participated in a U.S. cancer screening program; diagnosis was at least 3 yr after entry into screening program **Controls**: 1896 females in cancer screening program who did not develop cancer	**Evaluation**: interviews	**Estimation**: calculated RR for breast cancer unadjusted RR (95% CI) 1.0 for no (never) ethanol consumption 1.1 (0.9-1.3) for 0.1-13 g ethanol/wk 1.1 (0.9-1.3) for 14-91 g ethanol/wk 1.3 (1.0-1.7) for 92-182 g ethanol/wk 1.7 (1.2-2.4) for > 183 g ethanol/wk	RR adjusted for education, income, and reproductive factors; adjusted estimates not different from unadjusted estimates	IARC (1988) noted that effects were associated with alcohol use before age 30	Harvey et al. (1987)
case-control	**Cases**: 1118 breast cancer patients interviewed as part of the Third National Cancer Survey in the U.S. **Controls**: 3178 males and females with cancers not associated with alcohol or tobacco consumption	**Evaluation**: interviews	**Estimation**: calculated RR for breast cancer RR (95% CI not provided) 1.3 ($p < 0.05$) for consumption of < 1200 g ethanol/yr 1.6 ($p < 0.01$) for consumption of > 1200 g ethanol/yr	controlled for smoking, age, and race		William and Horm (1977)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
population-based case-control	**Cases:** 3498 U.S. females with newly diagnosed breast cancer **Controls:** 3157 females randomly chosen from same geographic areas Data from the Centers for Disease Control Cancer and Steroid Hormone Study	**Evaluation:** personal interviews by trained interviewers	**Estimation:** calculated adjusted RR using logistic regression RR (95% CI) 1.0 (0.8-1.1) for < 1 drink/wk 1.0 (0.8-1.2) for 1-3 drinks/wk 0.9 (0.7-1.1) for 4-7 drinks/wk 1.1 (0.9-1.3) for 8-14 drinks/wk 1.0 (0.8-1.4) for 15-21 drinks/wk 1.2 (0.9-1.6) for 22+ drinks/wk p for trend = 0.52	RR adjusted for age, age at first full-term pregnancy, parity, age at menarche, menopausal status, benign breast disease, family history of breast cancer, menopausal status, and pack-years of smoking		Chu et al. (1989)
Breast Cancer Cohort Studies						
prospective cohort	581,321 females enrolled in a U.S. prospective study in 1959 and followed for 12 yr (92%)	**Evaluation:** study participants completed a questionnaire	**Estimation**: calculated adjusted RR for breast cancer and alcohol consumption RR (95% CI) 1.00 for no alcohol consumption 0.96 (0.82-1.13) for occasional alcohol consumption 1.18 (1.03-1.36) for 1 whiskey equivalent/day 1.06 (0.86-1.30) for 2/day 1.28 (0.95-1.74) for 3/day 1.36 (0.90-2.07) for 4/day 2.10 (1.18-3.72) for 5/day 1.60 (1.00-2.56) for 6+/day	RR adjusted for age, education, age at first pregnancy, family history of breast cancer, meat consumption, and cigarette smoking		Garfinkel et al. (1988)
prospective cohorts combined	4335 invasive breast cancer cases from seven prospective studies in Canada, the Netherlands, Sweden, and the United States	**Evaluation:** food frequency questionnaires	**Estimation:** calculated pooled multivariate RR of breast cancer RR (95% CI) 1.09 (1.04-1.13) for an increment of 10 g/day of alcohol 1.41 (1.18-1.69) for intake of 30 to < 60 g alcohol/day versus nondrinkers Alcohol intake was positively associated with breast cancer risk	reproductive and anthropometric factors did not change the association		Smith-Warner et al. (1997)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
retrospective cohort	654 cases among 96,565 U.S. health plan-members (1964-1972) > 15 years at enrollment and followed until 1977	**Evaluation:** participants completed questionnaire	**Estimation**: calculated adjusted RR of breast cancer RR 1.0 for 0 drinks/day 1.38 for 3+ drinks/day (p trend = 0.035)	controlled for age, body mass index, reproductive factors		Hiatt and Bawol (1984)
prospective cohort	303 cases among 69,000 U.S. health plan-members; five yr follow-up	**Evaluation:** participants completed questionnaire	**Estimation**: calculated adjusted RR of breast cancer RR (95% CI) 1.0 for 0 drinks/day 2.2 (1.2-3.9) for past drinkers 1.5 (1.0-2.3) for 1-2 drinks/day 1.5 (0.8-2.8) for 3-5 drinks/day 3.3 (1.2-9.3) for ≥ 6 drinks/day	controlled for age, race, smoking, body mass index, cholesterol, reproductive factors		Hiatt et al. (1987)
prospective cohort	121 cases among 7,188 U.S. females age 25-74 yr who participated in the First National Health and Nutrition Examination Survey (1971-1975); median follow up 10 yr	**Evaluation:** participants completed questionnaire	**Estimation**: calculated adjusted RR of breast cancer RR (95% CI) 1.0 for no drinks in past year 1.4 (0.8-2.5) for > 0.1-1.2 drinks/day 1.6 (0.9-3.1) for 1.3-4.9 drinks/day 2.0 (1.1-3.7) for ≥ 5 drinks/day	controlled for age, education, body mass index, dietary fat, reproductive factors		Schatzkin et al. (1987)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
Laryngeal Cancer Case-Control Studies						
case-control	**Cases:** 326 laryngeal cancer patients **Controls:** 1134 matched by sex and age; approximately half of the controls reported drinking less than 100 g ethanol/wk	**Evaluation:** participants completed questionnaires	**Estimation:** calculated RR for laryngeal cancer based on alcohol consumption RR (95% CI not given) 1.0 for 0-100 g/week 1.5 for 101-200 g/week 3.2 for 201-300 g/week 4.1 for 301+ g/week	RR adjusted for tobacco		Olsen et al. (1985)
case-control	**Cases:** 814 male laryngeal cancer patients **Controls:** 3057 males from general population	**Evaluation:** interviews	**Estimation:** calculated RR for laryngeal cancer based on alcohol consumption RR (95% CI) Endolarynx (supraglottic) 1.0 for 0-20 g/day 0.88 (0.58-1.35) for 21-40 g/day 1.08 (0.74-1.58) for 41-80 g/day 1.68 (1.12-2.51) for 81-120 g/day 2.0 (1.33-3.02) for 121+ g/day Endolarynx (glottic and subglottic): 1.0 for 0-20 g/day 0.84 (0.49-1.44) for 21-40 g/day 1.05 (0.65-1.69) for 41-80 g/day 1.73 (1.05-2.86) for 81-120 g/day 3.40 (2.07-5.56) for 121+ g/day Epilarynx: 1.0 for 0-20 g/day 0.87 (0.29-2.65) for 21-40 g/day 1.53 (0.60-3.87) for 41-80 g/day 5.10 (2.09-12.44) for 81-120 g/day 10.64 (4.38-25.84) for 121+ g/day	RR adjusted for smoking, but adjustment did not affect crude RR		Tuyns et al. (1988)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 94 male laryngeal cancer patients **Controls:** 282 male patients not diagnosed with cancer or tobacco- and alcohol-related diseases; approximately half of the control group reported drinking <90 ml of alcohol per day	**Evaluation:** interviews	**Estimation:** calculated OR for laryngeal cancer based on alcohol consumption OR (95% CI) 1.0 for non-drinker 0.27 (0.10-0.72) for <90 mL/day 1.22 (0.60-2.48) for 90-180 mL/day 2.42 (1.18-4.93) for 180-360 mL/day 11.14 (3.84-32.37) for > 360 ml/day	adjusted for smoking		Choi and Kayho (1991)
case-control	**Cases:** 217 males with epilaryngeal cancer **Controls:** unknown number from national survey (~4000 males)	**Evaluation:** hospital chart records of alcohol and tobacco consumption compared to consumption by general population	**Estimation:** calculated RR for epilaryngeal cancer RR (95% CI) 1.0 for 0-39 g ethanol/day 1.9 (0.9-4.8) for 40-99 g ethanol/day 18.7 (8.1-42.9) for 100-159 g ethanol/day 101.4 (44-233.9) for 160+ g ethanol/day	RR adjusted for smoking The authors note that the controls may have underreported their alcohol consumption, leading to an overestimation of the RR for alcohol.	IARC (1988) noted that information on tobacco and alcohol use was obtained by different methods and in different interview situations for cases and controls	Brugere et al. (1986)
case-control	**Cases:** 832 male laryngeal cancer patients **Controls:** 1210 with cancers not reported to be related to alcohol or tobacco use; 23 of these did not have cancer	**Evaluation:** hospital admission records	**Estimation:** calculated OR for laryngeal cancer based on ethanol consumption OR (95% CI) 1.0 for 0 centiliters/wk 1.7 (1.0-3.2) for 1-35 cl/wk 1.8 (1.1-2.9) for 36-140 cl/wk 1.5 (0.8-2.9) for 141+ cl/wk	OR adjusted for smoking, age		Dosemeci et al. (1997)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 209 white male laryngeal cancer patients **Controls:** 209 matched for age, sex, hospital and educational/religious status; alcohol consumption was significantly lower than cases	**Evaluation:** interviews	**Estimation:** calculated RR for laryngeal cancer based on alcohol consumption RR (95% CI) (1 unit = 9.5 g ethanol) 1.0 for never drank or < 1 unit/day of mainly straight whiskey 1.8 (0.9-3.2) for 1-6 units/day 5.3 (2.5-11.2) for 7+ units/day 1.8 (1.0-2.9) for beer or wine, irrespective of amount consumed	RR adjusted for smoking	IARC (1988) noted that some of the tumors classified as laryngeal might have been pharyngeal.	Wynder et al. (1956; cited by IARC, 1988)
case-control	**Cases:** 224 male laryngeal cancer patients **Controls:** 414 males matched by year of interview, hospital status and age at diagnosis	**Evaluation:** interviews	**Estimation:** calculated RR for laryngeal cancer based on alcohol consumption RR (95% CI) 1.0 for < ~10 g/day 1.2 (0.8-1.9) for ~10-60 g/day 2.3 (1.5-3.4) for > 60 g/day	RR adjusted for smoking		Wynder et al. (1976; cited by IARC, 1988)
case-control	**Cases:** 184 male laryngeal cancer patients **Controls:** 184 males matched for age and area of residence	**Evaluation:** interviews	**Estimation:** calculated RR for laryngeal cancer based on alcohol consumption RR (90% CI) 4.4 (2.2-8.5) for <24 g/day 3.9 (2.1-7.3) for 24-58 g/day 4.8 (2.3-9.9) for > 60 g/day	RR adjusted for smoking		Burch et al. (1981; cited by IARC, 1988)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 154 males and females with laryngeal cancer **Controls:** 374 with other cancers	**Evaluation:** interviews	**Estimation:** calculated RR for laryngeal cancer based on alcohol consumption per week RR (95% not calculated) Extrinsic larynx: 1.0 for < 24 g 1.7 for 24-96 g 2.6 for 120-216 g 5.1 for 240-480 g 6.4 for > 480 g Intrinsic larynx 1.0 for < 24 g 1.1 for 24-96 g 0.7 for 120-216 g 2.0 for 240-480 g 2.2 for > 480 g	RR adjusted for smoking, socioeconomic group, marital status, dental care and history of tuberculosis		Elwood et al (1984; cited by IARC, 1988)
case-control	**Cases:** 365 male laryngeal cancer patients **Controls:** 1703 males	**Evaluation:** participants completed questionnaire	**Estimation:** calculated OR using unconditional multiple logistic regression for laryngeal cancer based on alcohol drinks (1 drink = 12 g of ethanol) per week OR (95% CI) 0.51 (0.27-0.96) for 1-13 0.35 (0.22-0.56) for 14-27 0.38 (0.24-0.61) for 28-41 0.76 (0.47-1.25) for 42-55 1.06 (0.68-1.65) for ≥ 56	RR adjusted for smoking		Franceschi et al. (1994)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
Liver Cancer Case-Control Studies						
case-control	**Cases**: 265 males and females with histologically confirmed primary liver cancer in New Jersey Response = 89.5% **Controls**: 530 persons matched to cases by age, race, sex, and county of residence; selected from hospital in which the cases were diagnosed and excluding patients diagnosed with hepatitis, cirrhosis, or other liver disease Response = 77%	**Evaluation**: interviews; 96% of case interviews were proxy interviews with family members of the deceased cases	**Estimation**: calculated adjusted Mantel-Haenszel RR for liver cancer and level of alcohol consumption RR (95% CI; no. cases/no. controls) for males 1.00 for abstainers 1.01 (0.48-2.12; 59/155) for 0-4000 mL ethanol/yr 1.17 (0.51-2.70; 44/87) for 4000-16000 mL ethanol/yr 2.52 (0.97-6.54; 29/30) for 16000-33000 mL ethanol/yr 1.96 (0.75-5.10; 32/54) for > 33000 mL ethanol/yr RRs higher for females; dose-response trends by level of alcohol consumption significant ($p < 0.05$) for males and females	RR adjusted for age and smoking		Stemhagen et al. (1983)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 194 patients with confirmed hepatocellular carcinoma **Controls:** 456 patients in cancer or trauma hospitals with diseases other than neoplasm or liver disease	**Evaluation**: interviews	**Estimation**: calculated adjusted RR for hepatocellular carcinoma (HCC) using logistic regression RR for HCC with cirrhosis 1.0 for 0-9 g ethanol/day 0.7 for 10-39 g ethanol/day 1.0 for 40-69 g ethanol/day 1.2 for 70+ g ethanol/day RR for HCC without cirrhosis 1.0 for 0-9 g ethanol/day 0.8 for 10-39 g ethanol/day 0.9 for 40-69 g ethanol/day 0.8 for 70+ g ethanol/day	RR adjusted for age, sex, viral antibody status, and smoking		Trichopoulos et al. (1987)
case-control	**Cases:** 165 from several U.S. hospitals **Controls:** 465 from same hospital as cases, excluding individuals with current diagnosis of tobacco and alcohol-related cancers	**Evaluation:** interviews	**Estimation**: calculated adjusted OR using logistic regression OR for males > 50 yr 1.00 for 0-1drinks/day 1.13 for 1-2 drinks/day 1.38 for > 3 drinks/day OR for females > 50 yr 1.00 for 0-1 drinks/day 1.87 for 1-2 drinks/day 3.48 for > 3 drinks/day test for trend in females statistically significant ($p < 0.05$)	OR adjusted for age at diagnosis, ethnic group, education, occupation, and religion		Yu et al. (1988)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases**: 187 Japanese males with newly diagnosed liver cancer **Controls**: 192 Japanese males admitted to gastroenterology clinics for checkups, without liver or alcohol-related diseases and age-matched to cases	**Evaluation:** interviews	**Estimation**: calculated adjusted RR for liver cancer using logistic regression RR (95 % CI) 1.0 for 0-2.7 x 10^5 mL total ethanol consumed (sake; referent) 1.0 (0.6-1.6) for 2.7 x 10^5 - 1.08 x 10^6 mL total ethanol consumed (sake) 2.2 (1.2-4.0) for $\geq$ 1.08 x 10^6 mL total ethanol consumed (sake) positive trend (p = 0.0273)	RR adjusted for age, HBsAg, history of blood transfusion, cigarette index, and family history of liver cancer		Tsukuma et al. (1990)
case-control	**Cases**: 204 Japanese patients diagnosed with hepatocellular carcinoma **Controls**: 410 persons without chronic liver disease in same region as cases who visited a public health center; matched to cases by sex and age	**Evaluation:** interviews	**Estimation:** calculated adjusted RR of hepatocellular carcinoma using logistic regression RR (95% CI) for males and females 1.0 for non-drinker (referent) 1.0 (0.6-1.7) for cumulative alcohol intake of 0.1-33.9 drink-years 1.1 (0.6-1.8) for cumulative alcohol intake of 34.0-76.6 drink-years 1.9 (1.1-1.3) for cumulative alcohol intake of 76.7+ drink-years drink-years categorized by quartiles among male controls positive trend (p = 0.01)	RR adjusted for sex, age; adjustment for HBsAg did not significantly change the estimates		Tanaka et al. (1992)
case-control	**Cases**: 83 males deceased from hepatocellular carcinoma and 15 males deceased from cholangiocarcinoma; identified through Swedish cancer registry **Controls**: two deceased population controls identified for each case in the National Population Register	**Evaluation:** relatives completed questionnaires; categorized cases into nondrinkers, light , moderate, heavy consumers of spirits	**Estimation:** calculated RR for hepatocellular carcinoma RR (95% CI) 1.0 for nondrinkers 2.1 (0.9-5.1) for light drinkers 2.9 (.99-8.7) for moderate drinkers 4.3 (1.8-10.8) for heavy drinkers		IARC(1988) noted: no hepatitis B serology	Hardell et al. (1984)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases**: 60 males and 26 females in five U.S. states diagnosed with liver cancer **Controls**: 110 males and 51 females; hospital patients without primary liver disease matched to cases by age, sex, and race	**Evaluation**: interviews	**Estimation**: calculated matched RR for liver cancer RR 1.0 for nondrinkers 1.4 for infrequent drinkers 2.3 for occasional drinkers 2.6 for regular drinkers (at least once/day) statistically significant trend test increased RRs for alcohol use after adjustment for smoking	gender, age, race, smoking		Austin et al. (1986)
case-control	**Cases**: 61 males in France with primary liver cancer **Controls**: 61 males admitted to hospitals for trauma; age-, sex-, and interviewer- matched to cases	**Evaluation:** personal interviews; obtained drinking history to 10 yr prior to interview; cases and controls reported equal ethanol intake	High, but equal, alcohol consumption among cases and controls.		IARC (1988) noted high but equal alcohol consumption among cases and controls	Schwartz et al. (1962; cited by IARC,1988)
case-control	**Cases**: 95 males and 12 females in Hong Kong with histologically confirmed primary liver cancer **Controls**: 94 males and 13 females matched to cases for age, sex, and hospital in Hong Kong	**Evaluation**: personal interviews; obtained socioeconomic status, birthplace, HBV exposure, dietary history and habits	**Estimation**: no data reported but the authors stated no significant positive association between liver cancer and alcohol intake			Lam et al. (1982)
case-control	**Cases**: 74 males and 16 females diagnosed with primary liver cancer **Controls**: 74 male and 16 female hospital patients with normal liver function age- and sex-matched to cases	**Evaluation:** categorization into 'heavy' and 'light' drinkers using mean ethanol intake per day heavy/light aflatoxin load per day was estimated by food items consumed	**Estimation:** calculated matched RR for liver cancer from combined effects of aflatoxin load and alcohol intake: RR 1.0 for light aflatoxin, light alcohol 3.9 ($p \leq 0.05$) for light aflatoxin, heavy alcohol 17.5 ($p = 0.05$) for heavy aflatoxin, light alcohol 35.0 ($p = 0.05$) for heavy aflatoxin, heavy alcohol	age, sex, hepatitis B infection	IARC (1988) noted interpretation is limited by lack of hepatitis B serology	Bulatao-Jayme et al. (1982)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
Liver cancer cohort studies						
cohort	5135 Japanese doctors followed 1965-1983	**Evaluation:** self-administered questionnaire in 1965	**Estimation**: calculated adjusted RR for death from liver cancer (19 yr follow-up) RR (95% CI) 1.4 (0.4-4.8) for ex-drinkers 1.5 (0.6-3.8) for occasional drinkers 2.0 (0.8-5.1) for daily drinkers of < 2 go of sake 2.7 (1.0-6.8) for daily drinkers of > 2 go of sake	RR adjusted for age and smoking but not hepatitis B infection	IARC (1988) noted no data on hepatitis B virus serology	Kono et al. (1986)
cohort	Danish Brewery workers cohort		**Estimation**: calculated RR for liver cancer RR; no. observed/no. expected 1.5; 29/19.2, significant			Jensen (1980; cited by IARC, 1988)
cohort	Finnish alcohol misusers 1944-1959 (205000) and alcoholics 1967-1970 (4370) cohorts; linked with Finnish cancer registry 1965-1970		**Estimation:** calculated RR for liver cancer RR; no. observed/no. expected 1.5; 66/44.3, $p < 0.05$ for alcohol misusers 2.5; 2/0.77, not significant for alcoholics	age		Hakulinen et al. (1974)
cohort	Japanese population; follow-up of 639 males in fishing area and 677 males in farming area; followed from 1958-1980	**Evaluation:** interviews at initiation of follow-up	**Estimation**: calculated SMR for death from liver cancer SMR Fishing Area Men 5.7 ($p < 0.001$) for < 1 units shochu 7.5 ($p < 0.001$) for 1-2 units shochu 20 ($p < 0.001$) for > 2 units shochu no effect of sake or shochu drinking on men in farming area, and no effect of sake drinking on men in fishing area	age, hepatitis B infection	IARC(1988) noted no data on hepatitis B virus serology	Shibata et al. (1986)

Abbreviations: OR = odds ratio; RR = relative risk; SMR = standardized mortality ratio; CI = confidence interval

4.0 EXPERIMENTAL CARCINOGENESIS

4.1 Studies Reviewed by IARC (1988)

One study reported no increased tumor incidence in rats administered alternating doses of pure ethanol in water (15% and 55%), farm apple brandy (15% and 55%), or industrial apple brandy (15% and 40%) as the drinking fluid for up to 23 mo. The higher concentrations were supplied on alternate days and controls were exposed to water alone. Other animal studies were considered inadequate for evaluation of carcinogenic effects of ethanol.

A number of adequate studies reported the tumor incidence in animals given ethanol in combination with a known carcinogen. Mice orally administered ethanol and *N*-nitrosodimethylamine (NDMA) had an increased incidence of nasal cavity tumors. Ethanol also enhanced the incidence of esophageal/forestomach tumors and lung tumors in mice given *N*-nitroso-diethylamine (NDEA) or *N*-nitrosodi-*n*-propylamine by oral administration. The incidence of benign tumors in the nasal cavity of rats was enhanced by ethanol administered in a liquid diet with *N*´-nitrosonornicotine. In addition, hamsters given *N*-nitrosopyrrolidine (NPyr) by intraperitoneal (i.p.) injection showed a higher incidence of nasal cavity and tracheal tumors and neoplastic liver nodules if ethanol was simultaneously administered. Rats exposed to vinyl chloride via inhalation had a higher incidence of liver tumors when ethanol was administered in the drinking water.

IARC (1988) concluded that there is inadequate evidence for the carcinogenicity of ethanol and alcoholic beverages in experimental animals. Earlier review groups (IARC, 1985, 1987) concluded that there is sufficient evidence for the carcinogenicity of acetaldehyde (the initial metabolite of ethanol) in experimental animals.

4.2 Studies Post-IARC (1988)

All tumor incidences are presented in ascending order from control to highest dose.

4.2.1 Mice

One recent study examined the effects of ethanol on mammary carcinogenesis (Hackney et al., 1992). The strain of mice treated have a high spontaneous mammary tumor incidence, but the mammary tumorigenesis was not enhanced by ethanol administered in drinking water, by gavage, or as part of a liquid diet. Groups were given ethanol at a rate of 15 g/kg/day in drinking water, 4 g/kg/day by gavage, or 20 g/kg/day in a defined diet. Compared to isocaloric controls, treatment groups showed either no change or a decrease in tumor incidence (Hackney et al., 1992).

Two other studies with mice provide evidence that coexposure to nitrosamines and ethanol potentiates the carcinogenicity of nitrosamines. In one study (Anderson et al., 1992), the incidence of lung tumors was significantly ($p<0.05$) greater in groups given NDMA (5 ppm) + ethanol (1%, 5%, or 10%) in drinking water than in a group given only NDMA (27/50, 47/49, 46/48, 49/50). A statistically significant increase in lung tumors was seen in mice exposed to NDMA (1 ppm) and 10% ethanol in drinking water for 48 or 72 wk and in mice given an intragastric (i.g.) dose of NDMA administered with an ethanol (5%, 10%, or 20%) solution.

Another coexposure study (Anderson et al., 1993) extended the nitrosamine exposure to include NDEA, NPyr, and N^6 - (methylnitroso) adenosine (MNAR). The NDEA + ethanol group

had a significantly ($p<0.01$) greater lung tumor multiplicity than the NDEA only group (5.8, 1.5). The incidence of forestomach tumors was also greater in the NDEA + ethanol group than in the NDEA-only group (16/50, 1/50). In addition, the NPyr + ethanol groups showed a significant ($p<0.01$) increase in the incidence of lung tumors compared to the NPyr- only groups, at 6.8 ppm NPyr (33/49, 20/49) and 40 ppm NPyr (47/48, 22/49). At the high dose of MNAR, the incidence of thymic lymphoma was significantly increased in the MNAR + ethanol group compared to the group treated with MNAR only (32/50, 21/49).

4.2.2 Rats

A study explored cancer metastasis in rats given ethanol prior to and during development of a primary tumor (Yirmiya et al., 1992). Rats were administered ethanol in a liquid diet followed by lung cancer induction by injection of murine lymphoma cells. The ethanol exposed group had significantly ($p<0.05$) more metastases, indicated by cell morphology, than control groups given a standard liquid or solid diet.

The influence of ethanol on the initiation stage of cancer induction by nitrosamines was investigated in several studies. In one study (Grubbs et al., 1988), rats were gavaged with two doses of ethanol and weeks later given dimethyl benzanthracene (DMBA) or methylnitrosourea (MNU). Ethanol-pretreated groups had a greater number of mammary cancers per rat after treatment with DMBA than groups not pretreated (high dose 5.6; low dose 5.4; sucrose 4.0; none 3.4).

Three studies examined mammary tumors in rats exposed to ethanol before, during and after treatment with DMBA or MNU. In one study (Singletary et al., 1991), groups were fed diets with ethanol as a percentage of calories before, and seven days after, treatment with DMBA, or only after DMBA treatment. Compared to the control group, the incidence of mammary tumors was significantly ($p<0.05$) greater in rats fed 20% ethanol before and after dosing with DMBA (47%, 82%). Likewise, in comparison to the control group, the incidence of mammary tumors in rats fed 15% ethanol was significantly ($p<0.05$) greater (49%, 83%). There was no significant difference, however, in the incidence of rats with mammary tumors from the group given 30% ethanol and the controls.

A similar study investigated dietary ethanol and the carcinogen MNU (Singletary et al., 1995). Groups were fed diets with ethanol as a percentage of calories before, during and seven days after treatment with MNU, or only after MNU treatment. There was a significant ($p<0.05$) difference in mammary tumor incidence between the 15% ethanol group and the control group, but there was no significant difference in the mammary tumor incidence between rats given 20% or 30% ethanol and the controls. A significant ($p<0.05$) difference in mammary adenocarcinomas per rat and in final palpable tumor number per rat was also observed between the 15% ethanol group and the control group. In addition, the 20% ethanol group had a significantly higher final palpable tumor incidence compared to the controls.

Finally, ethanol had no effect on mammary tumor incidence in rats given ethanol as a dietary caloric percentage before, during, and after treatment with DMBA (Rogers and Connor, 1990). A group was administered 10% of their calories as ethanol at age 24-28 days, 20% of their calories as ethanol at age 28-230 days, and DMBA (20 mg/kg) by gavage at age 55 days. In the control group, fat was substituted for ethanol.

Another study that investigated the incidence of DMBA-induced mammary tumors in rats pretreated with ethanol did not find that ethanol potentiated tumor incidence (McDermott et al.,

1992). Animals were administered ethanol (5%) in the drinking water from age 40 to 50 days and given an i.g. dose of DMBA (15 mg) at age 50 days. At age 116 days, the incidence of mammary tumors was greater in the control than in the treated group (18/18, 8/20).

Several studies examined tumor incidence in rats coexposed to a nitrosamine and ethanol. Cotreatment of rats with diethyl nitrosamine (DEN) and ethanol in drinking water resulted in an increase of esophageal tumors compared to tumors after exposure to only DEN (Aze et al., 1993). Groups were administered two doses of DEN (33 ppm, 50 ppm) or one dose of DEN (50 ppm) and ethanol (10%) in drinking water. The group coexposed to DEN and ethanol had a significant ($p<0.01$) number of rats with esophageal papilloma (1/26, 2/28, 10/26), esophageal carcinoma (0/26, 1/28, 8/26), and esophageal papilloma and carcinoma combined (1/26, 3/28, 15/26), compared to groups exposed to both levels of DEN alone.

Yamagiwa et al. (1991, 1994) investigated liver cancer in male and female rats simultaneously exposed to female hormones and ethanol. Groups were given by stomach tube ethynylestradiol (EE; 0.075 mg) and norethindrone acetate (NA; 6.0 mg) with and without ethanol (10%) in drinking water; liver examinations were made every two wk for 12 mo. The incidence of hepatocellular carcinoma was significantly ($p<0.05$) elevated at 12 mo. in females treated with NA, EE and ethanol compared to females treated with NA and EE only (2/25, 9/22). This increase in hepatocellular carcinoma was not seen in the males rats in the study.

In contrast, the incidence of glandular stomach carcinoma and duodenal carcinoma was significantly reduced in rats coadministered ethanol with the nitrosamine *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) in a drinking solution, compared to tumor induction by MNNG given without ethanol (Cerar and Pokorn, 1996). Groups of rats were given MNNG (100 μg/mL) in tap water, MNNG (100 μg/mL) in 11% ethanol, or MNNG (100 μg/mL) in wine. The solutions were administered for six mo followed by a normal diet until study termination at mo 13. The glandular stomach adenocarcinoma incidence in the group treated with only MNNG was significantly ($p=0.037$) increased compared to groups given MNNG in wine or in an ethanol solution (6/17, 1/18, 1/19). An analogous conclusion was drawn concerning duodenal adenocarcinoma (4/17, 0/18, 0/19; $p < 0.0005$).

In one study, rats were coexposed to ethanol and methyl-*n*-amylnitrosamine (MNAN) and then administered ethanol for life (Mirvish et al., 1994). Groups were given three i.p. injections of MNAN; one group was simultaneously administered ethanol in drinking water, which continued throughout the animals' lives. Histological examinations showed no change in the incidence of tumors in the esophagus, nasal cavity, tongue, forestomach, and thyroid between groups treated with MNAN and MNAN + ethanol.

4.2.3 Hamsters

A study with hamsters investigated cancer in the offspring of pregnant females exposed to ethanol early in gestation and later given the nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (Schuller et al., 1993). Offspring of the group transplacentally exposed to NNK and ethanol had a significantly ($p<0.01$) greater overall tumor incidence than both offspring exposed to NNK only and offspring of the control group (M: 8/16, 3/9, 0/12; F: 13/17, 6/15, 0/16).

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
Mice							
6-wk-old C3H/Ou mice; (strain known to develop mammary cancer spontaneously)	Expt I: 15 F Expt II: 10 F Expt III: 14 F	Expt I: 15 F Expt II: 16 F Expt III: 20 F	ethanol USP 95%	Expt I: semipurified solid diet and 15 g/kg/day ethanol in drinking water Expt II: isocaloric pair feeding semipurified diet and 4 g/kg/day ethanol by gavage five times per wk Expt III: isocaloric pair feeding of Lieber-DeCarli liquid diet and 20 g/kg/day ethanol in diet	65 wk	Expt I: rate of mammary tumor development delayed in treated group so the median incidence was 17 wk later than controls (p=0.03); control mice gained weight more rapidly and consumed more calories from solid food but both groups consumed approximately equal total daily calories Expt II: rate of mammary tumor development, weight gain, and calorie consumption similar in treated and control groups Expt III: no significant (p=0.10) difference in rate of mammary tumor development; weight gain same in both groups for 14 wk and then decreased in treated group	Hackney et al. (1992)

...perimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

...ain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
4-6-wk old A/JNCr mice	Expt I: four groups of 50 M Expt II: 12 groups of 50 M Expt III: nine groups of 30 M Expt IV: five groups of 25 M	Expt I: two groups of 25 M Expt II: four groups of 50 M Expt III: three groups of 30 M Expt IV: five groups of 25 M	ethanol; reagent grade NDMA (*N*-nitrosodimethylamine) technical grade	Expt I: groups given 0 or 5 ppm NDMA in drinking water and 0, 1, 5, or 10% ethanol in drinking water Expt II: groups given 1 ppm NDMA in drinking water and 0 or 10% ethanol in drinking water Expt III: groups given 0, 1, or 5 mg/kg NDMA single i.g. dose administered with 0, 5, 10, or 20% ethanol Expt IV: groups given 0 or 1 mg/kg NDMA by various routes (i.g., i.p., s.c., i.v.) and 0 or 10% ethanol in drinking water	Expt I: 4 wk then held 12 wk Expt II: 16, 32, 48, or 72 wk Expt III: 16 wk Expt IV: NDMA 5 x/wk for 4 wk; animal sacrifice at 32 wk	Expt I: the incidence of lung tumors was significantly ($p<0.05$) greater in all groups given NDMA + ethanol than in the group given NDMA only: NDMA + ethanol 0% 1% 5% 10% 27/50 47/49 46/48 49/50 Expt II: after 48 and 72 wk, the incidence of lung tumors was significantly ($p<0.05$) greater in groups given NDMA + ethanol than in the group given NDMA only: NDMA NDMA + ethanol 48 wks 32/48 45/49 72 wks 42/48 48/49 Expt III: the incidence of lung tumors was significantly ($p<0.05$) greater with 5 mg/kg NDMA + ethanol at all concentrations than in the group given NDMA only: NDMA + ethanol 0% 5% 10% 20% 15/30 27/30 30/30 30/30 Expt IV: no significant effects of ethanol with repeated doses of 1 mg NDMA/kg	Anderson et al. (1992)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
Expt I: 4-wk-old A/JNCr mice Expt II: 4-wk-old Swiss (NIH:Cr(S)) mice	Expt I: six groups of 50 M; one group of 25 M Expt II: five groups of 50 F	Expt I: one group of 25 M Expt II: one group of 50 F	ethanol; reagent grade NDEA (*N*-nitrosodiethylamine); analytical grade Npyr (*N*-nitrosopyrrolidine); analytical grade MNAR (N^6-(methylnitroso)adenosine; synthesized; purity n.p.	Expt I: groups given 0 or 6.8 ppm NDEA or 0, 6.8 or 40 ppm NPyr and 0 or 10% ethanol in sterilized distilled drinking water Expt II: groups given i.g. doses of 0, 60, or 120 mg MNAR/kg and 0 or 15% ethanol	Expt I: 4 wk; mice held 32 wk Expt II: three doses per wk for 12 wk; mice sacrificed when ill or at age 18 mo	Expt I: The NDEA-treated group showed a significant ($p< 0.01$) increase in lung tumors compared to untreated controls (42/50, 9/24). The NDEA + ethanol group had a significantly ($p<0.01$) greater lung tumor multiplicity than the NDEA group (5.8, 1.5). The incidence of forestomach tumors was also greater in the NDEA + ethanol group than in the NDEA only group (16/50, 1/50). The NPyr + ethanol groups showed a significant ($p<0.01$) increase in the incidence of lung tumors compared to the NPyr only groups at 6.8 ppm NPyr (33/49, 20/49) and 40 ppm NPyr (47/48, 22/49). However, the lung tumor incidence in the low dose NPyr + ethanol group was not significantly different from the incidence in the ethanol only group, so definitive interpretation is not possible. Expt II: Coexposure to ethanol significantly reduced survival time at the lower dose of MNAR. At the high dose of MNAR, the incidence of thymic lymphoma was significantly increased in the MNAR + ethanol group compared to the group treated with MNAR only (21/49, 32/50).	Anderson et al. (1993)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
Rats							
10-12-wk old Fischer 344 rats	one group of 9 or 10 M	two groups of 9-10 M	ethanol; purity n.p.	Treated group received a liquid diet with ethanol as 5% w/v and 35% ethanol-derived calories. Control groups received an isocaloric diet (pair-feeding) or normal rat chow and water. All groups were inoculated with murine lymphoma cells.	Lungs were removed and examined 3 wk after inoculation.	Ethanol-exposed rats had significantly ($p<0.05$) more metastases than both control groups.	Yirmiya et al. (1992)
35-day-old Sprague-Dawley rats	Expt I and Expt II: four groups of F; no. n.p.	Expt I and Expt II: one group of F; no. n.p.	ethanol; purity n.p. Expt I: DMBA (dimethylbenzanthracene); purity n.p. Expt II: MNU (methylnitrosourea); purity n.p.	Expt I: groups given two gavage doses of ethanol (3.5 g/kg; 7.0 g/kg); sucrose (isocaloric to the high dose of ethanol); or no treatment; then DMBA (10 mg) Expt II: ethanol treatment as above; MNU (50 mg/kg) by i.v.	Expt I: ethanol treatment for 3 wk; DMBA at age 58 days for 6 mo Expt II: ethanol treatment for 8 wk; MNU at age 93 days for 7 mo	Expt I: Both ethanol pretreated groups had a greater no. of mammary cancers per rat after treatment with DMBA than groups not pretreated (high dose-5.6; low dose-5.4; sucrose-4.0; none-3.4); statistical analyses n.p. Expt II: The group pretreated with the high dose of ethanol had a greater no. of mammary cancers per rat after treatment with MNU than groups not pretreated (hi dose-2.5; low dose-2.0; sucrose-1.7; none-2.0); statistical analyses n.p.	Grubbs et al. (1988)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
Expt I and II: 21-22-day-old Sprague-Dawley rats Expt III: 42-day-old Sprague-Dawley rats	Expt I: one group of 17 F Expt II: two groups of 26 and 31 F Expt III: two groups of 30 and 31 F	Expt I: one group of 15 F Expt II: one group of 33 F Expt III: one group of 31 F	ethanol; 95% purity DMBA; purity n.p.	Expt I: groups given a liquid diet; then given diets with ethanol at 0% or 20% of calories; i.g. administration of DMBA (30 mg/kg) Expt II: groups given a liquid diet; then given diets with ethanol at 0%, 10%, or 20% of calories; i.g. administration of DMBA (35.7 mg/kg) Expt III: groups given powdered control diet; administered DMBA (32.3 mg/kg); groups then given diets with ethanol at 0%, 15%, or 30% of calories	Expt I: liquid control diet to age 30 days; ethanol diet at age 30-57 days; DMBA at age 58 days; ethanol diet at age 58-65 days; powdered diet at age 65-78 days Expt II: liquid control diet to age 25 days; ethanol diet at age 25-52 days; DMBA at age 53 days; ethanol diet at age 53-60 days; powdered diet at age 60-79 days Expt III: powdered diet at age 42-56 days; DMBA at age 56 days; ethanol at age 63-203 days	Expt I: Compared to the control group, the incidence of mammary tumors was significantly ($p<0.05$) greater in rats fed 20% ethanol (47%, 82% respectively). Expt II: Compared to the control group, the incidence of mammary tumors was significantly ($p < 0.05$) greater in rats fed 20% ethanol (48%, 74% respectively), but there was no significant difference in the incidence of rats with mammary tumors between the low ethanol dose group and controls. On diets containing 0%, 10%, and 20% calories as ethanol, the incidence of tumor-bearing rats having adenocarcinomas was 78%, 82%, and 91%, respectively. Expt III: Compared to the control group, the incidence of mammary tumors was significantly ($p < 0.05$) greater in rats fed 15% ethanol (49%, 83% respectively), but there was no significant difference in the incidence of rats with mammary tumors in the group given 30% ethanol versus controls. On diets containing 0%, 15%, and 30% calories as ethanol, the incidence of tumor-bearing rats having adenocarcinomas was 74%, 93%, and 90%, respectively.	Singletary et al. (1991)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
Expt I: 23-day-old Sprague-Dawley rats Expt II: 38-day-old Sprague-Dawley rats	Expt I: three groups of 32 F Expt II: four groups of 32, 30, 30, and 30 F	Expt I: three groups of 32 F each Expt II: two groups of 32 F each	ethanol; purity 95% MNU; purity n.p.	Expt I: groups given a powdered diet; then given diets with ethanol at 0%, 15%, 20% or 30% of calories; then i.p. administration of MNU (30 mg/kg); then ethanol diet; then powdered diet Expt II: groups given powdered control diet; administered MNU (30 mg/kg); groups then given diets with ethanol at 0%, 15%, 20%, or 30% of calories	Expt I: powdered control diet to age 28 days; ethanol diet at age 28-49 days; MNU at age 50 days; ethanol diet at age 50-57 days; powdered control diet at age 57-72 days Expt II: powdered diet at age 38-51 days; MNU at age 51 days; ethanol diet at age 58-73 days	Expt I: Significant ($p<0.05$) difference in mammary tumor incidence between the control group (59%) and the 15% ethanol group (75%), but no significant difference in the mammary tumor incidence between controls and the group given 20% ethanol (66%) or in the group given 30% ethanol (69%). Expt II: Significant ($p<0.05$) difference in mammary adenocarcinomas per rat and in final palpable tumor no. per rat between 15% ethanol group and control group. The 20% ethanol group also had a statistically significant increased final palpable tumor incidence compared to controls, but there was no significant difference in the mammary tumor incidence between rats given 30% ethanol and controls.	Singletary et al. (1995)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
21-day-old Sprague-Dawley rats	two groups of 50 F	one group of 50 F	ethanol; purity n.p. DMBA; purity n.p.	Group 1: DMBA (20 mg/kg) by gavage and liquid diet with 20% calories as fat Group 2: DMBA (20 mg/kg) by gavage and liquid diet with 20% calories as fat; then 10% calories as ethanol; then 20% calories as ethanol Group 3: DMBA (20 mg/kg) by gavage and liquid diet with 20% calories as fat; then 10% calories as fat; then 20% calories as fat	Group 1: Rats at age 21-230 days Group 2: Rats given 20% calories as fat at 21-24 days of age, 10% calories as ethanol at age 24-28 days and 20% calories as ethanol at age 28-230 days Group 3: Rats given 20% calories as fat at 21-24 days of age, 10% calories as fat at age 24-28 days; 20% calories as fat at age 28-230 days DMBA in all groups at age 55 days	No significant difference in mammary tumors between groups	Rogers and Conner (1990)
40-day-old Sprague-Dawley rats	one group of 20 F	one group of 20 F	ethanol; lab grade DMBA; analytical purity	Group 1: ethanol (5%) in drinking water; then DMBA (15 mg) in sesame oil (1 mL) by i.g. Group 2: tap water; then DMBA (15 mg) in sesame oil (1 mL) by i.g.	Group 1: ethanol age 40-50 days Group 2: DMBA age 50 days diet and liquid age 50-170 days	Mammary tumors were reported in 100% of controls versus 40% of rats in the treated group ($p<0.001$) at age 116 days.	McDermott et al. (1992)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
5-wk-old Fischer 344 rats	Group 1: n=3 Group 2: n=30 Group 3: n=28 Group 4: n=30 All rats in study were male.	groups 2-4 controls for group 1	ethanol; purity > 99% DEN (diethylnitrosoamine); purity > 99%	Group 1: DEN (50 ppm) plus 10% ethanol in drinking water; then tap water Group 2: DEN (33 ppm) in drinking water; then tap water Group 3: DEN (50 ppm) in drinking water; then tap water Group 4: ethanol (10%) in drinking water; then tap water	Groups 1-4 treatment 8 wk; tap water 96 wk	Survival reduced at 104 wk in Group 1 (13%), Group 2 (57%), Group 3 (36%), and Group 4 (80%) Esophagus: Group 1 had a significant ($p < 0.01$) number of rats with papilloma, carcinoma, and papilloma and carcinoma combined compared to Groups 2 and 3. No tumor incidence in Group 4 given ethanol in drinking water without DEN: Papill. / Carcin. / Papill. + Carcin. Group 1 10/26 8/26 15/26 Group 2 1/26 0/26 1/26 Group 3 2/28 1/28 3/28 Group 4 0/28 0/28 0/28 Other tissues not examined.	Aze et al. (1993)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
4-wk-old Wistar JCL rats	Group 1: n=32 (5, 5, 5, 5, 12) Group 2: n=40 (5, 4, 5, 5, 21) Group 3: n=30 (5, 5, 5, 5, 10) Each group was subdivided for different treatment periods. All rats in the study were female.	Group 4: n=25 (5, 5, 5, 5, 5)	ethanol, EE (ethynyl estradiol); NA (norethinodrone acetate); all analytical purity	Group 1: EE (0.075 mg) and NA (6.0 mg) in olive oil (0.5 mL) by stomach tube Group 2: EE (0.075 mg) and NA (6.0 mg) in olive oil (0.5 mL) by stomach tube plus ethanol (10%) in drinking water Group 3: olive oil (0.5 mL) by stomach tube plus ethanol (10%) in drinking water Group 4: olive oil (0.5 mL) by stomach tube	groups treated for 2, 4, 6, 8, and 12 mo EE and NA administered daily; ethanol given 5/7 days per wk, pure water given in remaining two days per wk	The incidence of hepatocellular carcinoma was significantly ($p<0.05$) elevated at 12 mo in Group 2 treated with NA, EE and ethanol compared to Group 1 treated with EE and NA (8/21, 1/12 respectively). No hepatocellular carcinomas developed in Groups 3 and 4 during the study.	Yamagiwa et al. (1991)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
4-wk-old Wistar rats	Group 1: n=45 F (5, 5, 5, 5, 25) and 36M (4, 4, 4, 4, 20) Group 2: n=41 F (5, 4, 5, 5, 22) and 33M (4, 4, 4, 4, 17) Group 3: n= 30 F (5, 5, 5, 5, 10) and 24 M (4, 4, 4, 4, 8) Each group was subdivided for different treatment periods.	one group of 25 F (5, 5, 5, 5, 5) one group of 20 M (4, 4, 4, 4, 4)	ethanol, EE, NA; all analytical purity	Group 1: EE (0.075 mg) and NA (6.0 mg) in olive oil (0.5 mL) by stomach tube Group 2: EE (0.075 mg) and NA (6.0 mg) in olive oil (0.5 mL) by stomach tube plus ethanol (10%) in drinking water Group 3: olive oil (0.5 mL) by stomach tube plus ethanol (10%) in drinking water Group 4: olive oil (0.5 mL) by stomach tube	groups treated for 2, 4, 6, 8, and 12 mo EE and NA administered daily; ethanol given 5/7 days per wk, pure water given in remaining 2 days per wk	The incidence of hepatocellular carcinoma was significantly ($p<0.05$) elevated at 12 mo in the female group (Group 2) treated with NA, EE and ethanol compared to females in the group (Group 1) treated with NA and EE (9/22, 2/25). Males did not develop hepatocellular carcinoma except at 12 mo. in the group (Group 2) treated with NA, EE, and ethanol (2/17).	Yamagiwa et al. (1994)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
age n.p. Wistar rats	two groups of 20 M	one group of 20 M	MNNG (*N*-methyl-*N*-nitro-*N*-nitrosoguanidine), purity n.p.	Group 1: MNNG (100 µg/mL) in tap water Group 2: MNNG (100 µg/mL) in wine Group 3: MNNG (100 µg/mL) in 11% ethanol water solution one group for each treatment all solutions were administered as drinking fluid	0-6 mo for Group 1 0-6 mo plus 10 d for Groups 2-3 to equalize total MNNG consumption (Groups 2 and 3 consumed less liquid over 6 mo than Group 1) 6-13 mo only tap water for Group 1 6 mo plus 10 days-13 mo. only tap water for Groups 2-3	10% died before study termination at 13 mo: 3 in Group1, 2 in Group 2, 1 in Group 3. All organs except those in the central nervous system and skeleton were examined macroscopically. Glandular stomach: the adenocarcinoma incidence in Group 1 (6) was significantly (p=0.037) increased compared to Group 2 (1) and Group 3 (1); one sarcoma was found in Group 2. In the forestomach, the incidence of papilloma was not significantly different between groups - Group1 (1), Group 2 (0), Group 3 (1). Carcinoma of the forestomach was also identified in Group 1 (1), Group 2 (1), and Group 3 (2), but the difference was not significant. Duodenum: adenocarcinoma incidence in Group 1 (4) significantly ($p < 0.0005$) increased compared to Group 2 (0) and Group 3 (0)	Cerar and Pokorn (1996)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
6-wk-old MRC-Wistar rats	two groups of 40 and 25 M	one group of 10 M	ethanol; purity 95% MNAN (methyl-*n*-amylnitrosoamine); purity n.p.	Group 1: MNAN (25 mg/kg) by i.p. three times Group 2: MNAN (25 mg/kg) by i.p. three times and ethanol (20%) in drinking (distilled) water; then MNAN single i.p. (25 mg/kg) and ethanol (10%) in drinking water	Group 1: injection at 7, 8, 9 wk of age Group 2: injection of MNAN at age 7, 8 and 9 wks; ethanol (20%) continuously from age 6-8 wks; ethanol (10%) continuously from age 8-10 wks; then 5 days/wk for life	No significant difference in incidence of tumors in esophagus, nasal cavity, tongue, forestomach, and thyroid between group treated with MNAN and group treated with MNAN + ethanol	Mirvish et al. (1994)
Hamsters							
age n.p. Syrian golden hamsters	three groups of 4 pregnant F	4 F	ethanol; purity n.p. NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone); purity > 98%	Group 1: ethanol (10%) in drinking water Group 2: NNK (50 mg/kg) in distilled water by intratracheal instillation Group 3: ethanol in drinking water; NNK by intratracheal instillation control group given distilled water	Group 1: gestation days 5-16 Group 2: gestation day 15 Group 3: ethanol: gestation days 5-16; NNK: gestation day 15	survival similar between groups Offspring of the group transplacentally exposed to NNK and ethanol had a significantly ($p < 0.01$) greater overall tumor incidence (50% in males, 77% in females) than offspring exposed to NNK alone (33% in males, 40% in females) or offspring exposed to ethanol alone (5.9% in males, 4.3% in females). No control group offspring developed tumors during the study. A majority (10/17) of female offspring of the group treated with NNK and ethanol developed pancreatic tumors while female offspring of other treated groups developed no pancreatic tumors during the study.	Schuller et al. (1993)

5.0 GENOTOXICITY

Studies of the genotoxic effects of ethanol and alcoholic beverages published prior to 1988 have been reviewed by IARC (1988, pp. 135-159, see Appendix B). More recent studies are summarized in Section 5.2.

5.1 Genotoxicity Studies Reviewed by IARC (1988)

The peripheral blood lymphocytes of alcoholics showed increased frequencies of chromosomal aberrations when compared to nonalcoholics in studies that controlled for age, sex, duration of dependence, and smoking. Smoking alcoholics had a higher frequency of exchange-type aberrations than nonsmoking alcoholics. These aberration frequencies were also positively correlated to duration of alcohol dependence. Similar studies of sister chromatid exchange (SCE) or aneuploidy often did not control for confounding factors.

In rodents exposed to ethanol *in vivo*, inconsistent results were reported for chromosomal aberrations and SCE. Chromosomal aberrations were not induced in rats or hamsters, but one study showed chromosomal aberrations in rat embryos exposed *in vivo*. An increase in SCE was induced in mouse (but not hamster) bone-marrow, mouse embryo liver cells, and in rat peripheral blood lymphocytes exposed *in vivo*.

A high incidence of aneuploidy was seen in the fertilized eggs of female mice given ethanol after the predicted time of ovulation. Conflicting results were reported for induction of micronuclei and dominant lethal mutations in mice and rats administered ethanol.

Several studies examined the genotoxicity of ethanol and alcoholic beverages in human blood lymphocytes *in vitro*. In one study, chromosomal aberrations were induced in human lymphocytes treated *in vitro* with ethanol without exogenous metabolic transformation, but several similar studies were negative. Lymphocyte exposure to different types of alcoholic beverages did not produce chromosomal aberrations.

An increase in SCE was observed in human lymphocytes treated with ethanol or alcohol-free extracts of several alcoholic beverages. One study with ethanol showed a dose-related increase in SCE without exogenous metabolic activation, but another study found an SCE increase only after the addition of alcohol dehydrogenase. In a study of alcohol-free beverage extracts, the frequency of SCE was increased in the absence of an exogenous metabolic system.

5.2 Genotoxicity Studies Published after IARC (1988)

This section reviews only studies in human and other mammalian systems and *Drosophila*. An increase in the frequency of structural chromosomal aberrations was observed in mitogen-stimulated peripheral blood lymphocytes of abstinent alcoholics (Gattas and Saldanha, 1997). Abstinent alcoholics were abstinent from one month to 32 years (n = 55) while controls (n = 55) were selected at random and not screened for alcohol intake. Cytogenetic analyses showed that ex-chronic alcoholics had a threefold higher frequency of cells with structural chromosomal aberrations in peripheral lymphocytes than did controls.

An *in vivo* human study reported no relationship between reported alcohol intake and *hprt* mutant frequency in human T cells (Cole and Green, 1995). Blood samples were taken from 153 normal humans classified into four groups based on alcohol intake. Each donor had completed a questionnaire concerning alcohol consumption. Samples analyzed for *hprt* mutant frequency showed no significant difference in mutant frequency between groups, and there was no correlation between mutant frequency and alcohol consumption.

A study suggested that moderate wine consumption protects against hydrogen peroxide-induced DNA damage (Fenech et al., 1997). Blood samples were taken from four male volunteers just prior to wine consumption and at 1, 3, 8, and 24 hours after consumption of 300 mL of red or white wine. Volunteers were put on a plant polyphenol-free diet 48 hours prior to wine consumption to test the hypothesis that polyphenols in wine have a protective effect. Lymphocytes were exposed to hydrogen peroxide and the frequency of micronucleated cells was determined. Although an apparent protective effect was seen for both red and white wine, only with white wine consumption was there a statistically significant ($p = 0.0068$) inhibition (> 70%) of hydrogen peroxide-induced micronucleated cells observed one hour after consumption. In contrast, there was no effect among samples taken before the polyphenol-free diet, immediately before wine consumption, and 8 or 24 hours after wine consumption. The polyphenol effect is unclear because the white wine had a much lower level of total polyphenols than the red wine.

SCE frequencies were slightly higher in mouse (NIH male) bone marrow cells, 24 hours after i.p. inoculation with ethanol, tequila, or brandy (Piña-Calva and Madrigal-Bujaidar, 1993). Groups were inoculated with four doses of each liquid with the highest dose corresponding to 0.25-0.50% of a previously determined LD_{50}. All beverages at all doses, except ethanol at the lowest dose, produced significant ($p = 0.01$) increases in SCE frequencies compared to distilled water controls. With respect to cellular proliferation kinetics, no change was seen in the average generation time (AGT) for the tested substances.

A study investigated alterations in the synaptonemal complex (SC) of mouse spermatocytes after exposure of male mice to tequila and brandy (Piña-Calva et al., 1997). Three daily doses (1, 2, or 3 g/kg) of each beverage 20% diluted in distilled water were given by oral intubation for 21 days. Distilled water was the negative control and cyclophosphamide (20 mg/kg) served as a positive control. Tequila (2 and 3 g/kg) and brandy (3 g/kg) induced a significant ($p = 0.05$) increase in SC breaks.

The potential genetic toxicology of commercial beers was investigated using Chinese hamster ovary (CHO) cells and observation of SCE, chromosomal aberrations, and hypoxanthine-guanine phosphoribosyl transferase (HGPRT) mutation (Ivett et al., 1992). Concentrated organic residues from aliquots of commercial beers were prepared from resin extracted from a blend of four beers. For the SCE assay, cell cultures were treated with 0.75 μL/mL to 10 μL/mL of the extracts. The aberration assay used 1 μL/mL to 10 μL/mL, and the forward mutation assay used 2.5 μL/mL to 20 μL/mL. The SCE assay showed a significant increase in three of five samples without metabolic activation, but no increase after the addition of S9. The chromosome aberration and forward mutation assays were negative with or without metabolic activation of the extracts.

Several wines and a brandy were screened for potential genotoxicity with the Drosophila wing Somatic Mutation and Recombination Test (SMART) (Graf et al., 1994). *Drosophila melanogaster* larvae were fed three concentrations of each beverage for two durations and wing spots on the progeny of certain crosses were examined. Ethanol and water were separate controls. One of the five red wines showed significant genotoxic activity that was apparently unrelated to ethanol content because ethanol alone did not have a genotoxic effect.

6.0 OTHER RELEVANT DATA

6.1 Absorption, Distribution, and Metabolism in Humans and Experimental Animals

6.1.1 Absorption

Ethanol is absorbed from the gastrointestinal tract by simple diffusion (Wallgren and Barry, 1970; cited by IARC, 1988). Absorption from the stomach and upper intestine occurs within the first hour after ingestion (Halsted et al., 1973; cited by IARC, 1988). The absorption rate is decreased by food in the intestine and by delayed gastric emptying, as shown in studies of several animal species (Wallgren and Barry, 1970; cited by IARC, 1988).

A physiologically based pharmacokinetic model for ethanol absorption after inhalation by mice, rats, and humans was developed and validated with experimental data (Pastino et al., 1997). The model accurately predicted the blood ethanol concentrations in rats and mice exposed to 50, 200, and 600 ppm for up to six hours and in humans exposed to various concentrations of ethanol vapor for three hours.

6.1.2 Distribution

Animal studies show that, after diffusion into blood, ethanol is rapidly taken up into brain tissue (Harger et al., 1937; cited by IARC, 1988), but distribution to resting skeletal muscle is relatively slow (Harger and Hulpieu, 1956; cited by IARC, 1988). The rate of loss of ethanol from blood follows zero-order kinetics after intravenous administration in several species (Newman and Lehman, 1937; cited by IARC, 1988).

6.1.3 Metabolism

Ethanol is initially metabolized by oxidation to acetaldehyde through the alcohol dehydrogenase pathway (Smith et al., 1973; cited by IARC, 1988). Acetaldehyde is further metabolized to acetate by aldehyde dehydrogenase (Agarwal et al., 1981; cited by IARC, 1988). The rate of ethanol metabolism varies among individuals because of differences in genetically determined isoenzymes (Smith et al., 1973; cited by IARC, 1988). It has also been reported that some Orientals have a reduced rate of acetaldehyde metabolism (Ijiri, 1974; cited by IARC, 1988).

Acetaldehyde, the major intermediary metabolite of ethanol, is an animal carcinogen (IARC, 1988). A number of studies report the presence of acetaldehyde in alcohol consumers. Acetaldehyde was detected in the serum of Finnish women after intoxication (Fukunaga et al., 1993; cited by Longnecker, 1995) and as a DNA adduct in alcoholics (Fang and Vaca, 1997).

Chronic ethanol consumption results in an increased rate of ethanol metabolism to acetaldehyde (Nuutinen et al., 1984; cited by IARC, 1988), and enhances the metabolism of many drugs and halogenated hydrocarbons (Zimmerman, 1986; cited by IARC, 1988).

6.2 Modification of Toxicokinetics/Dynamics of Carcinogens

It is well known that acute or chronic consumption of ethanol influences the metabolism of other organic compounds, including drugs and some known carcinogens. The detection of nitrosamines in the urine of volunteers given ethanol and amines indicates nitrosamine metabolism is inhibited by ethanol (Eisenbrand et al., 1981; Spiegelhalder and Preussmann, 1985; both cited by IARC, 1988). When volunteers ingested ethanol immediately prior to inhalation of trichloroethylene, trichloroethylene levels in plasma increased twofold and urinary

excretion of a main metabolite (trichloroethanol) decreased (Müller et al., 1975; cited by IARC, 1988). Chronic consumption of ethanol increased the metabolism of many drugs and halogenated hydrocarbons to reactive intermediates (Zimmerman, 1986; cited by IARC, 1988) and caused otherwise nontoxic doses of chemicals (e.g. acetaminophen) to become toxic (Seeff et al., 1986; cited by IARC, 1988).

Reduced clearance of the nitrosamine NDMA with coexposure to ethanol was demonstrated for mice (Anderson et al., 1994; cited by Anderson et al., 1995) and patas monkeys (Anderson et al., 1992; cited by Anderson et al., 1995). Dose-dependent effects were observed for several toxicokinetic parameters, including maximum blood concentration, mean residence time, clearance, and area-under-blood-concentration vs. time curve (AUC) for the NDMA.

Hepatic pentobarbital hydroxylase activity in nonalcoholic volunteers doubled after 12 days of ethanol ingestion as 42% of total calories, suggesting an induction of cytochrome P450 (Rubin and Lieber, 1968; cited by IARC, 1988). Likewise, an increase in the smooth endoplasmic reticulum of hepatic cells was observed in volunteers given ethanol as up to 46% of total calories for 16-18 days (Lane and Lieber, 1966; cited by IARC, 1988). Studies with alcoholics also reveal enzyme induction by ethanol, if liver function is uncompromised. Increased levels of hepatic cytochrome P450 were detected in alcoholics with normal liver histology, but not in alcoholics with hepatitis or cirrhosis (Pelkonen and Sotaniemi, 1982; cited by IARC, 1988). Ethanol induced P450 enzymes in various animal tissues, including the liver, lung, intestines, and esophagus (Farinati et al., 1989; Lieber et al., 1987; both cited by Garro and Lieber, 1990).

The expression of a rat liver cytochrome P450 enzyme was reduced by chronic administration of alcohol (van den Wiel et al., 1993; cited by Longnecker, 1995). One study showed inductive and inhibitory effects of ethanol on hepatic mixed function oxidases in hamsters (Ioannides and Steele, 1986; cited by Garro and Lieber, 1990). Ethanol was also shown to be a competitive inhibitor of *N*-nitrosodimethylamine (DMN) demethylase activity in mice (Anderson et al., 1986; cited by Garro and Lieber, 1990). Reduced clearance of NDMA in experimental animals is consistent with competitive inhibition of P450 isoforms by ethanol (Anderson et al., 1995).

6.3 Formation of DNA-Reactive Molecules and DNA Adducts

In addition to acetaldehyde, chronic ethanol exposure can result in the formation of other DNA-reactive molecules, including oxygen radicals and lipid peroxidation products (Brooks, 1997; Garro and Lieber, 1990). Reactive oxygen intermediates, such as the hydroxyl radical, were detected in microsome preparations from experimental animals chronically administered ethanol. Lipid peroxidation products, produced from the reaction of oxygen intermediates and cellular lipids, were also identified in the livers of experimental animals after chronic exposure to ethanol. These molecules can produce DNA strand breaks, oxidative base damage, and form adducts with miscoding potential. Although DNA repair mechanisms are operative in most cells, chronic ethanol exposure places an additional burden on cells damaged during normal metabolism.

A recent study reported detection of DNA adducts of acetaldehyde in peripheral white blood cells of alcohol abusers (Fang and Vaca, 1997). Adduct levels in granulocyte and lymphocyte DNA (measured by ^{32}P-postlabeling using reversed-phase HPLC with on-line detection of radioactivity) were seven and 13-fold higher in alcoholic patients than in controls (p

< 0.001). In alcoholic patients, the average adduct level in granulocyte DNA was 60% higher than the level in lymphocyte DNA. Adduct levels in alcoholic patients indicated a large inter-individual variation.

NDMA-DNA adducts were increased in several tissues of patas monkeys given ethanol just prior to treatment with NDMA (Anderson et al., 1995). The adducts were greatly increased in tissues that are targeted in some human cancers, including the esophagus, ovary, and colon mucosa. In another study, the *in vivo* formation of rat mammary DMBA-DNA adducts was not influenced by chronic ethanol intake at 20% of calories before DMBA administration (Singletary et al., 1991; cited by Singletary, 1997).

The formation of O^6-methyldeoxyguanosine (O^6-MEdG) by the carcinogen *N*-nitrosomethylbenzylamine (NMBzA) was influenced by co-exposure of rats to ethanol (Yamada et al., 1992). Male Fischer rats were given a single intragastric dose of NMBzA in tap water containing 0-20% ethanol or in various alcoholic beverages adjusted to 4% alcohol. O^6-MEdG was increased in the esophagus, lung, and nasal mucosa of rats coadministered ethanol and NMBzA. Esophageal O^6-MEdG was increased in rats coexposed to NMBzA and various alcoholic beverages (pear brandy, sake, farm-made calvados, gin, Scotch whisky, white wine, Pilsner beer). Commercially distilled calvados and red burgundy wine produced significant increases in esophageal O^6-MEdG, indicating effects of ingredients other than ethanol in some alcoholic beverages.

6.4 Cell Proliferation

The proliferation of cells from which mammary adenocarcinomas develop in rats was increased by ethanol intake as 20-30% of calories (Singletary and McNary, 1994). Another recent study investigated the effect of ethanol on the growth of human breast cancer cells *in vitro* (Singletary and Yan, 1996; cited by Singletary, 1997). Ethanol at concentrations between 10-100 mM selectively stimulated the proliferation of estrogen receptor positive (ER+), but not estrogen receptor-negative (ER-) cells.

Increased cell proliferation was observed in the tongue, epiglottis, and forestomach of Wistar rats orally administered acetaldehyde (Homann et al., 1997). This proliferation was indicated by an enlarged basal layer of squamous epithelia in these tissues.

A review of alcohol-associated gastrointestinal cell proliferation in rats and humans concluded that chronic alcohol consumption produces mucosal hyperregeneration in certain sites (Simanowski et al., 1995). In rats chronically fed ethanol, cell proliferation was seen in the esophagus and in the rectum, but not in the colon. Esophageal cell proliferation depended on salivary gland function. In humans, there was an increased proliferative index in the rectal crypt. Ethanol produced cell proliferation in the esophageal epithelium of rats (Haentjens et al., 1987; cited by Garro and Lieber, 1990).

6.5 Cancer Susceptibility from Genetic Polymorphisms

A study strongly suggests that polymorphisms that increase acetaldehyde levels lead to an increased cancer risk (Harty et al., 1997). The risk of oral cancer associated with alcohol consumption was significantly increased in persons with a fast-metabolizing form of alcohol dehydrogenase. This enzyme converts ethanol to acetaldehyde. The immediate contact of acetaldehyde with oral tissues may initiate carcinogenesis.

Other studies also provide evidence of a genetic predisposition to acetaldehyde exposure and further implicate acetaldehyde in neoplasms associated with alcohol (Yokoyama et al., 1996a, 1996b; Yamamoto et al., 1993; all cited by Yokoyama et al., 1996c). The enzyme that metabolizes acetaldehyde, aldehyde dehydrogenase-2, was found to be inactive in a significant proportion of Japanese alcoholics who developed cancer of the upper aerodigestive tract.

Genetic polymorphisms (*Rsa*I and *Dra*I of *CYP2E1* and *Msp*I of *CYP1A1*) were compared among groups of Caucasian alcoholics and a control group (Lucas et al., 1996). Alcoholic groups were distinguished based on presentation of clinical symptoms from ethanol-related diseases, and groups were defined for esophageal cancer and upper aerodigestive tract cancer. The only significant difference was an increased frequency of the *Dra*I polymorphism in alcoholics, with or without ethanol-related diseases, compared with controls. In addition, among patients with the two alcohol-related cancers, the rare *Dra*I-C allele was three times less frequent in patients under age 45 than in older patients.

6.6 Suppression of DNA Repair

In rats, chronic and acute alcohol consumption increased the persistence of dimethylnitrosamine-induced hepatic O^6-methylguanine DNA adducts and acetaldehyde inhibited O^6-methylguanine transferase activity in rats and humans (Garro et al., 1986; Mufti et al., 1988; Espina et al., 1988; all cited by Garro and Lieber, 1990). This enzyme was also inhibited in neutered adult male rats by a single i.p. injection of 30% ethanol and a dose-response relationship was observed (Wilson et al., 1994).

6.7 Alcohol Metabolism by Microorganisms in the Upper Respiratory Tract

In humans, bacteria in the upper respiratory tract metabolize alcohol to acetaldehyde and can generate significant amounts of acetaldehyde that can persist in saliva for an extended period (Homann et al., 1997a; cited by Homann et al., 1997b). Acetaldehyde is considered to be a carcinogen in experimental animals (IARC, 1985). The direct contact of alcohol with tissues in the upper intestinal tract and subsequent conversion by microorganisms to acetaldehyde may contribute to the greater incidence of cancers in these anatomical regions among heavy consumers of alcoholic beverages (Homann et al., 1997b).

6.8 Other Carcinogens in Alcoholic Beverages

Some chemical compounds detected in alcoholic beverages are known or suspected animal or human carcinogens (Table 1-1). Urethan and nitrosamines are examples of compounds identified in all types of alcoholic beverages.

6.9 Dietary Factors

Cancer risk among malnourished alcoholics may be increased by their low intake of fruits and vegetables (Garro et al., 1990; cited by Longnecker, 1995). A lower consumption of carbohydrates among drinkers is the most common dietary difference between drinkers and nondrinkers (Colditz et al., 1991; cited by Longnecker, 1995), but this difference is unlikely to affect cancer risk. The levels of vitamin A in the liver were reduced by ethanol through increased mobilization of vitamin A from the liver to other organs and enhanced degradation of vitamin A by ethanol-induced P450 enzymes (Sato and Lieber, 1981, 1982; cited by Garro and Lieber, 1990). Vitamin A was associated with reduced cancer risk in epidemiological

investigations (Ziegler, 1989; cited by Garro and Lieber, 1990). Human data indicate that folate may influence neoplastic changes in association with alcohol, consistent with alcohol interference with absorption and utilization of folate. Men who reported high alcohol consumption and low folate intake had a high risk of rectal cancer (Freudenheim et al., 1991). Another study (Giovannucci et al., 1995) found an increased risk of total colon cancer in association with high alcohol but low folate intake.

Plasma β-carotene levels after recent alcohol intake were affected by liver damage (Ahmed et al., 1994). In cases without signs of liver damage, levels were increased following heavy alcohol consumption, while patients with alcoholic cirrhosis showed a decline in plasma ß-carotene levels after heavy alcohol intake. Another study (Albanes et al., 1996) suggests a possible interaction of alcohol and ß-carotene in the development of lung cancer.

6.10 Hormones

An epidemiology study of premenopausal women found a positive association between alcohol consumption and the estrogen precursor, androstenedione (Dorgan et al., 1994). Another study of premenopausal women (Reichman et al., 1993) reported that alcohol intake was associated with significant increases in plasma and/or urinary levels of several estrogenic hormones, including dehydroepiandrosterone sulfate, estrone, estradiol, and estriol. In a study of post-menopausal women (Hankinson et al., 1995), alcohol consumption was positively associated with estrone sulfate plasma levels, but not with estrone or estradiol.

7.0 MECHANISMS OF CARCINOGENESIS

At least two mechanisms may contribute to the carcinogenicity of alcoholic beverages. One of these is the carcinogenic activity of acetaldehyde, the initial metabolite of ethanol. A second possible mechanism is alteration of the metabolism of known environmental carcinogens such as nitrosamines.

While animal studies do not show that ethanol is a complete carcinogen, IARC (1985) concluded that there is sufficient evidence for the carcinogenicity of acetaldehyde in experimental animals. DNA adducts of acetaldehyde have been detected in lymphocytes of heavy drinkers. Acetaldehyde formation may be facilitated by microorganisms in the upper digestive tract, and a genetic predisposition to rapid acetaldehyde formation may also contribute to the carcinogenicity of alcoholic beverages (section 6).

Studies in humans and animals suggest that ethanol can promote the carcinogenic activity of known carcinogens. The metabolism and clearance of nitrosamines and trichloroethylene was reduced by prior or coexposure to ethanol (section 6). Animals exposed to known carcinogens had a higher cancer incidence with pre- or co-exposure to ethanol (section 4).

Two other possible mechanisms by which alcohol contributes to cancer are interference with folate metabolism and changes in hormone levels (section 6). Men who reported high alcohol consumption and low folate intake had a higher risk of rectal cancer (Freudenheim et al., 1991) and total colon cancer (Giovannucci et al., 1995). These results may reflect the fact that alcohol is an antagonist of methyl-group metabolism and can consequently affect DNA methylation (Giovannucci et al., 1995). An imbalance in DNA methylation is consistently observed in colonic neoplasia (Hoffman, 1984). Alterations of hormone levels by alcohol may

also mediate carcinogenesis since endogenous hormones are believed to play a role in the development of breast cancer (Harris et al., 1992). However, mechanisms are speculative and results of alcohol effects on plasma hormones in premenopausal women are inconsistent (Reichman et al., 1993; Dorgan et al., 1994).

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APPENDIX A

DESCRIPTION OF ONLINE LITERATURE SEARCHES FOR ALCOHOLIC BEVERAGE CONSUMPTION

DESCRIPTION OF ONLINE LITERATURE SEARCHES FOR ALCOHOLIC BEVERAGE CONSUMPTION

The search statement used in the biomedical databases MEDLINE, CANCERLIT, and TOXLINE, combined the terms alcoholic beverages OR beer OR wine OR spirits (allowing for both singular and plural forms) with "neoplasms + all/CT", which represents 658 Medical Subject Heading (MESH) terms for neoplasms. A similar search was done in EMBASE. These searches were done in October 1997. Duplicates were removed, and the 958 records were reduced to 777 by limiting to the period 1987-1997.

Current Contents searches in the 1200 Life Sciences journals edition had been done weekly for current awareness since April 1997, when a similar search was done only in TOXLINE with retrievals limited to reviews.

Searches for genetic toxicity information were done in the databases EMIC and EMICBACK.

Production and consumption information was sought in the commercial databases PROMT and the Chemical Economics Handbook. Internet searches led us to statistics from the Beer Institute, the Wine Institute, and the Statistical Abstract of the United States, and to an order form for the recent Report to Congress by the National Institute for Alcoholism and Alcohol Abuse.

APPENDIX B

IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK TO HUMANS: ALCOHOL DRINKING (VOLUME 44), 1988

APPENDIX C

REPORT ON CARCINOGENS (RoC), 9th EDITION
REVIEW SUMMARY

Report on Carcinogens (RoC), 9th Edition
Review Summary

Alcoholic Beverage Consumption

NOMINATION
Review based on letter from Dr. Hiroshi Yamasaki (IARC) recommending listing in the RoC based on IARC classification of Alcoholic Beverage Consumption as a known human carcinogen (IARC Vol. 44, 1988).

DISCUSSION
Alcoholic Beverage Consumption is causally related to cancers of the mouth, pharynx, larynx, and esophagus and may be causally related with cancers of the liver and breast. Studies indicate that the risk is most pronounced among smokers and at the highest levels of consumption. There is possible confounding of epidemiology studies by smoking, diet, and poor oral hygiene. However, these factors cannot account for the observed causal association between alcoholic beverage consumption and cancer. The effects of alcohol and smoking may be synergistic, which would put smokers at the highest risk for cancer development. Possible beneficial cardiovascular effects of low to moderate consumption of alcoholic beverages have been reported. The recommendations from the three NTP reviews of this nomination are as follows:

Review Committee	Recommendation	Vote
NIEHS (RG1)	list as known human carcinogen	6 yes/1 no
NTP EC Working Group (RG2)	list as known human carcinogen	7 yes/0 no
NTP Board RoC Subcommittee	list as known human carcinogen	9 yes/3 no/1 a*

*a-abstentions

Public Comments Received
A total of 19 public comments were received:

- 2 in favor of listing as a known to be human carcinogen
- 15 against listing in the RoC in any category
- 2 providing comments on the content of the background document prepared for the review of this nomination