5. Summary of Data Reported

5.1 Exposure data

The consumption of alcoholic beverages has been practiced as a part of human culture for centuries. In addition to ethanol and water, alcoholic beverages may also contain a multitude of other compounds derived from fermentation, contamination and the use of food additives or flavours. The normal by-products of fermentation, other than ethanol, are generally regarded as safe, but alcoholic beverages may contain contaminants that have been evaluated by the IARC as carcinogenic (e.g. nitrosamines and aflatoxins). However, contaminants are usually present at low concentrations and, over the past decades, these have been further reduced, at least in developed countries. For example, the concentration of nitrosamines in beer and that of lead in wine have declined significantly over the past 30 years.

Throughout the world, most alcoholic beverages are produced and consumed within the same country. Consumption has increased in developing regions, and the country that now has the highest total production is China, followed by India and Brazil. The trade in alcoholic beverages has increased over the last four decades, but its proportion has remained at approximately 0.5% of total world trade.

The consumption of alcoholic beverages can be divided into recorded consumption (estimated from sales, production and national taxation records) and unrecorded consumption (e.g. illegal production, smuggling, home production and private importation). Overall, recorded consumption has increased slightly over the past 20 years, but more substantial increases have occurred in China and some other developing countries. In contrast, an overall decline in recorded consumption is evident in several developed countries.

More than 1.9 billion adults (1.2 billion men and 750 million women) around the world were estimated to consume alcoholic beverages in 2002, and 22% of the men and 3% of the women drank 40 g alcohol or more per day. In all regions of the world, men drink more often and in larger quantities than women, but the gender differences

are largely culturally dependent; smaller differences are observed in Europe and larger differences in developing parts of the world. Consumption of alcohol is age-dependent: the frequency of drinking increases until middle age and the prevalence of heavy episodic drinking decreases over the adult life-span. Those of the lowest socioeconomic class tend to drink the cheapest beverage available in their respective countries.

A large variety of substances that are not intended for human consumption are nevertheless being consumed as alcohol (surrogate alcohol such as hair spray, after-shaves, lighter fluid and medicines). They usually contain very high concentrations of ethanol and may also contain higher alcohols and toxic concentrations of methanol.

In addition to international regulations such as the *Codex alimentarius*, countries tend to regulate traditional local alcoholic beverages (e.g. beer, whisky and vodka), but emerging products (e.g. alcopops) are initially subject to few regulations.

5.2 Human carcinogenicity data

The effect of alcoholic beverages on the risk for human cancer was last evaluated in the *IARC Monographs* series in 1988. At that time, it was concluded that there was *sufficient evidence* of carcinogenicity for cancers of the oral cavity, pharynx, larynx, oesophagus and liver. Since that time, several hundred additional epidemiological studies reported on the association between the consumption of alcoholic beverages and the risk for cancer at various sites. For the present Volume, the published evidence for 27 cancer sites was reviewed by the Working Group.

5.2.1 *Cancers of the oral cavity and pharynx*

A large body of evidence from epidemiological studies of different design and conducted in different populations consistently shows that consumption of alcoholic beverages is associated with a higher risk for both oral and pharyngeal cancer, and that the risk increases with increasing amounts of alcohol consumed. Compared with non-drinkers, regular consumption of about 50 g alcohol (ethanol) per day is associated with an approximately threefold increase in risk for these cancers. These associations were consistently found for the types of alcoholic beverage that are commonly drunk in the areas where the studies were conducted.

Tobacco smoking is an important cause of oral and pharyngeal cancer. The association of consumption of alcoholic beverages with these cancers was evident in both smokers and nonsmokers. The effects of smoking and consumption of alcoholic beverages appear to be multiplicative, such that the largest relative risks are seen in people who both smoke tobacco and drink alcoholic beverages.

Some data were available on the cessation of consumption and the risk for oral and pharyngeal cancer. The available evidence suggests that former drinkers have lower risks for oral and pharyngeal cancer than current drinkers of alcoholic beverages.

5.2.2 *Cancer of the larynx*

Studies of different design conducted in Asia, Europe, North America and South America have shown a consistent association between the consumption of alcoholic beverages and the risk for laryngeal cancer. This association increases with increasing amounts of alcoholic beverages consumed and, compared with non-drinkers, regular consumption of about 50 g alcohol per day is associated with an approximately two-fold increase in risk. These associations were observed for various types of alcoholic beverage.

Tobacco smoking is an important cause of laryngeal cancer. The association with the consumption of alcoholic beverages was evident in both smokers and nonsmokers. The effects of smoking and consumption of alcoholic beverages appear to be multiplicative and the largest relative risks are seen in smokers who also consume alcoholic beverages. There is little information on the duration or cessation of consumption of alcoholic beverages on the risk for laryngeal cancer.

5.2.3 *Cancer of the oesophagus*

More than 50 prospective and case–control studies from most regions of the world found a consistent association between the risk for oesophageal cancer (squamous-cell carcinoma) and the consumption of alcoholic beverages. The risk increases with increasing amounts of alcoholic beverage consumed and, compared with non-drinkers, regular consumption of about 50 g alcohol per day is associated with an approximately twofold increase in risk. The increased risk for oesophageal cancer was consistently observed for a range of different types of alcoholic beverage. However, the association, if any, is weak for adenocarcinoma of the oesophagus.

Of 13 cohort studies among the general population, 10 studies reported a statistically significant association between alcoholic beverage consumption and the risk for oesophageal cancer when controlled for tobacco smoking. Four cohort studies were based on special populations: three studies of alcoholics and one of brewery workers reported statistically significant associations.

Among 20 case–control studies published in the English literature, 18 (91%) studies adjusted for tobacco smoking. Sixteen of these 18 (81%) studies on the association between alcoholic beverage drinking and the risk for oesophageal cancer reported statistically significant associations. Among 18 case–control studies identified in the Chinese literature, eight (44%) studies reported a positive association with alcoholic beverage consumption. The evidence on the risk for oesophageal cancer in the Chinese literature is consistent with that in the English literature. In addition, the results from case–control studies are consistent with results from prospective cohort studies.

Data on adenocarcinoma of the oesophagus were available from one prospective study among alcoholics, one nested case–control study and eight case–control studies. Two case–control studies reported that an increased risk for adenocarcinoma of the

oesophagus is associated with a higher level of alcoholic beverage drinking, but the other eight studies did not.

Epidemiological evidence indicates that drinking alcoholic beverages is causally related to cancer of the oesophagus. There is no indication that the effect of alcoholic beverage consumption is dependent on the type of beverage. Tobacco smoking also increases the risk for oesophageal cancer and the effect of consumption of alcoholic beverages on this cancer is evident in both smokers and nonsmokers. The effects of smoking and consumption of alcoholic beverages appear to be multiplicative and the largest relative risks are seen in smokers who also consume alcoholic beverages.

The available data from molecular–genetic epidemiological studies provide ample evidence that the heterozygous aldehyde dehydrogenase 2 genotype — which leads to the accumulation of acetaldehyde, e.g. in the blood, saliva and liver — contributes substantially to the development of oesophageal cancers (squamous-cell carcinomas) that are related to the consumption of alcoholic beverages.

There is uncertainty about the effects of cessation of alcohol beverage intake and the duration of consumption on the risk for oesophageal cancer. The available evidence suggests that former drinkers have lower risks for oesophageal cancer than current drinkers.

5.2.4 *Cancer of the liver*

A large body of data derives from cohort studies, including cohorts of heavy drinkers, and case–control studies from most regions of the world, many of which were carried out in China. These studies provide firm evidence that the consumption of alcoholic beverages is an independent risk factor for primary liver cancer. Various types of alcoholic beverage consumed do not have substantially different effects on liver cancer.

Chronic infections with hepatitis viruses B and C are the major causes of liver cancer and the increased risk associated with alcoholic beverage intake has been found consistently among individuals infected with hepatitis viruses as well as among uninfected individuals. Quantification of the effect of alcohol on the risk for liver cancer cannot be achieved reliably since cirrhosis and other liver disorders that often predate liver cancer tend to lead to a decrease in or the cessation of consumption of alcoholic beverages many years before the occurrence of liver cancer.

5.2.5 *Cancer of the female breast*

More than 100 epidemiological studies conducted in all regions of the world have evaluated the association between the consumption of alcoholic beverages and female breast cancer, and have consistently found an increased risk with increasing intake. A pooled analysis of most of the data available worldwide in 2002, which included more than 58 000 women with breast cancer, found a linear increase in risk with increasing consumption of alcoholic beverages. Compared with non-drinkers, regular

consumption of about 50 g alcohol per day is associated with a relative risk for breast cancer of about 1.5; for regular consumption of 18 g alcohol per day, the relative risk is still significantly increased at 1.13. Broadly similar patterns of association were observed with different types of alcoholic beverage.

The risk for breast cancer is affected by a variety of hormonal and reproductive factors, and the effect of consumption of alcoholic beverages on the risk for breast cancer does not vary significantly by child-bearing patterns, menopausal status, use of oral contraceptives or hormone replacement therapy or having first-degree relatives with a history of breast cancer.

The effects of duration or cessation of consumption of alcoholic beverages on the risk for breast cancer are uncertain.

5.2.6 *Colorectal cancer*

More than 50 prospective and case–control studies reported on the association between consumption of alcoholic beverages and the risk for colon, rectal or colorectal cancer. Results of pooling the data from six cohort studies and those of recent meta-analyses suggest an increased risk for colorectal cancer with the consumption of alcoholic beverages. The association does not appear to be confounded by age, gender, race or ethnicity or body mass index, and some studies showed no confounding by diet or physical activity. Based on results of the pooled data from the six cohort studies and the recent meta-analysis of prospective cohort studies, regular consumption of about 50 g alcohol per day is associated with a relative risk for colorectal cancer of 1.4 compared with non-drinkers. However, there is uncertainty regarding the shape of the dose–response relationship. Based on the available data, the association is similar for colon and for rectal cancer and does not appear to vary by type of alcoholic beverage.

There is no consistent evidence that the association of colorectal cancer with the consumption of alcoholic beverages is modified by gender or by tobacco smoking. It is unclear whether obesity or dietary lifestyle factors, such as folate intake, modify the effect of alcoholic beverage intake on colorectal cancer, as few studies have examined these relationships.

The data on the effects of duration and cessation of consumption of alcoholic beverages on the risk for colorectal cancer are inadequate.

5.2.7 *Cancer of the lung*

Tobacco smoking is by far the most important cause of lung cancer. In most populations, there is a strong correlation between the use of tobacco and the consumption of alcoholic beverages. Therefore, the most important consideration in the interpretation of results from epidemiological studies of the consumption of alcoholic beverages and lung cancer is whether any observed association might be confounded by the effect of smoking.

Several studies have reported an increased risk for lung cancer associated with the consumption of alcoholic beverages, but it is not generally possible to exclude residual confounding by smoking. The findings from some of the studies that presented separate data on the risk for lung cancer in nonsmokers suggest a possible increased risk with consumption of alcoholic beverages, but others do not. No data relating to cessation of consumption of alcoholic beverages were available.

5.2.8 *Cancer of the stomach*

Epidemiological studies conducted in Asia, Europe and Latin America have reported inconsistent results on the risk for stomach cancer associated with the consumption of alcoholic beverages. Significantly increased risks were reported in some studies, including those from China, Japan, Poland and the Russian Federation.

In no study was it possible to stratify or adjust fully for lifetime infection with *Helicobacter pylori*, the most important known cause of non-cardia stomach cancer. Potential confounding by *H. pylori* infection is not, however, a major concern, since most of the population in areas where an association between consumption of alcoholic beverages and stomach cancer emerged had probably been infected by the bacteria. Of concern, however, is the likelihood that dietary deficiencies exist in these populations and that the consumption of alcoholic beverages may be accompanied by other unfavourable lifestyle factors, such low socioeconomic class and low intake of fresh fruit, vegetables and various micronutrients. Since insufficient allowance was made for these important lifestyle factors, the interpretation of the findings is not unequivocal.

5.2.9 *Cancer of the kidney*

Both cohort and case–control studies provide consistent evidence of no increase in the risk for renal-cell cancer with increasing consumption of alcoholic beverages. In several studies, increasing intake of alcoholic beverages was associated with a significantly lower risk for kidney cancer. These inverse trends were observed in both men and women and with multiple types of alcoholic beverage.

5.2.10 *Non-Hodgkin lymphoma*

The results of prospective cohort studies and evidence from some very large case–control studies showed an inverse association or no association between the consumption of alcoholic beverages and the risk for non-Hodgkin lymphoma. Most studies of non-Hodgkin lymphoma showed a lower risk for drinkers compared with non-drinkers. In general, there was no evidence of substantial differences in the effect between specific beverage types or for specific histological subtypes of non-Hodgkin lymphoma.

5.2.11 *Other sites*

For cancers of the pancreas, cervix, endometrium, ovary, vulva, vagina, male breast, urinary bladder, prostate, testis, brain and thyroid, for skin melanoma, Hodgkin disease, leukaemias and multiple myeloma, the evidence for an association between consumption of alcoholic beverages and risk for the site was generally sparse and/or inconsistent.

Although for some sites, e.g. cervix and prostate, some studies of special populations showed positive associations, bias and confounding could not be excluded. Some case–control studies indicated increased risks, but when, as for childhood brain cancer, testicular cancer and leukaemia, these were based on parental consumption of alcoholic beverages, it was not possible to exclude recall bias as an explanation of the association and, for several of the others, adequate adjustment for potential confounders had not been made.

When data were available, analysis by type of alcoholic beverage, dose, duration of consumption or histology or stratification by other risk factors did not reveal any consistent patterns for any of these sites. No reliable data related to the cessation of consumption of alcoholic beverages were available for most of these sites.

5.3 Animal carcinogenicity data

5.3.1 *Ethanol*

The effect of ethanol on the development of cancer depends on a variety of factors, including doses of ethanol and time of exposure, and also on animal species, strain and sex.

Ethanol was evaluated by a Working Group in 1988 and it was concluded that there was *inadequate evidence* for the carcinogenicity of ethanol in experimental animals. Most of the studies were criticized because of the small numbers of animals studied, the inadequate design of the experiments with uncontrolled dietary regimens, the short exposure to ethanol, low doses of ethanol and the failure to measure ethanol intake and/or concentrations in the blood. These concerns are also relevant for some of the studies that were published after 1988.

In a 2-year study, administration of ethanol to male mice in the drinking-water caused a dose-related increase in the incidence of hepatocellular adenomas and hepatocellular adenomas and carcinomas. In a lifetime study, administration of ethanol in the drinking-water resulted in an increase in the incidence of head and neck carcinomas in male and female rats and the incidence of forestomach carcinomas, testicular interstitial-cell adenomas and osteosarcomas of the head, neck and other sites in male rats. In another lifetime study, ethanol administered in the drinking-water induced mammary adenocarcinomas. In another study that used a genetically modified mouse model for intestinal cancer, administration of ethanol in the drinking-water increased

the incidence of intestinal tumours. Additional studies that encompassed oral and other routes of administration were also reviewed but were considered to be inadequate for the reasons noted above.

Many other studies were performed to determine whether ethanol modifies chemically induced carcinogenesis in various mouse and rat strains with a variety of carcinogens. Depending on the carcinogen and the animal model used, tumour-specific target organs included the mammary gland, oesophagus, forestomach, large intestine, liver, kidney, lung and thymus. Again, some of these studies were criticized because of the concerns mentioned above. However, in the majority of the studies, ethanol enhanced chemically induced carcinogenesis.

5.3.2 *Acetaldehyde*

Acetaldehyde was tested for carcinogenicity in rats by inhalation exposure and oral administration and in hamsters by inhalation exposure and intratracheal instillation. After inhalation exposure, acetaldehyde produced tumours of the respiratory tract, primarily adenocarcinomas and squamous-cell carcinomas of the nasal mucosa, in rats and laryngeal carcinomas in hamsters. Inhalation of acetaldehyde vapour enhanced the incidence of respiratory tract tumours induced by intratracheal instillation of benzo[*a*]pyrene. Intratracheal instillation of acetaldehyde did not increase tumour incidence in hamsters. Oral administration of acetaldehyde resulted in an increased incidence of tumours in several tissues. However, there was no obvious dose–response relationship.

Oral administration of acetaldehyde to rats did not potentiate the response induced by *N*-nitrosodiethylamine.

5.4 Mechanistic and other relevant data

5.4.1 *Ethanol*

Ethanol is absorbed rapidly from the upper gastrointestinal tract; a small fraction is cleared by first-pass metabolism, some of which probably occurs in the stomach and the remainder in the liver. Most of ethanol is eliminated in the liver, catalysed by alcohol dehydrogenases and to a much smaller degree by cytochrome P450 enzymes and catalase. The overall rate of elimination is affected to some extent by variation in alcohol dehydrogenase isozymes. Chronic consumption of alcoholic beverages induces cytochrome P450, but variants in this enzyme have not been clearly associated with differential susceptibility to alcoholism or ethanol-related pathology.

The presence of different alcohol dehydrogenase and aldehyde dehydrogenase isoenzymes determines tissue-specific differences in the metabolism of ethanol and acetaldehyde, and may contribute to tissue-specific susceptibilities to the toxicity of ethanol. The oesophagus and colon appear to express alcohol dehydrogenases (class IV (σ) alcohol dehydrogenase and alcohol dehydrogenase 1C, respectively), but have low

aldehyde dehydrogenase 2 activity, and hence may be susceptible to toxicity mediated by the metabolism of ethanol or exposure to acetaldehyde from other sources (saliva or microbes). Breast epithelium expresses class I alcohol dehydrogenase, but it is not clear whether it expresses aldehyde dehydrogenase 2; thus this tissue may also be susceptible to the oxidation products of ethanol.

Chronic ingestion of alcohol results in various adverse effects in the liver, such as fibrosis and cirrhosis. Although active alcohol dehydrogenase 1B and inactive aldehyde dehydrogenase 2 are a combination that protects against alcoholism, because of the undesired effects of accumulating acetaldehyde, polymorphisms in ethanol-metabolizing enzymes are unlikely to make a significant contribution to the development of alcoholic liver disease. The consumption of alcoholic beverages is detrimental in persons infected with the hepatitis C virus: alcoholic beverage drinking and the viral infection independently increase the risk for hepatocellular carcinoma.

In animal models, various types of ethanol-induced liver injury are observed that also occur in humans. Acute administration of ethanol causes hypoxia in the pericentral region of the liver lobule. Ethanol-induced liver pathology correlates with increased levels of cytochrome P450 2E1 and enhanced lipid peroxidation. Cytochrome P450 2E1-derived oxidants stimulate type I collagen synthesis in the liver and cause mitochondrial dysfunction and depolarization, which are key steps in apoptosis. Ethanol alters the permeability and microflora of the gut, which results in the release of endotoxins that can cause liver injury and inflammation.

The available data from molecular–genetic epidemiological studies suggest a positive association between the presence of *alcohol dehydrogenase 1B (*1/*1)* and the risk for upper aerodigestive tract cancer, but the mechanisms through which the functional polymorphism affects susceptibility to cancer have not been fully explained. The relationship between the *alcohol dehydrogenase 1B* genotype and cancer in other organs is inconclusive because the number of studies is small. Similarly, the evidence for a contribution of the *alcohol dehydrogenase 1C* polymorphism to the development of cancer in the upper aerodigestive tract is limited, and the relationship between the latter genotype and breast cancer is inconclusive because of the small number of studies.

Findings from studies that investigated the relationship between the *methylenetetrahydrofolate reductase* polymorphism *C677T* and the risk for colorectal cancer and adenoma indicate that high alcoholic beverage consumption increases the risk for colorectal cancer by influencing the metabolism of folate with respect to DNA methylation and DNA synthesis. A mechanistic interpretation regarding the role of polymorphisms of the methionine synthase and thymidylate synthase genes based on sparse data is difficult. The increased risk for breast, gastric and pancreatic cancer associated with the *methylenetetrahydrofolate reductase 677TT* genotype in persons with low folate and/or high alcoholic beverage intake suggests that alterations in the metabolism of folate may play a role in the occurrence of cancers at these sites.

Published results to date do not indicate that any particular DNA-repair gene variant has a dramatic effect on susceptibility to alcohol-related carcinogenesis, although

there are suggestions in the literature that genetic variation in the O^6-methylguanine–DNA methyltransferase gene, the X-ray repair cross-complementing gene (*XRCC-1*) and some nucleotide excision-repair genes may affect risk. With regard to the repair of oxidative DNA damage, two concordant studies showed an increased susceptibility to alcohol-related cancers in individuals who had the less active Cys 321 allele of the *oxoguanine glycosylase 1* gene. These results are of particular interest, since animal studies show that, in some cases, ethanol can increase oxidative DNA damage.

Ethanol has major effects on the metabolism and clearance of a variety of low-molecular-weight carcinogens and toxicants by cytochrome P450s 2E1, 1A1, 1A2, 2B6, 2C19 and 3A. In theory, ethanol may potentiate the tissue-specific effects of carcinogens by inducing cytochrome P450-dependent metabolism. However, most findings in experimental animals indicate that the more common mechanism is competitive inhibition of metabolism, especially in the liver, which results in increased dose delivery to peripheral target organs, an increase in DNA damage and enhancement of tumour formation, often five- to 20-fold. Such effects have been seen for many carcinogens and target organs. Evidence of this mechanism in humans is supportive but limited.

Alcoholic beverage consumption affects both male and female reproduction through the adverse regulation of levels of sex hormones and other effects on cells of the reproductive systems. There is a causal relationship between consumption of alcoholic beverages during pregnancy and the occurrence of adverse birth and developmental effects. Paternal exposure to alcoholic beverages has been associated with abnormalities in the offspring, such as decreases in birth weight and increases in ventricular septal defects. Animal models have convincingly supported the findings in humans; ethanol has deleterious effects on reproduction and causes skeletal and behavioural defects in the offspring of rodents when it is administered during gestation.

Numerous reports have shown that human alcoholics have a higher frequency of chromosomal aberrations, sister chromatid exchange and micronuclei in the peripheral lymphocytes and other cell types. Different types of DNA damage have been shown to occur in human tissues from subjects who consume alcoholic beverages; however, the relationship between oxidative stress-induced DNA lesions and alcoholic beverage consumption has not been well established.

Ethanol is not mutagenic in bacteria or *Drosophila*. It causes sister chromatid exchange in both lower organisms and mammalian cells, including human cells. The data from studies in animals suggest that ethanol causes DNA damage in target tissues.

5.4.2 *Acetaldehyde*

Acetaldehyde is formed metabolically from the oxidation of ethanol, and is further metabolized, predominantly by nicotinamide adenine dinucleotide-dependent aldehyde dehydrogenases, to acetic acid. The importance of aldehyde dehydrogenase in the oxidative pathway of ethanol is emphasized in drinkers of alcoholic beverages who are

deficient in this enzyme: the alcoholic flush reaction that they experience correlates with the accumulation of acetaldehyde in the blood.

In the absence of alcoholic beverage consumption, acetaldehyde ingested in food or generated by microbial fermentation is rapidly reduced to ethanol.

Acetaldehyde exerts toxic effects, mainly at the site of initial contact. Respiratory effects observed in studies in rats exposed to acetaldehyde by inhalation (for 13 weeks or 28 months) included degenerative changes in the olfactory and upper respiratory epithelium, metaplasia in the larynx and disturbances of the tracheal epithelium. When administered by intraperitoneal injection, acetaldehyde caused glycogenolysis, changes in the metabolic pathways and accumulation of lipids, cholesterol and free fatty acids in the liver. Effects on the pancreas and thyroid were also noted.

Acetaldehyde showed embryotoxic, fetotoxic and teratogenic effects in rats. In cultured cells of different origin, acetaldehyde affected lipid peroxidation, mitochondrial respiration and metabolism. In certain cell types, it reduced glutathione, increased intracellular calcium and induced DNA fragmentation, which are indicators of apoptosis.

The available data from molecular–genetic epidemiological studies provide ample evidence that the heterozygous *aldehyde dehydrogenase 2* genotype — which leads to the accumulation of acetaldehyde, e.g. in the blood, saliva and liver — contributes substantially to the development of oesophageal cancers (squamous-cell carcinomas) that are related to the consumption of alcoholic beverages.

While it is often difficult to differentiate clearly between the exact locations of tumours in the oropharyngolaryngeal area based on the available published data, there is strong evidence that the heterozygous *aldehyde dehydrogenase 2* genotype contributes to the development of cancers of the oropharyngolarynx as a whole that are related to the consumption of alcoholic beverages. The available epidemiological studies provide suggestive but inconclusive evidence for an association between the heterozygous *aldehyde dehydrogenase 2* genotype and hepatocellular carcinoma and inconclusive evidence for an association with colorectal cancer.

Acetaldehyde reacts with DNA to form various DNA adducts, and elevated levels of acetaldehyde-derived DNA adducts have been detected in white blood cells of individuals who are heavy alcoholic beverage drinkers. An important observation is that, with equivalent levels of tobacco smoking and consumption of alcoholic beverages, individuals who are deficient in aldehyde dehydrogenase 2 due the *aldehyde dehydrogenase 2*2* polymorphism had higher levels of acetaldehyde-related adducts in white blood cell DNA than individuals who have normal aldehyde dehydrogenase 2 activity. Aldehyde dehydrogenase 2-deficient individuals have been shown to be at higher risk for developing oesophageal cancer through alcoholic beverage consumption and also to have higher levels of acetaldehyde in the blood and saliva following alcoholic beverage drinking compared with aldehyde dehydrogenase 2-proficient individuals. Some of the DNA adducts that are increased after alcoholic beverage consumption are mutagenic in human cells. In addition, these adducts can undergo rearrangements in double-stranded DNA, which can result in the formation of DNA–protein cross-links

and DNA interstrand cross-links, which are mechanistically consistent with the generation of chromosomal aberrations. Elevated levels of chromosomal aberrations have been observed in human cells in culture after exposure to acetaldehyde as well as *in vivo* in human alcoholics.