GENERAL REMARKS

Part E of Volume 100 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* contains updated assessments of personal habits and indoor combustions that were first classified as *carcinogenic to humans (Group 1)* in Volumes 1–99.

Volume 100 – General Information

About half of the agents classified in Group 1 were last reviewed more than 20 years ago, before mechanistic studies became prominent in evaluations of carcinogenicity. In addition, more recent epidemiological studies and animal cancer bioassays have demonstrated that many cancer hazards reported in earlier studies were later observed in other organs or through different exposure scenarios. Much can be learned by updating the assessments of agents that are known to cause cancer in humans. Accordingly, IARC has selected A Review of Human Carcinogens to be the topic for Volume 100. It is hoped that this volume, by compiling the knowledge accumulated through several decades of cancer research, will stimulate cancer prevention activities worldwide, and will be a valued resource for future research to identify other agents suspected of causing cancer in humans.

Volume 100 was developed by six separate Working Groups:

Pharmaceuticals
Biological agents
Arsenic, metals, fibres, and dusts
Radiation
Personal habits and indoor combustions
Chemical agents and related occupations

Because the scope of Volume 100 is so broad, its *Monographs* are focused on key information. Each *Monograph* presents a description of a carcinogenic agent and how people are exposed, critical overviews of the epidemiological studies and animal cancer bioassays, and a concise review of the toxicokinetic properties of the agent, plausible mechanisms of carcinogenesis, and potentially susceptible populations, and life-stages. Details of the design and results of individual epidemiological studies and animal cancer bioassays are summarized in tables. Short tables that highlight key results appear in the printed version of Volume 100, and more extensive tables that include all studies appear on the website of the *IARC Monographs* programme (http://monographs.iarc.fr). For a few well-established associations (for example, tobacco smoke and human lung cancer), it was impractical to include all studies, even in the website tables. In those instances, the rationale for inclusion or exclusion of sets of studies is given.

Each section of Volume 100 was reviewed by a subgroup of the Working Group with appropriate subject expertise; then all sections of each *Monograph* were discussed together in a plenary session of the full Working Group. As a result, the evaluation statements and other conclusions reflect the views of the Working Group as a whole.

Volume 100 compiles information on tumour sites and mechanisms of carcinogenesis. This information will be used in two scientific publications that may be considered as annexes to this volume. One publication, Tumour Site Concordance between Humans and Experimental Animals, will analyse the correspondence of tumour sites among humans and different animal species. It will discuss the predictive value of different animal tumours for cancer in humans, and perhaps identify human tumour sites for which there are no good animal models. Another publication, Mechanisms Involved in Human Carcinogenesis, will describe mechanisms known to or likely to cause cancer in humans. Joint consideration of multiple agents that act through similar mechanisms should facilitate the development of a more comprehensive discussion of these mechanisms. Because susceptibility often has its basis in a mechanism, this could also facilitate a more confident and precise description of populations that may be susceptible to agents acting through each mechanism. This publication will also suggest biomarkers that could render future research more informataive. In this way, IARC hopes that Volume 100 will serve to improve the design of future cancer studies.

Specific remarks about the agents reviewed in this volume

Billions of people around the world are exposed to one or several of these agents as part of their everyday life. A common theme is that they cause adverse health effects at levels of exposure that are commonly experienced, and collectively are responsible for a disproportionately high portion of the global burden of cancer. At the same time, some of these agents, notably tobacco in all forms and alcoholic beverages, are also mostly discretionary, although marketing and societal influences have played an important role in promoting their use. Therefore, exposure to these agents is largely preventable, through a combination of individual action and governmental intervention, the latter being especially important, for example, in promoting smoking cessation or smoke-free indoor environments.

Tobacco consumption is the single largest cause of cancer in the world. Tobacco smoking was evaluated as providing *sufficient evidence of carcinogenicity* in humans in Volumes 38 (IARC, 1986) and 83 (IARC, 2004a). Some types of smokeless tobacco were evaluated in Volume 37 (IARC, 1985) as having *sufficient evidence of carcinogenicity* in humans; two decades later, Volume 89 (IARC, 2007) classified all types of smokeless tobacco in Group 1. In this volume, the tobacco-specific nitrosamines NNK and NNN were also classified in Group 1 based on strong mechanistic evidence in exposed humans (IARC, 2007). Betel quid, a preparation that includes areca nut with betel leaf and other ingredients, and often tobacco, is chewed by over 600 million people in southern Asia and in Asian-migrant communities across the world. Betel quid with tobacco was evaluated in Volume 37 as having *sufficient evidence of carcinogenicity* in humans, and this classification was reaffirmed and extended to betel quid without tobacco in Volume 85 (IARC, 2004b). In the latter volume, areca nut, the common ingredient in all betel quid preparations, was also classified in Group 1. Alcohol consumption, another major contributor to the global burden of cancer, was classified in Group 1 in Volumes 44 (IARC, 1988) and 96 (IARC, 2010a). Ethanol and acetaldehyde associated with alcoholic beverage

consumption were specifically mentioned as carcinogenic agents in the latter volume. Indoor smoke from solid fuels is yet another major contributor to the global burden of disease. The highest individual risks are seen in households that use unvented coal stoves for cooking and heating, an exposure that was classified in Group 1 in Volume 95 (IARC, 2010b). Finally, salted fish was evaluated in Volume 56 (IARC, 1993), with Chinese-style salted fish classified in Group 1.

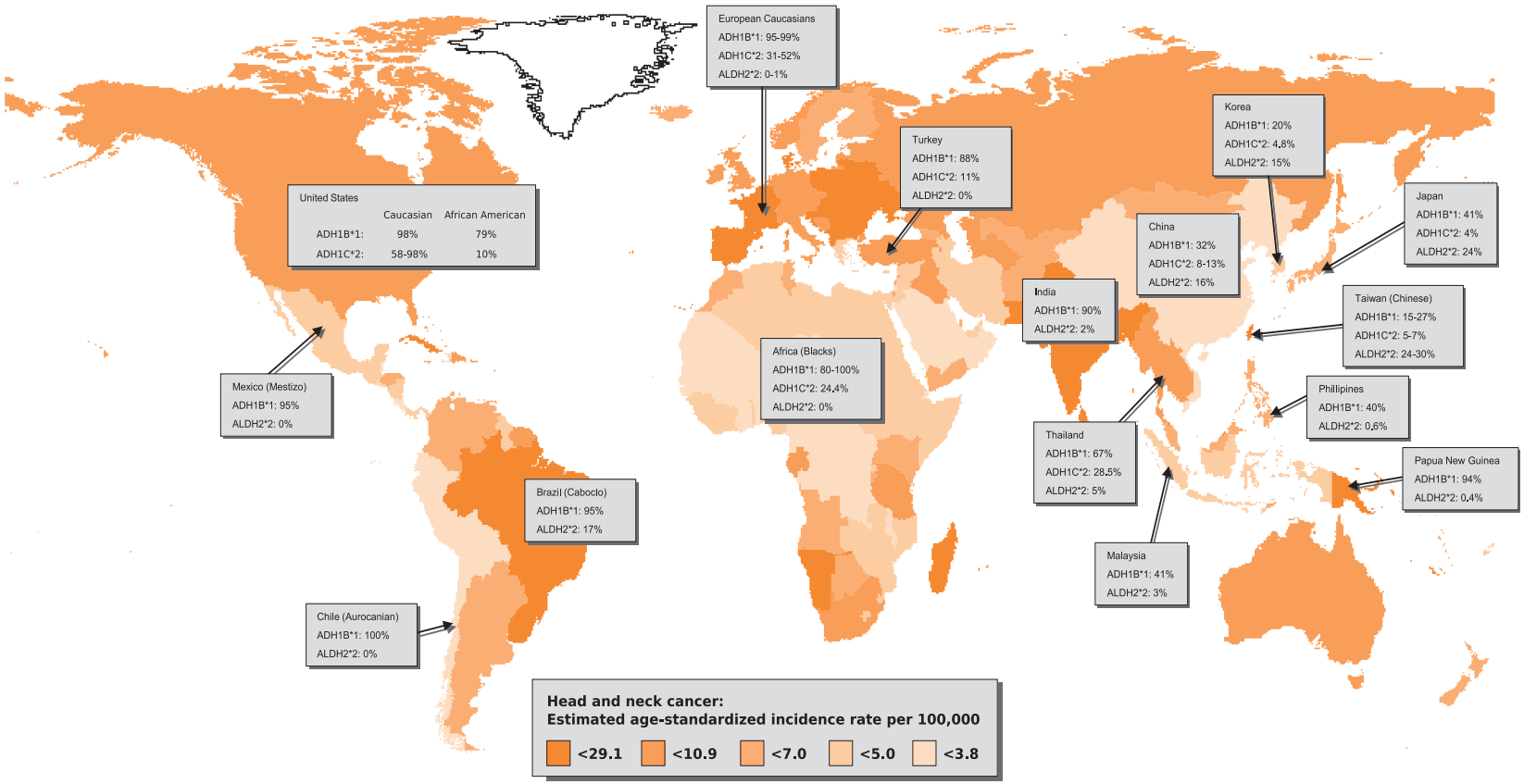
1. Alcoholic beverages, ethanol and acetaldehyde associated with their consumption

Consumption of alcoholic beverages is one of the top-10 exposures responsible for the burden of disease worldwide. Nearly two billion adults consume alcoholic beverages regularly, with an average daily consumption of 13 g ethanol (about one drink). The Working Group that evaluated alcohol consumption recently (IARC, 2010a) concluded that it causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver and female breast. With respect to the latter cancer type, the risk increases with increasing alcohol intake by about 10% per 10 g per day. Epidemiological evidence shows little indication that the carcinogenic effects depend on the type of alcoholic beverage.

The metabolism of ethanol, the key component in alcoholic beverages, can be essentially described as a two-step dehydrogenation process. In humans, the major enzymes involved are the alcohol dehydrogenases (ADH), which oxidize ethanol to its toxic intermediate, acetaldehyde, and the aldehyde dehydrogenases (ALDH), which detoxify acetaldehyde to acetate. The two groups of dehydrogenases exhibit genetic variations that confer wide differences in enzyme kinetics and substrate specificities and that vary widely across ethnicities (figure). Studies on the carcinogenicity of alcoholic beverages consumption give a striking example of a genetic polymorphism that strongly influences the response to a carcinogen. The variant *ALDH2*2* allele, which encodes an inactive subunit of the enzyme ALDH2, is highly prevalent in certain eastern-Asian populations (28–45%), but rare in other ethnic groups. Most homozygous carriers of this allele (*ALDH2*2/*2*) are abstainers or infrequent drinkers, because the complete deficiency of enzymatic activity would cause a strong facial flushing response, physical discomfort, and severe toxic reactions when consuming alcoholic beverages. In heterozygous carriers (*ALDH2*1/*2*), who have about 10% residual ALDH2 activity, these acute adverse effects are less severe, but these persons have higher levels of acetaldehyde in their blood and saliva after alcohol drinking, and higher levels of acetaldehyde-related DNA adducts in their lymphocytes compared with those with fully active enzyme (*ALDH2*1/*1* genotype). In addition, these individuals are at high risk for several alcohol-related aerodigestive cancers. Examining the role of acetaldehyde as a cause of aerodigestive cancers is further complicated by competing risk factors such as tobacco smoking, areca nut chewing, infection by HPV; in addition, this association may be modified by microflora present in the aerodigestive tract, which have high ADH but low ALDH enzyme activity (Chang *et al.*, 2011).

The previous Working Group acknowledged the important role of acetaldehyde in the development of alcohol-related cancer, especially of the esophagus, but refrained from making a formal evaluation of this metabolite. The Working Group for this Volume considered that the available epidemiological data clearly indicates that humans who are deficient in the oxidation of acetaldehyde to acetate have a substantially increased risk for development of alcohol-related cancers, and decided to make a separate evaluation for "acetaldehyde associated with alcoholic beverage consumption".

***ADH1B*1*& *ADH1C*2* (slow ethanol-oxidizing) & *ALDH2*2* (null) allele frequencies by population and incidence of head and neck cancer**



From Chang *et al.* (2011) (Supplementary figure)

2. Betel quid with and without tobacco, areca nut and smokeless tobacco

Smokeless tobacco and areca nut are consumed by millions of people across the globe and may be social practices deeply rooted in their respective cultures. In this *Monograph*, any product containing areca nut is referred to as 'betel quid', the most common name given for such products.

Smokeless tobacco and betel quid share many features. Both products are addictive (Warnakulasuriya, 2004; Chu, 2001), and most evidence suggests that users find it difficult to quit these behaviours. Both are typically used orally, being chewed and then spit out. Although generally considered as a social practice, both have other uses: for example, various forms of smokeless tobacco are used as a dentifrice in India. Both products are rarely used alone and are generally consumed with other constituents, added during manufacture or by the user. Notably, both may contain an additive that increases the pH of the product, which has the effect of unprotonating the psychoactive substance, thus making it readily bioavailable: nicotine in the case of smokeless tobacco and arecoline in the case of areca nut (for reviews, see Chu, 2001; Djordjevic *et al.*, 1995). Other additives to both smokeless tobacco and industrially manufactured betel quid may include flavourings and sweeteners.

2.1 Disentangling the effects of the various ingredients

Some populations use only areca nut and slaked lime in their betel quid. Since cancer bioassays have shown that slaked lime is not carcinogenic, studies from these populations provide evidence that areca nut is a cause of cancer in human populations. Studies of betel quids with a variety of other ingredients except tobacco provide evidence for the carcinogenicity to humans of betel quid without tobacco overall. Finally, studies that either assess specifically betel quid with tobacco, or that did not specify whether tobacco was added, or that combined individuals who may or may not include tobacco in their quid, together provide evidence for the carcinogenicity of betel quid with tobacco.

Areca nut and/or smokeless tobacco are highly prevalent in some cultures, e.g. in Sweden, up to 30% of men use smokeless tobacco. In 2002, it was estimated that 600 million people worldwide, primarily in the Indian sub-continent, used areca nut. In the successive IARC Monographs that have addressed either smokeless tobacco or areca nut, new formulations of these products and new populations with such habits have been reported.

New forms of these products are constantly being developed and introduced on the market in formulations that encourage initiation or maintenance of use of these products. For example, portion sizes and packaging render them more convenient for people to use, while flavourings may appeal to young persons.

Finally, no betel quid or tobacco product in any culture has been shown to be safe or free of risk of cancer. Despite the wide variation in added ingredients, method of preparation or manufacture of the product, mode of use and populations concerned, these products have been associated with an increased risk of cancer. Nevertheless, these products are promoted as "safe" alternatives to tobacco smoking and many people consider products such as *pan masala* to be safe. However, one study from North America found that smokers who had switched to smokeless tobacco had a higher death rate than men who quit tobacco entirely (Henley *et al.*, 2007).

2.2 Betel inflorescence

Betel inflorescence grows on Piper betel L. and is the male fruit, consumed with unripe areca nut in Taiwan, China. Betel inflorescence contains high levels of phenolic compounds including hydroxychavicol and safrole.

Of the different types of betel quid consumed in Taiwan, China, those that include betel inflorescence (*lao-hwa* quid) induced the highest risk for both oral leukoplakia and submucous fibrosis (Lee *et al.* 2003), and for oral and combined cancers of the oro- and hypopharynx (Ko *et al.* 1995; Chen *et al.* 2002).

Carcinogenic risk of betel inflorescence and mechanistic pathways should be examined in detail in the future.

2.3 Cancer burden

The magnitude of the risks associated with smokeless tobacco and betel quid vary, and can be very high. This, combined with the high prevalence of some behaviours in some parts of the world, leads to a very high cancer burden. In India for instance, the cancer burden from these habits meets or exceeds that of smoking.

3. Tobacco smoke: multiple exposures, multiple chemicals, multiple target sites

3.1 Tobacco smoke carcinogens

Tobacco smoke is the most pleiotropic carcinogen ever evaluated by the *IARC Monographs* Programme, with over 20 target sites to which it has been shown to be causally associated. The chemical compositions of mainstream smoke and sidestream smoke are qualitatively similar, although quantitatively different. Tobacco smoke contains over 60 chemicals or other agents that have been shown to be carcinogenic in rodents; for a dozen of those, there is also *sufficient evidence* of their carcinogenicity in humans.

For the agents present in tobacco smoke and that are classified as IARC Group 1 or Group 2A, the table below presents the target sites for which there is *sufficient* or *limited* evidence in humans.

3.2 Parental tobacco smoking

The prevalence of exposure to tobacco smoke from parental smoking varies by socioeconomic status and country, ranging up to 60% in some surveys. Exposure of the offspring may occur preconception, *in utero* or postnatally. Active smoking by either genitor preconception and maternal smoking during pregnancy both imply direct exposure to mainstream tobacco smoke of the germ cells (spermatozoa and ova) and of the foetus, respectively. In contrast, paternal smoking during pregnancy and parental smoking post-natally represent exposures to second-hand tobacco smoke.

How to evaluate separately the effect of the different exposures and time periods? Early studies generally only assessed the contribution of maternal exposures during pregnancy, whereas recent studies included assessments of exposure preconception, in particular from paternal smoking. Exposure may have occurred in all three periods even when a study reports on only one, or exposure may also be

Target sites associated with some carcinogenic chemical compounds and metals present in tobacco smoke

Agent	Tumour sites or types for which there is *sufficient* evidence in humans	Tumour sites or types for which there is *limited* evidence in humans
Chemicals		
1,3-Butadiene	Hematolymphatic organs	
2-Naphthylamine	Urinary bladder	
4-Aminobiphenyl	Urinary bladder	
Benzene	Acute non-lymphocytic leukaemia	Acute lymphocytic leukaemia, chronic lymphocytic leukaemia, multiple myeloma, non-Hodgkin lymphoma
Ethylene oxide		Breast, lymphoid tumours
Formaldehyde	Nasopharynx, leukaemia (particularly myeloid leukaemia)	Sinonasal cancer
o-Toluidine	Urinary bladder	
Vinyl chloride	Hepatocellular carcinoma, hepatic angiosarcoma	
Metals		
Arsenic and inorganic arsenic compounds	Lung, skin, urinary bladder	Kidney, liver, prostate
Beryllium and beryllium compounds	Lung	
Cadmium and cadmium compounds	Lung	Kidney, prostate
Chromium (VI) compounds	Lung	Nasal cavity and paranasal sinuses
Lead		Stomach
Nickel compounds	Lung, nasal cavity and paranasal sinuses	

Adapted from Cogliano *et al.* (2011)

reported as 'ever' exposed. In addition, parental smoking during each of these time periods tends to be correlated, in particular from the father, because father's smoking habits are less likely to change during pregnancy. Furthermore, paternal and maternal smoking habits are often correlated, and the risks may be increased when both parents smoke. Thus establishing a link between parental smoking and childhood cancer risk relates to several different exposures that are tightly correlated and difficult to disentangle.

The younger the child at diagnosis, the more direct prenatal exposures appear to be relevant compared to post-natal exposures. Stronger associations for cancer in offspring were observed from parental smoking preconception than from maternal smoking during pregnancy. Interestingly, the strongest and most consistent association was observed for hepatoblastoma, an embryonal tumour of presumably foetal origin, which has a median age of diagnosis of about 12 months. Cigarette smoke is a known germ-cell mutagen in mice and a likely germ-cell mutagen in humans. The effect of such mutagenicity on cancer risk in the offspring of smoking parents has now been demonstrated in human populations.

4. Coal Emissions

The use of coal in homes for cooking and heating is a major source of indoor air pollution in Asia, particularly in China. Emissions from the combustion of coal have been associated with a variety of health outcomes, especially lung cancer. The population at risk for illness from indoor air pollution numbers in the hundreds of millions in China alone, and possibly more than a billion worldwide. Women and children bear the largest share of the burden of disease from this exposure since they spend longer periods of time inside the home. Greater awareness of this exposure should be emphasized for these vulnerable groups. The development and implementation of appropriate improvement in ventilation and other strategies to reduce indoor air pollution in developing countries should be supported and encouraged from both the government and interested private parties in the commercial sector. The replacement of coal with cleaner fuels should also be a high priority. However, since many millions of people cannot afford to change the household fuels that they use, alternative efforts are necessary in the interim.

5. Salted fish

The Working Group has evaluated Chinese-style salted fish defined as salted fish consumed in Chinese populations, the majority of studies being from the Southern part of China. The evaluation of epidemiological studies has found *sufficient evidence* for an association with nasopharyngeal carcinoma, and *limited evidence* for an association with stomach cancer. The most consistent association between Chinese-style salted fish and nasopharyngeal carcinoma has been observed for ingestion during weaning or early childhood in the early studies; interestingly, the diet-related lifestyle changes that started in the second half of the 20th century in the Chinese populations, characterized by a large decrease in preserved food consumption and especially the decline in the habit of feeding young children with salted fish, coincides with the lower rate of nasopharyngeal cancer incidence observed in the most recent studies.

Defining a clear mechanism linking salted fish consumption with nasopharyngeal carcinoma has been hampered by the lack of data and by the fact that the composition of salted fish may greatly vary depending on the mode of preparation in different areas of Southern China. Possible mechanisms include the formation of *N*-nitrosamines and other *N*-nitroso compounds during the processing of the fish and/or endogenously after ingestion in the human body.

Another likely mechanism is the interaction between Chinese-style salted fish and Epstein-Baar virus (EBV). EBV involvement in the carcinogenesis of nasopharyngeal cancer in South-eastern China has been clearly demonstrated; its role is also suggested in gastric adenocarcinoma (see Volume 100B). Experimental data have shown that salted fish extracts can reactivate EBV in latently infected cells in vitro. This is an important finding, since EBV is known to be present in a latent form in almost every person unless reactivated.

Aqueous extracts of some other preserved food samples from Tunisia (e.g *harissa*, a spiced mixture) and Greenland (salted fish), two high risk areas for nasopharyngeal cancer, were also shown to activate EBV in cells in vitro. In addition, other preserved food whose consumption can potentially lead to *N*-nitroso compounds intake is consumed in many part of the world.

The Working Group recommends that IARC undertake a full review of the carcinogenic hazards of preserved food.

A summary of the findings of this volume appears in The Lancet Oncology (Secretan *et al.*, 2009).

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