International Agency for Research on Cancer

World Health Organization

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IARC STRENGTHENS ITS FINDINGS ON SEVERAL CARCINOGENIC PERSONAL HABITS AND HOUSEHOLD EXPOSURES

IARC has updated the cancer assessments of several personal habits and household exposures that cause cancer, including tobacco, areca nut, alcohol, and household coal smoke. The update was conducted with the advice of 30 scientists from 10 countries who met at IARC in October 2009. These assessments will be published as part E ("*Personal Habits and Household Exposures*") of Volume 100 of the IARC Monographs, which is compiling the information presently available on all of the more than 100 human carcinogens that have been identified to date. The other parts of Volume 100 cover (A)*Pharmaceuticals*, (B) *Biological Agents*, (C) *Metals, Arsenic, Dusts and Fibres*, (D)*Radiation*, and (F) *Chemical Agents and Related Occupations*.

Tobacco and cancer: new evidence, additional tumour sites

Tobacco smoking is the single largest cause of cancer worldwide, and over 1 billion people are current smokers. New studies provide sufficient evidence(1) to add cancers of the colon and rectum and of the ovary (mucinous type) to the already extensive list of cancers caused by tobacco smoking.(2)

Over 130 epidemiological studies on tobacco smoking and breast cancer were reviewed. Large cohort studies published during the past 5 years show a small positive association with breast cancer. Many chemicals present in tobacco smoke cause mammary gland tumours in animals; these carcinogens reach the breast in women and are stored in adipose tissue. These combined observations led the Working Group to conclude that tobacco smoking may be a cause of breast cancer.

Further, a causal link between parental smoking and childhood cancer has been established. Four recent studies showed that children born of parents who smoked (father and/or mother, during the preconception period and/or pregnancy) are at significantly higher risk of hepatoblastoma, a rare cancer thought to be of fetal origin. The United Kingdom Childhood Cancer Study reported relative risks for paternal-only or maternal-only smoking of 1.9 and 2.0, respectively, increasing to 4.7 (95% CI, 2-13) when both parents smoked. The evidence also suggests an increased risk of childhood leukaemia: particularly noteworthy, a meta-analysis of 11 studies found an association between pre-conception paternal smoking and childhood leukaemia.

Second-hand smoke

Second-hand smoke is carcinogenic to humans (Group 1), causing lung cancer. In addition, there is now some evidence for an association with cancers of the larynx and the pharynx. Since second-hand smoke contains most of the constituents of mainstream smoke, it may also be associated with other cancer sites.

Many types of smokeless tobacco are marketed for oral or nasal use, and all contain nicotine and tobacco-specific nitrosamines, including NNN (*N'*-nitrosonornicotine) and NNK (4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone). Hundreds of millions of people use smokeless tobacco, mainly in India and southeastern Asia, as well as in Sweden and the USA. In addition to previous conclusions that use of smokeless tobacco causes cancer of the oral cavity and pancreas, there is now sufficient evidence for cancer of the oesophagus.

Tobacco smoking, second-hand smoke and smokeless tobacco were all reaffirmed as carcinogenic to humans (Group 1), along with NNK and NNN.

Betel quid

Betel quid is chewed commonly in India and southeastern Asia: around 600 million people are estimated to chew, with a prevalence of up to 80% in some regions in India. Betel quid generally consists of areca nut, betel leaf, catechu and slaked lime, and tobacco is often added. Carcinogenic nitrosamines derived from the areca nut, the primary ingredient in betel quid, are formed in the saliva of chewers. Areca nut induces oral preneoplastic disorders that have a high propensity to progress to cancer. In some parts of India, cancer of the oral cavity is the most prevalent type of cancer. The Group 1 classification of betel quid with or without added tobacco, as well as of areca nut, was reaffirmed. In addition to cancer of the oral cavity, betel quid without

added tobacco is now associated with cancer of the oesophagus (sufficient evidence) and cancer of the liver (limited evidence(1))

Alcoholic beverages
Nearly 2 billion adults worldwide are estimated to consume alcoholic beverages regularly, with an average daily consumption of 13 g of ethanol (about one drink). Alcohol consumption has already been shown to cause cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver and female breast; there is now also some evidence for cancer of the pancreas. The relative risk of breast cancer increases with increasing alcohol intake by about 10% per 10g/day.(3)

Higher risk for East-Asian populations linked to alcohol metabolism
Alcohol consumption results in exposure to acetaldehyde, present in the beverage itself and also formed when the body breaks down alcohol. Alcohol is metabolised to acetaldehyde, (which is a genotoxic chemical), then this acetaldehyde is further metabolised to acetate (a harmless chemical) by enzymes known as aldehyde dehydrogenases (ALDH). A large proportion of people of east-Asian origin worldwide (up to 30% in some populations) has an inactive enzyme (known as *ALDH2*2*) that has only about 10% residual enzymatic activity. Carriers of the inactive enzyme are extremely slow to metabolise acetaldehyde, as a result, they experience higher internal levels of acetaldehyde and have much higher risks of oesophageal cancer and cancers of the head and neck compared with individuals with the active enzyme. The Working Group concluded that acetaldehyde associated with alcohol consumption is carcinogenic to humans (Group 1) and confirmed the classification in Group 1 of alcohol consumption and of ethanol in alcoholic beverages.

Indoor emissions from coal used for cooking and heating
About half of the world's population, mostly in low- and medium-resource countries, uses solid fuels for cooking or heating, often in poorly ventilated spaces. Indoor emissions from household combustion of coal was reaffirmed as carcinogenic to humans. Women and young children, who spend more time indoors, are most highly exposed.

Salted fish
Salt-preserved fish is consumed in several regions around the world, particularly in southeastern Asia. Chinese-style salted fish causes cancer of the nasopharynx, and may also cause cancer of the stomach. *N*-nitroso compounds are likely to form during processing and storage of the preserved fish as well as endogenously after ingestion, and may act as carcinogens. Reactivation of Epstein-Barr virus by chemicals present in salted fish may be another mechanism of carcinogenesis.

Tobacco smoking, alcohol consumption, and betel quid/areca nut chewing are highly prevalent and harmful activities for which exposure is preventable at the level of the individual. Although use of tobacco, alcohol, or betel quid/areca nut is often considered to be a voluntary or "lifestyle" behavior, these products, particularly tobacco and areca nut, are strongly addictive. In addition, marketing and societal factors influence many young people to take up these addictive habits. The choice to begin using these substances is often made in childhood, and addiction sustains their continued use.

[1] For a definition of IARC Monographs Group definitions and of evidence, see below at end of text.
[2] Tobacco smoking causes cancers of the oral cavity, oro-, naso-, and hypopharynx, oesophagus (adeno- and squamous cell carcinoma), stomach, colorectum, liver, pancreas, nasal cavity and paranasal sinuses, larynx, lung, uterine cervix, ovary (mucinous), urinary bladder, kidney (body and pelvis), ureter,and bone marrow (myeloid leukaemia).
[3] For example, a woman who consumes an average 20 grams of ethanol per day (about 1.5-2 drinks per day) would have a risk of breast cancer that is about 1.20 times the risk for a non-drinking woman, all other factors being equal.

Last minute: The highlights of meeting 100F of the IARC Monographs (*Chemical agents and related occupations*), which took place at the end of October, can be found at http://monographs.iarc.fr/

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ABOUT THE IARC MONOGRAPHS

What are the IARC Monographs?

The *IARC Monographs* identify environmental factors that can increase the risk of human cancer. These include chemicals, complex mixtures, occupational exposures, physical and biological agents, and lifestyle factors. National health agencies use this information as scientific support for their actions to prevent exposure to potential carcinogens. Interdisciplinary working groups of expert scientists review the published studies and evaluate the weight of the evidence that an agent can increase the risk of cancer. The principles, procedures, and scientific criteria that guide the evaluations are described in the Preamble to the IARC Monographs.

Since 1971, more than 900 agents have been evaluated, of which approximately 400 have been identified as carcinogenic or potentially carcinogenic to humans.

Definitions

Group 1: The agent is *carcinogenic to humans*.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is *probably carcinogenic to humans*.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is *possibly carcinogenic to humans*.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from

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mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

Definitions of evidence, as used in IARC Monographs for studies in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of

observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

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IARC Monographs website: http://monographs.iarc.fr/
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The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships.