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REVIEW

Preventable Exposures Associated With Human Cancers

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Information on the causes of cancer at specific sites is important to cancer control planners, cancer researchers, cancer patients, and the general public. The International Agency for Research on Cancer (IARC) Monograph series, which has classified human carcinogens for more than 40 years, recently completed a review to provide up-to-date information on the cancer sites associated with more than 100 carcinogenic agents. Based on IARC's review, we listed the cancer sites associated with each agent and then rearranged this information to list the known and suspected causes of cancer at each site. We also summarized the rationale for classifications that were based on mechanistic data. This information, based on the forthcoming IARC Monographs Volume 100, offers insights into the current state-of-the-science of carcinogen identification. Use of mechanistic data to identify carcinogens is increasing, and epidemiological research is identifying additional carcinogens and cancer sites or confirming carcinogenic potential under conditions of lower exposure. Nevertheless, some common human cancers still have few (or no) identified causal agents.

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Cancer includes many diseases, and the question often arises which exposures are associated with cancer of a specific organ or site. This information is important for rational planning of cancer control programs. It is also critical to the identification of potential confounding factors in the design and analysis of epidemiological studies and to the formulation of hypotheses concerning mechanistic pathways for experimental investigation. On a more personal level, patients and their families often wonder whether preventable environmental, occupational, dietary, or consumer exposures might have contributed to their disease. Information about exposures associated with cancer at specific sites is difficult to obtain because it is spread across hundreds of agent-specific assessments published by different health authorities at various times using different methods.

Recently, the International Agency for Research on Cancer (IARC) completed a review (1) of the more than 100 chemicals, occupations, physical agents, biological agents, and other agents that it has classified as carcinogenic to humans (Group 1; IARC classifies agents as carcinogenic to humans [Group 1], probably carcinogenic to humans [Group 2A], possibly carcinogenic to humans [Group 2B], not classifiable [Group 3], or probably not carcinogenic to humans [Group 4]) (2). To this end, IARC convened six Working Groups that included 160 scientists from 28 countries to critically review published epidemiological and experimental studies, to evaluate the carcinogenicity of each agent, to identify cancer sites where a causal association is established or credible, and to identify mechanistic events that are known or likely to be involved. This work will be published in 2011 as Volume 100 of the IARC Monographs (1), and summary information is already available (3–8). IARC's review provides up-to-date information on cancer sites associated with each human carcinogen.

There has been debate over the value of identifying cancer sites associated with an agent, with some scientists arguing that association with some cancer sites implies exclusion of a possible association with cancer at other sites (9,10). The crux of the matter is whether to regard a list of cancer sites restrictively, as a finite number of sites where carcinogenesis is possible, or expansively, as examples where strong evidence of an association exists at the time of evaluation (11). IARC has taken the expansive view, and its recent review provides information pertinent to this question.

In this article, we have brought together cancer site information on more than 100 human carcinogens identified through 40 years of IARC Monographs reviews, rearranged this information to list the known and suspected causes of cancer at various sites, and discussed some implications for the state-of-the-science of carcinogen identification. Other factors associated with an increased cancer risk not covered in the IARC Monographs, notably genetic traits, reproductive status, and some nutritional factors, are not included in this review.

Methods

For each agent that IARC classifies as carcinogenic to humans, we compiled lists of the cancer sites for which we have "sufficient evidence" or "limited evidence" of an association in humans. For the purposes of this analysis, sufficient evidence in humans means that a causal relationship has been established and that chance, bias, and confounding could be ruled out with reasonable confidence,

whereas limited evidence in humans means that a causal relationship was credible but that chance, bias, or confounding could not be ruled out with reasonable confidence (2). We took this information from the published summaries of IARC's review (3–8) and from the final drafts that the Working Groups developed for IARC Monographs Volume 100 (1).

To complete the list of cancer sites with limited evidence, we searched IARC Monographs Volumes 1–99 for agents that were classified as probably carcinogenic or possibly carcinogenic to humans. In most cases, the cancer site associations are clear and are based on the published summary and evaluation by the most recent Working Group that has classified an agent. For some agents with positive findings for several cancer sites, we made a judgment based on the IARC reviews about which cancer sites might be considered to have a credible causal relationship.

As we searched Volumes 1–99, we found earlier assessments of most carcinogens reviewed in Volume 100 (1). We identified the cancer sites with established causal relationships in the first volume in which an agent had been determined to be carcinogenic and compared these with the cancer sites that are currently considered to be established. After listing the cancer sites associated with each known or suspected carcinogen, we rearranged this information to list the known and suspected causes of cancer at each site, based on currently reviewed studies.

Results

We first list the cancer sites that IARC associates with each agent that it classifies as carcinogenic to humans (Table 1). For each agent, we list cancer sites for which IARC judges that there is sufficient evidence of an association and sites for which IARC judges that there is limited evidence of an association in its review. In some cases, cancer sites are described with a high level of precision, most notably for some biological agents that often infect specific target cells within an organ.

For several agents in Table 1, there is insufficient evidence for an association with any cancer sites in humans; these agents are classified as carcinogenic to humans because of strong mechanistic data and other information. Most of these agents occur in complex exposures for which it would be difficult for epidemiological studies to attribute causality to specific components; however, agent-specific biomarkers have been identified that associate them with tumor development in exposed humans. We separately list the agents that IARC classifies as carcinogenic to humans based on mechanistic or other relevant data, along with a summary of the rationale for each classification (Table 2).

In the next table (Table 3), we list the cancer sites that IARC associates with the agents that it classifies as probably carcinogenic or possibly carcinogenic to humans. It must be stressed that several of these evaluations are many years old and that subsequent research may support a different classification today. For example, in Supplement 7 (12), IARC listed 18 agents as having limited evidence of carcinogenicity in humans. Of these, 12 agents have been reevaluated and there is now sufficient evidence to consider five of them to be carcinogenic (beryllium and its compounds, cadmium and its compounds, crystalline silica dust, formaldehyde, and phenacetin), limited evidence for four (chloramphenicol, creosotes, ethylene oxide, and polychlorophenols), and "inadequate evidence" for three (acrylonitrile, diethyl sulfate, and phenytoin; here, inadequate evidence means that the available studies do not show the presence or absence of a causal association) (2).

The last table (Table 4) combines the IARC information from Tables 1 and 3 by cancer site rather than by agent. To accommodate the different degrees of precision with which cancer sites have been identified (eg, "liver cancer" for one agent and "hepatocellular carcinoma" for another), we have used designations that are more general in nature (liver cancer in this example) in Table 4. Information about specific histological types is presented in Tables 1 and 3.

Discussion

Tables 1–4 summarize and update some major conclusions from the first 40 years of IARC Monographs. To these, one might add other consensus findings for dietary and nutritional factors, including red meat and processed meat (convincing evidence for colorectal cancer), β-carotene (lung cancer), body fatness (breast, colorectal, endometrium, kidney, esophageal, and pancreatic cancers), abdominal fatness (colorectal cancer), and adult attained height (breast and colorectal cancers) (13).

From Tables 1–4, we might also gain new insights into the state-of-the-science of carcinogen identification. We discuss five major themes below.

Increased Use of Mechanistic Data

The use of mechanistic data to identify carcinogens is accelerating. Initially, IARC would classify an agent as carcinogenic to humans only when there was sufficient evidence in humans to support a causal association (14). Scientific understanding of the mechanisms of carcinogenesis, accompanied by the development of assays for studying mechanistic events involved in carcinogenesis, have given researchers new ways of establishing whether an agent is carcinogenic. Since 1991, IARC has allowed an agent to be classified as carcinogenic to humans if there is sufficient evidence in animal models and "strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity" [(15); sufficient evidence in animal models here means that a causal relationship has been established through an increased incidence of benign and malignant neoplasms in two or more species or independent studies, or in a single study to an unusual degree with regard to incidence, site, type of tumor, age at onset, or at multiple sites]. Under IARC's approach, classifications based on strong mechanistic evidence in exposed humans and classifications based on sufficient evidence from epidemiological studies of cancer in humans have been given similar confidence (2).

Some scientists would prefer that IARC be more conservative in classifying carcinogens based on mechanistic evidence. This alternative view holds that conclusions about the etiology of human cancers that are based on mechanistic evidence (in exposed humans [eg, biomarkers in a molecular epidemiological study], in human cell lines, in animals, or in animal cell lines) generally lack the certainty of conclusions based on epidemiological studies. Nevertheless, IARC's approach for using information on mechanisms of carcinogenesis has since been adopted by several national

Table 1. Agents that the International Agency for Research on Cancer has classified as carcinogenic to humans and associated cancer sites

Carcinogenic agent	Cancer sites with sufficient evidence in humans*	Cancer sites with limited evidence in humans	Earlier volumes that classified the agent as carcinogenic†
Chemicals and mixtures			
Acid mists, strong inorganic	Larynx	Lung	54 (1992)
Aflatoxins	Liver (hepatocellular carcinoma)		Suppl 7 (1987); 56 (1993); 82 (2002)
4-Aminobiphenyl	Urinary bladder		1 (1972); 99 (2010)
Aristolochic acid‡		Renal pelvis; ureter	§
Aristolochic acid, plants containing	Renal pelvis; ureter		82 (2002)
Benzene	Leukemia (acute nonlymphocytic)	Leukemia (acute lymphocytic, chronic lymphocytic, multiple myeloma, non-Hodgkin lymphoma)	7 (1974); 29 (1982)
Benzidine	Urinary bladder		1 (1972); 29 (1982); 99 (2010)
Benzidine, dyes metabolized to‡			99 (2010)
Benzo[*a*]pyrene‡			92 (2010)
Bis(chloromethyl)ether; chloromethyl methyl ether (technical grade)	Lung		4 (1974)
1,3-Butadiene	Hematolymphatic organs		97 (2008)
Coal tar pitch	Lung*; skin	Urinary bladder	3 (1973); 35 (1985)
Ethylene oxide‡		Breast; lymphoid tumors (non-Hodgkin lymphoma, multiple myeloma, chronic lymphocytic leukemia)	60 (1994); 97 (2008)
Formaldehyde	Leukemia (particularly myeloid)*; nasopharynx	Nasal cavity and paranasal sinus	88 (2006)
4,4′-Methylenebis(2-chloroaniline) (MOCA)‡			99 (2010)
Mineral oils, untreated or mildly treated	Skin		3 (1973); 33 (1984)
2-Naphthylamine	Urinary bladder		4 (1974); 99 (2010)
Tobacco-specific nitrosamines: N′-nitrosonornicotine (NNN) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)‡			89 (2007)
Shale oils	Skin		3 (1973); 35 (1985)
Soot	Lung*; skin	Urinary bladder	3 (1973); 35 (1985)
Sulfur mustard	Lung	Larynx	9 (1975)
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin	All cancers combined	Lung; non-Hodgkin lymphoma; soft tissue sarcoma	69 (1997)
3,4,5,3′,4′-Pentachlorobiphenyl (PCB-126)‡			§
2,3,4,7,8-Pentachlorodibenzofuran‡			§
Ortho-Toluidine	Urinary bladder		99 (2010)
Vinyl chloride	Liver (angiosarcoma, hepatocellular carcinoma)		7 (1974); 19 (1979); 97 (2008)
Occupations			
Aluminum production	Lung; urinary bladder		Sup 7 (1987); 92 (2010)
Auramine production	Urinary bladder		1 (1972); 99 (2010)
Coal gasification	Lung		34 (1984); 92 (2010)
Coal tar distillation	Skin		34 (1984); 92 (2010)
Coke production	Lung		34 (1984); 92 (2010)
Hematite mining (underground)‖	Lung		1 (1972)
Iron and steel founding	Lung		Sup 7 (1987)
Isopropyl alcohol production	Nasal cavity and paranasal sinus		15 (1977)
Magenta production	Urinary bladder		Sup 7 (1987); 57 (1993); 99 (2010)
Painting	Lung; mesothelioma*; urinary bladder*	Maternal exposure: childhood leukemia	47 (1989); 98 (2010)
Rubber production industry	Leukemia, lymphoma; lung; stomach; urinary bladder	Larynx; esophagus; prostate	28 (1982)
Welding¶	Eye (melanoma)		§
Metals			
Arsenic and inorganic arsenic compounds	Lung*; skin; urinary bladder*	Kidney; liver; prostate	2 (1973); 23 (1980); 84 (2004)
Beryllium and beryllium compounds	Lung		58 (1993)
Cadmium and cadmium compounds	Lung	Kidney; prostate	58 (1993)
Chromium (VI) compounds#	Lung	Nasal cavity and paranasal sinus	2 (1973); 23 (1980); 49 (1990)

(Table continues)

Table 1 (Continued).

Carcinogenic agent	Cancer sites with sufficient evidence in humans*	Cancer sites with limited evidence in humans	Earlier volumes that classified the agent as carcinogenic†
Nickel compounds**	Lung; nasal cavity and paranasal sinus		2 (1973); 11 (1976); 49 (1990)
Dusts and fibers			
Asbestos (all forms)	Larynx*; lung; mesothelioma; ovary*	Colorectum; pharynx; stomach	2 (1973); 14 (1977)
Erionite	Mesothelioma		42 (1987)
Leather dust††	Nasal cavity and paranasal sinus		25 (1981)
Silica dust, crystalline (in the form of quartz or crystobalite)	Lung		68 (1997)
Wood dust‡‡	Nasal cavity and paranasal sinus; nasopharynx*		25 (1981); 62 (1995)
Radiation			
Ionizing radiation (all types)§§			§
Alpha-particle emitters§§			78 (2001)
Radon-222 and its decay products	Lung	Leukemia	43 (1988)
Radium-224 and its decay products	Bone		78 (2001)
Radium-226 and its decay products	Bone; mastoid process; paranasal sinus		78 (2001)
Radium-228 and its decay products	Bone; mastoid process*; paranasal sinus*		78 (2001)
Thorium-232 and its decay products	Bile duct, extrahepatic*; gall bladder*; leukemia (excluding chronic lymphocytic leukemia); liver (including hemangiosarcoma)	Pancreas; prostate	78 (2001)
Plutonium	Bone; liver; lung	Other solid tumors	78 (2001)
Beta-particle emitters§§			78 (2001)
Phosphorus-32	Leukemia (acute)		78 (2001)
Fission products, including Strontium-90	Leukemia; solid cancers		§
Radioiodines, including Iodine-131	Thyroid	Bone and soft tissue; digestive tract; leukemia; salivary gland	78 (2001)
X radiation, gamma radiation	Bone*; brain and central nervous system*; breast (female); colon; kidney*; leukemia (excluding chronic lymphocytic leukemia); lung*; esophagus*; salivary gland*; skin (basal cell carcinoma)*; stomach; thyroid; urinary bladder*; exposure in utero: multiple sites*	Liver; multiple myeloma; non-Hodgkin lymphoma; ovary; pancreas; prostate; rectum	75 (2000)
Neutron radiation‡			75 (2000)
Solar radiation	Skin (basal cell carcinoma, squamous cell carcinoma, melanoma)	Eye (squamous cell carcinoma, melanoma); lip	55 (1992)
Ultraviolet radiation‡			§
Ultraviolet-emitting tanning devices	Eye (melanoma); skin (melanoma)	Skin (squamous cell carcinoma)	§
Biological agents			
Epstein—Barr virus	Burkitt lymphoma; Hodgkin lymphoma; lymphoma (extranodal NK/T-cell, nasal type); nasopharynx; non-Hodgkin lymphoma (immune suppression related)	Lymphoepithelial-like carcinoma; stomach	70 (1997)
Hepatitis B virus	Liver (hepatocellular carcinoma)	Liver (cholangiocarcinoma); non-Hodgkin lymphoma	59 (1994)
Hepatitis C virus	Liver (hepatocellular carcinoma); non-Hodgkin lymphoma*	Liver (cholangiocarcinoma)	59 (1994)
HIV type 1	Anus*; cervix*; eye (conjunctiva)*; Hodgkin lymphoma*; Kaposi sarcoma; non-Hodgkin lymphoma	Liver (hepatocellular carcinoma); penis; skin (non-melanoma); vagina; vulva	67 (1996)
Human papillomavirus type 16	Anus; cervix; oral cavity*; oropharynx*; penis*; tonsil*; vagina*; vulva*	Larynx	64 (1995); 90 (2007)
Human papillomavirus type 18	Cervix	Anus; larynx; oral cavity; penis; vulva	64 (1995); 90 (2007)
Human papillomavirus type 33	Cervix	Anus; vulva	90 (2007)

(Table continues)

Table 1 (Continued).

Carcinogenic agent	Cancer sites with sufficient evidence in humans*	Cancer sites with limited evidence in humans	Earlier volumes that classified the agent as carcinogenic†
Human papillomavirus types 31, 35, 39, 45, 51, 52, 56, 58, 59	Cervix		90 (2007)
Human T-cell lymphotropic virus type 1	Leukemia and/or lymphoma (adult T-cell)		67 (1996)
Kaposi sarcoma herpes virus	Kaposi sarcoma; lymphoma (primary effusion)	Lymph nodes (multicentric Castleman disease)	§
Clonorchis sinensis	Liver (cholangiocarcinoma)		§
Helicobacter pylori	Lymphoma (low-grade B-cell mucosa-associated lymphoid-tissue gastric lymphoma); stomach (noncardia carcinoma)		61 (1994)
Opisthorchis viverrini	Liver (cholangiocarcinoma)		61 (1994)
Schistosoma haematobium	Urinary bladder		61 (1994)
Personal habits			
Alcoholic beverages	Breast (female)*; colorectum*; larynx; liver (hepatocellular carcinoma); esophagus; oral cavity; pharynx	Pancreas	44 (1988); 96 (2010)
Acetaldehyde associated with consumption of alcoholic beverages	Aerodigestive tract, upper; esophagus		§
Ethanol in alcoholic beverages‡			96 (2010)
Areca nut‡			85 (2004)
Betel quid with tobacco	Esophagus*; oral cavity; pharynx*		37 (1985); 85 (2004)
Betel quid without tobacco	Esophagus*; oral cavity	Liver	85 (2004)
Coal, indoor emissions from household combustion	Lung		95 (2010)
Salted fish, Chinese style	Nasopharynx	Stomach	56 (1993)
Tobacco smoking	Bone marrow (myeloid leukemia)*; cervix*; colorectum*; kidney (body, renal pelvis); larynx; liver*; lung; nasal cavity and paranasal sinus*; esophagus (adenocarcinoma, squamous cell carcinoma); oral cavity; ovary (mucinous)*; pancreas; pharynx (nasopharynx, oropharynx, hypopharynx); stomach*; ureter*; urinary bladder; in smokers' children: hepatoblastoma*	Breast; in smokers' children: childhood leukemia (particularly acute lymphocytic)	38 (1986); 83 (2004)
Tobacco smoke, secondhand	Lung	Larynx; pharynx	83 (2004)
Tobacco, smokeless	Esophagus*; oral cavity; pancreas*		37 (1985); 89 (2007)
Pharmaceuticals			
Azathioprine	Non-Hodgkin lymphoma; skin (squamous cell carcinoma)		26 (1981)
Busulfan	Leukemia (acute myeloid)		Sup 4 (1982)
Chlorambucil	Leukemia (acute myeloid)		Sup 7 (1987)
Chlornaphazine	Urinary bladder		4 (1974)
Cyclophosphamide	Leukemia (acute myeloid)*; urinary bladder		26 (1981)
Cyclosporine	Non-Hodgkin lymphoma; skin (non-melanocytic)*; multiple other sites*		50 (1990)
Diethylstilbestrol	Exposure during pregnancy: breast*; exposure in utero: cervix (clear cell adenocarcinoma) and vagina (clear cell adenocarcinoma)	Exposure during pregnancy: endometrium; exposure in utero: cervix (squamous cell carcinoma) and testis	6 (1974); 21 (1979)
Estrogen menopausal therapy	Endometrium; ovary*	Breast	21 (1979); 72 (1999)
Estrogen–progestogen contraceptives (combined)	Breast*; cervix*; liver (hepatocellular carcinoma); note: reduced risk in endometrium, ovary		72 (1999); 91 (2007)

(Table continues)

Table 1 (Continued).

Carcinogenic agent	Cancer sites with sufficient evidence in humans*	Cancer sites with limited evidence in humans	Earlier volumes that classified the agent as carcinogenic†
Estrogen–progestogen menopausal therapy (combined)	Breast; endometrium (estrogen-induced risk decreases with number of days/month of progestogen use)		91 (2007)
Etoposide‡		Leukemia (acute myeloid)	§
Etoposide with cisplatin and bleomycin	Leukemia (acute myeloid)		76 (2000)
Melphalan	Leukemia (acute myeloid)		Sup 1 (1979)
Methoxsalen plus ultraviolet A	Skin (squamous cell carcinoma)		24 (1980)
MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)	Leukemia (acute myeloid); lung*		26 (1987)
Phenacetin	Renal pelvis; ureter		§
Phenacetin, analgesic mixtures containing	Renal pelvis; ureter*		Sup 4 (1982)
Semustine (methyl-CCNU)	Leukemia (acute myeloid)		Sup 7 (1987)
Tamoxifen	Endometrium; note: reduced risk in contralateral breast of breast cancer patients		66 (1996)
Thiotepa	Leukemia		50 (1990)
Treosulfan	Leukemia (acute myeloid)		26 (1981)

* Sufficient evidence became available for marked sites in this column after the agent had been classified as 'carcinogenic' in an earlier volume.

† Each agent was classified as carcinogenic to humans in Volume 100 (2011); to save space, Volume 100 is not listed in this column. In addition, Supplements 1 (1979), 4 (1982), and 7 (1987) updated all earlier volumes; supplements are listed only if a causal relationship was first established in the supplement.

‡ Aristolochic acid, ethylene oxide, and etoposide are classified as carcinogenic to humans with limited evidence from studies of cancer in humans but strong mechanistic evidence in exposed humans; thus, there are no cancer sites with sufficient evidence. Dyes metabolized to benzidine; benzo[*a*]pyrene; 4,4′-methylenebis(2-chloroaniline) (MOCA); N′-nitrosonornicotine (NNN) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK); 3,4,5,3′4′-pentachlorobiphenyl (PCB-126); 2,3,4,7,8-pentachlorodibenzofuran (2,3,4,7,8-PCDF); neutron radiation, ultraviolet radiation, ethanol in alcoholic beverages, and areca nut are classified as carcinogenic to humans with inadequate evidence from studies of cancer in humans but strong mechanistic evidence in exposed humans; thus, there are no cancer sites with sufficient evidence or limited evidence.

§ Classified as carcinogenic to humans for the first time in Volume 100.

‖ Potential causal agents include radon, crystalline silica dust, and diesel engine emissions.

¶ Volume 100 concluded that there is sufficient evidence for ocular melanoma in welders but left formal reclassification in Group 1 for a future volume that would consider all exposures during welding. Causal agents were not identified (See also "Welding fumes" in Table 3).

In Volume 2, the conclusion was for chromate production; in Supplement 1, the evaluation was more specifically for chromium and certain chromium compounds; in Supplement 7, for chromium (VI) compounds.

** In Volume 2, the conclusion was for nickel refining; in volume 49, the evaluation was more specifically for nickel compounds.

†† In Volume 25, the conclusion was that nasal adenocarcinoma and leukemia are causally associated with employment in the boot and shoe industry; in Volume 100, the leukemias were attributed to benzene, and a new evaluation was made for leather dust as the causal agent for the nasal cancers.

‡‡ In Volume 25, the conclusion was for employment in the furniture-making industry; in Volumes 62 and 100, the evaluation was made specifically for wood dust.

§§ Umbrella term encompassing several radionuclides listed next; no additional cancer sites were identified.

programs that identify suspected carcinogens (16–18). Its classification system makes clear which Group 1 classifications are based on sufficient evidence of cancer in humans and which rely on strong mechanistic evidence. Most classifications based on mechanistic data have occurred during the past few years (see Table 2). A few examples are discussed here.

Studies reviewed in 1997, in Volume 69 (19), showed that 2,3,7,8-tetrachlorodibenzo-*para*-dioxin binds to the aryl hydrocarbon receptor, which functions similarly in humans and experimental animals and signals a sequence of events that lead to changes in gene expression, cell replication, and inhibition of apoptosis. At that time, this mechanistic information led to the classification of this compound as a human carcinogen. When it was reviewed in Volume 100 (1), this compound was determined to also have sufficient epidemiological evidence to be considered carcinogenic to humans. This is the first carcinogen that was initially classified based on mechanistic data and subsequently by sufficient evidence from epidemiological studies. This example highlights the ability of mechanistic information to provide early robust evidence of carcinogenicity (8).

Plants of the genus *Aristolochia* were first evaluated in 2002, in Volume 82 (20), after a series of case reports from the 1990s had described rapidly progressing end-stage renal disease following ingestion of medicinal herbs derived from these plants. At the time, it was impossible to identify specific causal agents. When plants of the genus *Aristolochia* were reevaluated 6 years later in Volume 100 (1), mechanistic evidence of aristolochic acid–specific A:T→T:A transversions in the *TP53* tumor suppressor gene in renal disease patients led to the identification of aristolochic acid as the causal agent (3). It is encouraging to think that other carcinogens in the general environment might be identified with similar speed and confidence.

Table 2. Agents that the International Agency for Research on Cancer has classified as carcinogenic to humans based on mechanistic and other relevant data

Carcinogenic agent	Animal evidence	Mechanistic rationale for the classification as carcinogenic to humans	Volume and year
Ethylene oxide	Sufficient	Genotoxic in many systems; cytogenetic effects in lymphocytes of exposed workers	60 (1994)
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin*	Sufficient	Binding to aryl hydrocarbon receptor, leading to changes in gene expression, cell replication, and inhibition of apoptosis	69 (1997)
Neutron radiation	Sufficient	Ionizing events resulting in similar but more severe damage than from gamma rays	78 (2001)
Areca nut	Sufficient	Primary ingredient in all betel quid preparations; induces oral preneoplastic disorders with high propensity to progress to malignancy	85 (2004)
Tobacco-specific nitrosamines: N′-nitrosonornicotine (NNN) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	Sufficient	Uptake and metabolism, DNA and hemoglobin adducts in smokeless tobacco users	89 (2007)
Benzo[*a*]pyrene	Sufficient	Genotoxicity; specific diolepoxide-induced DNA adducts in exposed workers, *KRAS* mutations in nonsmokers exposed to coal smoke	92 (2010)
Ethanol in alcoholic beverages	Sufficient	Primary ingredient in all alcoholic beverages	96 (2010)
Benzidine, dyes metabolized to	Sufficient	Benzidine and its conjugates measured in urine of exposed workers and benzidine DNA adducts in exfoliated urothelial cells; genotoxicity	99 (2010)
4,4′-Methylenebis(2-chloroaniline)	Sufficient	Genotoxicity; DNA adducts and micronuclei in urothelial cells of exposed workers	99 (2010)
Acetaldehyde associated with consumption of alcoholic beverages	Sufficient	Substantially higher risks for cancers of the esophagus and upper aerodigestive tract in aldehyde dehydrogenase–deficient populations (genetic epidemiology studies)	100 (2011)
Aristolochic acid	Sufficient	Genotoxicity; A:T→T:A transversions in *TP53* of patients with severe renal nephropathy or urothelial tumors	100 (2011)
Etoposide	Inadequate†	Genotoxicity; translocations on *MLL* gene distinguish topoisomerase II inhibitors from alkylating agents	100 (2011)
3,4,5,3′,4′-Pentachlorobiphenyl (PCB-126)	Sufficient	Extensive evidence of action via the same aryl hydrocarbon receptor pathway as 2,3,7,8-TCDD	100 (2011)
2,3,4,7,8-Pentachlorodibenzofuran	Sufficient	Extensive evidence of action via the same aryl hydrocarbon receptor pathway as 2,3,7,8-TCDD	100 (2011)
Ultraviolet radiation	Sufficient	Specific C→T transition in human *TP53* in premalignant solar keratosis and skin tumors	100 (2011)

* 2,3,7,8-TCDD has since been classified in Group 1 based on sufficient evidence in humans.

† As with many pharmaceuticals and pesticides, few bioassays are published in the open scientific literature; this precludes a proper evaluation. Only one study, in *Nf1*-knockout mice, was identified.

Acetaldehyde associated with consumption of alcoholic beverages is the first example of a classification based on genetic epidemiological studies of metabolic enzyme activity. Alcohol is metabolized by the enzyme alcohol dehydrogenase to acetaldehyde, which in turn is metabolized by the enzyme aldehyde dehydrogenase. Studies of a polymorphism of aldehyde dehydrogenase showed that populations with a less active form of this enzyme accumulate acetaldehyde and have a substantially higher risk for cancers of the esophagus and of the upper aerodigestive tract (7). The information from genetic epidemiology studies does not fully explain the carcinogenicity of alcoholic beverages. Relationships between internal ethanol and acetaldehyde concentrations and other factors that may contribute to cancers associated with the consumption of alcoholic beverages continue to be explored.

Mechanistic information also aids in the very definition of the agents that are classified. Ingested nitrate or nitrite is probably carcinogenic under conditions that result in endogenous nitrosation, and shiftwork that involves circadian disruption has also been classified as probably carcinogenic (see Table 3). Endogenous

Table 3. Agents that the International Agency for Research on Cancer has classified as probably carcinogenic or possibly carcinogenic to humans and associated cancer sites

Suspected carcinogenic agent	Cancer sites with limited evidence in humans	Volume and year of latest IARC review
Androgenic (anabolic) steroids	Liver; prostate	Sup 7 (1987)
Art glass, glass containers and pressed ware (manufacture of)	Lung	58 (1993)
Biomass fuel (primarily wood), indoor emissions from household combustion of	Lung	95 (2010)
Bischloroethyl nitrosourea (BCNU)	Leukemia	Sup 7 (1987)
Carbon electrode manufacture	Lung	92 (2010)
Carpentry and joinery	Nasal cavity	Sup 7 (1987)
Chloramphenicol	Leukemia	50 (1990)
Alpha-Chlorinated toluenes and benzoyl chloride (combined exposures)	Lung	71 (1999)
Chlorophenoxy herbicides	Several sites	Sup 7 (1987)
4-Chloro-*ortho*-toluidine	Urinary bladder	99 (2010)
Cobalt metal with tungsten carbide	Lung	86 (2006)
Coffee	Urinary bladder; note: some evidence of reduced risk in large bowel	51 (1991)
Creosotes	Skin	92 (2010)
Dry cleaning	Esophagus; urinary bladder	63 (1995)
Engine exhaust, diesel	Lung; urinary bladder	46 (1989)
Frying, emissions from high temperature	Lung	95 (2010)
Hairdressers and barbers (occupational exposure)	Urinary bladder	99 (2010)
Human papillomavirus types 5 and 8 (in patients with *epidermodysplasia verruciformis*)	Skin (nonmelanoma)	100 (2011)
Human papillomavirus types 26, 53, 66, 67, 68, 70, 73, 82	Cervix	100 (2011)
Insecticides, nonarsenical (occupational exposures in spraying and application)	Lung	53 (1991)
Lead compounds, inorganic	Stomach	87 (2006)
Magnetic fields, extremely low frequency	Leukemia, childhood	80 (2002)
Mate drinking, hot	Gastrointestinal tract, upper (esophagus, pharynx, larynx)	51 (1991)
Mitoxantrone	Leukemia (acute myeloid)	76 (2000)
Nitrate or nitrite (ingested) under conditions that result in endogenous nitrosation	Stomach	94 (2010)
Nitrogen mustard	Leukemia; skin	Sup 7 (1987)
Petroleum refining (occupational exposures)	Leukemia; skin	45 (1989)
Pickled vegetables (traditional Asian)	Esophagus; stomach	56 (1993)
Polychlorinated biphenyls	Hepatobiliary tract	Sup 7 (1987)
Polychlorophenols or their sodium salts (combined exposures)	Non-Hodgkin lymphoma; soft tissue sarcoma	71 (1999)
Printing processes	Kidney; lung; oropharynx; urinary bladder	65 (1996)
Schistosoma japonicum	Colorectum; liver	61 (1994)
Shiftwork that involves circadian disruption	Breast	98 (2010)
Styrene	Lymphatic and hematopoietic neoplasms	82 (2002)
Talc-based body powder (perineal use)	Ovary	93 (2010)
Teniposide	Leukemia	76 (2000)
Tetrachloroethylene	Cervix; non-Hodgkin lymphoma; esophagus	63 (1995)
Textile manufacturing	Nasal cavity; urinary bladder	48 (1990)
Trichloroethylene	Liver and biliary tract; non-Hodgkin lymphoma	63 (1995)
Welding fumes	Lung	49 (1990)

nitrosation and circadian disruption mark the first uses of a mechanistic event in the wording of an evaluation statement. It is not hard to envision that further research may lead to evaluations of broader classes of agents that induce endogenous nitrosation or circadian disruption.

More Cancer Sites per Carcinogen

Further research often finds additional cancer sites. Among the 87 agents that had been causally associated with one or more cancer sites before Volume 100 (1), 25 are now associated with additional cancer sites with sufficient evidence and 13 more are associated with new sites with limited evidence (see Table 1). These new findings provide a compelling reason to regard every list of cancer sites as a work in progress, which may be amended if subsequent research provides strong evidence of additional cancer sites.

Some additional cancer sites may be of greater public health importance than the first sites identified for an agent. Alcohol consumption, for example, has been strongly associated with cancers of the liver and upper aerodigestive tract for a long time. Volume 96 (21) added associations with breast cancer and colorectal cancer, two of the most common cancers worldwide in terms of incidence and mortality. Thus, alcohol consumption appears to

Table 4. Preventable exposures associated with human cancers, as identified by the International Agency for Research on Cancer*

Cancer site	Carcinogenic agents with sufficient evidence in humans	Agents with limited evidence in humans
Lip, oral cavity, and pharynx		
Lip		Solar radiation
Oral cavity	Alcoholic beverages; betel quid with tobacco; betel quid without tobacco; human papillomavirus type 16; tobacco, smokeless; tobacco smoking	Human papillomavirus type 18
Salivary gland	X radiation, gamma radiation	Radioiodines, including Iodine-131
Tonsil	Human papillomavirus type 16	
Pharynx	Alcoholic beverages; betel quid with tobacco; human papillomavirus type 16; tobacco smoking	Asbestos (all forms); mate drinking, hot; printing processes; tobacco smoke, secondhand
Nasopharynx	Epstein–Barr virus; formaldehyde; salted fish, Chinese style; wood dust	
Aerodigestive tract, upper	Acetaldehyde associated with consumption of alcoholic beverages	
Digestive organs		
Esophagus	Acetaldehyde associated with consumption of alcoholic beverages; alcoholic beverages; betel quid with tobacco; betel quid without tobacco; tobacco, smokeless; tobacco smoking; X radiation, gamma radiation	Dry cleaning; mate drinking, hot; pickled vegetables (traditional Asian); rubber production industry; tetrachloroethylene
Stomach	*Helicobacter pylori*; rubber production industry; tobacco smoking; X radiation, gamma radiation	Asbestos (all forms); Epstein–Barr virus; lead compounds, inorganic; nitrate or nitrite (ingested) under conditions that result in endogenous nitrosation; pickled vegetables (traditional Asian); salted fish, Chinese style
Colon and rectum	Alcoholic beverages; tobacco smoking; X radiation, gamma radiation	Asbestos (all forms); *Schistosoma japonicum*
Anus	HIV type 1; human papillomavirus type 16	Human papillomavirus types 18, 33
Liver and bile duct	Aflatoxins; alcoholic beverages; *Clonorchis sinensis*; estrogen–progestogen contraceptives; hepatitis B virus; hepatitis C virus; *Opisthorchis viverrini*; plutonium; thorium-232 and its decay products; tobacco smoking (in smokers and smokers' children); vinyl chloride	Androgenic (anabolic) steroids; arsenic and inorganic arsenic compounds; betel quid without tobacco; HIV type 1; polychlorinated biphenyls; *Schistosoma japonicum*; trichloroethylene; X radiation, gamma radiation
Gall bladder	Thorium-232 and its decay products	
Pancreas	Tobacco, smokeless; tobacco smoking	Alcoholic beverages; thorium-232 and its decay products; X radiation, gamma radiation
Digestive tract, unspecified		Radioiodines, including Iodine-131
Respiratory organs		
Nasal cavity and paranasal sinus	Isopropyl alcohol production; leather dust; nickel compounds; radium-226 and its decay products; radium-228 and its decay products; tobacco smoking; wood dust	Carpentry and joinery; chromium (VI) compounds; formaldehyde; textile manufacturing
Larynx	Acid mists, strong inorganic; alcoholic beverages; asbestos (all forms); tobacco smoking	Human papillomavirus type 16; mate drinking, hot; rubber production industry; sulfur mustard; tobacco smoke, secondhand
Lung	Aluminum production; arsenic and inorganic arsenic compounds; asbestos (all forms); beryllium and beryllium compounds; bis(chloromethyl)ether; chloromethyl methyl ether (technical grade); cadmium and cadmium compounds; chromium (VI) compounds; coal, indoor emissions from household combustion; coal gasification; coal tar pitch; coke production; hematite mining (underground); iron and steel founding; MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture); nickel compounds; painting; plutonium; radon-222 and its decay products; rubber production industry; silica dust, crystalline; soot; sulfur mustard; tobacco smoke, secondhand; tobacco smoking; X radiation, gamma radiation	Acid mists, strong inorganic; art glass, glass containers and pressed ware (manufacture of); biomass fuel (primarily wood), indoor emissions from household combustion; carbon electrode manufacture; *alpha*-chlorinated toluenes and benzoyl chloride (combined exposures); cobalt metal with tungsten carbide; creosotes; engine exhaust, diesel; frying, emissions from high-temperature; insecticides, nonarsenical (occupational exposures in spraying and application); printing processes; 2,3,7,8-tetrachlorodibenzo-*para*-dioxin; welding fumes
Bone, skin, and mesothelium, endothelium, and soft tissue		
Bone	Plutonium; radium-224 and its decay products; radium-226 and its decay products; radium-228 and its decay products; X radiation, gamma radiation	Radioiodines, including Iodine-131
Skin (melanoma)	Solar radiation; ultraviolet-emitting tanning devices	

(Table continues)

Table 4 (Continued).

Cancer site	Carcinogenic agents with sufficient evidence in humans	Agents with limited evidence in humans
Skin (other malignant neoplasms)	Arsenic and inorganic arsenic compounds; azathioprine; coal tar distillation; coal tar pitch; cyclosporine; methoxsalen plus ultraviolet A; mineral oils, untreated or mildly treated; shale oils; solar radiation; soot; X radiation, gamma radiation	Creosotes; HIV type 1; human papillomavirus types 5 and 8 (in patients with *epidermodysplasia verruciformis*); nitrogen mustard; petroleum refining (occupational exposures); ultraviolet-emitting tanning devices
Mesothelium (pleura and peritoneum)	Asbestos (all forms); erionite; painting	
Endothelium (Kaposi sarcoma)	HIV type 1; Kaposi sarcoma herpes virus	
Soft tissue		Polychlorophenols or their sodium salts (combined exposures); radioiodines, including Iodine-131; 2,3,7,8-tetrachlorodibenzo-*para*-dioxin
Breast and female genital organs		
Breast	Alcoholic beverages; diethylstilbestrol; estrogen–progestogen contraceptives; estrogen–progestogen menopausal therapy; X radiation, gamma radiation	Estrogen menopausal therapy; ethylene oxide; shiftwork that involves circadian disruption; tobacco smoking
Vulva	Human papillomavirus type 16	HIV type 1; human papillomavirus types 18, 33
Vagina	Diethylstilbestrol (exposure in utero); human papillomavirus type 16	HIV type 1
Uterine cervix	Diethylstilbestrol (exposure in utero); estrogen–progestogen contraceptives; HIV type 1; human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59; tobacco smoking	Human papillomavirus types 26, 53, 66, 67, 68, 70, 73, 82; tetrachloroethylene
Endometrium	Estrogen menopausal therapy; estrogen–progestogen menopausal therapy; tamoxifen	Diethylstilbestrol
Ovary	Asbestos (all forms); estrogen menopausal therapy; tobacco smoking	Talc-based body powder (perineal use); X radiation, gamma radiation
Male genital organs		
Penis	Human papillomavirus type 16	HIV type 1; human papillomavirus type 18
Prostate		Androgenic (anabolic) steroids; arsenic and inorganic arsenic compounds; cadmium and cadmium compounds; rubber production industry; thorium-232 and its decay products; X radiation, gamma radiation
Testis		Diethylstilbestrol (exposure in utero)
Urinary tract		
Kidney	Tobacco smoking; X radiation, gamma radiation	Arsenic and inorganic arsenic compounds; cadmium and cadmium compounds; printing processes
Renal pelvis and ureter	Aristolochic acid, plants containing; phenacetin; phenacetin, analgesic mixtures containing; tobacco smoking	Aristolochic acid
Urinary bladder	Aluminum production; 4-aminobiphenyl; arsenic and inorganic arsenic compounds; auramine production; benzidine; chlornaphazine; cyclophosphamide; magenta production; 2-naphthylamine; painting; rubber production industry; *Schistosoma haematobium*; tobacco smoking; *ortho*-toluidine; X radiation, gamma radiation	4-Chloro-*ortho*-toluidine; coal tar pitch; coffee; dry cleaning; engine exhaust, diesel; hairdressers and barbers (occupational exposure); printing processes; soot; textile manufacturing
Eye, brain, and central nervous system		
Eye	HIV type 1; ultraviolet-emitting tanning devices; welding	Solar radiation
Brain and central nervous system	X radiation, gamma radiation	
Endocrine glands		
Thyroid	Radioiodines, including Iodine-131; X radiation, gamma radiation	
Lymphoid, hematopoietic, and related tissue		
Leukemia and/or lymphoma	Azathioprine; benzene; busulfan; 1,3-butadiene; chlorambucil; cyclophosphamide; cyclosporine; Epstein–Barr virus; etoposide with cisplatin and bleomycin; fission products, including strontium-90; formaldehyde; *Helicobacter pylori*; hepatitis C virus; HIV type 1; human T-cell lymphotropic virus type 1; Kaposi sarcoma herpes virus; melphalan; MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture); phosphorus-32; rubber production industry; semustine (methyl-CCNU); thiotepa; thorium-232 and its decay products; tobacco smoking; treosulfan; X radiation, gamma radiation	Bischloroethyl nitrosourea (BCNU); chloramphenicol; ethylene oxide; etoposide; hepatitis B virus; magnetic fields, extremely low frequency (childhood leukemia); mitoxantrone; nitrogen mustard; painting (childhood leukemia from maternal exposure); petroleum refining (occupational exposures); polychlorophenols or their sodium salts (combined exposures); radioiodines, including Iodine-131; radon-222 and its decay products; styrene; teniposide; tetrachloroethylene; trichloroethylene; 2,3,7,8-tetrachlorodibenzo-*para*-dioxin; tobacco smoking (childhood leukemia in smokers' children)

(Table continues)

Table 4 (Continued).

Cancer site	Carcinogenic agents with sufficient evidence in humans	Agents with limited evidence in humans
Multiple or unspecified sites		
Multiple sites (unspecified)	Cyclosporine; fission products, including strontium-90; X radiation, gamma radiation (exposure in utero)	Chlorophenoxy herbicides; plutonium
All cancer sites (combined)	2,3,7,8-Tetrachlorodibenzo-*para*-dioxin	

* This table does not include factors not covered in the IARC Monographs, notably genetic traits, reproductive status, and some nutritional factors.

contribute substantially more to the worldwide cancer burden than was previously thought (22), although light to moderate alcohol consumption has been associated with some benefits related to heart disease, stroke, and diabetes (benefits that are reversed with occasional or regular heavy drinking) (23).

Another implication of the identification of additional cancer sites is that many agents cause cancer via multiple mechanistic pathways. For example, the recent addition, in Volume 100 (1), of leukemia (particularly myeloid leukemia) as a formaldehyde-associated malignancy has encouraged researchers to investigate a broader range of mechanisms than before, when formaldehyde research was focused on cancers of the upper respiratory tract. Similar implications follow from the new associations between non-Hodgkin lymphoma and hepatitis B and C viruses, which infect hundreds of millions of people worldwide.

Simultaneous consideration of agents that act at the same cancer site can suggest new research hypotheses. For example, does the association of ovarian cancer with talc-based body powder and asbestos suggest that a physical mechanism can induce this cancer in some cases? Is the limited association of hepatitis B virus with non-Hodgkin lymphoma stronger now that there is sufficient evidence of a strong association with hepatitis C virus? Is there a mechanistic pathway to link salted fish consumption and Epstein–Barr virus in the development of nasopharyngeal and stomach cancer because both of these cancers have been associated with both of these agents?

More Sensitive Indications of Carcinogenic Potential

Further research has confirmed carcinogenic potential under conditions of lower exposure. Some old evaluations explicitly restricted their applicability to a small set of high-exposure conditions. For example, IARC's 1973 asbestos classification in Volume 2 (24) was based on studies of miners and millers and explicitly ruled out risks from other exposures. Volume 100 (1), however, cites a growing body of studies that indicate increased risks of lung cancer and mesothelioma from environmental exposures to asbestos. Similarly, the California Environmental Protection Agency restricted its 1988 listing of alcoholic beverages as carcinogenic only "when associated with alcohol abuse" (25). Some subsequent studies, however, have shown that moderate alcohol consumption statistically significantly increases breast cancer risk (22). Even without an explicit restriction, there is sometimes a tendency to recognize carcinogenic potential only in circumstances that have been well studied. For example, IARC's 1988 radon classification in Volume 43 (26) was based on studies of underground miners, and debate ensued about whether radon in homes poses a hazard. Volume 100 (1) finds that studies of residential exposure alone provide sufficient evidence of lung cancer. Similarly, the carcinogenicity of secondhand tobacco smoke was confirmed several decades after the carcinogenicity of tobacco smoke was established in smokers, whereas today it is well accepted [Volume 83; (27)].

These examples suggest that it might be prudent to be more circumspect about statements that limit a cancer hazard only to the high-exposure conditions that have been studied. Although this practice is sometimes defended as describing where the data exist, it can and has delayed recognition of carcinogenic potential in other circumstances. It is difficult for epidemiological studies to detect a cancer hazard when exposures occur mostly at lower levels, such as additives or contaminants of food, water, air, or consumer products. Epidemiological and experimental studies of high-exposure conditions often provide the first evidence of a hazard that applies to lower exposures as well.

A Growing List of New Carcinogens

New research continues to find additional human carcinogens. During the decades ending in 1980, 1990, 2000, and 2010, respectively, there were 23, 27, 24, and 25 agents classified as carcinogenic to humans for the first time, and 11 more were so classified in Volume 100 [(1); see Table 1]. Some designations of new carcinogens were not based on conclusions found first in the Monographs but reflected the expansion of the IARC program to include additional types of agent already known to be carcinogenic. For example, tobacco smoking and alcoholic beverages were evaluated for the first time during 1986–1988, biological agents during 1994–1997, and ionizing radiation during 2000–2001, many decades after these agents had been recognized as human carcinogens.

The diversity of carcinogenic agents that have been identified more recently puts these "bursts" of new classifications in perspective. New carcinogenic agents from Volumes 90–99 (21,28–36) have included 10 additional human papillomavirus types, estrogen–progestogen menopausal therapy, benzo[*a*]pyrene, indoor coal emissions, ethanol in alcoholic beverages, 1,3-butadiene, dyes metabolized to benzidine, 4,4′-methylenebis(2-chloroaniline), and *ortho*-toluidine (see Table 1). Except for indoor coal emissions and ethanol, which had not been evaluated before, these agents had been classified as probably carcinogenic or possibly carcinogenic, indicating that continued research on suspected carcinogens can lead to a more definitive classification.

Estimation of the proportion of the worldwide cancer burden represented by these agents is outside the scope of the IARC Monographs or of this review. Although tobacco, diet, infectious agents, and estrogenic compounds are responsible for a substantial fraction of cancers at some sites, it is also likely that many human carcinogens remain to be identified. This is suggested by the continuing identification of carcinogenic agents throughout the 40-year history of the IARC Monographs, by mechanistic understanding that many cancers are caused by multiple factors acting jointly, and by the large number of probable and possible carcinogens identified by experimental studies. A recent review identified more than 200 chemicals that induce mammary gland tumors in experimental animals (37). Most of these have been classified by IARC as carcinogenic, probably carcinogenic, or possibly carcinogenic to humans, but there were too few women in the epidemiological studies to permit conclusions about their potential to cause breast cancer. Better linkage between experimental results and human carcinogenicity should lead to the identification of human carcinogens on the basis of experimental results.

Some occupations classified as carcinogenic to humans have had subsequent reviews attribute their carcinogenicity to specific chemical or physical agents. These include chromate production and nickel refining, whose carcinogenicity is now attributed to chromium (VI) and nickel compounds, respectively (see Table 1). Other examples are boot and shoe manufacture and repair (respiratory tract cancers are now attributed to leather dust; and leukemia, to benzene), furniture and cabinet making (respiratory cancers from wood dust), and chimney sweeping (lung and skin cancers from soot). These and other occupations should be regarded as carcinogenic to humans whenever there is exposure to the carcinogenic agents identified in those workplaces. Attributing carcinogenicity to specific agents helps national agencies develop regulations to prevent exposure to these agents wherever they are found, in the workplace or in the general environment.

Remaining Research Needs

Some common human cancers have few (or no) identified causal agents. There are wide disparities in the number of agents that are causally associated with the more common human cancers (see Table 4). In 2008, the 10 most frequent cancers worldwide (in both sexes combined) were cancers of the breast, prostate, lung, colorectum, cervix, stomach, liver, uterus, esophagus, and ovary (38). For several of these cancer sites, only a few causal factors have been identified, and none has been found for prostate cancer. A few less-prevalent cancers do not appear in these tables, for example, those of the small intestine, thymus, heart, and endocrine glands other than the thyroid and salivary glands. There is a need for etiological research to identify additional causal factors for common and uncommon human cancers.

Future Directions

IARC's review of human carcinogens, to be published in six parts in 2011(1), will include full Monographs on the more than 100 agents classified by IARC as carcinogenic to humans. These Monographs critically review the epidemiological studies, cancer bioassays in animals, and information on toxicokinetics and mechanisms of carcinogenesis.

Subsequent workshops will synthesize this information for related scientific publications. An analysis of tumor concordance between humans and experimental animals will explore the predictive value of animal tumors and identify human cancers for which currently there are not good animal models. This analysis could encourage development of predictive mechanistic models for these cancers. A review of mechanisms involved in human carcinogenesis will synthesize information on mechanistic events that are known to be or likely to be involved in human carcinogenesis. It will also suggest populations and developmental stages that may be especially susceptible to certain mechanistic events, as well as identify biomarkers that could be incorporated into future epidemiological study designs. The ultimate objective is to facilitate the identification of carcinogens based on mechanistic information in the absence of cancer studies in animals or in humans.

Every Group 1 agent can be considered to represent cancers that might have been prevented had scientists been able to predict cancer hazards earlier or had public health authorities been willing to act more quickly when scientific information became available. Volume 100 (1) of the IARC Monographs will be a bridge from epidemiological studies that identify carcinogens after decades of human exposure to experimental studies that can screen suspected carcinogens before humans are exposed. The information in this article, together with the more detailed Monographs that IARC will publish in Volume 100, should stimulate researchers worldwide to create links between epidemiological and experimental results and lead to more rapid and more confident identification of carcinogens.

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Notes

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