Special Report: Policy

A review of human carcinogens—Part F: Chemical agents and related occupations

In October, 2009, 23 scientists from six countries met at the International Agency for Research on Cancer (IARC) to reassess the carcinogenicity of several chemical and occupational exposure circumstances previously classified as "carcinogenic to humans" (Group 1) and to identify additional tumour sites and mechanisms of carcinogenesis (table). These assessments will be published as the sixth and last part of Volume 100 of the IARC Monographs.[1]

Four aromatic amines and two related industrial processes were reaffirmed as Group-1 carcinogens based on sufficient evidence that they cause urinary bladder cancer in humans. The Group-1 classification of dyes metabolised to benzidine and of 4,4′-methylenebis(2-chloroaniline) was based on sufficient evidence in animal models and strong mechanistic evidence.[2]

Exposure to polycyclic aromatic hydrocarbons (PAHs) causes cancers of the skin and lung in humans. Various PAH-related industries and PAH-containing complex mixtures were confirmed as Group-1 carcinogens. Although there are no epidemiological studies of benzo[a]pyrene, carcinogenicity in many animal species and strong mechanistic evidence justified its classification in Group 1.[3]

The carcinogenicity to humans of other chemicals and exposure scenarios was reaffirmed (table). For ethylene oxide, the epidemiological evidence was limited, but there is sufficient evidence for its carcinogenicity in rodents. Additionally, ethylene oxide is genotoxic and mutagenic in many in-vitro tests and in-vivo studies in animals, and its cytogenetic effects in lymphocytes of exposed workers provided strong support for its classification in Group 1.[4]

Workers in the rubber-manufacturing industry have an increased risk for leukaemia, lymphoma, and cancers of the urinary bladder, lung, and stomach. Due to the diversity and complexity of the exposures in this industry, it is difficult to identify causative agents, but there is strong evidence of genotoxic effects in these workers.[5]

The Working Group reviewed more than 100 epidemiological studies of benzene and confirmed its carcinogenicity, with sufficient evidence for ANLL, and limited evidence for ALL, CLL, MM, and NHL (for abbreviations, see table footnote). The Working Group also found limited evidence of an association between maternal exposure to painting—before and during pregnancy—and an increased risk of childhood leukaemia in the offspring.

Dioxin (2,3,7,8-tetrachlorodibenzo-*para*-dioxin, TCDD) was classified in Group 1 in 1997, based on limited evidence of carcinogenicity in humans,

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	Tumour sites or types with sufficient evidence in humans	Tumour sites or types with limited evidence in humans	Evidence of genotoxicity as the main mechanism
Aromatic amines			
4-Aminobiphenyl	Urinary bladder	..	Strong
Benzidine	Urinary bladder	..	Strong
Dyes metabolised to benzidine	..	..	Strong*
4,4′-Methylenebis(2-chloroaniline)	..	..	Strong*
2-Naphthylamine	Urinary bladder	..	Strong
Ortho-toluidine	Urinary bladder	..	Moderate
Auramine production	Urinary bladder	..	Weak/lack of data†
Magenta production	Urinary bladder	..	Weak/lack of data†
PAH-related exposures			
Benzo[a]pyrene	..	..	Strong*
Soot (chimney sweeping)	Skin, lung	Urinary bladder	Moderate
Coal gasification	Lung	..	Strong
Coal-tar distillation	Skin	..	Strong
Coke production	Lung	..	Strong
Coal-tar pitches (paving, roofing)	Lung	Urinary bladder	Strong
Aluminium production	Lung, urinary bladder	..	Weak/moderate†‡
Other chemicals			
Aflatoxins	Hepatocellular carcinoma	..	Strong
Benzene	ANLL	ALL**, CLL**, MM**, NHL**	Strong
Bis(chloromethyl)ether/chloromethyl methylether	Lung	..	Moderate/strong
1,3-Butadiene	Haematolymphatic organs	..	Strong
Dioxin (2,3,7,8-TCDD)	All cancers combined**	Lung, STS, NHL	See text§
2,3,4,7,8-Pentachlorodibenzofuran	..	..	See text*§
3,3′,4,4′,5-Pentachlorobiphenyl (PCB-126)	..	..	See text*§
Ethylene oxide	..	Lymphoid tumours (NHL, MM, CLL), breast	Strong*
Formaldehyde	Nasopharynx Leukaemia¶**	Sinonasal cancer	Strong Moderate
Sulfur mustard	Lung	Larynx	Strong
Vinyl chloride	Hepatic angiosarcoma, hepatocellular carcinoma	..	Strong

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	Tumour sites or types with sufficient evidence in humans	Tumour sites or types with limited evidence in humans	Evidence of genotoxicity as the main mechanism
(Continued from previous page)			
Other complex exposures			
Iron and steel founding	Lung	..	Weak/moderate
Isopropyl alcohol manufacture using strong acids	Nasal cavity	..	Weak/lack of data
Mineral oils	Skin	..	Weak/lack of data
Occupational exposure as a painter	Lung, urinary bladder, pleural mesothelioma	Childhood leukaemia‖	Strong‡
Rubber-manufacturing industry	Leukaemia, lymphoma**, urinary bladder, lung**, stomach**	Prostate, larynx, oesophagus	Strong‡
Shale oils	Skin	..	Weak/lack of data
Strong inorganic acid mists	Larynx	Lung	Weak/lack of data

ANLL=acute non-lymphocytic leukaemia. ALL=acute lymphocytic leukaemia. CLL=chronic lymphocytic leukaemia. MM=multiple myeloma. NHL=non-Hodgkin lymphoma. STS=soft-tissue sarcoma. *Agents classified in Group 1 on the basis of mechanistic information. †Weak evidence in workers, but strong evidence for some chemicals in this industry. ‡Due to the diversity and complexity of these exposures, other mechanisms may also be relevant. §Strong evidence for an aryl hydrocarbon receptor (AhR)-mediated mechanism. ¶Particularly myeloid leukaemia. ‖After maternal exposure (before or during pregnancy, or both). **New epidemiological findings.

Table: **Evidence for carcinogenicity in humans and for genotoxicity as the main mechanism of the Group-1 agents assessed**

sufficient evidence in rodents, and strong evidence in humans and animals for a mechanism via initial binding to the aryl hydrocarbon receptor (AhR), which leads to changes in gene expression, cell replication, and apoptosis.[6] There is now sufficient epidemiological evidence for all cancers combined, making TCDD the first agent classified initially in Group 1 based on sufficient animal data and mechanisms, to be later confirmed by increased cancer incidence in humans. This highlights the ability of mechanistic information to provide robust evidence of carcinogenicity.

Like TCDD, 2,3,4,7,8-pentachlorodibenzofuran and 3,3',4,4',5-pentachlorobiphenyl (PCB-126) are complete carcinogens in experimental animals,[7,8] and there is extensive evidence that they act through the same AhR-mediated mechanism. The Working Group classified these two chemicals in Group 1.

The Working Group unanimously reaffirmed the classification of formaldehyde in Group 1, based on sufficient evidence in humans of nasopharyngeal cancer. A possible association with leukaemia was previously considered "strong but not sufficient",[9] because of the lack of a plausible mechanism. The epidemiological evidence has become stronger: a recent study[10] found that embalming was significantly associated with an increased risk for myeloid leukaemia, with significant trends for cumulative years of embalming (p_{trend}=0·020) and for increasing peak formaldehyde exposure (p_{trend}=0·036). In addition, a recent study[11] of a small group of exposed workers showed numerical chromosomal aberrations in myeloid progenitor cells (chromosome 7 monosomy, chromosome 8 trisomy) consistent with myeloid leukaemia, and haematological changes in peripheral blood that are indicative of effects on the bone marrow. The Working Group concluded that, overall, there is sufficient evidence for leukaemia, particularly myeloid leukaemia.

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Conflicts of interest
BDG is a consultant on toxic tort cases involving benzene. MTS has received consulting and expert testimony fees from law firms representing both plantiffs and defendants in cases involving exposure to benzene and consulting fees from government agencies assessing the health risks associated with benzene exposure. The other Monograph Working Group Members declared no conflicts of interest.

Invited Specialists
None

The IARC authors declared no conflicts of interests. Attending the meeting as Representatives were E Pasquier (French Agency for Environmental and Occupational Health and Safety [AFSSET]), A Huici-Montagud (European Commission Directorate General for Employment, Social Affairs and Equal Opportunities), and D DeVoney (US Environmental Protection Agency). Attending the meeting as Observers were M G Bird (ExxonMobil Corp, USA), A Bracco (European Tyre and Rubber Manufacturers' Association, Belgium), J Collins (Formaldehyde Council, USA), P Crosignani (International Society of Doctors for the Environment, Switzerland), S Gabriel (German Social Accident Insurance BGIA, Germany), P Gelbke (European Chemical Industry Council CEFIC, Belgium), P Infante (private consultant, USA), R J Lewis (International Institute of Synthetic Rubber Producers, USA), K Mundt (International Paint and Printing Ink Council, USA), and G Swaen (American Chemistry Council and American Petroleum Institute, USA; CONCAWE and ECETOC, Belgium).

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ED_002435_00003559-00002