Carcinogenicity of benzene

In October, 2017, a Working Group of 27 scientists from 13 countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to finalise their evaluation of the carcinogenicity of benzene. This assessment will be published in Volume 120 of the *IARC Monographs*.[1]

Benzene, an aromatic hydrocarbon, is a ubiquitous air pollutant, arising mostly from anthropogenic sources, notably combustion. It is a component of gasoline, vehicle exhaust, industrial emissions, and tobacco smoke, and was used historically as a solvent in industry and consumer products. The uses of benzene as a solvent are now restricted in many countries, but it is still produced in high volumes for use primarily as a chemical intermediate. Occupational exposure to benzene can occur in diverse industries, including petroleum, chemical production, and manufacturing, and in some countries still occurs in industries where high levels were observed historically, such as shoemaking, painting, printing, and rubber manufacturing. The population at large can be exposed to benzene in polluted air and water and through the use of benzene-containing products. Benzene concentrations in workplace and outdoor air have declined over time; the Working Group noted concentrations less than 3·00 and 0·005 mg/m^3 in workplace and outdoor air, respectively, in high-income countries, but higher levels have been reported in some low-income and middle-income countries.

Benzene has been classified as carcinogenic to humans (IARC group 1) since 1979, on the basis of sufficient evidence that it causes leukaemia.[2] This evaluation was reaffirmed specifically for acute myeloid leukaemia (AML) and acute non-lymphocytic leukaemia in 2009;[3] positive associations with acute lymphocytic leukaemia, chronic lymphocytic leukaemia, multiple myeloma, and non-Hodgkin lymphoma were also recognised at that time. The present evaluation was undertaken to review new epidemiological and mechanistic evidence as well as to explore the potential to characterise quantitative relationships for cancer risk and for biological endpoints related to cancer mechanisms.

The current Working Group confirmed the carcinogenicity of benzene on the basis of sufficient evidence in humans, sufficient evidence in experimental animals, and strong mechanistic evidence. The Working Group focussed its review of epidemiological studies on those in which occupational or environmental exposure to benzene was specifically identified. Important new evidence came from several large occupational cohort studies.[4–6] In adult humans, benzene causes acute non-lymphocytic leukaemia, including AML. The previous observations of limited evidence for chronic lymphocytic leukaemia, multiple myeloma, and non-Hodgkin lymphoma were also confirmed. New data were also available from several recent studies that showed positive associations between AML in children and environmental exposure to benzene.[7,8] Positive associations with exposure to benzene were also observed for chronic myeloid leukaemia and for lung cancer in several studies. Small minorities of the Working Group concluded that the evidence of carcinogenicity was inadequate for lung cancer and sufficient for non-Hodgkin lymphoma.

In male and female mice, several whole-body inhalation studies (eg, the study by Farris and colleagues[9]) reported the induction of tumours of the haematopoietic and lymphoid tissues, Zymbal gland carcinoma, squamous cell carcinoma of the preputial gland, forestomach squamous cell carcinoma, and lung adenoma. There were four oral administration studies (by gavage; eg, studies by The National Toxicity Program[10] and Maltoni and colleagues[11]) and two intraperitoneal injection studies in male and female mice. The oral administration studies reported the induction of tumours of the haematopoietic and lymphoid tissues, lung alveolar or bronchiolar adenoma and carcinoma, hepatocellular adenoma and carcinoma, squamous cell carcinoma of the Zymbal gland, adenoma and carcinoma of the Harderian gland, preputial gland carcinoma, ovarian tumours, malignant mammary gland tumours in females only, forestomach squamous cell tumours, and pheochromocytoma of the adrenal gland. In one intraperitoneal injection study, the offspring of injected dams developed liver tumours and tumours of the haematopoietic and lymphoid tissues.[12]

Four oral administration studies (by gavage) in male and female rats,[10,11] and one whole-body inhalation study in pregnant female rats and their male and female offspring[11] have been published. Benzene caused tumours of the haematopoietic and lymphoid tissues, Zymbal gland carcinoma, oral cavity squamous cell carcinoma, and forestomach carcinoma in situ in gavage studies and in the offspring after inhalation. Hepatocellular carcinomas were induced in offspring in the inhalation study, and skin carcinoma and endometrial stromal polyps were induced in gavage studies.

In several studies using three different genetically modified mouse models of different genetic backgrounds, benzene induced tumours of the haematopoietic and lymphoid tissues by oral administration, whole-body inhalation, or skin application; benzene also caused sarcomas of the subcutis in one oral administration study and skin papillomas in two skin application studies.

Benzene is easily absorbed, widely distributed, and extensively metabolised, yielding a complexity

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The Working Group Members declare no competing interests.

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of reactive electrophiles via multiple metabolic pathways in various tissues, including bone marrow. It exhibits many of the key characteristics of carcinogens.[13] In particular, strong evidence, including in exposed humans, shows that benzene is metabolically activated, induces oxidative stress, is genotoxic, is immunosuppressive, and causes haematotoxicity. In addition, strong evidence from experimental studies shows that benzene causes genomic instability, inhibiting topoisomerase II; modulates receptor-mediated effects relevant to aryl hydrocarbon receptor, and induces apoptosis.

In benzene-exposed humans, epoxide-protein and benzoquinone-protein adducts are formed in blood. Additionally, benzene induces oxidative stress in exposed humans, human cells, and mouse bone marrow. In studies of occupationally exposed humans, benzene induces oxidative DNA damage, DNA strand breaks, gene mutations, chromosomal aberrations, and micronuclei. Specific cytogenetic changes induced in exposed humans include aneuploidy, translocations, and various other structural chromosome changes. In the bone marrow of experimental animals exposed in vivo, benzene induces DNA adducts, chromosomal aberrations, and micronuclei. Similarly, in human cells in vitro, benzene or its metabolites induce DNA adducts, DNA damage, and chromosomal aberrations.

Many studies in exposed humans have demonstrated haematotoxicity, ranging from decreased white blood cell counts at lower exposures to aplastic anaemia and pancytopenia at higher exposures. Benzene-induced haematotoxicity is associated with future risk of developing haematological malignancy or related disorders. Although no human studies of benzene exposure directly examined changes in immune function, multiple experimental animal studies demonstrate haematotoxicity and consistent immunosuppressive effects on humoural and cell-mediated functional assays.

The Working Group investigated the shape and slope of the exposure–response function for AML in metaregression analyses of six published occupational cohort studies with suitable data. The relationship of benzene exposure with the log relative-risk was well described by a linear model. The slope was moderately sensitive to whether a cohort study of rubber hydrochloride workers, which had the highest exposure estimates, was included in the model. In the majority of human studies that reported exposure–response information for benzene and endpoints relevant to the key characteristics of carcinogens (ie, micronuclei,[14] chromosomal aberrations,[15] and leukocyte counts,[16] an exposure–response gradient was reported.

We declare no competing interests.

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