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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

GENERAL REMARKS

This one-hundred-and-twentieth volume of the *IARC Monographs* presents an evaluation of the carcinogenic hazard to humans of exposure to benzene.

The conclusions of this volume represent the sixth evaluation of the carcinogenicity of benzene by an *IARC Monographs* Working Group. Successive evaluations published in Volumes 7 (IARC, 1974), 29 (IARC, 1982), and 100F (IARC, 2012) and Supplements 1 (IARC, 1979) and 7 (IARC, 1987) considered progressively larger and more complex volumes of data and yielded consistent, yet steadily broader and more compelling, conclusions about the carcinogenicity of benzene.

The available data were sparse at the time of the first evaluation (IARC, 1974). The Working Group determined that the available evidence from studies of experimental animals did not permit a conclusion to be drawn, but found suggestive evidence from epidemiological case reports and one case–control study that benzene causes leukaemia in humans; the current system of formal classifications of evidence had not yet been introduced at that time (it was introduced in Volume 17). Benzene was reviewed again in Supplement 1, which updated Volumes 1–20. With formal classifications then in place, the evidence in experimental animals was found to be *inadequate*, and the human epidemiological evidence, now supplemented by several occupational cohort studies and case–control studies in addition to case reports, was found to be *sufficient*. In the overall evaluation, benzene was found to be *carcinogenic to humans* (Group 1), a finding that has stood since that time.

Additional data had become available when benzene was reviewed again for Volume 29 (IARC, 1982). The Working Group now found the evidence in experimental animals to be *limited* and concluded that the modestly expanded epidemiological evidence established a causal relationship between exposure to benzene and development of acute myeloid leukaemia.

With further growth of the database during the 1980s, the evidence in experimental animals was found to be *sufficient* when benzene was evaluated again for Supplement 7 (IARC, 1987). Although mechanistic evidence was not yet formally incorporated into overall evaluations at that time, induction of chromosomal aberrations in exposed humans and of chromosomal aberrations and micronuclei in rodents was also noted in the summary report.

The volume of evidence had grown substantially larger and more complex by 2009, when the evaluation of benzene was updated for Volume 100F (IARC, 2012). The Working Group confirmed the previous findings of *sufficient evidence* of carcinogenicity in humans and experimental animals and, for the first time, presented *strong evidence* of multiple genotoxic effects based on a review of extensive mechanistic data. In humans, the Working Group concluded

that benzene causes acute myeloid leukaemia/acute non-lymphocytic leukaemia (both terms were used in epidemiological studies reviewed in that volume) and found *limited* evidence that benzene causes acute lymphocytic leukaemia, chronic lymphocytic leukaemia, non-Hodgkin lymphoma, and multiple myeloma.

The current evaluation was undertaken with two principal goals: (i) to incorporate new epidemiological and experimental evidence, including a large number of mechanistic studies in exposed humans, and (ii) to assess quantitative exposure–response relationships of exposure to benzene with both human cancer risks and relevant biological end-points in exposed humans. Such quantitative evaluations were recommended as an adjunct to future *Monographs* by an Advisory Group on quantitative risk characterization (IARC, 2014).

In the current evaluation, the Working Group again confirmed the carcinogenicity of benzene based on *sufficient evidence* of carcinogenicity in humans, *sufficient evidence* of carcinogenicity in experimental animals, and *strong* mechanistic evidence. The Working Group's evaluation of the accumulated evidence from human epidemiological studies focused on studies in which occupational or environmental exposure to benzene was specifically identified. The findings fully supported the previous conclusion that benzene causes acute non-lymphocytic leukaemia – including acute myeloid leukaemia – in adults, as well as the previous observations of *limited evidence* for chronic lymphocytic leukaemia, non-Hodgkin lymphoma, and multiple myeloma. On the basis of new data available since the last review, the Working Group also found *limited* evidence that benzene causes chronic myeloid leukaemia and lung cancer, and acute myeloid leukaemia in children. The Working Group's review of the large body of mechanistic studies took into account the key characteristics of carcinogens (Smith et al., 2016). The Working Group affirmed the *strong evidence* that benzene is genotoxic, and found that it also exhibits many other key characteristics of carcinogens, including in exposed humans. In particular, benzene is metabolically activated to electrophilic metabolites; induces oxidative stress and associated oxidative damage to DNA; is genotoxic; alters DNA repair or causes genomic instability; is immunosuppressive; alters cell proliferation, cell death, or nutrient supply; and modulates receptor-mediated effects.

The evidence reviewed for this evaluation, the Working Group's conclusions, and their analysis of exposure–response relationships are detailed in this volume. A summary of the key findings has appeared in *The Lancet Oncology* (Loomis et al., 2017).

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