USE OF MECHANISTIC EVIDENCE FROM OCCUPATIONAL STUDIES IN CANCER HAZARD IDENTIFICATION: THE EXPERIENCE OF THE IARC MONOGRAPHS PROGRAMME

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Over the past 50 years, the Monographs Programme of the International Agency for Research on Cancer (IARC) has evaluated the potential carcinogenic hazard of more than 1000 agents. Through 129 volumes, 121 agents have been classified as ‘carcinogenic’ (Group 1), 89 as ‘probably carcinogenic’ (Group 2A), 318 as ‘possibly carcinogenic’ (Group 2B), and 499 as ‘not classifiable as to carcinogenicity’ (Group 3). Many Group 1 agents derived their ‘sufficient evidence of cancer in humans’ from studies of exposed workers. Since 1991, it has been possible to classify an agent in Group 1 based on strong mechanistic evidence in exposed humans and sufficient evidence from cancer bioassays when human cancer evidence was less-than-sufficient. In the recently revised Preamble for the IARC Monographs, mechanistic evidence has gained increased prominence as an individual evidence stream, reflecting advances in mechanistic toxicology and molecular epidemiology. The Preamble revision introduces new possibilities for carcinogen identification from robust mechanistic studies in exposed humans. Specifically, strong evidence that an agent exhibits ‘key characteristics’ (KCs) of carcinogens in exposed humans can lead explicitly to a Group 2A evaluation when evidence of cancer in humans is limited. Further, classification in Group 2B can be based on strong evidence of KCs in exposed humans alone. Thus, especially for agents for which cancer studies in experimental systems are impracticable (e.g., work as a firefighter), mechanistic studies in exposed humans can increasingly play a crucial role in cancer hazard identification. We will address critical aspects of study design, exposure assessment, and KC-related endpoints anticipated to be influential in future Monographs evaluations of mechanistic studies.