

GENERAL REMARKS ON THE SUBSTANCES CONSIDERED

This eighty-eighth volume of *IARC Monographs* evaluates the available evidence on the carcinogenic potential in humans of formaldehyde, 2-butoxyethanol and 1-*tert*-butoxypropan-2-ol. Formaldehyde, a potential carcinogen that is found in the workplace and in the environment, has been studied the most widely and has been evaluated three times previously. In Volume 29 (IARC, 1982), the experimental animal data were evaluated as having *sufficient evidence* and the epidemiological studies as having *inadequate evidence* of carcinogenicity. In Supplement 7 (IARC, 1987), these data were updated and an overall evaluation was made that formaldehyde is *probably carcinogenic to humans* (Group 2A), based on *limited evidence* of carcinogenicity from studies in humans and *sufficient evidence* of carcinogenicity from studies in experimental animals. Formaldehyde was reconsidered again in Volume 62 (IARC, 1995), when the existing classification was reaffirmed. It is being re-evaluated this time following a recommendation from an Advisory Group (IARC, 2003) that identified formaldehyde as a high priority for future re-evaluation, based on the availability of complex mechanistic data and the anticipated publication of new epidemiological studies that became available soon afterwards. The same Advisory Group also identified 2-butoxyethanol and other glycol ethers as high priorities, based on the availability of new carcinogenesis bioassays conducted by the US National Toxicology Program. This is the first evaluation that IARC has made of the two glycol ethers.

A theme common to these three evaluations is the consideration of mechanistic information to develop and evaluate hypotheses on the sequence of steps that lead to the induction of tumours in experimental animals. The hypothesized mechanisms described in this volume provide an interesting set of cases that range from a vast literature on respiratory tract tumours in rats induced by the inhalation of formaldehyde to some more tentative hypotheses on the various tumours observed in animals following exposure to glycol ethers. Both types of mechanistic datasets were of use in the evaluation process.

This evaluation emphasizes the importance of mechanistic information in the classification of carcinogens. For example, the Working Group considered the extensive scientific database on the mechanisms by which formaldehyde can induce cancer in humans. The extensive mechanistic data for formaldehyde-induced respiratory cancer provide strong support for the empirical observation of nasopharyngeal cancer in humans. In contrast, the lack of such information on possible mechanisms by which formaldehyde

might increase the risk for leukaemia in humans tempered the interpretation of the epidemiological data on that cancer.

The evaluations in this volume also reveal that the Working Group grappled with questions of interpretation and scientific judgement. A recurring issue was the criteria that characterize a rare tumour or an unusual set of observations that can carry greater weight than a typical bioassay result. Another issue was how to introduce additional information to resolve difficult questions; for example, how to consider the results of historical controls or alternative statistical tests. When the Working Group tried to, but could not reach, consensus on a question of interpretation or scientific judgement, the evaluation presents the differing positions favoured by its members.

Although the *IARC Monographs* focus on a qualitative assessment of the carcinogenic potential of an agent, subsequent predictions of the risks for cancer from formaldehyde could consider pertinent information on mechanisms of carcinogenesis, including dose-dependent cytotoxicity and genotoxicity. Information on human biomarkers may facilitate a comparison of the relative susceptibility of animals and humans, as well as describe the variation in the susceptibility of different human populations.

It is important to note that an evaluation of an agent as *not classifiable as to its carcinogenicity to humans* is not a determination of safety, with respect to both cancer and effects other than cancer. Rather, it can indicate the need for further testing and information, particularly when there is widespread human exposure or another reason for public health concern. In these cases, it is important that investigators who represent different scientific disciplines and perspectives conduct further research.

References

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