

# Recent Publications

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## **The evaluation of carcinogenic risks: selected pharmaceuticals**

Toxicological data established in animal models serve as the unique but decidedly uncertain basis for predicting the safety of candidate drugs for human use. Any doubts about the relevance of short-term dose-related animal toxicity demonstrated in a promising compound are almost immediately resolved during the course of initial dose-ranging studies in humans. However, no information will emerge, until long after a successfully-developed compound has been marketed, that can either confirm or refute the relevance of positive findings in experimental mutagenicity or carcinogenicity studies.

New drugs, and particularly those that are destined to be administered for prolonged periods, enter into routine use on the basis of their projected risks and their observed benefits. This implies a mandatory need for open-ended assessment of longer-term risks. Since 1969, this need has been satisfied with respect to carcinogenicity by the Monographs Programme of the International Agency for Research on Cancer (IARC) on the evaluation of carcinogenic risks to humans. The programme is broadly based since it covers, in addition to individual chemicals, hazards related to complex environmental and occupational exposures and to other agents including radiation and viruses. However, the 50th volume of this series, which has just been published, is concerned exclusively with drugs.

The objective of the programme is to prepare, with the help of an international working group of experts, critical reviews and evaluations of evidence on the carcinogenicity of specific exposures with the primary purpose of assisting national and international authorities in making risk assessments and in formulating decisions concerning necessary preventive measures. The topics — in this instance, drug substances — are selected on the basis of two criteria: well-defined human exposure and some evidence or suspicion of carcinogenicity.

The current volume comprises monographs on five antineoplastic agents, four antimicrobial agents (ampicillin, chloramphenicol, nitrofurantoin and nitrofurantoin), two diuretics (furosemide and hydrochlorothiazide), cimetidine, paracetamol and dantron (a laxative). For a high proportion of these substances insufficient evidence is as yet available to enable a definitive judgement to be made. But when the working group considers that the facts warrant a positive conclusion, the decision is unequivocally expressed.

It comes as no surprise to find that most of the selected cytostatic agents are "probably" carcinogenic in humans. Of greater moment is the decision to categorize the immunosuppressive agent, ciclosporin, unambiguously as carcinogenic. A high incidence of lymphoma has now been recorded in each of four prospective cohort studies of organ transplant recipients and, in some instances, regression of the tumour has followed withdrawal of the drug. Ciclosporin is used extensively in the prevention and treatment of graft-versus-host reactions in bone-marrow transplantation, and for preventing the rejection of kidney, heart and liver transplants. It is also being used in a more exploratory context in the management of many chronic non-malignant conditions in which immunological factors may have a pathogenetic role. Its carcinogenic potential clearly needs to be weighed in the balance before definitive decisions are taken regarding its place in the broader spectrum of medicine.

The IARC monographs are already widely used by governments and regulatory bodies. They would reach a far wider audience of interested professionals if they were to be made available in a less cumbersome form. They would slip very conveniently into a CD-ROM. We look forward to a decision to produce them in electronic format.

*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 50 — Pharmaceutical Drugs.* International Agency for Research on Cancer, Lyon, France, 1990.