GENERAL REMARKS ON THE SUBSTANCES CONSIDERED

This sixty-sixth volume of *IARC Monographs* comprises evaluations on a number of pharmaceutical drugs. Pharmaceutical drugs were considered previously in Volumes 13, 24 and 50 and Supplement 7 of the *Monographs* series (IARC, 1977, 1980, 1987, 1990). Several of the compounds — diazepam, oxazepam, clofibrate and phenytoin — have been evaluated by previous working groups. All available relevant data including mechanistic data on these compounds are included in the new evaluations. The primary objective of the evaluation process in *IARC Monographs* is hazard or risk identification, although protective effects on cancer occurrence, where pertinent, have been mentioned in the monographs.

Several of the pharmaceuticals considered in this volume are benzodiazepines or benzodiazepine analogues. This class of drugs has been extensively prescribed since the late 1950s for the treatment of anxiety and as sedatives or anticonvulsants, and for other conditions. The specific drugs of this type considered in this volume are *diazepam*, *doxefazepam*, *estazolam*, *oxazepam*, *prazepam*, *ripazepam* and *temazepam*. In addition, a diphenylhydantoin, *phenytoin*, which is another anticonvulsant, was evaluated in this volume.

Three triphenylethylene antioestrogenic drugs were considered that are at various stages of development: *tamoxifen* has been used extensively since the early 1980s, *toremifene* is just being introduced and *droloxifene* is under development for the treatment of breast cancer.

Clofibrate and *gemfibrozil* are cholesterol-lowering drugs that have been used in the treatment of patients at high risk for cardiovascular disease.

Pharmaceutical drugs, in contrast to industrial chemicals or environmental contaminants, are designed to have pharmacological properties which are beneficial. Decisions on the appropriate use of these compounds may involve risk/benefit considerations that go beyond the scope of the *Monographs* programme. It is important to note that pharmaceutical agents are developed and used because of their beneficial biological properties. Sometimes, these biological properties could be also responsible for increased risk of certain diseases including cancer.

The circumstances, magnitude and routes of human exposure for pharmaceuticals are usually easier to evaluate than for environmental or occupational agents. Thus, exposure–response relationships for pharmaceuticals often have more precision. Nevertheless, there are many complicating factors for pharmaceuticals that were considered by the Working Group. A unique feature of the data available on pharmaceuticals is that there is a wealth of information on pharmacokinetic and pharmacodynamic effects in humans obtained in well-controlled studies.

Considerable attention was given to the monograph sections on 'Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms'. Of particular interest are the mechanistic underpinnings responsible for significant cancer findings in experimental and epidemiological studies. Although complete knowledge of the mechanism of carcinogenicity of pharmaceuticals is difficult to attain, we can discern, in some cases, the mode of action. This information can lead to biologically-based comparisons which are essential for determining how best to use experimental data in identifying human risks. Comparative data on metabolism, interactions with critical cellular targets (DNA adducts, receptor binding), alterations in gene structure and expression and early tissue responses such as cell proliferation can be especially helpful in strengthening the scientific basis for overall evaluations of carcinogenic risk. Confidence in evaluations is enhanced when there is sound scientific information available from several levels: exposure, animal toxicity and cancer studies, clinical and epidemiological studies and some knowledge of mechanism derived from human, experimental animal and isolated cell systems.

Worldwide, diazepam is the most widely prescribed of the benzodiazepines. For this reason, nearly all studies on the carcinogenicity in humans of the seven benzodiazepines evaluated relate to diazepam. For the others, the evaluation of carcinogenic risk had to rest solely on cancer studies in animals. The drugs that were associated with tumours in animals generally increased only the incidence of rodent liver tumours, a response whose significance to human risk is not clear. Moreover, these effects generally occurred at exposures of the rodents well above the human therapeutic doses. Information from mechanistic studies indicated that these drugs are non-genotoxic and that, if carcinogenic, they operate through a promoting mechanism. Information from human studies to fully evaluate the likelihood that this mechanism will occur in humans was unfortunately lacking.

There were several reports indicating that tamoxifen is a potential hazard in increasing the risk of endometrial cancer. Tamoxifen is recognized as one of the most effective drugs for the treatment of breast cancer and is one of a small group of pharmaceuticals recognized by the World Health Organization as an essential drug for this disease (WHO, 1994). It is currently being evaluated in a number of chemoprevention trials to determine whether it reduces the incidence of breast cancer in otherwise healthy women judged to be at increased risk for development of breast cancer. The Working Group reviewed all the published scientific data on second primary tumours reported in patients who had been treated with tamoxifen for breast cancer. The group further weighed the evidence for carcinogenic effects of tamoxifen in experimental animals, and evaluated possible biological mechanisms of carcinogenesis. It was the totality of the evidence that had to be considered by the Working Group in reaching their final evaluation.

Clofibrate and gemfibrozil, in addition to their therapeutic effects, cause peroxisome proliferation and neoplasia in the livers of rats and mice. All data on exposure and studies of cancer in humans and experimental animals were evaluated. Furthermore, all other data relevant to mechanisms of carcinogenesis were evaluated. Specifically, data were considered, on a case-by-case basis, with regard to (a) the potential for any liver

tumour response in mice or rats to be secondary to peroxisome proliferation and (b) the potential for those effects to be observed in humans. The role of peroxisome proliferation and hepatocellular proliferation induced by chemicals such as the fibrate drugs in the development of hepatic cancer was recently addressed by an IARC Working Group (IARC, 1995).

References

IARC (1977) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 13, *Some Miscellaneous Pharmaceutical Substances*, Lyon

IARC (1980) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 24, *Some Pharmaceutical Drugs*, Lyon, pp. 39-58

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, pp. 161-165, pp. 171-172

IARC (1990) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 50, *Pharmaceutical Drugs*, Lyon

IARC (1995) *Peroxisome Proliferation and its Role in Carcinogenesis* (IARC Technical Report No. 24), Lyon

WHO Consultation (1994) Essential drugs for cancer chemotherapy. *Bull. World Health Org.*, **72**, 893-898