METHODS

The data on animal and human carcinogenicity for each of the agents for which information on carcinogenicity in humans was available were reviewed and evaluated before the meeting by members of the Working Group, who prepared draft summaries of the findings. During the meeting of the Working Group, these summaries and evaluations were discussed, modified as appropriate and adopted. Overall evaluations of carcinogenicity to humans for these agents were made by the Working Group on the basis of the combined evidence from: human carcinogenicity data, animal carcinogenicity data, the conclusions of the December 1986 Working Group on studies on genetic and related effects, and other relevant data judged to be of sufficient importance to affect the making of the overall evaluation.

The criteria for evaluating the degree of evidence for carcinogenicity in humans and in experimental animals and for making the overall evaluation of carcinogenicity to humans are those described in the Preamble to this volume (see pp. 29-32), which represents the conclusions of two working groups which met in September/October 1986 and in January 1987.

Some closely-related chemicals were evaluated as groups, as at previous meetings, when such an approach was biologically plausible and when the available evidence did not permit separate evaluation of each individual chemical within the group. For groups of chemicals categorized into Group 1 ('The agent is carcinogenic to humans'), the evaluation was considered to apply to the group as a whole and not necessarily to all chemicals within the group. If and when further evidence is obtained, separate evaluations may be made for individual chemicals, possibly into different categories.

Evaluations of carcinogenicity to humans were sometimes made for a group of human exposures, e.g., industrial processes and therapeutic combinations. Under such circumstances, the composition of different mixtures, and consequently their biological effects, are likely to vary with settings and conditions. Although the degree of evidence for carcinogenicity has been characterized with all possible specificity, it is difficult to be specific for such variable human exposures, which are also likely to change considerably over time, e.g., with the introduction of new processes. The Working Group therefore recognizes that the evaluation of a complex situation may not apply to all constituents or to every combination or to every point in time.

Other relevant data, including the results of tests for genetic and related effects (see Supplement 6 [IARC, 1987]), were used by the Working Group in making the overall evaluation of carcinogenicity to humans of an agent when one of the following sets of information was available:

(1) the agent produces genetic or related effects in exposed humans (i.e., indicative of DNA or chromosomal damage) and also gives positive results in a range of other types of assays;

or

(2) the agent is active in a broad spectrum of assays for genetic and related effects, including those involving mammalian cells, and there is evidence from structure-activity and/or metabolism studies that the agent itself reacts covalently with DNA or is likely to be converted to a reactive form in humans.

This information was used in two ways:

(1) to classify in Group 2A, as a probable human carcinogen, an agent for which there is *sufficient evidence* of carcinogenicity in experimental animals, which would otherwise have been classified in Group 2B as a possible human carcinogen; and

(2) to classify in Group 2B, as a possible human carcinogen, an agent for which there is *limited evidence* of carcinogenicity in experimental animals, which would otherwise have been classified in Group 3.

In using the above information, it was recognized that certain known carcinogens are not detected in currently used assays for genetic and related effects.

Overall evaluations of carcinogenicity to humans for agents for which no data on carcinogenicity in humans were available were made on the basis of the combined evidence from animal carcinogenicity tests and from other relevant data that fell into one of the two categories described above. The overall evaluation was generally based on the summary and evaluation of the most recent monograph on that agent. The same procedure was used in the case of three agents (benzoyl peroxide, polyvinyl chloride and selenium and selenium compounds) for which a previous evaluation of *inadequate evidence* for carcinogenicity in humans had been made.

Prior to Volume 20 of the Monographs, the evaluations of *sufficient*, *limited*, *inadequate* and *no evidence* of carcinogenicity were not used. However, an ad-hoc group which was convened in 1978 re-evaluated all chemicals evaluated in Volumes 1-19 of the monographs and listed those for which there was considered to be *sufficient evidence* of carcinogenicity in experimental animals according to the criteria established at that time. All chemicals for which there is *sufficient evidence* of carcinogenicity in experimental animals were re-evaluated by the present group.

For agents for which there were no data on carcinogenicity in humans and which were evaluated in Volumes 1-19 of the *IARC Monographs*, prior to the development of criteria for defining *limited* and *inadequate evidence* of carcinogenicity, no formal re-evaluation was made. However, on the basis of data presented in the summaries in those volumes, an attempt was made in conjunction with the Secretariat to judge whether the available data at that time would have met the present criteria for *limited* and *inadequate evidence.*

With regard to compounds for which there are no data on carcinogenicity in humans, the Working Group also examined data from short-term tests and other relevant biological data in *Monographs* volumes 14-42. Only those compounds for which data were *limited* or *sufficient* in animal studies were considered for recategorization on the basis of the procedures described above for using data on genetic and related effects.

When additional published data of significant importance to affect the evaluation of *sufficient evidence* of carcinogenicity in experimental animals (upgrading to or

downgrading from) were available to the Working Group, new summaries and evaluations of the data in experimental animals were prepared (see p. 389), and these were used in making the overall evaluations.

Only one agent was categorized as probably not carcinogenic to humans (Group 4). More agents did not fall into this category partly because one of the criteria used for selecting agents to be considered in the *Monographs* series is that there be a suspicion for the carcinogenicity of the agents on the basis of either epidemiological or experimental observations. Therefore, the monographs tend to represent a selection of agents for which positive findings have been reported in the literature.

The epidemiological evidence for diazepam, fluorides (inorganic, used in drinking-water) and prednisone appeared to be suitable for classification as 'suggesting lack of carcinogenicity' in humans. The different reasons why it could not be so described are given in the texts on each compound.

For two chemicals, ferric oxide and methyl parathion, there was considered to be 'evidence suggesting lack of carcinogenicity' in experimental animals, but there were insufficient supporting data to allow their classification into Group 4.

References

IARC (1982) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Supplement 4, *Chemicals, Industrial Processes and Industries Associated with Cancer in Humans (IARC Monographs, Volumes 1 to 29)*, Lyon

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Supplement 6, *Genetic and Related Effects: An Updating of Selected* IARC Monographs *from Volumes 1 to 42*, Lyon