METHODS

The data on each chemical were reviewed in detail before the meeting by two members of the group; the animal studies by an experimentalist and the human studies by an epidemiologist. Data that had become available since the publication of the relevant monograph were included in this review.

Separate assessments of the human and animal evidence of carcinogenicity were debated and adopted by the Working Group. An overall evaluation of carcinogenicity for humans was made based on the combined evidence. Brief descriptions of the data used to support the assessments and the evaluations appear in the Appendix. The reader is encouraged to consult these notes together with the summary Table 3. For each chemical the appropriate volume in the *Monographs* series is given and also, where applicable, papers that have been published subsequently.

Assessment of evidence for carcinogenicity from experimental animal studies

These assessments were classified in five groups:

i. *Sufficient evidence* of carcinogenicity indicates that there is an increased incidence of malignant tumours: (a) in multiple species or strains, or (b) in multiple experiments (preferably with different routes of administration or using different dose levels), or (c) to an unusual degree with regard to incidence, site or type of tumour, or age at onset. Additional evidence may be provided by data concerning dose-response effects, as well as information on mutagenicity or chemical structure.

ii. *Limited evidence* of carcinogenicity means that the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain, or experiment; or (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) the neoplasms produced often occur spontaneously or are difficult to classify as malignant by histological criteria alone (e.g., lung and liver tumours in mice).

iii. *Inadequate evidence* indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect

iv. *Negative evidence* means that within the limits of the tests used, the chemical is not carcinogenic. The number of negative studies is small, since in general, studies that show no effect are less likely to be published than those suggesting carcinogenicity.

v. *No data* indicates that data were not available to the Working Group.

The categories *sufficient evidence* and *limited evidence* refer only to the strength of the experimental evidence that these chemicals are (or are not) carcinogenic and not to the extent of their carcinogenic activity. The classification for any chemical may change as new information becomes available.

Assessment of evidence for carcinogenicity from human studies

Evidence of carcinogenicity from human studies comes from three main sources:

1. Case reports of individual cancer patients who were exposed to the chemical or process.
2. Descriptive epidemiological studies in which the incidence of cancer in human populations was found to vary spatially or temporally with exposure to the agents.
3. Analytical epidemiological (case-control and cohort) studies in which individual exposure to the chemical or group of chemicals was found to be associated with an increased risk of cancer.

Three criteria must be met for a causal association to be inferred between exposure and human cancer (3):

1. There is no identified bias which could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance.

In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies are concordant in showing the association, when the association is strong, when there is a dose-response relationship, or when a reduction in exposure is followed by a reduction in the incidence of cancer.

The degrees of evidence for carcinogenicity in human studies were categorized as :

i. *Sufficient evidence* of carcinogenicity indicates a causal association between exposure and human cancer.

ii. *Limited evidence* of carcinogenicity indicates a possible carcinogenic effect in humans, although the data are not sufficient to demonstrate a causal association.

iii. *Inadequate evidence* of carcinogenicity indicates that the data are qualitatively or quantitatively insufficient to allow any conclusion regarding carcinogenicity for humans.

Dividing lines were by no means firmly drawn between *sufficient evidence* and *limited evidence* from animal studies and between *inadequate evidence* and *limited evidence* from both human and animal studies. When differences of opinion occurred among the members of the Working Group, the classification was made by majority vote.

Evaluation of the carcinogenic risk to humans

Presently, no objective criteria exist to interpret the animal data directly in terms of human risk. Thus, in the absence of ***sufficient evidence*** from human studies, evaluation of the carcinogenic risk to humans was based on consideration of both the epidemiological and experimental evidence. Furthermore, the breadth of the categories for human and animal evidence defined above allows substantial variation within each, and the decisions reached by the group regarding overall risk incorporated these differences, even though they could not always be adequately reflected in the placement of a chemical into a particular category in the Table3. The evidence in support of these decisions is summarized in the notes for each chemical in the Appendix.

The chemicals, groups of chemicals, or industrial processes were placed into one of three groups:

Group 1

The chemical, group of chemicals, or industrial process is carcinogenic for humans. This category was used only when there was *sufficient evidence* to support a causal association between the exposure and cancer.

Group 2

The chemical or group of chemicals is probably carcinogenic for humans. This category includes chemicals for which the evidence of human carcinogenicity is almost 'sufficient' as well as chemicals for which it is only suggestive. To reflect this range this category has been divided into higher (group A) or lower (group B) degrees of evidence. The data from experimental animal studies played an important role in assigning chemicals to category 2, and particularly to those in group B.

Group 3

The chemical or group of chemicals cannot be classified as to its carcinogenicity for humans.