GENERAL REMARKS

Part A of Volume 100 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* considers all pharmaceutical agents that were first classified as *carcinogenic to humans (Group 1)* in Volumes 1–99.

Volume 100 – General Information

About half of the agents classified in Group 1 were last reviewed more than 20 years ago, before mechanistic studies became prominent in evaluations of carcinogenicity. In addition, more recent epidemiological studies and animal cancer bioassays have demonstrated that many cancer hazards reported in earlier studies were later observed in other organs or through different exposure scenarios. Much can be learned by updating the assessments of agents that are known to cause cancer in humans. Accordingly, IARC has selected *A Review of Human Carcinogens* to be the topic for Volume 100. It is hoped that this volume, by compiling the knowledge accumulated through several decades of cancer research, will stimulate cancer prevention activities worldwide, and will be a valued resource for future research to identify other agents suspected of causing cancer in humans.

Volume 100 was developed by six separate Working Groups:

Pharmaceuticals
Biological agents
Arsenic, metals, fibres, and dusts
Radiation
Personal habits and indoor combustions
Chemical agents and related occupations

Because the scope of Volume 100 is so broad, its *Monographs* are focused on key information. Each *Monograph* presents a description of a carcinogenic agent and how people are exposed, critical overviews of the epidemiological studies and animal cancer bioassays, and a concise review of the toxicokinetic properties of the agent, plausible mechanisms of carcinogenesis, and potentially susceptible populations, and life-stages. Details of the design and results of individual epidemiological studies and animal cancer bioassays are summarized in tables. Short tables that highlight key results appear in the printed version of Volume 100, and more extensive tables that include all studies appear on the website of the *IARC Monographs* programme (http://monographs.iarc.fr). For a few well-established associations (for example, tobacco smoke and human lung cancer), it was impractical to include all studies, even in the website tables. In those instances, the rationale for inclusion or exclusion of sets of studies is given.

Each section of Volume 100 was reviewed by a subgroup of the Working Group with appropriate subject expertise; then all sections of each *Monograph* were discussed together in a plenary session of the full Working Group. As a result, the evaluation statements and other conclusions reflect the views of the Working Group as a whole.

Volume 100 compiles information on tumour sites and mechanisms of carcinogenesis. This information will be used in two scientific publications that may be considered as annexes to this volume. One publication, *Tumour Site Concordance between Humans and Experimental Animals*, will analyse the correspondence of tumour sites among humans and different animal species. It will discuss the predictive value of different animal tumours for cancer in humans, and perhaps identify human tumour sites for which there are no good animal models. Another publication, *Mechanisms Involved in Human Carcinogenesis*, will describe mechanisms known to or likely to cause cancer in humans. Joint consideration of multiple agents that act through similar mechanisms should facilitate the development of a more comprehensive discussion of these mechanisms. Because susceptibility often has its basis in a mechanism, this could also facilitate a more confident and precise description of populations that may be susceptible to agents acting through each mechanism. This publication will also suggest biomarkers that could render future research more informative. In this way, IARC hopes that Volume 100 will serve to improve the design of future cancer studies.

Specific remarks about the review of pharmaceutical agents in this volume

The subgroups on cancer in humans recognized a number of methodological issues complicating the evaluation of some of the studies reviewed, including:

- The widespread use of combination chemotherapy regimens, making it more difficult to isolate the effect of a particular drug.
- Particularly in patients with primary cancers with longer expected survivals, subsequent treatments are commonly given after the initial therapy was not successful, making it more difficult to attribute the development of other malignancies to the initial drug(s) used.
- The variable period of follow-up in patients treated for advanced cancer, many of whom will die in a short period of time due to their primary disease. Hence, the 'real' incidence of second cancers produced by a particular treatment may be underestimated.
- Second cancers can occur either late and sporadically (such as radiation-associated sarcomas, the incidence of which may be increased by concurrent chemotherapy) or have 'peaks' in their time-to-onset (such as alkylating-agent-induced leukaemias, which tend to occur 4–7 years post-exposure with lower incidence before and after). It is therefore critical to assess whether the analytical method appropriately took these different patterns in account.
- Patients who have already developed one cancer may be more prone to the carcinogenic effects of treatment because of inherited polymorphisms in DNA-repair mechanisms or drug-metabolizing enzymes. It is therefore difficult to extrapolate the effect estimates to patients receiving these same drugs for non-malignant disorders such as autoimmune diseases. This is of particular relevance because such individuals often live for decades, and the estimates of carcinogenic potential certainly should influence the choice of treatments. And, because these patients are often treated with a series of regimens in sequence, the same issues arise

as noted above with regard to isolating the effect to a single drug or treatment. Furthermore, some of these diseases (e.g. inflammatory bowel diseases) have an increased 'background' incidence of some cancers.

- The immunosuppression resulting from drugs such as ciclosporin and azathioprine is permissive of the development of new malignancies in transplant recipients. This mechanism should be distinguished from genotoxic effects.

Some anti-neoplastic agents included in this volume have been superseded by newer drugs, and combination therapies. It is important that these new drugs and combinations be evaluated in future volumes. The older agents are included here in order to maintain the historical record of agents known to cause cancer in humans. In addition, because much is often known about the mechanisms through which pharmaceuticals act, the updated *Monographs* in this volume will provide data for subsequent analyses on tumour–site concordance, and on mechanisms involved in human carcinogenesis.

Acute myeloid leukaemia that develops in patients who had been treated with alkylating agents frequently exhibits distinctive characteristics that allow it to be distinguished from acute myeloid leukaemia induced by other agents (such as etoposide or topoisomerase II inhibitors) or that occurs spontaneously. One hallmark of alkylating-agent-induced leukaemia is that it frequently exhibits a clonal loss of either chromosome 5 or 7 or a loss of part of the long arm of one of these chromosomes.

Although the *Monographs* evaluate whether agents can pose a cancer hazard to humans, the Working Group noted that there is evidence that the potency to cause acute myeloid leukaemia varies among the anti-neoplastic agents considered in this volume. In particular, cyclophosphamide, one of the most widely used anti-neoplastic agents, presents a lower risk of leukaemia at therapeutic dose levels than other anti-neoplastic agents that act by an alkylating mechanism.

During the discussion of methoxsalen in combination with ultraviolet radiation, the Working Group noted that some vegetables naturally contain methoxsalen, and that handling such vegetables can result in exposure to methoxsalen. There have been reports of photosensitivity and skin lesions in grocery workers (especially those who frequent tanning salons) and in farmworkers, and this may reflect the possibility of hidden occupational or environmental exposure to methoxsalen in combination with ultraviolet radiation.

The information on sequential estrogen–progestogen contraceptives (classified in Group 1 in Supplement 7, IARC, 1987) is included in the *Monograph* on combined estrogen–progestogen contraceptives, and the evaluation for combined administration is applicable to sequential administration.

Estrogen–progestogen contraceptives have been available for several decades primarily in the form of an oral pill. In consequence, the epidemiological studies followed women who took these contraceptives in oral form. Estrogen–progestogen contraceptives are now being marketed also in the form of a skin patch or a vaginal insert, but it is too soon for cancer studies of these newer methods of administration to have been completed. Because estrogen–progestogen contraceptive skin patches and vaginal inserts use the same types of hormones that are present in oral contraceptives, there is a likelihood that they pose similar cancer hazards.

Although estrogen–progestogen contraceptives and estrogen–progestogen menopausal therapy are discussed in separate *Monographs*, it is important to keep in mind that they use the same types of hormones. The *Monograph* on estrogen–progestogen menopausal therapy discusses recent studies of women who have used both hormonal regimens at different stages of life, and the results are not entirely predictable from looking at the two separately. It will be important to continue to follow

these women in order to understand the effects of prolonged exposure to these exogenous hormones through different stages of life.

Separate sections of this volume are devoted to estrogen-only menopausal therapy, estrogen–progestogen menopausal therapy, combined oral contraceptives, diethylstilbestrol, and tamoxifen. This structure precludes a detailed comparison of the carcinogenicity of these different hormonal products in any single section. Such a comparison can provide information not readily apparent from separate considerations of individual products, and is provided here.

Estrogen products given with and without a progestogen have markedly different carcinogenic or anti-carcinogenic effects, and the same regimens may have markedly different effects in different organs and at different stages of women's lives. Great caution should therefore be exercised in applying observations on the carcinogenic effects of one product on one organ to its possible carcinogenic effect in another organ; and similar caution should be exercised in applying observations on the carcinogenicity of one hormonal product to another, apparently similar, product.

For example, estrogen used without a progestogen by menopausal women clearly increases the risk of endometrial cancer, but estrogen given in combination with at least 21 days of a progestogen each month or cycle does not increase this risk, and may actually reduce the risk of endometrial cancer. Another example of contrasting effects is the increased breast cancer risk associated with menopausal estrogen plus progestogen use, and a much weaker or more delayed increased risk with the use of unopposed estrogen. Unlike in the endometrium, in the breast, progestogens, in the presence of estrogens, stimulate mitotic activity, presumably by activating estrogen receptors. This provides a plausible explanation for the greater risk associated with estrogen–progestogen menopausal treatment than with estrogen treatment alone. Another possible explanation is that estrogen alone tends to be given to women who have had a hysterectomy, whereas estrogen–progestin combination therapy is recommended only for women with an intact uterus. Women who have had a hysterectomy (with or without an oophorectomy) have lower levels of endogenous ovarian hormones than women who have not, and are at lower risk of breast cancer based on very low levels of endogenous estrogens and progestogens.

In epidemiological studies, estimates of relative risk are generally used as measures of the statistical association between an exposure and risk of a disease. Relative risks do not indicate absolute increases or decreases in risk. If the underlying risk in the absence of the exposure of interest is small, then even large relative risks will not indicate a large absolute increase in risk. For example, although the relative risk of breast cancer is increased in current and recent users of oral contraceptives, who tend to be young and therefore at low risk of breast cancer, the absolute increase in risk is very small.

Some *Monographs* in this volume conclude that an agent causes one type of cancer while reducing the risk of another. This does not constitute a recommendation for use in cancer prevention, and it is outside the scope of the *Monographs* to offer medical advice.

Phenacetin, etoposide, and plants containing aristolochic acid

Although the intent of Volume 100 is not to identify new carcinogenic agents, the Working Group was mindful of the statement in the Preamble that "When the available epidemiological studies

pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk [part B, section 6(a)]."

During discussion of analgesic mixtures containing phenacetin, the Working Group concluded that phenacetin itself (previously classified in Group 2A in Supplement 7, IARC, 1987) should now be classified in Group 1, noting that the other components of analgesic mixtures containing phenacetin (namely phenazone, aspirin, codeine phosphate, and caffeine) could not explain the increased risks of cancers of the renal pelvis and the ureter.

When reviewing antineoplastic drugs, the Working Group noted that acute myeloid leukaemia induced by alkylating agents, such as busulfan, frequently exhibits clonal loss (partial or total) of either chromosome 5 or 7, thereby distinguishing it from acute myeloid leukaemia induced by topoisomerase II inhibitors, such as etoposide. The latter shows clonal balanced translocations involving the *MLL* gene on chromosome 11 (11q23). Following this line of reasoning, the Working Group classified etoposide itself in Group 1 (previously classified in Group 1 in combination with cisplatin and bleomycin, IARC, 2000).

For different reasons, during discussion of plants of the genus *Aristolochia*, the Working Group concluded that aristolochic acid (previously classified in Group 2A in Volume 82, IARC, 2002) should now be classified in Group 1 based on strong evidence that aristolochic acid-specific DNA adducts and *TP*53 transversions have been found in humans who ingested material from these plant species.

As a result, these three chemical agents have been added to the list of carcinogens classified in Group 1.

The latter evaluation of aristolochic acid in Group 1 shows the promise that mechanistic studies can bring to the identification of carcinogenic hazards. Every reference cited in the section on mechanistic and other relevant data was published after the 2002 *Monograph* on plants of the genus *Aristolochia*. In only six years, these studies were able to convincingly demonstrate that aristolochic acid is the specific agent responsible for the high risk of cancers of the renal pelvis and ureter in people who ingested material from these plant species. It is encouraging to think that other environmental or occupational cancer clusters might be investigated with such speed and resolved with similar confidence.

A summary of the findings of this volume appears in *The Lancet Oncology* (Grosse *et al.*, 2009).

References

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