5. Summary of Data Reported and Evaluation

5.1 Exposure

Use of regimens in which a progestogen is added to post-menopausal oestrogen therapy has been increasing in order to reduce the increased risk for endometrial cancer observed with oestrogens alone. Regimens vary with respect to dose and timing of oestrogen and progestogen administration and in the number of days on which the progestogen is given per month. Several routes of administration are used, including oral (as tablets), injection, implantation, percutaneous application and intrauterine administration. The frequency and type of hormonal supplementation used vary widely within and between countries.

5.2 Human carcinogenicity

Breast cancer

Separate information on the effects of use of post-menopausal oestrogen–progestogen therapy was provided in only a minority of the studies on the risk for breast cancer. The results of nine cohort and five case–control studies that did include such information and the findings of a pooled analysis of the original data from these and other studies indicate that the increased relative risk observed with long-term use of post-menopausal oestrogen–progestogen therapy is not materially different from that for long-term use of oestrogens alone. The available information on long-term use of the combination is, however, limited. The data are insufficient to assess the effects of past use and of different progestogen compounds, doses and treatment schedules.

Endometrial cancer

The relationship between use of post-menopausal oestrogen–progestogen therapy and the risk for endometrial cancer was addressed in four follow-up and four case–control studies. In comparison with women who did not use hormonal therapy, the risk of women who did was no different or modestly increased, but the increase was smaller than that for women who used oestrogens alone. In the two studies that were recent and large enough to evaluate different durations of progestogen supplementation during each cycle, an increase in risk was found relative to non-users when the progestogen was added to the cycle for 10 days or fewer. The risk for endometrial cancer associated with different monthly durations of progestogen supplementation per cycle and different doses of progestogen supplementation remains unclear.

Ovarian cancer

One cohort and one case–control study are available on the possible relationship between use of post-menopausal oestrogen–progestogen therapy and the risk for ovarian cancer. The limited data suggest no association.

Liver cancer

One cohort study suggested that there is no association between use of post-menopausal oestrogen–progestogen therapy and the risk for liver cancer.

Other cancers

Very few studies were available of the risks for colorectal cancer, cutaneous malignant melanoma or thyroid cancer that allowed a distinction between use of post-menopausal oestrogen–progestogen and oestrogen therapy. They do not suggest an increased risk, but all included few exposed subjects.

5.3 Carcinogenicity in experimental animals

Only one study was available on combined oestrogen and progestogen therapy, in which conjugated equine oestrogens were tested with medroxyprogesterone acetate. Oral administration of this combination or of the conjugated oestrogens alone in the diet of ovariectomized female rats which had been given 7,12-dimethylbenz[*a*]anthracene, a known mammary carcinogen, increased the incidence of mammary tumours to a level equal to that in non-ovariectomized controls treated with the carcinogen.

5.4 Other relevant data

Combinations of oestrogens and progestogens are absorbed rapidly and reach maximal serum concentrations quickly. The proportion of absorbed hormones that becomes biologically available depends on the extent of enterohepatic circulation and metabolic transformation of pro-drugs. Oestrogens and progestogens may affect each other's disposition. Many progestogens have oestrogenic activity and can modify the effects of oestrogens. The addition of progestogens to therapy may decrease cell proliferation in human endometrium

over that with oestrogen alone. The extent of the cell proliferation response depends on the doses of oestrogen and progestogen, increasing with higher doses of oestrogen and decreasing with more progestogen, as compared with oestrogen alone.

In ovariectomized cynomolgus monkeys, the conjugated oestrogen–progestogen combination caused a higher incidence of mammary gland hyperplasia than did conjugated equine oestrogens alone. No information was available on whether the effect of oestrogen–progestogen combinations on the mammary gland is modified by sequential exposure to progestogens, by body weight or by the recency or duration of exposure in experimental animals. Similarly, no information was available on the possible relationship between exposure to oestrogen–progestogen combinations and the degree of malignancy of breast tumours.

No information was available on the genotoxic effects of formulations similar to those used in post-menopausal oestrogen–progestogen therapy.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of post-menopausal oestrogen–progestogen therapy.

There is *inadequate evidence* in experimental animals for the carcinogenicity of conjugated equine oestrogens plus progestogen.

Overall evaluation

Post-menopausal oestrogen–progestogen therapy is *possibly carcinogenic to humans (Group 2B).*