5. Summary of Data Reported and Evaluation

5.1 Exposure

Progestogen-only contraceptives have been available worldwide for over 40 years. Intramuscular depot injections and subcutaneous implants are the most common routes of administration in developing countries, where there is the widest use. Oral progestogen-only 'mini pills' are used primarily in Europe and North America, but fewer women use these preparations than parenterally administered progestogens and combined oral contraceptives.

5.2 Human carcinogenicity

Breast cancer

Data on injectable progestogen-only contraceptives were available from two case–control studies and a pooled analysis of original data, overall including about 350 women with breast cancer who had used these drugs. Data on oral progestogen-only contraceptives were available from a pooled analysis of original data on 725 women with breast cancer who had used these drugs. Overall, there is no evidence of an increased risk for breast cancer.

Endometrial cancer

One case–control study addressed the relationship between use of oral progestogen-only contraceptives and risk for endometrial cancer; less than 2% of the control women had used these preparations. Women with endometrial cancer were less likely to have used oral progestogen-only contraceptives than control women but not significantly so.

The effects of use of depot medroxyprogesterone acetate on the risk for endometrial cancer have been evaluated in one cohort and one case–control study. No reduction in risk

was seen in the cohort study, whereas a strong reduction was observed in the case–control study. Although the evidence is based on small numbers of women, the results of these studies suggest that women who use progestogen-only contraceptives have a reduced risk for endometrial cancer.

Cervical cancer

There is little evidence that use of depot medroxyprogesterone acetate or other progestational injectable contraceptives alters the risk for either squamous-cell carcinoma or adenocarcinoma of the uterine cervix.

Ovarian cancer

One case–control study addressed use of progestogen-only oral contraceptives, and one case–control study specifically addressed any use of depot medroxyprogesterone acetate. Neither showed any alteration in risk, either overall or in relation to duration of use.

Liver cancer

Two case–control studies have addressed the association between risk for liver cancer and use of injectable progestogen-only contraceptives. In neither study did the risk for liver cancer differ significantly between women who had ever or never used these contraceptives. Both studies were conducted in areas endemic for hepatitis viruses.

Cutaneous malignant melanoma

One case–control study of cutaneous malignant melanoma showed no increase in risk among users of progestogen-only contraceptives.

5.3 Carcinogenicity in experimental animals

Medroxyprogesterone acetate has been tested for carcinogenicity in mice by subcutaneous implantation of pellets or injection and in dogs by subcutaneous or intramuscular administration. In mice, it induced mammary adenocarcinomas; in dogs, it induced mammary hyperplasia, nodules and benign mammary tumours. Tumour development in other organs and tissues of these animals was not reported.

Medroxyprogesterone acetate was tested in combination with some known carcinogens. With 7,12-dimethylbenz[*a*]anthracene or *N*-methyl-*N*-nitrosourea, it increased the incidence of mammary adenocarcinomas in mice and shortened the latency to tumour appearance. Medroxyprogesterone acetate enhanced the incidence of cervical invasive squamous-cell carcinomas in mice treated with 3-methylcholanthrene. It decreased the incidence of endometrial adenocarcinoma in mice previously treated with *N*-methyl-*N*-nitrosourea plus oestradiol.

Two studies in dogs and one study in cats treated by veterinarians for suppression of oestrus and compared with untreated animals indicated that medroxyprogesterone acetate increases the risk for developing benign and malignant mammary tumours in both species.

Levonorgestrel was tested by implantation into the uterus of rabbits, with no indication of carcinogenicity. In combination with *N*-nitrosobis(2-oxopropyl)amine, levonorgestrel did not enhance the incidence of renal dysplastic lesions or tumours in hamsters.

5.4 Other relevant data

Use of depot injections of progestogens or subcutaneous implants of controlled-release devices results in sustained levels of hormone release over long periods. Progestogens used in this way vary in their spectrum of hormonal activities. In addition to progestational activity, levonorgestrel has some oestrogenic activity. In contrast, medroxyprogesterone acetate has no marked oestrogenic activity but has some androgenic activity. Both compounds can modify oestrogenic effects. Progestogen-only contraceptives have growth potentiating effects in the human mammary gland, as indicated by elevated rates of cell proliferation. No data were available on the genetic activity of these progestogens in humans, but norethisterone induced some changes in DNA and chromosomes in experimental systems. Progesterone induced cell transformation in mammalian cells *in vitro*. Early studies on use of depot medroxyprogesterone acetate during pregnancy suggested that genital malformations were induced in the fetus, but the results of later studies provided no support for that suggestion. Medroxyprogesterone acetate administered to men can reduce testosterone levels and semen production.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of progestogen-only contraceptives.

There is *sufficient evidence* in experimental animals for the carcinogenicity of medroxyprogesterone acetate.

Overall evaluation

Progestogen-only contraceptives are *possibly carcinogenic to humans (Group 2B)*.