5. Summary of Data Reported and Evaluation

5.1 Exposure

Oral contraceptives have been used since the early 1960s and are now used by about 90 million women worldwide. 'The pill' is given as a combination of an oestrogen and a progestogen or as sequential therapy. Since the 1970s, progestogen-only pills have been available. Continuous development of the formulas and the development of new progestogens have allowed for lower dosages with fewer acute side-effects, while offering effective, convenient contraception.

The oestrogen component of combined oral contraceptives is either ethinyloestradiol or mestranol, and the progestogens used are cyproterone acetate, desogestrel, ethynodiol diacetate, gestodene, levonorgestrel, lynoestrenol, megestrol, norethisterone, norethisterone acetate, norethynodrel, norgestimate and norgestrel. Currently, the most commonly used oestrogen is ethinyloestradiol, and commonly used progestogens are levonorgestrel and norethisterone.

Large differences exist in the worldwide use of oral contraceptives. These products were already being used extensively in the 1960s in northern Europe (e.g. the Netherlands, Sweden and the United Kingdom) and the United States. Extensive use of oral contraceptives by adolescents was documented in Sweden and the United Kingdom as early as 1964. Very little use of oral contraceptives is reported in Japan, the countries of the former Soviet Union and most developing countries. Contraceptive use also differs in relation to religion, ethnicity, educational level, use before or after marriage and use before or after first pregnancy.

The type of oral contraceptives prescribed differs between countries, and both the type of oral contraceptive and the doses of oestrogens and progestogens have changed between and within countries over time.

Oral contraceptives may be used for emergency post-coital contraception, and the components of oral contraceptives are used to treat peri- and post-menopausal symptoms and a number of other conditions.

It is important to stress that use of oral contraceptives is a recent human activity, and the health benefits and adverse effects in women have not yet been followed over a complete generation, even though they are some of the most widely used drugs in the

world. Women who began using oral contraceptives before the age of 20 in the 1960s are only now reaching the ages (50–60 years) at which the incidences of most malignancies begin to increase.

Oestrogens and progestogens belonging to the same chemical groups may have different oestrogenic, androgenic and progestogenic effects. Little is known about the long-term health risks and potential protective effects of the individual components. The effects become increasingly complex as women grow older, as they may be exposed to different types and doses of hormones, starting with oral contraceptives and progressing to post-menopausal hormonal therapy.

5.2 Human carcinogenicity

Breast cancer

More than 10 cohort and 50 case–control studies have assessed the relationship between use of combined oral contraceptives and the risk for breast cancer. The studies included over 50 000 women with breast cancer. The weight of the evidence suggests a small increase in the relative risk for breast cancer among current and recent users, which is, however, unrelated to duration of use or type or dose of preparation. By 10 years after cessation of use, the risk of women who used oral contraceptives appears to be similar to that of women who never used them. Important known risk factors do not account for the association. The possibility that the association seen for current and recent users is due to detection bias has not been ruled out. Even if the association is causal, the excess risk for cancer associated with patterns of use that are typical today is very small.

Cervical cancer

Five cohort and 16 case–control studies of use of combined oral contraceptives and invasive cervical cancer have been published; these consistently show a small increase in relative risk associated with long duration of use. These associations were also seen in four studies in which some analyses were restricted to cases and controls who had human papillomavirus infections. Biases related to sexual behaviour, screening and other factors cannot be ruled out as possible explanations for the observed associations.

Endometrial cancer

Three cohort and 16 case–control studies addressed the relationship between use of combined oral contraceptives and the risk for endometrial cancer. The results of these studies consistently show that the risk for endometrial cancer of women who have taken these pills is approximately halved. The reduction in risk is generally stronger the longer the oral contraceptives are used and persists for at least 10 years after cessation of use. Few data are available on the more recent, low-dose formulations.

Use of sequential oral contraceptives which were removed from the consumer market in the 1970s was associated with an increased risk for endometrial cancer.

Ovarian cancer

Four cohort and 21 case–control studies addressed the relationship between ovarian cancer and use of combined oral contraceptives. Overall, these studies show a consistent reduction in the risk for ovarian cancer with increasing duration of use. The reduction is about 50% for women who have used the preparations for at least five years, and the reduction seems to persist for at least 10–15 years after use has ceased. Few data are available on the more recent, low-dose formulations. A reduction in risk for ovarian tumours of borderline malignancy is also observed.

Cancers of the liver and gall-bladder

Two case–control studies of benign hepatocellular tumours showed a strong relationship with duration of use of combined oral contraceptives. Three cohort studies showed no significant association between use of combined oral contraceptives and the incidence of or mortality from liver cancer, but the expected numbers of cases were very small, resulting in low statistical power. Long-term use of combined oral contraceptives was associated with an increase in risk for hepatocellular carcinoma in all nine case–control studies conducted in populations with low prevalences of hepatitis B and C viral infection and chronic liver disease, which are major causes of liver cancer, and in analyses in which women with these factors were excluded. Few data are available for the more recent, low-dose formulations. In the two case–control studies conducted in populations with a high prevalence of infection with hepatitis viruses, there was no increase in risk for hepatocellular carcinoma associated with use of combined oral contraceptives, but there was little information on long-term use.

Little information was available on the association between use of combined oral contraceptives and the risk for cholangiocarcinoma or cancer of the gall-bladder.

Colorectal cancer

Four cohort investigations and 10 case–control studies provided information on use of combined oral contraceptives and risk for colorectal cancer. None showed significantly elevated risks in women who used these preparations for any length of time. Relative risks lower than 1.0 were found in nine studies, and the risk was significantly reduced in two.

Cutaneous malignant melanoma

Four cohort investigations and 16 case–control studies provided information on use of combined oral contraceptives and the risk for cutaneous malignant melanoma. The relative risks were generally close to 1.0 and not related to duration of use.

Thyroid cancer

Ten case–control studies provided information on use of combined oral contraceptives and the risk for cancer of the thyroid gland. In general, there was no elevation in the risk associated with oral contraceptive use.

5.3 Carcinogenicity in experimental animals

Oestrogen–progestogen combinations

Several combinations of oral contraceptives have been tested alone and together with known carcinogens in mice, rats and monkeys. Consistent tumorigenic effects that are seen with various combinations which are important for classifying the degree of evidence for carcinogenicity of this class of compounds are as follows.

The incidences of pituitary adenoma in male and female mice were increased by administration of mestranol plus chlormadinone acetate, mestranol plus ethynodiol diacetate, ethinyloestradiol plus ethynodiol diacetate, mestranol plus norethisterone, ethinyloestradiol plus norethisterone (females only) and mestranol plus norethynodrel, which also increased the incidence of pituitary adenomas in female rats.

The incidence of benign mammary tumours was increased in mice by ethinyloestradiol plus chlormadinone acetate (in intact and castrated males) and by mestranol plus norethynodrel (only in castrated males). In rats, the incidence of benign mammary tumours was increased by administration of ethinyloestradiol plus norethisterone acetate. This combination did not cause tumour formation in any tissue in one study in monkeys.

The incidence of malignant mammary tumours was increased in male and female mice by ethinyloestradiol plus megestrol acetate and in rats by ethinyloestradiol plus ethynodiol diacetate (males and females), mestranol plus norethisterone (females) and mestranol plus norethynodrel (females).

In female mice, the incidence of malignant uterine tumours (non-epithelial) was increased by ethinyloestradiol plus ethynodiol diacetate and the incidence of vaginal or cervical tumours by norethynodrel plus mestranol. In mice treated with 3-methylcholanthrene to induce genital tumours, ethinyloestradiol plus lynoestrenol, ethinyloestradiol plus norgestrel and mestranol plus norethynodrel increased the incidence of uterine tumours; however, this occurred only at the highest doses of ethinyloestradiol plus lynoestrenol and ethinyloestradiol plus norgestrel that were tested. Lower doses inhibited tumorigenesis induced by 3-methylcholanthrene alone.

In rats, the incidence of benign liver tumours (adenomas) was increased by mestranol plus norethisterone (males) and by ethinyloestradiol plus norethisterone acetate (males); the latter combination also increased the incidence of hepatocellular carcinomas in females. Liver foci, which are putative preneoplastic lesions, were induced in rats by mestranol plus norethynodrel. In rats initiated for hepatocarcinogenesis with *N*-nitrosodiethylamine, mestranol plus norethynodrel increased the formation of altered hepatic foci.

Oestrogens

The synthetic oestrogens ethinyloestradiol and mestranol have been tested extensively alone and together with known carcinogens in mice, rats, hamsters, dogs and monkeys.

The incidence of pituitary adenomas was increased by ethinyloestradiol and mestranol in male and female mice and by ethinyloestradiol in female rats.

The incidences of malignant mammary tumours in male and female mice and female rats were increased by ethinyloestradiol and mestranol; however, mestranol did not increase the incidences of mammary tumours in dogs in a single study.

Ethinyloestradiol increased the incidence of cervical tumours in female mice.

In one mouse strain, ethinyloestradiol increased the incidences of hepatocellular adenomas. In female rats, ethinyloestradiol and mestranol increased the numbers of altered hepatic foci. Ethinyloestradiol increased the incidence of adenomas in males and females and of hepatocellular carcinomas in females, whereas mestranol increased the incidence of hepatic nodules and carcinomas combined in female rats.

The incidence of microscopic malignant kidney tumours was increased in hamsters exposed to ethinyloestradiol.

In mice initiated for liver carcinogenesis and exposed to unleaded gasoline, ethinyloestradiol increased the number of altered hepatic foci; however, when given alone after the liver carcinogen, it reduced the number of spontaneous foci.

In female rats initiated for liver carcinogenesis, ethinyloestradiol and mestranol increased the number of altered hepatic foci and the incidences of adenomas and carcinomas. Ethinyloestradiol also increased the incidences of kidney adenomas, renal-cell carcinomas and liver carcinomas in rats initiated with *N*-nitrosoethyl-*N*-hydroxyethylamine. In hamsters initiated with *N*-nitrosobis(2-oxopropyl)amine, ethinyloestradiol increased the incidence of renal tumours and the multiplicity of dysplasias.

Progestogens

Various progestogens have been tested alone and together with known carcinogens in mice, rats and dogs.

The incidence of pituitary adenomas was increased by norethisterone in female mice and by norethynodrel in male and female mice and male rats.

The incidence of malignant mammary tumours was increased in female mice by lynoestrenol, megestrol acetate and norethynodrel. In female rats, lynoestrenol and norethisterone slightly increased the incidence of malignant mammary tumours. Norethisterone also slightly increased the incidence of malignant mammary tumours in male rats, while norethynodrel increased the incidence of both benign and malignant mammary tumours in male rats. In dogs, chlormadinone acetate, lynoestrenol and megestrol acetate increased the incidence of benign and malignant mammary tumours; however, lynoestrenol had a protective effect at a low dose but enhanced tumour incidence at two higher doses. Levonorgestrel did not increase the incidence of mammary tumours in one study in dogs.

In female mice treated with 3-methylcholanthrene to induce uterine tumours, norethynodrel further increased the tumour incidence.

In male mice treated with chlormadinone acetate, ethynodiol diacetate, lynoestrenol, norethisterone or norethisterone acetate, the incidence of liver adenomas was increased. Megestrol acetate increased the incidence of adenomas in female mice. Cyproterone acetate increased the incidences of liver adenomas and hepatocellular carcinomas in male and female mice, but at doses exceeding the maximum tolerated dose. In rats, the inci-

dence of liver adenomas was increased by norethisterone acetate (males and females), norethisterone (males), norethynodrel and cyproterone acetate (males and females). The numbers of altered hepatic foci in female rats were also increased by norethisterone acetate and cyproterone acetate. In rats treated with *N*-nitrosodiethylamine to initiate hepatocarcinogenesis, norethynodrel increased the number of altered hepatic foci. Norethynodrel alone was shown to increase the incidence of hepatocarcinomas in male rats.

Levonorgestrel in combination with *N*-nitrosobis(2-oxopropyl)amine did not enhance the incidence of renal dysplastic lesions or tumours in hamsters.

5.4 Other relevant data

After single or multiple doses, oestrogens and progestogens in combined oral contraceptives are rapidly absorbed and reach maximal serum levels quickly. The proportion of the absorbed hormone that becomes biologically available depends on the extent of enterohepatic circulation and metabolic transformation of pro-drugs. Interactions between some of these hormones affect their disposition and that of the oestrogen or progestogen with which they are combined. Several progestogens also exhibit some oestrogenic activity and can thus modify the effects of the oestrogens. In three studies, women taking oestrogen–progestogen combinations had increased epithelial cell proliferation in the breast, and in one of these studies the effect was related to the dose of oestrogen in the presence of progestogen. The constituents of combined oral contraceptives may stimulate rat hepatocyte cell proliferation *in vitro* and *in vivo*, and this growth potentiation may be selectively effective in preneoplastic hepatocytes. In addition to the major routes of metabolism, a minor proportion of oestrogen may be metabolized to catechol intermediates, with significant potential for formation of reactive intermediates and damage to DNA. Some of the constituents of combined oral contraceptives can cause changes in DNA at the nuclear level in some experimental systems. Most, but not all, human studies show effects of this type, which occur at conventional therapeutic doses of combined oral contraceptives. When given during pregnancy, combined oral contraceptives can cause developmental abnormalities of the genital tract of offspring. There is evidence for other malformations, but this is controversial and not considered proven.

5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of combined oral contraceptives.

This classification is based on an increased risk for hepatocellular carcinoma in the absence of hepatitis viruses observed in studies of predominantly high-dose preparations.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethinyloestradiol plus ethynodiol diacetate and mestranol plus norethynodrel.

There is *limited evidence* in experimental animals for the carcinogenicity of ethinyloestradiol plus megestrol acetate, mestranol or ethinyloestradiol plus chlormadinone

acetate, mestranol plus ethynodiol diacetate, mestranol plus lynoestrenol, mestranol or ethinyloestradiol plus norethisterone and ethinyloestradiol plus norgestrel.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethinyloestradiol and mestranol.

There is *sufficient evidence* in experimental animals for the carcinogenicity of norethynodrel and lynoestrenol.

There is *limited evidence* in experimental animals for the carcinogenicity of chlormadinone acetate, cyproterone acetate, ethynodiol diacetate, megestrol acetate, norethisterone acetate and norethisterone.

There is *inadequate evidence* in experimental animals for the carcinogenicity of levonorgestrel and norgestrel.

Overall evaluation

Combined oral contraceptives are *carcinogenic to humans (Group 1).*

There is also conclusive evidence that these agents have a protective effect against cancers of the ovary and endometrium.