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Hormonal Contraception and Post-menopausal Hormonal Therapy

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ORAL CONTRACEPTIVES, COMBINED (Group 1)

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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 ethinylloestradiol 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 ethinylloestradiol, 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 incidence 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 ethinylloestradiol plus ethynodiol diacetate and mestranol plus norethynodrel.

There is *limited evidence* in experimental animals for the carcinogenicity of ethinylloestradiol plus megestrol acetate, mestranol or ethinylloestradiol plus chlormadinone acetate, mestranol plus ethynodiol diacetate, mestranol plus lynoestrenol, mestranol or ethinylloestradiol plus norethisterone and ethinylloestradiol plus norgestrel.

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

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: [Suppl. 7 \(1987\)](#)

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HORMONAL CONTRACEPTIVES, PROGESTOGENS ONLY (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

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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 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)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: [Suppl. 7 \(1987\)](#)

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POST-MENOPAUSAL OESTROGEN THERAPY (Group 1)

For definition of Groups, see [Preamble Evaluation](#).

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5. Summary of Data Reported and Evaluation

5.1 Exposure

The numbers of women who have used post-menopausal oestrogen therapy vary between countries and within regions of individual countries. The prevalence of use has been greater in the United States than in most other countries; use of oestrogen therapy after the menopause is rare in developing countries but is increasing. Conjugated equine oestrogens are the most widely prescribed preparation for oestrogen therapy for women in the United States, but oestradiol and its esters have greater use in most of Europe. Oral administration is the most popular route, but percutaneous methods are becoming commoner; use of injections, the first form of post-menopausal oestrogen therapy, has been declining.

5.2 Human carcinogenicity

Breast cancer

Information on the relationship between post-menopausal oestrogen therapy and risk for breast cancer is available from many epidemiological studies. A pooled analysis of the original data from 51 of those studies and a review of data from 15 cohort and 23 case–control studies showed that in the majority of the studies there is a small increase in risk with longer duration of use (five years or more) in current and recent users. Although there is far less information about women who used post-menopausal oestrogen therapy and then ceased use, the increase in risk appears to cease several years after use has stopped. The increase in risk is predominantly for small localized carcinomas of the breast. There are insufficient data to determine whether the risk varies with type of compound or dose.

Endometrial cancer

Three cohort and more than 30 case–control studies consistently showed an association between use of post-menopausal oestrogen therapy and an increased risk for endometrial cancer. The risk increases with increasing duration of use. It decreases with time since last use but remains higher than that of untreated women for at least 10 years.

Cervical cancer

Only one cohort and two case–control studies were available on the relationship between use of post-menopausal oestrogen therapy and the risk for invasive cervical cancer; in none of them were the possible confounding effects of oncogenic human papillomaviruses considered. On balance, the limited evidence available suggests that post-menopausal oestrogen therapy is not associated with an increased risk for invasive cervical carcinoma. The results provide some suggestion that post-menopausal oestrogen therapy is associated with a reduced risk for cervical cancer, but the finding could be due to more active screening for pre-invasive disease among women who have received post-menopausal oestrogen therapy.

Ovarian cancer

The four cohort and 12 case–control studies that addressed the risk for ovarian cancer (largely epithelial)

among women undergoing post-menopausal oestrogen therapy gave mixed results. One cohort study and one large case–control study showed a significant excess risk for ovarian cancer in women who used this therapy, but a pooled analysis of the individual data from case–control studies showed no excess risk. There is therefore no clear association between post-menopausal oestrogen therapy and the risk for ovarian cancer.

Cancers of the liver and gall-bladder

The two cohort and two case–control studies that addressed the association between use of post-menopausal oestrogen therapy and the risk for cancers of the liver or biliary tract showed no alteration in risk.

Colorectal cancer

Seven cohort and 12 case–control studies have provided information on use of post-menopausal oestrogen therapy and the risk for colorectal cancer. The risk was not increased and appeared to be reduced in one-half of the studies. The reduced risk tended to be observed among recent users and did not appear to be related to duration of use.

Cutaneous malignant melanoma

One cohort and nine case–control studies addressed the risk for cutaneous malignant melanoma in relation to use of post-menopausal oestrogen therapy. Most suggested no alteration in risk.

Thyroid cancer

Seven case–control studies that provided information on thyroid cancer and use of post-menopausal oestrogen therapy suggested no effect on risk.

5.3 Carcinogenicity in experimental animals

Conjugated oestrogens

Hydrolysed conjugated equine oestrogens, equilin and d-equilenin were tested in male hamsters by subcutaneous implantation. The hydrolysed oestrogens and equilin induced microscopic renal carcinomas, whereas d-equilenin was inactive.

Oestradiol

Oestradiol and its esters were tested in mice by oral administration, in mice, rats, hamsters, guinea-pigs and monkeys by subcutaneous injection or implantation and in mice by neonatal exposure.

Oral administration of oestradiol to mice bearing murine mammary tumour virus increased the incidences of uterine (endometrial and cervical) adenocarcinomas and mammary tumours. Its subcutaneous administration to mice resulted in increased incidences of mammary, pituitary, uterine, cervical, vaginal and lymphoid tumours and interstitial-cell tumours of the testis.

Invasive pituitary tumours were induced in rats treated with oestradiol dipropionate. In hamsters, a high incidence of malignant kidney tumours occurred in intact and castrated males and in ovariectomized females treated with oestradiol, but not in intact females. In guinea-pigs, diffuse fibromyomatous uterine and abdominal lesions were observed. Subcutaneous injections to neonatal mice resulted in precancerous and cancerous cervical and vaginal lesions in later life and an increased incidence of mammary tumours. The 4-hydroxy metabolite of oestradiol induced renal-cell carcinomas in castrated male hamsters.

Oestradiol was tested in two-stage carcinogenesis models in mice with the known carcinogens *N*-methyl-*N*-nitrosourea, *N*-ethyl-*N*-nitrosourea or 3-methylcholanthrene and in two-stage carcinogenesis models in rats with *N*-methyl-*N*-nitrosourea, 2-acetylaminofluorene, *N*-nitrosodiethylamine, 7,12-dimethylbenz[*a*]anthracene or *N*-butyl-*N*-nitrosourea. In mice, oestradiol enhanced the incidences of endometrial adenomatous hyperplasia, atypical hyperplasia and adenocarcinomas induced by *N*-methyl-*N*-nitrosourea and *N*-ethyl-*N*-nitrosourea. A continuously high serum concentration of oestradiol and a low concentration of progesterone appeared to be important for the development of endometrial adenocarcinomas in mice. Oestradiol suppressed the development of uterine cervical carcinomas induced by 3-methylcholanthrene. In rats, large doses of oestradiol alone or oestradiol with progesterone suppressed the development of mammary carcinomas induced by *N*-methyl-*N*-nitrosourea. Combined treatment of ovariectomized rats with oestradiol and *N*-methyl-*N*-nitrosourea-induced vaginal polyps. In a two-stage model of liver carcinogenesis in rats, oestradiol showed no initiating activity. It did not show promoting effects in the livers of rats initiated with *N*-nitrosodiethylamine. In one study pretreatment with oestradiol increased the number of liver foci positive for γ -glutamyl transferase induced by *N*-nitrosodiethylamine. Oestradiol did not affect mammary tumour development in intact or ovariectomized female rats treated with 7,12-dimethylbenz[*a*]anthracene. Oestradiol benzoate enhanced the incidence of mammary tumours in rats treated with γ -rays.

Oestriol

Oestriol was tested for carcinogenicity by subcutaneous implantation in one study in castrated mice and in one study in hamsters. In mice, oestriol increased the incidence and accelerated the appearance of mammary tumours in both male and female mice. In hamsters, oestriol produced kidney tumours.

In female mice, oestriol slightly increased the incidence of *N*-methyl-*N*-nitrosourea-induced endometrial adenocarcinomas. In several studies in female rats, oestriol inhibited the induction of mammary tumours by 7,12-dimethylbenz[*a*]anthracene when administered before the carcinogen; continuous treatment with oestriol resulted in a decreased incidence of mammary tumours. In one study in female rats, oestriol inhibited the induction of mammary carcinomas when administered 13–15 days after irradiation with γ -rays.

Oestrone

Oestrone was tested for carcinogenicity by oral administration in two studies in castrated male mice. The incidence of mammary tumours was increased. In one study in which oestrone was administered by skin application to mice, the incidence of mammary tumours was increased in males and that of pituitary tumours in animals of each sex. In studies in which oestrone was tested by subcutaneous and/or intramuscular administration, mammary tumours were induced in male mice, and the average age at the time of appearance of mammary tumours in female mice was reduced. In castrated male and female rats, subcutaneous injection of oestrone resulted in mammary tumours.

In three studies of subcutaneous or intramuscular administration, oestrone benzoate induced mammary tumours in male mice. In one study in rats, subcutaneous injection of oestrone benzoate induced mammary and pituitary tumours in animals of each sex. In several studies involving subcutaneous implantation of oestrone, the incidences of mammary and lymphoid tumours were increased in mice, and those of mammary and pituitary tumours were increased in rats. In one study of rats, implantation of low-dose oestrone pellets induced adrenal cortical tumours, but high-dose pellets reduced the incidence. In intact and castrated male hamsters, implantation of oestrone resulted in malignant kidney tumours. The oestrone metabolite, 4-hydroxyoestrone, induced kidney tumours at a low incidence in castrated male hamsters.

Oestrone-3,4-quinone, a metabolite of oestrone, was tested for carcinogenicity by direct injection into the mammary glands of rats fed a high-fat diet. There were no significant differences in mammary tumour incidence or multiplicity in comparison with controls that did not receive the metabolite.

The incidence of endometrial adenocarcinomas induced by *N*-methyl-*N*-nitrosourea in the uterine corpus of mice was significantly increased in those receiving an oestrone-containing diet; furthermore, the incidences of preneoplastic endometrial lesions in the *N*-methyl-*N*-nitrosourea-treated and untreated uterine corpora were significantly increased in mice receiving the oestrone-containing diet. In one study in female toads,

subcutaneous administration of oestrone enhanced the incidence of hepatocellular carcinomas induced by subcutaneous injection of *N*-nitrosodimethylamine.

5.4 Other relevant data

Oestrogens administered orally are absorbed rapidly and achieve maximum serum levels quickly. Although the major route of metabolism for oestrogens inactivates them and facilitates their excretion, a minor metabolic pathway activates a small proportion of oestrogen to catechol intermediates, with significant potential for damaging DNA, and may also yield reactive oxygen species that damage DNA. Some oestrogens, including conjugated oestrogens, have been reported to have genotoxic activity in experimental systems. At higher concentrations, which may or may not involve receptor mediation, oestrogens have been reported to induce changes in DNA and chromosomes. Oestradiol binds to oestrogen receptors with higher affinity than oestriol or oestrone. Oestrogens can increase the number of proliferating cells in the human endometrium *in vivo*. It has been reported that oestrogens increase cell proliferation in normal breast cells in monkeys and in cultured human breast cancer cells. At higher concentrations, oestrogens stimulated cell proliferation in rat liver *in vivo* and in cultured rat hepatocytes *in vitro*. No information was available on whether the effect of oestrogens on the mammary gland is modified by body weight or by the recency or duration of exposure to oestrogens in experimental systems. Similarly, no information was available on the possible relationship between exposure to oestrogens and the degree of malignancy of breast tumours.

5.5 Evaluation

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

There is *sufficient evidence* in experimental animals for the carcinogenicity of oestradiol and oestrone.

There is *limited evidence* in experimental animals for the carcinogenicity of conjugated equine oestrogens, equilin and oestriol.

There is *inadequate evidence* in experimental animals for the carcinogenicity of d-equilenin.

Overall evaluation

Post-menopausal oestrogen therapy is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: [Suppl. 7 \(1987\)](#)

POST-MENOPAUSAL OESTROGEN–PROGESTOGEN THERAPY (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

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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)*.

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Previous evaluation: [Suppl. 7 \(1987\)](#)

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