OESTROGENS, PROGESTINS AND COMBINATIONS

I. INTRODUCTORY REMARKS

IARC Monographs Volume 21[1] should be consulted for a general discussion of sex hormones and cancer. The principles considered in that volume remain applicable. Attention is drawn to specific points previously noted therein as 'General Conclusions on Sex Hormones':

'Steroid hormones are essential for the growth, differentiation and function of many tissues in both animals and humans. It has been established by animal experimentation that modification of the hormonal environment by surgical removal of endocrine glands, by pregnancy or by exogenous administration of steroids can increase or decrease the spontaneous occurrence of tumours or the induction of tumours by applied carcinogenic agents.... The incidence of tumours in humans could be altered by exposure to various exogenous hormones, singly or in combination.'

These statements make explicit the facts that oestrogens and progestins occur naturally, and that the hormonal milieu and dose-effect relationships are generally inextricably involved in the carcinogenic effects of oestrogens and progestins.

In this section, we describe the human epidemiology, carcinogenicity studies in animals, and other relevant data for oestrogens and progestins alone and in combination. The human epidemiological data reflect the patterns of use of oestrogens and progestins and their combinations in medical practice, i.e., the available information concerns specific products used for particular indications. Although many of the products have the same constituents (or a similar class of constituents), doses vary among products and the compounds and doses have changed over time. The operating principle is to determine the ability of the chemical to produce cancer or other genetic and related effects without the strictures of mode of human use or the magnitude of the doses. Thus, there is a basic incongruity between the human data and the animal carcinogenicity data. As noted earlier, however, the effects of these chemicals in humans appear, at least in most cases, to be linked to the hormonal milieu.

In this section, the current status of 'evidence for carcinogenicity to humans' is described only for diethylstilboestrol, oestrogen replacement therapy, medroxyprogesterone acetate, sequential oral contraceptives, combined oral contraceptives and oestrogen-progestin replacement therapy. There is little evidence that various oestrogens and progestins differ in

their effects on cancer risk when the effect is an oestrogenic/progestinic effect, and the reader should therefore consult the descriptions of other oestrogens and progestins.

The reader should also be aware that diethylstilboestrol, dienoestrol, hexoestrol and chlorotrianisene are nonsteroidal oestrogens, and their carcinogenic effects may not be due solely to their oestrogenic action.

Reference

[1]*IARC Monographs, 21*, 131-134, 1979

II. OESTROGENS

NONSTEROIDAL OESTROGENS (Group 1*)

Evidence for carcinogenicity to humans (*sufficient*)

Diethylstilboestrol (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Diethylstilboestrol (DES) causes clear-cell adenocarcinoma of the vagina and cervix in women exposed *in utero*. There is sufficient evidence that administration of oestrogens for the control of symptoms of the climacteric is causally related to an increased incidence of endometrial carcinoma; DES is no different from other oestrogens in this respect[1].

There is also clear evidence that administration of DES in large doses during pregnancy increases the subsequent risk of breast cancer and that DES increases the risk of testicular cancer in males exposed *in utero*.

In four follow-up studies[2-5] of exposed and nonexposed groups of women, the possible effects of DES exposure during pregnancy on subsequent breast cancer risk have been evaluated. All have shown an increased risk in exposed women. Two were randomized trials[2,3]. In one[2], there were 32 (4.6%) breast cancers among 693 women exposed to an average total dose of 12 g DES, and 21 (3.1%) breast cancers among 668 control (placebo) women. In the other[3], there were four (5.0%) breast cancers among 80 women exposed to an average total dose of DES of 16 g (plus ethisterone, average total dose, 14 g), compared to none of 76 controls; all 156 women were diabetic. In two studies, an exposed group and a 'matched' unexposed group were followed up[4,5]. One[4] showed 118 (4.4%) breast cancer cases in 2680 women exposed to a mean DES dose of 5 g, and 80 (3.1%) among 2566 control women. The other[5] similarly showed 38 (2.5%) breast cancer cases among 1531 women exposed to a mean DES dose of 2 g, and 24 (1.7%) cases among the 1404 control women. The overall relative risk from these four studies is 1.5 ($p = 0.001$).

A further group of 408 DES-exposed women (median dose, 1.5 g) was followed up, and the eight breast cancer cases found were contrasted to the 8.1 cases expected on the basis of

*This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group (see also Methods, p. 38).

local breast cancer incidence rates[6]. If this study is considered together with the four studies described above, the overall relative risk is 1.4 ($p = 0.0016$).

In all five papers[2-6], the possibility is discussed that there may be a long (15-20 years) 'latent' period before the first 'DES-induced' breast cancer would be seen. Clear evidence was found in a study[4] in which there was no difference in the breast cancer rates of exposed and nonexposed women until 22 years after exposure, but an increasing difference thereafter. Similarly, in another study[3], there was no case in the exposed group in the first 18 years after exposure. In a further study[5], the relative risk was 1.3 before age 50 and 1.7 thereafter; and, in another[6], three cases were reported with 5.1 expected before age 50 and five cases *versus* 3.0 expected thereafter. In contrast, however, a randomized study[2] showed 11 exposed cases and five nonexposed cases during the first 15 years of follow-up, compared to 21 exposed cases and 16 nonexposed cases thereafter. Further data are required to settle this issue.

The four follow-up studies[2-5] of exposed and nonexposed women also included information on other possibly 'hormone-related' cancers. The occurrence of endometrial cancer was not increased in any study. The study[2] of 693 women exposed to DES and 668 controls showed increases in the occurrence of cancer of the ovary (4 exposed, 1 nonexposed), cancer of the cervix (7 exposed, 3 nonexposed) and cancer of the colon-rectum (2 exposed, 1 nonexposed); there was also a risk for cancer at these sites in the study of 1531 women exposed to DES and 1404 controls[5] (6 exposed, 2 nonexposed; 9 exposed, 6 nonexposed; 11 exposed, 7 nonexposed for the three sites, respectively). A third study[4] showed, in contrast, no elevation of rates for cancer at any other site, and there were seven deaths from cervical cancer in the control group and none in the exposed group, suggesting that matching in the control group was 'inadequate'; the authors could not identify the matching problem, and, in particular, they found that the two groups were well matched on educational level. The data are too few to draw any firm conclusions.

A greater frequency of abnormalities of the reproductive tract has been found in males exposed prenatally to DES in comparison with nonexposed controls, although the data are few. Cryptorchidism, a major risk factor for testicular cancer, is one of the associated lesions[1]. Cancer of the testis has been investigated in five case-control studies of fetal exposure to DES[7-11]. One[7] showed that 5.1% (4/78) of cases and 1% of controls had been exposed to hormones (in all likelihood DES) for bleeding; the second[8] similarly found that 5.8% (11/190) *versus* 2.3% (7/304) had had such exposure; the third[9] found 1.9% (2/108) *versus* 0 (0/108) exposed to DES; the fourth[10] found 1.0% (2/202) *versus* 1.0% (2/206) exposed to DES; and the fifth[11] found 1.9% (4/211) *versus* 0.9% (2/214) exposed to DES. The combined relative risk is 2.5 ($p = 0.014$).

A number of unusual tumours have been reported in women exposed to DES *in utero*: a fatal adenocarcinoma of the endometrium at age 26[12]; a pituitary adenoma at age 18[13]; an invasive squamous-cell carcinoma of the cervix at age 21[14]; an invasive adenosquamous-cell carcinoma of the cervix at age 27[15]; and an ovarian teratoma at age 12[16].

There has been no further report to add to the six cases of primary breast cancer in males with prostatic cancer treated with DES[1]. A case has been reported of a Leydig-cell tumour developing in a man treated with DES at 1 mg per day for 2.5 years[17]. There has been a case

report of hepatic angiosarcoma in a man treated over a long period with DES for prostatic cancer[1,18], and a second case report of a hepatoma in a prostatic cancer patient treated with DES at 3 mg per day for 4.5 years (to diagnosis of hepatoma)[1,19]. Three renal carcinomas have been reported after exposure to DES for prostatic cancer[20,21].

B. Evidence for carcinogenicity to animals (*sufficient*)

DES has been tested in mice, rats, hamsters, frogs and squirrel monkeys, producing tumours principally in oestrogen-responsive tissues[1]. Female newborn mice injected with DES developed epidermoid carcinomas and granular-cell myoblastomas of the cervix and squamous carcinomas of the vagina[22]. Mice treated prenatally with DES developed adenocarcinomas of the uterus, cervix and vagina, epidermoid carcinomas of the uterine cervix and vagina and ovarian and mammary tumours[23-28]. Female mice fed diets containing DES developed cervical and endometrial adenocarcinomas, mammary adenocarcinomas, osteosarcomas and mesotheliomas[29-33]. Mice treated subcutaneously with DES had a slightly increased incidence of lymphomas and subcutaneous fibrosarcomas[34,35]. Prenatal exposure to DES potentiated mammary tumorigenesis in rats given 7,12-dimethylbenz[*a*]anthracene at about 50 days of age[36]. Rats given DES by subcutaneous pellet developed mammary and pituitary tumours. When these animals were also treated with X-rays or neutrons, they developed a higher incidence of mammary tumours[37-39]. In other studies (subcutaneous, transplacental, oral), rats treated with DES developed mammary, hepatic and pituitary tumours[40-44]. When hamsters were treated prenatally with DES, females developed endometrial adenocarcinoma, squamous-cell papillomas of the cervix and vagina, and a mixed Mullerian tumour of the cervix (myosarcoma); in males, a leiomysarcoma of the seminal vesicles and a Cowper's gland adenoma were found[45]. Male hamsters castrated as adults and given DES subcutaneously developed renal tumours[46,47].

C. Other relevant data

No data were available on the genetic and related effects of DES in humans.

DES induced chromosomal aberrations in bone-marrow cells of mice treated *in vivo*, but data on induction of sister chromatid exchanges and micronuclei were equivocal; it induced sister chromatid exchanges in one study in rats. Unusual nucleotides were found in kidney DNA following chronic treatment of hamsters with DES. Aneuploidy was induced in human cells *in vitro*, but data on induction of sister chromatid exchanges, chromosomal aberrations and mutation were inconclusive; it induced DNA strand breaks, but not unscheduled DNA synthesis, except in a single study. Tests for transformation in rat and Syrian hamster embryo cells gave positive results, while results for mouse cells were negative. Aneuploidy and DNA strand breaks were induced in rodent cells *in vitro*, but results for chromosomal aberrations, micronuclei and sister chromatid exchanges were equivocal; DES did not induce mutation or unscheduled DNA synthesis, except in a single study in Syrian hamster embryo cells. It did not inhibit intercellular communication of Chinese hamster V79 cells. It induced aneuploidy in fungi, but, in most studies, it did not induce mutation, recombination or gene conversion. It did not induce mutation in a variety

of bacterial and insect systems, but it was mutagenic in plants. DNA damage was not induced in fungi or bacteria. DES induced single-strand breaks in bacteriophage DNA in the presence of a horseradish peroxidase activation system[48].

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[48]*IARC Monographs, Suppl. 6*, 250-256, 1987

Dienoestrol

A. Evidence for carcinogenicity to animals (*limited*)

Dienoestrol was tested in female guinea-pigs by subcutaneous injection and in female mice by intravaginal administration. Although these experiments indicated induction of 'uterine tumours' in guinea-pigs and of ovarian tumours in mice, they were regarded as inadequate[1]. Renal tumours were produced by administration of α-dienoestrol in male hamsters castrated as adults[2,3]. In noninbred rats, dienoestrol given prenatally and neonatally did not increase tumour incidence[4].

B. Other relevant data

No data were available on the genetic and related effects of dienoestrol in humans.

There are two stable stereoisomers of dienoestrol — Z,Z-dienoestrol (*cis,cis*-dienoestrol, β-dienoestrol) and E,E-dienoestrol (*trans,trans*-dienoestrol, α-dienoestrol). E,E-Dienoestrol is the principal constituent of dienoestrol-containing medications, whereas Z,Z-dienoestrol is a metabolite of diethylstilboestrol. Z,Z-Dienoestrol induced sister chromatid exchanges in human fibroblasts *in vitro*. Z,Z-Dienoestrol, but not E,E-dienoestrol, transformed cultured hamster cells. Z,Z-Dienoestrol produced single-strand breaks in hamster cells in the absence of an exogenous metabolic system, whereas both Z,Z- and E,E-dienoestrol gave weakly positive results in tests for unscheduled DNA synthesis in hamster cells, only in the presence of a metabolic system. Z,Z-Dienoestrol did not induce single-strand breaks in bacteriophage DNA in the presence of a horseradish peroxidase activation system. Z,Z-Dienoestrol and E,E-dienoestrol were not mutagenic to bacteria[5].

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[5]*IARC Monographs, Suppl. 6*, 245-247, 1987

Hexoestrol

A. Evidence for carcinogenicity to animals (*sufficient*)

Hexoestrol was tested for carcinogenicity in intact male hamsters and in males castrated as adults by subcutaneous implantation as a pellet, producing renal tumours, some of which were described as renal carcinomas, in 85-100% of tested animals[1-3].

B. Other relevant data

No data were available on the genetic and related effects of hexoestrol in humans. Unusual nucleotides were found in kidney DNA of hamsters treated with hexoestrol *in vivo*. The compound was not mutagenic to bacteria[4].

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[4]*IARC Monographs, Suppl. 6*, 336-337, 1987

Chlorotrianisene

A. Evidence for carcinogenicity to animals (*inadequate*)

Chlorotrianisene was tested in only one experiment in rats by oral administration. The data were insufficient to evaluate the carcinogenicity of this compound[1].

B. Other relevant data

No data were available to the Working Group.

Reference

[1]*IARC Monographs, 21*, 139-146, 1979

STEROIDAL OESTROGENS (Group 1*)

Evidence for carcinogenicity to humans (*sufficient*)

Oestrogen replacement therapy (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

A number of studies, utilizing a variety of designs, have shown a consistent, strongly positive association between exposure to a number of oestrogenic substances and risk of endometrial cancer, with evidence of positive dose-response relationships both for strength of medication and duration of use[1]. Consistent findings have also been seen in more recent studies[2-16]. The rise and fall of incidence of endometrial cancer in several areas of the USA was compatible with trends in oestrogen use[1,15].

Of the 20 epidemiological studies of oestrogen replacement therapy and breast cancer risk[16-35], nine show a positive relation between oestrogen use and breast cancer[17-20,22-24,28,33]. The increased risks tend to be small; for example, a 50% increase was found with 20 years of menopausal oestrogen replacement therapy use[24]. All except one[33] of the positive studies involved use of population controls (eight of the nine studies with population controls gave positive results), and most showed increased risk after prolonged use or after ten or more years since initial exposure. One study showed a positive association with current oestrogen use[28].

*This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group (see also Methods, p. 38).

One possible reason that studies with hospital controls gave negative results and those with population controls positive results is that oestrogen replacement therapy may be used more frequently in hospitalized women than in the general population. However, in two studies involving use of both hospital and population control groups, one giving positive[29] and the other largely negative[25] results, similar results were obtained when hospital and population controls were used to estimate the relative risk. Three of the studies with negative results[26,27,34] probably did not permit the authors to address satisfactorily the question of long-term use of oestrogen replacement therapy. The large hospital-based study that showed a positive finding used as controls subjects with a large spectrum of acute conditions unrelated to any of the known or suspected risk factors for breast cancer[33].

One cohort study of 1439 women initially treated for benign breast disease showed increased risk for women who took exogenous oestrogens after biopsy, but not for those who had taken them before biopsy. The increased risk in the former group appeared to be associated with epithelial hyperplasia or calcification in the initial lesion[35].

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Conjugated oestrogens

A. Evidence for carcinogenicity to animals (*limited*)

Conjugated oestrogens were tested inadequately in rats by oral administration in one study[1]. In male hamsters castrated as adults, equilin administered as a subcutaneously implanted pellet produced renal tumours in 6/8 treated animals. In contrast, *d*-equilenin administered similarly did not induce renal tumours[2,3].

B. Other relevant data

No data were available on the genetic and related effects of conjugated oestrogens in humans.

A commercial preparation of conjugated oestrogens did not induce chromosomal aberrations in human lymphoblastoid cells *in vitro* or in Chinese hamster V79 cells exposed in diffusion chambers implanted into mice after oestrogen treatment. It was not mutagenic to bacteria[4].

References

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[4]*IARC Monographs, Suppl. 6*, 187, 1987

Oestradiol-17β and esters

A. Evidence for carcinogenicity to animals (*sufficient*)

Oestradiol-17β and its esters were tested in mice, rats, hamsters and guinea-pigs by oral and subcutaneous administration. Administration to mice increased the incidences of mammary, pituitary, uterine, cervical, vaginal, testicular, lymphoid and bone tumours[1-5]. In rats, there was an increased incidence of mammary and/or pituitary tumours[1,6]. Oestradiol-17β produced a nonstatistically significant increase in the incidence of foci of altered hepatocytes and hepatic nodules induced by partial hepatectomy and administration of *N*-nitrosodiethylamine in rats[7]. In hamsters, a high incidence of malignant kidney tumours occurred in intact and castrated males[1,8-10] and in ovariectomized females, but not in intact females[1]. In guinea-pigs, diffuse fibromyomatous uterine and abdominal lesions were observed[1].

B. Other relevant data

No data were available on the genetic and related effects of oestradiol-17β in humans.

Oestradiol-17β did not induce chromosomal aberrations in bone-marrow cells of mice treated *in vivo*. Unusual nucleotides were found in kidney DNA of treated hamsters. It induced micronuclei but not aneuploidy, chromosomal aberrations or sister chromatid exchanges in human cells *in vitro*. In rodent cells *in vitro*, it induced aneuploidy and unscheduled DNA synthesis but was not mutagenic and did not induce DNA strand breaks or sister chromatid exchanges. Oestradiol-17β was not mutagenic to bacteria[11].

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[11]*IARC Monographs, Suppl. 6*, 437-439, 1987

Oestriol

A. Evidence for carcinogenicity to animals (*limited*)

Oestriol was tested by subcutaneous implantation in castrated mice and in rats and hamsters. It increased the incidence and accelerated the appearance of mammary tumours in both male and female mice and produced kidney tumours in hamsters[1].

B. Other relevant data

No data were available on the genetic and related effects of oestriol in humans. It did not induce aneuploidy in cultured lymphocytes from one pregnant woman; results for induction of sister chromatid exchanges were inconclusive. No effect was seen in lymphocytes from one man[2].

References

[1]*IARC Monographs, 21*, 327-341, 1979

[2]*IARC Monographs, Suppl. 6*, 440-441, 1987

Oestrone

A. Evidence for carcinogenicity to animals (*sufficient*)

Oestrone was tested in mice by oral administration, in mice, rats and hamsters by subcutaneous injection and implantation, and in mice by skin painting. Its administration resulted in an increased incidence of mammary tumours in mice, in pituitary, adrenal and mammary tumours in rats, and in renal tumours in both castrated and intact male hamsters[1]. Oestrone implanted subcutaneously as a pellet produced renal tumours in 80% of treated male hamsters castrated as adults[2,3].

B. Other relevant data

No data were available on the genetic and related effects of oestrone in humans. It was not mutagenic to Chinese hamster cells *in vitro*[4].

References

[1]*IARC Monographs, 21*, 343-362, 1979

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[3]Li, J.J. & Li, S.A. (1984) Estrogen-induced tumorigenesis in hamsters: roles for hormonal and carcinogenic activities. *Arch. Toxicol., 55*, 110-118

[4]*IARC Monographs, Suppl. 6*, 442-443, 1987

Ethinyloestradiol

A. Evidence for carcinogenicity to animals (*sufficient*)

Ethinyloestradiol was tested in mice, rats, dogs and monkeys by oral administration and in rats by subcutaneous injection. In mice, it increased the incidences of pituitary tumours and of malignant mammary tumours in both males and females and produced malignant tumours of the uterus and cervix in females[1]. In rats, it increased the incidence of liver-cell tumours[1,2], pituitary chromophobe adenomas[2] and mammary adenocarcinomas[2,3]. Ethinyloestradiol administered as a subcutaneous injection of pellets produced a low but increased incidence of renal tumours in hamsters castrated as adults[4,5]. In rats, it induced foci of altered hepatocytes, a presumed preneoplastic lesion; when administered following initiation of hepatocarcinogenesis with *N*-nitrosodiethylamine, ethinyloestradiol enhanced the development of foci of altered hepatocytes and of hepatic nodules[6]. In female rats given partial hepatectomy and treated with *N*-nitrosodiethylamine, ethinyloestradiol potentiated the development of foci of altered hepatocytes and of hepatocellular carcinomas[7]. In *N*-nitrosodiethylamine-initiated rats, ethinyloestradiol increased the number of γ-glutamyl transpeptidase-positive hepatic foci[8]. Dietary administration of ethinyloestradiol combined

with subcutaneous injections of 3,2′-dimethyl-4-aminobiphenyl caused a high incidence of prostatic carcinomas in male rats[9]. In rats, ethinyloestradiol significantly enhanced the development of tumours of the liver and kidneys induced by several agents[10].

B. Other relevant data

No data were available on the genetic and related effects of ethinyloestradiol alone in humans. See, however, the summary of data for combined oral contraceptives (p. 297).

Ethinyloestradiol did not induce chromosomal aberrations in human lymphocytes, chromosomal aberrations or mutation in Chinese hamster cells or unscheduled DNA synthesis in rat hepatocytes *in vitro*. Studies on cell transformation were inconclusive. It was weakly active in an assay for inhibition of intercellular communication in Chinese hamster V79 cells. It did not induce sex-linked recessive lethal mutations in *Drosophila* or mutation in yeast and did not induce mutation or DNA damage in bacteria[11].

References

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[11]*IARC Monographs, Suppl. 6*, 293-295, 1987

Mestranol

A. Evidence for carcinogenicity to animals (*sufficient*)

Mestranol was tested in mice, rats, dogs and monkeys by oral administration. It increased the incidence of pituitary tumours and malignant mammary tumours in mice[1,2] and increased the incidence of malignant mammary tumours in female rats. Studies in monkeys were still in progress; although no tumour had been observed after seven years, no conclusive evaluation could be made[1]. Feeding of mestranol to rats following partial hepatectomy and treatment with *N*-nitrosodiethylamine enhanced the development of foci of altered hepatocytes and of hepatocellular carcinomas[3,4]. No significant increase in mammary tumour occurrence was seen in dogs treated with mestranol[5,6].

B. Other relevant data

No data were available on the genetic and related effects of mestranol alone in humans. See, however, the summary of data for combined oral contraceptives (p. 297).

Mestranol did not induce DNA strand breaks in hepatocytes of rats or chromosomal aberrations in bone-marrow cells of mice treated *in vivo*. It did not induce chromosomal aberrations in human lymphocytes *in vitro*. It was weakly active in an assay for inhibition of intercellular communication in Chinese hamster V79 cells. It did not induce unscheduled DNA synthesis in cultured rat hepatocytes or sex-linked recessive lethal mutations in *Drosophila*. It was not mutagenic to bacteria[7].

References

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III. PROGESTINS (Group 2B)

Evidence for carcinogenicity to humans (*inadequate*)

Medroxyprogesterone acetate (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

The results of one cross-sectional study of the development of breast nodules in women given medroxyprogesterone acetate was difficult to interpret because of methodological considerations[1]. Two small cohort studies in the USA showed relative risks (and 95% confidence limits) of breast cancer in women exposed to medroxyprogesterone acetate of 0.69 (0.3-1.4)[2] and 1.1 (0.5-2.4)[3], but both included only women with short-term exposure and limited duration of follow-up. A case-control study of 30 women with breast cancer and 179 controls[4] yielded a relative risk of 1.0 (no confidence limits given) for use of medroxyprogesterone acetate at some time. Preliminary analyses of a collaborative case-control study in Thailand, Kenya and Mexico sponsored by the World Health Organization[5], based on 427 cases (39 'ever' users) and 5951 controls (557 'ever' users), provided estimates of relative risk (and 95% confidence limits) for breast cancer of 1.0 (0.7-1.5) in women who 'ever' used medroxyprogesterone acetate, 1.1 (0.7-1.9) for users for 1-12 months, 1.2 (0.7-2.2) for users for 13-36 months and 0.8 (0.4-1.7) for users for $\geqslant$37 months.

Medroxyprogesterone acetate causes reversible changes in the endometrium, from proliferative to secretory or suppressed[4]. In one small cohort study, one case of uterine leiomyosarcoma was found, with 0.83 cancers of the uterine corpus expected, giving a relative risk of 1.2 [0.03-6.7][2]. In the collaborative study[5], the estimated relative risk for endometrial cancer in 'ever' users of medroxyprogesterone acetate was 0.3 (0.04-2.4), based on 57 cases, only one of which was exposed, and 316 matched controls (30 exposed).

In one small cohort study[2], one ovarian cancer case occurred in a medroxyprogesterone acetate user, with 1.16 expected, giving a relative risk of 0.86 [0.02-4.6]. Preliminary analysis of data from the collaborative study[5], based on 105 cases (seven exposed) and 637 matched controls (74 exposed) yielded a relative risk for ovarian cancer of 0.7 (0.3-1.7) in 'ever' users of medroxyprogesterone acetate.

The results of two cohort studies of dysplasia and of carcinoma *in situ* of the uterine cervix in women given medroxyprogesterone acetate were conflicting and difficult to interpret because of methodological problems[1]. Preliminary results from the collaborative study[5], based on 920 cases of invasive cervical carcinoma (126 exposed to medroxyprogesterone acetate) and 5833 controls (545 exposed) yielded estimated relative risks of 1.2 (0.9-1.5) in 'ever' users, after controlling for parity, history of vaginal discharge, age at first sexual relationship, number of sexual partners, number of prior Pap smears and use of an intrauterine device and oral contraceptives. Relative risks in users for 1-12, 13-24, 25-60 and $\geqslant$61 months were estimated to be 1.4 (1.0-2.0), 1.2 (0.7-2.0), 0.6 (0.4-1.1) and 1.4 (0.9-2.2), respectively.

Preliminary analyses of data from the collaborative study[5] showed the relative risk for primary liver cancer (all histological types combined) in women who had ever used

medroxyprogesterone acetate to be 1.0 (0.4-2.8), based on 57 cases (seven exposed) and 290 controls (34 exposed).

B. Evidence for carcinogenicity to animals (*sufficient*)

Medroxyprogesterone acetate was tested by intramuscular injection in dogs and by subcutaneous implantation in mice. It induced adenocarcinomas of the mammary gland in one study in female mice[6], and produced malignant mammary tumours in dogs[1]. After four years of intramuscular treatment of dogs with a human contraceptive dose, a dose-related increase in the incidence of mammary nodules was seen; the incidence of mammary-gland nodules at that time was comparable with that seen in dogs given progesterone at 25 times the canine luteal level[7]. Female dogs treated with medroxyprogesterone acetate for at least one year had a significant increase in the incidence of large and small mammary nodules as compared with control animals in one study[8], and a dose-related increase in the incidence of large mammary nodules was found in another after intramuscular administration[9].

C. Other relevant data

No data were available on the genetic and related effects of medroxyprogesterone acetate alone in humans. See, however, the summary of data for combined oral contraceptives (p. 297). Medroxyprogesterone acetate induced sister chromatid exchanges in mouse cells *in vitro*[10].

References

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[10]*IARC Monographs, Suppl. 6*, 359-360, 1987

Chlormadinone acetate

A. Evidence for carcinogenicity to animals (*limited*)

Chlormadinone acetate was tested in mice, rats and dogs by oral administration. In dogs, it produced mammary tumours in one study[1] and increased the incidence of mammary-gland hyperplasia and mammary nodules in another[2].

B. Other relevant data

No data were available on the genetic and related effects of chlormadinone acetate alone in humans. See, however, the summary of data for combined oral contraceptives (p. 297). Chlormadinone acetate did not induce chromosomal aberrations in cultured human lymphocytes and was not mutagenic to bacteria[3].

References

[1]*IARC Monographs, 21*, 365-375, 1979

[2]El Etreby, M.F. & Gräf, K.-J. (1979) Effect of contraceptive steroids on mammary gland of beagle dog and its relevance to human carcinogenicity. *Pharmacol. Ther., 5*, 369-402

[3]*IARC Monographs, Suppl. 6*, 148-149, 1987

Dimethisterone

A. Evidence for carcinogenicity to animals (*inadequate*)

Dimethisterone was reported to have been tested in monkeys in one study. No increase in tumour incidence was found[1].

B. Other relevant data

No data were available on the genetic and related effects of dimethisterone in humans. It did not induce chromosomal aberrations in cultured human lymphocytes[2].

References

[1]Weikel, J.H., Jr & Nelson, L.W. (1977) Problems in evaluating chronic toxicity of contraceptive steroids in dogs. *J. Toxicol. environ. Health, 3*, 167-177

[2]*IARC Monographs, Suppl. 6*, 260-261, 1987

Ethynodiol diacetate

A. Evidence for carcinogenicity to animals (*limited*)

Ethynodiol diacetate was tested in mice and rats by oral administration. It increased the incidence of benign liver tumours in male mice and of mammary tumours in castrated male mice, and produced benign mammary tumours in male rats[1].

B. Other relevant data

No data were available on the genetic and related effects of ethynodiol diacetate alone in humans. See, however, the summary of data for combined oral contraceptives (p. 297). Ethynodiol diacetate did not induce sex-linked recessive lethal mutations in *Drosophila*[2].

References

[1]*IARC Monographs, 21*, 387-398, 1979

[2]*IARC Monographs, Suppl. 6*, 308-309, 1987

17α-Hydroxyprogesterone caproate

A. Evidence for carcinogenicity to animals (*inadequate*)

17α-Hydroxyprogesterone caproate was tested in rabbits by repeated intramuscular injection, giving inconclusive results[1]. It was reported to have accelerated the growth of a transplantable cervical tumour line in mice[2].

B. Other relevant data

No data were available to the Working Group.

References

[1]*IARC Monographs, 21*, 399-406, 1979

[2]Umancheeva, A.F., Novikova, A.I. & Anisomov, V.N. (1981) Stimulating effect of pregnancy on the growth of cervical cancer (Russ.). *Akush. Ginekol., 1*, 53-55

Lynoestrenol

A. Evidence for carcinogenicity to animals (*inadequate*)

Lynoestrenol was tested by oral administration in mice and rats. It induced a slight increase in the incidence of benign liver-cell tumours in male mice and of malignant mammary tumours in female mice. In female rats, a slight but nonsignificant increase in the incidence of malignant mammary tumours was observed after administration of lynoestrenol[1].

B. Other relevant data

No data were available to the Working Group.

References

[1]*IARC Monographs, 21*, 407-415, 1979

Megestrol acetate

A. Evidence for carcinogenicity to animals (*limited*)

Megestrol acetate was tested by oral administration in mice, rats, dogs and monkeys. It produced nodular hyperplasia, and benign and malignant mammary tumours in dogs[1]. No tumour was reported in monkeys[2].

B. Other relevant data

No data were available on the genetic and related effects of megestrol acetate alone in humans. See, however, the summary of data for combined oral contraceptives (p. 297). Megestrol acetate did not induce chromosomal aberrations in cultured human lymphocytes[3].

References

[1]*IARC Monographs, 21*, 431-439, 1979

[2]Weikel, J.H., Jr & Nelson, L.W. (1977) Problems in evaluating chronic toxicity of contraceptive steroids in dogs. *J. Toxicol. environ. Health, 3*, 361-362, 1987

[3]*IARC Monographs, Suppl. 6*, 361-362, 1987

Norethisterone

A. Evidence for carcinogenicity to animals (*sufficient*)

Norethisterone and its acetate were tested by oral administration in mice and rats, and by subcutaneous implantation in mice. In mice, norethisterone and its acetate increased the incidence of benign liver-cell tumours in males; norethisterone increased the incidence of pituitary tumours in females and produced granulosa-cell tumours in the ovaries of females. Norethisterone increased the incidence of benign liver-cell tumours and benign and malignant mammary tumours in male rats[1]. Rats fed 3-4 mg/kg bw per day norethisterone acetate (about 100 times the daily human dose) for two years had an increased incidence of neoplastic nodules of the liver; an increase in the incidence of uterine polyps was seen in females[2]. In rats given weekly intramuscular injections for 104 weeks of norethisterone enanthate at doses of 10, 30 and 100 mg/kg bw (20, 60 and 200 times the daily human contraceptive dose), there was a dose-related increase in pituitary-gland tumours in males, whereas in females no effect on pituitary glands was observed with the lowest dose and a reduction in pituitary tumours was observed with the highest dose. Benign mammary tumours were observed in males at all doses, but there was little effect in females; the incidence of malignant mammary tumours was greatly increased in both males and females given the two higher dose levels and was dose-related. A dose-related increase in the incidence of liver tumours was also seen in animals of each sex[3].

B. Other relevant data

No data were available on the genetic and related effects of norethisterone alone in humans. See, however, the summary of data for combined oral contraceptives (p. 297).

Aneuploidy was observed in oocytes of mice treated with high doses of norethisterone acetate. In a test for dominant lethal mutations in which female mice were exposed orally to norethisterone acetate, no increase was seen in one strain of mice, and a second strain showed an increase only when females were mated within two weeks after treatment. The compound did not induce aneuploidy or chromosomal aberrations in cultured human lymphocytes. Neither norethisterone nor its acetate was mutagenic to bacteria[4].

References

[1] *IARC Monographs, 21*, 441-460, 1979

[2] Schardein, J.L. (1980) Studies on the components of an oral contraceptive agent in albino rats. II. Progestogenic component and comparison of effects of the components and the combined agent. *J. Toxicol. environ. Health, 6*, 895-906

[3] El Etreby, M.F. & Neumann, F. (1980) *Influence of sex steroids and steroid antagonists on hormone-dependent tumors in experimental animals.* In: Iacobelli, S., King, R.J.B., Lindner, H.R. & Lippman, M.E., eds, *Hormones and Cancer*, New York, Raven Press, pp. 321-336

[4] *IARC Monographs, Suppl. 6*, 427-429, 1987

Norethynodrel

A. Evidence for carcinogenicity to animals (*limited*)

Norethynodrel was tested by oral administration in mice and rats and by subcutaneous implantation in mice. It increased the incidence of pituitary tumours in mice of each sex and that of mammary tumours in castrated males of one strain. It also increased the incidence of benign and malignant liver-cell, pituitary and mammary (benign and malignant) tumours in male rats[1]. Feeding of norethynodrel to rats following partial hepatectomy and treatment with *N*-nitrosodiethylamine increased the number of γ-glutamyl transpeptidase-positive hepatic foci at four months, but there was no significant difference by nine months[2].

B. Other relevant data

No data were available on the genetic and related effects of norethynodrel alone in humans. See, however, the summary of data for combined oral contraceptives (p. 297). Norethynodrel did not induce aneuploidy in human cells in culture or unscheduled DNA synthesis in rat hepatocytes *in vitro*. It inhibited intercellular communication in Chinese hamster V79 cells. The compound was not mutagenic to bacteria[3].

References

[1]*IARC Monographs*, *21*, 461-477, 1979

[2]Yager, J.D., Jr & Yager, R. (1980) Oral contraceptive steroids as promoters of hepatocarcinogenesis in female Sprague-Dawley rats. *Cancer Res.*, *40*, 3680-3685

[3]*IARC Monographs*, *Suppl. 6*, 430-431, 1987

Norgestrel

A. Evidence for carcinogenicity to animals (*inadequate*)

Norgestrel was tested by oral administration in mice and rats. No increase in the incidence of tumours was observed in either species[1].

B. Other relevant data

No data were available on the genetic and related effects of norgestrel alone in humans. See, however, the summary of data for combined oral contraceptives (p. 297). Norgestrel gave inconclusive results in tests for sex-linked recessive lethal mutations in *Drosophila*. It was not mutagenic to bacteria[2].

References

[1]*IARC Monographs*, *21*, 479-490, 1979

[2]*IARC Monographs*, *Suppl. 6*, 432-433, 1987

Progesterone

A. Evidence for carcinogenicity to animals (*sufficient*)

Progesterone was tested by subcutaneous and by intramuscular injection in mice, rabbits and dogs, and by subcutaneous implantation in mice. It increased the incidences of ovarian, uterine and mammary tumours in mice. Neonatal treatment with progesterone enhanced the occurrence of precancerous and cancerous lesions of the genital tract and increased mammary tumorigenesis in female mice[1]. Dogs treated with progesterone for four years at one to 25 times the luteal-phase levels for that species developed a dose-related incidence of mammary-gland nodules[2].

B. Other relevant data

No data were available on the genetic and related effects of progesterone in humans.

Progesterone did not induce dominant lethal mutations in mice or chromosomal aberrations in rats treated *in vivo*. It did not induce chromosomal aberrations or sister chromatid exchanges in cultured human cells, nor chromosomal aberrations or DNA strand breaks in rodent cells. Studies on transformation of rodent cells *in vitro* were inconclusive: a clearly positive result was obtained for rat embryo cells, a weakly positive result for mouse cells and a negative result for Syrian hamster embryo cells. Progesterone was not mutagenic to bacteria[3].

References

[1]*IARC Monographs*, *21*, 491-515, 1979

[2]Frank, D.W., Kirton, K.T., Murchison, T.E., Quinlan, W.J., Coleman, M.E., Gilbertson, T.J., Feenstra, E.S. & Kimball, F.A. (1979) Mammary tumors and serum hormones in the bitch treated with medroxyprogesterone acetate or progesterone for four years. *Fertil. Steril.*, *31*, 340-346

[3]*IARC Monographs*, *Suppl. 6*, 479-481, 1987

IV. OESTROGEN-PROGESTIN COMBINATIONS

SEQUENTIAL ORAL CONTRACEPTIVES (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Case reports of endometrial cancer occurring at an unusually young age in users of sequential oral contraceptives provide evidence that these preparations can cause endometrial cancer[1]. Three case-control studies have provided the following estimates of the relative risk (and 95% confidence intervals) for endometrial cancer in women who had used sequential oral contraceptives: 2.2 (0.6-7.3)[2], 2.1 (0.8-5.8)[3] and [1.9 (0.7-5.3)][4]. One study[2]

showed a relative risk of 7.3 (1.4-38.8) in users of a preparation that contained a relatively large amount of a potent oestrogen (0.1 mg ethinyloestradiol) and only a weak progestin (25 mg dimethisterone); another[4] showed a relative risk of 4.6 in users of more than two years' duration. The finding of an increased risk for endometrial cancer in relation to sequential oral contraceptives is in contrast with a reduction in risk for endometrial cancer found in association with the use of combined oral contraceptives (see below).

B. Evidence for carcinogenicity to animals (*inadequate* for dimethisterone in combination with ethinyloestradiol)

Dimethisterone and oestrogen

When dimethisterone and ethinyloestradiol were given sequentially to female dogs by oral administration, a few palpable mammary nodules were reported to have occurred in treated (4/16) and in untreated animals (2/16)[5].

C. Other relevant data

No adequate data were available on the genetic and related effects of sequential oral contraceptives in humans. See, however, the summaries of data on individual compounds commonly found in sequential oral contraceptives: chlormadinone acetate (p. 291), dimethisterone (p. 291), ethinyloestradiol (p. 286) and mestranol (p. 288).

References

[1]*IARC Monographs, 21*, 111-112, 133, 1979

[2]Weiss, N.S. & Sayvetz, T.A. (1980) Incidence of endometrial cancer in relation to the use of oral contraceptives. *New Engl. J. Med., 302*, 551-554

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[4]Henderson, B.E., Casagrande, J.T., Pike, M.C., Mack, T., Rosario, I. & Duke, A. (1983) The epidemiology of endometrial cancer in young women. *Br. J. Cancer, 47*, 749-756

[5]*IARC Monographs, 21*, 233-255, 377-385, 1979

COMBINED ORAL CONTRACEPTIVES (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

There is sufficient evidence that combined oral contraceptives cause benign and malignant liver tumours. There is also conclusive evidence that these agents protect against cancers of the ovary and endometrium.

Liver cancer

Numerous case reports and series of hepatic-cell adenomas occurring almost exclusively in women who had used combined oral contraceptives strongly suggest that such benign

tumours may result from exposure to these products[1]. Two case-control studies[1] have shown that risk of hepatic-cell adenomas increases strongly with duration of use and have provided estimates of the relative risk in users for more than seven and nine years duration of 500[2] and 25[3], respectively. The many reports of focal nodular hyperplasia occurring in users of oral contraceptives could also represent a causal relationship, but these lesions also occur in men and older women, and no case-control study on these populations has been conducted.

Reports of hepatocellular carcinomas occurring in conjunction with liver-cell adenomas in users of oral contraceptives have been published[1]. In addition, three case-control studies of hepatocellular carcinomas, one in the USA[4] and two in the UK[5,6], have shown strong trends of increasing risk with duration of use. Relative risks (95% confidence limits) in the three studies in users of more than five, eight and eight years' duration, respectively, were estimated to be [13.5 (1.2-152.2)][4], 7.2 (2.0-25.7)[5] and 20.1 (2.3-175.7)[4], respectively. When data for all three studies are combined, relative risks of 2.5 (1.1-5.5) and 10.0 (3.7-27.2) in 'ever' users and users for more than five to eight years (depending on the study) were derived by the Working Group. Although all three case-control studies of liver cancers and oral contraceptives are small and have methodological deficiencies that could have resulted in biased results, the magnitude of the relative risks and the consistency of the results provide strong evidence that the results are not spurious. Case reports of cholangiocarcinoma in users of oral contraceptives have also been published, but one case-control study of 11 cases[6] showed no association with use of oral contraceptives [(relative risk, 0.3 in women who ever used oral contraceptives; 0.9 in users of four or more years)].

Ovarian cancer

Ten case-control studies have provided the following estimates of the relative risk (95% confidence limits) for ovarian cancer in women who had ever used combined oral contraceptives: 0.6 [0.3-1.1][7], [0.7 (0.4-1.1)][8], 0.8 (0.4-1.5)[9], 0.5 (0.2-1.5)[10], 0.6 [0.4-1.0][11], 0.7 (0.4-1.1)[12], 0.4 (0.2-1.0)[13], 0.6 (0.4-0.9)[14], 0.6 (0.4-0.9)[15] and 0.6 (0.4-1.0)[16]. Six of these studies assessed risk in relation to duration of use, and five provide at least some evidence that the risk declines with years of exposure, although this trend is less striking than that for endometrial cancer (see below). Relative risks in women who had used combined oral contraceptives for up to or more than five, five, seven and nine years were found in four different studies to be 0.3 (0.1-0.8)[14], 0.4 (0.2-0.6)[15], 0.6 [0.3-1.4][8] and 0.4 (0.2-1.3)[11].

Endometrial cancer

Five case-control studies have provided the following estimates of the relative risk (95% confidence limits) for endometrial cancer in women who had ever used combined oral contraceptives: 0.5 (0.1-1.0)[17], 0.4 (0.2-0.8)[18], 0.4 [0.2-1.2][19], 0.5 (0.3-0.8)[20] and 0.6 (0.2-1.3)[16]. Three of these[18-20], and two others[21,22], assessed risk in relation to duration of use, and all showed a decline in risk with duration of exposure. Relative risks in users of five or more years' duration were estimated in two studies to be 0.3 (0.1-1.3)[19] and 0.6 (0.4-0.9)[20], and one study showed a relative risk of 0.1[22] in women with six or more years of use.

Cervical cancer

Four case-control studies[23-26] of cervical squamous dysplasia provide estimates of relative risk in women who had ever used combined oral contraceptives ranging from 1.2 to 3, and the lower limit of the 95% confidence limits of two of the estimates was greater than 1.0. Relative risks (95% confidence limits) from three cohort studies were [5.0 (1.2-20.8)][1], 1.5 [(0.8-2.6)][27] and 1.1 [(0.8-1.7)][28]. Relative risks for squamous dysplasia were found to increase with duration of use in two[24,26] of three case-control studies in which risk in relation to length of exposure was considered, and those for women who had used oral contraceptives for more than four years were found in two cohort studies to be [4.9 (1.1-21.8)[1]] and 2.0 [(1.1-3.6)][27].

Four case-control studies of cervical carcinoma *in situ*[1,23-25] provide estimates of relative risk in women who had ever used combined oral contraceptives ranging from 0.6 to 1.1[25], with 95% confidence limits that include 1.0; but one additional such study yielded an estimated relative risk of [1.6 (1.2-2.0)][1], and estimates from three cohort studies were [3.7 (1.5-9.0)][1], 1.6 [(0.8-3.0)][27] and 1.2 (0.8-1.7)[28]. One case-control study showed a strong increase in risk for carcinoma *in situ* with duration of use[24], but two others did not[1,25]. Relative risks in users of more than four years' duration were estimated in two cohort studies to be [5.4 (2.1-13.7)][1] and 1.7 [(0.9-3.2)][27]. Another cohort study[1] showed the risk of progression from dysplasia to carcinoma *in situ* to be six times greater in users than in nonusers of oral contraceptives.

Three case-control studies of invasive cervical cancer yielded relative risks in women who had ever used combined oral contraceptives of 1.2 (1.0-1.4)[29], 1.5 (1.1-2.1)[30] and 1.7 (0.8-3.6)[16]; and three cohort studies gave incidence rates of invasive cervical cancer per 1000 women years in users and nonusers of oral contraceptives of 0.20 and 0[27], 0.15 and 0.07[31] and 0.12 and 0[28]. All three case-control studies also showed that risk increased with duration of use; and the two in which relative risks were assessed in women who had used oral contraceptives for more than five years gave values of 1.5 (1.1-2.1)[29] and [1.9 (1.3-2.7)][30].

There is evidence that one or more sexually transmitted, infective agents play an important role in the development of cervical cancer. Since this agent(s) has not been unequivocally identified, and, in particular, was not considered in the studies under review, surrogate measures were used to reflect degree of sexual activity and to adjust for this. Any observed effect of oral contraceptives on risk of cervical cancer may therefore be confounded by an association of oral contraceptive use with exposure to the putative infective agent. Since the specific factor by which the analysis should be adjusted is not known, the Working Group considered that adjusting for age at first intercourse and number of sexual partners may not be sufficient to remove the confounding and, therefore, that they could not regard a causal association of oral contraceptives and cervical cancer as proven.

Breast cancer

Relative risks for breast cancer in women who had ever used combined oral contraceptives have been assessed in 18 case-control studies[1,16,32-43] and in seven cohort studies[1,44-47]. All provide point estimates of relative risk close to unity, with 95% confidence

intervals that include 1.0. Six case-control studies have provided estimates of the relative risk in women who had used combined oral contraceptives for more than a decade: four[36,39,40,43] yield relative risks between 0.7 and 1.1 with 95% confidence limits that included 1.0 in users of ten or more years' duration; another[48] provides a relative risk estimate of 2.2 (1.2-4.0) in users of 12 or more years' duration; and one[42] gives a relative risk of 0.6 (0.4-0.9) in women who had used oral contraceptives for 15 or more years. Eight case-control studies[16,36-38,40,42,43,48] and two cohort studies[44,45] give estimated relative risks for breast cancer ten or more to 20 or more years after initial exposure to combined oral contraceptives, and all are close to 1.0, with 95% confidence intervals that include unity. Eleven case-control studies have assessed risk for breast cancer among women who had used combined oral contraceptives before their first full-term pregnancy. The results are inconsistent, six studies[39,40,43,47,49,50] showing no significant elevation in risk, three[34,37,51] showing a significant trend of increasing risk with duration of use, and two[48,52] showing an increased risk without a significant trend. The reasons for these discrepant findings have not been identified. Five case-control studies have assessed risk in women who had used combined oral contraceptives before 25 years of age. The initial study of this issue showed a strong trend of increasing risk with years of use before age 25[53]. A subsequent study from Sweden[54] showed a relative risk of 3.3 in women who had ever used oral contraceptives at age 20-24, but ascertainment of prior use was not comparable for cases and controls, rendering this finding suspect. Another study from Norway and Sweden[48] gave a relative risk of 2.7 in women who had used oral contraceptives for eight or more years before the age of 25, but the confidence limits for this included 1.0 (0.7-11.0), and no consistent trend of increasing risk with duration of use was observed. The fourth study, from New Zealand[43], showed a nonsignificant ($p = 0.4$) trend of declining risk with duration of use before age 25 and estimated the relative risk in users of six or more years to be 0.6. The fifth study[50] gave relative risks of 1.0 to 1.3 in six categories of duration of use (<12, 13-48 and >48 months in women less than 20 and in women 20-24 years of age) but no trend of increasing risk with duration of use. Risk was also initially reported to be particularly enhanced by use before age 25[53] of oral contraceptives with a high progestogen potency, but the authors' classification has been disputed; and results from a large collaborative study in the USA do not confirm their findings[50].

Other tumours

The relative risk for malignant melanoma in women who had ever taken oral contraceptives has been estimated in eight case-control[1,55-61] and three cohort[55,62,63] studies. Values from all the case-control studies were close to unity, with 95% confidence limits that included 1.0. Values from the three cohort studies were 0.3 [0.1-0.8][55], 1.5 (0.7-2.9)[62] and 3.5 (1.4-9.0)[63]. The reasons for these widely discrepant results are unknown. Trends of increasing risk with duration of use have been observed in some investigations but not in others. The two case-control studies in which analyses were performed to estimate the relative risk in users of more than two[56] and five[59] years' duration, ten or more years after initial exposure, showed elevated risks of 2.3 (0.8-6.9) and 1.5 (1.0-2.1), respectively. Two case-control studies showed trends of increasing risk specifically for superficial spreading

melanoma with increasing duration of use[57,60], although a third did not[63]. Also, two studies have shown relative risks for superficial spreading-type melanoma to be increased in users of five or more years' duration after latent periods of over ten[59] and 12[57] years: [1.6 (1.0-2.6)] and 4.4 (2.0-9.7), respectively.

Two case-control studies and two prospective studies have shown no increase in risk for pituitary adenomas[1,64,65].

Women who took oral contraceptives after evacuation of a hydatidiform mole were reported in one study[1] subsequently to have developed trophoblastic tumours more frequently than women who had used other methods of contraception after a molar evacuation, but this was not confirmed in another investigation[66].

A single case-control study showed a reduction in risk for carcinomas of the colon and rectum with duration of use of combined oral contraceptives[67], but two cohort studies showed no alteration in risk for these neoplasms in users[63,68].

A protective effect of combined oral contraceptives against both fibroadenoma and fibrocystic disease of the breast has been found in many investigations[1,63,69-72], although a single recent study found an increase in risk for the latter condition in postmenopausal women[73]. One study showed no protective effect of oral contraceptives against fibrocystic disease with atypical histological features[1], but one subsequent investigation did[70].

A reduction in risk for retention cysts of the ovary has been documented in two cohort studies and in one case-control study[1]. A reduction in risk for uterine leiomyoma has been documented in one case-control study[74].

B. Evidence for carcinogenicity to animals (*sufficient* for norethynodrel in combination with mestranol; *limited* for chlormadinone acetate in combination with mestranol or ethinyloestradiol, for ethynodiol acetate in combination with mestranol or ethinyloestradiol, for megestrol acetate in combination with ethinyloestradiol, for norethisterone in combination with mestranol or ethinyloestradiol, for progesterone in combination with oestradiol-17β, and for investigational contraceptives; *inadequate* for lynoestrenol in combination with mestranol and for norgestrel in combination with ethinyloestradiol)

Chlormadinone acetate and oestrogens

Chlormadinone acetate, in combination with mestranol, was tested for carcinogenicity by oral administration to mice; an increased incidence of pituitary tumours was observed in animals of each sex. Oral administration of chlormadinone acetate in combination with ethinyloestradiol to mice resulted in an increased incidence of mammary tumours in intact and castrated males[75].

Ethynodiol diacetate and oestrogens

Following oral administration of ethynodiol diacetate plus mestranol to mice, increased incidences of pituitary tumours were observed in animals of each sex. Ethynodiol diacetate plus ethinyloestradiol was tested for carcinogenicity by oral administration to mice and rats.

In mice, it induced increased incidences of pituitary tumours in animals of each sex and of malignant tumours of connective tissues of the uterus. In rats, malignant mammary tumours were produced in animals of each sex[76].

Lynoestrenol and oestrogens

Lynoestrenol, in combination with mestranol, was tested in mice and female rats by oral administration. A slight, nonsignificant increase in the incidence of malignant mammary tumours was observed in female mice[77].

Megestrol acetate and oestrogens

Megestrol acetate plus ethinyloestradiol was tested for carcinogenicity by oral administration to mice and rats. In mice, increased incidences of malignant mammary tumours were observed in animals of each sex. No increase in tumour incidence was observed in rats[78].

Norethisterone and oestrogens

Norethisterone acetate plus ethinyloestradiol was tested for carcinogenicity by oral administration to mice, rats and monkeys. In mice, pituitary tumours were observed in animals of each sex. In rats, increased incidences of benign mammary tumours were found in males in one study and of benign liver-cell and mammary tumours in animals of each sex in the other[79]. Norethisterone acetate plus ethinyloestradiol administered orally to rats induced endometrial carcinomas[80]. Oral administration of norethisterone acetate plus ethinyloestradiol to female rats for 12 months resulted in hyperplastic nodules of the liver in all animals and a hepatocellular carcinoma in one (preliminary results)[81]. Norethisterone acetate and ethinyloestradiol given orally to monkeys for ten years did not produce malignant tumours[82].

Norethisterone plus mestranol was tested for carcinogenicity in mice and rats by oral administration. In mice, pituitary tumours developed in animals of each sex. In rats, an increased incidence of malignant mammary tumours was found in females. Norethisterone plus ethinyloestradiol, tested in mice by oral administration, induced an increased incidence of pituitary tumours in females[79].

Norethynodrel and oestrogens

Norethynodrel in combination with mestranol was tested for carcinogenicity in mice, rats, hamsters and monkeys orally and by subcutaneous implantation. Increased incidences of pituitary, mammary, vaginal and cervical tumours were found in female mice and of pituitary tumours in male mice. In castrated male mice, the combined treatment resulted in an increase in the incidence of mammary tumours. In rats, benign liver-cell tumours were observed in males and pituitary tumours and malignant mammary tumours in animals of each sex. A study of hamsters was of too short a duration to be considered for evaluation.

The combined treatment given to *Macaca mulatta* monkeys for five years did not increase the incidence of mammary tumours[83].

Norgestrel and oestrogens

Norgestrel plus ethinyloestradiol was tested for carcinogenicity in mice and rats by oral administration. No increase in the incidence of tumours was observed in either species[84].

Progesterone and oestrogen

Neonatal exposure of mice to progesterone plus oestradiol-17β resulted in an increased incidence of mammary tumours[85].

Investigational oral contraceptives

Three investigational oral contraceptives (ethynerone, chloroethynyl norgestrel or anagestone acetate plus mestranol) were tested for carcinogenicity by oral administration to dogs. An increased incidence of malignant mammary tumours was observed after treatment with chloroethynyl norgestrel plus mestranol or with anagestone acetate plus mestranol; no difference in the total number of mammary-gland nodules was observed with these two contraceptives. One dog given ethynerone plus mestranol had 14 malignant mammary fibrosarcomas[86].

C. Other relevant data

The results reported in the available studies relate to a variety of different oral contraceptives.

Several studies showed no increase in the incidence of structural chromosomal changes in lymphocytes taken from women after oral contraceptive use (norethisterone with mestranol or ethynodiol diacetate with mestranol). In contrast to an earlier report, no increase in the incidence of sister chromatid exchanges was observed in 52 women taking oral contraceptives as compared with 63 controls when results were adjusted for smoking[87].

No significant difference in the frequency of abnormal karyotypes or in sex ratio was seen in a study of spontaneous abortuses of women who had taken oral contraceptives; the contraceptives used were norgestrel, norethisterone acetate or medroxyprogesterone acetate in combination with ethinyloestradiol; or ethynodiol diacetate, megestrol acetate or lynoestrenol in combination with mestranol. Similarly, a large cohort study showed no increase in risk for chromosomal anomalies in live births and abortuses of oral contraceptive users[87].

High doses of one oral contraceptive (lynoestrenol and mestranol) administered to two strains of female mice induced dominant lethal mutations, whereas high doses of another (norethisterone and ethinyloestradiol) did not. In a later report using even higher doses of the oral contraceptive that induced dominant lethal mutations and another (norethisterone acetate and ethinyloestradiol), the same authors reported no increase in the incidence of dominant lethal, recessive lethal or visible mutations in mice. Combinations of progestins

(norethynodrel and ethynodiol diacetate) and oestrogens (mestranol and ethinyloestradiol) did not induce sex-linked recessive lethal mutations in *Drosophila*[87].

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OESTROGEN-PROGESTIN REPLACEMENT THERAPY (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Progestins, when administered for at least ten days per 28-day oestrogen replacement therapy cycle, prevent adenomatous hyperplasia, a precursor of endometrial carcinoma, and cause regression of pre-existing adenomatous hyperplasia in some patients[1]. When administered alone, progestins are effective in the treatment of carcinoma *in situ* of the endometrium[2] and of more advanced disease[3,4].

Progestins increase the conversion of oestradiol-17β to oestrone, a biologically less active oestrogen[5], and they reduce the concentration of oestrogen receptors[6]. Maximal mitotic activity in the endometrium occurs during the follicular phase of the cycle; luteal-phase progesterone effectively stops mitotic activity and causes differentiation of endometrial cells to a secretory state[7].

Support for a protective effect of progestins against endometrial cancer risk is obtained from the results of studies of the effects of oral contraceptives on endometrial cancer risk (see p. 298). Case-control studies have consistently shown that, whereas ingestion of sequential oral contraceptives containing an oestrogen alone throughout most of the menstrual cycle increases risk, ingestion of combined oral contraceptives, in which each pill contains an oestrogen and a progestin, substantially decreases risk.

The effect of progestins on the breast is markedly different from that on the endometrium. Endometrial cancer risk is considerably reduced with combined oral contraceptives (see p. 298), but there is no evidence of a reduced risk of breast cancer, even after long periods of combined oral contraceptive use[8]. Maximal mitotic activity in breast tissue occurs during the luteal phase of the normal menstrual cycle in the face of maximal progesterone levels[9]. These results concerning the effects of combined oral contraceptives suggest strongly that progestins do not have an antioestrogen, anticancer effect on the breast. A number of studies[10-12] have addressed the relationship between oestrogen-progestin replacement therapy and cancer, but in each instance either the small size of the study or apparently inadequate study design or data analysis prevent conclusions from being drawn.

B. Other relevant data

No data were available to the Working Group.

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