



WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Volume 21 Sex Hormones (II)

Summary of Data Reported and Evaluation

Oestrogens

Chlorotrianisene

Conjugated oestrogens

Dienoestrol

Diethylstilboestrol and diethylstilboestrol dipropionate

Ethinylestradiol

Mestranol

Oestradiol-17 β , oestradiol-3-benzoate, oestradiol dipropionate, oestradiol-17- β -valerate and polyoestradiol phosphate

Oestriol

Oestrone and oestrone benzoate

Progestins

Chlormadinone acetate

Dimethisterone

Ethinodiol diacetate

17 α -Hydroxyprogesterone caproate

Lynoestrenol

Medroxyprogesterone acetate

Megestrol acetate

Norethisterone and norethisterone acetate

Norethynodrel

Norgestrel

Progesterone

Androgens

Testosterone, testosterone oenanthate and testosterone propionate

Other

Clomiphene and clomiphene citrate

Last updated: 6 April 1998

CHLOROTRIANISENE

VOL.: 21 (1979) (p. 139)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

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

5.2 Human data

No case reports or epidemiological studies on chlorotrianisene alone were available to the Working Group. Case reports and epidemiological studies on steroid hormones used in oestrogen-progestin contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

The available experimental data are insufficient to evaluate the carcinogenicity of chlorotrianisene in animals. Studies in humans strongly suggest that the administration of oestrogens is causally related to an increased incidence of endometrial carcinoma; there is no evidence that chlorotrianisene is different from other oestrogens in this respect.

Subsequent evaluation: [Suppl. 7 \(1987\) \(Nonsteroidal oestrogens\)](#)

CONJUGATED OESTROGENS

VOL.: 21 (1979) (p. 147)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Conjugated oestrogens (Premarin^R) were tested in only one experiment in rats by oral administration. The data were insufficient to evaluate the carcinogenicity of this compound.

5.2 Human data

Case reports and epidemiological studies on steroid hormones used in oestrogen treatment have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'. Because most of the studies which concerned endometrial carcinoma involved the use of conjugated oestrogens, the evidence in humans that administration of these agents is causally related to an increased risk of developing this cancer is particularly convincing.

5.3 Evaluation

The available experimental data are insufficient to evaluate the carcinogenicity of conjugated oestrogens in animals. Studies in humans strongly suggest that the administration specifically of conjugated oestrogens is causally related to an increased incidence of endometrial carcinoma.

Subsequent evaluation: [Suppl. 7 \(1987\) \(Steroidal oestrogens\)](#)

DIENOESTROL

VOL.: 21 (1979) (p. 161)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Dienoestrol was tested in female guinea-pigs by subcutaneous injection and in female mice by intravaginal administration. Although pointing to the induction of 'uterine tumours' in guinea-pigs and ovarian tumours in mice, these experiments were insufficient to evaluate the carcinogenicity of this compound.

5.2 Human data

No case reports or epidemiological studies on dienioestrol alone were available to the Working Group. Case reports and epidemiological studies on steroid hormones used in oestrogen treatment have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

The available experimental data are insufficient to evaluate the carcinogenicity of dienioestrol in animals. Studies in humans strongly suggest that the administration of oestrogens is causally related to an increased incidence of endometrial carcinoma; there is no evidence that dienioestrol is different from other oestrogens in this respect.

Subsequent evaluation: [Suppl. 7 \(1987\) \(Nonsteroidal oestrogens\)](#)

DIETHYLSTILBOESTROL AND DIETHYLSTILBOESTROL DIPROPIONATE

VOL.: 21 (1979) (p. 173)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Diethylstilboestrol was tested in mice and rats by oral administration; in mice by local application; in mice, rats, hamsters and monkeys by subcutaneous implantation; and in mice, hamsters and dogs by subcutaneous injection. It was also tested by prenatal exposure in mice and hamsters and by neonatal exposure in mice and rats. Its administration to mice resulted in an increased incidence of mammary and lymphoid tumours in both males and females, and of interstitial-cell tumours of the testis in males and ovarian tumours in females; cervical and vaginal tumours were observed in females, including those exposed prenatally and on the first day of life. In rats, increased incidences of pituitary, mammary and bladder tumours (in conjunction with calculi) were observed. In hamsters, a high incidence of renal tumours was observed in castrated males and females and in intact males, but not in intact females. Following prenatal exposure of hamsters, tumours of the uterus, cervix and vagina were observed in female offspring, and tumours of the accessory sex organs occurred in males. In squirrel monkeys, malignant mesotheliomas of the uterine serosa were observed.

In another study, rats were given s.c. injections of 0.015-0.6 mg/kg bw DES on days 13, 16, 18 and 20 of pregnancy and/or 0.2-10 mg/kg bw DES for 3 weeks *post partum*. Genital tumours (2 vaginal squamous-cell carcinomas, 1 endometrial adenocarcinoma, 1 ovarian adenocarcinoma) were observed among 10 female offspring. None of the controls developed such tumours (Vorherr *et al.*, 1979).

Another study has been reported in which male Syrian golden and European hamsters were implanted subcutaneously with a 25-mg DES pellet. The animals developed adenomas and adenocarcinomas of the kidney and adenohipophysis and adenomas of the testes and adrenal glands. European hamsters, which are more sensitive, also developed liver tumours (adenomas, cholangiocellular carcinomas and hepatocellular carcinomas) (Reznik-Schüller, 1979).

In most studies by pellet implantation, an accurate assessment of the effective carcinogenic dose could not be made. After oral administration, the lowest statistically significant dose that produced mammary carcinomas in mice was about 6 µg/kg bw per day. This dose is similar to that of diethylstilboestrol used in humans in the control of symptoms of the climacteric (10 µg/kg bw per day) and 30 times less than the dose given for the control of mammary or prostatic cancer (300 µg/kg bw per day).

Diethylstilboestrol dipropionate was tested by subcutaneous injection in rats and frogs, producing pituitary tumours in rats and tumours of the haematopoietic tissue in frogs.

Subcutaneous injection of polydiethylstilboestrol phosphate in hamsters produced renal tumours.

Diethylstilboestrol is embryo-lethal for pre- and postimplantation embryos in some species and causes teratogenic effects on the genital tract, which may be of significance for the carcinogenicity observed in these tissues.

5.2 Human data

Diethylstilboestrol taken during pregnancy has been shown to be causally associated with an increase in vaginal and cervical clear-cell adenocarcinoma in daughters, primarily in those between the ages of 10 and 30 years. The risk appears to be in the order of 0.14-1.4/1000 exposed daughters up to the age of 24 years. Because of the young age of the population at risk, further estimates of cancer risk cannot be made at this time.

Non-neoplastic epithelial and structural changes of the female genital tract have frequently been observed in the daughters of women exposed to diethylstilboestrol during pregnancy; these changes include transverse fibrous cervical and vaginal septa, vaginal adenosis and cervical ectropion. Non-malignant structural changes have been reported in the reproductive tracts of male children of exposed women; but the effect of diethylstilboestrol on fertility, if any, is uncertain. Cryptorchidism and hypoplastic testes observed in one study have been shown to be related to exposure to diethylstilboestrol; these conditions can predispose to malignant changes, but an increased risk of malignancy in males has not been demonstrated.

There appears to be an increased risk of endometrial carcinoma in young women with Turner's syndrome who were treated with diethylstilboestrol.

A few cases have been reported of breast cancer in men treated with diethylstilboestrol for metastatic prostatic carcinoma. Although a modest excess of breast cancer was observed in one study of mothers exposed to diethylstilboestrol, the difference from that in controls was not statistically significant.

Evidence strongly suggests that the administration of oestrogens for the control of symptoms of the climacteric is causally related to an increased incidence of endometrial carcinoma; diethylstilboestrol is no different from other oestrogens in this respect.

5.3 Evaluation

Diethylstilboestrol is causally associated with the occurrence of cancer in humans. There is also *sufficient evidence* for its carcinogenicity in experimental animals.

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

Previous evaluation: [Vol. 6 \(1974\)](#)

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

Last updated: 6 April 1998

ETHINYLOESTRADIOL

VOL.: 21 (1979) (p. 233)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Ethinylloestradiol was tested in mice, rats, dogs and monkeys by oral administration and in rats by subcutaneous injection; in most studies it was administered in combination with progestins.

When administered alone to mice, it increased the incidence of pituitary tumours and malignant mammary tumours in both males and females and produced malignant tumours of the uterus and its cervix in females. In rats, it increased the incidence of benign liver-cell tumours in both males and females and produced malignant liver-cell tumours in females.

When ethinylloestradiol was given in combination with certain progestins, excess incidences of malignant tumours of the uterine fundus were observed in female mice and of benign and/or malignant mammary tumours in male rats; in female rats, the combinations reduced but did not prevent the incidence of malignant liver-cell tumours when compared with that produced by ethinylloestradiol alone. In dogs, no tumours that could be attributed to the treatment were found. The study in monkeys was still in progress at the time of reporting: no tumours had been found after 5 years of observation.

Mammary fibroadenomas were produced in female rats following subcutaneous injection of a combination of ethinylloestradiol with megestrol acetate.

Ethinylloestradiol is embryolethal for preimplantation embryos in some species.

5.2 Human data

No case reports or epidemiological studies on ethinylloestradiol alone were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen-progestin contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of ethinylloestradiol in experimental animals. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard ethinylloestradiol as if it presented a carcinogenic risk to humans. The use of oral contraceptives containing ethinylloestradiol in combination with progestins has been related causally to an increased incidence of benign liver adenomas and a decreased incidence of benign breast disease. Studies also strongly suggest that the administration of oestrogens is causally related to an increased incidence of endometrial carcinoma; there is no evidence that ethinylloestradiol is different from other oestrogens in this respect.

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

Previous evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(Steroidal oestrogens\)](#)

Last updated: 6 April 1998

MESTRANOL

VOL.: 21 (1979) (p. 257)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Mestranol was tested in mice, rats, dogs and monkeys by oral administration; in most studies it was administered in combination with progestins. When administered alone, it increased the incidences of pituitary tumours in both sexes of one strain of mice and increased the incidence of malignant mammary tumours in castrated males of two further strains and in males and females of another strain. It also produced an increased incidence of malignant mammary tumours in female rats.

Studies in dogs and monkeys are still in progress. Although no tumours have been observed in either species after 7 years, no conclusive evaluation can yet be made.

In experiments in which mestranol was administered to female mice in combination with norethynodrel, pituitary tumours and vaginal and cervical squamous-cell carcinomas were produced; in male mice, an increased incidence of mammary tumours was observed following administration of mestranol in combination with norethynodrel or ethynodiol diacetate. Combinations with norethynodrel or norethisterone resulted in an excess of benign liver-cell tumours in male rats and increased the incidence of malignant mammary tumours in rats of both sexes.

In dogs, administration of combinations with various synthetic progestins led to the formation of mammary tumours. In monkeys given these combinations as well as combinations with norethynodrel or ethynodiol diacetate, no mammary nodules were observed after 5 and 7 years of experimentation, respectively. These experiments are still in progress.

It was also tested in combination with norethynodrel by subcutaneous administration in mice, rats and hamsters; it produced an increased incidence of mammary tumours in female mice.

Mestranol is embryo-lethal for pre- and postimplantation embryos in some species.

5.2 Human data

No case reports or epidemiological studies on mestranol alone were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen-progestin oral contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of mestranol in experimental animals. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard mestranol as if it presented a carcinogenic risk to humans. The use of oral contraceptives containing mestranol in combination with progestins has been related causally to an increased incidence of benign liver adenomas and a decreased incidence of benign breast disease. Studies also strongly suggest that the administration of oestrogens is causally related to an increased incidence of endometrial carcinoma; there is no evidence that mestranol is different from other oestrogens in this respect.

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

Previous evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\) \(Steroidal oestrogens\)](#)

Last updated: 7 April 1998

OESTRADIOL-17 β , OESTRADIOL 3-BENZOATE, OESTRADIOL DIPROPIONATE, OESTRADIOL-17 β -VALERATE AND POLYOESTRADIOL PHOSPHATE

VOL.: 21 (1979) (p. 279)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Oestradiol-17 β and its esters were tested in mice, rats, hamsters, guinea-pigs and monkeys by subcutaneous injection or implantation and in mice by oral administration. Its subcutaneous administration resulted in increased incidences of mammary, pituitary, uterine, cervical, vaginal and lymphoid tumours and interstitial-cell tumours of the testis in mice. In rats, there was an increased incidence of mammary and/or pituitary tumours. In hamsters, a high incidence of malignant kidney tumours occurred in intact and castrated males and in ovariectomized females, but not in intact females. In guinea-pigs, diffuse fibromyomatous uterine and abdominal lesions were observed. Oral administration of oestradiol-17 β in mice led to an increased mammary tumour incidence. Subcutaneous injections in neonatal mice resulted in precancerous and cancerous cervical and vaginal lesions in later life and an increased incidence of mammary tumours.

Oestradiol-17 β has teratogenic actions on the genital tract and possibly on other organs and impairs fertility.

5.2 Human data

No case reports or epidemiological studies on oestradiol-17 β alone were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen-progestin oral contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of oestradiol-17 β in experimental animals. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard oestradiol-17 β as if it presented a carcinogenic risk to humans. Studies in humans strongly suggest that the administration of oestrogens is causally related to an increased incidence of endometrial carcinoma; there is no evidence that oestradiol-17 β is different from other oestrogens in this respect.

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

Previous evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\) \(Steroidal oestrogens\)](#)

OESTRIOL

VOL.: 21 (1979) (p. 327)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones](#).)

5.1 Experimental data

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.

Oestriol is embryo-lethal, especially for preimplantation embryos, in some species.

5.2 Human data

No case reports or epidemiological studies on oestriol alone were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen-progestin oral contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

There is *limited evidence* for the carcinogenicity of oestriol in experimental animals. Studies in humans strongly suggest that the administration of oestrogens is causally related to an increased incidence of endometrial carcinoma; there is no evidence that oestriol is different from other oestrogens in this respect.

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

Previous evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\) \(Steroidal oestrogens\)](#)

OESTRONE AND OESTRONE BENZOATE

VOL.: 21 (1979) (p. 343)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones](#).)

5.1 Experimental data

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, as well as bladder tumours in association with stones, in rats; and in renal tumours in both castrated and intact male hamsters.

Oestrone benzoate increased the incidence of mammary tumours in mice following its subcutaneous injection.

Oestrone is embryolethal for preimplantation embryos in some species.

5.2 Human data

No case reports or epidemiological studies on oestrone alone were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen-progestin oral contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of oestrone in experimental animals. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard oestrone as if it presented a carcinogenic risk to humans. Studies in humans strongly suggest that the administration of oestrogens is causally related to an increased incidence of endometrial carcinoma; there is no evidence that oestrone is different from other oestrogens in this respect.

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

Previous evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\) \(Steroidal oestrogens\)](#)

CHLORMADINONE ACETATE

VOL.: 21 (1979) (p. 365)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Chlormadinone acetate was tested in mice, rats and dogs by oral administration. When given alone to dogs, chlormadinone acetate produced mammary tumours. When given to mice in combination with mestranol, it increased the incidence of pituitary tumours in animals of both sexes; in combination with ethinyloestradiol, it increased the incidence of mammary tumours in intact and castrated male mice of one hybrid strain.

Chlormadinone acetate has been reported to be embryolethal and teratogenic when given during the organogenesis stage in some species.

5.2 Human data

No case reports or epidemiological studies on chlormadinone acetate alone were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen-progestin contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

There is *limited evidence* for the carcinogenicity of chlormadinone acetate in dogs. In humans, oral contraceptives containing oestrogens in combination with progestins have been related causally to an increased incidence of benign liver adenomas and a decreased incidence of benign breast disease.

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

Previous evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(Progestins; Combined oral contraceptives\)](#)

DIMETHISTERONE

VOL.: 21 (1979) (p. 377)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Dimethisterone was tested in dogs in combination with ethinyloestradiol by oral administration. No increase in incidence of mammary tumours was found.

5.2 Human data

No case reports or epidemiological studies on dimethisterone alone were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen-progestin oral contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

Owing to the lack of experimental and human data on dimethisterone alone, no evaluation of the carcinogenicity of dimethisterone could be made. In humans, oral contraceptives containing oestrogens in combination with progestins have been related causally to an increased incidence of benign liver adenomas and a decreased incidence of benign breast disease.

Previous evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(Progestins\)](#)

Last updated: 6 April 1998

ETHYNODIOL DIACETATE

VOL.: 21 (1979) (p. 387)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Ethynodiol diacetate was tested in mice, rats and monkeys alone or in combination with oestrogens by oral administration. In castrated male mice, it increased the incidence of mammary tumours, and in male rats it produced benign mammary tumours. In combination with oestrogens, it increased the incidence of pituitary tumours in mice and of malignant mammary tumours in male and female rats. The study in monkeys is still in progress.

Ethynodiol diacetate was reported to be embryolethal for pre- and postimplantation embryos and to have teratogenic effects in some species.

5.2 Human data

No case reports or epidemiological studies on ethynodiol diacetate alone were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen-progestin oral contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

There is *limited evidence* for the carcinogenicity of ethynodiol diacetate in animals. In humans, oral contraceptives containing oestrogens in combination with progestins have been related causally to an increased incidence of benign liver adenomas and a decreased incidence of benign breast disease.

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

Previous evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\) \(Progestins; combined oral contraceptives\)](#)

17 α -HYDROXYPROGESTERONE CAPROATE

VOL.: 21 (1979) (p. 399)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

17 α -Hydroxyprogesterone caproate was tested in rabbits by repeated intramuscular injection. The data were insufficient to evaluate the carcinogenicity of this compound.

5.2 Human data

No case reports or epidemiological studies on 17 α -hydroxyprogesterone caproate were available to the Working Group.

5.3 Evaluation

The available experimental and human data are inadequate to evaluate the carcinogenicity of 17 α -hydroxyprogesterone caproate.

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

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

LYNOESTRENOL

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

VOL.: 21 (1979) (p. 407)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones](#).)

5.1 Experimental data

Lynoestrenol was tested by oral administration in mice and rats, alone or in combination with mestranol. It did not increase the incidence of tumours.

5.2 Human data

No case reports or epidemiological studies on lynoestrenol alone were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen-progestin oral contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

No evaluation of the carcinogenicity of lynoestrenol could be made. In humans, oral contraceptives containing oestrogens in combination with progestins have been related causally to an increased incidence of benign liver adenomas and a decreased incidence of benign breast disease.

Subsequent evaluation: [Suppl. 7 \(1987\) \(Progestins; combined oral contraceptives\)](#)

Last updated: 7 April 1998

MEDROXYPROGESTERONE ACETATE

VOL.: 21 (1979) (p. 417)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Medroxyprogesterone acetate was tested in mice and dogs by intramuscular administration. It produced mammary tumours in dogs.

Medroxyprogesterone acetate was reported to have teratogenic effects in some species.

5.2 Human data

One epidemiological study concerning the development of breast nodules and two studies concerning the development of dysplasias and carcinoma *in situ* of the uterine cervix have been reported. The results of these studies were conflicting and difficult to interpret because of methodological problems. Epidemiological studies on steroid hormones used in oestrogen-progestin oral contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

There is *limited evidence* for the carcinogenicity of medroxyprogesterone acetate in dogs. Epidemiological studies on medroxyprogesterone acetate are inadequate for an evaluation of the carcinogenicity of this compound in humans.

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

Previous evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\) \(Medroxyprogesterone acetate; progestins\)](#)

MEGESTROL ACETATE

VOL.: 21 (1979) (p. 431)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones](#).)

5.1 Experimental data

Megestrol acetate alone or with ethinyloestradiol was tested in mice, rats and dogs by oral administration and in rats by subcutaneous administration. It produced mammary tumours in dogs when tested alone and in mice when tested in combination with ethinyloestradiol. Experiments in which it was tested in rats in combination with ethinyloestradiol were negative or inadequate.

5.2 Human data

No case reports or epidemiological studies on megestrol acetate alone were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen-progestin oral contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

There is *limited evidence* for the carcinogenicity of megestrol acetate in dogs. In humans, oral contraceptives containing oestrogens in combination with progestins have been related causally to an increased incidence of benign liver adenomas and a decreased incidence of benign breast disease.

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

Subsequent evaluation: [Suppl. 7 \(1987\) \(Progestins; combined oral contraceptives\)](#)

NORETHISTERONE AND NORETHISTERONE ACETATE

VOL.: 21 (1979) (p. 441)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Norethisterone and its acetate alone or in combination with oestrogens were tested in mice, rats and dogs by oral administration and in mice by subcutaneous implantation. When administered alone to mice, norethisterone increased the incidence of benign liver-cell tumours in males and of pituitary tumours in females and produced granulosa-cell tumours of the ovary in females. Administration of norethisterone acetate alone increased the incidence of benign liver-cell tumours in male mice. In male rats, administration of norethisterone alone increased the incidence of benign liver-cell tumours.

Norethisterone in combination with mestranol, or the acetate in combination with ethinyloestradiol, increased the incidence of pituitary tumours in mice of both sexes; norethisterone in combination with ethinyloestradiol increased the incidence of pituitary tumours in female mice. In combination with mestranol it increased the incidence of benign liver-cell tumours in male rats and of malignant mammary tumours in animals of both sexes. Norethisterone acetate in combination with ethinyloestradiol increased the incidence of benign mammary tumours in male rats in one study and increased the incidence of benign liver-cell and mammary tumours in rats of both sexes in a further study.

A study in dogs in which it was given in combination with ethinyloestradiol is still in progress.

Norethisterone is embryo-lethal in some species and produces virilization in female foetuses.

5.2 Human data

No case reports or epidemiological studies on norethisterone or norethisterone acetate alone were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen-progestin oral contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

There is *limited evidence* for the carcinogenicity of norethisterone and of its acetate in animals. In humans, oral contraceptives containing oestrogens in combination with progestins have been related causally to an increased incidence of benign liver adenomas and a decreased incidence of benign breast disease.

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

Previous evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\) \(Progestins; combined oral contraceptives\)](#)

NORETHYNODREL

VOL.: 21 (1979) (p. 461)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Norethynodrel was tested in mice, rats and monkeys alone or in combination with mestranol by oral administration. It was also tested alone in mice by subcutaneous implantation, and in combination with mestranol in mice, rats and hamsters by subcutaneous injection.

When given alone, norethynodrel increased the incidence of pituitary tumours in mice of both sexes and of mammary tumours in castrated males of one strain; it also increased the incidence of liver-cell, pituitary and mammary tumours in male rats.

When given in combination with mestranol, it increased the incidence of pituitary, mammary, vaginal and cervical tumours in female mice, of pituitary tumours in male mice, of mammary tumours in castrated male mice, of benign liver-cell tumours in male rats and of malignant mammary tumours in rats of both sexes. The study in hamsters was of too short duration to be considered for evaluation.

Oral administration of norethynodrel in combination with mestranol to *Macaca mulatta* monkeys for 5 years did not increase the incidence of mammary tumours; the study is still in progress.

Norethynodrel was reported to be embryolethal in some species and to have teratogenic effects in mice.

5.2 Human data

No case reports or epidemiological studies on norethynodrel alone were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen-progestin oral contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

There is *limited evidence* for the carcinogenicity of norethynodrel alone and in combination with mestranol in experimental animals. In humans, oral contraceptives containing oestrogens in combination with progestins have been related causally to an increased incidence of benign liver adenomas and a decreased incidence of benign breast disease.

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

Previous evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\) \(Progestins; combined oral contraceptives\)](#)

NORGESTREL

VOL.: 21 (1979) (p. 479)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Norgestrel was tested in mice and rats alone or in combination with ethinyloestradiol by oral administration. There was no increase in the incidence of tumours in either species.

Norgestrel is embryolethal for pre- and postimplantation embryos in rats.

5.2 Human data

No case reports or epidemiological studies on norgestrel alone were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen-progestin oral contraceptive preparations have been summarized in the section, 'Oestrogens and Progestins in Relation to Human Cancer'.

5.3 Evaluation

The available data in experimental animals and humans are insufficient to evaluate the carcinogenicity of norgestrel. In humans, oral contraceptives containing oestrogens in combination with progestins have been related causally to an increased incidence of benign liver adenomas and a decreased incidence of benign breast disease.

Previous evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\) \(Progestins; combined oral contraceptives\)](#)

Last updated: 7 April 1998

PROGESTERONE

VOL.: 21 (1979) (p. 491)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Progesterone was tested by subcutaneous and intramuscular injection in mice, rats, rabbits and dogs and by subcutaneous implantation in mice and rats. It was tested alone in mice and dogs; in rats and rabbits it was always given in combination with other sex hormones.

When given alone, progesterone increased the incidence of ovarian, uterine and mammary tumours in mice; the data from dogs were insufficient to evaluate carcinogenicity.

Neonatal treatment with progesterone enhanced the occurrence of precancerous and cancerous lesions of the genital tract and resulted in increased mammary tumorigenesis in female mice.

5.2 Human data

No case reports or epidemiological studies on exogenous progesterone were available to the Working Group.

5.3 Evaluation

There is *limited evidence* for the carcinogenicity of progesterone in experimental animals. In the absence of epidemiological data, no evaluation of the carcinogenicity of progesterone to humans can be made.

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

Previous evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(Progestins\)](#)

TESTOSTERONE, TESTOSTERONE OENANTHATE AND TESTOSTERONE PROPIONATE

VOL.: 21 (1979) (p. 519)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Testosterone and its esters were tested in mice, rats and hamsters, by subcutaneous injection and/or implantation, and in rabbits by intramuscular injection.

Testosterone propionate implanted subcutaneously in mice induced cervical-uterine tumours, which metastasized in some cases; in rats, metastasizing prostatic adenocarcinomas were induced in males.

Neonatal treatment of female mice by subcutaneous injection of testosterone induced lesions of the genital tract and increased the mammary tumour incidence when the animals were adult. 5 β -Dihydrotestosterone, which is considered to be hormonally inactive in adults, also increased the incidence of mammary tumours in mice when given neonatally by subcutaneous injection.

Testosterone is embryo-lethal in pre- and postimplantation embryos and causes virilization in female offspring.

5.2 Human data

No case reports or epidemiological studies on testosterone alone were available to the Working Group. There are limited data concerning the possible long-term effects of androgenic-anabolic steroids, which are related to testosterone. An association between these synthetic androgenic steroids and the occurrence of hepatocellular carcinomas has been suggested, but the evidence is inconclusive.

5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of testosterone in experimental animals. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard testosterone as if it presented a carcinogenic risk to humans. The only related data in humans, although insufficient for an evaluation, concern the possible long-term effects of androgenic anabolic-steroids.

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

Subsequent evaluation: [Vol. 6 \(1974\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\) \(Androgenic \(anabolic\) steroids\)](#)

CLOMIPHENE AND CLOMIPHENE CITRATE

VOL.: 21 (1979) (p. 551)

5. Summary of Data Reported and Evaluation

(N.B. - This section should be read in conjunction with the General Remarks on Sex Hormones and with the [General Conclusions on Sex Hormones.](#))

5.1 Experimental data

Clomiphene citrate was inadequately tested in one experiment in newborn rats by subcutaneous injection; uterine and ovarian tumours were reported.

Clomiphene citrate is embryolethal for pre- and postimplantation embryos in several species and has various teratogenic effects in rats.

5.2 Human data

There are a few case reports of the occurrence of malignant and benign tumours at various sites in patients treated with clomiphene citrate, but there is no evidence of a causal relationship.

No definite association between clomiphene citrate administration and congenital defects in humans has been demonstrated.

5.3 Evaluation

The available experimental and human data are insufficient to evaluate the carcinogenicity of clomiphene citrate.

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