



WORLD HEALTH ORGANIZATION  
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

## Volume 6 Sex Hormones

### Summary of Data Reported and Evaluation

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#### Oestrogens

Diethylstilboestrol (stilboestrol)  
Ethinylestradiol  
Mestranol  
Oestradiol-17 $\beta$   
Oestriol  
Oestrone

#### Progestins

Progesterone

#### 17-Hydroxyprogesterones

Chlormadinone acetate  
Medroxyprogesterone acetate

#### 19-Nortestosterone Derivatives

Dimethisterone  
Ethinodiol diacetate  
Norethisterone and norethisterone acetate  
Norethynodrel  
Norgestrel

#### Androgens

Testosterone

# DIETHYLSTILBOESTROL (STILBOESTROL)

VOL.: 6 (1974) (p. 55)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section '[General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

Diethylstilboestrol (DES) was tested in mice by oral administration, local application and subcutaneous injection, in mice, rats, hamsters and squirrel monkeys by subcutaneous implantation and in hamsters by subcutaneous injection. 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 cervical and vaginal tumours in females, including those exposed only on the first day of life. In rats, increased incidences of pituitary, mammary and bladder tumours 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. In squirrel monkeys, malignant mesotheliomas of the uterine serosa were observed.

DES treatment in most cases increased the incidence of mammary tumours in strains of mice having a spontaneous incidence of these tumours, which may be related to the presence of a virus; testicular tumours occurred in strains having a particular genetic susceptibility to such tumours. No evidence of a possible role of a virus has been shown in rats. Bladder tumours occurred only in rats in which bladder calculi were present.

In most cases, an accurate assessment of the effective carcinogenic dose in implantation studies is not possible. However, in oral administration studies, the lowest statistically significant dose ( $p < 0.01$ ) producing mammary carcinomas in mice was about 0.15 µg/day (6 µg/kg bw/day). This dose is similar to that used in humans in the control of menopausal symptoms by DES (10 µg/kg bw/day) and 30 times less than the dose given for the control of mammary or prostatic cancer (300 µg/kg bw/day).

### 5.2 Human carcinogenicity data

The administration of diethylstilboestrol to women during pregnancy is associated with an increased risk of vaginal or cervical adenocarcinoma in their exposed female offspring. There may also be an increased risk of endometrial carcinoma in women with gonadal dysgenesis treated with this drug. It is possible that the administration of the drug therapeutically to men with carcinoma of the prostate increases the risk of breast cancer.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\)](#)

# ETHINYLOESTRADIOL

VOL.: 6 (1974) (p. 77)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section '[General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

Ethinylloestradiol was tested in mice and rats by the oral route; in most cases it was administered in combination with progestins. 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 uterine fundus and the 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 some progestins, excess incidences of malignant tumours of the uterine fundus in female mice and of benign and/or malignant mammary tumours in male rats were observed; 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.

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

### 5.2 Human carcinogenicity 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" in this volume.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\)](#)

# MESTRANOL

VOL.: 6 (1974) (p. 87)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section '[General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

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

In experiments where mestranol was administered to female mice in combination with norethynodrel (as Enovid), pituitary, mammary, vaginal and cervical tumours were produced. In rats, combinations with norethynodrel and norethisterone produced an excess of benign liver-cell tumours in male rats and increased the incidence of malignant mammary tumours in rats of both sexes.

The results in dogs and monkeys were difficult to assess since the studies were still in progress at the time of reporting.

### 5.2 Human carcinogenicity data

No case reports or epidemiological studies on the effects of mestranol alone were available to the Working Group. Epidemiological studies on steroid hormones in oestrogen-progestin contraceptive preparations have been summarized in the section "Oestrogens and Progestins in Relation to Human Cancer" in this volume.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\)](#)

# OESTRADIOL-17 $\beta$

VOL.: 6 (1974) (p. 99)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section ' [General Conclusions on Hormones](#)!.)

### 5.1 Animal carcinogenicity data

Oestradiol-17 $\beta$  was tested in mice, rats, hamsters and guinea-pigs by subcutaneous injection or implantation. Its administration resulted in an increased incidence 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 pituitary tumours. In hamsters, malignant kidney tumours occurred with a high incidence in intact or castrated males and in ovariectomized but not in intact females. In guinea-pigs, diffuse fibromyomatous abdominal lesions of uncertain histological interpretation were observed. Subcutaneous injections in neonatal mice resulted in precancerous and cancerous vaginal lesions in later life.

The studies in monkeys could not be assessed since they were limited in group size and duration.

Oestradiol-17 $\beta$  treatment increased the incidence of mammary and pituitary tumours in strains of mice having a spontaneous incidence of these tumours. The spontaneous occurrence can be related either to the presence of a virus or to a particular genetic susceptibility. No evidence of the possible role of a virus has been ascertained for rats.

The role of the hormonal balance in the development and persistence of these tumours and possible synergisms with other carcinogenic factors in increasing the incidence of lymphoid tumours has been discussed (see section, "General Remarks on the Sex Hormones", in this volume).

### 5.2 Human carcinogenicity data

No case reports or epidemiological studies were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen treatment have been summarized in the section, "Oestrogens and Progestins in Relation to Human Cancer" in this volume.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\)](#)

# OESTRIOL

**VOL.:** 6 (1974) (p. 117)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section '[General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

Since oestriol has not been adequately tested in experimental animals, no assessment can be made.

### 5.2 Human carcinogenicity data

No case reports or epidemiological studies were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen treatment have been summarized in the section, "Oestrogens and Progestins in Relation to Human Cancer", in this volume.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\)](#)

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# OESTRONE

VOL.: 6 (1974) (p. 123)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section '[General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

Oestrone was tested orally in mice; by subcutaneous injection and by implantation in mice, rats and hamsters; and by skin-painting in mice. Its administration resulted in an increased incidence of mammary tumours in mice; in pituitary, adrenal and mammary tumours and bladder tumours in association with stones in rats; and in renal tumours in both castrated and intact male hamsters.

Oestrone treatment increased the incidence of mammary tumours in strains of mice having a spontaneous incidence of the tumours which may be related to the presence of a virus. No evidence of a possible role of a virus has been demonstrated in rats.

### 5.2 Human carcinogenicity data

No case reports or epidemiological studies were available to the Working Group. Epidemiological studies on steroid hormones used in oestrogen treatment have been summarized in the section, "Oestrogens and Progestins in Relation to Human Cancer", in this volume.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\)](#)

# PROGESTERONE

VOL.: 6 (1974) (p. 135)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section '[General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

Progesterone was tested by subcutaneous or intramuscular injection in mice, rats, rabbits and dogs and by subcutaneous implantation in mice and rats. It was tested alone only in mice and dogs; in rats and rabbits it was always given in combination with other chemicals; in mice it was also tested in combination with other carcinogens.

When given alone, it increased the incidence of ovarian, uterine or mammary tumours in mice, while the experiment in dogs was of insufficient duration to allow an assessment to be made.

The administration of progesterone to intact or castrated mice and rats and to rabbits in combination with polycyclic aromatic hydrocarbons or with 2-acetylaminofluorene and/or oestrogen variously affected the incidence and the histological type of the tumours produced by these known carcinogens (mainly mammary, uterine and vaginal tumours). In particular, progesterone enhanced the incidence of tumours produced by these known carcinogens, but only when given after and not before their administration.

### 5.2 Human carcinogenicity data

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

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\) \(Progestins; Combined oral contraceptives\)](#)

# CHLORMADINONE ACETATE

VOL.: 6 (1974) (p. 149)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section '[General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

Chlormadinone acetate was tested by the oral route in mice, rats and dogs. In mice it was also tested in combination with oestrogen.

Given alone, it produced no increase in the incidence of tumours in mice or in rats but resulted in mammary tumours in dogs. The significance of the tumours in dogs is discussed in the section, "General Remarks on the Sex Hormones", in this volume.

In combination with mestranol, the incidence of pituitary tumours was increased in mice of both sexes; in combination with ethinyloestradiol, it increased the incidence of mammary tumours in intact and castrated males of one hybrid strain.

### 5.2 Human carcinogenicity 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', in this volume.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\) \(Progestins; Combined oral contraceptives\)](#)

# MEDROXYPROGESTERONE ACETATE

VOL.: 6 (1974) (p. 157)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section '[General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

Medroxyprogesterone acetate was tested by the intramuscular route in dogs and produced malignant mammary tumours. Full details were not available to the Working Group. The significance of the finding in dogs is discussed in the section, "General Remarks on the Sex Hormones", in this volume.

### 5.2 Human carcinogenicity data

No case reports or epidemiological studies on medroxyprogesterone 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", in this volume.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\)](#)

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# DIMETHISTERONE

VOL.: 6 (1974) (p. 167)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section '[General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

No data were available to the Working Group.

### 5.2 Human carcinogenicity data

No case reports or epidemiological studies 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", in this volume.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\)](#)

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# ETHYNODIOL DIACETATE

VOL.: 6 (1974) (p. 173)

## 5. Comments on Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section ' [General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

Ethynodiol diacetate was tested alone or in combination with oestrogens by the oral route in mice and rats. Given alone, it did not increase the incidence of tumours in female mice or female rats; 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 malignant mammary tumours in some groups of male and female rats.

### 5.2 Human carcinogenicity 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 contraceptive preparations have been summarized in the section, "Oestrogens and Progestins in Relation to Human Cancer", in this volume.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\) \(Progestins; Combined oral contraceptives\)](#)

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# NORETHISTERONE AND NORETHISTERONE ACETATE

VOL.: 6 (1974) (p. 179)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section '[General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

Norethisterone or its acetate were tested in mice by oral administration and by subcutaneous implantation and in rats by oral administration. When administered alone to mice norethisterone increased the incidence of benign liver-cell tumours in males, of pituitary tumours in females and produced a low incidence of microscopic ovarian tumours in females. The acetate alone only increased the incidence of benign liver-cell tumours in males.

Norethisterone in combination with mestranol, or the acetate in combination with ethinyloestradiol, increased the incidence of pituitary tumours in both sexes. In addition, norethisterone in combination with ethinyloestradiol increased the incidence of pituitary tumours in female mice.

In rats, norethisterone alone increased the incidence of benign liver-cell tumours in males. In combination with mestranol it increased the incidence of benign liver-cell tumours in males and of malignant mammary tumours in both sexes. Norethisterone acetate in combination with ethinyloestradiol increased the incidence of benign mammary tumours in males in one study and increased the incidence of benign liver-cell and mammary tumours in both sexes in a further study.

### 5.2 Human carcinogenicity data

No case reports or epidemiological studies on norethisterone or its acetate alone were available. 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", in this volume.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\) \(Progestins; Combined oral contraceptives\)](#)

# NORETHYNODREL

VOL.: 6 (1974) (p. 191)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section '[General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

Norethynodrel was tested alone or in combination with mestranol by the oral route in mice and rats. Alone, it was also tested by subcutaneous implantation in mice; and in combination with mestranol, by subcutaneous injection in rats. A subcutaneous injection study in hamsters and a feeding study in monkeys were of too limited duration to be considered for evaluation.

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.

In combination with mestranol, it increased the incidence of pituitary, 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.

### 5.2 Human carcinogenicity 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 contraceptive preparations have been summarized in the section, "Oestrogens and Progestins in Relation to Human Cancer", in this volume.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\)](#) ([Progestins](#); [Combined oral contraceptives](#))

# NORGESTREL

VOL.: 6 (1974) (p. 201)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section ' [General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

Norgestrel was tested in one experiment only in mice and rats by the oral route. There was no increase in the incidence of tumours in either species compared with that in controls. Comparable results were obtained when norgestrel was administered in combination with ethinyloestradiol.

### 5.2 Human carcinogenicity 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 contraceptive preparations have been summarized in the section, "Oestrogens and Progestins in Relation to Human Cancer", in this volume.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\) \(Progestins; Combined oral contraceptives\)](#)

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# TESTOSTERONE

VOL.: 6 (1974) (p. 209)

## 5. Summary of Data Reported and Evaluation

(N.B.: This section should be read in conjunction with the section '[General Conclusions on Hormones](#)'.)

### 5.1 Animal carcinogenicity data

Testosterone was tested by subcutaneous injection and/or implantation in mice, rats and hamsters.

Testosterone implanted subcutaneously induced cervical-uterine tumours in mice, which metastasized in some cases. The only study in rats was considered inadequate in numbers of animals.

The incidences of leukaemia and of liver-cell and breast tumours in untreated mice of some strains were decreased by testosterone treatment, but the incidence of mammary tumours was increased by neonatal treatment of females of a mammary-tumour-virus-bearing strain.

Three distinctive types of neoplasm were induced in hamsters by a combination of oestrogen and testosterone: a tumour of the uterine endometrium, a tumour of the vas deferens-epididymis and a basal-cell epithelioma of the flank. They remained dependent on oestrogen and testosterone for continued growth.

### 5.2 Human carcinogenicity data

No adequate epidemiological data on testosterone alone were available to the Working Group.

**Subsequent evaluations:** [Vol. 21 \(1979\)](#); [Suppl. 7 \(1987\)](#)

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