

## Ethynodiol Diacetate

Ethynodiol diacetate is a synthetic progestin. It is used in combination with an estrogen as a drug for female contraception in the U.S., and alone in other countries (IARC, 1999). People may be exposed to the chemical intentionally through its use as a drug. Occupational exposure of the chemical may occur during manufacturing and handling processes.

Ethynodiol diacetate passed the animal data screen, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

### Epidemiological data

Exposure to oral contraceptives containing ethynodiol diacetate in combination with an estrogen:

- Case-control studies
  - Studies of breast cancer: Pike *et al.* (1983); Armstrong (1986)
- Case series
  - Liver tumors: Ansari *et al.* (1978); Chan and Detmer (1977)

### Animal carcinogenicity data

- Ethynodiol diacetate feeding studies in mice
  - Lifetime study in female (C3HxRIII) F<sub>1</sub> mice: Rudali *et al.* (1972); Rudali (1975)
  - Lifetime study in castrated male (C3HxRIII) F<sub>1</sub> mice: Rudali *et al.* (1972); Rudali (1975)
  - 80-week studies in male and female CF-LP mice: Committee on Safety of Medicines (1972)
- Ethynodiol diacetate feeding studies in rats
  - Two-year studies in male and female rats: Committee on Safety of Medicines (1972)
- Ethynodiol diacetate + mestranol (Ovulen) feeding studies in mice
  - Lifetime study in male (C3HxRIII) F<sub>1</sub> mice: Rudali (1975)
  - Lifetime study in castrated male (C3HxRIII) F<sub>1</sub> mice: Rudali *et al.* (1972); Rudali (1975)
  - Lifetime study in female (C3HxRIII) F<sub>1</sub> mice: Rudali (1975)
  - Lifetime study in castrated female (C3HxRIII) F<sub>1</sub> mice: Rudali (1975)

- 80-week studies in male and female CF-LP mice: Committee on Safety of Medicines (1972)
- Ethynodiol diacetate + mestranol (Ovulen) feeding studies in rats
  - Two-year studies in male and female rats: Committee on Safety of Medicines (1972)
- Ethynodiol diacetate + ethinyloestradiol feeding studies in mice
  - 80-week studies in male and female CF-LP mice: Committee on Safety of Medicines (1972)
- Ethynodiol diacetate + ethinyloestradiol feeding studies in rats
  - Two-year studies in male and female rats: Committee on Safety of Medicines (1972)

### Other relevant data

- Genotoxicity: Siddique and Afzal (2004), reviewed in IARC (1979, p. 393)
- Metabolism: Ethynodiol diacetate is metabolized to norethisterone (IARC, 1979 p. 393-394), which is listed under Proposition 65 as a carcinogen.

### Reviews

- IARC (1979)
- IARC (1999)

### References<sup>1</sup>

Ansari AH, Ravry MJ, Stanton PE, Hanafi M (1978). Liver tumors and oral contraceptives. *Fertil Steril* **29**(6):643-50.

Armstrong BK (1986). Oral contraceptives and breast cancer. *Lancet*. **1**:552-3

Chan CK, Detmer DE (1977). Proper management of hepatic adenoma associated with oral contraceptives. *Surg Gynecol Obstet* **144**(5):703-6.

Committee on Safety of Medicines (1972). Carcinogenicity tests of oral contraceptives, by Her Majesty's Stationery Office, London, UK.

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<sup>1</sup> Copies of these listed references, as either the abstract, the relevant sections of the publication, or the complete publication, have been provided to members of the Carcinogen Identification Committee. These references have been provided in the order in which they are discussed in this document.

International Agency for Research on Cancer (IARC, 1979). IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. **21**:387-98. Lyon, France.

International Agency for Research on Cancer (IARC, 1999). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. **72**, Lyon, France.

Pike MC, Henderson BE, Krailo MD, Duke A, Roy S (1983). Breast cancer and oral contraceptives: reply to critics. *Lancet* **2**, 926-30.

Rudali G, Coezy E, Chemama R (1972). Mammary carcinogenesis in female and male mice receiving contraceptives or gestagens. *J Natl Cancer Inst* **49**(3):813-9.

Rudali G (1975). Induction of tumors in mice with synthetic sex hormones. *Gann Monograph on Cancer Res* **17**:243-252.

Siddique YH, Afzal M (2004) Evaluation of genotoxic potential of synthetic progestin ethynodiol diacetate in human lymphocytes *in vitro*. *Current Science* 86(8):1161-1165.