

S U M M A R Y

A literature search conducted to evaluate the teratological effect of sex hormones used in early pregnancy yielded 27 publications on this topic, of which 22 show either statistically significant increase in abnormality or a trend in the same direction. Statistical reassessment of the remaining studies also show a trend in this direction. In a small number of studies the methodology might be considered inappropriate.

4 unpublished surveys also revealed positive trend.

In 1971 - and 1972, the Authorities in Sweden and in Finland banned the sales of HPT products, and between 1971 - 1975 five further countries have issued warning notices; all prior to that from the DHSS. During the same interval several inter-governmental circulars were issued on this topic by the WHO.

It is proposed that irrespective of discerning opinion, the weight of existing evidences are sufficient to justify:

- a) placing the onus of proof of safety of HPT products on the manufacturers.
2. b) an earlier warning by the CSM.

These are considered especially relevant in HPT.products, as they were used for diagnostic purposes when alternative reliable diagnostic tests for pregnancy were available.

The above might also be considered to vindicate the observation made in 1967.

Ovid MEDLINE(R) 1950 to July Week 1 2008

1. Norethindrone/
2. Ethinyl Estradiol/
3. Teratogens/
4. Abnormalities, Drug-Induced/
5. 1 or 2
6. 3 or 4
7. 5 and 6

<1>

Unique Identifier

18054974

Status

MEDLINE

Authors

Zha J. Sun L. Zhou Y. Spear PA. Ma M. Wang Z.

Authors Full Name

Zha, Jinmiao. Sun, Liwei. Zhou, Yiqi. Spear, Philip A. Ma, Mei. Wang, Zijian.

Institution

State Key Laboratory of Environmental Aquatic Chemistry, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, P.O. Box 2871, Shuangqing Rd 18, Haidian District, Beijing, 100085, PR China.

Title

Assessment of 17alpha-ethinylestradiol effects and underlying mechanisms in a continuous, multigeneration exposure of the Chinese rare minnow (*Gobiocypris rarus*).

Source

Toxicology & Applied Pharmacology. 226(3):298-308, 2008 Feb 1.

Abstract

17alpha-Ethinylestradiol (EE(2)) is a synthetic estrogen used primarily in birth control pills and in hormone replacement therapy. Owing to its occurrence in surface waters at concentrations frequently greater than 1 ng/l and its projected future use, EE(2) is expected to pose a significant risk to aquatic organisms. This study was conducted to obtain long-term exposure data necessary for the establishment of water quality criteria and to investigate mechanisms associated with toxic effects. In a multigeneration experiment, Chinese rare minnows (*Gobiocypris rarus*) were constantly exposed to environmentally relevant concentrations of the synthetic estrogen EE(2). Mortality, deformities, reproductive parameters, plasma vitellogenin and histopathology were assessed. The results showed that, in the F(0) generation, all endpoints were significantly affected at concentrations higher than 0.2 ng/l EE(2). No F(1) phenotypic males developed to maturity at 0.2 ng/l and, when adult females of this exposure group were crossed with unexposed males, no F(2) fertile eggs were produced. Kidney histopathology and ultrastructure suggest anomalies possibly associated with increased vitellogenin accumulation. We concluded that the reproduction of the F(1) minnows was completely inhibited at the lowest concentration tested, 0.2 ng/l EE(2), a concentration frequently detected in surface waters. Growth effects may be related to increased energy requirements including the energy used in VTG synthesis. Reproductive effects are presumably associated with male feminization and the occurrence of testis-ova in males; however, ovarian degeneration observed in females may also have contributed to reproductive failure.

Publication Type

Journal Article. Research Support, Non-U.S. Gov't.

<2>

Unique Identifier

17203781

Status

MEDLINE

Authors

Kirigaya A. Hayashi S. Iguchi T. Sato T.

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Institution

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Title

Developmental effects of ethinylestradiol on reproductive organs of female mice.

Source

In Vivo. 20(6B):867-73, 2006 Nov-Dec.

Abstract

Reproductive organs in female mice are susceptible to exposure to estrogenic substances especially during development. In the present study, C57BL/6J female mice were exposed to the synthetic estrogens ethinylestradiol (EE2) or diethylstilbestrol (DES), 10-100 or 6.7-67 microg/kg bw, respectively, in utero from day 10 to 18 of pregnancy, and their effects were analyzed at 30 and 40 days of age. Both EE2 and DES reduced the survival rate of fetuses and newborns in a dose-dependent manner. Polyovular follicles (PF) were found in the ovaries of all groups at 30 days of age including oil-injected controls. However, the incidence of PF was significantly higher in the 50 microg/kg EE2- and 33.3 microg/kg DES-exposed mice than the control. In vaginal epithelia of the in utero EE2 exposed, ovariectomized mice, stratification and cornification were encountered even 10 days after ovariectomy. Especially, vaginae in the ovariectomized mice given high dose of EE2 or DES in utero showed ovary-independent proliferation of the epithelium. Thus, it is clear that prenatal exposure to EE2 or DES induces reproductive abnormalities, including PF, ovary-independent vaginal epithelial stratification and cornification.

Publication Type

Journal Article. Research Support, Non-U.S. Gov't.

<3>

Unique Identifier

974713

Status

MEDLINE

Authors

Frost O.

Authors Full Name

Frost, O.

Title

Tracheo-oesophageal fistula associated with hormonal contraception during pregnancy.

Source

British Medical Journal. 2(6042):978, 1976 Oct 23.

Publication Type

Case Reports. Journal Article.

<4>

Unique Identifier

974708

Status

MEDLINE

Authors

Gal I.

Authors Full Name

Gal, I.

Title

Hormonal pregnancy tests and congenital malformations.

Source

British Medical Journal. 2(6042):1014-5, 1976 Oct 23.

Other Abstract

Some general practitioners are still using hormonal pregnancy tests despite the warning notice by the Committee on Safety of Medicines. In view of the possible fetal damage, this practice requires further action. 12 different preparations have been used. Only Primodos and Norlestrin are still available. These products are also used for the symptomatic treatment of secondary amenorrhea. The manufacturers' data sheets have been revised but the warning notice should be reinforced. A change in the name of the products is suggested.

Publication Type

Letter.

<5>

Unique Identifier

12831336

Status

MEDLINE

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Title

Acne: comparing hormonal approaches to antibiotics and isotretinoin. [Review] [31 refs]

Source

Expert Opinion on Pharmacotherapy. 4(7):1097-103, 2003 Jul.

Abstract

Acne is a common and disfiguring disease affecting a significant proportion of the general population. In milder cases topical therapy is sufficient. However, in more severe cases where papulopustular or nodulocystic acne is present, there is a need of systemic treatment. The latter include antibiotics, anti-androgens and retinoids. A systematic review of the literature was performed of systemic monotherapy using these drugs. Because of the significant methodological variability of the studies examined, it was not possible to make a meta-analysis. Instead the overall effects were assessed by calculating mean weighted effects across different reported effect variables. Isotretinoin scored 85 +/- 10% improvement compared with the baseline, whereas tetracyclines and cyproterone acetate plus ethinyloestradiol were less effective (54 +/- 3% versus 65 +/- 4% improvement compared with baseline, respectively). Moreover, studies suggested that isotretinoin reduces the risk of acne relapse in the few studies that included a follow-up period. A number of restrictions limit the general use of these drugs as monotherapy, e.g., potential teratogenicity. There is a continued need for effective drugs for the therapy of acne, although judicious combined use of existing topical and systemic therapies offers great relief to many patients. In addition, methodological problems in previous studies prevent adequate synthesis of existing knowledge within the framework of evidence-based medicine. There is therefore a demand for future standardisation of further acne studies to enable direct comparison of different treatment efficacies. [References: 31]

Publication Type

Comparative Study. Journal Article. Review.

<6>

Unique Identifier

6952745

Status

MEDLINE

Authors

De-Wei Z.

Authors Full Name

De-Wei, Z.

Title

Research activities in the field of oral contraceptives in the People's Republic of China.

Source

Acta Obstetricia et Gynecologica Scandinavica - Supplement. 105:51-60, 1982.

Publication Type

Journal Article.

<7>

Unique Identifier

2941890

Status

MEDLINE

Authors

Keller P.J.

Authors Full Name

Keller, P J.

Title

[Hormonal contraception using depot preparations]. [Review] [26 refs] [German]

Source

Therapeutische Umschau. 43(5):395-9, 1986 May.

Publication Type

Comparative Study. English Abstract. Journal Article. Review.

<8>

Unique Identifier

12883093

Status

MEDLINE

Authors

Sawaki M. Noda S. Muroi T. Mitoma H. Takakura S. Sakamoto S. Yamasaki K.

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Title

In utero through lactational exposure to ethinyl estradiol induces cleft phallus and delayed ovarian dysfunction in the offspring.

Source

Toxicological Sciences. 75(2):402-11, 2003 Oct.

Abstract

Most of the attention currently focused on endocrine-active chemicals is directed to their effects on the development of offspring exposed to them in utero or during the neonatal period. Pregnant Crj:CD(SD)IGS rats were given ethinyl estradiol (EE) orally in doses of 0.5-50 microg/kg/day from gestational day 7 to postnatal day 18, and their offspring were examined for its effects. Our previous study according to a similar protocol demonstrated the occurrence of cleft phallus in the female offspring exposed to 50 microg/kg of EE in utero and during the lactation period. The present study was designed to assess (1) the reproducibility of the induction of cleft phallus, (2) the fertility of female rats with cleft phallus, and (3) whether any delayed effects, possibly delayed anovulation, were induced. At 50 microg/kg cleft phallus was observed in almost all of the female offspring, and slight retardation of body weight gain was detected in both sexes. At 15-17 weeks of age the animals with cleft phallus could copulate and had fertility comparable to the control group. At 6 months of age, on the other hand, 6/8 of the female offspring at 50 microg/kg exhibited

abnormal cyclicity, including persistent estrus, and histological examination revealed follicular cysts and absence of corpora lutea in the ovaries of the rats with persistent estrus. These findings are consistent with delayed anovulation syndrome. The results suggest that observation of cyclicity at 6 months old is able to detect possible delayed ovarian dysfunction induced by perinatal exposure to chemicals.

Publication Type

Journal Article. Research Support, Non-U.S. Gov't.

<9>

Unique Identifier

12831336

Status

MEDLINE

Authors

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Authors Full Name

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Department of Medicine, Roskilde Hospital, University of Copenhagen, Denmark.

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Title

Acne: comparing hormonal approaches to antibiotics and isotretinoin. [Review] [31 refs]

Source

Expert Opinion on Pharmacotherapy. 4(7):1097-103, 2003 Jul.

Abstract

Acne is a common and disfiguring disease affecting a significant proportion of the general population. In milder cases topical therapy is sufficient. However, in more severe cases where papulopustular or nodulocystic acne is present, there is a need of systemic treatment. The latter include antibiotics, anti-androgens and retinoids. A systematic review of the literature was performed of systemic monotherapy using these drugs. Because of the significant methodological variability of the studies examined, it was not possible to make a meta-analysis. Instead the overall effects were assessed by calculating mean weighted effects across different reported effect variables. Isotretinoin scored 85 +/- 10% improvement compared with the baseline, whereas tetracyclines and cyproterone acetate plus ethinyloestradiol were less effective (54 +/- 3% versus 65 +/- 4% improvement compared with baseline, respectively). Moreover, studies suggested that isotretinoin reduces the risk of acne relapse in the few studies that included a follow-up period. A number of restrictions limit the general use of these drugs as monotherapy, e.g., potential teratogenicity. There is a continued need for effective drugs for the therapy of acne, although judicious combined use of existing topical and systemic therapies offers great relief to many patients. In addition, methodological problems in previous studies prevent adequate synthesis of existing knowledge within the framework of evidence-based medicine. There is therefore a demand for future standardisation of further acne studies to enable direct comparison of different treatment efficacies. [References: 31]

Publication Type

Comparative Study. Journal Article. Review.

<10>

Unique Identifier

12759103

Status

MEDLINE

Authors

Sawaki M. Noda S. Muroi T. Mitoma H. Takakura S. Sakamoto S. Yamasaki K.

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Title

Evaluation of an in utero through lactational exposure protocol for detection of estrogenic effects of ethinyl estradiol on the offspring of rats: preliminary trial.

Source

Reproductive Toxicology. 17(3):335-43, 2003 May-Jun.

Abstract

As a preliminary trial of an in utero through lactational exposure protocol, ethinyl estradiol, 0, 0.5, 5, or 50 micro g/kg/day, was administered by gavage to pregnant Crj: CD (SD) IGS BR rats from gestational day (GD) 7 to day 18 after delivery to evaluate the efficacy of this protocol and to estimate optimal endpoints. The dams showed no abnormalities. Cleft phallus was observed in female offspring at 50 micro g/kg. Other than a retardation of body weight gain in both sexes at 50 micro g/kg/day, no other abnormal findings were detected. The fact that cleft phallus was the only change induced suggests that the protocol is applicable to the detection of effects of estrogenic chemicals given to pregnant rats on offspring development and that the morphology of the female external genitalia may be a useful endpoint.

Publication Type

Journal Article. Research Support, Non-U.S. Gov't.

<11>

Unique Identifier

12151635

Status

MEDLINE

Authors

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Title

Transgenerational and developmental exposure of Japanese medaka (*Oryzias latipes*) to ethinylestradiol results in endocrine and reproductive differences in the response to ethinylestradiol as adults.

Source

Toxicological Sciences. 68(2):389-402, 2002 Aug.

Abstract

17alpha-Ethinylestradiol (EE), a synthetic estrogen found in birth control pills, has been detected in the effluent of municipal wastewater treatment plants in several countries. Because EE was designed to be extremely potent at the estrogen receptor (ER), environmental exposure to low concentrations has the potential to disrupt the development of normal endocrine and reproductive function when exposure occurs during critical periods in development. Japanese medaka, *Oryzias latipes*, were used to evaluate the effect of exposure to EE during development on adult reproduction and endocrine function and the sensitivity of these animals to estrogen exposure as adults. To determine if the response to exogenous estrogen stimulation was diminished or sensitized, adults resulting from the developmental exposure groups were reexposed to EE at respectively higher concentrations. Hatchling exposure produced no changes in adult vitellogenin (VTG) content in the liver or circulating steroid concentrations, nor was reproduction affected. Reexposure of these adults inhibited reproduction, increased hepatic VTG and ER, and increased estrogen concentration measured in male plasma. Parental exposure produced permanent changes in hepatic content of ER and VTG in the adults resulting from exposure during

gametogenesis and was related to a diminished response of males to subsequent estrogen exposure. The potential for this transgenerational exposure to decrease the responsiveness of males to EE is supported by comparing the concentration-response curves for hepatic VTG and ER in males exposed in ovo and as hatchlings. Our results indicate that the relationship between biomarkers and estrogen exposure will be altered by the timing and frequency of exposure.

Publication Type

Journal Article. Research Support, Non-U.S. Gov't. Research Support, U.S. Gov't, Non-P.H.S..

<12>

Unique Identifier

11502156

Status

MEDLINE

Authors

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Title

Pharmacology and toxicology of ethinyl estradiol and norethindrone acetate in experimental animals. [Review] [93 refs]

Source

Regulatory Toxicology & Pharmacology. 34(1):53-61, 2001 Aug.

Abstract

For over 30 years various combinations of synthetic estrogens and progestins have been used in oral contraceptive formulations. Ethinyl estradiol (EE) and norethindrone acetate (NA) are common synthetic hormones used in oral contraceptives such as Loestrin, Brevicon, Ortho-Novum, Norlestrin, and Norinyl. In recent years these oral contraceptives have been considered for development in other therapeutic indications. Given the use of these agents for other clinical indications with different and larger target populations, an updated comprehensive review of the toxicology literature of estrogens and progestins is warranted. This review will summarize available data on the pharmacology and toxicology of estrogens and progestins with an emphasis on the specific synthetic hormones EE and NA. Ethinyl estradiol and norethindrone acetate alone or in combination, possess low acute and chronic toxicity. In some studies, EE and/or NA increased the incidence of specific tumors in susceptible strains of rodents and dogs, but not monkeys. These agents are not teratogenic when given in combination. Alone EE and NA have clastogenic properties. Overall, the animal data demonstrates that long-term exposure to EE and NA formulations pose very little health risks to humans. Copyright 2001 Academic Press. [References: 93]

Publication Type

Comparative Study. In Vitro. Journal Article. Review.

<13>

Unique Identifier

9685884

Status

MEDLINE

Authors

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Institution

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Title

In vitro cytotoxicity and teratogenicity of norethisterone and levonorgestrel released from hollow nylon monofilaments.

Source

Journal of Controlled Release. 50(1-3):179-86, 1998 Jan 2.

Abstract

Direct delivery of progestogens to the uterus may be of use in the treatment of dysfunctional uterine bleeding and the sequelae of the menopause as it has the potential to overcome the problems of systemic administration. This study characterised the release of norethisterone and levonorgestrel into an aqueous medium from hollow nylon fibres with dimensions suitable for easy insertion through the post-menopausal cervix. Cell culture techniques were used to assess potential cytotoxic and teratogenic effects. The results demonstrated that the hollow fibres released norethisterone and levonorgestrel at mean rates of 0.5 and 0.6 micrograms/day over 14 days, respectively. There were indications, however, that both steroids were toxic to endometrial cells at concentrations of approximately 5 micrograms/ml, and both drugs showed signs of potential teratogenicity at 10 micrograms/ml. Delivery of the same doses of norethisterone using the hollow fibres reduced the effects on the endometrial and fetal cells. Delivery of levonorgestrel from the hollow fibres had no effect on the endometrial cell toxicity but potentiated the effects on the fetal cells. These results suggest that the hollow nylon fibres may be of use for the delivery of norethisterone to the uterus but that they are inappropriate for the delivery of levonorgestrel.

Publication Type

Journal Article.

<14>

Unique Identifier

7750279

Status

MEDLINE

Authors

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Department of Human Genetics and Teratology, National Institute of Hygiene, Budapest, Hungary.

Title

A changing pattern in the association of oral contraceptives and the different groups of congenital limb deficiencies.

Source

Contraception. 51(1):19-24, 1995 Jan.

Abstract

A case-control study on different groups of isolated congenital limb deficiency was performed in a ten-year population-based and revised Hungarian data set. A higher rate of one contraceptive pill type with relatively high dose (ethynodiol diacetate 1.0 mg + ethinyloestradiol 0.05 mg) used in the periconceptional period was found in the mothers of cases with terminal transverse defect (adjusted relative odds 1.9 with 95% confidence interval of 1.1-3.4). This risk is minimised by the use of recent low-dose pills.

Other Abstract

In Hungary, researchers analyzed 1975-1984 population-based and revised data on 537 children with isolated congenital limb deficiency (CLD) (i.e., cases with at least 1 affected limb) and data on 537 age-matched controls with no CLD. They wanted to determine the association between periconceptional use of oral contraceptives (OCs) and CLD. Personal examination and/or medical documents confirmed reported diagnoses. They separated the isolated CLD cases into terminal transverse CLD, amniogenic CLD, radial and tibial CLD, ulnar-fibular CLD, split hand and/or foot CLD, and intercalary CLD. Periconceptional use of Bisecurin (relatively high dose of 1 mg ethynodiol diacetate and 0.05 mg ethinyl estradiol) was significantly associated with terminal

transverse CLD (adjusted odds ratio [AOR] = 1.9; $p = 0.03$). It was also significantly associated with monomelic CLD (AOR = 1.6; 9.6% vs. 2.9%; $p = 0.0015$). The monomelic cases comprised 19 terminal transverse cases, 6 amniogenic cases, 7 radial cases, 3 atypical split hand cases, and 2 ulnar cases. 19 of the 20 terminal transverse cases were monomelic. Periconceptional use of Continuin (0.5 mg ethynodiol diacetate alone) was associated, but not significantly so, with terminal transverse CLD (6 cases vs. 1 control; $p = 0.06$). These findings suggest that use of OCs with a high dose of ethynodiol diacetate increases the risk of terminal transverse defect. Use of low dose OCs likely minimizes this risk.

Publication Type
Journal Article.

<15>

Unique Identifier
2727933

Status
MEDLINE

Authors

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Division of Reproductive and Developmental Toxicology, National Center for Toxicological Research, Jefferson, Arkansas 72079.

Title

Transplacental estrogen responses in the fetal rat: increased uterine weight and ornithine decarboxylase activity.

Source

Teratology. 39(3):253-60, 1989 Mar.

Abstract

The synthetic estrogens, diethylstilbestrol (DES) and ethynylestradiol (EE2), are more potent than 17 beta-estradiol (E2) in inducing uterine weight gain in the neonatal rat, due to the binding of E2 to serum alpha-fetoprotein (AFP). However, all three hormones are equipotent in inducing neonatal uterine ornithine decarboxylase (ODC) activity. The present study assessed estrogen potency in fetal rats. Pregnant CD rats were injected sc daily on gestation days (GD) 16-20 with DES, EE2, or E2 in sesame oil. Both DES and EE2, but not E2, significantly increased uterine weight at birth, to more than twice that of controls. In addition, implants which continuously release E2 only slightly increased uterine weight at birth. Alternatively, dams were given a single estrogen injection on GD 20 and were sacrificed at various times after injection. Peak fetal uterine ODC activity occurred at 6-8 hours after maternal injection for all three estrogens. E2 had a relative potency about tenfold less than either DES or EE2 in stimulating fetal ODC activity, in contrast to equal potencies of the three estrogens in the postnatal rat uterus. Similar patterns were found following direct fetal injection with E2 or DES. In summary, these data demonstrate a transplacental induction of fetal uterine ODC activity and uterine weight gain by both DES and EE2. In addition, the lack of correlation between these endpoints in response to E2 suggests that they may be useful as selective indicators of potential toxicity of both natural and synthetic estrogens.

Publication Type
Journal Article.

<16>

Unique Identifier
2976719

Status
MEDLINE

Authors

Tews G. Arzt W. Mursch-Edlmayr G.

Authors Full Name

Tews, G. Arzt, W. Mursch-Edlmayr, G.

Title

[Pregnancy carried to term following administration of cyproterone acetate in the 1st trimester].

[German]

Source

Gynakologische Rundschau. 28(4):193-7, 1988.

Publication Type

Case Reports. English Abstract. Journal Article.

<17>

Unique Identifier

3352817

Status

MEDLINE

Authors

Wolffers I.

Authors Full Name

Wolffers, I.

Title

[Problems with high-dose estrogen/progestin combinations such as Mestrogen, in India]. [Dutch]

Source

Nederlands Tijdschrift voor Geneeskunde. 132(1):29-31, 1988 Jan 2.

Publication Type

Journal Article.

<18>

Unique Identifier

3672376

Status

MEDLINE

Authors

Yasuda Y. Konish H. Tanimura T.

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Institution

Department of Anatomy, Kinki University School of Medicine, Osaka, Japan.

Title

Ovarian follicular cell hyperplasia in fetal mice treated transplacentally with ethinyl estradiol.

Source

Teratology. 36(1):35-43, 1987 Aug.

Abstract

The occurrence of follicular cell hyperplasia was studied by light and electron microscopy in fetal mouse ovaries exposed to ethinyl estradiol (EE) from day 11 through day 17 of pregnancy. Pregnant mice were given EE in olive oil (0.02, or 0.2 mg/kg of body weight) and were sacrificed on day 18. The female fetuses were examined for ovarian histogenesis. Follicular cell hyperplasia was detected in both of the experimental groups, but the incidence was statistically significant only in fetuses exposed to 0.2 mg/kg of EE. Light and electron microscopic observations of the ovaries showed that the hyperplasia was located in the medullary region, and the follicular cells showed pleomorphism. Accumulation of abundant lipid droplets, enlarged rough endoplasmic reticulum with granular material, dense bodies, and vague masses of fibrous structures were seen in the cytoplasm. These morphological observations indicate that hyperplasia of follicular cells in fetal mouse ovaries at term can be induced by prenatal treatment with EE.

Publication Type

Journal Article. Research Support, Non-U.S. Gov't.

<19>

Unique Identifier

2958120

Status

MEDLINE

Authors

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Title

[Deficiencies of the mullerian ducts induced by norethindrone in the female chick embryo].

[French]

Source

Comptes Rendus des Seances de la Societe de Biologie et de Ses Filiales. 181(3):300-6, 1987.

Abstract

Norethindrone produces two effects on mullerian ducts (MD) of female chick embryos. It induces the loss of the lower end of both ducts, as a result of a stop in their development, before 8 days. After 12 days NET causes regressions of the upper part of the MD particularly of the oviduct. NET like estrogens are the only known substances which present these both properties.

Publication Type

English Abstract. Journal Article.

<20>

Unique Identifier

3563930

Status

MEDLINE

Authors

Hendrickx AG. Korte R. Leuschner F. Neumann BW. Prahalada S. Poggel A. Binkerd PE.

Gunzel P.

Authors Full Name

Hendrickx, A G. Korte, R. Leuschner, F. Neumann, B W. Prahalada, S. Poggel, A. Binkerd, P E. Gunzel, P.

Title

Embryotoxicity of sex steroidal hormone combinations in nonhuman primates: I. Norethisterone acetate + ethinylestradiol and progesterone + estradiol benzoate (Macaca mulatta, Macaca fascicularis, and Papio cynocephalus).

Source

Teratology. 35(1):119-27, 1987 Feb.

Abstract

Two sex steroid hormone combinations which have been used clinically as tests for detection of early pregnancy were examined for embryotoxic effects in macaques and baboons. Norethisterone acetate and ethinyl estradiol (NEA + EE) were orally administered to rhesus and cynomolgus monkeys and baboons at dosages ranging from one to 1,000 times the human dose equivalent (HDE) during days 20-50 of pregnancy. Progesterone and estradiol benzoate (P + EB) were delivered by two to six intramuscular injections to rhesus and cynomolgus monkeys between gestational days 20 and 35 at 0.1-25 X HDE. Fetuses were examined following cesarean section at 100 +/- 2 days (NEA + EE) or at term (P + EB). The results showed increased embryoletality over controls at 100-1,000 X HDE (NEA + EE) and at 10 and 25 X HDE (P + EB). Besides growth retardation, isolated cases of minor nongenital malformations were observed only in cynomolgus monkeys following treatment with both hormone combinations mainly at embryoletal dose levels and were considered spontaneous in nature. Virilization of female cynomolgus fetuses following

NEA + EE treatment was manifested as two cases of clitoral enlargement in the 300 X HDE group and two cases of increased anogenital distance with reduced vaginal opening in the 1,000 X HDE group. The highest dose of NEA + EE was also maternally toxic, as two maternal deaths occurred at the end of the treatment period. One dead female cynomolgus fetus exposed to P + EB (10 X HDE) also exhibited masculinized external genitalia.(ABSTRACT TRUNCATED AT 250 WORDS)

Publication Type

Journal Article.

<21>

Unique Identifier

2874623

Status

MEDLINE

Authors

Yasuda Y. Konishi H. Tanimura T.

Authors Full Name

Yasuda, Y. Konishi, H. Tanimura, T.

Title

Leydig cell hyperplasia in fetal mice treated transplacentally with ethinyl estradiol.

Source

Teratology. 33(3):281-8, 1986 Jun.

Abstract

Pregnant female mice were given ethinyl estradiol on days 11 through 17 of gestation. On day 18 the dams were killed and the male fetuses were examined for testicular differentiation. Three of 12 males from dams treated with the highest dose of ethinyl estradiol showed cryptorchid testes with uterine tubes. Light and electron microscopic evaluation of the testes, both cryptorchid and normal, demonstrated foci of hyperplasia of Leydig cells showing cytoplasmic and nuclear pleomorphism, increase in lipid droplets, and decrease in smooth endoplasmic reticulum and ribosomes when compared to testes from control fetal mice. Morphometric determinations of the testes indicated that the number of Leydig cells in a unit area (mm²) in the interstitial tissue showed a dose-response relationship to ethinyl estradiol in the normal testes. The number of Leydig cells in the testes exposed to the highest dose of estrogen showed a significant difference between cryptorchid and normal testes: the former had fewer Leydig cells than the latter. These morphological observations indicate that hyperplasia of Leydig cells of fetal mouse testis at term can be induced by transplacental treatment with ethinyl estradiol and suggest that a malignant transformation into a Leydig cell tumor is possible.

Publication Type

Journal Article.

<22>

Unique Identifier

2941890

Status

MEDLINE

Authors

Keller P.J.

Authors Full Name

Keller, P J.

Title

[Hormonal contraception using depot preparations]. [Review] [26 refs] [German]

Source

Therapeutische Umschau. 43(5):395-9, 1986 May.

Publication Type

Comparative Study. English Abstract. Journal Article. Review.

<23>

Unique Identifier

3987922

Status

MEDLINE

Authors

Resseguie L.J. Hick J.F. Bruen J.A. Noller K.L. O'Fallon W.M. Kurland L.T.

Authors Full Name

Resseguie, L. J. Hick, J. F. Bruen, J. A. Noller, K. L. O'Fallon, W. M. Kurland, L. T.

Title

Congenital malformations among offspring exposed in utero to progestins, Olmsted County, Minnesota, 1936-1974.

Source

Fertility & Sterility. 43(4):514-9, 1985 Apr.

Abstract

Comparison of a cohort of 988 offspring exposed in utero to exogenous progestins with a matched cohort of unexposed offspring did not result in detection of an association of congenital anomalies with exposure. The conclusions are based primarily on outcomes of pregnancy with exposure to progesterone and 17 alpha-hydroxyprogesterone caproate, and may not apply to androgenic progestins. Offspring exposed to combinations of progestins and estrogens were excluded from this study and may have a different distribution of anomalies.

Publication Type

Journal Article. Research Support, U.S. Gov't, P.H.S..

<24>

Unique Identifier

6676180

Status

MEDLINE

Authors

Joshi N.J. Ambani L.M. Munshi S.R.

Authors Full Name

Joshi, N. J. Ambani, L. M. Munshi, S. R.

Title

Evaluation of teratogenic potential of a combination of norethisterone and ethinyl estradiol in rats.

Source

Indian Journal of Experimental Biology. 21(11):591-6, 1983 Nov.

Publication Type

Journal Article.

<25>

Unique Identifier

6613580

Status

MEDLINE

Authors

Czeizel A. Pazsy A. Pusztai J. Nagy M.

Authors Full Name

Czeizel, A. Pazsy, A. Pusztai, J. Nagy, M.

Title

Aetiological monitor of congenital abnormalities: a case-control surveillance system.

Source

Acta Paediatrica Hungarica. 24(1):91-9, 1983.

Abstract

An Aetiological Monitor of Congenital Abnormalities was launched in Hungary on 1 January 1980 with the purpose to obtain aetiological information parallel with the reporting of congenital abnormalities. A questionnaire is sent to all mothers having babies with well defined major congenital abnormalities within one month after being reported to the Register. Diseases during pregnancy, drugs taken during pregnancy as well as employment and type of work made by the pregnant are studied. According to the data of the first year, progestogens were taken in 33.4% and oestrogen in 10.8% of all pregnancies. Other data indicate that the drugs studied mean either no teratogenic risk or, if there is any risk, it is very small.

Publication Type

Journal Article.

<26>

Unique Identifier

6867943

Status

MEDLINE

Authors

Prahalada S. Hendrickx AG.

Authors Full Name

Prahalada, S. Hendrickx, A G.

Title

Embryotoxicity of Norlestrin, a combined synthetic oral contraceptive, in rhesus macaques (*Macaca mulatta*).

Source

Teratology. 27(2):215-22, 1983 Apr.

Abstract

Thirty timed-mated pregnant rhesus monkeys received Norlestrin (Norethindrone acetate, 2.5 mg, and ethinyl estradiol, 0.05 g per tablet, Parke-Davis) orally at four different dose levels. The dose levels were 5, 10, 25 and 50 mg/day/monkey and the doses were administered during early (days 21-35), late (days 33-46), and throughout (days 21-46) organogenesis, except for the 50-mg-dose-group animals, which were treated only during early organogenesis (days 21-35). All except the animals in the 60-mg-dose group were allowed to go to term (165 days gestation). Pregnancy for the animals in the 50-mg-dose group was terminated by cesarean section on day 50 of gestation and the fetuses were fixed, serially sectioned, and examined histologically. No teratogenicity was observed. However, the prenatal mortality rate (38.5%) was higher for the Norlestrin-treated animals than in the control colony (21%). Eight animals aborted between days 40 and 78 of gestation and two other cases resulted in stillbirths at 139 and 165 days of gestation. There was a higher incidence of abortion (44.4%) in the 25-mg-dose group. Norlestrin treatment during early organogenesis also resulted in a higher abortion rate (37.5%) compared to treatment during late organogenesis (22.2%) abortions. No morphological abnormalities were found in infants observed at birth or in juvenile monkeys which died of natural causes or in those that were sacrificed over a period of two years. No histopathology was observed in the 50-day-old fetuses examined by serial section. Examination of endogenous maternal serum estrogen and progesterone levels in Norlestrin-treated monkeys (25 mg/day, days 21-35) suggested that placental steroidogenesis was not affected; however, the lower levels of estrogen in maternal serum suggested that the ovarian steroidogenesis was affected. Although the precise pathogenesis of this selective embryolethality is not known, several observations in this study suggest a direct generalized embryotoxic effect. Thus, this study for the first time has demonstrated that, while Norlestrin may be embryolethal at 100 times the human contraceptive dose equivalent (25 mg/day) in the rhesus monkey, nevertheless it does not affect the offspring which survive the exposure.

Publication Type

Journal Article. Research Support, U.S. Gov't, P.H.S..

<27>

Unique Identifier

6952745

Status

MEDLINE

Authors

De-Wei Z.

Authors Full Name

De-Wei, Z.

Title

Research activities in the field of oral contraceptives in the People's Republic of China.

Source

Acta Obstetrica et Gynecologica Scandinavica - Supplement. 105:51-60, 1982.

Publication Type

Journal Article.

<28>

Unique Identifier

7268640

Status

MEDLINE

Authors

Yasuda Y. Kihara T. Nishimura H.

Authors Full Name

Yasuda, Y. Kihara, T. Nishimura, H.

Title

Effect of ethinyl estradiol on development of mouse fetuses.

Source

Teratology. 23(2):233-9, 1981 Apr.

Abstract

Pregnant ICR/JCL mice were given orally 0.02, 0.3, or 2.0 mg/kg body weight/day of ethinyl estradiol in olive oil or vehicle alone on day 11 through day 17 of pregnancy. Pregnant mice of another group received a single oral dose of ethinyl estradiol on day 8 or day 11 of pregnancy. A lethal effect on fetuses of both groups with single and continuous exposure to ethinyl estradiol was observed in a dose-response relationship. Growth suppression of fetuses was only found at term in a dose-response relationship following continuous exposure to ethinyl estradiol. Hypertrophic nipples were seen in 42% of surviving female fetuses prenatally exposed to 2.0 mg/kg of ethinyl estradiol singly on day 11 of gestation. There was not an increase in other congenital malformations in any of the treated groups. These findings indicate that administered ethinyl estradiol can affect the developing mouse embryo but the embryotoxic doses in the mouse are substantially greater than the usual therapeutic or contraceptive doses in the human.

Publication Type

Journal Article. Research Support, Non-U.S. Gov't.

<29>

Unique Identifier

120838

Status

MEDLINE

Authors

Anonymous.

Title

Norethisterone and norethisterone acetate. [Review] [58 refs]

Source

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 21:441-60, 1979 Dec.

Other Abstract

This monograph on norethisterone and its acetate (NOR) includes chemical and physical data (synonyms and trade names), structural and molecular formulae and molecular weight of NOR, chemical and physical properties of NOR, and the production, use, occurrence, and analysis of NOR. Production of NOR and its acetate, both of which are not known to occur naturally, occurs via conversion of estrone to its methyl ester which is reduced to estradiol 3-methyl ether with lithium aluminum hydride; NOR acetate is synthesized by acetylating NOR with acetic anhydride in pyridine. NOR has been used for human medicine in a variety of ways: 1) to treat amenorrhea, 2) to treat dysfunctional uterine bleeding, and 3) for treating endometriosis. It has also been used to treat premenstrual tension and dysmenorrhea. Medicinal use of NOR acetate is similar to that for NOR. Analytical procedures for determining NOR as a bulk chemical are presented tabularly. Biological data relevant to the evaluation of carcinogenic risk to humans are presented briefly. With experimental animals, when administered alone NOR and/or its acetate increased the incidence of benign liver tumors in male mice and of pituitary tumors in females; females also suffered granulosa-cell ovarian tumors. NOR in combination with an estrogen increased incidence of pituitary tumors in mice of both sexes. NOR is embryolethal in some species and produces virilization in female fetuses. It is concluded that there is limited evidence for the carcinogenicity of NOR and its acetate in animals. Human studies are not available, but NOR is implicated causally as a progestogenic element in side effects of combined oral contraceptive usage. [References: 58]

Publication Type

Journal Article. Review.

<30>

Unique Identifier

120833

Status

MEDLINE

Authors

Anonymous.

Title

Ethinylestradiol. [Review] [72 refs]

Source

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 21:233-55, 1979 Dec.

Other Abstract

This monograph on ethinylestradiol (EE) includes chemical and physical data (synonyms and trade names), structural and molecular formulae and molecular weight of the substance, chemical and physical properties of EE, and the production, occurrence, use, and analysis of EE. Production of EE, which has not been reported to occur naturally, occurs by treatment of estrone with potassium acetylide in liquid ammonia. EE is 1 of the most active estrogens known when administered orally; it is used in human medicine for 1) estrogen replacement therapy, 2) functional menstrual disorders, 3) postpartum breast engorgement, 4) dysfunctional uterine bleeding, 5) prostatic carcinoma, and 6) for advanced breast cancer in postmenopausal women. Its largest use is as an oral contraceptive, administered in combination therapy with a progestin. Typical analytical methods for EE are presented tabularly. Biological data relevant to the evaluation of carcinogenic risk to humans are presented in brief. Mice, rats, dogs, and monkeys have been used in experiments of EE by the oral route, and rats have been studied using subcutaneous injection. When administered alone, EE increased the incidence of pituitary tumors and malignant mammary tumors in both sexes and malignant cervical and vaginal tumors in females. Rats showed increased incidence of benign liver tumors in both sexes and malignant liver tumors in females. When combined with a progestin, EE produced mammary fibroadenomas in female rats, via subcutaneous infection. EE is embryolethal for preimplantation embryos in some species. Therefore, there is sufficient evidence for the carcinogenicity of EE in experimental animals. No human studies were available on EE alone, but since it is used in combined oral contraceptives, carcinogenic risks associated with these are associated causally with EE. [References: 72]

Publication Type

Journal Article. Review.

<31>

Unique Identifier

469899

Status

MEDLINE

Authors

Wallace ME. Badr FM. Badr RS.

Authors Full Name

Wallace, M E. Badr, F M. Badr, R S.

Title

Studies in mice on the mutagenicity of two contraceptive drugs.

Source

Journal of Medical Genetics. 16(3):206-9, 1979 Jun.

Abstract

An experiment is described which tests for visible and invisible mutants in mice treated with four different doses each of the contraceptives Gynanovlar and Lyndiol. The results show that there is no reason to suppose that either substance has an appreciable mutagenic effect, expressed as an increase of antenatal and postnatal lethals or visibles. The substrain CBA/CagCam, used throughout, has an incidence of 0.27% of singly occurring abnormalities, mainly of the appendicular skeleton, which distinguishes it from the parent CBA strain and its axial variation described by Gruneberg (1963).

Publication Type

Journal Article.

<32>

Unique Identifier

724353

Status

MEDLINE

Authors

Mills JL. Bongiovanni AM.

Authors Full Name

Mills, J L. Bongiovanni, A M.

Title

Effect of prenatal estrogen exposure on male genitalia.

Source

Pediatrics. 62(6 Pt 2):1160-65, 1978 Dec.

Publication Type

Journal Article.

<33>

Unique Identifier

846706

Status

MEDLINE

Authors

Gardo S.

Authors Full Name

Gardo, S.

Title

[The use of limovanil in pregnancy]. [Hungarian]

Source

Orvosi Hetilap. 118(11):660, 1977 Mar 13.

Publication Type
Journal Article.

<34>

Unique Identifier
1011335

Status
MEDLINE

Authors
Rundle FW.
Authors Full Name
Rundle, F W.

Title
Cervical teratoma.

Source
Journal of Otolaryngology. 5(6):513-8, 1976 Dec.

Abstract

Cervical teratomas are rare tumors in an unusual location. A neck mass in a newborn was excised when it enlarged disproportionately; histologically, it was a teratoma. Teratomas may occur because of an alteration in sterol chemistry; conception in this case occurred while the mother was ingesting estrogens. Retinal tissue, an unusual finding, was present in this teratoma. Symptoms in cervical teratomas are secondary to interference with deglutition and respiration. Treatment is surgical excision.

Publication Type
Case Reports. Journal Article.

<35>

Unique Identifier
974713

Status
MEDLINE

Authors
Frost O.
Authors Full Name
Frost, O.

Title
Tracheo-oesophageal fistula associated with hormonal contraception during pregnancy.

Source
British Medical Journal. 2(6042):978, 1976 Oct 23.

Publication Type
Case Reports. Journal Article.

<36>

Unique Identifier
974708

Status
MEDLINE

Authors
Gal I.
Authors Full Name
Gal, I.

Title
Hormonal pregnancy tests and congenital malformations.
Source

British Medical Journal. 2(6042):1014-5, 1976 Oct 23.

Other Abstract

Some general practitioners are still using hormonal pregnancy tests despite the warning notice by the Committee on Safety of Medicines. In view of the possible fetal damage, this practice requires further action. 12 different preparations have been used. Only Primodos and Norlestrin are still available. These products are also used for the symptomatic treatment of secondary amenorrhea. The manufacturers' data sheets have been revised but the warning notice should be reinforced. A change in the name of the products is suggested.

Publication Type

Letter.

<37>

Unique Identifier

936986

Status

MEDLINE

Authors

Kullander S. Kallen B.

Authors Full Name

Kullander, S. Kallen, B.

Title

A prospective study of drugs and pregnancy. 3. Hormones.

Source

Acta Obstetrica et Gynecologica Scandinavica. 55(3):221-4, 1976.

Abstract

Results from a prospective study in Malmö performed in 1963-65 are used to discuss the possible role of hormonal drugs in human fetal maldevelopment. Appr. 2 per cent of all women had a child born were treated with gestagens during early pregnancy and slightly more had used Primodos as a pregnancy test. No harmful effect on embryonic development can be demonstrated.

Other Abstract

A prospective study of 6376 pregnancies was conducted to determine whether there is any association between drug usage and incidence or severity of effects on the fetus. Gestagens were given where bleeding or previous miscarriage indicated a present threatening miscarriage. Both such conditions are associated with higher than normal incidence of malformed infants. The study did not show a teratogenic effect of the gestagens. Hormonal preparations used to diagnose pregnancy, Primodos in this case, also seem to have no teratogenic effect. The only hormone treatment which showed an unambiguous relationship with pregnancy outcome was insulin; pregnancy wastage in these instances was due to the diabetes and not to the insulin.

Publication Type

Journal Article.

<38>

Unique Identifier

47000

Status

MEDLINE

Authors

Jaffe P. Liberman MM. McFadyen I. Valman HB.

Authors Full Name

Jaffe, P. Liberman, M M. McFadyen, I. Valman, H B.

Title

Letter: Incidence of congenital limb-reduction deformities.

Source

Lancet. 1(7905):526-7, 1975 Mar 1.

Publication Type

Journal Article.

<39>

Unique Identifier
4594858

Status

MEDLINE

Authors

Kucera J.

Authors Full Name

Kucera, J.

Title

[Congenital defects due to drugs]. [Review] [9 refs] [Czech]

Source

Ceskoslovenska Pediatrie. 28(12):664-6, 1973 Dec.

Publication Type

Journal Article. Review.

<40>

Unique Identifier
4361633

Status

MEDLINE

Authors

Herbst AL.

Authors Full Name

Herbst, A L.

Title

Exogenous hormones in pregnancy. [Review] [28 refs]

Source

Clinical Obstetrics & Gynecology. 16(4):37-50, 1973 Dec.

Other Abstract

Various changes that have been observed after intrauterine exposure to exogenous hormones are presented. Often, alterations observed after exogenous maternal hormone therapy consist of varying degrees of masculinization of the female genitalia. The following specific drug interactions are described in some detail: 1) effects of progestational agents and androgens on female genitalia; 2) relationship of corticosteroids to the development of cleft palate; and 3) effects of synthetic estrogens (e.g., diethylstilbestrol) on the female reproductive tract. The discussion closes with a review of the association of therapy with such drugs to the delayed appearance of clear-cell adenocarcinoma of the genital tract in young women. [References: 28]

Publication Type

Journal Article. Review.

<41>

Unique Identifier
4573581

Status

MEDLINE

Authors

Sever LE.

Authors Full Name

Sever, L E.

Title

Hormonal pregnancy tests and spina bifida.

Source

Nature. 242(5397):410-1, 1973 Apr 6.

Publication Type

Journal Article.

<42>

Unique Identifier

4691941

Status

MEDLINE

Authors

Boue A. Boue J.

Authors Full Name

Boue, A. Boue, J.

Title

Actions of steroid contraceptives on gametic material.

Source

Geburtshilfe und Frauenheilkunde. 33(2):77-85, 1973 Feb.

Publication Type

Journal Article.

<43>

Unique Identifier

4569422

Status

MEDLINE

Authors

Gal I.

Authors Full Name

Gal, I.

Title

Risks and benefits of the use of hormonal pregnancy test tablets.

Source

Nature. 240(5378):241-2, 1972 Nov 24.

Publication Type

Journal Article.

<44>

Unique Identifier

4104009

Status

MEDLINE

Authors

Gardner LI. Assemany SR. Neu RL.

Authors Full Name

Gardner, L I. Assemany, S R. Neu, R L.

Title

Syndrome of multiple osseous defects with pretibial dimples.

Source

Lancet. 2(7715):98, 1971 Jul 10.

Publication Type

Journal Article.

Title: Risks and benefits of the use of hormonal pregnancy test tablets.

POPLINE Document Number: 722029

Author(s):

Gal I

Source citation:

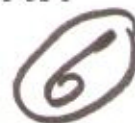
Nature, November 24, 1972;240:241-242.

Abstract:

A brief summary of the risks involved in the use of hormonal pregnancy test tablets is presented. 100 mothers of spina bifida cases (index group) were matched to control mothers as closely as possible according to age, reproductive history, course of pregnancy, and sex of the baby. The most important possible teratological factor detected was the frequent use of "Primodos" (10 mg norethisterone acetate plus .02 mg ethinyl estradiol) or "Amenorone Forte" (50 mg ethisterone plus .05 mg ethireylestradiol) tablets for diagnosis of pregnancy in the index group. The test had been used in 19 index mothers and in only 4 control mothers, a significant difference (p equals .01 to .001). These results suggest that the pregnancy test might have contributed to or acted as a trigger factor in producing the malformation in 1 in 8 cases. These data indicate the need for fundamental biological studies into the possible harmful effects of hormonal preparations in early pregnancy. It is concluded that unnecessary risks are being taken by diagnosing pregnancy with an in vivo method when many other reliable in vitro methods are available.

Keywords:

Comparative Studies
Pregnancy Tests
Congenital Abnormalities
Side Effects
Norethindrone Acetate
Ethinyl Estradiol
Studies
Research Methodology
Laboratory Procedures
Laboratory Examinations and Diagnoses
Examinations and Diagnoses
Neonatal Diseases and Abnormalities
Diseases
Treatment
Norethindrone
Contraceptive Agents, Progestin
Contraceptive Agents, Female
Contraceptive Agents
Contraception
Family Planning
Contraceptive Agents, Estrogen



Library Detail

Title: Duogynon, Primados

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Event Date

Summary: Various cases of birth defects because of use of Primados during pregnancy. Schering recalls product after decade of protest. Duogynon still available in W. Germany. Worldwide sales annually DM 15 mio. Recalls in Sweden, Finland, Italy, Holland, Australia, Spain. Original report (1967) in "Nature" verified by Schering, British study: causality established. Schering, Germany ignores warning, maintains own tests with mice show no causality. In Nov. 1973 Schering no longer advised use of Duogynon during pregnancy, did not, however, inform public why. Product "Primados" supplied with warning label in May 1975. Suit is being prepared for filing. Berlin State attorney sued three leading employees of Schering in 1979. Product liability.

Related Topics: