Toxicological Summary for: 17α-Ethinylestradiol

CAS: 57-63-6

Synonyms: Ethinyl estradiol; Ethinylestradiol; 17-α ethinyl estradiol; 17-α EE; EE2; 17-ethinylestradiol; ethynylestradiol; 17α-ethynyl-1,3,5(10)-estratriene-3,17β-diol;19-nor-17α-pregna-1,3,5(10)-trien-20-yn-3,17-diol (IUPAC)

Acute Non-Cancer Health Based Value (nHBV_{Acute}) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value (nHBV_{Short-term}) = 0.0005 µg/L

(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)

(Short-term Intake Rate, L/kg-d)

= (1.7 x 10^{-7} mg/kg-d) x (0.8*) x (1000 µg/mg)

(0.285 L/kg-d)**

= 0.00048 rounded to 0.0005 µg/L

* Relative Source Contribution: MDH 2008, Section IV.E.1. MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate Relative Source Contributions (RSCs) (MDH 2008, Appendix K). Typically an RSC of 0.5 is utilized for nonvolatile contaminants for the acute and short-term durations and an RSC of 0.2 is used for subchronic and chronic durations. Given the limited potential for exposure from other sources, an RSC of 0.8 was selected rather than applying the default RSC value. For individuals who take 17α-ethinylestradiol by prescription, the additional exposure from drinking water will be negligible.


Reference Dose/Concentration: (POD x DAF)/Total UF = 1.7 x 10^{-7} mg/kg-d (Sprague-Dawley rat)

Source of toxicity value: determined by MDH in 2016

Point of Departure (POD): 0.00050 mg/kg-d (LOAEL, Delclos et al. 2014)

Human Equivalent Dose (MDH, 2011): Not adjusted due to interspecies differences and life-stage differences in toxicokinetics

Total uncertainty factor: 3000

Uncertainty factor allocation: 10 for interspecies differences, 10 for intraspecies variability, and 10 for LOAEL-to-NOAEL, 3 for database uncertainty regarding potential latent effects

Critical effect(s): Male mammary gland hyperplasia, decreased ovary weight, increased uterine weight, delayed vaginal opening

Co-critical effect(s): In humans: reduced fertility (prevention of ovulation), increased sex hormone binding globulin, decreased

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corticosteroid-binding globulin, decreased follicle-stimulating hormone, decreased luteinizing hormone, breast development (gynecomastia) in infants

In laboratory animals: Decreased body weight gain in adults, post-implantation loss, increased resorptions, decreased number of live pups/litter, decreased fetal/neonatal survival, reduced pup body weight and body weight gain, histopathology in female sex organs (uterus, ovaries and clitoral gland), latent uterine atypical focal hyperplasia, increased malformations in female external genitalia, increased number of female nipples, changes in sexually dimorphic behaviors, decreased fertility, early female pubertal onset, effects on estrous cyclicity, ovarian dysfunction, increased gestation length, changes in male reproductive organ weights and histopathology effects in various male reproductive organs, increased male mammary gland terminal end buds and density, decreased testosterone, decreased epididymal sperm counts, increased pituitary gland weight

Additivity endpoint(s): Developmental (E), Female reproductive system (E), Male reproductive system (E)

Subchronic Non-Cancer Health Based Value \( (nHBV_{Subchronic}) = 0.0002 \mu g/L \)

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(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor}) = (1.4 \times 10^{-8} \text{mg/kg-d}) \times (0.8^*) \times (1000 \mu g/mg) \\
(0.070 \text{L/kg-d})^{**} \]

\[
= 0.00016 \text{rounded to } 0.0002 \mu g/L
\]

*Rationale for selecting RSC of 0.8 – same explanation as that provided for the short-term duration (see above)


Reference Dose/Concentration: \( (POD \times DAF)/Total \text{ UF} = 1.4 \times 10^{-8} \text{mg/kg-d (Sprague-Dawley rat)} \)

Source of toxicity value: determined by MDH in 2016

Point of Departure (POD): \( 4.2 \times 10^{-5} \text{mg/kg-d (BMDL}_{10}, \text{NTP 2010a)} \)

Human Equivalent Dose (MDH, 2011): \( \text{POD } \times \text{DAF} = 4.2 \times 10^{-5} \text{mg/kg-d } \times 0.01 = 4.2 \times 10^{-7} \text{mg/kg-d (DAF chemical-specific basis)} \)

Total uncertainty factor: 30

Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability

Critical effect(s): Mammary gland hyperplasia in adult males
Co-critical effect(s): None
Additivity endpoint(s): Developmental

Chronic Non-Cancer Health Based Value (nHBV\textsubscript{Chronic}) = nHBV\textsubscript{Subchronic} = 0.0002 µg/L

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\frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{\text{(Chronic Intake Rate, L/kg-d)}}
\]

\[
= \frac{(1.4 \times 10^{-8} \text{ mg/kg-d}^{**}) \times (0.8^{*}) \times (1000 \text{ µg/mg})}{(0.044 \text{ L/kg-d})^{***}}
\]

\[
= 0.00025, \text{ rounded to 0.0003 µg/L}
\]

*Rationale for selecting RSC of 0.8 – same explanation as that provided for the short-term duration (see above)
**See the subchronic information above for details about the reference dose

The Chronic nHBV must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Subchronic nHBV of 0.0002 µg/L. Additivity endpoints: Developmental

Cancer Health Based Value (cHBV) = Not Derived

After carefully reviewing the available data MDH concluded that the non-cancer HBVs are sufficiently protective for potential cancer effects.

Cancer classification: IARC Group 1, Carcinogenic to humans
Slope factor: Not available
Source of slope factor: Not Applicable
Tumor site(s): Endometrium, ovary, mammary

Volatile: No

Summary of Guidance Value History:
The HBVs for 17α-ethinylestradiol are new. No previous values exist.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):
Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.
Ethinylestradiol is used as a human contraceptive for its ability to disrupt the human endocrine system at human contraceptive doses over 260 times higher than the short-term RfD and over 9,000 times higher than the sub/chronic RfD. Endocrine-mediated effects on a variety of male and female endocrine-responsive tissues form the basis for all of the RfDs. In humans, hormonal effects including increased sex hormone binding globulin and angiotensinogen with decreased corticosteroid binding globulin and follicle-stimulating hormone were reported at doses more than 300 times higher than all of the RfDs. In laboratory animal studies, steroid hormonal effects including reduced testosterone, luteinizing hormone, follicle-stimulating hormone, prolactin, progesterone and increased serum estradiol have been reported at doses more than 100 times higher than all of the RfDs. Thyroid hormones were affected in adult rats at doses more than 350 times higher than the subchronic RfD. No effects on thyroid hormones were found in neonatal animals. Increased pituitary gland weight was reported at doses more than 2,800 times higher than the subchronic RfD.

Ethinylestradiol produced decreased bone marrow DNA synthesis and blood cell progenitor cells in rats, indicating a potential impact on the immune system at doses over 2,000 times higher than all of the RfDs. Other immune system effects occurring at doses more than 1,000 times higher than the subchronic RfD included increased natural killer cell activity, increased spleen cell proliferation related to cell-mediated immunity, decreased spleen cell numbers (B, T, and NK cells), and increased relative spleen weight. Significant, but inconsistent increases in thymus weight were reported in adult rat offspring at doses over 140 times higher than the subchronic RfD.

The short-term RfD is based, in part, on male and female developmental effects reported in laboratory animal studies. The sub/chronic RfDs are based on male mammary gland hyperplasia, considered an aberrant developmental effect for males. Epidemiological studies have found no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy and also do not suggest any overt birth defects effects when taken inadvertently during early pregnancy. However, potential for subtle, long-term effects from gestational exposure in humans has not been fully evaluated. In a clinical study of children whose mothers used oral contraceptives during lactation (starting at age 2 months), no effects on intellectual or behavioral development were found when children were followed up to age 8 years. A few adverse effects in nursing infants whose mothers were taking ethinylestradiol have been reported, including jaundice and breast enlargement. These effects in nursing infants occurred at maternal doses more than 2,000 times higher than the short-term RfD and more than 30,000 times higher than the subchronic RfD.

Ethinylestradiol is a human contraceptive drug that is used deliberately for its ability to disrupt human reproduction by inhibiting ovulation. Oral contraceptives given during nursing may also interfere with...
lactation by decreasing the quantity and quality of breast milk. The lowest human contraceptive dose is 260 times higher than the short-term RfD and over 9,000 times higher than the sub/chronic RfDs. The short-term RfD is based, in part, on female reproductive system effects in laboratory animals.

Neurobehavioral developmental effects related to feminization or masculinization of behaviors were reported in rats exposed to doses more than 100 times higher than the short-term RfD and 30,000 higher than the subchronic RfD. Effects included changes in saccharin and sodium preferences and decreased female rearing behavior. Increased activity and startle responses were reported in rat offspring. In a clinical study of children whose mothers used oral contraceptives during lactation (starting at age 2 months), no effects on intellectual or behavioral development were found when children were followed up to age 8 years.

Resources Consulted During Review:


http://www.drugs.com/breastfeeding/contraceptives-oral-combined.html


National Toxicology Program (NTP). (2010a). Multigenerational Reproductive Toxicology Study Of Ethinyl Estradiol (Cas No. 57-63-6) In Sprague-Dawley Rats Retrieved from 


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