

Toxicological Summary for: 17 α -Ethinylestradiol

CAS: 57-63-6

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

Acute Non-Cancer Health Risk Limit (nHRL_{Acute}) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Risk Limit (nHRL_{Short-term}) = 0.0005 μ g/L

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

$$= \frac{(1.7 \times 10^{-7} \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ } \mu\text{g/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

$$= 0.000468 \text{ rounded to } \mathbf{0.0005 \text{ } \mu\text{g/L}}$$

* 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 17 α -ethinylestradiol by prescription, the additional exposure from drinking water will be negligible.

** Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	(POD x DAF)/Total UF = 1.7×10^{-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 applied (doses directly given to neonatal animals were not adjusted due to interspecies 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 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 Risk Limit (nHRL_{Subchronic}) = 0.0002 µg/L

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

$$= \frac{(1.4 \times 10^{-8} \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 0.000151 \text{ rounded to } \mathbf{0.0002 \text{ µg/L}}$$

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

**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration: (POD x DAF)/Total UF = 1.4 x 10⁻⁸ mg/kg-d (Sprague-Dawley rat)
 Source of toxicity value: determined by MDH in 2016
 Point of Departure (POD): 4.2 x 10⁻⁵ mg/kg-d (BMDL₁₀, NTP 2010a)
 Human Equivalent Dose (MDH, 2011): POD x DAF = 4.2 x 10⁻⁵ mg/kg-d x 0.01 = 4.2 x 10⁻⁷ 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 Risk Limit (nHRL_{Chronic}) = 0.0002 µg/L

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

$$= \frac{(1.4 \times 10^{-8} \text{ mg/kg-d}^{**}) \times (0.8^*) \times (1000 \text{ } \mu\text{g/mg})}{(0.045 \text{ L/kg-d})^{***}}$$

= 0.000248, rounded to **0.0002 µg/L**

Additivity endpoint(s): Developmental

*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

*** Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Cancer Health Risk Limit (cHRL) = Not Derived

After carefully reviewing the available data MDH concluded that the non-cancer HRLs 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 were new in 2016. No previous values exist. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in the Chronic duration HBV no longer being set to the Subchronic duration HBV. However, the Chronic duration HBV remains the same value. In November 2023, the guidance values were adopted into Minnesota Rules, 4717.7860, as Health Risk Limits (HRLs).

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.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes ¹	Yes ²	Yes ³	Yes ⁴	Yes ⁵

Comments on extent of testing or effects:

¹Ethinylestradiol 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.

²Ethinylestradiol 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.

³The 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.

⁴Ethinylestradiol 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.

⁵Neurobehavioral 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:

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