

Adopted as Rule: November 2023

Toxicological Summary for: Venlafaxine

CAS: 93413-69-5 (free base)

99300-78-4 (HCl salt, Effexor XR)

Synonyms: Venlafaxine-HCl (Effexor XR); 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol (IUPAC)

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

Short-term Non-Cancer Health Risk Limit (nHRL_{Short-term}) = 10 µg/L

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

$$= \frac{(0.0054 \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

$$= 14.9 \text{ rounded to } \mathbf{10 \text{ µg/L}}$$

* MDH utilizes the U.S. EPA Exposure Decision Tree (U.S. EPA 2000) to select appropriate RSCs, ranging from 0.2 to 0.8. An RSC greater than 0.8 may be warranted for those who have no other route of exposure besides drinking water because of the unlikelihood of exposure from any other sources. However, without additional information a specific value cannot be determined at this time. Therefore, the recommended upper limit default of 0.8 was utilized. For those who take venlafaxine according to prescription the additional drinking water exposure will be negligible. For nursing infants whose mothers are taking venlafaxine, the drinking water exposure from supplemental bottle-feeding will also 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:	0.0054 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	0.54 mg/kg-d (LOAEL, lowest starting dose of 37.5 mg/d from Wyeth Pharmaceuticals, 2014a)
Human Equivalent Dose (MDH, 2011):	n/a
Total uncertainty factor:	100
Uncertainty factor allocation:	10 for intraspecies variability and 10 for use of LOAEL
Critical effect(s):	Developmental (persistent pulmonary hypertension and nervous system effects), gastrointestinal system (nausea, constipation), male reproductive effects (decreased libido, abnormal orgasm, erectile dysfunction, ejaculation failure/disorder), and nervous system effects (effects on serotonin hormone receptor interaction, sweating, abnormal dreams, and dizziness, and neuroendocrine-mediated increases in blood pressure)
Co-critical effect(s):	None

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

Subchronic Non-Cancer Health Risk Limit (nHRL_{Subchronic}) = Short-term HRL = 10 µg/L

$$\frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Subchronic intake rate, L/kg-d})}$$
$$= \frac{(0.0054 \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$
$$= 58 \text{ rounded to } 60 \text{ µg/L}$$

*Refer to RSC explanation provided for the short-term non-cancer health risk limit.

** 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: 0.0054 mg/kg-d (human)
Source of toxicity value: MDH, 2014
Point of Departure (POD): 0.54 mg/kg-d (LOAEL, lowest starting dose of 37.5 mg/d and lowest dose tested in a 6-month clinical trial, Cobalt Pharmaceutical Co. 2014, Emslie et al. 2007a, Emslie et al. 2007b)
Human Equivalent Dose (MDH, 2011): n/a
Total uncertainty factor: 100
Uncertainty factor allocation: 10 for intraspecies variability and 10 for use of LOAEL
Critical effect(s): Cardiovascular system (neuroendocrine-mediated increases in blood pressure), developmental (persistent pulmonary hypertension and nervous system effects), gastrointestinal system (constipation), male reproductive effects (effects on orgasm, ejaculation failure, decreased libido), and nervous system (effects on serotonin hormone receptor interaction, abnormal dreams, sweating, and neuroendocrine-mediated increases in blood pressure)
Co-critical effect(s): Nervous system (mydriasis or dilation of pupils)
Additivity endpoint(s): Cardiovascular system, Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)

**The Subchronic nHRL must be protective of the acute, and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 10 µg/L.
Additivity endpoints: Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)**

Chronic Non-Cancer Health Risk Limit (nHRL_{Chronic}) = Short-term HRL = 10 µg/L

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

$$= \frac{(0.0054 \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 96 \text{ rounded to } 100 \text{ µg/L}$$

*Refer to RSC explanation provided for the short-term non-cancer health risk limit.

** 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:	0.0054 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	0.54 mg/kg-d (LOAEL, lowest starting dose of 37.5 mg/d, and lowest dose tested in a 6-month clinical trial Cobalt Pharmaceutical Co. 2014, Emslie et al. 2007a, Emslie et al. 2007b)
Human Equivalent Dose (MDH, 2011):	n/a
Total uncertainty factor:	100
Uncertainty factor allocation:	10 for intraspecies variability and 10 for use of LOAEL
Critical effect(s):	Cardiovascular system (neuroendocrine-mediated increases in blood pressure), developmental (persistent pulmonary hypertension in newborns and nervous system effects), gastrointestinal system (constipation), male reproductive effects (effects on orgasm, ejaculation failure, decreased libido), and nervous system (effects on serotonin hormone receptor interaction, abnormal dreams, sweating, and neuroendocrine-mediated increases in blood pressure)
Co-critical effect(s):	Nervous system (mydriasis or dilation of pupils)
Additivity endpoint(s):	Cardiovascular system, Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)

The Chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 10 µg/L. Additivity endpoints: Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)

Cancer Health Risk Limit (cHRL) = Not Applicable

Volatile: No

Summary of Guidance Value History:

There are no previous drinking water guidance values for venlafaxine. All values are new. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values. 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:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	Yes	Yes	Yes	Yes
Effects?	Yes ¹	Yes ²	Yes ³	Yes ⁴	Yes ⁵

Note: 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. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

Comments on extent of testing or effects:

¹Neuroendocrine effects related to serotonin and norepinephrine are identified as critical effects. Serotonin receptor interactions are the basis for the intended pharmacological action of venlafaxine and many of the adverse effects. Significant neuroendocrine-mediated increases in systolic blood pressure related to norepinephrine have been reported in some clinical trials and are considered as a critical effect. Doses more than 200 times higher than the RfD have been associated with sustained hypertension (defined as supine diastolic blood pressure (SDBP) ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for 3 consecutive therapy visits). Other endocrine system effects have been described as “limited” and have generally occurred only at doses greater than those required for antidepressant therapeutic effects. Menstrual disorders in humans have been identified at doses over 200 times higher than the RfD. Inappropriate antidiuretic hormone secretion (SIADH) in the kidney has been reported as an adverse event in dehydrated patients. Rare reports of endocrine effects at therapeutic doses over 200 times higher than the RfD include galactorrhea, goiter, hyper- and hypothyroidism, thyroid nodule, thyroiditis, and increased prolactin.

²Venlafaxine has been reported to have only limited effects on the immune system that generally occur at doses greater than those required for therapeutic antidepressant effects (more than 200 times higher than the RfD). Since depression is associated with alterations in immune function, the effects of antidepressants on the immune system have been of interest, primarily from the perspective of restoring immune function in depressed patients. Some reports suggest that antidepressant treatment, including venlafaxine, may have a beneficial anti-inflammatory effect. In laboratory mice, effects on various pro-inflammatory cytokines were reported when mice were exposed to venlafaxine at HED doses more than 150 times higher than the RfD.

³Developmental toxicity in humans is identified as a critical endpoint with effects in newborns exposed during the third trimester of pregnancy as a result of maternal antidepressant therapy. Effects on newborns exposed to therapeutic doses during the third trimester can be life-threatening and require hospitalization. Effects may include respiratory distress at birth and/or tachypnea, persistent pulmonary hypertension, cyanosis, apnea, seizures, tremor, irritability, temperature instability, vomiting, hypoglycemia, and changes in muscle tone. Exposure during pregnancy at doses more than 200 times higher than the RfD did not adversely affect behavior or IQ of children at age 3 to 6 years. In laboratory animals, developmental toxicity including decreased fetal size and pup weight, increased stillborn pups, and increased pup deaths during early lactation were reported at doses over 1,400 times higher than the RfD.

⁴Male reproductive toxicity effects in humans are identified as critical effects for all durations. Female reproductive toxicity, including amenorrhea, dysmenorrhea or other menstrual disorders have been reported in humans at doses over 200 times higher than the RfD.

⁵Nervous system effects are identified as critical effects for all durations. Venlafaxine is a neurologically-active drug with intended pharmacological effects on the nervous system.

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