



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 Based Value (nHBV_{Acute}) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value (nHBV_{Short-term}) = 10 µg/L

(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)
(Short-term intake rate, L/kg-d)

$$= \frac{(0.0054 \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ } \mu\text{g/mg})}{(0.289 \text{ L/kg-d})}$$

$$= 14.9 \text{ rounded to } 10 \text{ } \mu\text{g/L}$$

* 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.

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 Based Value (nHBV_{Subchronic}) = Short-term HBV = 10 µg/L

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

$$= \frac{(0.0054 \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ µg/mg})}{(0.077 \text{ L/kg-d})}$$

$$= 56 \text{ rounded to } 60 \text{ µg/L}$$

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

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

Chronic Non-Cancer Health Based Value (nHBV_{Chronic}) = Short-term HBV = 10 µg/L

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

$$= \frac{(0.0054 \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ µg/mg})}{(0.043 \text{ L/kg-d})}$$

$$= 100 \text{ µg/L}$$

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

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 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 Short-term nHBV of 10 µg/L. Additivity endpoints: Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)

Cancer Health Based Value (cHBV) = Not Applicable

Volatile: No

Summary of Guidance Value History: There are no previous drinking water guidance values for venlafaxine. All values are new.

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.

⁴ Male 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.

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

References:

- Archer, D. F., J. V. Pinkerton, C. J. Guico-Pabia, E. Hwang, R. F. Cheng and I. Study (2013). Cardiovascular, cerebrovascular, and hepatic safety of desvenlafaxine for 1 year in women with vasomotor symptoms associated with menopause (reviewed abstract only). *Menopause* 20(1): 47-56.
- Basterzi, A. D., K. Yazici, V. Buturak, B. Cimen, A. Yazici, G. Eskandari, et al. (2010). Effects of venlafaxine and fluoxetine on lymphocyte subsets in patients with major depressive disorder: a flow cytometric analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 34(1): 70-75 (abstract reviewed).
- Boucher, N., G. Koren and L. Beaulac-Baillargeon (2009). Maternal use of venlafaxine near term: correlation between neonatal effects and plasma concentrations. *Ther Drug Monit* 31(3): 404-409.
- Broy, P. and A. Berard (2010). Gestational exposure to antidepressants and the risk of spontaneous abortion: a review. *Curr Drug Deliv* 7(1): 76-92.
- Cobalt Pharmaceutical Company (2014). Canada Drug Products Monograph, Venlafaxine XR, March 3, 2014.
- Coleman, K. A., V. Y. Xavier, T. L. Palmer, J. V. Meaney, L. M. Radalj and L. M. Canny (2012). An indirect comparison of the efficacy and safety of desvenlafaxine and venlafaxine using placebo as the common comparator (reviewed abstract). *CNS Spectr* 17(3): 131-141.
- da-Silva, V. A., S. P. Altenburg, L. R. Malheiros, T. G. Thomaz and C. J. Lindsey (1999). Postnatal development of rats exposed to fluoxetine or venlafaxine during the third week of pregnancy. *Braz J Med Biol Res* 32(1): 93-98.
- Denys, D., S. Fluitman, A. Kavelaars, C. Heijnen and H. G. Westenberg (2006). Effects of paroxetine and venlafaxine on immune parameters in patients with obsessive compulsive disorder. *Psychoneuroendocrinology* 31(3): 355-360 (abstract reviewed).
- Dubovicky, M., E. Csaszarova, Z. Brnoliakova, E. Ujhazy, J. Navarova and M. Mach (2012). Effect of prenatal administration of venlafaxine on postnatal development of rat offspring. *Interdiscip Toxicol* 5(2): 92-97.

- ECHA (European Chemicals Agency). (2014). "CAS 93413-62-8 Search using The Global Portal to Information on Chemical Substances (eChemPortal), hosted by OECD (Organization for Economic Cooperation and Development)." Retrieved 5/23/2014, from http://apps.echa.europa.eu/registered/data/dossiers/DISS-a215f3ac-24b3-0295-e044-00144f67d031/DISS-a215f3ac-24b3-0295-e044-00144f67d031_DISS-a215f3ac-24b3-0295-e044-00144f67d031.html
- Emslie, G. J., R. L. Findling, P. P. Yeung, N. R. Kunz and Y. Li (2007a). Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. *J Am Acad Child Adolesc Psychiatry* 46(4): 479-488.
- Emslie, G. J., P. P. Yeung and N. R. Kunz (2007b). Long-term, open-label venlafaxine extended-release treatment in children and adolescents with major depressive disorder. *CNS Spectr* 12(3): 223-233.
- Findling, R. L., J. Groark, D. Chiles, S. Ramaker, L. Yang and K. A. Tourian (2014). Safety and tolerability of desvenlafaxine in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol* 24(4): 201-209.
- Ghanizadeh, A., R. D. Freeman and M. Berk (2013). Efficacy and adverse effects of venlafaxine in children and adolescents with ADHD: a systematic review of non-controlled and controlled trials. *Rev Recent Clin Trials* 8(1): 2-8.
- Hill, L. and K. C. Lee (2013). Pharmacotherapy considerations in patients with HIV and psychiatric disorders: focus on antidepressants and antipsychotics. *Ann Pharmacother* 47(1): 75-89 (abstract reviewed).
- HSDB. (2014). "National Library of Medicine HSDB Database: Venlafaxine." Retrieved May 2014, 2014, from <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~SDa5al:1>
- Hulisz, D., Lagzdins, M. (2008). Drug-Induced Hypertension. *U.S. Pharmacist* 33(9): HS11-HS20.
- Ilett, K. F., L. P. Hackett, L. J. Dusci, M. J. Roberts, J. H. Kristensen, M. Paech, et al. (1998). Distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk. *Br J Clin Pharmacol* 45(5): 459-462.
- Ilett, K. F., J. H. Kristensen, L. P. Hackett, M. Paech, R. Kohan and J. Rampono (2002). Distribution of venlafaxine and its O-desmethyl metabolite in human milk and their effects in breastfed infants. *Br J Clin Pharmacol* 53(1): 17-22.
- Iwata, N., K. A. Tourian, E. Hwang, L. Mele and C. Vialet (2013). Efficacy and safety of desvenlafaxine 25 and 50% shaded blockmg/day in a randomized, placebo-controlled study of depressed outpatients (abstract reviewed). *J Psychiatr Pract* 19(1): 5-14.
- Kamath, J. and V. Handratta (2008). Desvenlafaxine succinate for major depressive disorder: a critical review of the evidence. *Expert Rev Neurother* 8(12): 1787-1797.

- Kjaersgaard, M. I., E. T. Parner, M. Vestergaard, M. J. Sorensen, J. Olsen, J. Christensen, et al. (2013). Prenatal antidepressant exposure and risk of spontaneous abortion - a population-based study. *PLoS One* 8(8): e72095.
- Lee, K. M. and Y. K. Kim (2006). The role of IL-12 and TGF-beta1 in the pathophysiology of major depressive disorder. *Int Immunopharmacol* 6(8): 1298-1304 (abstract reviewed).
- Liebowitz, M. R., K. A. Tourian, E. Hwang, L. Mele and I. Study (2013). A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/day in adult outpatients with major depressive disorder. *BMC Psychiatry* 13: 94.
- Minnesota Department of Health (MDH). (2011). "MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses." from <http://www.health.state.mn.us/divs/eh/risk/guidance/hedrefguide.pdf>.
- Nakhai-Pour, H. R., P. Broy and A. Berard (2010). Use of antidepressants during pregnancy and the risk of spontaneous abortion (abstract reviewed). *CMAJ* 182(10): 1031-1037.
- Nulman, I., G. Koren, J. Rovet, M. Barrera, A. Pulver, D. Streiner, et al. (2012). Neurodevelopment of children following prenatal exposure to venlafaxine, selective serotonin reuptake inhibitors, or untreated maternal depression. *Am J Psychiatry* 169(11): 1165-1174.
- Park, P., J. Caballero and H. Omidian (2014). Use of serotonin norepinephrine reuptake inhibitors in the treatment of attention-deficit hyperactivity disorder in pediatrics. *Ann Pharmacother* 48(1): 86-92.
- Polen, K. N., S. A. Rasmussen, T. Riehle-Colarusso, J. Reefhuis and S. National Birth Defects Prevention (2013). Association between reported venlafaxine use in early pregnancy and birth defects, national birth defects prevention study, 1997-2007. *Birth Defects Res A Clin Mol Teratol* 97(1): 28-35.
- Rampono, J., S. Teoh, L. P. Hackett, R. Kohan and K. F. Ilett (2011). Estimation of desvenlafaxine transfer into milk and infant exposure during its use in lactating women with postnatal depression. *Arch Womens Ment Health* 14(1): 49-53.
- Sansone, R. A. and L. A. Sansone (2014). Serotonin norepinephrine reuptake inhibitors: a pharmacological comparison. *Innov Clin Neurosci* 11(3-4): 37-42.
- Shea, M. L., L. D. Garfield, S. Teitelbaum, R. Civitelli, B. H. Mulsant, C. F. Reynolds, 3rd, et al. (2013). Serotonin-norepinephrine reuptake inhibitor therapy in late-life depression is associated with increased marker of bone resorption. *Osteoporos Int* 24(5): 1741-1749.
- Snyder, S., RA Trenholm, EM Snyder, GM Bruce, RC Pleus, and JDC Hemming, (2008). Toxicological Relevance of EDCs and Pharmaceuticals in Drinking Water. AWWA Research Foundation.
- Sopko, M. A., Jr., M. J. Ehret and M. Grgas (2008). Desvenlafaxine: another "me too" drug? *Ann Pharmacother* 42(10): 1439-1446.

- Steinhorn, R. H. (2010). Neonatal pulmonary hypertension. *Pediatr Crit Care Med* 11(2 Suppl): S79-84.
- Tynan, R. J., J. Weidenhofer, M. Hinwood, M. J. Cairns, T. A. Day and F. R. Walker (2012). A comparative examination of the anti-inflammatory effects of SSRI and SNRI antidepressants on LPS stimulated microglia. *Brain Behav Immun* 26(3): 469-479 (abstract reviewed).
- U.S. Environmental Protection Agency - Office of Research and Development. (1988). "Recommendations for and Documentation of Biological Values for Use in Risk Assessment." from <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855>.
- U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). "Recommended Use of Body Weight^{3/4} as the Default Method in Derivation of the Oral Reference Dose." from <http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf>.
- U.S. FDA. (2007). "U.S. Food and Drug Administration - Center for Drug Evaluation and Research. Risk Assessment and Risk Mitigation Reviews for NDA 21-992 for Pristiq (Desvenlafaxine Succinate).", from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021992s000TOC.cfm.
- U.S. FDA. (2008). "U.S. Food and Drug Administration - Center for Drug Evaluation and Research. Pharmacology Reviews for NDA 21-992 for Pristiq (Desvenlafaxine Succinate) Extended Release Tablets. from Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.", from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021992s000TOC.cfm.
- Uguz, F., M. Sahingoz, S. A. Kose, O. Ozbebit, C. Sengul, Y. Selvi, et al. (2012). Antidepressants and menstruation disorders in women: a cross-sectional study in three centers. *Gen Hosp Psychiatry* 34(5): 529-533.
- Vidal, R., E. M. Valdizan, M. T. Vilaro, A. Pazos and E. Castro (2010). Reduced signal transduction by 5-HT₄ receptors after long-term venlafaxine treatment in rats. *Br J Pharmacol* 161(3): 695-706.
- Vollmar, P., S. Nessler, S. R. Kalluri, H. P. Hartung and B. Hemmer (2009). The antidepressant venlafaxine ameliorates murine experimental autoimmune encephalomyelitis by suppression of pro-inflammatory cytokines. *Int J Neuropsychopharmacol* 12(4): 525-536 (abstract reviewed).
- Wyeth Pharmaceuticals Inc. a subsidiary of Pfizer Inc. (2014a). "EFFEXOR XR - Venlafaxine hydrochloride capsule, extended release FDA label." from <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=53c3e7ac-1852-4d70-d2b6-4fca819acf26>.
- Wyeth Pharmaceuticals Inc. a subsidiary of Pfizer Inc. (2014b). "Pristiq Extended Release (desvenlafaxine succinate) Drug Label." from <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=0f43610c-f290-46ea-d186-4f998ed99fce>.