Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Web Publication Date: January 2015
Expiration Date: January 2020

Toxicological Summary for: Desvenlafaxine

CAS: **93413-62-8 (free base)**
386750-22-7 (succinate salt, Pristiq)
300827-87-6 (HCl salt)
93414-04-1 (fumarate salt)

Synonyms: Desvenlafaxine succinate (Pristiq); Desvenlafaxine-HCl; Desvenlafaxine fumarate; 4-[2-dimethylamino-1-(1-hydroxycyclohexyl) ethyl] phenol

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

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 20 µg/L

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

$$= \frac{\text{(0.0071 mg/kg-d) x (0.8*) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 19.7 rounded to **20 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 desvenlafaxine according to prescription the additional drinking water exposure will be negligible. For nursing infants whose mothers are taking desvenlafaxine, the drinking water exposure from supplemental bottle-feeding will also be negligible.

Reference Dose/Concentration:	0.0071 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	0.71 mg/kg-d (LOAEL, based on the lowest therapeutic dose of 50 mg/d, Wyeth Pharmaceuticals Inc. 2014b)
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, decreased appetite, weight loss); male reproductive effects (erectile dysfunction,

	ejaculation failure/disorder, decreased libido), nervous system (effects on serotonin hormone receptor interaction, abnormal dreams, sweating, dizziness, insomnia, mydriasis, blurred/abnormal vision, 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 = 20 µg/L

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

$$= \frac{\text{(0.0071 mg/kg-d) x (0.8*) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 74 rounded to 70 µg/L

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

Reference Dose/Concentration:	0.0071 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	0.71 mg/kg-d (LOAEL, based on the lowest therapeutic dose of 50 mg/d, Wyeth Pharmaceuticals Inc. 2014b)
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 sustained hypertension), developmental (persistent pulmonary hypertension and nervous system effects), gastrointestinal system (constipation, decreased appetite, weight loss); male reproductive effects (erectile dysfunction, ejaculation failure/disorder, decreased libido), nervous system (effects on serotonin hormone receptor interaction, abnormal dreams, sweating, dizziness, insomnia, mydriasis, blurred/abnormal vision, and neuroendocrine-mediated increases in blood pressure)
Co-critical effect(s):	None
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 20 µg/L. Additivity endpoints: Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)
Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = Short-term HBV = 20 µg/L

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

$$= \frac{\text{(0.0071 mg/kg-d) x (0.8*) x (1000 µg/mg)}}{\text{(0.043L/kg-d)}}$$

= 132 rounded to 100 µg/L

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

Reference Dose/Concentration:	0.0071 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	0.71 mg/kg-d (LOAEL, based on the lowest therapeutic dose of 50 mg/d, Wyeth Pharmaceuticals Inc. 2014b)
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 sustained hypertension), developmental (persistent pulmonary hypertension and nervous system effects), gastrointestinal system (constipation, decreased appetite, weight loss); male reproductive effects (erectile dysfunction, ejaculation failure/disorder, decreased libido), nervous system (effects on serotonin hormone receptor interaction, abnormal dreams, sweating, dizziness, insomnia, mydriasis, blurred/abnormal vision, and neuroendocrine-mediated increases in blood pressure)
Co-critical effect(s):	None
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 20 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 desvenlafaxine. All values are new.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	No	Yes	Yes	Yes
Effects?	Yes[1]	Secondary Observations[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:

[1]Neuroendocrine effects related to serotonin and norepinephrine are identified as critical effects. Serotonin receptor interactions are the basis for the intended pharmacological action of desvenlafaxine and many of the adverse effects. Significant neuroendocrine-mediated increases in systolic blood pressure and sustained hypertension related to norepinephrine have been reported in some clinical trials and are identified as critical effects. Sustained hypertension is 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 reported to be limited and are generally at doses greater than required for antidepressant therapeutic effects. Inappropriate antidiuretic hormone secretion (SIADH) in the kidney has been reported as an adverse event in dehydrated patients. Increased blood levels of prolactin have been reported infrequently (<2%) in patients; however, a causal link to desvenlafaxine has not been established. In laboratory animals, desvenlafaxine affected estrous cycles in females at a dose over 900 times higher than the RfD. There were no effects on male prolactin or testosterone levels reported up to a dose approximately 10,000 times higher than the RfD.

[2]The effects of desvenlafaxine on the immune system have not been directly tested or reported. However, based on lack of secondary observations in spleen, thymus, or bone marrow in multiple laboratory animal studies and lack of reported immunotoxicity in humans, the immune system is not considered a potential target. Additionally, a structurally-related drug, venlafaxine, was reported to have limited effects on the immune system generally at doses greater than required for antidepressant effects. Therefore, the RfDs are considered protective for this endpoint.

[3]Developmental 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. In laboratory animals, developmental toxicity including increased pre-implantation loss, decreased fetal body weight, decreased pup birth weight, decreased pup viability occurred at doses over 4,800 times higher than the RfD.

[4] Male reproductive toxicity effects in humans are identified as critical effects for all durations. In laboratory animals, female reproductive toxicity including disrupted estrous cycles, increased

time-to-mating, and decreased fertility index occurred at doses over 3,000 times higher than the RfD.

[5] Nervous system effects are identified as critical effects for all durations. Desvenlafaxine 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 5050% 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 Weight¾ 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 Adminstration - 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 hydrochoride 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.