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-term}) = 20 \, \mu g/L

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

\begin{align*}
= (0.0071 \, \text{mg/kg-d}) \times (0.8^*) \times (1000 \, \mu g/mg) \\
= 19.7 \text{ rounded to } 20 \, \mu g/L
\end{align*}

* 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, weight loss, and breast enlargement)}
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 (\(nHBV_{\text{subchronic}}\)) = Short-term HBV = 20 \(\mu\)g/L

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

\[
= (0.0071 \text{ mg/kg-d) x (0.8*) x (1000 \mu g/mg)}
\]

\[
= 74 \text{ rounded to 70 \(\mu\)g/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}) = \text{Short-term HBV} = 20 \, \mu g/L

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

\[
= (0.0071 \, \text{mg/kg-d}) \times (0.8^*) \times (1000 \, \mu g/mg) \\
\times (0.043 L/kg-d)
\]

\[= 132 \, \text{rounded to 100 µg/L}\]

*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
- 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 (erecile 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:

<table>
<thead>
<tr>
<th>Tested?</th>
<th>Endocrine</th>
<th>Immunotoxicity</th>
<th>Development</th>
<th>Reproductive</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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:


