Toxicological Summary for: Mestranol

CAS: 72-33-3

Synonyms: 3-Methoxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17-ol; (17alpha)-3-Methoxy-19-norpregna-1,3,5(10)-trien-20-yn-17-ol; Ethinylestradiol 3-methyl ether; 17alpha-Ethinylestradiol 3-methyl ether, EEME, MeEE

Mestranol (MeEE) is the 3-methyl ether of 17α-ethinylestradiol (EE2). MeEE is not initially biologically active as a contraceptive hormone but it is rapidly demethylated in the liver to form the biologically active EE2. A dose of 50 µg of MeEE is considered to be bioequivalent to 35 µg of EE2 as a result of a 70% conversion efficiency in the liver (e.g., 35 µg/0.70 = 50 µg) (Brody et al. 1989). The relative bioequivalence is the basis for the different contraceptive dose levels for MeEE and EE2 used to achieve the same effect in adult humans.

HBVs are available for 17α-ethinylestradiol (EE2). The Minnesota Department of Health (MDH) recommends adjusting the reference doses (RfDs) derived for EE2 by a factor of 0.7 to account for relative bioequivalence and then deriving Risk Assessment Advice (RAAs) for MeEE based on the adjusted RfDs.

The following are MeEE RfDs, based on RfDs for EE2 adjusted for relative bioequivalence according to the following equation:

\[ RfD_{MeEE} = \frac{RfD_{EE2}}{0.7} \]

Acute \( RfD_{MeEE} \) = Not derived. Insufficient data.

Short-term \( RfD_{MeEE} \) = Short-term \( RfD_{EE2}/0.7 \) = \( 1.7 \times 10^{-7}/0.7 \) = \( 2.4 \times 10^{-7} \) mg/kg-d

Subchronic \( RfD_{MeEE} \) = Subchronic \( RfD_{EE2}/0.7 \) = \( 1.4 \times 10^{-8}/0.7 \) = \( 2.0 \times 10^{-8} \) mg/kg-d

Chronic \( RfD_{MeEE} \) = Chronic \( RfD_{EE2}/0.7 \) = \( 1.4 \times 10^{-8}/0.7 \) = \( 2.0 \times 10^{-8} \) mg/kg-d

The following recommendation represents Risk Assessment Advice (RAA) for mestranol using adjusted RfDs and the same duration-based algorithms applied to derive 17α-ethinylestradiol HBVs:

Acute \( nRAA_{MeEE} \) = Not derived. Insufficient data.

Short-term \( nRAA_{MeEE} \) = 0.0007 µg/L

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

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\[
= (2.4 \times 10^{-7} \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ µg/mg}) \\
(0.285 \text{ L/kg-d})
\]
\[
= 0.00067 \text{ rounded to } \boxed{0.0007} \text{ µg/L}
\]
Additivity endpoints: Developmental (E), Female reproductive system (E), Male reproductive system (E)*

Subchronic nRAA\textsubscript{MeEE} = 0.0002 µg/L

\[
\frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Subchronic Intake Rate, L/kg-d})}
\]
\[
= (2.0 \times 10^{-6} \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ µg/mg}) \\
(0.070 \text{ L/kg-d})
\]
\[
= 0.00023 \text{ rounded to } \boxed{0.0002} \text{ µg/L}
\]
Additivity endpoints: Developmental*

Chronic nRAA\textsubscript{MeEE} = subchronic nRAA\textsubscript{MeEE} = 0.0002 µg/L

\[
\frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Chronic Intake Rate, L/kg-d})}
\]
\[
= (2.0 \times 10^{-8} \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ µg/mg}) \\
(0.044 \text{ L/kg-d})
\]
\[
= 0.00036, \text{ rounded to } 0.0004 \text{ µg/L}
\]
Additivity endpoints: Developmental*

The Chronic nRAA must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nRAA is set equal to the Subchronic nRAA of 0.0002 µg/L. Additivity endpoints: Developmental

Cancer cRAA\textsubscript{MeEE} – Not derived. Non-cancer HBVs are considered protective.

*For additional information on the derivation of RfDs, RSC and HBVs for 17α-ethinylestradiol, critical/co-critical effects, and relevant additivity endpoints see: Toxicological Summary for: 17α-Ethinylestradiol (http://www.health.state.mn.us/divs/eh/risk/guidance/gw/ethinylestrsumm.pdf)

Volatile: No
Summary of Guidance Value History:
The RAA values for mestranol are new. No previous values exist.

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.

<table>
<thead>
<tr>
<th>Tested for specific effect?</th>
<th>Endocrine</th>
<th>Immunotoxicity</th>
<th>Development</th>
<th>Reproductive</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

| Effects observed? | Yes¹ | Yes¹ | Yes¹ | Yes¹ | Yes¹ |

Comments on extent of testing or effects:
¹The pharmacological activity of mestranol is due to the conversion to 17α ethinylestradiol in the liver. See the Summary Sheet for 17α ethinylestradiol for information on the endocrine, immunotoxicity, developmental, reproductive and neurotoxicity effects at Toxicological Summary for: 17α- Ethinylestradiol (http://www.health.state.mn.us/divs/eh/risk/guidance/gw/17aethinyl.pdf)

Resources Consulted During Review:


Snyder, S., RA Trenholm, EM Snyder, GM Bruce, RC Pleus, and JDC Hemming,. (2008). Toxicological Relevance of EDCs and Pharmaceuticals in Drinking Water. In AWWA Research Foundation (Ed.).


