Toxicological Summary for N, N-Diethyl-3-methylbenzamide (DEET):
CAS: 134-62-3
Synonyms: N,N-Diethyl-m-toluamide; Diethyltoluamide
Trade Names: DEET; OFF; Cutter; Repel

Acute Non-Cancer Health Risk Limit (nHRL\textsubscript{acute}) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Risk Limit (nHRL\textsubscript{short-term}) = 200 µg/L

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

\[
= (0.23 \text{ mg/kg/d}) \times (0.2^*) \times (1000 \mu g/mg) \\
(0.289 L/kg-d)
\]

= 159 rounded to 200 µg/L

* MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the potential exposure to DEET through sources other than water (e.g., use of products containing DEET) an RSC of < 0.2 may be warranted. However, without additional information a specific value cannot be determined. Therefore, the lower limit default of 0.2 recommended in the EPA Exposure Decision Tree (EPA 2000) was utilized.

Reference Dose / Concentration: 0.23 mg/kg-d (rats)
Source of toxicity value: MDH, 2012
Point of Departure: 100 mg/kg-d (NOAEL, 2 generation study, MRID 41368401 as cited in EPA 1989 & EPA 1998a. LOAEL = 250 mg/kg-d )

Human Equivalent Dose Adjustment: 23 mg/kg-d (100 mg/kg-d x 0.23) (MDH, 2011)
Total uncertainty factor: 100
UF allocation: 3 interspecies extrapolation (toxicodynamics), 10 intraspecies variability, 3 database insufficiencies (additional characterization of neurotoxicity and immunotoxicity is warranted)

Critical effect(s): Decreased pup body weight
Co-critical effect(s): Changes in activity level, increased response time
Additivity endpoint(s): Developmental, Nervous system

Subchronic Non-Cancer Health Risk Limit (nHRL\textsubscript{subchronic}) = Short-term nHRL = 200 µg/L

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

\[
= (0.12 \text{ mg/kg/d}) \times (0.2^*) \times (1000 \mu g/mg)
\]

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(0.077 L/kg-d)

= 312 rounded to 300 µg/L

* MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential exposure to DEET through sources other than water (e.g., use of products containing DEET) an RSC of < 0.2 may be warranted. However, without additional information a specific value cannot be determined. Therefore, the lower limit default of 0.2 recommended in the EPA Exposure Decision Tree (EPA 2000) was utilized.

Reference Dose / Concentration: 0.12 mg/kg-d (hamsters)
Source of toxicity value: MDH, 2012
Point of Departure: 61 mg/kg-d (NOAEL, 90-day study in hamsters (MRID 41344101 1989 as cited by US EPA 1998a and 1990a).
Human Equivalent Dose Adjustment: 11.6 mg/kg-d (61 mg/kg-d x 0.19) (MDH, 2011)
Total uncertainty factor: 100
UF allocation: 3 interspecies extrapolation (toxicodynamics), 10 intraspecies variability, 3 database insufficiencies (additional characterization of neurotoxicity and immunotoxicity is warranted)
Critical effect(s): Decreased body weight and food consumption
Co-critical effect(s): Decreased pup body weight, increased response time, decreased vertical activity, increased liver weight
Additivity endpoint(s): Developmental, Hepatic (liver) system, Nervous system

The Subchronic nHRL must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 200 µg/L. Additivity endpoints: Development, Nervous system

Chronic Non-Cancer Health Risk Limit (nHRL_{chronic}) = Short-term nHRL = 200 µg/L

\[
\begin{align*}
\text{Chronic Non-Cancer Health Risk Limit (nHRL}_{\text{chronic}}) & = \text{Short-term nHRL} = 200 \ \mu g/L \\
& = \left( \frac{\text{Reference Dose, mg/kg/d}}{\text{Relative Source Contribution}} \times \text{Conversion Factor} \right) \\
& \times \left( \frac{\text{Chronic intake rate, L/kg/d}}{\text{Conversion Factor}} \right) \\
& = (0.23 \text{ mg/kg/d}) \times (0.2^*) \times (1000 \ \mu g/mg) \\
& \times (0.043 \text{ L/kg-d}) \\
& = 1070 \text{ rounded to } 1000 \ \mu g/L
\end{align*}
\]

* MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential exposure to DEET through sources other than water (e.g., use of products containing DEET) an RSC of < 0.2 may be warranted. However, without additional information a specific value cannot be determined. Therefore, the lower limit default of 0.2 recommended in the EPA Exposure Decision Tree (EPA 2000) was utilized.

Reference Dose / Concentration: 0.23 mg/kg-d (rats)
Source of toxicity value: MDH, 2012
Point of Departure: 90 mg/kg-d (NOAEL, chronic neurological assessment of F2 offspring from the 2 generation study, Schoenig et al 1993. LOAEL = 225 mg/kg-d as cited by EPA 1998)
Human Equivalent Dose Adjustment: 23 mg/kg-d (90 mg/kg-d X 0.26) (MDH, 2011)
Total uncertainty factor: 100
UF allocation: 3 interspecies extrapolation, 10 intraspecies variability, 3 database
Critical effect(s): Increased motor activity
Co-critical effect(s): Increased response time, decreased vertical activity, decreased pup weight, increased liver weight, decreased adult body weight
Additivity endpoint(s): Developmental, Hepatic (liver) system, Nervous system

The Chronic nHRL must be protective of the short-term exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 200 µg/L. Additivity endpoints: Development, Nervous system.

Cancer Health Risk Limit (cHRL) = Not Applicable
Cancer classification: Group D (EPA 1998a)

Volatile: No

Summary of health-based guidance history:
Short-term, Subchronic and Chronic Health-Based Values (HBVs) were issued in February 2011. MDH reevaluated the HBVs in 2012 to incorporate HED methodology. The resulting HBVs did not change. The HBVs were adopted as HRLs in 2013.

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

<table>
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<th>Tested?</th>
<th>Endocrine</th>
<th>Immunotoxicity</th>
<th>Development</th>
<th>Reproductive</th>
<th>Neurotoxicity</th>
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<td>No</td>
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<td>Yes</td>
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<table>
<thead>
<tr>
<th>Effects?</th>
<th>Secondary Observations</th>
<th>Endocrine</th>
<th>Immunotoxicity</th>
<th>Development</th>
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<td>Yes²</td>
<td>Yes³</td>
<td>Yes⁴</td>
<td>Yes⁵</td>
<td></td>
</tr>
</tbody>
</table>

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 No studies directly assessing endocrine effects have been conducted. Male and female reproductive tract effects (see footnote 4) have been reported; however, it is not clear whether these effects are the result of endocrine activity.

2 A single 14-day subcutaneous injection study has been conducted. A decrease in the antibody plaque-forming (PFC) response was reported. It should be noted that oral exposure would result in first pass metabolism of DEET in the liver to a greater extent than subcutaneous injection. The subcutaneous dose level at which decreased PFC response was noted is slightly lower than the oral exposure points of departure used for the short-term, subchronic and chronic duration RfDs. However they are ~30-60-fold higher than the RfD values. A database UF was incorporated in to the short-term, subchronic and chronic duration RfDs, in part, to address the need for additional characterization of immunological effects.
Three developmental studies and a 2 generation reproductive/developmental study have been conducted. The developmental studies did not report developmental effects except at doses that resulted in severe toxicity (e.g., increased mortality) in the pregnant animals. The 2-generation study reported decreased pup body weight during lactation at the highest dose tested. Decreased pup body weight forms the basis of the short-term RfD. Decreased pup body weight occurred at a dose level similar to the subchronic and chronic point of departures. This effect is included as a health endpoint for these durations.

An 8-week study in dogs and a 90 day study in hamsters reported decreased organ weight or histological changes in the testes/epididymis weights. However, these effects were not reported in the 1 year dog study at similar dose levels. Macroscopic and histologic evaluation of females exposed in the 1 year dog study reported an increased incidence of mild hyperplasia of the epithelia of the uterus and uteruses distended with fluid. The male and female reproductive tract effects above were reported at dose levels more than 7-fold higher than the short-term, subchronic or chronic duration point of departures. The doses at which the effects were observed are more than 700-fold higher than the short-term, subchronic and chronic RfDs. No effects on reproductive parameters (e.g., fertility, organ weights) were reported in the 2 generation reproductive study conducted in rats.

Two neurotoxicity studies in rats have been conducted. One was an acute (single exposure) study and one was a chronic (~9 month) study. Changes in reaction time and activity levels were observed. The results of the acute study were insufficient to determine a point of departure with confidence. The results of this study, however, were used as part of the justification for incorporating a database uncertainty factor in to the derivation of the RfD. The results of the chronic study were utilized as the basis of the chronic duration RfD. General toxicity studies, particularly in dogs, have also observed neurological effects (e.g., tremors, excessive salivation). A database UF was incorporated into the short-term, subchronic and chronic RfD derivation to address concerns that additional characterization of neurotoxicity is warranted.

References:


California Environmental Protection Agency-OEHHA Toxicity Criteria Database. from http://www.oehha.ca.gov/risk/ChemicalDB/index.asp.


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