Chemical Name: Acetone  
CAS: 67-64-1  
Synonyms: propanone, β-ketopropane, dimethyl ketone, dimethylformaldehyde, DMK, 2-propanone, propan-2-one

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

Short-term Non-Cancer Health Risk Limit (nHRL_{short-term}) = 9000 μg/L

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

\[
= \frac{(5 \text{ mg/kg/d}) \times (0.5) \times (1000 \mu g/mg)}{(0.289 \text{ L/kg-d})}
\]

\[= 8561 \text{ rounded to } 9000 \mu g/L\]

Reference Dose / Concentration: 5.0 mg/kg-day (laboratory animal - rats)  
Source of toxicity value: MDH 2010  
Point of Departure: 1485 mg/kg-d (NOAEL, Dietz, et al. 1991; NTP, 1991)  
Human Equivalent Dose Adjustment: Insufficient data  
Total uncertainty factor: 300  
UF allocation: UF of 10 was applied to account for intraspecies variation; for interspecies extrapolation, 3 was used for toxicokinetic differences; the toxicodynamics component was 1 because humans are not anticipated to be more susceptible than rats to the nephrotoxic effects. Studies show that both humans and rodents metabolize acetone, at low doses, in the liver and by extrahepatic pathway followed by excretion at a higher concentration. UF of 10 was used to account for database uncertainty. The database lacks a multigenerational study and adequate studies of the oral neurotoxicity, developmental and developmental neurotoxicity. 

Critical effect(s): Increased kidney weight (consistent with nephropathy seen in rats during the 13-week Dietz study)  
Co-critical effect(s): None  
Additivity endpoint(s): Renal (kidney) system  
Secondary effect(s): Bone marrow effects; centrilobular hepatocellular hypertrophy (liver effects); decreased survival, decreased reproductive index, and increased gestation duration (reproductive effects)
Subchronic Non-Cancer Health Risk Limit (nHRL\textsubscript{subchronic}) = 8000 μg/L

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Subchronic intake rate, L/kg/d)

= (3 mg/kg/d) x (0.2) x (1000 μg/mg)
(0.077 L/kg-d)

= 7792 rounded to 8000 μg/L

Reference Dose / Concentration: 3.0 mg/kg-day (laboratory animal -rats)
Source of toxicity value: MDH 2010
Point of Departure: 900 mg/kg-d (NOAEL, Dietz, et al. 1991; NTP, 1991)
Human Equivalent Dose Adjustment: Insufficient data
Total uncertainty factor: 300
UF allocation: UF of 10 was applied to account for intraspecies variation; for interspecies extrapolation, 3 was used for toxicokinetic differences; the toxicodynamics component was 1 because humans are not anticipated to be more susceptible than rats to the nephrotoxic effects. Studies show that both humans and rodents metabolize acetone, at low doses, in the liver and by extrahepatic pathway followed by excretion at a higher concentration. UF of 10 was used to account for database uncertainty. The database lacks a multigenerational study and adequate studies of the oral neurotoxicity, developmental and developmental neurotoxicity. Additionally, the database uncertainty factor also accounts for non-biologically significant changes and inconsistent dose-responses in hematological parameters at doses ≤ 900 mg/kg-day that may be indicative of precursor events for development of hematological toxicity (i.e., macrocytic anemia).

Critical effect(s): Nephropathy – Renal (kidney) system, changes in hematological (blood) parameters consistent with bone marrow toxicity
Co-critical effect(s): Tubular degeneration of kidneys - renal (kidney system)
Additivity endpoint(s): Renal (kidney) system, Hematological (blood) system
Secondary effect(s): Increased testes weights, decreased sperm motility, increased incidence of abnormal sperm, and depressed caudal weight (Reproductive effects); excessive salivation (neurological)

Chronic Non-Cancer Health Risk Limit (nHRL\textsubscript{chronic}) = 4000 μg/L

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Chronic intake rate, L/kg/d)
\[
\frac{= (0.9 \text{ mg/kg/d}) \times (0.2) \times (1000 \mu g/mg)}{(0.043 \text{ L/kg-d})} = 4186 \text{ rounded to } 4000 \mu g/L
\]

Reference Dose / Concentration: 0.90 mg/kg-day (laboratory animal - rats)
Source of toxicity value: MDH 2010 (same as EPA, IRIS 2003)
Point of Departure: 900 mg/kg-d (NOAEL, Dietz, et al. 1991; NTP, 1991)
Human Equivalent Dose Adjustment: Insufficient data
Total uncertainty factor: 1000
UF allocation: UF of 10 was applied to account for intraspecies; for interspecies extrapolation, 3 was used for toxicokinetic differences; the toxicodynamics component was 1 because humans are not anticipated to be more susceptible than rats to the nephrotoxic effects. Studies show that both humans and rodents metabolize acetone, at low doses, in the liver and by extrahepatic pathway followed by excretion at a higher concentration. UF of 10 was used to account for database uncertainty. The database lacks a multigenerational study and adequate studies of the oral neurotoxicity, developmental and developmental neurotoxicity. Additionally, the database uncertainty factor also accounts for non-biologically significant changes and inconsistent dose-responses in hematological parameters at doses \( \leq 900 \text{ mg/kg-day} \) that may be indicative of precursor events for development of hematological toxicity (i.e., macrocytic anemia). The database contains oral subchronic studies but lacks chronic studies. A subchronic to chronic uncertainty factor of 3 is used due to uncertainty about increased severity of effects from increased duration of oral exposure to acetone. Based on information provided in the IRIS summary, a value of 3 rather than 10 is justified because effects from chronic exposure to acetone are not likely to be dramatically different than during subchronic exposure because acetone is produced endogenously, there are multiple pathways of acetone elimination – excretion, exhalation, and metabolism – and acetone does not accumulate in the body.

Critical effect(s): Nephropathy – Renal (kidney) system, changes in hematological (blood) parameters consistent with bone marrow toxicity
Co-critical effect(s): Tubular degeneration of kidneys - renal (kidney system).
Additivity endpoint(s): Renal (kidney) system, Hematological (blood) system
Secondary effect(s): Increased testes weights, decreased sperm motility, increased incidence of abnormal sperm, and depressed caudal weight (Reproductive effects); excessive salivation (neurological)

Cancer Health Risk Limit (cHRL) = Not Applicable
Cancer classification: No cancer classification is available for acetone
Slope factor: Not applicable
Source of slope factor: Not applicable
Tumor site(s): Not applicable

Volatile: Yes (moderate volatility)

Summary of changes since 1993/1994 HRL promulgation:
The 2011 HRL_{chronic} (4000 μg/L) is approximately 6 times higher than the 1993/94 HRL value (700 μg/L) as the result of: 1) utilizing more recent intake rates which incorporate higher intake rates during early life, 2) a 9-fold increase in the RfD value, and 3) rounding to one significant digit.

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>Effects?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes – Secondary Observations</td>
<td>Yes</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. Decreased pup survival was observed after pregnant rats were exposed to acetone at 3500 mg/kg-day by oral gavage which is 1.5 times higher than the short-term LOAEL of 2328 mg/kg-day (EHRT 1987 as cited by ATSDR 1994). Offspring exposed to acetone through inhalation during gestation experienced decreased fetal weight and increased incidence of fetal malformations. During another developmental inhalation study in mice, no developmental effects were seen in the offspring (Mast et al, 1988).

2. Reproductive effects from exposure to acetone observed during an oral gavage study in pregnant rats included a decreased reproductive index and increase in the gestation duration at 3500 mg/kg-day (EHRT 1987 as cited by ATSDR 1994). Male rats exposed to acetone through drinking water for 13 weeks experienced an increase in relative testes weight, decreased caudal and epididymal weights, depressed sperm motility, and increased incidence of abnormal sperm at 3400 mg/kg-day (decreased testes weights could have been due to an overall decrease in body weight) (Dietz 1991). No reproductive effects were seen when male rats exposed to acetone in drinking water for 6-week prior to mating (Larsen et al. 1991). The reproductive effects observed in both studies occurred at approximately 1.5 times the short-term LOAEL of 2328 mg/kg-day and approximately 2 times higher than the subchronic/chronic LOAEL of 1700 mg/kg-day.

3. A couple of neurotoxicity studies were conducted for oral exposure to acetone with only one reporting very minimally evoked visual potentials in rats at 650 mg/kg-day (approximately 3 times lower than the subchronic/chronic LOAEL of 1700 mg/kg-day). Excessive salivation was also observed in rats exposed to acetone in drinking water at 2500 mg/kg-day (1.5 times the subchronic/chronic LOAEL of 1700 mg/kg-day).
Narcotic-like effects have been reported after humans have inhaled or ingested acetone which include lethargy, minimal responsiveness, and comatose condition. Excessive salivation has also been observed in animals following acetone ingestion. Neurotoxicity observed in animals following inhalation of acetone include: inhibition of avoidance behavior, effects on fixed ratio and fixed interval response rates, and central nervous system depression measured by tests of unconditioned performance and reflexes.

References:


California Water Resources Control Board http://www.waterboards.ca.gov/water_issues/programs/water_quality_goals/


Environmental Protection Agency (EPA). ACToR: Aggregated Computational Toxicology Resource (http://actor.epa.gov/)


EPA National Center for Environmental Assessment http://cfpub.epa.gov/ncea/cfm/archive_whatsnew.cfm


EPA Office of Pesticide Programs http://www.epa.gov/pesticides/reregistration/status.htm

EPA Toxicity and Exposure Assessment for Children's Health (TEACH) http://www.epa.gov/teach/

EPA Voluntary Children's Chemical Evaluation Program (VCCEP) http://www.epa.gov/oppt/vccep/pubs/chemmain.htm


International Agency for Research on Cancer (IARC). Agents Reviewed by the IARC. [Link]

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International Toxicity Estimates for Risk (ITER). [Link]


National Toxicology Program. NTP Report on the Toxicity Studies of Acetone in F344/N Rats and B63CF1 Mice (Drinking Water Studies). January 1991. [Link]

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WHO Recommended Classification of Pesticides by Hazard. 2004. [Link]

World Health Organization. [Link] (search Chapter 8 Chemical Aspects and Chapter 12 Chemical Fact Sheets for chemical name)