Minnesota Department of Health

Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Adopted as Rule: November 2015

Toxicological Summary for: Acetaminophen

CAS**: 103-90-2**

Synonyms: N-(4-hydroxyphenyl)acetamide, Tylenol, Paracetamol, Paracetol, Acetamide, N-(4-hydroxyphenyl)-, 4'-Hydroxyacetanilide, 4-(acetylamino)phenol, 4-acetamidophenol, Acetanilide, 4'-hydroxy-, p-Acetamidophenol, p-Acetaminophenol, p-Acetylaminophenol, p-Hydroxyacetanilide, APAP

Acute Non-Cancer Health Risk Limit (nHRLAcute) = 200 µg/L (Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)

$$\text{(Acute intake rate, L/kg-d)} = \frac{\text{(0.25 mg/kg-d) x (0.2*) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 173 rounded to **200 µg/L**

*MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential non-water sources of exposure from multiple products available for infants and children an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals.

Reference Dose/Concentration	0.25 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	7.4 mg/kg-d (NOAEL, based on the human minimum therapeutic dose for infants at 40 mg/dose for up to 5.4 kg infant (McNeil Consumer Healthcare 2010)
Human Equivalent Dose (MDH, 2011	Not applicable
Total uncertainty factor:	30
Uncertainty factor allocation:	10 for intraspecies variability; 3 for database uncertainty (additional studies to evaluate gestational and early life exposures and to adequately characterize the dose-response and adversity of cyclooxygenase (COX) enzyme inhibition are warranted)
Critical effect(s):	Hepatotoxicity in humans
Co-critical effect(s):	Liver effects in animals (increased serum liver enzymes, reduced hepatic glutathione, liver histopathological changes); acute liver failure in humans.
Additivity endpoint(s):	Hepatic (liver) system

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 200 µg/L

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

$$= \frac{(0.25 \text{ mg/kg-d}) \times (0.2^*) \times (1000 \text{ µg/mg})}{(0.289 \text{ L/kg-d})}$$

= 173 rounded to **200 µg/L**

*See footnote for acute section for RSC rationale

Reference Dose/Concentration	0.25 mg/kg-d (human)
Source of toxicity value	MDH, 2014
Point of Departure (POD)	7.4 mg/kg-d (NOAEL, based on the human minimum therapeutic dose for infants at 40 mg/dose for up to 5.4 kg infant (McNeil Consumer Healthcare 2010)
Human Equivalent Dose (MDH, 2011):	Not applicable
Total uncertainty factor:	30
Uncertainty factor allocation:	10 for intraspecies variability; 3 for database uncertainty (additional studies to evaluate gestational and early life exposures and to adequately characterize the dose-response and adversity of cyclooxygenase (COX) enzyme inhibition are warranted)
Critical effect(s):	Hepatoxicity and increased serum liver enzymes (ALT) in humans and animals
Co-critical effect(s):	Acute liver failure, hepatotoxicity, increased serum liver enzymes (ALT, AST) in humans and animals; decreased hepatic glutathione (GSH), and liver histopathological changes in animals
Additivity endpoint(s):	Hepatic (liver) system

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = $nHRL_{Short\text{-}term}$ = 200 µg/L

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

$$= \frac{(0.28 \text{ mg/kg-d}) \times (0.2) \times (1000 \text{ µg/mg})}{(0.077 \text{ L/kg-d})}$$

= 727 rounded to 700 µg/L

Reference Dose/Concentration	0.28 mg/kg-d (human)
Source of toxicity value	MDH, 2014
Point of Departure (POD):	27.8 mg/kg-d (LOAEL based on dosing of 1950 mg/day, McNeil Consumer Healthcare 2010)
Human Equivalent Dose (MDH, 2011):	Not applicable
Total uncertainty factor:	100
Uncertainty factor allocation:	10 for intraspecies variability; 3 for use of minimal LOAEL instead of NOAEL; 3 for database uncertainty (additional studies evaluating gestational and early life exposures and to adequately characterize the dose-response and adversity of cyclooxygenase (COX) enzyme inhibition are warranted)
Critical effect(s):	Increased serum liver enzymes (ALT) in humans and animals

Co-critical effect(s):	Liver effects in animals (hepatotoxicity, increased bilirubin, reduced hepatic glutathione, liver histopathological changes); and humans (acute liver failure)
Additivity endpoint(s):	Hepatic (liver) system

The Subchronic nHRL must be protective of the acute, and 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: Hepatic (liver) system

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = $nHRL_{Short\text{-}term}$ = 200 µg/L

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

$$= \frac{\text{(0.093 mg/kg-d) x (0.2) x (1000 µg/mg)}}{\text{(0.043L/kg-d)}}$$

= 433 rounded to 400 µg/L

Reference Dose/Concentration:	0.093 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	27.8 mg/kg-d (LOAEL based on dosing of 1950 mg/day, McNeil Consumer Healthcare 2010)
Human Equivalent Dose (MDH, 2011):	Not applicable
Total uncertainty factor:	300
Uncertainty factor allocation:	10 for intraspecies variability; 3 for use of minimal LOAEL; 3 use of subchronic human data for chronic duration; 3 for database uncertainty (additional studies evaluating gestational and early life exposures and to adequately characterize the dose-response and adversity of cyclooxygenase (COX) enzyme inhibition are warranted)
Critical effect(s):	Increased serum liver enzymes (ALT) in humans.
Co-critical effect(s):	Liver effects in animals (increased serum liver enzymes ALT, reduced glutathione, liver histopathological changes); Kidney effects in animals (increased severity of nephropathy); Thyroid effects in animals (thyroid follicular cell hyperplasia)
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system, Thyroid

The Chronic nHRL must be protective of the acute, short-term, and subchronic 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: Hepatic (liver) system

Cancer Health Risk Limit (cHRL) = **Not Applicable. Not classified as a carcinogen by IARC, U.S. FDA, NTP, U.S. EPA or California OEHHA**

Volatile: **No**

Summary of Guidance Value History:
Health-based guidance values for acetaminophen were published in 2011. Acetaminophen was re-evaluated in 2014 to incorporate more recent toxicity information. The re-evaluation did not result in quantitative changes; therefore, the 2014 Health-Based Values (HBVs) were identical to the 2011 guidance values. The re-evaluation did provide some additional information regarding health effects identified in the Health Standards Statute (see below). The 2014 HBVs were adopted into rule as HRLs in 2015.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	Yes	Yes	Yes	Yes
Effects?	Yes[1]	Yes[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] Thyroid hyperplasia was reported in a 2-yr dietary study in mice at human equivalent doses approximately 150 times higher than the chronic RfD of 0.093 mg/kg-day. No effects on thyroid hormones were found in a small short-term study in humans at a dose over 170 times higher than the short-term RfD or in mice at a dose 26 times higher than the short-term RfD. One epidemiology study reported a weak association between increased risk of cryptorchidism in offspring of mothers who used acetaminophen during pregnancy. Thyroid was identified as a co-critical endpoint for the chronic duration; however, the chronic HRL was set to the short-term value and, therefore, is considered protective for possible thyroid effects.

In vitro studies reported decreased testosterone production in fetal rat and adult human testes exposed to acetaminophen but no effects on fetal testosterone production by human fetal testes *in vitro*. In human fetal testes explants, decreased insulin-like factor 3 (INSL3) levels were reported. The biological relevance of *in vitro* testes studies is unknown and testosterone effects for acetaminophen have not been evaluated *in vivo*.

In humans taking oral contraceptives, acetaminophen may increase circulating ethinylestradiol after ingestion of a single acetaminophen dose (approximately 14 mg/kg-day or approximately 50 times higher than the acute, short-term and subchronic RfDs and 150 times higher than the chronic RfD). Acetaminophen was negative in mouse and rat uterotrophic assays at human equivalent doses greater than 600 times higher than the acute/short-term RfDs.

[2] A limited number of animal studies have reported that acetaminophen suppressed humoral and cellular immunity at doses that were either toxic to the liver or over 150 times higher than the RfDs. Acetaminophen was associated with suppression of serum neutralizing antibody response, increased

nasal symptoms, and a rise in circulating monocytes in human volunteers infected with intranasal rhinovirus type 2 in a small double-blind, placebo-controlled human clinical trial at doses over 200 times higher than the RfDs. Acetaminophen may cause bronchoconstriction in individuals with aspirin-induced asthma at doses more than 50 times higher than the RfDs. There are conflicting epidemiology data regarding a possible association with prenatal or early life exposure to acetaminophen and childhood asthma. The most common limitation in these epidemiology studies was the lack of control for “indication for use” (i.e. infection, fever, or illness may have been important confounders that were not considered and data was not adjusted accordingly) and doses were not adequately characterized.

[3]Multiple human studies have reported no increase in developmental effects from acetaminophen use during pregnancy and the overall weight-of-evidence suggests that acetaminophen is not a developmental toxicant in humans. There are conflicting human data regarding associations between acetaminophen use during pregnancy and risk of gastroschisis in offspring. No other malformation has been shown to be causally associated with single-ingredient acetaminophen. Recent human studies reported possible weak associations between acetaminophen use during pregnancy and increased risk of asthma, increased risk of autistic disorder from acetaminophen use after measles-mumps-rubella vaccination; and increased risk of cryptorchidism (undescended testes) in offspring. At the present time there is insufficient evidence for a casual association and further studies are needed before these recent findings can be linked to acetaminophen.

Experimental animal studies do not suggest increased malformations from therapeutic use of acetaminophen during pregnancy. One laboratory animal study reported decreased body weight gain in offspring and decreased survival of offspring at a human equivalent dose over 500 times higher than the acute RfD. In another study, effects on survival and body weight gain in offspring, persisting to adulthood, and sperm abnormalities occurred at human equivalent doses approximately 200 times higher than the acute and short-term RfDs.

[4] No effects on pregnancy or offspring were reported in several laboratory animal studies at human equivalent doses up to over 500 times higher than the acute and short-term RfDs. In a continuous breeding animal study, effects on reduced fertility and reproduction were observed at human equivalent dose 800 times higher than the acute and short-term RfDs.

[5]Acetaminophen is not considered to be a neurotoxicant based on lack of secondary observations in animal studies. In laboratory animals, clinical neurotoxicity symptoms were reported only at very high doses over 1,700 times higher than the RfDs. No effects were reported at doses 1,000 times higher than the RfDs. An acute subcutaneous injection study in neonatal animals reported altered locomotor activity and failure to acquire spatial learning in adulthood; however, the relevance of injection studies for oral exposure is questionable. A few epidemiology studies reported associations between acetaminophen during pregnancy and higher risk of hyperkinetic disorders, ADHD medication use, and ADHD-like behaviors, decreased motor skill development, communication skills, and externalizing or internalizing behaviors in children. One epidemiology study reported no association between exposures during pregnancy and IQ or attention deficits in children. However, these epidemiology studies have several limitations, including lack of dose characterization, and cannot be used to establish a causal relationship between acetaminophen use and neurotoxicity in humans.

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