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: Sulfamethazine

CAS: **57-68-1 and 1981-58-4 (sodium salt)**

Synonyms: Sulfadimidine; 4-Amino-N-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide; Benzenesulfonamide, 4-amino-N-(4,6-dimethyl-2-pyrimidinyl)-; Sulfanilamide, N(sup 1)-(4,6-dimethyl-2-pyrimidinyl)-; Sulfanilamide, N1-(4,6-dimethyl-2-pyrimidinyl); sulphamethazine; sulphadimidine; sulfadine; 4-amino-N-4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide, monosodium salt, SMZ

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

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 100 µg/L

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

$$= \frac{\text{(0.04 mg/kg/d) x (0.8)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 111 rounded to **100 µg/L**

* MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate Relative Source Contributions (RSCs) (MDH 2008, Appendix K). Typically an RSC of 0.5 is utilized for nonvolatile contaminants for the acute and short-term durations and an RSC of 0.2 is used for subchronic and chronic durations. Given the limited potential for exposure from other sources, an RSC of 0.8 was selected rather than applying the default RSC value. For individuals who take sulfonamide antibiotics by prescription, the additional exposure from drinking water will be negligible.

Reference Dose/Concentration:	0.04 mg/kg-d (Sprague-Dawley CR/CD rats)
Source of toxicity value:	MDH 2013
Point of Departure (POD):	5 mg/kg-d (NOAEL, McClain 1993 and 1995)
Human Equivalent Dose (HED):	5 x 0.23 = 1.2 mg/kg-d (MDH 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Thyroid follicular cell hypertrophy
Co-critical effect(s):	None
Additivity endpoint(s):	Thyroid

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = $HRL_{Short-term}$= 100 µg/L

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

= $\frac{(0.017 \text{ mg/kg/d}) \times (0.8)^{*} \times (1000 \text{ µg/mg})}{(0.077 \text{ L/kg-d})}$

= 177 rounded to **200 µg/L**

* Rationale for selecting an RSC of 0.8 - same explanation as that provided for the short-term duration (see above).

Reference Dose/Concentration:	0.017 mg/kg-d (Fischer 344 rats)
Source of toxicity value:	MDH, 2013
Point of Departure (POD):	2.2 mg/kg-d (NOAEL, Littlefield et al. 1990)
Human Equivalent Dose (HED):	2.2 x 0.23 = 0.51 mg/kg-d (MDH 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Thyroid follicular cell hyperplasia
Co-critical effect(s):	Thyroid follicular cell hypertrophy, increased thyroid weight, increased serum thyroid stimulating hormone (TSH), decreased pup bodyweight at weaning
Additivity endpoint(s):	Developmental, Thyroid (E)

The Subchronic HRL must be protective of the acute and short-term exposures that occur within the acute and short-term periods and therefore, the Subchronic HRL is set equal to the Short-term HRLof 100 µg/L. Additivity endpoints: Thyroid.

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = $HRL_{Short-term}$ = 100 µg/L

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

= $\frac{(0.019 \text{ mg/kg/d}) \times (0.8)^{*} \times (1000 \text{ µg/mg})}{(0.043 \text{L/kg-d})}$

= 354 rounded to **400 µg/L**

* Rationale for selecting an RSC of 0.8 - same explanation as that provided for the short-term duration (see above).

Reference Dose/Concentration:	0.019 mg/kg-d (Fischer 344 rats)
Source of toxicity value:	MDH, 2013
Point of Departure (POD):	2.4 mg/kg-d (NOAEL, Littlefield et al. 1990)
Human Equivalent Dose (HED):	2.4 x 0.24 = 0.58 mg/kg-d (MDH 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability

Critical effect(s):	Thyroid follicular cell hyperplasia
Co-critical effect(s):	Thyroid follicular cell hypertrophy, increased thyroid weight, increased serum thyroid stimulating hormone (TSH), decreased pup bodyweight at weaning
Additivity endpoint(s):	Developmental, Thyroid (E)

The Chronic HRL must be protective of the acute, short-term, and subchronic exposures that occur within the acute, short-term, and subchronic periods and therefore, the Chronic HRL is set equal to the Short-term HRL of 100 µg/L. Additivity endpoints: Thyroid.

Cancer Health Risk Limit (cHRL) = Not Applicable

Volatile: No

Summary of Guidance Value History:
No previous guidance values exist. The non-cancer health-based values presented above represent new values. Health based values developed in 2014 were adopted into rule as HRLs in November 2015.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	Yes	Yes	Yes	No
Effects?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	No[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]In laboratory animals, sulfamethazine (SMZ) increased thyroid stimulating hormone (TSH) and decreased thyroid hormone (T4). Thyroid hormones were not affected in non-human primates at administered doses over 17,000 times higher than the subchronic RfD. Thyroid and pituitary hormone effects were identified as critical and co-critical effects.

[2]Immunotoxicity studies for SMZ in animals or humans are not available; however, the sulfonamide antibiotic drug class is generally known to cause hypersensitivity immune reactions in humans and dogs based on clinical experience. SMZ forms the same types of reactive metabolites that have been related to sulfonamide hypersensitivity. Immunotoxic effects include skin rashes, hives, and serious life-threatening hypersensitivity reactions. Sulfonamide hypersensitivity is considered to be related to drug metabolism deficiencies and/or variability among sensitive individuals. Immunotoxicity is addressed through the use of an uncertainty factor of 10 to account for sensitive populations.

[3]Human infants exposed to sulfonamides *in utero* or during the first 2 months after birth have increased risk of kernicterus, a bilirubin-induced permanent brain dysfunction. Exposed infants have a greater risk for jaundice and hemolytic anemia. Malformations (i.e., cleft palate, hydroureter and hydronephrosis) occurred in laboratory animals exposed to SMZ *in utero* at doses over 2,900 times higher than the

short-term RfD. Developmental effects were identified as co-critical for the subchronic and chronic durations.

[4]Reproductive performance and fertility were decreased in rats at HED doses over 4,000 times higher than the RfDs. No reproductive effects were reported in laboratory animals at doses over 1,900 times higher than the RfDs.

[5]Neurotoxicity has not been directly evaluated for SMZ. For a similar sulfonamide, SMX, no effects on neurological clinical signs were observed in chronic studies with non-human primates and rats at doses 4,000 times or more than the RfD. The thyroid plays and important role in normal neurodevelopment, so the RfDs based on thyroid effects are considered protective.

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