2013 Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
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Chemical Name: Sulfamethoxazole
CAS**:** 723-46-6
Synonyms: 3-(p-aminophenylsulfonamido)-5-methylisoxazole; benzenesulfonamide, 4-amino-N-(5-methyl-3-isoxazolyl)-; Gantanol; N(1)-(5-methyl-3-isoxazolyl)sulfanilamide; 5-methyl-3-sulfanilamidoisoxazole; Radonil; Sinomin; sulfamethalazole; Sulfamethoxazol; sulfamethoxizole; sulfamethylisoxazole; sulfanilamide, N(1)-(5-methyl-3-isoxazolyl)-; 3-sulfanilamido-5-methylisoxazole; sulfisomezole, sulphamethoxazole, SMX

The database for sulfamethoxazole (SMX) consists of several oral studies of various durations. Many of the studies had limitations (e.g., insufficient data reporting) that prevented development of a chemical specific guidance value for drinking water.

HBVs are available for a related sulfonamide, sulfamethazine (SMZ). SMZ and SMX have similar chemical structures, similar metabolites, share similar metabolic pathways, and have comparable toxicological profiles. The Minnesota Department of Health (MDH) recommends the use of HBVs for SMZ to evaluate the potential health risks associated with exposure to SMX. The following recommendation represents Risk Assessment Advice (RAA):

- Acute – Not Derived;
- Short-term – 100 ug/L, Additivity endpoints: Thyroid
- Subchronic – 100 ug/L*, Additivity endpoints: Thyroid
- Chronic – 100 ug/L*, Additivity endpoints: Thyroid
- Cancer – not applicable

*Set at short-term value

For additional information on the derivation of HBVs for SMZ and relevant additivity endpoints see: SMZ Chemical Summary Sheet

Volatile: No

Summary of Guidance Value History:
No previous guidance values exist. The non-cancer risk assessment advice presented above represents new values.

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 humans receiving co-trimoxazole (combination of sulfamethoxazole (SMX) with trimethoprim), decreased thyroid hormones, T4 and T3, were reported without effects on TSH. However, other human studies of SMX in combination with trimethoprim reported no thyroid hormone effects (note: in humans, SMX is co-administered with trimethoprim; however, trimethoprim is not considered to be a thyroid toxicant). The lowest human therapeutic dose level (23 mg/kg bw-d) for SMX (a LOAEL for potential adverse thyroid effects in humans) is over 575 times higher than the RfDs for the surrogate chemical, SMZ. In laboratory animals, SMX increased serum TSH and decreased T4. Thyroid hormone effects were identified as critical and co-critical effects for the surrogate chemical, SMZ.

[2]In humans, therapeutic doses of SMX (in combination with trimethoprim) are associated with immunotoxicity, including skin rashes and hives. Serious, potentially life-threatening, hypersensitivity reactions have also occurred. The risk for hypersensitivity is thought to be related to drug metabolism deficiencies and/or variability among sensitive individuals. The lowest therapeutic dose for SMX in humans (23 mg/kg bw-d), considered a human LOAEL for adverse immune effects, is over 575 times higher than the RfDs for the surrogate chemical, SMZ. SMX hypersensitivity has also occurred in dogs lacking the ability to detoxify sulfonamides at estimated HEDs about 250 times higher than the short-term RfD for the surrogate chemical, SMZ.

[3]Human infants exposed to SMX (in combination with trimethoprim) *in utero* or during the first 2 months after birth have increased risk of kernicterus, a bilirubin-induced permanent brain dysfunction. Also, exposed infants have a greater risk for jaundice and hemolytic anemia (note: in humans, SMX is co-administered with trimethoprim, which also causes developmental effects, so the combination drug may have greater developmental toxicity than SMX alone). Malformations, including cleft palate, occurred in laboratory animals exposed *in utero* to high doses of SMX alone. Developmental effects were identified as co-critical for the subchronic and chronic exposure durations for the surrogate chemical, SMZ.

[4]Reproductive toxicity of SMX, including effects on reproductive performance and fertility, occurred in animal studies only at high doses about 7,800 times higher than the RfD for the surrogate chemical, SMZ.

[5] Neurotoxicity has not been directly evaluated for SMX. Potential adverse human reactions to antibiotics containing SMX (in combination with trimethoprim) listed on the drug labeling include neurological and psychiatric effects (e.g., aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache, hallucinations, depression, apathy, and nervousness). No effects on neurological clinical signs were observed in chronic SMX studies with non-human primates and rats at doses over 4,000 times higher than the RfDs for the surrogate chemical, SMZ. The lowest therapeutic dose level (23 mg/kg bw-d) for SMX in humans (a LOAEL for nervous system effects in humans) is over 575 times higher than the RfDs for the surrogate chemical, SMZ.

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