EXECUTIVE SUMMARY

TETRAMETHYLSUCCINONITRILE – Oral Risk Assessment CAS # 3333-52-6			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
NOAEL (no observed adverse effects level)	Not identified	mg/kg-day	
Oral RfD (oral reference dose)	Not calculated	mg/kg-day	
TAC (total allowable concentration)	0.01	mg/L	Based on a qualitative risk assessment under NSF/ANSI 61 (2010).
SPAC (single product allowable concentration)	0.01	mg/L	Based on a qualitative risk assessment under NSF/ANSI 61 (2010).
STEL (short term exposure level)	0.01	mg/L	Based on a qualitative risk assessment under NSF/ANSI 61 (2010).

KEY STUDY	Johannsen, F.R. and G.J. Levinskas. 1986. Subchronic toxicity of tetramethylsuccinonitrile. Fundam Appl Toxicol. 7(1):41-8.
CRITICAL EFFECT	A critical effect was not identified and a qualitative risk assessment was conducted due to the lack of sufficient information to reliably conduct a quantitative risk assessment.
UNCERTAINTY FACTORS	Since a quantitative risk assessment was not performed, no uncertainty factors were used.
TOXICITY SUMMARY	A qualitative risk assessment was conducted according to the guidelines established in Annex A of NSF/ANSI 60 (2009a) and 61 (2010) due to limited oral data in humans or laboratory animals to perform a quantitative risk assessment. Oral toxicity data for tetramethylsuccinonitrile in humans were not identified. Male SD rats that received tetramethylsuccinonitrile via gavage or drinking water for 13 weeks had increased kidney weights accompanied by degenerated proximal and distal convoluted tubules with hyaline droplet formation. α-2μ-Globulin-associated histochemical staining was not included in the evaluation. Increased liver weights were also seen in the absence of associated hepatic histopathology after subchronic gavage but not drinking water exposure in rats. Standardized two-generation reproduction or developmental toxicity studies were not identified. Maternal toxicity along with reduced crown-rump length in offspring was seen in hamsters that received single intraperitoneal injections of tetramethylsuccinonitrile on GD 8. Neither chronic data nor *in vivo* genotoxicity data were identified. Tetramethylsuccinonitrile was not mutagenic in *Salmonella typhimurium* or L5178y mouse lymphoma cells. Based on U.S. EPA (2005) guidelines for carcinogen risk assessment, there is *inadequate information to assess carcinogenic potential* of exposure to tetramethylsuccinonitrile in humans, due to the limited availability of chronic human epidemiological data and lack of carcinogenicity data in animals. The subchronic drinking water study was the longest-term drinking water study in laboratory animals. Although the weight of evidence was insufficient to attribute the kidney effects in male rats to α-2μ-globulin-associated nephropathy, there is low confidence in the benchmark dose estimate of 2.4 mg/kg-day for increased mean relative kidney weight in male rats since the data were a poor fit. NSF considered the weight of evidence from these studies, and from structurally similar compounds to support the use of this qualitative risk assessment in the absence of a key study from which to perform a quantitative risk assessment.
CONCLUSIONS	The weight of evidence suggests that repeated oral exposure to 0.01 mg/L or less of tetramethylsuccinonitrile is protective of human health.