Chloramine-T (trihydrate) & *p*-Toluenesulfonamide

CAS #s 7080-50-4, 127-65-1 & 70-55-3

ORAL RISK ASSESSMENT DOCUMENT

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EXECUTIVE SUMMARY

Chloramine-T (CAS#s 7080-50-4 (trihydrate), 127-65-1) & *p*-TSA (CAS# 70-55-3)– Oral Risk Assessment			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
NOAEL (no-observed-adverse-effect level)	30	mg/kg-day	From a 90-day oral feeding study for chloramine-T trihydrate in rats
$NOAEL_{HED}$ (NOAEL oral human equivalent dose)	5.8	mg/kg-day	Adjusted using $BW^{3/4}$ due to lack of relevant chemical-specific toxicokinetic data (as anhydrous chloramine-T)
Oral RfD (oral reference dose)	0.02	mg/kg-day	From a 90-day feeding study in rats, with an uncertainty factor of 300 (as anhydrous chloramine-T)
TAC (total allowable concentration)	0.1	mg/L	For a 70 kg adult drinking two L/day using a 20% relative source contribution for drinking water
SPAC (single product allowable concentration)	0.1	mg/L	Equivalent to TAC as directly added to water for disinfection purposes (outside of U.S.)
STEL (short term exposure level)	2	mg/L	From a 28-day study of chloramine-T trihydrate in rats with a LOAEL of 300 mg/kg-day

EXPOSURE SUMMARY	Chloramine-T (in trihydrate form) is a disinfectant with water uses limited to aquaculture (globally) and emergency water treatment (outside the U.S.). It may be used as a chemical intermediate in food processing and as disinfectant in dental, medicinal, and veterinary applications. *p*-TSA is the degradant of disinfection and primary metabolite of chloramine-T. *p*-TSA is used in chemical synthesis, industrial applications, in food contact adhesives, and in investigational medicine. Exposure results from oral, dermal, and inhalation routes.
KEY STUDY	90-day oral toxicity of chloramine-T trihydrate in Wistar rats. (1971 TNO study summary by ECHA, 2018)
CRITICAL EFFECT	Statistically significant increased relative kidney weights in male and female rats with increased incidence of calcareous deposits in the kidneys of female rats
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD include: • **3x** for interspecies extrapolation • **10x** for intraspecies extrapolation • **10x** for subchronic to chronic extrapolation The total uncertainty factor is therefore **300x**.
TOXICITY SUMMARY	Human occupational exposure studies and case reports indicate risk of occupational asthma and dermal sensitization from exposure to chloramine-T disinfectant products. Chloramine-T powders and concentrated solutions are considered irritating. Chloramine-T and *p*-TSA are of moderate acute toxicity with oral LD50 values ranging from 381.6 to 4700 mg/kg in the rat, mouse, and rabbit. Rapid absorption and metabolism of chloramine-T leads to formation of *p*-toluenesulfonamide (*p*-TSA) upon ingestion, which is subsequently partially oxidized to 4-sulphamoylbenzoic acid and excreted primarily in the urine. Complete elimination occurs within 5 days of oral exposure. Chloramine-T has shown no mutagenic activity in bacterial reverse mutation assays with or without metabolic activation. *p*-TSA has given positive results in tester strain TA98 with metabolic activation; however, several subsequent, guideline compliant, independent, replicates with TA98 were negative. Additional relevant *in vivo* assays were negative. Based on the lack of guideline compliant carcinogenicity studies in humans or animals, it is concluded that there is "*Inadequate Information to Assess Carcinogenic Potential*" according to US EPA guidelines (2005). 28-day and 90-day feeding studies in rats were available for chloramine-T (trihydrate). The 28-day study resulted in a LOAEL of 300 mg/kg-day with increased relative kidney and liver weights observed at all dose levels and in both sexes. Increased relative kidney weights in both sexes and increased incidence of calcareous deposits in kidneys of female rats were reported at 100 mg/kg-day in the 90-day study, resulting in a NOAEL of 30 mg/kg-day. Four additional 90-day feeding studies were available for *p*-TSA in rats, mice, and dogs, with NOAELs ranging from 30 – 780 mg/kg-day. Reproductive and developmental toxicity studies were available only for *p*-TSA and a single developmental study for chloramine-T, with indication for adverse effects co-occurring with maternal toxicity (reduced body weights in dams and offspring; increased fetal mortality, increased post-implantation losses and resorption rates, and at high exposure level delayed balanopreputial separation and vaginal opening). No teratogenic effects were observed other than vertebral anomalies in one rabbit study that was correlated with reduced fetal body weight. The lowest LOAEL from these studies was 65 mg/kg.
CONCLUSIONS	Based on a quantitative approach utilizing the available guideline-compliant or robust study summaries available from multiple regulatory authority reviews for chloramine-T and *p*-TSA, these drinking water action levels are protective of public health.

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated disinfectant chloramine-T and its primary degradant and metabolite, *p*-toluenesulfonamide, in drinking water, as drinking water treatment chemicals evaluated under NSF/ANSI 60 (2017). Both non-cancer and cancer endpoints have been considered, and risk assessment methodology developed by the U.S. Environmental Protection Agency (U.S. EPA) has been used.

Non-cancer endpoints are evaluated using the reference dose (RfD) approach (Barnes and Dourson, 1988; Dourson, 1994; U.S. EPA, 1993; U.S. EPA, 2002), which assumes that there is a threshold for these endpoints that will not be exceeded if appropriate uncertainty factors (Dourson et al., 1996; U.S. EPA, 2002; WHO/IPCS, 2005) are applied to the highest dose showing no significant effects. This highest dose is derived from human exposure data when available, but more often is derived from studies in laboratory animals. Either the no-observed-adverse-effect level (NOAEL) taken directly from the dose-response data, or the calculated lower 95% confidence limit on the dose resulting in an estimated 10% increase in response (the LED_{10} or $BMDL_{10}$ from benchmark dose programs) can be used (U.S. EPA, 2017). The lowest-observed-adverse-effect level (LOAEL) can also be used, with an additional uncertainty factor, although the benchmark dose approach is preferred in this case. The RfD is expressed in mg/kg-day. It is defined by the U.S. EPA as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (Barnes and Dourson, 1988; U.S. EPA, 1993; U.S. EPA, 2011a).

NSF International uses the RfD to derive three product evaluation criteria for non-cancer endpoints. The total allowable concentration (TAC), generally used to evaluate the results of extraction testing normalized to static at-the-tap conditions, is defined as the RfD multiplied by the 70 kg weight of an average adult assumed to drink two liters of water per day. A relative source contribution (RSC), to ensure that the RfD is not exceeded when food and other non-water sources of exposure to the chemical are considered, is also applied in calculating the TAC. The relative source contribution should be data derived, if possible. Alternately, a 20% default contribution for water can be used (U.S. EPA, 1991a). The TAC calculation is then as follows:

$$\text{TAC (mg/L)} = \frac{[\text{RfD (mg/kg-day)} \times 70\text{ kg}] - [\text{total contribution of other sources (mg/day)}]}{2\text{ L/day}}$$

or

$$\text{TAC (mg/L)} = \frac{\text{RfD (mg/kg-day)} \times 70\text{ kg}}{2\text{ L/day}} \times 0.2\text{ (RSC)}$$

The single product allowable concentration (SPAC), used for water treatment chemicals and for water contact materials normalized to flowing at-the-tap conditions, is the TAC divided by the estimated total number of sources of the substance in the drinking water treatment and distribution system. In the absence of source data, a default multiple source factor of 10 is used. This accounts for the possibility that more than one product in the water and/or its distribution system could contribute the contaminant in question to drinking water.