P-TERT-BUTYLPHENOL

CAS # 98-54-4

ORAL RISK ASSESSMENT DOCUMENT

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TABLE OF CONTENTS

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EXECUTIVE SUMMARY

p-tert-Butylphenol – Oral Risk Assessment CAS # 98-54-4			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
$BMDL_{10HED}$ (human equivalent benchmark dose, lower bound, at 10% response)	12	mg/kg-day	From a two-generation reproduction study in rats
Oral RfD (oral reference dose)	0.04	mg/kg-day	From a two-generation reproduction study in rats with a 300x total uncertainty factor
TAC (total allowable concentration)	0.3	mg/L	Based on a 0.032 L/kg-day adult intake using a 20% relative source contribution factor for drinking water.
SPAC (single product allowable concentration)	0.03	mg/L	From the TAC, using the default 10 sources of *p-tert*-butylphenol in drinking water
STEL (short term exposure level)	1	mg/L	From a two-generation reproduction study in rats, a total uncertainty factor of 100x, and a 0.228 L/kg drinking water intake factor for bottle fed infants.

EXPOSURE SUMMARY	Human exposure to *p-tert*-butylphenol may occur through its use as a component of resins, adhesives, and epoxy coatings, including those used in food contact articles and drinking water components.
KEY STUDY	Clubb S and Jardine L. 2006. *p-tert*-Butylphenol two generation reproduction study in rats. Charles River Laboratories Study Number 493595.
CRITICAL EFFECT	Decreased ovarian weights in F_0 female rats
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD include: • 3x for interspecies extrapolation • 10x for intraspecies extrapolation • 3x for subchronic to chronic extrapolation • 1x for LOAEL to NOAEL • 3x for database deficiencies The total uncertainty factor is therefore 300x
TOXICITY SUMMARY	*p-tert*-Butylphenol has low acute toxicity in rats, with LD_{50} values of 2,500-4,000 mg/kg. The neat substance is moderately irritating to skin and highly irritating to eyes, and human exposure may result in melanocyte depigmentation. *p-tert*-Butylphenol exhibits weak estrogenic activity *in vitro*. In a uterotrophic assay in immature female rats increased uterine weights were observed at all dose after subcutaneous injection of *p-tert*-butylphenol with a LOAEL of 100 mg/kg-day. In the same study, an initial increase followed by a dose-responsive decrease in uterine weights was observed when *p-tert*-butylphenol was administered in the presence of ethinyl estradiol. In a repeat dose reproductive / developmental screening test in rats, there were no adverse systemic, reproductive, or developmental effects observed at doses up to 200 mg/kg-day. In a two-generation reproduction study in rats using doses of 0, 70, 200, and 600 mg/kg-day, there was a significant decrease in body weight gain and food consumption in male and female parents, and reductions in litter size and pup weights in F1 and F2 offspring at doses of ≥ 200 mg/kg-day. Biologically significant, dose-dependent reduction of relative weights of ovaries and adrenal glands and increased vaginal epithelium atrophy was also seen in females at ≥ 200 mg/kg-day. The NOAEL for parental and developmental effects was 70 mg/kg-day. Oral *p-tert*-butylphenol caused forestomach hyperplasia and forestomach papillomas in male hamsters at a dietary dose of ~1,250 mg/kg-day for 20 weeks; a 5% reduction in mean body weight which was not biologically significant, and a 20% increase in liver weight, not associated with any histopathology was considered adaptive. Forestomach hyperplasia developed in rats given *p-tert*-butylphenol alone at ~750 mg/kg-day for 51 weeks, and treatment with *p-tert*-butylphenol promoted the development of forestomach tumors in rats if first initiated by treatment with N-methyl-N'-nitrosoguanidine. A significant 16% decrease in mean body weight was also observed. These effects of *p-tert*-butylphenol were attributed to cytotoxicity at high doses and are not considered relevant to human cancer risk assessment. *p-tert*-Butylphenol was not mutagenic or clastogenic in bacterial or mammalian cells with and without activation. A chromosomal aberration assay in Chinese hamster lung cells reported structural chromosomal aberrations in the presence of metabolic activation and polyploidy with and without activation; it was aneugenic when evaluated by the fluorescence *in situ* hybridization technique. The substance was negative when evaluated in an *in vivo* bone marrow micronucleus test in mice. When evaluated according to US EPA (2005) guidelines, there is *inadequate information to assess carcinogenic potential* due to the lack of standardized chronic exposure data.
CONCLUSIONS	Based on the available toxicity data, selection of the most sensitive endpoint as the critical effect, and the applied uncertainty factors, the derived drinking water action levels are protective of the public health.

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated contaminant ***p-tert*-butylphenol** in drinking water, as an extractant from one or more drinking water system components evaluated under NSF/ANSI/CAN 61 (2019), or as a contaminant in a drinking water treatment chemical evaluated under NSF/ANSI/CAN 60 (2019). 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 and are described in NSF/ANSI/CAN 600 (2019).

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 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 and is based on an adult intake of 0.032 L/kg-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:

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

or

$$\text{TAC (mg/L)} = \frac{\text{RfD (mg/kg-day)}}{0.032 \text{ L/kg-day}} \times 0.2 \text{ (RSC)}$$

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.