BENZYL ALCOHOL

CAS # 100-51-6

ORAL RISK ASSESSMENT DOCUMENT

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EXECUTIVE SUMMARY

Benzyl Alcohol – Oral Risk Assessment CAS # 100-51-6			
PARAMETER	**LEVEL**	**UNITS**	**CALCULATED:**
NOAEL (no-observed-adverse-effect level)	143	mg/kg-day	From a 2-year bioassay in mice.
Oral RfD (oral reference dose)	0.5	mg/kg-day	From a 2-year bioassay in mice.
TAC (total allowable concentration)	3	mg/L	For a 70 kg adult drinking 2 L/day, with a 20% source contribution for water
SPAC (single product allowable concentration)	0.3	mg/L	Based on 10 sources of benzyl alcohol in drinking water
STEL (short term exposure level)	10	mg/L	For a 10 kg child drinking 1 L/day

KEY STUDY	NTP. 1989. National Toxicology Program Toxicology and Carcinogenesis Studies of Benzyl Alcohol (CAS No. 100-51-6) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP Technical Report 343. National Institutes of Health Publication No. 89-2599.
CRITICAL EFFECT	The chronic study did not identify any statistically significant toxic responses to benzyl alcohol administration in either rats or mice to serve as the critical effect. At higher dose levels than were used in the chronic study, lethargy and progressively more severe neurotoxic responses with increasing dose were observed.
UNCERTAINTY FACTORS	• 10x for interspecies extrapolation, as there are insufficient data to establish a data-derived uncertainty factor • 10x for intraspecies extrapolation, as there are insufficient data to establish a data-derived uncertainty factor • 1x for duration of exposure, as a lifetime exposure study was used as the key study • 1x for LOAEL to NOAEL extrapolation, as a NOAEL was used • 3x for database deficiencies, as there are no two-generation reproduction or standard developmental toxicity studies The total uncertainty factor is, therefore, 300x.
TOXICITY SUMMARY	Studies in rats and mice dosed by gavage with benzyl alcohol at levels up to 2,000 mg/kg-day resulted in progressive lethargy, sedation, and death. No associated histopathology was seen in these animals. There was no evidence of any cumulative toxic effect of benzyl alcohol exposure based on studies in rats and mice of 16 days to 2 years duration. Benzyl alcohol was not mutagenic in standard *in vitro* tests, and there was no evidence of cancer in rats or in mice after two years of exposure. Benzyl alcohol is rapidly absorbed and metabolized to benzoic acid in humans. With the exception of rare, mild sensitization reactions, a 4.5 mg/kg-day intravenous dose appears to be without adverse effect in adults. Medical use of benzyl alcohol as a preservative in flushing solutions for intravascular catheters and injectable medications resulted in metabolic acidosis, gasping respiration, and some deaths in low birth weight newborns. The problem was recognized and the use of benzyl alcohol as a preservative was severely limited in fluids used for these patients.
CONCLUSIONS	Benzyl alcohol is a relatively nontoxic compound in adults and children. Care must be taken not to give newborns, especially those of birth weight ≤ 2,500 g, an inadvertent parenteral dose that exceeds their immature metabolizing capabilities. The TAC, SPAC, and STEL levels for oral benzyl alcohol exposure derived in this assessment are considered protective of human health.

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated contaminant **benzyl alcohol** in drinking water, as an extractant from one or more drinking water system components evaluated under NSF/ANSI 61 (2002), or as a contaminant in a drinking water treatment chemical evaluated under NSF/ANSI 60 (2002). 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), which assumes that there is a threshold for these endpoints that will not be exceeded if appropriate uncertainty factors (Dourson et al., 1996) are applied to the highest dose showing no significant adverse 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 from benchmark dose programs) can be used (U.S. EPA, 2001). 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 generally expressed in mg/kg-day. The RfD 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, 1999a).

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 multiplied by the 70 kg weight of an average adult assumed to drink 2 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 level (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.