

di-tert-BUTYL PEROXIDE
CAS # 110-05-4
ORAL RISK ASSESSMENT DOCUMENT



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EXECUTIVE SUMMARY

Di-tert-Butyl Peroxide – Oral Risk Assessment CAS # 110-05-4			
PARAMETER	LEVEL	UNITS	CALCULATED:
NOAEL (no-observed-adverse-effect level)	Not identified		
Oral RfD (oral reference dose)	Not identified		
TAC (total allowable concentration)	0.01	mg/L	Based on a qualitative risk assessment under NSF/ANSI 61 (2002).
SPAC (single product allowable concentration)	0.01	mg/L	Based on a qualitative risk assessment under NSF/ANSI 61 (2002).
STEL (short term exposure level)	0.01	mg/L	Based on a qualitative risk assessment under NSF/ANSI 61 (2002).
KEY STUDIES	Zeiger, E., B. Anderson, S. Haworth, T. Lawlor, and K. Mortelmans. 1988; and Microbiological Associates, Inc. 1996.		
CRITICAL EFFECT	There were insufficient data to identify a critical toxicological effect for this chemical.		
UNCERTAINTY FACTORS	Since a quantitative risk assessment was not performed, no uncertainty factors were used.		
TOXICITY SUMMARY	Di-tert-butyl peroxide was negative in two <i>Salmonella</i> reverse mutation assays. A mouse bone marrow micronucleus assay produced weakly positive results at one dose level in two assays, but results of one of the assays was within the range of historical control results. Di-tert-butyl peroxide was also a weak inducer of short-term indices of tumor promotion, although it was not a tumor promoter in a 60-week dermal study. However, lack of human data and of oral data in laboratory animals, as well as very weak positive responses in several genetic toxicity studies, indicate that <i>data are inadequate for an assessment of human carcinogenic potential</i> of di-tert-butyl peroxide. Floyd and Stokinger (1958) reported results of numerous experiments on the acute and subacute non-cancer effects of di-tert-butyl peroxide. The acute toxicity of the chemical is low, with an oral LD₅₀ > 25,000 mg/kg and an intraperitoneal LD₅₀ of 3,210 mg/kg. In a seven-week study during which five rats were dosed three times per week at one fifth of the oral LD₅₀ (5,000 mg/kg), one rat died during the second week and another during the third week. The three survivors failed to gain weight normally. Histopathology of rats dosed with organic peroxides revealed mild liver effects of questionable relevance to treatment. Non-lethal effects of orally administered di-tert-butyl peroxide are therefore limited to decreased body weight gain and possible liver effects, based on available studies. The number of toxicological endpoints examined was not sufficient to meet current guidelines for a repeated dose study from which a critical effect could be selected and an oral RfD calculated.		
CONCLUSIONS	The available data are inadequate to quantitatively describe the risk to human health posed by di-tert-butyl peroxide. Based on genetic toxicity and dermal tumor promotion data suggesting that the carcinogenic potential of the chemical is weak or absent, a qualitative risk level of 0.01 mg/L is adequately protective of human health based on a weight of evidence approach consistent with NSF/ANSI 61 (2002), Table A3.		

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated contaminant **di-tert-butyl peroxide** 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 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 LED₁₀ or BMDL from benchmark dose programs) can be used (U.S. EPA, 2001a). 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, 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 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.

Finally, a short-term-exposure level (STEL), at a higher level than the TAC, may be calculated for contaminants such as solvents expected to extract at higher levels from new product, but also expected to decay rapidly over time. The STEL is calculated from the NOAEL or the LED₁₀ of an animal study of 14- to 90-days duration, with uncertainty factors appropriate to the duration of the study. The contaminant level must decay to the TAC or below under static conditions, or to the SPAC or below under flowing conditions within 90 days, based on the contaminant decay curve generated from over-time laboratory extraction data.

Endpoints related to cancer are evaluated using modeling to fit a curve to the appropriate dose-response data (U.S. EPA, 1996a; U.S. EPA, 1999b). If there is sufficient evidence to use a non-linear model, the LED₁₀ or BMDL, divided by the anticipated exposure, is calculated to give a margin of exposure. If there is insufficient evidence to document non-linearity, a linear model drawing a straight line from the LED₁₀ or BMDL to zero, is used as a default. If a linear model (generally reflecting a genotoxic carcinogen) is used, a target risk range of 10⁻⁶ to 10⁻⁴ is considered by the U.S. EPA to be safe and protective of public health (U.S. EPA, 1991a). For the purposes of NSF/ANSI 60 (2002) and 61 (2002), the TAC is set at the 10⁻⁵ risk level, and the SPAC is set at the 10⁻⁶ risk level. Use of a higher risk level is not ruled out but would generally require documentation of a benefit to balance the additional risk.

The minimum data set for a quantitative risk assessment is described in NSF/ANSI 60 (2002) and 61 (2002) Annex A as consisting of a gene mutation assay, a chromosomal aberration assay, and a subchronic toxicity study. If the subchronic study is not available, a qualitative risk assessment may be performed under the requirements of Annex A, Table A3. These requirements specify that the TAC may be set at 10 µg/L (0.01 mg/L) if the weight of evidence review of the required genetic toxicity studies and all other relevant toxicity data concludes that the chemical is not a hazard to human health at that level. Further, the TAC may be set up to 50 µg/L (0.05 mg/L) if, in addition, there is a repeated dose study of less than subchronic duration that is of suitable quality.

The RfD, TAC, SPAC, and STEL values derived in this document are based on available health effects data and are intended for use in determining compliance of products with the requirements of NSF/ANSI 60 (2002) and 61 (2002). Application of these values to other exposure scenarios should be done with care and with a full understanding of the derivation of the values and of the comparative magnitude and duration of the exposures. These values do not have the rigor of regulatory values, as data gaps are generally filled by industry or government studies prior to regulation. Data gaps introduce uncertainty into an evaluation and require the use of additional uncertainty factors to protect public health.

The general guidelines for this risk assessment include those from the National Research Council (1983) and from The Presidential/Congressional Commission on Risk Assessment and Risk Management (1997a, 1997b). Other guidelines used in the development of this assessment may include the following: Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), draft revised Guidelines for

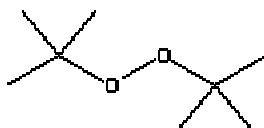
Carcinogen Risk Assessment (U.S. EPA, 1999b), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991b), Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996b), Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1998), Recommendations for and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988), and Health Effects Testing Guidelines (OPPTS series 870, U.S. EPA 1996c; 40 CFR Part 798, U.S. EPA, 2002a).

The literature search strategy employed for this compound was based on the Chemical Abstract Service Registry Number (CASRN) and at least one common name. As a minimum, the following data banks were searched:

- ChemID Plus
- Registry of Toxic Effects of Chemical Substances (RTECS)
- Hazardous Substances Data Bank (HSDB)
- GENE-TOX
- Environmental Mutagen Information Center (EMIC)
- Developmental and Reproductive Toxicology (DART/ETIC)
- TOXLINE
- Toxicology Literature from Special Sources (TOXLIT)
- CANCERLIT
- Chemical Carcinogenesis Research Information System (CCRIS)
- Medline (via PubMed)
- Integrated Risk Information System (IRIS)
- Syracuse Research Corporation Online Toxic Substance Control Act Database (TSCATS)

2.0 PHYSICAL AND CHEMICAL PROPERTIES

Di-tert-butyl peroxide is an organic peroxide with synonyms of tert-butyl peroxide, bis(1,1-dimethylethyl)peroxide (ChemFinder, 2002), bis(tert-butyl)peroxide, di-tert-butyl peroxyde, di-tert-butylperoxid, perossido di butile terziario, peroxide de butyle tertiaire, di-tert-butyl hydroperoxide, and t-butyl peroxide (NIST, 2001). It has trade or common names of TBP, Cadox, DTBP (ChemFinder, 2002), Trigonox b, Cadox tbp, and UN 2102 (NIST, 2001). It has the following structure, and physical and chemical properties listed in Table 1:



Di-tert-butyl peroxide is one of the more stable peroxides, having a half-life of 10 hours at 126 °C (Gimenez-Conti et al., 1991). It is expected to form the butoxy free radical as the primary radical (Gimenez-Conti et al., 1991). However, the butoxy free radical is reported to be unstable (HSDB, 2002) and study of its photodecomposition resulted in identification of acetone, ethane, carbon monoxide, methane, biacetyl, and tert-butyl alcohol (Volman and Graven, 1953). Acetone