BENZOPHENONE

CAS # 119-61-9

ORAL RISK ASSESSMENT DOCUMENT

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EXECUTIVE SUMMARY

BENZOPHENONE – Oral Risk Assessment CAS# 119-61-9			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
LOAEL (lowest observed adverse effect level)	41	mg/kg-day	From a two-year feeding study in B6C3F1 mice
$LOAEL_{HED}$ (human equivalent LOAEL dose)	6.1	mg/kg-day	From the LOAEL with body weight scaling to the ¾ power
Oral RfD (oral reference dose)	0.02	mg/kg-day	From the $LOAEL_{HED}$ in B6C3F1 mice with a 300x total uncertainty factor
TAC (total allowable concentration)	0.1	mg/L	Based on an adult intake rate of 0.032 L/kg-day using a 20% relative source contribution for drinking water
SPAC (single product allowable concentration)	0.01	mg/L	From the TAC, using the default 10 sources of benzophenone in drinking water
STEL (short term exposure level)	0.3	mg/L	From a two-generation reproduction study adjusted for an infant intake rate of 0.228 L/kg-day

EXPOSURE SUMMARY	The general population may be exposed to benzophenone through food and drinking water, since it is used as a direct and indirect food additive and as a UV stabilizer in coatings with water contact, respectively.
KEY STUDIES	NTP (National Toxicology Program). 2006. Toxicology and carcinogenesis studies of benzophenone (CAS No. 119-61-9) in F344/N rats and B6C3F1 mice. NTP TR 533. NIH Publication No. 06-4469. National Toxicology Program, Research Triangle Park, NC. Published by Rhodes et al., 2007. Hoshino, N., E. Tani, Y. Wako, and K. Takahashi. 2005. A two-generation reproductive toxicity study of benzophenone in rats. J Toxicol Sci. 30(Spec No.):5-20.
CRITICAL EFFECTS	The critical effect of long-term benzophenone ingestion was considered increased syncytial alteration and chronic active inflammation of hepatocytes secondary to chronic enzyme induction in male B6C3F1 mice. Splenic lymphoid follicular hyperplasia in male and female B6C3F1 mice and splenic cell proliferation in female B6C3F1 mice were also observed as critical effects. Increased severity of chronic progressive nephropathy in rats occurred at slightly higher but comparable point of departure.
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD include: • 3x for interspecies extrapolation • 10x for intraspecies extrapolation • 1x for subchronic to chronic extrapolation • 10x for LOAEL to NOAEL (syncytial alteration; 1x for splenic endpoints) • 1x for database deficiencies The total uncertainty factor is therefore 300x (syncytial alteration; 30x for splenic endpoints)
TOXICITY SUMMARY	Human data were not identified. The target organs after dietary exposure in F344 rats and B6C3F1 mice were the kidneys, liver, spleen and hematopoietic system. Dietary benzophenone exacerbated the severity of chronic progressive nephropathy. While there is evidence that liver tumors in mice resulting from chronic nuclear receptor agonism (CAR and PXR) may not be human relevant, scientific consensus is lacking and thus the liver lesions observed in mice and rats that are known to be a consequence of chronic enzyme induction (e.g. syncytial hepatocytes, necrosis, inflammation) are considered human relevant precursors to liver tumor formation after chronic exposure. The low incidence of histiocytic sarcomas that originated from the liver after prolonged high dietary doses was likely secondary to systemic toxicity. The modest (≤10%), decrease in anogenital distance in F_1 female but not F_0 female or male offspring suggests a potential weak estrogenic mode of action but is uncertain due to the lack of dose-response. *In vitro* endocrine assays indicate weak estrogen receptor activity for benzophenone and *p*-hydroxybenzophenone, and androgen receptor antagonism for *p*-hydroxybenzophenone with estimated human equivalent administered doses equivalent to or higher than the observed systemic reference doses. The decreased incidence of mammary tumors and thyroid hyperplasia in female rats was likely secondary to reduced body weight rather than the endocrine disruption potential of the major metabolite, *p*-hydroxybenzophenone. There is *suggestive evidence of carcinogenic potential* based on hepatic and hematopoietic tumors in mice. However, the human relevant mode of action (liver lesions as a result of chronic enzyme induction) is expected to have a threshold based on the lack of genotoxicity for benzophenone and thus is of low risk to humans at environmentally-encountered exposure levels. Since a reliable benchmark dose (BMD) estimate for chronic active inflammation and syncytial hepatocytes in mice could not be obtained due to the nature of the dataset, the point of departure for the RfD was the $LOAEL_{HED}$ of 6.1 mg/kg-day. The STEL was based on a $BMDL_{10HED}$ of 2 mg/kg-day for proximal tubule epithelial regeneration in F_0 adult male SD rats from a two-generation reproduction study.
CONCLUSIONS	Based on selection of the most sensitive critical effects in the most sensitive sex and species, the drinking water levels are protective of public health. Additional toxicokinetic and mode of action information to establish key events in target tissues would increase the confidence and reduce the uncertainty in the risk levels derived herein.

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated contaminant **benzophenone** 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.