ADIPIC ACID

CAS # 124-04-9

ORAL RISK ASSESSMENT DOCUMENT

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EXECUTIVE SUMMARY

Adipic Acid – Oral Risk Assessment CAS # 124-04-9			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
NOAEL (no-observed-adverse-effect level)	400	mg/kg-day	From 33-week and chronic repeated dose studies in rats
Oral RfD (oral reference dose)	4	mg/kg-day	From 33-week and chronic repeated dose studies in rats with a 100x total uncertainty factor
TAC (total allowable concentration)	30	mg/L	For a 70 kg adult drinking 2 L/day using a 20% relative source contribution for drinking water
SPAC (single product allowable concentration)	3	mg/L	From the TAC, using the default 10 sources of adipic acid in drinking water
STEL (short term exposure level)	100	mg/L	From a 19-week repeated dose study, for a 10 kg child drinking 1 L/day

KEY STUDY	Lang, K., and Bartsch, A-R. 1953. Über den stoffwechsel und die verträglichkeit der adipinsäure. Biochem Zeitschrift 323:462-468; with support from Horn, H.L., E.G. Holland, and L.W. Hazelton. 1957. Safety of adipic acid as compared with citric and tartaric acid. Agric Food Chem 5(10):759-762.
CRITICAL EFFECT	A weight of evidence NOAEL was established based on effects including reduced survival, diarrhea, decreased body weight during growth, and intestinal and liver pathology.
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD include: • 10x for interspecies extrapolation • 10x for intraspecies extrapolation • 1x for subchronic to chronic extrapolation • 1x for LOAEL to NOAEL • 1x for database deficiencies The total uncertainty factor is therefore 100x.
TOXICITY SUMMARY	Adipic acid has been used as a direct food additive for several decades. The JECFA Acceptable Daily Intake (ADI) is 0-5 mg/kg. Bolus oral doses of up to 10 g (~140 mg/kg for a 70 kg adult) adipic acid were tolerated by humans. Several repeated dose oral studies in rats, from five weeks to lifetime duration, have been conducted on adipic acid resulting in NOAEL values in the range of 400-3,000 mg/kg-day. Decreased body weight was observed in most studies with survival, diarrhea, chronic intestinal inflammation, regeneration activity in the principal part of the kidney, and enlargement of liver cell nuclei and occasionally whole cell volume observed in some instances at high doses. Some of these effects may have been related to administration of adipic acid in a wheat/milk diet, or to acidity of the chemical. Although the feeding studies were old and did not include all the endpoints required under current guidelines, few adverse effects were noted in the examined hematology and clinical parameters, or in the macroscopic and microscopic examination of many organs and tissues after lifetime exposure. The limited correlation of toxicity with exposure duration likely resulted from the rapid (within a few hours) and extensive (~ 70%) metabolism of adipic acid to carbon dioxide. Adipic acid is normally metabolized by the mammalian fatty acid β-oxidation pathway. Developmental toxicity studies in rats, mice, hamsters, and rabbits have been performed with adipic acid. No adverse effects were noted in dams or fetuses at maternal doses approaching 300 mg/kg-day given during the period of organogenesis. Adipic acid was not mutagenic in *Salmonella typhimurium* reverse mutation assays. Chromosomal aberration assays, although uniformly negative, had sufficient protocol deficiencies based on current guidelines to preclude a conclusion regarding clastogenicity. A chronic study in rats did not detect any treatment-related tumors, but used an inadequate number of animals and assessed too few endpoints to meet current guidelines. Due to deficiencies in the only available chronic study as well as in the genetic toxicity studies, the *data are inadequate for an assessment of human carcinogenic potential* under current regulatory guidelines.
CONCLUSIONS	Based on the studies reviewed, the metabolic pathway for adipic acid, and the uncertainty factors applied, the TAC, SPAC, and STEL drinking water action levels derived in this document are protective of public health.

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated contaminant **adipic acid** in drinking water, as an extractant from one or more drinking water system components evaluated under NSF/ANSI 61 (2005), or as a contaminant in a drinking water treatment chemical evaluated under NSF/ANSI 60 (2005). 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, 2003a). 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, 2003b).

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.