2-CHLORO-1,4-BENZENEDIAMINE

CAS # 615-66-7

ORAL RISK ASSESSMENT DOCUMENT

NSF International
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EXECUTIVE SUMMARY

2-CHLORO-1,4-BENZENEDIAMINE – Oral Risk Assessment CAS # 615-66-7			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
$BMDL_{10}$ (95% confidence limit at 10% response level)	15	mg/kg-day	From a chronic feeding study in rats
Oral RfD (oral reference dose)	0.05	mg/kg-day	From the $BMDL_{10}$ with a 300x total uncertainty factor
TAC (total allowable concentration)	0.3	mg/L	For a 70 kg adult drinking 2 L/day, with a 20% relative source contribution for drinking water
SPAC (single product allowable concentration)	0.03	mg/L	From the TAC, assuming 10 potential sources of 2-chloro-1,4-benzenediamine in drinking water
STEL (short term exposure level)	0.5	mg/L	From a chronic rat feeding study and based on a 10 kg child drinking 1 L/day.

KEY STUDY	NTP/NCI (National Toxicology Program/National Cancer Institute). 1978a. Bioassay of 2-Chlorophenylenediamine Sulfate for Possible Carcinogenicity. Technical Report Series No. 113 DHEW Publication No. (NIH) 78-1368, U.S. Department of Health Education and Welfare, National Cancer Institute, Bethesda, MD 20014.
CRITICAL EFFECT	Transitional cell hyperplasia of the kidney and renal pelvis in male rats.
UNCERTAINTY FACTORS	Uncertainty factors applied in calculating the oral RfD are as follows: • 10x for interspecies extrapolation • 10x for intraspecies extrapolation • 1x for extrapolation from a less-than-lifetime study to lifetime duration • 1x for extrapolation from a LOAEL to a NOAEL • 3x for database deficiencies. The total uncertainty factor is, therefore, 300x.
TOXICITY SUMMARY	No oral data in humans were available. 2-Chloro-1,4-benzenediamine sulfate did not cause a statistical increase in any tumor type in rats or mice after chronic dietary administration. However, transitional cell hyperplasia of the kidney and renal pelvis was observed in male and female rats at increased incidence compared to controls. The incidence of renal epithelial hyperplasia was dose related in males, but a NOAEL could not be identified. Hepatic focal necrosis was observed in male mice at an increased incidence compared to controls, but the incidence was not dose-related. No kinetic and limited metabolism studies in humans and laboratory animals were identified for 2-chloro-1,4-benzenediamine. In the *Salmonella typhimurium* reverse mutation assay, 2-chloro-1,4-benzenediamine sulfate produced dose-related increases in revertant colonies of more than twice the background level at higher doses but in the absence of cytotoxicity. 2-Chloro-1,4-benzenediamine was negative in the *in vivo* alkaline single cell assay (Comet assay) and in the alkaline elution assay for the detection of hepatic DNA damage. The limited genotoxicity data identified for 2-chloro-1,4-benzenediamine or its sulfate salt precluded definitive conclusions regarding its genotoxic potential. However, structure-activity relationship studies suggest that the genotoxic or carcinogenic potential of 2-chloro-1,4-benzenediamine is less than that of 4-chloro-1,2-benzenediamine or 4-chloro-1,3-benzenediamine. Further, no statistical increases in tumors were observed after chronic feeding. The *data are inadequate for an assessment of human carcinogenic potential* of 2-chloro-1,4-benzenediamine or its sulfate salt. For the purposes of this risk assessment, 2-chloro-1,4-benzenediamine was considered a non-carcinogen. A NOAEL could not be identified for the critical effect of transitional cell hyperplasia of the kidney and renal pelvis in male rats. A $BMDL_{10}$ of 15 mg/kg-day was determined, since the incidence was dose-related. This effect was considered non-neoplastic, since the rats were treated for at least 24 months, as recommended by current U.S. EPA health effects testing guidelines, and the effect did not progress into renal tumors.
CONCLUSIONS	The drinking water action levels developed in this risk assessment are protective of public health since they were developed based on chronic oral data for 2-chloro-1,4-benzenediamine sulfate from the most sensitive endpoint and laboratory animal species.

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated contaminant **2-chloro-1,4-benzenediamine** in drinking water, as an extractant from one or more drinking water system components evaluated under NSF/ANSI 61 (2004), or as a contaminant in a drinking water treatment chemical evaluated under NSF/ANSI 60 (2004). 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) 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.