1,2-EPOXYBUTANE – Oral Risk Assessment CAS # 106-88-7			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
$BMDL_{05}$ (95% confidence limit at 5% response level)	8.9	mg/kg-day	From a chronic inhalation study in rats
10^{-5} Cancer Risk Level	0.002	mg/kg-day	From the $BMDL_{05}$
Oral Slope Factor	0.01	$mg/kg\text{-}day^{-1}$	From the $BMDL_{05}$
Drinking Water Unit Risk (at the 1 x 10^{-5} cancer risk level)	0.02	$\mu g/L^{-1}$	From the oral slope factor
TAC (total allowable concentration)	0.06	mg/L	For a 70 kg adult drinking 2 L/day
SPAC (single product allowable concentration)	0.006	mg/L	From the TAC, assuming 10 potential sources of 1,2-epoxybutane in drinking water
STEL (short term exposure level)	0.06	mg/L	The STEL is set equal to the TAC for a chemical presumed to be a linear carcinogen.

EXPOSURE SUMMARY	Human exposure to 1,2-epoxybutane may occur in its production and use as a monomer, chemical intermediate, or stabilizer. Exposure can also occur through drinking water, since it has been detected in the extract water of products tested according to NSF/ANSI 61 (2010) at normalized concentrations up to 30 ppb.
KEY STUDY	Dunnick, J.K., S.L. Eustis, W.W. Piegorsch and R.A. Miller. 1988. Respiratory tract lesions in F344/N rats and B6C3F1 mice after inhalation exposure to 1,2-epoxybutane. Toxicol. 50(1):69-82. NTP (National Toxicology Program). 1988. Toxicology and Carcinogenesis Studies of 1,2-Epoxybutane in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Report #329, NIH Publication # 88-2585.
CRITICAL EFFECT(S)	Portal of entry irritation, inflammation, cytotoxicity were observed in F344 rats that inhaled 1,2-epoxybutane and these effects progressed to tumors after chronic inhalation.
UNCERTAINTY FACTORS	No uncertainty factors were applied in this risk assessment, since an oral RfD was not determined. The carcinogenic effects observed in chronic animal studies were analyzed using linear extrapolation.
TOXICITY SUMMARY	Although oral data are preferred for the derivation of drinking water levels, data for 1,2-epoxybutane were limited to inhalation or dermal bioassays. Inflammatory lesions of the respiratory tract of F344 rats and B6C3F1 mice were associated with an increased incidence of nasal papillary adenomas and alveolar/bronchiolar adenomas and/or carcinomas in rats after chronic inhalation of 1,2-epoxybutane. Inhalation of 1,2-epoxybutane during pregnancy was associated with maternal toxicity in rats and rabbits in the absence of signs of developmental toxicity. The weight of evidence suggests that 1,2-epoxybutane is genotoxic *in vitro*. Limited *in vivo* genotoxicity data were identified. Recognizing the lack of oral data, the possibility that equivalent portal of entry tumors would be observed after oral exposure can not be discounted. The increased incidence of nasal but not alveolar/bronchiolar atrophy in treated rats may explain the lack of an increase in nasal carcinomas in rats and suggests that the toxic moiety that reached the alveolar/bronchiolar epithelium was sufficient to initiate the progression of a malignant response but insufficient to induce cell death. Since a genotoxic mode of action cannot be excluded due to positive *in vitro* genotoxicity data, it was assumed that a dual mode of action involving both DNA-reactive and cytotoxic effects of 1,2-epoxybutane contribute to respiratory tumor development. Thus, a 10^{-5} cancer risk level based on respiratory tumor development was extrapolated from the chronic inhalation $BMDL_{05}$ of 8.9 mg/kg-day based on the combined incidence of alveolar/bronchiolar adenomas and carcinomas in male rats. The human equivalent dose used to estimate the benchmark dose level conservatively assumed a regional gas dose ratio of 1 and 50% inhalation absorption due to the lack of kinetic data to quantitatively estimate these parameters. The 10^{-5} cancer risk level is considered to be representative and protective of potential portal of entry carcinogenicity after chronic oral exposure.
CONCLUSIONS	Chronic exposure to 1,2-epoxybutane is associated with tumor development at the portal of entry. The weight of evidence supports that 1,2-epoxybutane demonstrates *suggestive evidence of carcinogenic potential*. The drinking water action levels developed in this risk assessment are protective of public health since they were based on chronic data from the most sensitive endpoint and laboratory animal species. Additional information regarding the toxicity and kinetics of 1,2-epoxybutane after oral exposure would increase the confidence and reduce the uncertainties associated with the risk levels derived herein.