EXECUTIVE SUMMARY

γ-Butyrolactone – Oral Risk Assessment CAS # 96-48-0			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
LOAEL (lowest-observed-adverse-effect level)	12.5	mg/kg	From a single dose human neurotoxicity study
Oral RfD (oral reference dose)	0.1	mg/kg-day	From a single dose human neurotoxicity study
TAC (total allowable concentration)	4	mg/L	For a 70 kg adult drinking 2 L/day, with a data derived Relative Source Contribution of 0.14 mg/day
SPAC (single product allowable concentration)	0.4	mg/L	For a 70 kg adult drinking 2 L/day
STEL (short term exposure level)	4	mg/L	Calculation for a 10 kg child drinking 1 L/day superseded by the TAC

KEY STUDY	Ferrara, S.D., R. Giorgetti, S. Zancaner, R. Orlando, A. Tagliabracci, F. Cavarzeran, P. Palatini. 1999. Effects of Single Dose of Gamma-Hydroxybutyric Acid and Lorazepam on Psychomotor Performance and Subjective Feelings in Healthy Volunteers. Eur J Clin Pharmacol 54: 821-827.
CRITICAL EFFECTS	Neurotoxic effects in humans, including dizziness, a sense of dullness, uncontentedness, and decreased anxiety.
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD include: • 1x for interspecies extrapolation • 10x for intraspecies extrapolation • 3x for extrapolation from a LOAEL to a NOAEL • 1x for study duration • 3x for database deficiencies The total uncertainty factor is therefore 100x.
TOXICITY SUMMARY	γ-Butyrolactone is metabolized in the body within minutes to γ-hydroxybutyrate; therefore, its toxicity can be assessed based on that of both γ-butyrolactone and γ-hydroxybutyrate. The critical effects in humans associated with γ-hydroxybutyrate administration involve changes in behavior. The critical study evaluated behavioral changes associated with oral administration of 12.5 mg/kg or 25 mg/kg bolus doses of γ-hydroxybutyrate to human volunteers. In the 25 mg/kg dose group, 66% of subjects reported adverse side effects of dizziness and a sense of dullness, while 50% of subjects in the 12.5 mg/kg dose group reported these effects. Also, changes in mood were observed at both doses. Based on this, a LOAEL of 12.5 mg/kg γ-hydroxybutyrate was established. Another human study found that volunteers reported feeling drowsy at doses ranging from 35 to 63 mg/kg γ-hydroxybutyrate. Bolus doses greater than 50 mg/kg led to coma. This second study showed evidence that γ-hydroxybutyrate administration leads to neurophysiological abnormalities, as inconsistent electroencephalographic trends were observed. Based on drowsiness reported at all dose levels, a LOAEL of 35 mg/kg was established. Abnormal electroencephalographic patterns indicative of generalized nonconvulsive seizures, in addition to behavioral and body temperature alterations, were observed in single dose neurotoxicity studies with monkeys and rats. In repeated dose rat and mouse studies, lethality, reduced body weight gain, reduced body weight, and behavioral alterations were observed. Reduced testicular weight was observed in a 3-week reproductive toxicity study with male rats. Several genotoxicity studies demonstrated that γ-butyrolactone is not genotoxic in standard short-term tests. There was equivocal evidence that γ-butyrolactone elicits carcinogenic effects in male mice, with a statistically significant increase in the occurrence of focal hyperplasia of the adrenal medulla in male $B6C3F_1$ mice orally administered 262 mg/kg-day γ-butyrolactone. However, there was no evidence of carcinogenicity in male or female rats or in female mice. Subsequent review of the mouse data for γ-butyrolactone by the National Toxicology Program concluded that this chemical was unlikely to be carcinogenic.
CONCLUSIONS	Exposure to γ-butyrolactone elicits neurotoxic effects in humans, monkeys, and rats. The critical acute study for this risk assessment was chosen because it is a human study and because the neurotoxic effects induced by γ-hydroxybutyrate occurred at doses lower than any dose used in any of the repeated-dose animal studies. Based on the uncertainty factors used to account for intraspecies extrapolation, database deficiencies, and extrapolation from a LOAEL to a NOAEL, the drinking water action levels derived in this risk assessment are considered protective of public health.