EXECUTIVE SUMMARY

2-Ethylhexanoic Acid – Oral Risk Assessment CAS # 149-57-5			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
NOAEL (no-observed-adverse-effect level)	100	mg/kg-day	From developmental toxicity studies in rats and rabbits.
Oral RfD (oral reference dose)	0.1	mg/kg-day	From a developmental toxicity study in rats.
TAC (total allowable concentration)	0.7	mg/L	From a developmental toxicity study in rats, for a 70 kg adult drinking 2L/day with a 20% relative source contribution for drinking water.
SPAC (single product allowable concentration)	0.07	mg/L	From the TAC, with the default 10 drinking water sources.
STEL (short term exposure level)	10	mg/L	From a developmental toxicity study in rats, for a 10 kg child drinking 1L/day.

KEY STUDY	Hendrickx, A.G., P.E. Peterson, R.W. Tyl, L.C. Fisher, L.J. Fosnight, M.F. Kubena, M.A. Vrabanic, and G.V. Katz. 1993. Assessment of the developmental toxicity of 2-ethylhexanoic acid in rats and rabbits. Fundam Appl Toxicol 20:199-209.
CRITICAL EFFECT	Multiple developmental findings in rats, and maternal toxicity in rabbits.
UNCERTAINTY FACTORS	Uncertainty factors applied in calculating the oral RfD are as follows: • 10x for interspecies extrapolation • 10x for intraspecies extrapolation • 10x for extrapolation from a less-than-lifetime study to lifetime duration • 1x for extrapolation from a LOAEL to a NOAEL • 1x for database deficiencies. The total uncertainty factor is therefore 1000x.
TOXICITY SUMMARY	Oral 2-ethylhexanoic acid produced signs of liver effects in two-week and subchronic studies in F-344 rats and B6C3F1 mice. These effects included increased absolute and/or relative liver weight, hepatocyte hypertrophy, and changes in cholesterol and triglyceride levels and were most likely due to peroxisome proliferation, which was positively identified. Peroxisome proliferation and activation of PPARα were given limited weight in this risk assessment, because humans and non-human primates do not respond in this manner while some rodents are highly susceptible. Inhibition of the urea cycle was suggested in one occupational report and in a 20-day rat study, but no adverse consequences of urea cycle disturbance were observed in subchronic rat or mouse studies. Oral 2-ethylhexanoic acid was a developmental toxin in rats, producing an increased incidence of skeletal malformations and variations, as well as dilated lateral ventricles of the brain with or without tissue compression. Clubfoot was observed in another rat study. Developmental toxicity of 2-ethylhexanoic acid had a weak relationship to maternal zinc status in rats. This relationship was taken into account, along with potential urea cycle disturbances, in selection of the intraspecies uncertainty factor, as both zinc status and urea cycle efficiency of the general population vary. Maternal deaths were seen in rabbits, consistently at doses ≥ 500 mg/kg-day and occasionally at lower doses, in the absence of fetotoxicity. Developmental toxicity was specific to the (R)-enantiomer, the (S)-enantiomer being largely inactive when tested in mice. Stereospecificity was not incorporated into this risk assessment because potential drinking water exposure is to the optically inactive 1:1 racemic mixture. 2-Ethylhexanoic acid was not mutagenic in reverse mutation assays but produced a very small but statistically significant increase in sister-chromatid exchanges. No chromosomal aberration or micronucleus assays were located. Results of chronic oral studies on 2-ethylhexanol, metabolized in part to 2-ethylhexanoic acid, were considered negative in rats and male mice. A statistically significant increase in hepatocellular carcinomas was observed in female mice when compared with the concurrent 0.005% aqueous polyoxyl-35 castor oil vehicle control group but not when compared with a concurrent water control group, leading the authors to conclude that the carcinogenic potential of 2-ethylhexanoic acid in female mice was weak or equivocal. The postulated mode of action was peroxisome proliferation. Based on the lack of human epidemiology data and of chronic studies of 2-ethylhexanoic acid in laboratory animals, the *data are inadequate for an assessment of human carcinogenic potential* under U.S. EPA (2005) guidelines.
CONCLUSIONS	Based on the selected critical effects, consideration of the entire data set, and the uncertainty factors applied, the TAC, SPAC, and STEL levels are protective of the public health.