EXECUTIVE SUMMARY

TRIS (2-BUTOXYETHYL) PHOSPHATE – Oral Risk Assessment CAS # 78-51-3			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
$BMDL_{10}$ (10% Benchmark Dose Level)	51	mg/kg-day	From an 18-week dietary study in Sprague-Dawley rats
Human Equivalent $BMDL_{10}$	15	mg/kg-day	From the $BMDL_{10}$ with body weight scaling to the ¾ power
Oral RfD (oral reference dose)	0.05	mg/kg-day	From the human equivalent $BMDL_{10}$ with a 300x total uncertainty factor
TAC (total allowable concentration)	0.4	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)	0.04	mg/L	From the TAC, using the default 10 sources of tris (2-butoxyethyl) phosphate in drinking water
STEL (short term exposure level)	2	mg/L	From a 14-week dietary study, for a 10 kg child drinking 1 L/day

EXPOSURE SUMMARY	The principle route of general population exposure to tris (2-butoxyethyl) phosphate is through food and drinking water since it is used as an indirect food additive and is an ingredient in synthetic rubbers, respectively.
KEY STUDIES	Reyna, M.S. and D.G. Thake. 1987a. Eighteen Week Feeding Study of Tributoxyethyl Phosphate (TBEP) Administered to Sprague-Dawley Rats. Study Number 84103. Monsanto Environmental Health Laboratory, St Louis, Mo. Submitted to the U.S. EPA under TSCA Section 8D. EPA Document No. 86-910000297; OTS0530087. Saitoh, M., T. Umemura, Y. Kawasaki, J. Momma, Y. Matsushima, M. Matsumoto, N. Eshita, K. Isama, and M. Kaniwa. 1994. [Subchronic toxicity study of tributoxyethyl phosphate in Wistar rats]. Eiser Shikensko Hokoku (Japanese). 112: 27–39.
CRITICAL EFFECT(S)	Increased liver weights and periportal hepatocyte hypertrophy occurred in rats repeatedly fed tris (2-butoxyethyl) phosphate for up to 18 weeks. Reductions in blood cholinesterase were inconsistently observed with reductions in erythrocyte or brain acetylcholinesterase and thus may not be toxicologically significant.
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD include: • 3x for interspecies extrapolation • 10x for intraspecies extrapolation • 3x for subchronic to chronic extrapolation • 1x for LOAEL to NOAEL • 3x for database deficiencies The total uncertainty factor is therefore 300x.
TOXICITY SUMMARY	Due to the lack of oral toxicity data in humans, an oral risk assessment for tris (2-butoxyethyl) phosphate relies on data in laboratory animals. Increased liver weights and periportal hepatocyte hypertrophy were observed in rats after repeated oral exposure. Reductions in plasma or serum cholinesterase in rats were not consistently observed with reductions in erythrocyte or brain acetylcholinesterase and thus may not be toxicologically significant. While there were no kinetic or metabolism data to explore gender-related differences in toxicity, greater plasma butyrylcholinesterase and hepatic enzyme activity in female rats may contribute to the increased susceptibility of exposed male rats to liver lesions (i.e. due to lower hepatic metabolism and plasma cholinesterase activity). Although the liver effects may represent an adaptive response to metabolizing high tris (2-butoxyethyl) phosphate doses since they were not observed or were attenuated in recovery studies, the lack of a chronic study or metabolism data precludes assessment of key events for this mode of action. The weight of evidence suggests that tris (2-butoxyethyl) phosphate is not genotoxic *in vitro*. *In vivo* genotoxicity data were not identified. Tris (2-butoxyethyl) phosphate was not mutagenic or associated with chromosomal aberrations in standardized assays *in vitro*. Due to the lack of a two-year bioassay, there is *inadequate information to assess carcinogenic potential*. Effects on conduction nerve velocity in rats were inconsistent and thus difficult to interpret. Compared to the $BMDL_{20}$ for cholinesterase inhibition (80 mg/kg-day), there was a better statistical fit and thus higher degree of confidence in the $BMDL_{10}$ for hepatocyte hypertrophy (51 mg/kg-day) as the point of departure for the RfD. Allometric scaling was applied to the $BMDL_{10}$ to estimate a human equivalent $BMDL_{10}$ of 15 mg/kg-day. The human equivalent dose estimate could be further refined if chemical-specific toxicokinetic data become available.
CONCLUSIONS	Additional data to substantiate an adaptive liver response (which may be less relevant to humans) are needed to determine the human relevance of the hepatic changes in rats fed tris (2-butoxyethyl) phosphate.