EXECUTIVE SUMMARY

N-Nitrosomorpholine – Oral Risk Assessment CAS # 59-89-2			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
Human Equivalent $BMDL_{10}$ (95% confidence limit at 10% response level)	0.025	mg/kg-day	From the incidence of hepatocellular carcinoma in female rats in a chronic study, with allometric body weight$^{3/4}$ scaling
Oral Slope Factor	4.0	mg/kg-day^{-1}	From the human equivalent $BMDL_{10}$
Oral Slope Factor – life-stage adjusted	10	mg/kg-day^{-1}	From the human equivalent $BMDL_{10}$, adjusted for life stage
Drinking Water Unit Risk – life-stage adjusted (at the 1 x 10^{-5} cancer risk level)	2.9 x 10^{-4}	µg/L $^{-1}$	From the oral slope factor, adjusted for life stage
TAC – life-stage adjusted (total allowable concentration)	40	ng/L	For a 70 kg adult drinking 2 L/day, adjusted for life stage
SPAC – life-stage adjusted (single product allowable concentration)	4	ng/L	From the TAC, assuming 10 potential sources of *N*-nitrosomorpholine in drinking water
STEL – life-stage adjusted (short term exposure level)	40	ng/L	The STEL is set equal to the TAC for a chemical presumed to be a linear carcinogen

EXPOSURE SUMMARY	Exposure to *N*-nitrosomorpholine is mainly incidental to use of tobacco and in occupations where rubber and rubber chemicals are manufactured, processed, stored or sold. Exposure potentially occurs from ingestion of certain foods and drinking water, and *N*-nitrosomorpholine may be formed endogenously from nitrosation of dietary morpholine (HSDB, 2012).
KEY STUDY	Lijinsky, W., R.M. Kovatch, C.W. Riggs and P.T. Walters. 1988. Dose-response study with *N*-nitrosomorpholine in drinking water of F-344 rats. Cancer Res. 48(8): 2089-2095.
CRITICAL EFFECT	Hepatocellular neoplasias were observed at an increased incidence compared to controls in female F344 rats that received *N*-nitrosomorpholine in drinking water for 100 weeks.
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, and risk values were modified to adjust for the potential differential risk of early postnatal-lifestage exposure.
TOXICITY SUMMARY	Epidemiological studies of rubber industry workers support an association between exposure to nitrosamines, including *N*-nitrosomorpholine, and cancers of the esophagus, oral cavity, and pharynx. *N*-Nitrosomorpholine is among approximately 300 *N*-nitrosamines known to be carcinogenic in animals. Studies have been designed to evaluate tumor development in rats, mice, and hamsters, and associated pathological changes, as well as the influence of dose rate, dose route, and total dose. The principal target organs for carcinogenicity following oral exposure are the liver, esophagus, nasal cavity, lung, and kidneys. Animal studies have also examined noncancer effects on the liver from single or repeated exposure. *N*-Nitrosomorpholine is mutagenic to bacterial and mammalian cells *in vitro*, induces chromosomal aberrations *in vitro*, and hepatic micronuclei were induced in rats *in vivo* in the presence of mitogenic stimulation. *N*-Nitrosomorpholine generated reactive oxygen species and oxidative DNA damage *in vitro*. *In vivo*, unscheduled DNA synthesis was induced in rats treated orally with *N*-nitrosomorpholine, and there was no increase in 8-hydroxydeoxyguanosine formation in rat liver following intraperitoneal administration. *N*-Nitrosomorpholine induces somatic cell mutations in *Drosophila melanogaster in vivo*. Several DNA adducts of *N*-nitrosomorpholine have been identified. The most sensitive target tissue and species was the liver in rats. Due to the weight-of-evidence supporting a mutagenic mode of carcinogenic action, a lifestage adjusted 10^{-5} cancer risk level was extrapolated from the chronic drinking water study human equivalent $BMDL_{10}$ of 0.025 mg/kg-day, which was based on the incidence of hepatocellular carcinomas in female F344 rats.
CONCLUSIONS	*N*-Nitrosomorpholine is classified by IARC as a *possible human carcinogen* and the weight of evidence supports the classification *likely to be carcinogenic to humans* using U.S. EPA guidelines for carcinogen risk assessment. The drinking water action levels derived in this risk assessment are protective of public health since they were based on linear extrapolation from chronic oral data for *N*-nitrosomorpholine using a sensitive endpoint and laboratory animal species, and take into account potential increased susceptibility from early postnatal-life exposure.