EXECUTIVE SUMMARY

N-NITROSOPIPERIDINE – Oral Risk Assessment CAS # 100-75-4			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
$BMDL_{10}$ (95% confidence limit at 10% response level)	0.034	mg/kg-day	From the incidence of hepatocellular adenoma or carcinoma in combined male and female rats in a chronic study
10^{-5} Cancer Risk Level – life-stage adjusted	1.4×10^{-6}	mg/kg-day	From the $BMDL_{10}$, adjusted for life stage
Oral Slope Factor	2.9	$mg/kg\text{-}day^{-1}$	From the $BMDL_{10}$
Oral Slope Factor – life-stage adjusted	7.4	$mg/kg\text{-}day^{-1}$	From the $BMDL_{10}$, adjusted for life stage
Drinking Water Unit Risk – life-stage adjusted (at the 1×10^{-5} cancer risk level)	2.1×10^{-4}	$\mu g/L^{-1}$	From the oral slope factor, adjusted for life stage
TAC – life-stage adjusted (total allowable concentration)	50	ng/L	For a 70 kg adult drinking 2 L/day, adjusted for life stage
SPAC – life-stage adjusted (single product allowable concentration)	5	ng/L	From the TAC, assuming 10 potential sources of N-nitrosopiperidine in drinking water
STEL – life-stage adjusted (short term exposure level)	50	ng/L	The STEL is set equal to the TAC for a chemical presumed to be a linear carcinogen

EXPOSURE SUMMARY	General population exposure to *N*-nitrosopiperidine potentially occurs from tobacco smoke, food, and drinking water. It is also formed endogenously from nitrosation of dietary piperidine. Occupational exposure has been associated with rubber manufacture and processing (HSDB, 2012).
KEY STUDIES	Gray, R., Peto, R., Brantom, P., and Grasso, P. 1991. Chronic nitrosamine ingestion in 1040 rodents: The effect of the choice of nitrosamine, the species studied, and the age of starting exposure. *Cancer Research* 51(23 II): 6470-6491.
CRITICAL EFFECT	Hepatocellular neoplasias were observed at an increased incidence compared to controls in male and female rats that received *N*-nitrosopiperidine in drinking water for two years.
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-lifestage exposure.
TOXICITY SUMMARY	*N*-Nitrosopiperidine is among approximately 300 *N*-nitrosamines known to be carcinogenic in nonhuman primates or rodents. The principal target organs for *N*-nitrosopiperidine carcinogenicity are liver, upper digestive tract and respiratory tract. Studies have been designed to evaluate tumor development in rats, mice, hamsters, guinea pigs, and nonhuman primates, and associated pathological changes, as well as the influence of dose rate, dose route, and total dose. *N*-Nitrosopiperidine is mutagenic to bacterial and mammalian cells *in vitro*, induces chromosomal aberrations, DNA damage and unscheduled DNA synthesis *in vitro*, and induces somatic cell mutations in *Drosophila melanogaster in vivo*. Micronucleated reticulocytes were not induced by *N*-nitrosopiperidine in an *in vivo* assay with mice. Several DNA adducts of *N*-nitrosopiperidine have been identified *in vitro*. *N*-Nitrosopiperidine generates reactive oxygen species and stimulates apoptosis *in vitro*. Evaluations based on *in vitro* gene expression indicate that exposure at 40 mM affects pathways involved in embryogenesis, immune system response, cell cycle regulation, cell proliferation, and oxidative stress. 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 $BMDL_{10}$ of 0.034 mg/kg-day, which was based on the incidence of hepatocellular adenomas or carcinomas of male and female Colworth rats. Cross-species dose scaling ($BW^{3/4}$) was not applied since the toxic moeity is a reactive intermediate that reacts within the target tissue and never leaves the tissue in which it is formed.
CONCLUSIONS	*N*-Nitrosopiperidine 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*-nitrosopiperidine using a sensitive endpoint and laboratory animal species and strain, and take into account potential increased susceptibility from early life exposure.