EXECUTIVE SUMMARY

Titanium (CAS # 7440-32-6) and Titanium Dioxide (CAS # 13463-67-7)
Oral Risk Assessment

PARAMETER	Ti LEVEL[1]	UNITS	DERIVED:
NOAEL (no-observed-adverse-effect level)	2,680	mg/kg-day	From a 2-year titanium dioxide feeding study in rats.
Oral RfD (oral reference dose)	3	mg/kg-day	From a 2-year titanium dioxide feeding study in rats.
TAC (total allowable concentration)	90	mg/L	From a 2-year titanium dioxide feeding study in rats, for a 70 kg adult consuming 2 L/day, with a 20% Relative Source Contribution for drinking water.
SPAC (single product allowable concentration)	9	mg/L	From the TAC, assuming the default 10 sources of titanium in drinking water.
STEL (short term exposure level)	90	mg/L	Set equal to the TAC.

[1] The solubility of titanium or titanium dioxide in actual use as a direct or indirect drinking water additive should not be exceeded.

KEY STUDY	NCI (National Cancer Institute). 1978. Bioassay of Titanium Dioxide for Possible Carcinogenicity. NTIS PB288780.
CRITICAL EFFECT	No significant adverse responses at either of the tested doses
UNCERTAINTY FACTORS	Uncertainty factors applied in calculating the oral RfD are as follows: • 10x for interspecies extrapolation • 10x for intraspecies extrapolation • 1x for study duration, since a chronic study was used • 1x for extrapolation from a LOAEL to a NOAEL, since a NOAEL was used • 10x for database deficiencies The total uncertainty factor is, therefore, 1000x.
TOXICITY SUMMARY	While there are no experimental data by the oral route in humans, titanium is the ninth most abundant element and humans are routinely exposed to it as a natural, direct and indirect food additive. A statistically significant reduction in survival of female mice fed titanium dioxide for two years (NCI, 1978) was of questionable biological significance due to exceptionally high survival of control females, and represented the only significant toxicological effect seen in rats or mice in the 2-year studies. Neoplastic responses to long-term titanium exposure in laboratory animals were observed after high-dose titanium dust inhalation in rats. Those lesions, in addition to the non-neoplastic responses to titanium inhalation exposure in laboratory animals and humans, were attributed to excessive dust accumulation in the lung. Statistically increased neonatal deaths and runts were seen in the second generation of a three-generation reproduction study (Schroeder and Mitchener, 1971), in which rats were exposed to titanium in their drinking water. This study, however, was not conducted according to guidelines and had insufficient experimental detail for use in risk assessment. Titanium compounds did not induce gene mutations in microbial assays or in the mouse lymphoma assay. Titanium dioxide did not induce structural chromosomal aberrations *in vitro* or *in vivo*, but did induce micronuclei both *in vitro* and *in vivo*, suggesting that it induces micronuclei through chromosome loss (aneuploidy).
CONCLUSIONS	Based on positive clastogenicity data and negative cancer bioassays in rats and mice, there is *inadequate information to assess the carcinogenic potential* of titanium and titanium dioxide to humans by the oral route. The concern associated with positive clastogenicity (micronucleus) data is reduced because dietary titanium failed to induce neoplastic lesions following chronic oral exposure in rats or mice. Any significance to the positive micronucleus data or to results of the three-generation reproduction study have been addressed by incorporating appropriate uncertainty factors in the oral risk value calculations. There is limited evidence of carcinogenicity in laboratory animals following inhalation and intramuscular exposure to high levels of titanium dioxide or titanium, but the adverse effects are not considered relevant to drinking water (oral) exposure. It is not appropriate to use the derived oral risk values for titanium tetraiodide, titanium tetrabromide, titanium tetrachloride, titanium tetrafluoride or organotitanium compounds as their chemical, physical, and biological properties differ from those of titanium and titanium dioxide evaluated in this document. Inorganic titanium compounds not specifically excluded are either not manufactured in the United States or have limited available data. Those compounds shall be evaluated on a case-by-case basis to determine whether use of the derived oral risk values is appropriate. The derived TAC, SPAC, and STEL values for titanium and titanium dioxide are protective of public health.