EXECUTIVE SUMMARY

Lanthanum Carbonate Oral Risk Assessment CAS #587-26-8			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
Lowest Therapeutic Dose in Humans	5.4	mg/kg-day	From the dose used to control hyperphosphatemia in hemodialysis patients
Oral RfD (oral reference dose)	0.5	mg/kg-day	From the lowest therapeutic dose in humans with a 10x total uncertainty factor
TAC (total allowable concentration)	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)	0.4	mg/L	From the TAC, using 10 sources of La in drinking water.
STEL (short term exposure level)	Not applicable		A STEL for La exposure through the use of lanthanum carbonate was not developed since metals are not anticipated to demonstrate decay over time.

EXPOSURE SUMMARY	Lanthanum (La) carbonate is used to reduce inorganic phosphorous or arsenic concentrations in drinking water and for other proprietary uses.
KEY STUDY	Multiple clinical trials were collectively considered key studies. These trials have administered La carbonate to individuals with compromised renal function to control hyperphosphatemia for up to six years.
CRITICAL EFFECT	The lowest therapeutic dose of La carbonate associated with pharmacological activity (reduced serum or urine phosphate) contains 375 mg/day La (5.4 mg/kg-day), recognizing that reduced blood or urine phosphate in and of itself has not been shown to be an adverse effect.
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD include: • 1x for interspecies extrapolation • 1x for intraspecies extrapolation • 3x for LOAEL to NOAEL extrapolation • 3x for subchronic to chronic extrapolation • 1x for database deficiencies The total uncertainty factor is therefore 10x.
TOXICITY SUMMARY	Although clinical trials for La carbonate focus on its efficacy for treating hyperphosphatemia in hemodialysis patients (rather than dose-response relationships of potential systemic toxicity), they are useful in that they provide evidence that La (as the carbonate) concentrations up to 43 mg/kg-day can be tolerated by a sensitive subpopulation (those with compromised renal function) without appreciable evidence of adverse effects for up to six years. Repeated gavage exposure to La carbonate in laboratory animals from 13 weeks to two years was associated with mineralized foci and epithelial hyperplasia of the glandular and non-glandular stomach in rats and mice, which progressed to stomach adenomas in mice. The weight of evidence suggests that La carbonate has low genotoxic potential *in vitro.* The mode of action of the stomach tumors was considered to be a non-genotoxic, threshold mode of action involving repeated chemical irritation at the portal of entry. Due to insufficient epidemiology data for La compounds in humans, the *data are inadequate for an assessment of human carcinogenic potential* based on U.S. EPA (2005a) guidelines for carcinogen risk assessment. The RfD of 0.5 mg/kg-day was based on the lowest therapeutic dose of La used to control hyperphosphatemia (5.4 mg/kg-day) after application of a 10x composite uncertainty factor. A LOAEL to NOAEL factor of 3x was applied since reduced blood or urine phosphate in and of itself has not been shown to be an adverse effect. A study duration extrapolation factor of 3x was applied due to the persistent accumulation and long biologic half-life of La once it enters tissues and the lack of longer-term (more than six years) clinical data to confirm the lack of adverse effects, particularly on the liver or bone. These organs demonstrated the highest tissue La concentrations. This RfD is comparable to an RfD of 0.6 mg/kg-day based on the $BMDL_{10}$ of 62 mg/kg-day for the precursor effect, stomach epithelial hyperplasia, in female rats receiving La carbonate via gavage for 26 weeks, after a 100x composite uncertainty factor is applied to account for interspecies (3x) and intraspecies (10x) extrapolation and database deficiencies (3x).
CONCLUSIONS	Since the drinking water action levels derived in this risk assessment were based on the lowest clinical dose in a sensitive subpopulation, they are protective of public health. The present assessment applies to La carbonate, which dissociates to the La^{+3} ion in the stomach. This evaluation does not apply to the nitrate or chloride salts of La.